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Integrative Oncology: Implementing Patient-Centred Care

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CONTENTS

EXECUTIVE SUMMARY

INTEGRATIVE ONCOLOGY: IMPLEMENTING PATIENT-CENTRED CARE

"I was 30 when I received the news from my specialist. He said they found something in my blood work; that it was leukaemia. He started talking about the disease and treatment options, but I wasn't taking it in, I just watched him fan out brochures for different drugs on his desk, pointing at graphs and side effect profiles. I caught the vital information. I'd know in the first three months if treatment was going to work. I'd be taking medication for the rest of my life. Having children in future was unlikely. There was no time to retrieve eggs. I had to make a decision about the treatment plan on the spot. I had to book in a bone marrow aspiration as soon as possible.

I made the decision, I booked the procedure, I paid the bill and walked out of the hospital. Now what?"

Reading stories told by patients faced with this reality, a common theme that arises is one of feeling left out of the picture. In the whirlwind of appointments and a flood of information, the patient can feel like they have taken a back seat to this part of themselves which is proliferating, beyond control.

However, there is so much more to the patient journey than the mechanisms of carcinogenesis and cancer treatment. By definition, patient-centred care ensures that the patient's values guide the treatment approach. It prioritises physical comfort, emotional wellbeing and social support.[1] Bringing the patient to the centre of care ensures their experience is infused with a sense of dignity and humanity.

Here, natural health care Practitioners are in a place where they can walk with patients through this seismic shift in their lives; seeing the patient in front of them, hearing their story and playing an integral role as part of the team accompanying the patient on their journey.

"To restore the human subject at the centre – the suffering, afflicted, fighting, human subject – we must deepen a case history to a narrative or tale; only then do we have a 'who' as well as a 'what', a real person, a patient, in relation to disease – in relation to the physical."

- Oliver Sacks MD

For Practitioners this can be daunting, but by facing it with humility and curiosity, this challenge can be incredibly rewarding too. This is a unique opportunity for Practitioners to walk with their patients in appreciation of their journey.

The goal of this seminar is to arm Practitioners with the tools and confidence they need to support their patient's experience of cancer therapy, reduce the side effects of treatment, and optimise treatment efficacy. This seminar will increase your understanding of how cancer develops and the mechanisms of cancer therapy, facilitating effective communication with the patient's primary care physician. Furthermore, this seminar will highlight where Practitioners have an opportunity to utilise their skills in holistic care, improving diet and lifestyle factors which support patients to live well through this period of time. Finally, learn the integral role of supporting mental health in patient centred care and integrative oncology, and the important role of the natural health care Practitioner as a key part of the support team.

Hallmarks of Cancer

The word cancer, originating from the Greek word for crab, refers to the long tendrils radiating out from the centre of a tumour – starkly different in appearance to the well-organised nature of healthy tissue. The cause of this abnormal cell growth has been a subject of enquiry for centuries. In 1775, Percivall Pott demonstrated the association between chimney soot and scrotal cancer, and so began the understanding of how exposure to some chemicals leads to carcinogenesis. Since then, viruses and hereditary conditions associated with the development of cancer have been discovered, offering explanations which sometimes sound contradictory. Regardless of the cause, some shared features appear to be required for the development of the myriad of conditions collectively known as cancer.

These features were laid out in a seminal article written by researchers Hanahan and Weinberg in 2000, and were named the six hallmarks of cancer, described below:

- Sustained proliferation: Unlike normal cells, cancer cells can proliferate in the absence of growth factors. This hallmark involves oncogenes (see page 7), which can up-regulate receptors and increase the production of, or mimic, growth signals;
- Growth suppressor evasion: Normal cells contain antigrowth signals which divert cells from proliferation towards quiescence or differentiation. Mutations in tumour suppressor genes (see page 10) can deactivate growth suppressors, or cause cells to be unresponsive to their action;
- Replicative immortality: In cancer, there is an uncoupling of a cell's growth programing, and the signals the cell receives from its environment. Mutations in tumour suppressor genes can enable cells to replicate unchecked for generations. Cancer cells also display an upregulation of telomerase, an enzyme that offsets cellular aging;
- Sustained angiogenesis: Tumours cannot live without an abundant supply of blood and nutrients. In order to survive they display increased expression of endothelial growth factors;
- Apoptosis evasion: Programed cell death (apoptosis) protects healthy tissue by halting proliferation in the face of critical malfunction. Apoptosis can involve oncogenes and mutations in tumour suppressor genes, but also involves changes in mitochondrial death signalling; and
- Invasion and metastasis: One of the most well-known characteristics of cancer cells is their ability to invade other tissue. This process involves alterations in cell adhesion molecules and degradation of the extra cellular matrix.[2]

Twenty years later, these six hallmarks still stand up to scrutiny, although they have since gained two 'emerging hallmarks' and two 'enabling characteristics' (Figure 1).

Emerging hallmarks:

- Dysregulated energetics: Cancer cells display altered energy metabolism and mitochondrial function, fuelling cellular proliferation (explored in more detail on page 29); and
- Immune evasion: Immune surveillance ensures that transformed cells are destroyed, however, cancer cells actively evade detection and attack from the immune system (explored in more detail on page 15).

Enabling characteristics:

- Genetic instability: Cancer cells display an increased rate of mutation and reduced deoxyribonucleic acid (DNA) repair, which allows for further mutations and enables alterations characteristic of the other hallmarks; and
- Inflammation: Tumour associated inflammation enhances tumourigenesis and progression. Furthermore, inflammation contributes to the other hallmarks; for instance by upregulating growth factors and altering the extracellular matrix, thereby encouraging angiogenesis and invasion and metastasis (explored in more detail on page 21).[3]

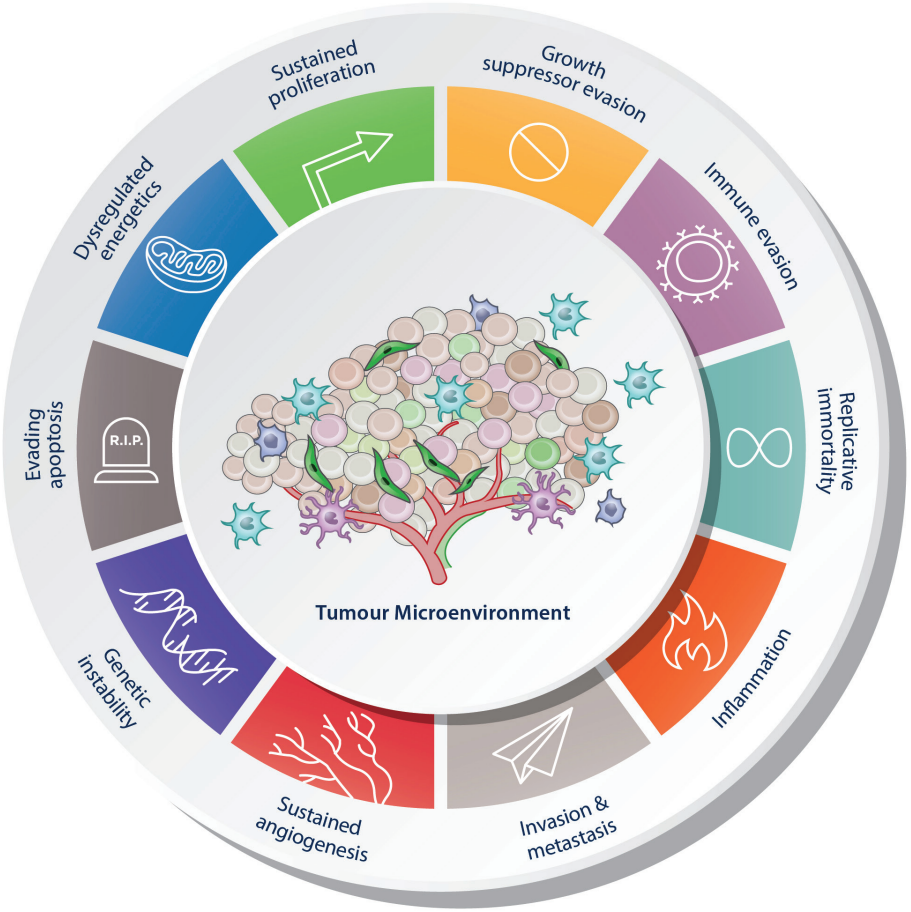


Figure 1: The six hallmarks, two emerging hallmarks and two enabling characteristics of cancer.

It has become clear that cancer is more than just the sum of the cancer cells. The tumour microenvironment (TME) contains extracellular matrix, blood vessels and cell types which enable tumour progression, such as inflammatory immune cells and fibroblasts. Together, the contents of the TME contribute to the hallmarks of cancer to promote and protect the tumour.[4]

The Accelerators: Oncogenes

The journey towards the discovery of oncogenes, that is, genes which have the potential to cause cancer, began in 1909 when a poultry farmer presented researcher Peyton Rous with a hen exhibiting a large growth. When Rous took some of the tumour and processed it, removing all solid material, the remaining liquid was able to induce tumours in other chickens. This seemed to indicate that the tumour was due to a 'filterable agent', i.e. something of non-cellular origin. Later, this filterable agent was identified and named: a retrovirus called Rous sarcoma virus (RSV). To explain this phenomenon, Huebner and Todaro proposed the oncogene hypothesis in 1969. They suggested that viruses contained genes which could transform cells, thus leading to cancer development. After much investigation, it was found that an RSV gene called Src was kick-starting mutations in these unfortunate chickens. Intriguingly, while the virus caused unchecked replication in the chicken's cells, Src seemed to be dispensable for viral replication, leading to questions about its origins. Researchers were able to determine that Src was in fact stolen by the virus from avian origin. That is to say, this gene already existed in the chicken without causing cancer. It was only when RSV caused Src to be over expressed, that it became problematic.[5]

From Proto-oncogene to Oncogene

It is now understood that oncogenes originate from genes called proto-oncogenes, which regulate normal, healthy cellular growth and division. However when proto-oncogenes are altered, they can become oncogenes, leading to sustained proliferation and cancer. The mutations that produce oncogenes are referred to as gain-of-function mutations. This means that usually only one gene copy needs to be affected in order to create problems. These mutations tend to be acquired (rather than inherited), and can be caused by carcinogens such as radiation, smoke and other environmental toxins. Some viruses, such as human papilloma virus (HPV), can also produce oncogenes.

A proto-oncogene can become an oncogene by missense mutations, gene amplification or translocation.[6] A missense mutation will cause a change to a gene small enough that it produces a protein which is ever so slightly different from the product of an un-mutated gene. In the case of a proto-oncogene, a missense mutation can shift the gene in a way that causes it to be an oncogene (Figure 2).

Figure 2: A missense mutation, results in a protein that is slightly different from the product of a proto-oncogene.

A good example of oncogenic, gain-of-function, missense mutations, are that of the RAS genes (HRAS, NRAS and KRAS), which were in fact, the first oncogenes to be discovered. KRAS is the oncogene most commonly associated with human cancer, being mutated in 25% to 30% of tumours.[7] Normally, the RAS proto-oncogenes produce Ras* proteins, which require activation in order to initiate cell growth and differentiation. This occurs when a particular growth factor binds to their respective receptor, causing a cascade of events which activates the Ras protein (Figure 3). When RAS genes are mutated, they produce a protein that doesn't need to be activated to move the cell cycle forward. It does so independent of growth factor binding, leading to sustained and unchecked proliferation.[8]

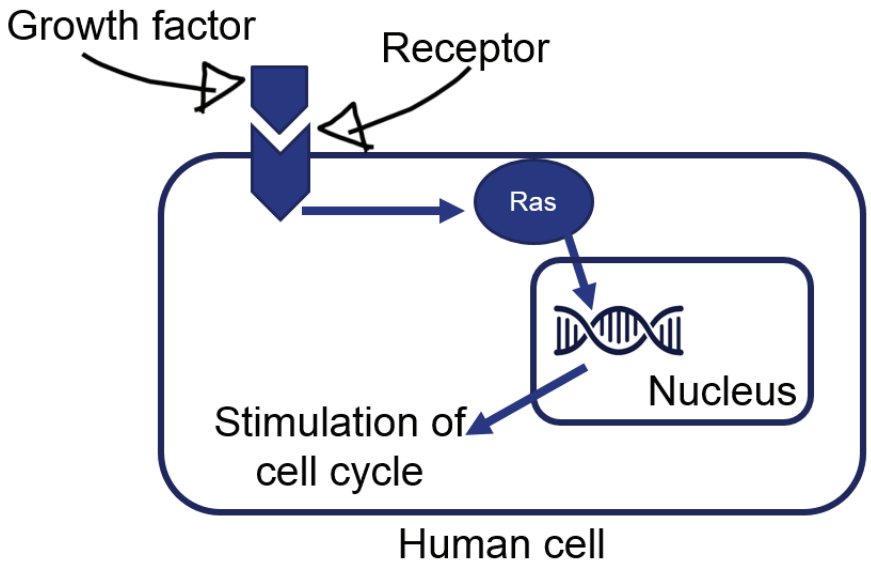


Figure 3: Ras usually requires the binding of growth factors to growth factor receptors for activation.

Amplification occurs when a gene is copied, with each gene copy producing a corresponding amount of protein (Figure 4). If amplification occurs in a proto-oncogene it becomes an oncogene, driving the cell cycle forward, leading to sustained proliferation.[9] For example, the gene HER2 is a proto-oncogene that promotes cell proliferation and opposes apoptosis. Human epidermal growth factor receptor 2 (HER2) is amplified in 15% to 20% of breast cancers,[10] and is associated with more aggressive disease and poorer prognosis. Identification of the HER2 oncogene has opened the way for targeted treatments, specific for HER2 positive breast cancer.

* RAS denotes the gene, while Ras denotes the protein produced by the gene.

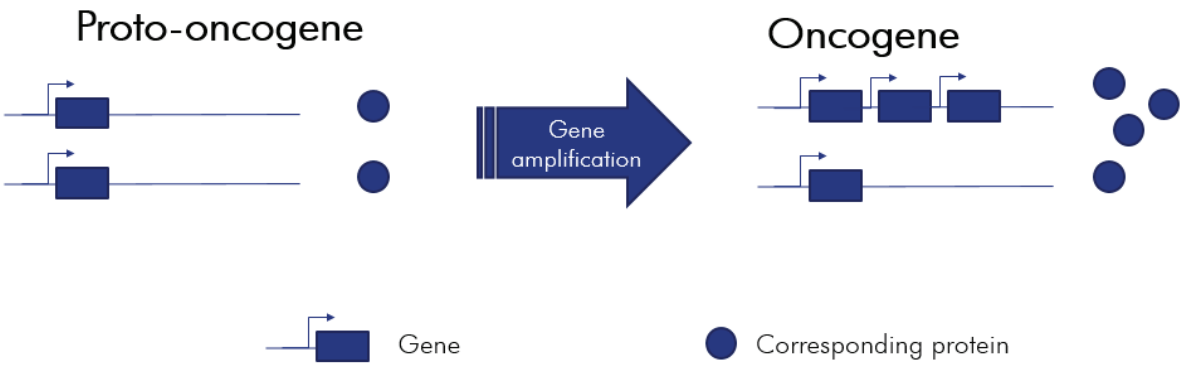


Figure 4: Gene amplification leads to an increase in protein production which drives proliferation.

Translocation is another mechanism by which a proto-oncogene becomes an oncogene. Proto-oncogenes have gene promotors that are highly regulated, only switching on the gene when the cell cycle needs to be pushed forward (seen on the top, left-hand side of Figure 5). If this gene is translocated to a promotor specific to a gene that needs to always be switched on (for example, a house keeping gene), it will likewise be constantly expressed, becoming an oncogene (seen on the bottom, right-hand side of Figure 5).[11]

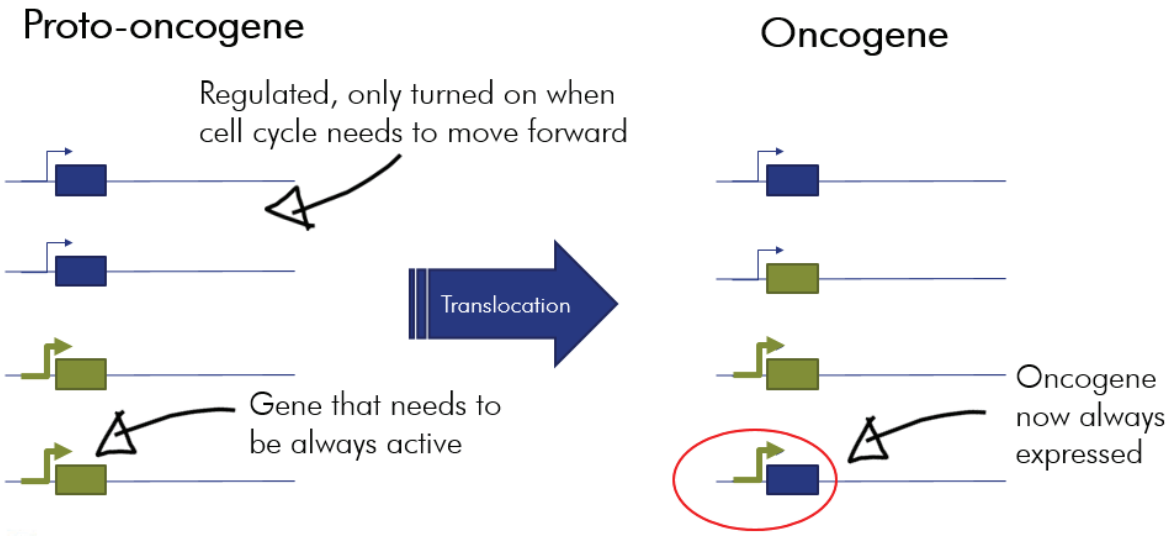


Figure 5: When a proto-oncogene is translocated to a promotor which is always switched on, it becomes an oncogene.

Box 1: Viral Oncogenes

Chickens are not the only ones at risk of cancer-causing viruses. Some viruses contain oncogenes, which, when inside a human cell, can drive sustained proliferation. Viral oncogenes can do this by activating proto-oncogenes within the human cell, so they are always expressed. They can also inhibit tumour suppressor genes. HPV, for instance, contains the oncogene E6, which produces a protein that binds to and inactivates p53. This protein, expressed by the p53 tumour suppressor gene, normally prevents proliferation and promotes apoptosis. It's inhibition by HPV explains why this virus is associated with higher rates of cervical cancer (as well as cancer of the anus, vulva, vagina, penis and oropharynx). In fact, two types of HPV cause 70% of cervical cancer.[12]

Broken Brakes: Tumour Suppressor Genes

While oncogenes lead to sustained proliferation by putting the cell cycle pedal to the floor, in cancer, tumour suppressor genes lose their ability to hit the brakes. Mutated tumour suppressors originate from genes that regulate cell cycle arrest, apoptosis, senescence, DNA repair and differentiation.[13] The tumour suppressor gene p53, known as the 'guardian of the genome', is the most commonly mutated gene in human cancer, being present in more than half of cases.[14]

RB1, the first tumour suppressor gene to be identified, codes for the Rb protein, which prevents cell cycle progression. Mutations in RB1 are associated with many cancers, but it is most well-known for being involved in retinoblastoma. For a long time a geneticist called Alfred G. Knudson had studied patients with retinoblastoma, a type of retinal cancer, meticulously recording information about the occurrence of tumours. He noticed that heritable retinoblastoma occurred early in life, and had a bilateral presentation, with multiple tumours. Nonheritable retinoblastoma on the other hand, occurred later in life, and had a unilateral presentation, with one tumour. This discrepancy can be explained by the two-hit hypothesis, proposed by Knudson in 1971 (Figure 6). The loss-of-function that occurs in mutated tumour suppressor genes is recessive. When this occurs in one allele it isn't enough to cause carcinogenesis. Those with heritable retinoblastoma inherit, through the germline, a mutation in RB1 which is present in every cell. This is the first-hit. It only takes a second-hit for cancer to develop. However, those with non-heritable retinoblastoma need to incur both hits to the RB1 gene, explaining why it typically occurs at a later age.[15]

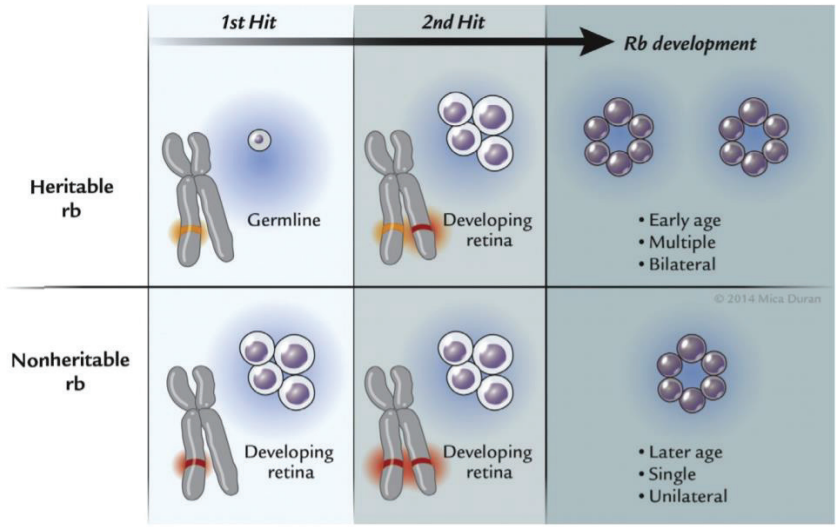


Figure 6: The two-hit hypothesis, as shown in the development of retinoblastoma.[16]

While the two-hit hypothesis has been a helpful model for understanding the link between mutations in tumour suppressor genes and cancer, it has been criticised for being too simplistic. Studies of tumour suppressor genes show that the 'second-hit' may not in fact be a mutation. For instance, gene expression can be inhibited through epigenetic mechanisms or abnormal transcription factor regulation. Furthermore, the proteins that are coded for by a tumour can undergo degradation or be 'mislocalised', essentially preventing the end product from regulating the cell cycle.[17]

Box 2: Questioning 100 Years of Mutation Theory

The somatic mutation theory, which places genetic mutations as the initiator of malignancy, began in 1914 and has been the dominant theory of carcinogenesis since. It postulates that cancer begins with a mutation which gives a cell a growth advantage. The cell then clones itself, accumulating DNA mutations that continue to encourage proliferation. Here, mutations are central, and necessary for cancer to develop. However, this theory has been challenged and some have suggested that the presence of mutations in tumour samples may be misrepresented as the underlying cause of cancer.[18] Critics of the somatic mutation theory point out that several studies surveying tumours found zero genetic mutations.[19] On the other hand, approximately 10% of the healthy population over 65 years old display driver mutations that are often seen in leukaemia. In fact, all cells in all people display small mutations in cells which similarly clone themselves, forming a mosaic of slightly differing genetic material.[20]

The tissue organisation theory has been proposed as an alternative to the somatic mutation theory. In this model, DNA mutations are a by-product of carcinogenesis, rather than its cause. Instead, dysfunctional tissue organisation leads to cancer development and genetic instability. The proponents of this theory cite evidence of dysfunctional morphostats, signals that keep tissues differentiated and well organised; altered mechanical forces, which play a role in tissue development; and bioelectric changes, as possible alternatives to mutation driven carcinogenesis. Supporting this theory is the existence of compounds such as chloroform, which induce tumours, without damaging DNA. Instead, these compounds seem to lead to carcinogenesis by disrupting gap junctions.[21]

While it is often repeated that cancer is a genetic disease, it is far from definitive that mutations are the cause of cancer. There is no doubt that genetic instability plays a role in carcinogenesis, however there are other important systems at work.

A Brief History of Modern Oncology

Whilst genetic mutations have largely been the focus of the causes of cancer, this unfortunately provides little benefit in treating existing cancers. For more than 70 years, oncology has primarily focused on inhibiting the cell cycle as means of strangling this rampant cell proliferation. Over the decades, the three prongs of attack in oncology – surgery, chemo- and radiotherapy - have yielded intermittent result. In particular, chemotherapy has lost some horrific battles, but slowly, trial by trial, it is slightly winning the war.[22] Along this journey there have been some additions to the oncologists' toolkit that have produced dramatic results, albeit often only in specific cancers.

For example, imatinib has been an overwhelming success for the treatment of chronic myelogenous leukaemia (CML).[23] Likewise, trastuzumab, a 'targeted therapy', has been a game changer for aggressive, early stage, and HER2-positive breast cancer. Additionally, the relatively recent deployment of immunotherapies, such as PD-L1 inhibitors, have yielded significant benefits to a wide range of advanced cancers.[24]

The successes of traditional therapies, peppered with the occasionally quantum leap, over the decades have now cumulated in meaningful results for cancer patients. For instance, the five-year survival rate in Australia has extended for almost all cancers over the past 30 years (Figure 7).[25]

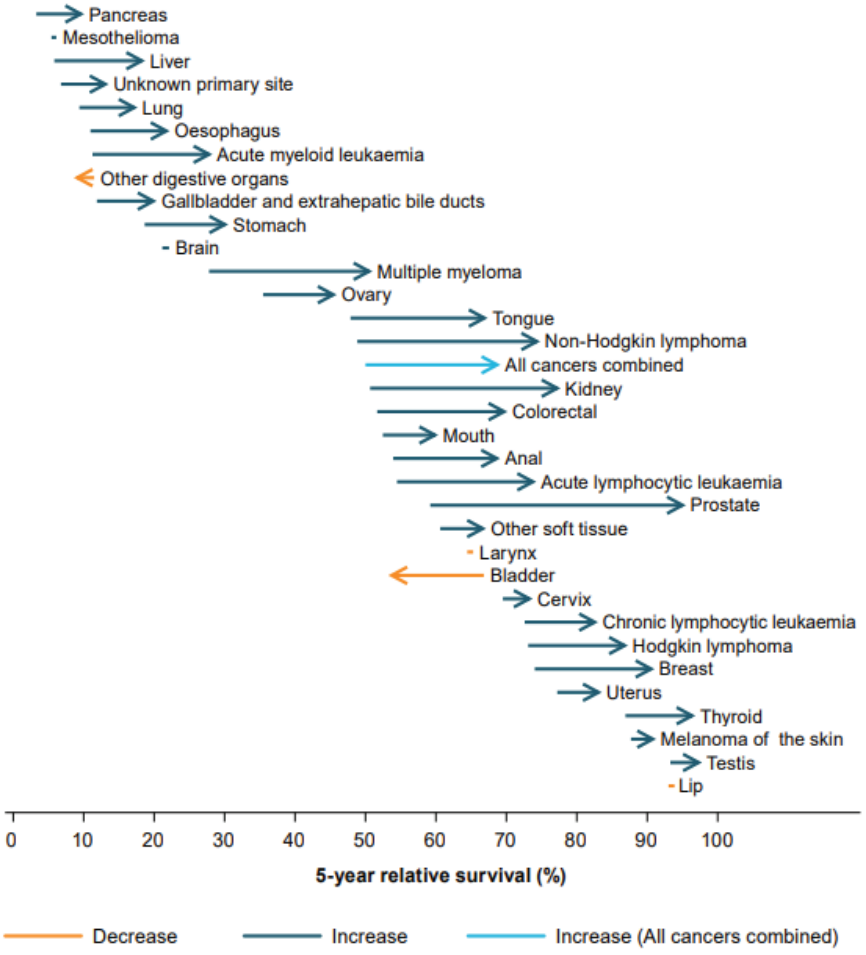


Figure 7: Australian five-year survival of cancers between 1986-1990 and 2011-2015.[26]

Conquer the Dividing

Despite the expanding toolkit in oncology, chemotherapy is often a core treatment for many cancer patients. Chemotherapy is a broad term for a number of drugs that act to inhibit the cell cycle, i.e. cell division. The cell cycle is typically broken down into five distinct stages: two growing phases (gap [G1 and G2]), a DNA synthesis phase (S), the cell division phase (M [mitosis]) and a resting phase (G0). Chemotherapies are an eclectic mix of drugs that are difficult to group. One approach is to group the class of chemotherapies based on how they inhibit the cell cycle (Figure 8). Appendix 1 further outlines the classes and common use of chemotherapies to help Practitioners better understand the regime a cancer patient may undertake.

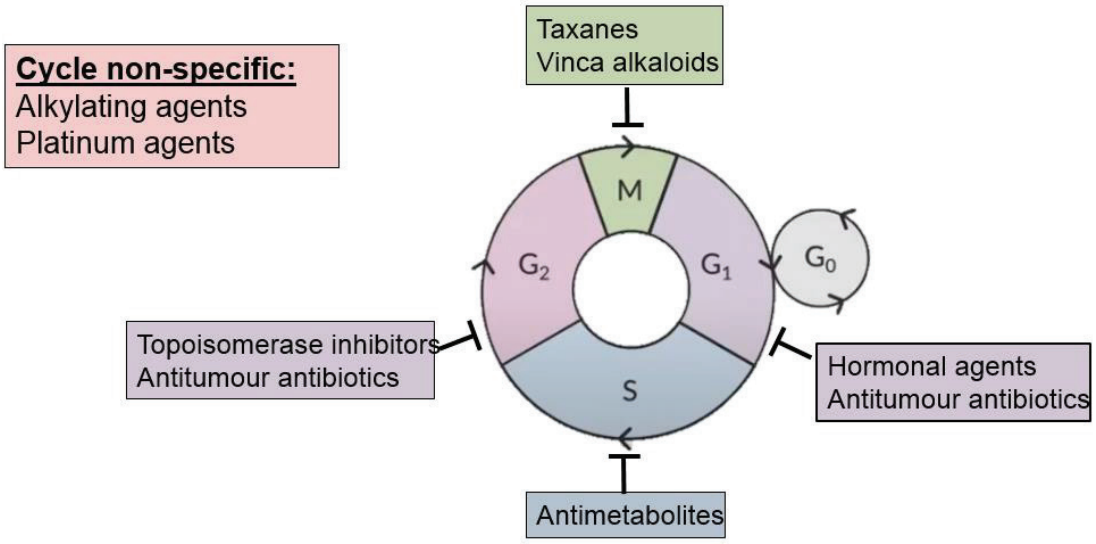


Figure 8: Chemotherapies act to inhibit the cell cycle.

In addition, both chemo- and radiotherapy cause oxidative stress, DNA damage and subsequent cellular apoptosis, as part of the mechanism of action. They do this to varying degrees as listed in Table 1.[27] For more information about oxidative stress and the use of antioxidants during cancer, see page 27.

Table 1: Cancer treatments that induce oxidative stress.[28]

High oxidative stress	Low oxidative stress
Radiotherapy	Vinca alkaloid
Alkylating agents	Taxanes
Anthracyclines	Anti-metabolites
Epipodophyllotoxins	
Platinum coordinated complexes	
Camptothecins	

Defeat the Tumour Before the Body is Defeated

As Practitioners and patients are undoubtedly aware, the use of chemotherapy often comes at a heavy cost. Traditional chemotherapies are non-discriminatory, rather than 'targeted,' and thus will inhibit all cell division – whether it's a cancer cell or a healthy cell. The view is, as cancer cells divide more rapidly than normal cells, the body will lose less in this war of attrition; defeat the tumour before the body is defeated. Additionally, chemo- and radiotherapy induce oxidative stress, genomic instability and inflammation. These insults not only also add to a long list of side effects from chemotherapy (Table 2) but some researchers fear that these stressors also may contribute to cancer reoccurrence in the future.[29,30]

Table 2: Common side effects from chemo- and radiotherapy.[31]

Side effect	Prevalence	Mechanism/contributing factors
Fatigue	50-90%	Inflammation, anaemia, pain, stress
Anxiety and depression	80%	Stress of cancer diagnosis and therapy, uncontrolled pain, metabolic abnormalities e.g. anaemia, endocrine abnormalities, medications
Sleep issues	50-90%	Medication side effect, stress, altered diurnal rhythm, physical inactivity, pain, environmental
Pain and neuropathy	≥40%	Can originate from primary and metastatic sites or from treatment
Anorexia and cachexia	50-80%	Systemic inflammation, nutritional insufficiency
Nausea and vomiting	~60%	Medication side effects
Mucositis	40-60%	Inflammation, neutropaenia, barrier degeneration

This information is in no way to discourage the use of traditional therapies; as it is highlighted above, the overall benefits of modern oncology has been life changing. However, it is important to recognise the costs as well as the benefits of therapy, and more importantly, to identify where complimentary therapies may play a role to mitigate these side effects.

Adverse Effects of Chemotherapy Lowered With AHCC™

When it comes to addressing the side effects of cancer therapy, active hexose correlated compound (AHCC™), a derivative of shiitake mushroom, offers a safe and effective strategy.

Along with the gastrointestinal (GI) complaints listed above, diarrhoea, constipation[32] and hepatotoxicity[33] can be common adverse effect of chemotherapy. AHCC™ has shown to be hepatoprotective and when taken alongside chemotherapy, at a dose of 3 g/d over four weeks, significantly lowered elevated alanine transferase (ALT) levels in 85% of patients with various cancers.[34] Furthermore, patients experienced less appetite suppression, changes in bowel movements, nausea and vomiting when supplementing with AHCC™.[35]

Importantly, AHCC™ may also assist with improving patient quality of life (QOL), which is commonly impacted throughout cancer therapy. Treatment with AHCC™ at 6 g/d significantly improved mental stability, general physical health and engagement in everyday activities for patients with hepatocellular carcinoma.[36]

Some cancer therapies suppress bone marrow function, and therefore the production of red and white blood cells (WBC), referred to as myelosuppression. This adverse effect can lead to serious health complications including infections, thrombocytopenia and severe anaemia. Myelosuppression is managed with blood transfusions, yet a trial using AHCC™ supplementation dramatically prevented this requirement. A group of 25 patients with advanced head and neck cancer receiving chemotherapy plus 3 g/d of AHCC™ daily required 81% less blood transfusions.[37]

Another study observed less incidence of thrombocytopenia cases when 3 g/d of AHCC™ was provided in the second cycle of chemotherapy, when compared with the first cycle without AHCC™. In addition, neutropenia was reduced and neutrophil count was markedly increased in the second cycle compared with the first cycle (Figure 9).[38] Granulocyte colony-stimulating factor (G-CSF) is used to boost low WBC counts, however this treatment is not without side effects. AHCC™ at a dose of 1 g/d for 12 weeks, significantly lowered the requirement of G-CSF in breast cancer patients (stages I, IIA and IIIB) receiving concomitant chemotherapy.[39]

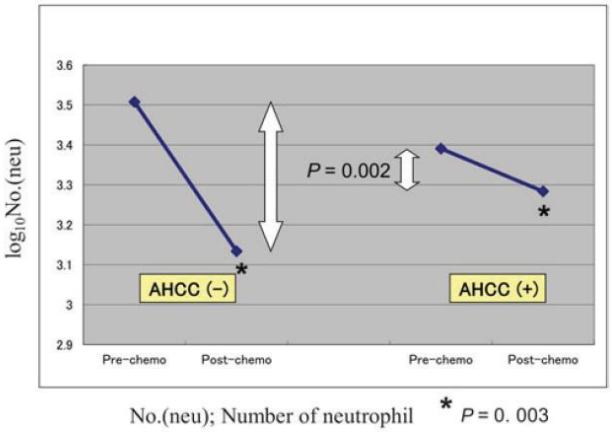


Figure 9: Addition of AHCC™protected against diminished neutrophil counts post chemotherapy.[40]

Zingiber officinale (ginger) is well-known for its anti-inflammatory and anti-emetic effects, and has demonstrated potential in supporting patients on chemotherapy. For example, alongside chemotherapy treatment, ginger extract, at doses ranging from 500 mg/d to 1.2 g/d can reduce nausea.[41,42] In a randomised double-blind placebo-controlled trial, 1 g/d of ginger, when combined with an anti-emetic, significantly attenuated anticipatory, acute and delayed vomiting in breast cancer patients.[43] For many individuals receiving treatment, compounding the misery of digestive side effects is profound fatigue. Interestingly, ginger has been found to assist with this presentation, as 1.2 g/d ginger extract for five days during chemotherapy resulted in 29% less fatigue, improving patients' QOL during therapy.[44]

Furthermore, in animal studies, ginger has shown to be protective against cisplatin-induced hepatotoxicity, where supplementation lowered the liver enzymes ALT and aspartate aminotransferase (AST). Additionally, it reduced lipid abnormalities, which are often associated with chemotherapy.[45]

The combination of *AHCC™ and Ginger* can offer multiple benefits for cancer patients, helping to offset some of the side effects of cancer treatment. This can have huge implications for patients' long-term health outcomes by improving their ability to continue on their treatment and reducing the limitation that side effects cause to dosing. To understand how AHCC™ can further benefit patients undergoing treatment for cancer, a deeper exploration of one of the hallmarks of cancer, immune evasion, is required.

The Concept of Immune Surveillance in Cancer

For over 100 years, immunological and biological researchers have studied the interaction between the immune system and cancer. A brief look at history reveals the developments from research that have allowed for a greater understanding of how the immune system interacts with tumour cells.

- 1891 – American surgeon William Coley noted the effects of immunity in tumours. Coley injected live *Streptococcus pyogenes* directly into the lymphosarcoma of a patient, which resulted in the tumour regressing;[47]
- 1909 – Noble prize winning physician and scientist Paul Erlich proposed that the immune system protected the host against cancer;
- 1967 – Virologist Frank McFarlane Burnet and biologist Lewis Thomas, proposed the *immunosurveillance hypothesis*, postulating that the immune system controlled tumour development; and
- 2002 – Robert D Schreiber's group developed the *immunoediting theory* which permanently changed the understanding of immune function in relation to cancer. This theory highlighted how the immune system may control the development of cancer, or paradoxically shape the immunogenicity of cancer cells making them more resistant to anti-tumour immunity.[48]

A Snapshot of the Three E's of Immunoediting

The immunoediting theory comprises of three phases which determines the fate of the tumour.

1. Elimination
2. Equilibrium
3. Escape

Elimination – The Domination of Anti-Tumour Immunity

This phase continually occurs in the body[50] and supports the immunosurveillance theory whereby anti-tumour immunity dominates.[51,52,53] Elimination is dependent upon the collaboration of the innate, adaptive and complement immune systems.[54] Key players include cytotoxic natural killer (NK) cells,[55,56] type one dendritic cells (DC1),[57,58] $CD4^+$ T cells and $CD8^+$ T cells.

NK cells police the internal environment for abnormalities[59] and as such, play a vital role in controlling tumour growth and metastasis, with higher rates of malignancies being associated with inadequate NK cell populations and/or function.[60] When in cytotoxic attack mode, NK cells attach to tumours and release granules called perforins and granzymes. Perforins pierce the cell membrane and granzymes cause tumour cell apoptosis.[61] However, before this can occur the NK cell relies on two ways to recognise the tumour:

1. Through receptor mediated activity between the NK cell and the tumour,[62] or
2. From the release of interleukins (IL) and chemokines from tumours or DC1.[63]

Receptor mediated activity depends on the interactions between two receptor types on the NK cell. The receptor can either be stimulatory, which, when activated, sends the NK cell into a killing frenzy, or inhibitory, which acts as molecular brakes shutting off NK cell cytotoxic function. The major histocompatibility complex (MHC) class I receptor, common on host cells, sends signals to the NK cell inhibitory receptor that this is 'self', reducing the risk of autoimmunity.[64,65] Certain tumours may down-regulate, degrade or invert this receptor, thus upon policing, the NK cell does not receive the brake signal and launches an attack. Attack may also occur from an overexpression of tumour stress molecules which override inhibitory receptor activity and heighten stimulatory receptor responses.[66] Lastly, NK cells possess an additional receptor that picks up immunoglobulin G (IgG) antibodies, which can initiate tumour cell death.[67]

Signaling molecules, either directly from the tumour or from DC1 assist NK cells to identify tumour cells. In fact, an important relationship exists between NK cells and DC1 with both supporting the recruitment and function of one another to the tumour site. This was demonstrated in a melanoma animal model where genetically depleted NK cell mice had lower populations of DC1 cells at the tumour site.[68] Further, an abundance of DC1 within the tumour microenvironment (TME) is associated with accelerated tumour elimination and better chances of survival.[69] In addition, DC1 secretes IL-12 which elevates NK cell synthesis of interferon (INF)-γ,[70] recruiting macrophages for cleanup and repair.[71]

DC1 also activates antigen-specific $CD4^+$ T cells via MHC II ligands, and shifts $CD8^+$ T cells into cytotoxic mode through IL-12 secretion,[72] the cytokine associated with a prolonged immune response.[73] Furthermore, patients with melanoma who had higher populations of DC1 were more responsive to a type of immunotherapy, known as anti-programmed death-1 (PD-1) therapy, which enhances T cell function (Figure 10).[74]

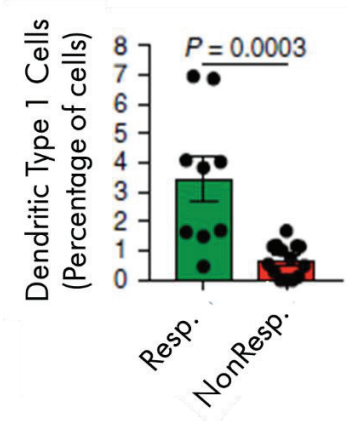


Figure 10: DC1 cell populations in melanoma cancer patients receiving anti-PD-1 therapy.[75]

Cytotoxic CD4+ T cells both alone, and in conjunction with CD8+ T cells, mediate the adaptive immune anti-tumour response.[76] A growing body of evidence indicates tumour antigen-specific CD4+ T cells play a pivotal role in coordinating tumour eradication by facilitating:

- Activation and maturation of dendritic cells;
- Synthesis of cytokines essential for differentiation or maintenance of T-cell responses;
- Activation of B cells to produce tumour antigen-specific antibodies; and
- Together with DC1, enhancement of CD8+ T cell cytotoxicity.[77]

CD8+ T cells function similarly to NK cells, having stimulatory and inhibitory receptors, as well as releasing cytotoxic granules, tumour necrosis factor (TNF)-α and INF-γ. CD8+ T cells become cytotoxic after activation by CD4+ T cells and DC1, playing a vital role in tumour elimination and equilibrium.

Equilibrium – The Road to Escape

During this phase the immune system holds the tumour in a state of functional dormancy, restricting their transition into the growth phase.[78,79] Unfortunately, the longer the tumour stays in this dormant phase, the greater its chances of becoming resistant to immune control due to its ability to edit or alter gene expression of proteins that would normally be recognised by the immune system.[80,81]

High proportions of CD8+ T cells and NK cells are required to maintain equilibrium.[82,83] A balance between cytokines IL-12, a promotor of immune persistence, and IL-23, a promotor of tumour growth, play an important role in determining who will win the fight.[84] However, continued pressure from the immune system may drive the tumour cells to undergo both genetic and epigenetic changes resulting in a generation of cancer cells that can resist immune recognition and invoke immunosuppression.[85]

Escape – The Strength of the Tumour

Several factors, including those discussed below, contribute to the exponential growth of the tumour and the development of the TME,[86] features of the escape phase.

Poor immunogenicity: Mutations within cancer cells may lower or completely stop expression of specific antigens recognised by the immune system. In other cancers, MHC I receptor expression may be retracted or degraded allowing it to dodge the cytotoxic CD8+ T cell.[87,88]

Immune suppression: This results from a combination of inflammatory proteins and antigens produced directly from the tumour, and from the recruitment of additional cells which build the TME. Some mechanisms exploited by tumours include:

- High expression of IL-6 which is involved in proliferation, migration and angiogenesis. The continued secretion of IL-6 interrupts MHC II antigen presentation which suppresses CD4+ T cell mediated immunity[89];
- Tumour secretion of IL-6 increases DC and macrophage release of arginase which reduces CD4+ T cell-mediated immunity[90] and blunts cytotoxic CD8+ T cell function.[91] Thus, tumour synthesis of IL-6 slows anti-tumour immunity[92] allowing for exponential tumour growth (Figure 11);

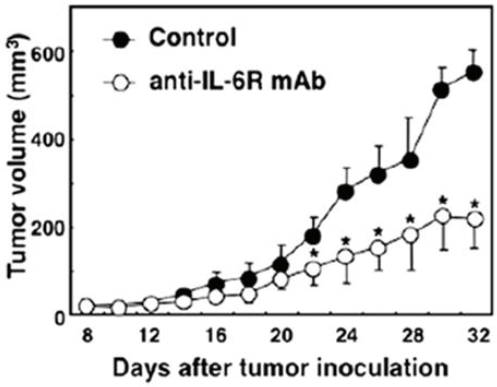


Figure 11: Tumour growth with and without anti-IL-6 antibodies.[93]

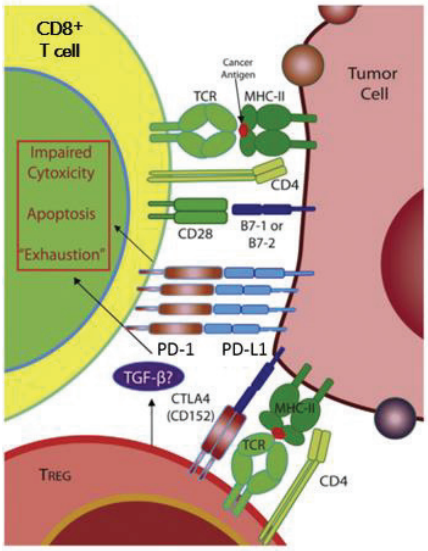
- Production of prostaglandin (PG) E2 affects communication between DC1 and NK cells,[94,95] blocking the expression of NK cell receptors allowing tumours to remain hidden[96];
- Secretion of lactate by the tumour inhibits DC1 functions[97];
- The expression of a transmembrane protein that sends a 'don't eat me' signal to macrophages[98];
- The synthesis of transforming growth factor beta (TGF-β) which lowers NK cell tumour recognition and communication with DC1 cells[99];
- Recruitment of cells including immune cells to build the TME (Table 3). Like a police officer corrupted by the crime lords, certain immune cells act to both protect the tumour from NK and CD8⁺ T cells, and secrete substances to enhance tumour growth[100,101]; and
- Induced CD8⁺ T cell exhaustion.[102]

Tumours Exhaust CD8⁺ T Cells

Tumour cells and the TME induce T cell exhaustion, which occurs due to the overexpression of inhibitory ligands such as programmed death ligand-1 (PD-L1) that bind with inhibitory receptors (PD-1 receptors) on CD8⁺ T cells.[103,104] Persistent tumour antigen stimulation results in an up-regulation of PD-1 receptors on T cells applying molecular brakes. With no foot on the accelerator, the CD8⁺ T cell has poor cytotoxic activity (Figure 12).[105] This is seen in cancer patients where higher percentages of exhausted CD8⁺ T cells are associated with a poorer prognosis.[106]

Exhausted T cells:

- Increased inhibitory receptors
- Lowered IFN-γ and TNF-α
- Reduced proliferation
- Poor killing ability



TCR: T cell receptor; MHC: Major histocompatibility complex; CTLA4: Cytotoxic T-lymphocyte-associated protein 4; PD-1: Programmed death-1; PD-L1: Programmed death ligand-1

Figure 12: Tumours induce CD8⁺ T cell exhaustion.

Table 3: TME demographics.

TME Cell Types	Function
Tumour associated macrophages (TAMs)	• Shift from M1 to M2-like phenotype under the influence of the tumour (discussed further on page 22); and • Secrete TGF-β, IL-10 and proteolytic enzymes involved in extracellular matrix (ECM) remodelling.[108]
Myeloid derived suppressor cells (MDSCs)	• Consists of macrophages, granulocytes and immature dendritic cells; • Secrete extracellular L-arginase which inhibits T cell function; and • Increase reactive oxygen species/ reactive nitrogen species production.[109]
Tumour associated neutrophils (TANs)	• Tumour secreted TGF-β induces polarisation from anti-tumour to pro-tumour behaviour; and • Expresses arginase and pro-angiogenic factors.[110]
Immature/tolerogenic DC1	• Synthesises and releases TGF-β; and • Up-regulates indoleamine 2,3-dioxygenase enzyme activity increasing kynurenine levels which is toxic to NK and $CD8^+$ T cells.[111,112,113,114]
T regulatory cells (Treg)‡	Inhibits $CD8^+$ T cell and NK cell activity via: • Inhibitory cytokine (TGF-β,[115] IL-10) secretion[116]; • Metabolic disruption via competition for IL-2[117,118]; • Cytolysis via perforins and granzymes; and • Secretion of kynurenine.[119]
Angiogenic vascular cells (endothelial cells, pericytes and cancer associated fibroblasts)	• Major components of tumour connective tissue.[120] • Provide support, regulate proliferation, angiogenesis, metastasis and immunogenicity.[121] • Fibroblasts utilise lactate produced by tumour[122]; • Regulate ECM remodelling; and • Release proinflammatory cytokines that induce Treg cells from $CD4^+$T cells in TME.[123]
Cancer stem cells (CSC)	• Form new CSC allowing for tumour growth and metastasis.[124]

As discussed, the development of cancer is a continual tug of war between anti-tumour immunity and pro-tumour immunity with the stealthy cancer able to recruit certain immune cells in its TME to support exponential growth. Thus, addressing factors that negatively affect immunity, such as poor diet and chronic inflammation, may assist in promoting a powerful immune system, favouring a balance towards cancer elimination.

AHCC™ Boosts Critical Anti-Tumour Immunity

As previously described, innate and adaptive immune cells are recruited to attack and eliminate cancer cells. Therapeutics such as AHCC™ may serve to promote immune stimulation, as demonstrated in numerous human and animal studies.[125,126,127,128,129,130,131,132,133,134,135] For example, AHCC™ at 3 g/d for four weeks was shown to increase circulating populations of both dendritic cells (DC) and DC1 (Figure 13).[136] The increase in DC1 is notable since they are critical for anti-tumour immunity and potentiate the cytotoxic function of NK cells.[137]

‡ High populations of Tregs are associated with poor prognosis in some cancers and better outcomes in others. Literature suggests the outcome depends on factors such as Treg heterogeneity and the balance of other T cell populations.

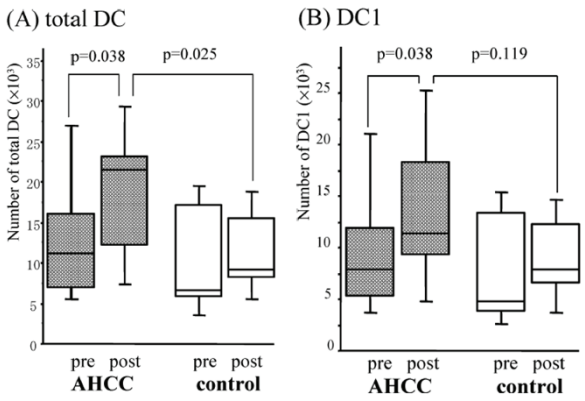


Figure 13: AHCC™ raises DC and DC1 populations associated with tumour protection.[138]

AHCC™ has also demonstrated value in combination with chemotherapy in an animal model of liver cancer. AHCC™ and the anticancer drug 5-fluorouracil (5-FU) produced better outcomes compared 5-FU alone. The addition of AHCC™ resulted in (Table 4):

- Increased NK cell populations (>50%);
- Greater $CD4^+$:$CD8^+$ ratio (associated with better immunological activity); and
- Lowered tumour weight and volume and increased the apoptosis index of the tumour.[139]

Table 4: AHCC™ supplementation potentiated the effects of 5-FU in an animal hepatoma model.

Group	CD^+ (%)	NK (%)	$CD4^+/CD8^+$ (%)
Control	8.7	6.7	2.5
5-FU	9.6	5.0	2.8
5-FU + AHCC™	10.3	10.5	3.9

The effects of AHCC™ on $CD8^+$ T cell numbers have also been observed in trials after three weeks[141] and eight weeks of supplementation at 3 g/d. In the latter trial, the investigation revealed additional increases in $CD4^+$ T cells and INF-γ secretion.[142] Since adequate levels of $CD4^+$ and $CD8^+$ T cells and INF-γ is essential for cancer elimination, supporting these immune cells may assist in tipping the balance towards anti-tumour immunity victory.

This information considered, the immune enhancing effects of AHCC™ may be well indicated in conditions of immunosuppression such as cancer.

AHCC™ Improves Survival Rates

AHCC™ not only improves the side effects of cancer therapy and immune function. Increased survival time has also been observed in cancer studies using AHCC™ in both humans and animals.[143,144,145,146,147,148,149,150] Forty-four patients with advanced liver cancer, known for poor survival rates, self-administered either placebo or 6 g/d of AHCC™ until the end of life. At six weeks the placebo group had a 50% mortality rate compared with no fatalities in the AHCC™ group.[151] In another study, post hepatocellular carcinoma surgery patients self-administered either 3 g/d of AHCC™ or placebo, until the end of life. Hepatocellular carcinoma recurred in 39 of the AHCC™ group compared with 72 in the placebo group. Further, the AHCC™ group had 26% less deaths compared with the placebo group (Figure 14).[152]

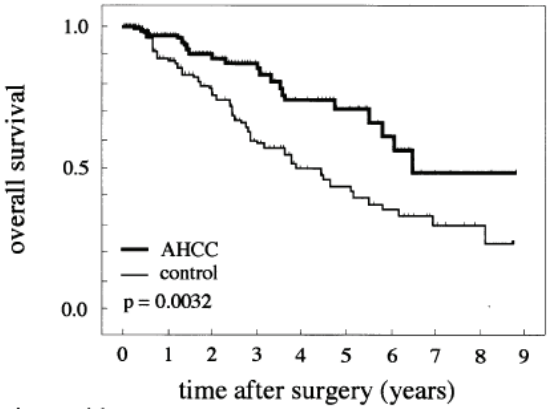


Figure 14: AHCC™ improved overall survival rates in hepatocellular carcinoma patients post liver resection.[153]

In conjunction with standard chemotherapy, 3 g/d of AHCC™ significantly improved survival rates of patients with gastric cancer (stage II and IIIA) and with colon cancer (stage I, II and IIIA). Further, when compared with treatment centres where AHCC™ therapy was not implemented, the AHCC™ groups had greater five year survival rates (Table 5).[154]

Table 5: AHCC™ improves survival rates in gastric cancer (stage II and IIIA) and colon cancer patients (stage I,II and IIIA) compared with institutions not utilising AHCC™.[155]

	5 Year Survival % AHCC™ Study	5 Year Survival % Other Japanese Institutions
Stage II gastic cancer	92.3	74.9 – 75.9
Stage IIIA gastric cancer	82.8	53.6 – 61.7
Stage I colon cancer	100	93 – 100
Stage II colon cancer	100	81 – 88
Stage IIIA colon cancer	95.2	73 – 76

For further information about *AHCC™ and Ginger* please refer to the technical data or call the Clinical Support Team on 1800 777 648 (Australia) or 0508 227 733 (New Zealand) or email clinicalsupport@metagenics.com.au.

The Inflammatory Hallmark of Cancer

Everyone knows the pain, redness and swelling of inflammation. Acute inflammation can clear infections, heal wounds and maintain tissue homeostasis, but chronic inflammation sets a grim scene for chronic diseases, including the malignant transformation of susceptible cells and tumourogenesis. Consequently, the smouldering environment continues to feed tumour-associated inflammation and endows cancer cells with their hallmarks of genomic instability, metabolic reprogramming, growth and survival, angiogenesis, immune suppression, invasion and metastasis (Figure 15).[156,157]

Only a few cancers are associated with inherited mutations, with the vast majority, approximately 90%, caused by environmental exposures and somatic (acquired) mutations.[158] Alcohol, tobacco, radiation, pollutants and high-calorie diets are just a few recognised carcinogens.[159] Some chronic infections are also known carcinogens, such as HPV (leading to cervical cancer) and *Helicobacter pylori* (leading to gastric cancer).[160,161] Linking these diverse carcinogens is their potential to fuel chronic inflammation, either locally in tissues, or systemically.[162]

Interestingly, while some chronic inflammatory diseases increase the risk of certain cancers, others do not. For instance, it remains unclear exactly why inflammatory bowel disease or chronic hepatitis are tumour promoting, yet rheumatoid arthritis and psoriasis do not significantly promote cancer.[163]

On the other hand, being overweight or obese significantly increases the risk of 14 types of cancer, including oesophageal adenocarcinoma, stomach cardia, colon, rectum, liver, gallbladder, pancreas, breast, endometrium, ovary, advanced/fatal prostate, kidney, thyroid and multiple myeloma. Additionally, colon and postmenopausal breast and endometrial cancer risk increases with physical inactivity.[164] Reason being, adipose tissue is more than simply fat storage, but a complex regulator of inflammation and metabolism. Excessive adipose tissue is carcinogenic as it up-regulates certain growth factors and hormones (e.g. oestrogen), and causes metabolic-induced inflammation (meta-inflammation). Adipose expansion can also differentiate adipose-derived tumour supporting cells, which can migrate, infiltrate and progress tumour activity.[165]

Furthermore, in a cruel twist, anti-cancer treatments can incite inflammation and perpetuate the disease, but more on this soon.

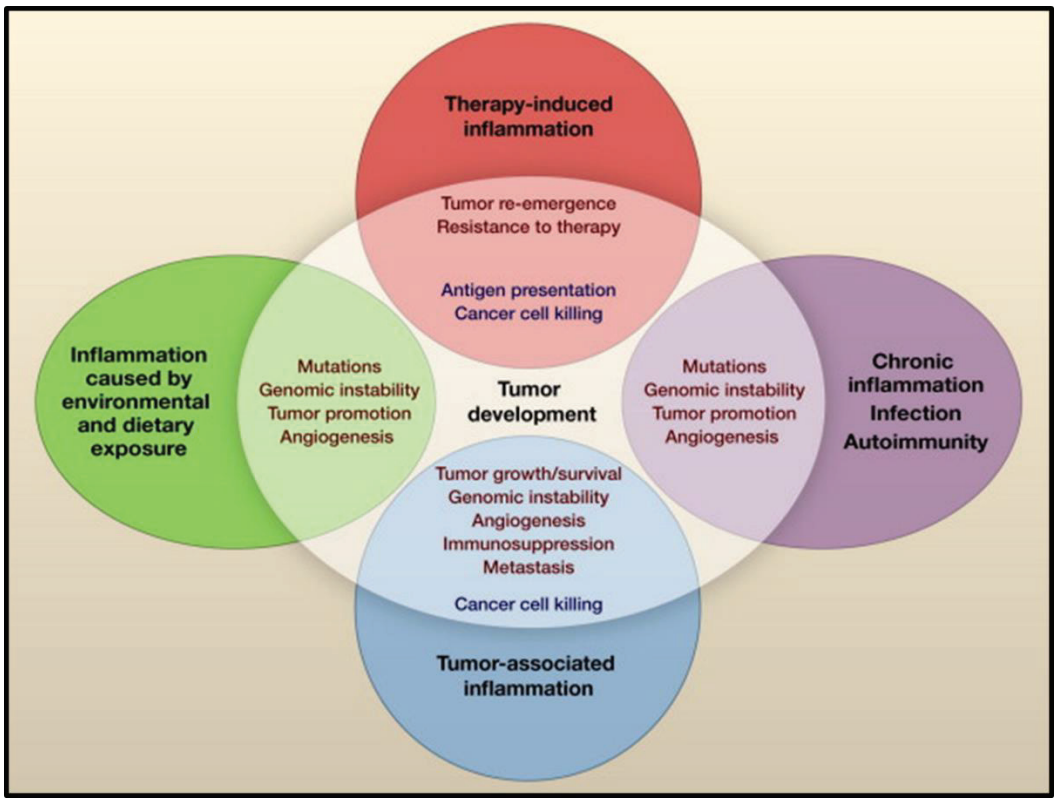


Figure 15: Key inflammatory inputs for tumour development.
The central circle lists the hallmarks endowed to cancer cells by each inflammatory input.[166]

The Chilling Consequences of Tumour-Associated Inflammation

Host immunity creates an incredibly hostile environment for cancer. As described earlier, the elimination phase is characterised by amassing immune cells, polarised in their most proinflammatory phenotypes, unleashing every immune defence available. If cancer cells survive this onslaught, they can take immune cells as prisoners and re-educate them as the equilibrium phase ensues, which can last for several years.[167] Ever-weakening IFN-γ secreting immune cells attempt to apply pressure, but may only serve to strengthen tumour resistance and develop evasion, whilst increasing genetic instability and mutations.[168] The resulting TME is characterised by suppressed immunity and low-grade inflammation, explaining why tumours can be described as 'wounds that won't heal'.[169]

Macrophages: Classical and Alternative Activation

Macrophages can direct opposing proinflammatory or anti-inflammatory tone depending upon their environment. That is, these immune cells set the inflammatory tone of all tissues, including tumours. They achieve this extraordinary plasticity by polarising to proinflammatory M1 macrophages via classical activation or M2 macrophages via alternative activation, which correspond to the T helper 1 (Th1) and T helper 2 (Th2) polarisation of T cells respectively.[170] Under normal conditions, macrophages undergo rapid M1 classical activation to coordinate innate immunity to overcome injuries and infections. As pathogens are cleared and healing commences, M1 macrophages undergo M2 alternative activation to coordinate the resolution of inflammation, scavenge tissue debris and promote angiogenesis to restore homeostasis.[171]

Importantly, in the TME M1 macrophages *are suppressed*. Once summoned to infiltrate and attack cancer cells, the inflammatory environment suppresses and forces them into an *atypical M2* phenotype, called an M2-like tumour-associated macrophages (TAMs). Unfortunately TAMs sustain an inflammatory and immune-suppressed microenvironment.[172,173] They are categorised according to the functions they perform, including angiogenesis promoting; metastases promoting; immunosuppressive; and cancer stem cell promoting – each with highly specific and mixed functionality (Figure 16).[174] Due to their high plasticity, TAMs can shift between subtypes based on tumour-specific signals and stimuli.[175] TAMs are a key component of most, but not all cancers, and their quantity and phenotype (e.g. immunosuppressive) is associated with poor patient prognosis.[176]

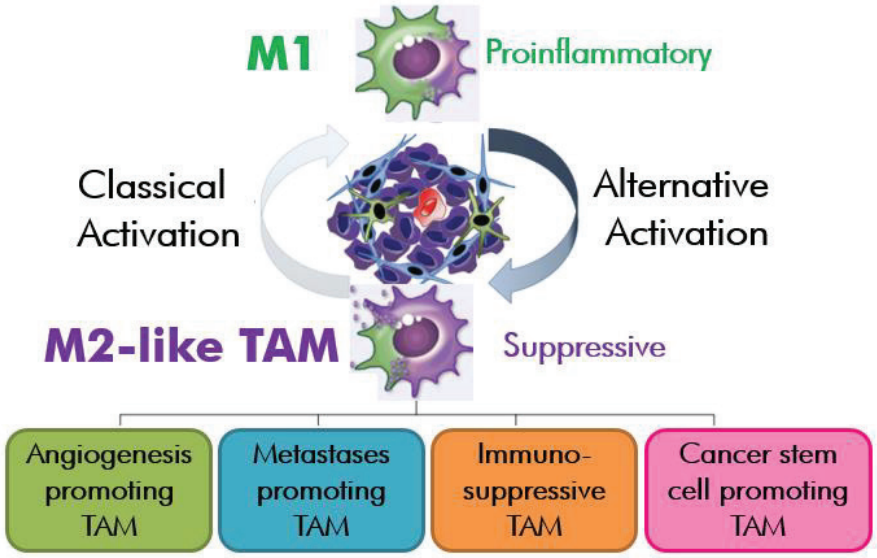


Figure 16: Macrophage plasticity and characterization.[177]

The chemotherapy checkpoint inhibitors, anti-PD1 and anti-PD-L1, *remodel TAMs* to reinvigorate anti-tumour cytotoxic $CD8^+$ T cells, with significant therapeutic efficacy in a subset of patients.[178] Also, paclitaxel, widely used to treat solid tumours by acting on cell-cycle arrest, stimulate TLR (toll-like receptor)-4 and reactivate immunity against cancer by guiding TAMs toward the M1 anti-tumour phenotype.[179] Unfortunately, the inflammatory side effects of such immune stimulation can cause excessive coagulation or cytokine storms, hindering the application of certain therapies.[180]

Cancer surgery (including biopsy), chemotherapy, and/or radiation can all induce proinflammatory and immunosuppressive responses that can increase metastatic outgrowth and tumour recurrence.[181] Even anesthesia can impair the resolution of inflammation.[182] Additionally, chemotherapy-generated cell death can provoke tumour growth,[183] and surgical wounding can impair the efficacy of chemotherapy.[184]

Dial Down Dangerous Inflammation

These challenges in oncology turn attention to anti-inflammatory strategies. Non-steroidal anti-inflammatory drugs (NSAIDs), steroidal anti-inflammatory drugs and statins have known efficacy in decreasing morbidity, counteracting chemo-resistance, suppressing tumour progression and improving survival.[185]

Prostate cancer, significantly progressed by inflammation, is shown to be impeded by NSAIDs, metformin and statins with well-defined anti-tumour activity. Furthermore, dietary soy isoflavones, vitamin D, pomegranate, green tea and resveratrol are indicated to slow the progression of prostate cancer. Whilst these anti-inflammatory approaches are unlikely to prevent progression in all patients, new research is indicating they may enhance the efficacy of cancer surgery and chemotherapy.[186,187]

Specialised Pro-Resolving Mediators – Reprogramming the TME

Specialised pro-resolving mediators (SPMs), comprised of lipoxins, resolvins, protectins, and maresins, are endogenously synthesised molecules that orchestrate the resolution of inflammation without suppressing immunity.[188] Specifically, SPMs activate the polarisation of M2 macrophages and the resolution of inflammation. However, chronic inflammation, meta-inflammation and ageing present significant blockades to endogenous SPM synthesis.[189] Likewise, it appears SPM synthesis is suppressed by tumour-associated inflammation. As aforementioned, the inflammatory TME suppresses attacking M1s into tumour-promoting M2-like TAMs.

Interestingly, inducing SPM synthesis via supplementation and/or low-dose NSAIDs, promotes **anti-tumour immunity** via dual anti-inflammatory and pro-resolving activity. In particular, lipoxins and resolvins have an 'adaptogenic' effect to reverse cancer biology, compared to resolving non-cancer inflammation, as briefly outlined in Table 6.[190] Emerging SPM research now reveals how inducing these pro-resolving lipid mediators can beneficially modify immunity in target tumour cells, the TME and pre-cancerous lesions (Figure 17).[191]

Therefore, supplementing *Specialised Pro-Resolving Mediators* is highly indicated to resolve this chronic inflammation.

Table 6: Comparing the effects of SPMs in inflammation and tumours.[192]

SPM	Functions in Inflammation	Functions in Cancer
Lipoxin	• Increased M2 polarisation • Decreased neutrophil infiltration • Decreased angiogenesis • Decreased pain signal	• TAMs to M1 phenotype • Decreased tumour cell proliferation • Decreased tumour cell invasion • Decreased angiogenesis • Decreased tumour cell migration
Resolvin E-series	• Decreased antigen presenting cells and T cell priming • Decreased pain signal • Decreased fibroblast proliferation	• Decreased tumour growth
Resolvin D-series	• Decreased antigen presentation • Decreased pain signals • Increased M2 polarisation and efferocytosis • Increased Treg recruitment and T cell apoptosis	• Decreased tumour cell escape • Decreased tumour growth • Increased NK cell function and survival

Furthermore, the therapeutic effects of omega-3 observed in various cancer types, including breast, colorectal, gastric, pancreatic, oesophageal, prostate, lung, head and neck cancers, and cancer cachexia[193] are now understood to be driven via SPMs' anti-neoplastic effects.[194] Recent research reveals in animal cancer models that NSAIDs and/or SPMs (specifically resolvins), administered *pre-operatively*, but not post-operatively, prevented micrometastases in multiple tumour resection models, resulting in long-term survival. This pre-operative delivery of resolvins specifically inhibited metastases and induced T cell responses. Synergy was demonstrated when SPMs and NSAIDs were combined, by amplifying anti-tumour activity and preventing surgery- or chemotherapy-induced micrometastases, therefore preventing tumour recurrence and prolonging survival.[195]

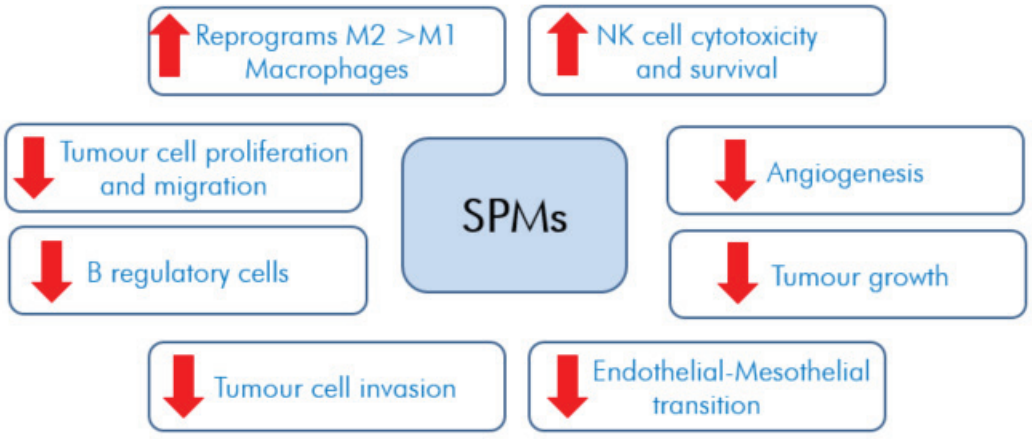


Figure 17: Summary of anti-cancer actions and mechanisms of SPMs.[196]

For further information about *Specialised Pro-Resolving Mediators* please refer to the technical data or call the Clinical Support Team on 1800 777 648 (Australia) or 0508 227 733 (New Zealand) or email clinicalsupport@metagenics.com.au.

PEA Soothes Painful Nerves

Chemotherapy-induced peripheral neuropathy (CIPN) affects 30% to 40% of treated patients, often serving as a painful reminder of treatment.[197] Palmitoylethanolamide (PEA) as a standalone therapy or in conjunction with pharmaceutical analgesics,[198,199,200,201] is shown to enhance patient QOL and relieve the intensity of several painful neuropathies, with no serious side effects reported.[202,203,204,205,206]

Safety and efficacy was demonstrated in 20 multiple myeloma patients experiencing neuropathy whilst undergoing chemotherapy (thalidomide and bortezomib). After eight weeks of PEA (300 mg twice daily), pain scores reduced by 24% compared to controls, indicating significant protection of nerve function.[207]

Another example of efficacy was reported in a prostate cancer case study, where a patient developed significant neuropathy after receiving his second dose of the antineoplastic agent sagopilone. Despite requiring tramadol and pregabalin, the patient still reported 7 out of 10 pain. PEA was added at a dose of 600 mg twice daily and after three weeks of supplementation the patient's pain score reduced to 1 to 2 out of 10. Six months later, he could discontinue analgesics, with only occasional use of paracetamol.[208]

The debilitating long-standing condition CIPN affects both QOL and the patient's ability to withstand the chemotherapy. PEA offers relief from neuropathy, protects nerves against damage and enhances treatment compliance whilst being well tolerated.[209]

For further information about *Highly Bioavailable Palmitoylethanolamide (PEA) With Endocannabinoid Action* please refer to the technical data on page 216 or call the Clinical Support Team on 1800 777 648 (Australia) or 0508 227 733 (New Zealand) or email clinicalsupport@metagenics.com.au.

Treatment Considerations for Integrative Oncology

Considering the discussion above, Table 7 outlines the treatment considerations for every cancer patient. These therapies can be used alongside cancer therapy, to reduce side effects and improve patient outcomes.

Table 7: Considerations for cancer patients.

Considerations	Indications
AHCC™ and Ginger	Reduce side effect of cancer therapy, including: • Nausea and vomiting • Changes in bowel function • Appetite suppression • Myelosuppression Improve QOL Hepatoprotective Improve immunosurveillance
Highly Bioavailable Palmitoylethanolamide (PEA) With Endocannabinoid Action	Reduce chemotherapy induced peripheral neuropathy Reduce pain Improve QOL
Specialised Pro-Resolving Mediators	Reduce tumour sustaining inflammation Improve resolution
Microbiome support – see below	
Further considerations:	Diet and lifestyle interventions can reduce side effects and improve QOL and patient outcomes: • Diet: see page 32 • Exercise: see page 36 • Sleep: see page 37 • Psycho-oncology: see page 38 For novel and emerging therapies see page 43

Microbial Health

Given the role of immune surveillance and inflammation in the development of cancer, it is probably no surprise to Practitioners that the gut microbiome has been investigated as a target for cancer management. Indeed, it seems that the gut microbiome not only influences a patient's risk of developing cancer, but it can also alter patient response to cancer treatment.[210]

There are some key organisms and functions of the gut microbiome which appear to reduce cancer risk. For instance, the production of short chain fatty acids, in particular butyrate, induces cell differentiation and apoptosis and is believed to limit cancer development. Likewise, certain organisms metabolise phytochemicals such as polyphenols, flavonoids and glucosinolates to compounds which reduce DNA damage and inflammation, while inhibiting tumour growth. On the other hand, pathogenic microbes have been found in the TME interacting with cancer cells and encouraging growth. For instance, particular strains of *Escherichia coli*, found more often in the mucosa of those with colorectal cancer compared to healthy controls, produce a toxic metabolite which increases the production of growth factors. Pathogenic organisms also produce a host of metabolites that cause inflammation and DNA damage.[211] Therefore, looking after the health of patient's microbiome may reduce the risk of carcinogenesis. However, for those patients who present already having developed cancer, the health of the gut microbiome is still an important consideration.

Chemotherapeutic agents can lead to dramatic alterations in the composition and function of patients' gut microbiome. For instance, the abundance of gut bacteria was 100-fold lower in paediatric patients undergoing treatment for acute myeloid leukaemia, compared to healthy controls. Furthermore, diversity was dramatically reduced. Authors determined that the changes seen in the subject's microbiome could not be explained by changes in diet or by the use of prophylactic antibiotics, but instead were a result of chemotherapy.[212] In patients with non-Hodgkin's lymphoma undergoing myeloablative conditioning, overall diversity and butyrate producing organisms were reduced, while organisms associated with inflammatory pathways were increased after treatment. Further, patients' capacity for amino-acid and carbohydrate metabolism were reduced, while glycan metabolism was enriched, a profile that has been associated with intestinal inflammation. Chemotherapy induced dysbiosis and the resulting inflammation may be at least in part responsible for the mucositis that many patients develop.[213] This is supported by a study in melanoma patients receiving anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) treatment. Immune-mediated colitis is a common side effect of check point inhibitors such as anti-CTLA-4 treatment. In this study, increased levels of organisms in the Bacteroidetes phylum were correlated with resistance to colitis development.[214]

Mucositis is not the only chemotherapy side effect which may be influenced by the health of the gut microbiome. While research is preliminary, animal models have implicated gut dysbiosis, and the associated gut barrier dysfunction and systemic inflammation, in the development of cancer cachexia.[215] Likewise, it has been suggested that disruption of the gut-brain axis may exacerbate neurocognitive symptoms such as chemotherapy induced cognitive impairment.[216]

Finally, the health of the gut microbiome may impact patient response to treatment. Increased microbial diversity in patients with melanoma receiving anti-PD-1 immunotherapy was associated with a more favourable treatment response, including prolonged progression free survival.[217] On the other hand, in patients with metastatic renal cell carcinoma who were being treated with immune checkpoint inhibitors, antibiotic use reduced progression free survival and overall survival.[218]

Lactobacillus rhamnosus (LGG®) offers a safe and gentle solution for patients going through cancer therapy. Given to patients receiving 5-fluorouracil based chemotherapy for colorectal cancer, 10 to 20 billion colony forming units (CFU) of LGG® daily reduced abdominal discomfort and severe diarrhoea frequency, compared to those who did not receive the probiotic. Furthermore, patients receiving the probiotic experienced less bowel toxicity, and required fewer chemotherapy dose reductions and less hospital care.[219]

While LGG® has an excellent safety profile, it is important to note that probiotics should not be used during haematopoietic stem cell transplants (HSCT). In one study a greater number of patients receiving LGG® developed graft-versus-host-disease, a serious complication of HSCT, compared to those who did not.[220] This study was very small (with 20 in the treatment group and 11 in the control), but given the severity of the complication, caution is advised. High gut microbiome diversity has been associated with higher overall three year survival rates for patients undergoing HSCT,[221] therefore if possible, improving patients gut health with probiotics and prebiotics prior to treatment would be a reasonable approach.

There has also been some concern raised over the possible development of systemic infections in immunocompromised patients due to probiotic use, a pertinent consideration for those undergoing cancer treatment. With its wide consumption, LGG® has compelling evidence in favour of its safety. Safety surveillance data from Finland, where LGG® use is very common, reveals that *Lactobacilli* represented only 0.02% of positive blood cultures. Furthermore, while LGG®-like isolates were found in 11 out of 89 strains, on closer inspection they were found to be phenotypically different.[222] Moreover, studies of probiotic supplementation in recipients of solid organ transplants, as well as other immunocompromised patients, found no evidence of systemic infection.[223] On the other hand,

while still relatively rare, there have been reports of *Saccharomyces cerevisiae boulardii* positive fungaemia found in patients taking probiotics.[224]

Taking all of this into account, a conservative safety approach is detailed in Table 8.

Table 8: Probiotic safety considerations.

Neutrophil Count	Probiotic Safety Considerations
Normal neutrophil count 2,500 to 6,000	Strain specific, quality probiotics generally regarded as safe. Consider *Strain Specific Probiotics for Gut Microbiota Restoration and Support* post cancer therapy to rebuild. Avoid probiotics if undergoing haematopoietic stem cell transplants.
Low neutrophil count 500 to 2,500	Consider strain specific, quality probiotics with considerable safety profile, such as *Double Strength, Researched, Authentic LGG®*. Avoid use of *S. boulardii.* Avoid probiotics if undergoing haematopoietic stem cell transplants.
Neutropaenia <500	Avoid probiotic use until neutropaenia is resolved.

Box 3: The Antioxidant Controversy

Few topics generate as much controversy as the use of supplemental antioxidants (AO) in cancer. Contention arises due to questions surrounding safety, efficacy and more prominently the therapeutic co-administration of AO with chemo- and radiotherapy. While a plethora of research exists both for and against the use of AO in cancer, unfortunately, no definitive guidelines exist.

Over the years, results from various human clinical trials suggest that AO may, at times, contribute to, rather than impede tumour progression. The research often used to support this refers to the ATBC (Alpha-Tocopherol, Beta-Carotene Cancer Prevention) study on the deleterious impact of beta-carotene (20 mg/d) on tumour progression in male smokers.[225,226] This study generated numerous conversations, leading to the questioning of the study design, outcomes and biomechanics of nutritionals, all of which contributed to further exploration. A few years later, more than 18,000 smokers, former smokers and workers previously exposed to asbestos were recruited for the CARET. The trial once again investigated the effect of beta-carotene supplementation on lung cancer incidence.[227] Alarmingly, this trial was discontinued 21 months early due to an increase in the risk of both lung cancer diagnosis and mortality.[228]

Results from the above studies appear to support the discontinuation of AO supplementation in cancer. However, upon assessing all of the data, it appears that this may only be true in specific circumstances, such as in patients exposed to cigarette smoke. Whereas the same nutrient in an otherwise healthy individual may offer cellular protection.[229] For instance a number of epidemiological studies such as the Physician Health Study, the Linxian trial, and a pooled analysis of seven epidemiological cohort studies have reported associations of increased AO plasma levels with decreased cancer risk.[230]

Thus, the benefit of supplemental AO for the prevention of cancer may depend on patients' exposure, hinting at the complexity of this topic. When it comes supplemental AO in patients who have already developed cancer, and who are undergoing cancer therapy, the issue appears even more nuanced.

Estimations note that up to 81% of cancer patients take some form of vitamin and/or mineral supplement,[231] perhaps seeking the protection that antioxidants ostensibly offer from oxidative stress. However, the generation of oxidative stress, DNA damage and subsequent cellular apoptosis is exactly how some chemo- and radiotherapy exert their effect (Figure 18).[232] This is desirable if this damage occurs in a cancer cell. Unfortunately, ROS are not selective, and normal cells

succumb to collateral damage. Furthermore, as discussed on page 13 anticancer drugs often cause a variety of adverse effects, and induction of ROS has been reported as one of the contributing factors.[233] While it may seem prudent to utilise AO to mitigate damage to healthy cells and reduce side effects, it is important to note that most anticancer treatments have a narrow therapeutic index, therefore even a modest decrease in ROS may diminish tumour eradication.[234,235,236]

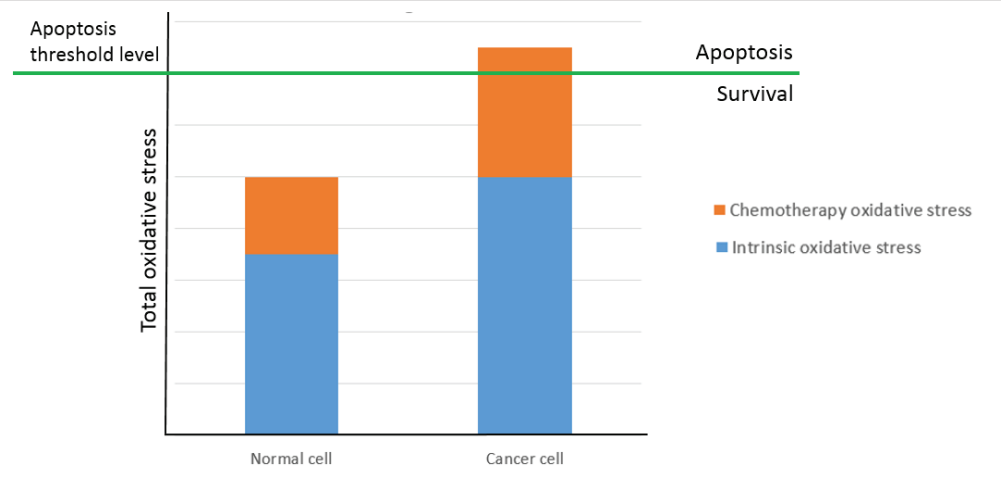


Figure 18: Chemotherapeutic agents induce oxidative stress and cellular apoptosis.[237]

To date there are only a handful of randomised controlled trials using AO supplements during radiation therapy.[238] This research supports the notion that the effectiveness of radiation is decreased with the simultaneous use of AO.[239] This seems to be especially true for patients undergoing radiotherapy for head and neck cancer; while antioxidants may mitigate side effects, such as mucositis, overall survival was compromised.[240,241] Consequently, recommendations remain firm that high dose antioxidant supplementation, over and above the recommended daily intake (RDI), should be avoided during radiation therapy, especially in patients with head and neck cancer.[242,243]

Please see page 43, to discover how photobiomodulation could offer safe and effective relief from side effects associated with chemo- and radiotherapy in patients with head and neck cancer. Research on antioxidant use alongside chemotherapy is more positive. In 2018, a research review published the outcomes of 174 peer-reviewed original articles, comprised of 93 clinical trials investigating the use of AO alongside chemotherapy.[244] This review concluded that, AO supplementation during chemotherapy offers higher therapeutic efficiency and increased survival times in patients.[245] Furthermore, research has indicated that the co-administration of certain antioxidants with chemotherapy drugs may assist in mitigating side effects.[246,247,248] For example, a small human clinical trial found that 53% of patients reported that alpha-lipoic acid effectively reduced the severity of oxaliplatin-related peripheral sensory neuropathy.[249]

Fork in the Road

Despite recent intensive research on dietary AO supplementation during cancer therapy, dispute still exists and this remains an area which requires more investigation. While it is recommended that antioxidants are avoided alongside radiotherapy, especially in patients undergoing radiotherapy for head and neck cancer, recommendations for patients on chemotherapy remain less clear. Therefore, Practitioners should use their discretion when it comes to the supplementation of AO in these patients. A safe, albeit conservative approach, can be taken with the provision of antioxidants through a whole-food diet.[250] The Wellness Diet provides the framework to optimise nutrient intake, assisting patients in meeting the RDI of nutrients for optimal health and healing. For more information on how diet can be utilised during cancer therapy, please see page 32. Fortunately, as discussed above, there is much that can be achieved using safe and effective ingredients, alongside cancer treatment to reduce side effects and improve patient outcomes.

For information regarding the use of intravenous vitamin C, which has a vitally different mechanism of action to oral AO supplementation, please see page 47.

Deregulated Cellular Energetics

In 1931 Nobel Prize laureate Otto Warburg suggested, controversially, that cancer may be a metabolic disease. Warburg observed that cancer cells displayed impaired cellular respiration. He proposed that even in an oxygen replete environment, cancer cells alter their metabolism, increasing glucose uptake, up-regulating glycolysis and fermenting large amounts of glucose into lactate. This process, now known as aerobic glycolysis, was later termed the Warburg effect.[251,252,253,254,255] More recently, Thomas Seyfried and others have continued the debate that cancer is a metabolic disease, questioning whether altered cellular metabolism precedes cancer development or, whether it is a consequence of the disease process itself.[256] Indeed, almost 100 years later, deregulated cellular energetics is recognised as an emerging hallmark of cancer.[257,258]

Aerobic Glycolysis: The Warburg Effect

It has been well-established that in the presence of oxygen normal cells produce energy to carry out cellular processes via oxidative phosphorylation. When glucose is consumed it enters the cytosol and is converted to pyruvate via glycolysis. Pyruvate then enters the mitochondrial pathway of oxidative phosphorylation under aerobic conditions, yielding roughly 36 units of adenosine triphosphate (ATP), the cellular energy currency.[259] When oxygen is scarce, normal cells rely on anaerobic glycolysis rather than oxidative phosphorylation for their energy supply.[260] Anaerobic glycolysis is a less energy efficient pathway, yielding only two ATP. However, when it comes to the metabolism of cancer cells, their cellular processes are deregulated, and they behave very differently to healthy cells, giving them a specific metabolic signature. Even in an oxygen replete environment, cancer cells preferentially utilise glycolysis, converting glucose into pyruvate, but rather than entering the mitochondria for oxidative phosphorylation, more than 85% of pyruvate is shunted towards increased lactate production (Figure 19).[261]

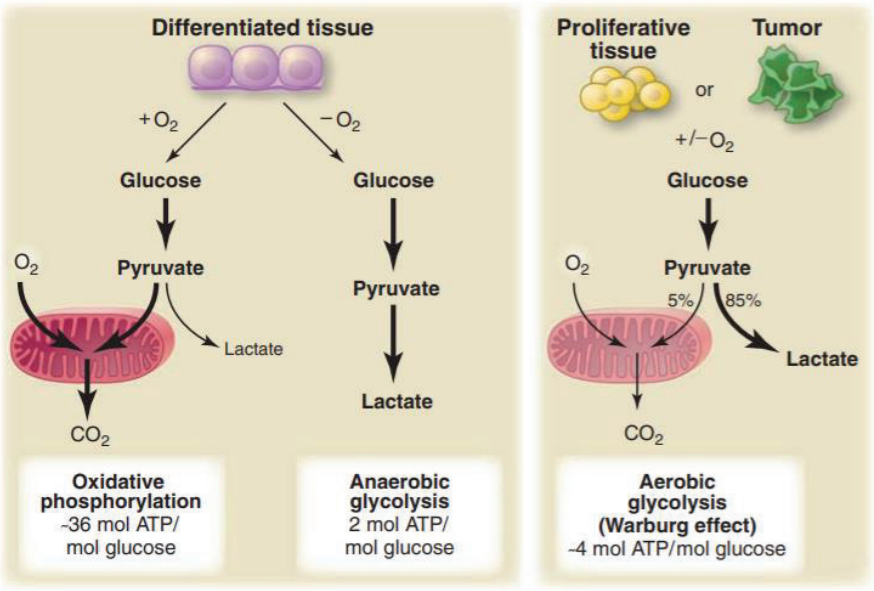


Figure 19: Schematic representation of the differences between oxidative phosphorylation, anaerobic glycolysis, and aerobic glycolysis (the Warburg effect).[262]

To compensate for the reduction in ATP production, cancer cells increase their uptake of glucose via the over-expression of glucose transporters such as GLUT-1 to meet their demands of rapid growth, proliferation and survival.[263,264] While mitochondrial capacity is reduced, some mitochondria remain functional, with oxidative phosphorylation continuing to some extent inside the cancer cell.[265]

Due to the altered metabolism during aerobic glycolysis, intracellular levels of both lactate and reactive oxygen species (ROS) increase, which has the potential to cause cellular damage and cell death. Interestingly, cancer cells have a dual approach to managing both the increase in ROS and lactate that can promote cancer cell survival and progression. Firstly, cancer cells have the ability to increase glutathione levels as part of their antioxidant defence mechanism, with lactate playing a key role in redox balance.[266] Secondly, the increase in lactate is used for manufacturing of nucleotides, amino acids and lipids, providing the essential building blocks for cell division, proliferation and the creation of daughter cells.[267,268]

Interestingly, cancer cells' addiction to glucose consumption has been put to good use in a clinical setting, with position emission tomography scans detecting glucose uptake in 80% to 90% of solid tumours.[269,270]

The Role of Lactate in the Tumour Microenvironment

While the Warburg effect plays a central role in cancer cell metabolism, the TME may provide a dual metabolic benefit, allowing cancer cells to both survive and evade detection.[271] As mentioned above, there are several steps involved in the metabolism of glucose to lactate within a cancer cell, these include:

1. Increased glucose uptake via the amplified expression of glucose transporters like GLUT-1 for the biosynthesis of macromolecules such as amino acids, nucleotides and fatty acids for the formation of daughter cells;
2. Increased glycolytic enzyme expression and activity;
3. Decreased mitochondrial function, diverting pyruvate away from the tricarboxylic acid (TCA) cycle and into the production of lactate; and
4. Increased lactate production within the cytosol, accumulation and finally the release of lactate into the TME.[272]

Lactate continues to have an effect beyond the confines of the cancer cell, and is an important factor in carcinogenesis.[273] Lactate release and subsequent uptake through monocarboxylate transporters (MCT1 and MTC4), into the TME has been suggested to drive angiogenesis and tumour growth.[274]

The export of lactate out of the cytosol into the TME triggers a cascade of events.[275,276] To start with, lactate increases local acidity which stimulates vascular endothelial growth factor (VEGF), triggering angiogenesis and promoting proliferation and migration of cancer cells.[277] Lowering the pH also has the ability to decrease T cell activity and alter cytokine release, helping to reduce immune detection.[278,279]

Beyond lactate there are other metabolic processes which provide substrates for the continued growth of cancer. Below we explore how metabolic coupling displayed in the reverse Warburg effect can provide an additional metabolic advantage.

The Reverse Warburg Effect

First postulated by Pavlides et al. in 2009,[280] the reverse Warburg effect is a phenomena where aerobic glycolysis is switched on in non-cancerous stromal cells within the TME. This allows cancer cells to metabolically couple with neighbouring stroma cells, meaning cancer cells are able to source additional fuel from the surrounding environment. Cancer cells initiate this process through the release of ROS, corrupting neighbouring stroma cells and inducing oxidative stress.[281] Stroma cells, in particular cancer associated fibroblasts (CAF), essentially become manufacturing plants of nutrient dense by-products such as lactate,[282] which are then shuttled back into the cancer cell via MCT1 to drive further growth of the tumour.[283,284,285,286] Upon re-entering the cancer cell, lactate is converted to pyruvate, up-regulating oxidative phosphorylation to meet energy demands, providing further metabolic benefit.[287]

All Roads Lead to Rome

Interestingly, the Warburg effect is not consistent across all cancer types. One of the fascinating aspects of cancer cell metabolism is the ability to metabolically rewire fuel sources to continue survival. Regardless of the fuel source, all roads lead to Rome, with all nutrients, glucose, glutamine or lipids, being used to increase biomass for cell division and proliferation and the production of daughter cells.

Two Modes of Metabolism for Growth: Nutrient Uptake and Nutrient Scavenging

Cancer cells use two modes of metabolism to acquire cellular building blocks to sustain growth. The first is nutrient uptake, usually involving glucose and glutamine, resulting in de novo synthesis of amino acids, fatty acids and nucleotides for growth.[288] The second is nutrient scavenging. As cancer cells grow and proliferate they begin their process of evading detection, migrating away from blood vessels, nutrient supply and oxygen supply, entering into a nutrient-poor and hypoxic microenvironment.[289] In this scenario, nutrient scavenging occurs, with cancer cells accessing the required nutrients through macropinocytosis, where the cancer cells engulf extracellular material to source the proteins and lipids they require.[290]

The Glutamine Addiction

One of the main amino acids that feeds cancer is glutamine. Certain cancers are addicted to glutamine, and will source it from multiple avenues to feed their hunger. Glutamine is used primarily as a fuel for the biosynthesis of amino acids, nucleotides and fatty acids to generate new daughter cells, as well as being a source of ATP production.[291] Interestingly, glutamine also plays an important role in glutathione production and the redox status of a cancer cell.[292]

Glutamine demand can exceed the supply required for periods of rapid growth in cancer. It can be obtained via several pathways to drive growth in the TME, including:

- Macropinocytosis of skeletal muscle;
- Secretion of glutamine by adipocytes; or
- CAF that take up glutamate the cancer cells excrete and convert it back into free glutamine.[293]

Regardless of the source, the aim is to support the rapidly proliferation cells.

Box 4: Can We Supplement with Glutamine?

While we are generally aware of the beneficial role that glutamine has in the human body, we have also learnt that it can be used as a fuel source for cancer cells through complex biochemical pathways, driving cancer growth and progression. This raises the question, if cancer cells utilise glutamine to fuel growth, can we safely supplement cancer patients with glutamine?

As we know, cancer metabolism is complex, and our current understanding of cancer cell metabolism is still evolving. Cancer cells have the ability to access the glutamine they require through multiple avenues, including the breakdown of skeletal muscle when demand outweighs supply. However, research has shown that glutamine supplementation can be beneficial for cancer patients, countering some of the complications that can arise from cancer therapy such as oral mucositis (OM), reducing gastrointestinal side effects and improving cancer induced peripheral neuropathy (CINP).[294,295,296] Furthermore, glutamine plays an important role in immune function, which is required to help the body fight back against cancer.[297]

Two systematic reviews have investigated the benefits of glutamine supplementation for cancer patients. The first assessed glutamine intake for patients with colon and colorectal cancer, and found that glutamine was beneficial in reducing gut mucositis, improved wound healing after surgery, and helped to manage other gastrointestinal side effects from chemotherapy such as diarrhoea.[298] A second systematic review found in favour of oral glutamine supplementation in adults undergoing chemo and/or radiotherapy for reducing the incidence and severity of mucositis as well as weight loss, with 30 g/d of glutamine given up to seven days before treatment.[299] Preliminary research has also been conducted showing benefit for oral glutamine in reducing CIPN symptoms in those on oxaliplatin or high-dose paclitaxel.[300]

In addition to the use of oral glutamine in practice, whey protein is commonly used as a supplement in cancer patients. Whilst there are some concerns around its potential to increase systemic glutathione, *in vitro* and *in vivo* research demonstrates potential anti-cancer effects, helping to prevent muscle wasting, providing a cost effective therapy.[301]

Overall, both glutamine and whey protein supplementation may be beneficial for cancer patients, reducing some of the side effects of cancer therapy and supporting immune function and recovery.

Fats as a Fuel Source

Fatty acids are also an essential component for cellular proliferation, and can be synthesised in several different ways, through:

- *De novo* synthesis, producing non-essential fatty acids from the primary nutrients glucose and glutamine;
- Cholesterol and the transfer of free fatty acids into a cell; or
- Using acetate as a substrate for fatty acid synthesis.

Melanoma is a typical example of a form of cancer which utilises fats to fuel its growth.[302]

Metabolic Switching

Research is discovering that certain cancer cells have a preference for either glucose, glutamine or fat as their primary fuel source, but some cancers can metabolically switch preference, depending on the type and stage of cancer.

An example of this was observed in a recent clinical trial conducted on patients with acute myeloid leukaemia. Researchers were able to demonstrate that leukaemia stem cells (LSC) displayed a preference for amino acid uptake for survival, but that their metabolic

preference may change after relapse to favour fatty acid metabolism.[303] This study highlights the ability of cancer cells to switch metabolism and display metabolic flexibility even with cancer progression.

Box 5: Live By The Sword, Die By The Sword

Interestingly, in addition to changes in energy metabolism, cancer cells also appear to alter the balance between oxidative stress and endogenous AO protection in order to favour cell survival. It is well-established that cancer cells exhibit higher levels of oxidative stress during all stages of malignancy. In fact, cancer cells rely on the signalling capabilities of ROS for cell migration, proliferation, and survival.[304,305] Therefore, it is critical for cancer cells to maintain an optimal level of ROS to facilitate tumour progression.[306,307] On the other hand, cancer stem cells (CSC), small subpopulations of surviving primary cancer cells, have another trick up their sleeves. They exhibit increased expression of AO enzymes such as superoxide dismutase, catalase and glutathione S-transferases, offsetting ROS induced cellular damage. Ultimately this results in a highly drug resistant population of cancer cells.[308]

What Should a Cancer Patient Eat?

You only have to google the 'best form of diet for cancer' to be taken down a rabbit warren of multiple dietary recommendations. Current dietary guidelines provided for cancer patients by The Cancer Council of Australia recommend eating a healthy balanced diet, consuming small meals more frequently, with a possible increase in calories and protein over time.[309] For further advice, patients are then directed to their doctor or dietitian.[310]

Emerging research is now suggesting that what a cancer patient consumes could become part of their cancer therapy. It makes sense that if cancer fuel sources are restricted, there is the possibility that metabolic pathways that drive tumour growth and progression may be hindered. To investigate the impact of diet on cancer, the following section will discuss the current level of evidence for three popular dietary groups: ketogenic diets, vegan/plant-based diets and fasting.

Ketogenic Diets Attempting to Kick Cancer to the Curb

Ketogenic diets (KD) have been used as a therapy for chronic diseases for over a century. In the 1920s, KD were recommended for the management of epilepsy.[311] More recently, KD have been investigated for their impact on cellular metabolism and potential anti-tumour effect.[312]

A KD is defined as a diet high in fat and low in carbohydrates, with low to moderate levels of protein. Containing in some cases up to 90% fat, this diet is designed to drive cells to utilise fats as their primary energy source, shifting metabolism away from aerobic glycolysis.[313] As a result, there is a rise in serum ketone bodies, which cancer cells find difficult to metabolise, further restricting their fuel source.[314]

Research suggests that KD are a potentially safe therapy for cancer patients,[315] offering multiple benefits, including:

- Targeting the metabolism of cancer cells;
- Mimicking the metabolic alterations seen with fasting;
- Lowering the availability of glucose; and
- Increasing ROS,[316] which has the ability to affect the TME.

Although KD are one of the first diets that come to mind in connection to cancer management, there have been concerns around recommending them alongside chemotherapy due to a lack of human clinical trials.[317] To alleviate some of these concerns, a 2020 systematic review investigated the use of ketogenic diets in oncology.

A total of 12 papers reviewing 13 clinical studies were included in the review, two of which were randomised controlled trials.[318] The studies investigated the use of KD in a range of cancers including high-grade gliomas, and gastrointestinal and gynaecological cancers.[319] A table including the specific type of cancer, details on the intervention and outcome can be found in Appendix 2. The overall finding was a beneficial effect on body composition, with KD leading to the maintenance of skeletal muscle mass in both overweight and frail individuals.[320] In addition, four studies found KD had a beneficial effect on overall survival and/or progression free survival in cancer patients.[321]

Research into the benefits of KD on cancer have been spearheaded by Professor Thomas Seyfried, who has investigated their impacts on high-grade gliomas.[322,323,324] Through his research, he has developed a novel form of therapy known as the 'Press/Pulse Theory'.[325] The 'Press' component involves the use of a restrictive KD throughout cancer treatment, whilst the 'Pulse' component is the use of cancer therapy drugs along with hyperbaric oxygen therapy. This approach is designed to stimulate multiple metabolic signalling pathways, targeting the elimination of cancer cells while maintaining optimal function of healthy cells.[326]

Overall, while human studies examining KD in cancer are encouraging, larger randomised clinical trials need to be conducted before firm clinical recommendations can be made.

A Plant-Based Diet Does It Again

It has long been thought that plant-based diets convey a protective effect against cancer.[327] Vegan diets in particular have been investigated for their benefits on reducing cancer incidence, with specific research in the area of prostate[328] and colorectal cancers.[329] To be specific, research has suggested that plant-based diets have the ability to alter cellular metabolic processes, down-regulating carbohydrate metabolism,[330] lowering glucose levels[331] and activating insulin-like growth factor (IGF)-1.[332,333,334]

More recently, consuming a vegan diet has been shown to significantly lower the incidence of total cancer,[335] with large population studies suggesting it could reduce the incidence by up to 19% compared to an omnivorous diet.[336]

In 2008, a landmark paper by plant-based researcher Dean Ornish suggested that simple diet and lifestyle modifications were powerful enough to alter gene expression, hinder tumourigenesis and the TME, and therefore cancer progression.[337]

The GEMINAL (Gene Expression Modulation by Intervention with Nutrition and Lifestyle) pilot study by Ornish investigated the impact of diet and lifestyle modification, specifically a plant-based diet, on prostate cancer.[338] Thirty male participants were placed on a low-fat, wholefood, plant-based diet and were asked to participate in moderate exercise and stress management techniques as well as a psychological support group for three months.[339] Prostate needle biopsies were taken at baseline and at the end of the intervention to compare ribonucleic acid (RNA) samples before and after.[340] When samples were compared, researchers discovered that pathways involved in tumourigenesis and protein metabolism were significantly modified, with the up-regulation of 48 and down-regulation of 453 transcripts after the intervention.[341] Interestingly, on further examination, they found that certain pathways regulating cellular metabolism were also down-regulated, in particular down-regulation of IGF gene pathways such as IGF-1 receptor as well as genes relating to fat and carbohydrate metabolism.[342] This pilot study revealed the impact that a plant-based diet, alongside specific lifestyle interventions, can have on prostate gene expression, cancer cell metabolism and the TME.[343]

As aforementioned, plant-based diets have been associated with a lower incidence of colorectal cancer. Researchers have indicated the increased consumption of plant-based, wholefood and a decrease in red meat consumption may be, in part, responsible for this observation.[344] Not surprisingly, concerns have been raised regarding consumption of animal products and processed meat in relation to cancer. Recent research has examined this association, with a particular focus on the role of methionine.

Absolute Methionine Dependency

In humans, methionine is an essential amino acid, commonly found in animal products, particularly red meat and eggs, whilst the lowest source is found in plant-based proteins such as legumes and nuts.[345] Hence, vegan/plant-based diets are naturally lower in methionine.[346]

Dietary methionine exerts a range of metabolic functions throughout life, displaying a dose dependant effect on health depending on the age of the individual.[347] Methionine is necessary for normal development during the first 1000 days from birth and beyond into adolescence.[348] As adults, the requirement for higher levels are no longer needed, and in contrast, dietary methionine restriction (MR) is associated with health benefits such as extending lifespan, preventing obesity, improving metabolic health and inhibiting tumour growth (Figure 20).[349]

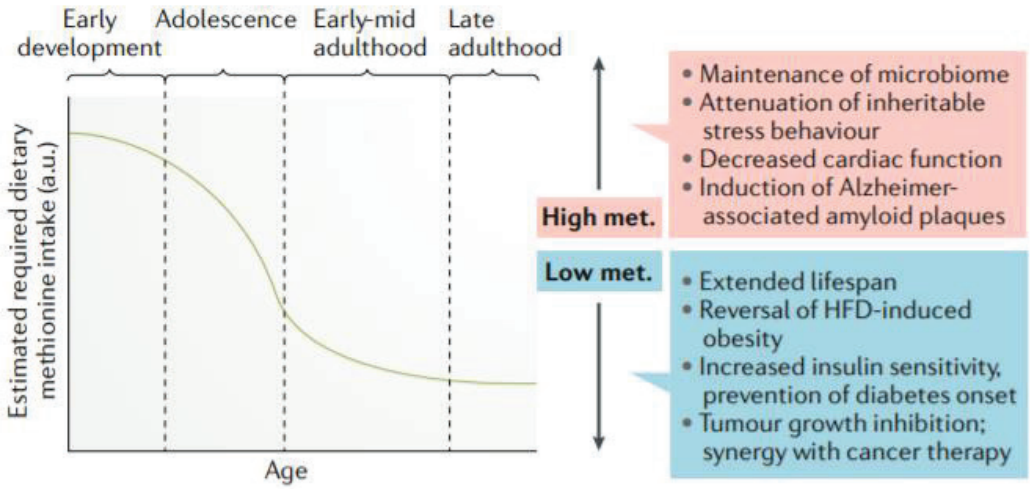


Figure 20: Dietary methionine intake has age-dependent effects on health.[350]

In April 1974, a landmark *in vitro* study was published which showed for the first time that when methionine is removed from the growth medium, normal cells continue to grow whilst cancer cells die.[351] This study was one of the first of its kind, demonstrating that many cancer cells display an 'absolute methionine dependency'.[352]

Methionine is involved in a range of cellular metabolic functions.[353] These include one-carbon metabolism, maintaining the redox balance and status intracellularly, as well as the synthesis of nucleotides,[354] all of which are important factors in cancer development and progression. As such, the idea of cancer cells being methionine dependent, along with the potential anti-tumour effects of MR piqued researchers' interest, questioning whether restricting cellular uptake through diet or blocking uptake through medication could lead to a new form of cancer management. Animal models and a small selection of human trials have investigated whether restricting methionine intake influences cancer growth, and if a MR diet is safe in those with cancer.

A pre-clinical trial was conducted to investigate the anti-tumour activity of MR with breast cancer.[355] Researchers suggested that through 'metabolic priming', a process of utilising a MR diet prior to cancer therapy, would essentially prime the cancer cells rendering them more susceptible to the cytotoxic effect of the drugs.[356] In an *in vivo* setting, metastatic triple-negative breast cancer (TNBC) cells were transferred to mice to test this theory.[357] Researchers compared the impact of a MR diet, a TNF-related apoptosis-inducing ligand-receptor 2 (TRAIL-R2) agonist lexatumumab or a combination of the two on tumour growth and progression.[358] Results showed that while MR and lexatumumab alone had little impact on inhibiting tumour growth, the combination of the two was able to suppress both the initial tumour and the subsequent lung metastasis.[359] It was suggested that MR metabolically primed TNBC, allowing increased expression of TRAIL-R2 receptors, rendering them more susceptible to the TRAIL-R2 agonist.[360]

Further, small trials with MR diets in humans have also shown promise. For example, eight patients with varying metastatic solid tumours were placed on a MR diet (2 mg of methionine/kg/d) for up to 39 weeks.[361] Results showed that plasma levels of methionine fell within two weeks, with the trial determining MR diets to be safe in this small group.[362]

Although MR is a fascinating area of research, and our understanding of the benefits of MR is advancing, more research in human clinical trials need to be conducted to further determine efficacy and clinical guidelines.

When the Going Gets Tough, the Tough Get Fasting

When cells are deprived of nutrients, as is the case during short-term fasting (STF), certain cellular metabolic pathways involved in growth are halted, and energy diverted into repairing processes.[363] As a result, STF has the ability to lower glucose, IGF-1 and insulin, whilst activating autophagy. In healthy cells, fasting activates a process known as differential stress resistance, whereby this lowering/down-regulation activates stress resistance genes in the bid to protect the cell from the impact of chemotherapy.[364,365] For cancer cells though, this down-regulation leads to a reduction in fuel supply, leading to an increase in ROS intracellularly, ultimately leading to cell death.[366,367] STF prior to chemotherapy and/or radiotherapy may reduce DNA damage and protect healthy cells from the impact of oxidative stress, reducing the toxicity of cancer therapy, and increasing treatment efficacy with reduced side effects for cancer patients.[368]

Whilst the idea of long-term fasting can be a difficult concept for most to consider, STF is more achievable, which improves patient compliance.[369] The fasting mimicking diet (FMD) is a form of STF that is being proposed as a clinical version of fasting to be employed

alongside chemotherapy cycles.[370] The FMD lasts between one to five days in total[371] and consists of a very low-calorie diet (300 to 1000 calories per day), and includes tailored soups, teas, juices, nut bars and specific supplements to reduce the risk of nutritional deficiencies.[372]

Animal models and human trials are now revealing the clinical benefits of STF/FMD, and demonstrating how short cycles of low-calorie fasting can be safe and effective when used in conjunction with cancer therapy.[373,374,375] A case report reviewed patients with varying forms of cancers (breast, prostate, ovarian, uterine, non-small cell carcinoma of the lungs, and oesophageal adenocarcinoma) who voluntarily fasted between 48 to 140 hours prior to and 5 to 56 hours during chemotherapy.[376] Clinically significant reductions in fatigue and weakness were seen in those who underwent chemotherapy and fasting.[377] In addition, vomiting and diarrhoea were also reduced in those that fasted, with only minor side effects of hunger and light-headedness being reported.[378]

Following this, a randomised controlled pilot study confirmed the above findings. Thirty-four cancer patients were recruited and randomised to complete STF in the first half of their chemotherapy, followed by a normal diet, whilst the second group followed a normal diet switching to a STF diet in the second half of their treatment.[379] The fasting period was 36 hours before chemotherapy and 24 hours post chemotherapy.[380] Results showed that STF was able to improve QOL markers and reduced fatigue.[381]

It must be noted that although animal models of fasting show promise, human trials are limited for the use of the FMD in oncology, and according to leading researchers in the area, more trials need to be conducted to provide firm evidence for clinical recommendations. With this in mind, several clinical trials on FMD and cancer are currently underway.[382]

It's a Non-Sandwich Related Wrap

When it comes to cellular metabolism and cancer, it is important to remember that while many cancer cells utilise glucose as a primary fuel for aerobic glycolysis, this is not the case for every type of cancer. It is important, therefore, to be informed about the type and stage of cancer your patient presents with, and then conduct research to obtain a better understanding of its metabolism, which can help you decide on the best dietary measures for your patient.

While the ketogenic, vegan/plant-based and fasting-mimicking/STF diets show promise for targeting a range of metabolic pathways, when we consider the current guidelines from the Cancer Council of Australia, we can confidently recommend a wholefood diet high in plant-based foods, with moderate levels of protein as our first line recommendation for cancer patients. The Metagenics Wellness Diet offers clear guidelines on a healthy eating plan that can be downloaded from the Metagenics website, www.metagenics.com.au or www.metagenics.co.nz.

Further to dietary recommendations, non-dietary solutions to target metabolic pathways can also be considered. Jane McLelland, author of *How to Starve Cancer* has also integrated herbs, nutrients and off-label medications that can alter metabolic pathways, with top recommendations for natural ingredients including berberine, quercetin, chromium, epigallocatechin gallate (EGCG), curcumin and resveratrol.[383] One of the highlights of these recommendations is the use of berberine which appears to impact all major fuel sources that feed cancer: glucose, glutamine and fat. Research on berberine is promising, with animal studies indicating it may help to target many roads that impact cancer cell metabolism. Some potential actions that have been noted include berberine's anti-inflammatory affect, inhibiting proliferation and metastasis, inducing autophagy and apoptosis.[384,385,386,387,388,389,390]

Box 6: Nutritional Resuscitation and Recovery

Whilst sophisticated cancer therapies are saving more lives, many cancers become chronic diseases. As the side effects of surgery, radiation and chemotherapy frequently results in malnutrition and metabolic derangements, many cancer patients need to recover from prolonged inadequate nutrient intake. Subsequently, chronic inflammation and loss of muscle mass (cachexia), negatively affects QOL, physical function and treatment tolerance.[391]

For patients recovering from cancer and its treatments, supplementing the diet with nutrient-dense smoothies can be particularly helpful. For example, blending *Undenatured Whey Protein Isolate* with *High Absorption Multi Mineral with Apple Cider Vinegar* effectively delivers pure essential amino acids for anabolic muscle growth, with bioavailable minerals to provide the basic nutrients for immune system function, musculoskeletal strength and metabolic health.

Cancer and Exercise

Years of research have highlighted the benefits of exercise for cancer patients (Figure 21).[392] This accumulation of data has shown that exercise targets and improves almost every conceivable outcome from reducing cancer incidence,[393] to inhibiting tumour growth,[394] alleviating cancer-related adverse events,[395] improving anti-cancer treatment efficacy,[396] lowering the risk of recurrence,[397] and improving QOL in patients.[398] Moreover, exercise has been proven to be safe, feasible, and effective, even in the most fragile and advanced-stage cancer patient.[399]

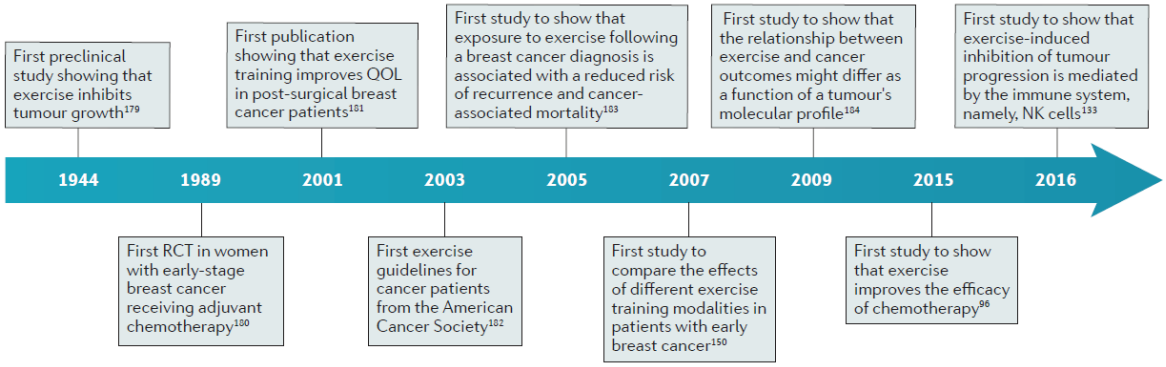


Figure 21: Highlights of research examining the effects of exercise in cancer.[400]

More than 100 clinical exercise intervention studies have shown that exercise-induced alterations in the systemic environment influence key regulatory mechanisms in the TME, from angiogenesis to immune regulation and metabolism.[401] During exercise, the rise in heart rate and blood pressure drives blood circulation, which increases tumour perfusion and has an impact upon the health of the TME due to increased angiogenesis and intratumoural vascularisation, reducing tumour hypoxia (Figure 22).[402,403] This may at first seem to be an undesirable consequence, however, improving oxygen and blood flow to the TME, has the beneficial effect of improving treatment efficiency and recovery.

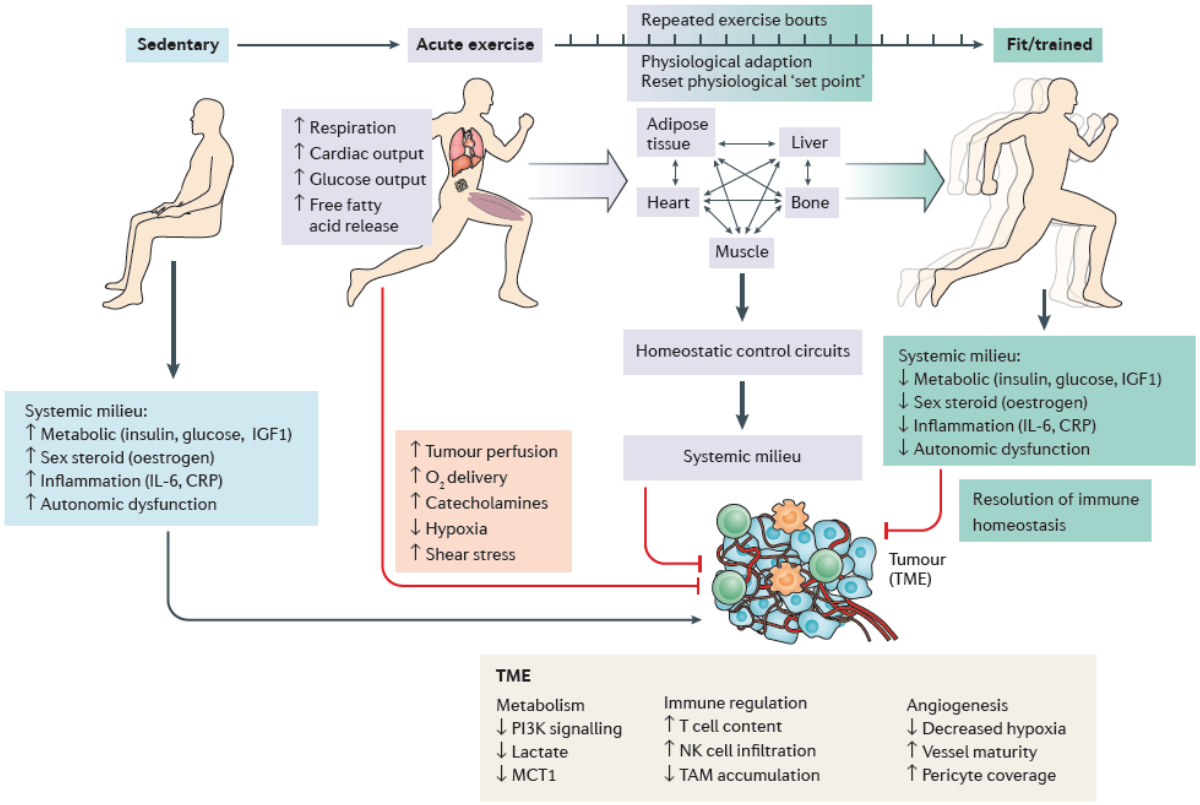


Figure 22: Exercise regulation of the TME.[404]

During exercise, enhanced blood perfusion and temperature increases improve drug delivery within the TME.[405] The increased integrity and structure of the vascular system within the TME supports the delivery of chemo- and radiotherapy – treatments that work to reduce tumour cell volume via the generation of reactive oxidative species to exert their therapeutic effect.[406] Furthermore, due to the beneficial effect of exercise on the health of cells overall, commonly reported side effects are significantly reduced, with patients often reporting improved tolerance and better recovery from treatment.[407,408]

Presently, exercise plays a strikingly limited role in clinical oncology. This might be due to a lack of recognition of the positive effects of exercise on cancer.[409] However, considering the research, exercise may be recommended to patients as a targeted approach to regulate cancer progression and formation, as well as ameliorate cancer-associated adverse events, and improve treatment efficacy.[310] Table 9 outlines evidence based exercise recommendations to address specific cancer patients concerns.

Table 9: Exercise recommendation for cancer patients.[411]

Exercise Recommendations for Cancer Patients 30 minutes x 5 days (150 min) exercise per week.[412]	
Specific Side Effect	**Exercise**
Anxiety and/or depression	30 to 60 minutes of moderate-intensity exercise 3 times per week for 12 weeks
Fatigue	30 minutes of moderate-intensity aerobic exercise 3 times per week
Quality of life	Combined 30 minutes of moderate-intensity exercise plus 2 sets of 12 to15 repetitions of resistance exercise 2 to 3 times per week for at least 12 weeks
Lymphoedema	A supervised resistance exercise program completed 2 to 3 times per week
Physical function	30 to 60 minutes of moderate-intensity aerobic exercise, 2 sets of 8 to 12 repetitions of resistance exercises, 3 times per week for 8 to 12 weeks

The Importance of a Good Night's Rest

Up to 75% of newly diagnosed or recently treated cancer patients, report experiencing sleep disturbances.[413] This loss of circadian homeostasis is thought to not only promote cancer development, but also contribute to poor therapeutic outcomes and sadly early mortality.[414]

Circadian disruption, specifically night-shift work, may also increase the risk of developing cancer, notably breast cancer.[415,416] A study in the International Journal of Cancer found a relationship between women's irregular work schedules and the incidence of breast cancer.[417] Researchers compared 1,200 female night-shift workers who had developed breast cancer between 2005 and 2008, with 1,300 women who did not have a cancer diagnosis. They found that the rate of breast cancer was 30% higher for the women who had worked night-shift for approximately four years, with a notable link if the women had been working night-shifts prior to her first pregnancy.[418] Men are not exempt, with published results linking shift work with an increased incidence of prostate cancer.[419] Researchers suspect that this increase in cancer risk is mediated by a disruption in the protective nature of melatonin.[420,421]

Accumulating research notes that chronic disruption of the circadian rhythm tips the balance between tumour-suppressive and tumour-progressive gene expression to favour tumour growth.[422] The underlying mechanisms to date are not yet clear,[423] however several hypotheses have been put forward including: exposure to light during the night eliminating the nocturnal anti-carcinogenic effects of melatonin,[424] disturbed functioning of the biological clock genes that control cell proliferation,[425] and a weakening of the immune system due to sleep disturbances.[426]

Improved circadian rhythm on the other hand, has been shown to improve treatment efficacy. Randomised clinical trials including patients undergoing treatment for advanced-stage cancers, including metastatic ovarian, lung, colorectal, and breast cancers using conventional chemotherapeutic drugs has provided evidence that better therapeutic outcomes, including host tolerability, is improved with circadian rhythmicity.[427] Utilising Metagenics Circadian Rhythm Reset Protocol can help to support patients sleeping patterns throughout their cancer journey.

Psycho-oncology – a Central Part of Cancer Care

"Psycho-oncology is a cancer treatment. If empirical evidence of the impact of psychological intervention on overall survival is hard to demonstrate, there is ample evidence of its positive effect on quality of life, pain reduction, and cancer treatment side-effect management. For patients it is clearly not about just extending overall survival, but about living well the time that we live with cancer. Psycho-oncology holds a central place in each step of the path from diagnosis to recovery, and for those who like me live with advanced disease, all the way to the terminal phases of cancer."

– Cancer patient Patricia Garcia-Petro, 2013[428]

The development of psycho-oncology parallels the shift towards improving quality of life and palliative care for cancer patients, as opposed to simply increasing survival and life expectancy.[429] Psycho-oncology focuses on enhancing wellbeing and reducing distress, as well as supporting patients to find a sense of meaning in their life. Research demonstrates that patients who experience more meaning in life generally, have better psychological wellbeing and quality of life, with less distress after a cancer diagnosis than those whose life lacks meaning.[430]

The main areas of psycho-oncologic care include pain, fatigue, sexual issues and fear of cancer progression and/or recurrence. There are many proven strategies to support cancer patients and their carers, including meaning-centered psychotherapy (MCP), positive reframing and coping skills, mindfulness-based meditation and training, as well as relaxation and slow breathing techniques.[431]

"Psycho-oncological care needs to be fully acknowledged as a central part of cancer treatment."

– Cancer patient Patricia Garcia-Petro 2013[432]

The Cancer Personality Debunked

"Even today the cancer social identity remains highly stigmatised by our society and the discrimination one may experience because of the cancer membership can actually lead to increased levels of stress and damage health even more. In a way, with cancer, it feels like you have to pay your bill twice as you have to deal with the cancer and you have to deal with the stigma of cancer."

– Cancer patient Patricia Garcia-Petro 2013[433]

The cancer stereotype has been described as a personality with depressed mood, social conformism and controlled expression of needs and emotions.[434] This characterisation is not only incorrect but has had the unfortunate impact of marginalising cancer patients, leading many to feel self-guilt and attribute their diagnosis to previous misdemeanours.

Rather, the psychological experiences of cancer patients are usually the consequence rather than the cause of the disease.[435] The psychological significance of cancer diagnosis as well as the physiological impact of the disease and its treatments, considerably affect the neuroendocrine and immune systems with potential implications for mental health and behaviour.[436]

Phase Models Help us Understand What Patients are Going Through

As Practitioners, we may not be able to fully appreciate the distress and turmoil cancer patients face, however, understanding the phases of dealing with a severe and potentially terminal illness can help us to support patients on their emotional journey.

Utilising the work of both Elizabeth Kubler-Ross (five-phase model)[437] and Monika Renz (the four stages of maturation),[438] Figure 23 outlines the typical phases a cancer patient may go through on their journey with the disease and its treatment, potentially coming to terms with their own mortality.

Figure 23: The process of maturation when dealing with illness.[439,440]

As this combined model illustrates, the patient may initially experience disbelief along with shock and denial. Then emotions surge as reality sets in, resulting in a vacillation between anger, grief and despair, with many experiencing this rollercoaster cycle of emotions repeatedly. Bargaining is associated with pleading, such as making life transformative changes in the hope it will increase recovery and survival. The next step may be depression, giving up and surrendering to despondency and impotence in relation to the situation, whilst the last phase is associated with transformation, acceptance and letting go. This involves the spiritual dimension and often patients will develop a new mental attitude and even experience 'happiness and wellbeing in the midst of illness.'[441]

It is important to acknowledge that not all patients will enter into this process in a linear way. Each patient may go into one or more of these phases at any stage, not necessarily progressively, and the outcomes will vary individually. It is up to us as Practitioners to respect and support the process, wherever our patients may be on their journey.

"How a patient copes with reality and illness altogether makes up the quality of his or her hope"[442]

Adjustment to Cancer: Anxiety and Distress

Difficulties adjusting to cancer diagnosis is a normal response, as would be expected with any type of severe, life threatening and potentially fatal disease. It is therefore not surprising that many individuals with cancer experience a variety of challenging emotional reactions, including anxiety and fear in response to the stress associated with cancer screening, diagnosis, treatment and/or recurrence.[443]

Whilst most cancer patients do not exhibit or progress to develop specific mental disorders,[444] they and their carers will understandably require ample information, guidance and support at every stage of their journey to manage anxiety and related emotions such as fear and dread. The power of informed decision making cannot be overestimated and the role of any healthcare Practitioner is to empower their patients with knowledge for their health and wellbeing.

The Distress Thermometer – Open up Communication

A useful screening tool that has been utilised by oncology nurses and other healthcare professionals in hospital settings is the Distress Thermometer. Whilst not all patients will want or need psycho-oncological interventions, their need for support on other levels including daily practical matters, may go unrecognised and therefore not be adequately understood and met. The Distress Thermometer specifically provides the opportunity for patients to voice their concerns, identify areas where immediate support is needed, and to indicate if further referral to psychosocial services is required.[445]

In the context of cancer, distress has been defined as "a multifactorial unpleasant experience of a psychological (i.e. cognitive, behavioural, emotional), social, spiritual, and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and treatment. Distress extends along a continuum (Figure 24), ranging from common normal feelings of vulnerability, sadness and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis."[446]

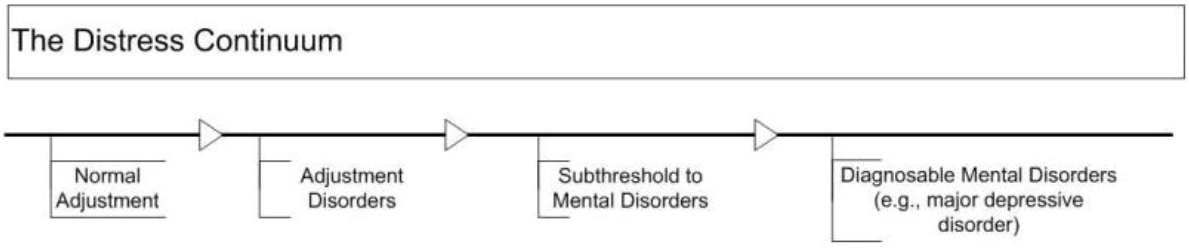


Figure 24: Psychosocial distress exists on a continuum that ranges from normal adjustment issues to syndromes that may result in a diagnosable mental disorder.[447]

The term 'distress' is preferred when describing the impact of cancer diagnosis on both patients and caregivers alike. 'Distress' carries less stigma for most people than words like anxiety or depression, which may pathologise many normal responses to being diagnosed with cancer.[448]

A copy of the Distress Thermometer is provided in Appendix 3.

It also needs to be acknowledged that the degree of distress may change during different stages of the disease and treatment. As such, using the Distress Thermometer can be a valuable means to 'check in' with your patient, identifying the particular stressors and needs at each stage of their journey.

Stress and Health Risk Behaviours Increase Cancer Risk

The combination of early life stress/trauma, along with chronic ongoing stress, increases the likelihood of health risk behaviours as a coping mechanism. Chronic stress is associated with risky health behaviour such as smoking, physical inactivity, poor diet and sleep deprivation. This in turn may increase the risk of progression and recurrence of cancer. There is a bidirectional relationship between high-risk behaviours such as alcohol and substance abuse with chronic stress and allostatic load, subsequently leading to disease burden.[449]

The Importance of Psychosocial Support

Psychosocial approaches include cognitive behavioural therapy (CBT) techniques, stress management, specific coping strategies, psychotherapy, crisis intervention, couple and family therapy, group therapy, self-help groups and relaxation-based interventions such as meditation, progressive relaxation, guided imagery and hypnosis. Some of these specific techniques are described in more detail below.

CBSM Reduces Breast Cancer Mortality and Recurrence

Cognitive-behavioural stress management (CBSM) interventions for cancer patients not only reduce anxiety and depression but are also associated with reduced leukocyte, proinflammatory and pro-metastatic gene expression in the first year of primary treatment.[450] Cancer patients who continue CBSM coping techniques and skills report reduced stress symptoms and have longer survival. In turn, there is also reduced pressure on inflammatory and tumour-promoting pathways.[451]

In 240 women recovering from surgery and undergoing adjuvant treatments for non-metastatic breast cancer, a 10-week group-based CBSM program was associated with better emotional and physical wellbeing compared to controls at follow up eleven years later.[452]

The CBSM program involved 90-minute sessions once per week, utilising techniques such as cognitive reframing, stress evaluation, training on effective coping skills, assertiveness and anger management, as well as encouraging optimum use of social support and relaxation techniques. The overall aim was to reduce stress and support psychological adaptation and coping skills. Women in the control group received a one day psychoeducational self-help seminar and general information about health and breast cancer care. They also received handouts containing abbreviated sections of the CBSM modules but were not otherwise taught these techniques.[453]

The CBSM intervention was associated with long-term clinical as well as psychological benefits. Further, it reduced the risk of all-cause mortality and prolonged survival compared to controls (Figure 25).[454]

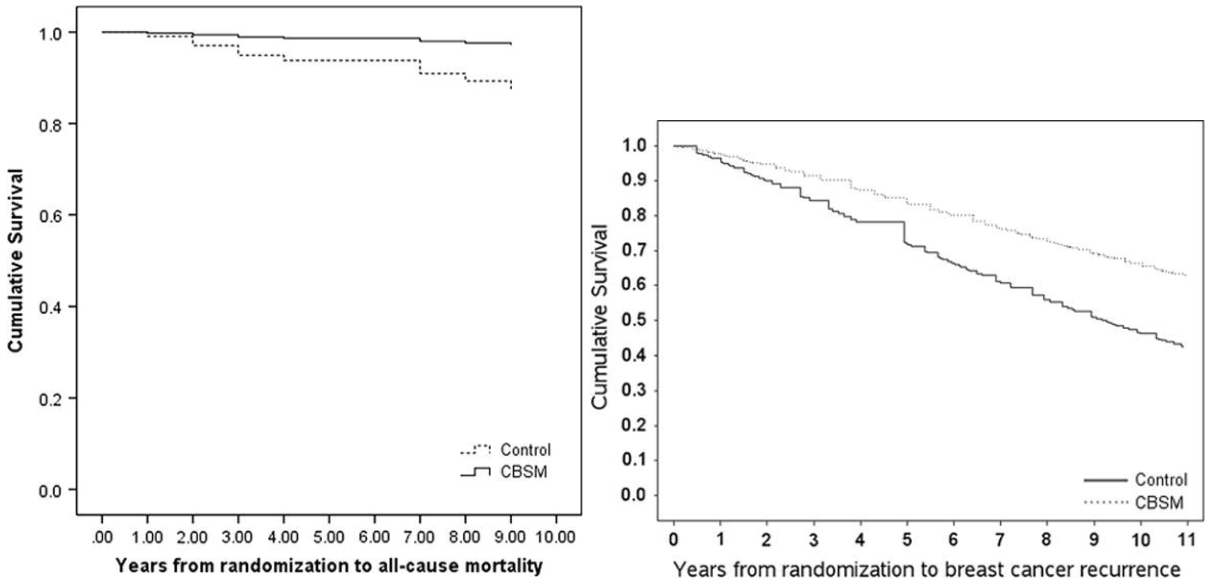


Figure 25: Left - general survival difference and Right - breast cancer specific survival difference between CBSM and control groups.

The Stress and Cancer Connection

The potential impact of chronic stress leads to changes in neuroendocrine function and is associated with increased inflammation and immune dysregulation, which may increase cancer progression and negatively impact QOL and survival. Conversely, the positive impact of stress management, including social support, skills such as CBSM techniques, meditation and relaxation, as well as pharmacologic and/or herbal and nutritional support may serve to modulate these negative impacts and consequently improve QOL and positive health outcomes.[465]

Activation of the sympathetic nervous system (SNS) by stress releases neurotransmitters, which act on β-adrenergic receptors on tumour cells and tumour-associated immune cells to promote metastasis.[457] Reducing stress improves survival and health outcomes in cancer patients.[458]

A recent Australian study suggests that beta-blockers, commonly used to treat high blood pressure and anxiety, could prevent the spread of cancer cells by reducing the impact of stress. Sixty breast cancer patients who were due to undergo surgery received the beta-blocker propranolol, or placebo, one week prior to their operation. The results demonstrated that the use of beta-blockers down-regulated biomarkers associated with metastatic potential, indicating the likelihood of reducing cancer recurrence.[459]

Beta-blockers are also associated with longer overall survival in ovarian cancer patients. A study conducted to investigate the impact of beta-blockers on clinical outcomes was conducted with 269 women (median age 63 years) with epithelial ovarian, primary peritoneal or fallopian tube cancers, collectively referred to as EOC. These women were either receiving adrenergic beta-1 receptor (ADRB1) selective agents (71.7%) or non-selective beta agonists, primarily prescribed for hypertension as well as arrhythmia and post-myocardial infarction management. The median overall survival (OS) for patients receiving any beta-blocker was 47.8 months compared to 42 months for non-users. For those on non-selective beta-blockers the median OS was 94.9 months compared to 38 months for those receiving ADRB1 selective agents (Figure 26).[460]

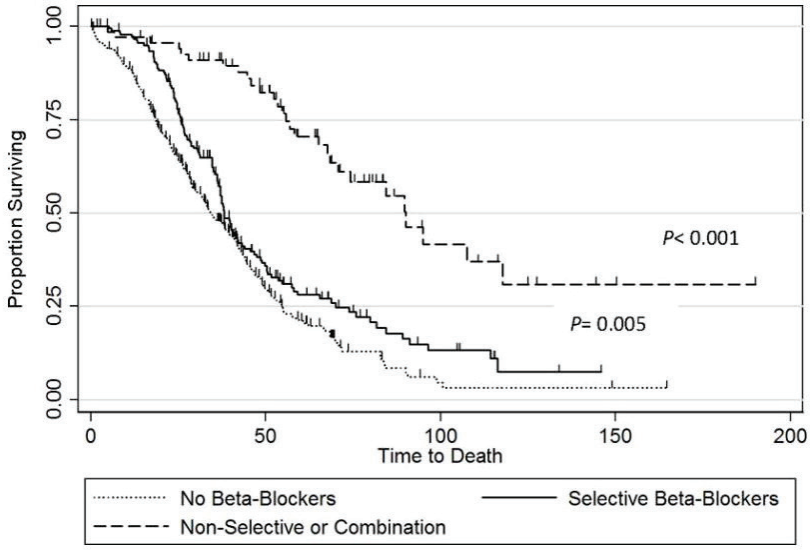


Figure 26: Beta-blockers associated with increased survival in cancer patients.[461]

MBSR Alters Cortisol and Immune Patterns in Cancer Patients

"MBSR gave me a new perspective that allowed me to distinguish the thoughts about the cancer situation from the actual experience in the body"

– Cancer patient Patricia Garcia-Petro, 2013[462]

A study was conducted to investigate the continuing effects of an eight-week mindfulness based stress reduction program (MBSR) with 49 breast cancer patients and 10 patients with prostate cancer on QOL, symptoms of stress and mood. The MBSR program involved meditation, relaxation, gentle yoga and daily home practice. Immune, endocrine and autonomic nervous system markers, as well as blood pressure (BP) and heart rate (HR) were all monitored at baseline, post-intervention and 6- and 12-month follow up.[463]

The results demonstrated a reduction in symptoms of stress as well as a decrease in cortisol levels, both of which were sustained in the follow-up period (Figure 27). A decline in inflammatory cytokines and a decrease in both systolic blood pressure (SBP) and HR were also positively correlated with self-reported symptoms of stress.[464]

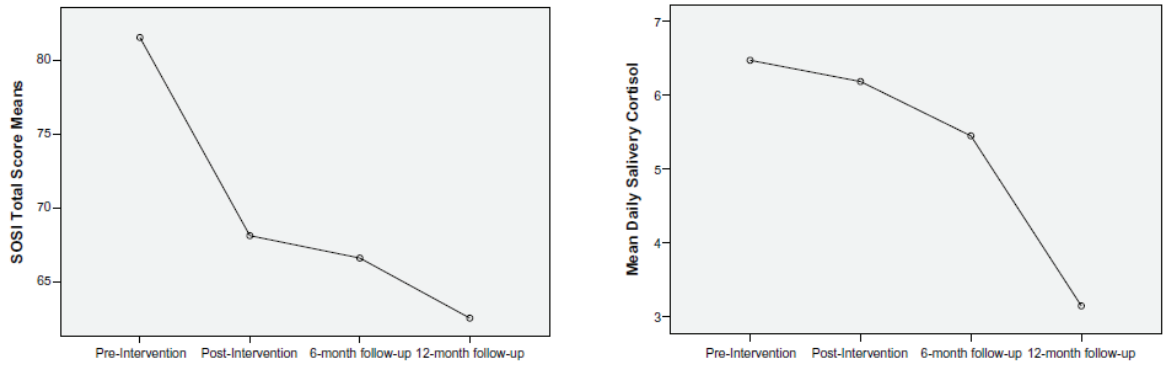


Figure 27: MBSR lowers symptoms of stress inventory (SOSI [left]) and cortisol (right) in cancer patients.[465]

Fear of Cancer Recurrence

Not surprisingly, fear of cancer recurrence (FCR) is cited as one of the most common concerns of cancer survivors and their carers.[466] The prevalence of FCR can be as high as 70% and is rated as one of the most poorly addressed needs.[467]

CBT can reduce the severity of FCR in cancer survivors with evidence provided in several studies. One of the more well-known interventions is the SWORD study which investigated the efficacy of blended CBT (bCBT) in 88 survivors of breast, prostate and colorectal cancers with high FCR. The bCBT was provided over a three month period and involved five individual one hour face-to-face sessions, and three 15 minute e-consultations with access to a website.

Patients without access to a website received three 15 minute telephone consultations and a workbook with identical content. The intervention utilised techniques such as psycho-education, cognitive restructuring and behavioural modification. The control group received care as usual (CAU).[468] Approximately one third of the participants receiving bCBT had clinically significant improvement, evaluated as a reduction in FCR severity, while no improvement was noted in the control group.

In another study, the effectiveness of a comprehensive intervention consisting of CBT-based coping strategies and an information manual to manage uncertainty around cancer recurrence was evaluated in 509 breast cancer survivors. The women in the intervention group were taught to recognise their own triggers of uncertainty and utilise coping strategies such as relaxation, distraction and calming self-talk to deal with these. The manual provided a resource to assist with pain, lymphoedema, fatigue and other symptoms. The study found that the 244 women in the intervention group regularly utilised the coping strategies to contend with triggers of fear of breast cancer recurrence and long-term treatment side effects. The majority of women in this group reported these strategies were very helpful.[469]

Support with Natural Medicine

The Mood and Stress Questionnaire (MSQ) is another useful clinical screening tool to elicit levels of stress and identify which herbal and nutritional support is best indicated. This can be downloaded from the Metagenics website at www.metagenics.com.au or www.new.metagenics.co.nz.

Table 10 outlines some general recommendations for specific nervous system support for cancer patients, which may be implemented at any stage during treatment. Whilst many ingredients used to support the nervous system can be safely co-prescribed alongside chemo- and radiotherapy, each patient and their situation will essentially be unique and we recommend prescribing with the support of the patient's oncologist. Table 10 also provides the general cautions and contraindications for the formulas indicated, however for a more detailed exploration of individual ingredients please consult the Technical Data or call the Clinical Support Team on 1800 777 648 (Australia) or 0508 227 733 (New Zealand) or email clinicalsupport@metagenics.com.au.

Table 10: Nervous system support for cancer patients.

Clinical Indication	Catchphrase	Cautions and Considerations
General stress management	*Meta Mag® Magnesium, Taurine and Glutamine for Stress*	Check with a patient's oncologist before recommending a formula containing antioxidants.
	Vitamins B5, B6 and C for Stress and Adrenal Health	Seek approval from a patient's oncologist before prescribing folate and a formula containing antioxidants.
Depresssion	*BCM-95™ Turmeric and Saffron for Depression*	Check with a patient's oncologist before recommending a formula containing antioxidants. Note: mixed evidence on the effects of curcumin alongside chemotherapy – use with caution and only under the supervision of the patient's oncologist.
Anxiety	*Herbal Support for Hyper HPA and Stress*	As kudzu is oestrogenic, avoid use in hormone sensitive/dependant cancers.
Chemotherapy "brain fog"	*Lipid and Tocotrienols for Healthy Cell Membranes and Cognition*	Safe to use alongside chemo- and radiotherapy.
	Choline	
	Bacopa/Gingko Complex	
Metagenics Stress Less Program		Call the Clinical Support Team for specific support.

Cancer is understandably a topic of critical and ongoing research, and as such there are many novel and emerging therapies and tools, some more grounded in evidence than others. What follows is a comprehensive update on the state-of-play, which may improve Practitioner awareness of the options available to cancer patients.

Photobiomodulation – Shining the Light on Cancer

Photobiomodulation (PBM) therapy, previously known as low-level laser therapy (LLLT), is the use of red or near-infrared light (NIR) to stimulate healing and repair damage caused by injury or disease.[470] The therapeutic results of PBM is owed to its actions on the mitochondria, as these energy powerhouses contain photosensitive chromophores, organelles that absorb light. PBM activates the endogenous chromophores by stimulating the mitochondrial enzyme cytochrome oxidase C.[471] This leads to both reduction of oxygen and the disassociation of nitric oxide (NO), thus increasing the mitochondrial membrane potential and ATP synthesis. In turn, this activates signalling pathways to stimulate anti-inflammatory processes, cell metabolism and repair, amongst other healing mechanisms. Figure 28 demonstrates how NIR activates the mitochondria resulting in profound effects on gene expression to promote healing and repair.[472]

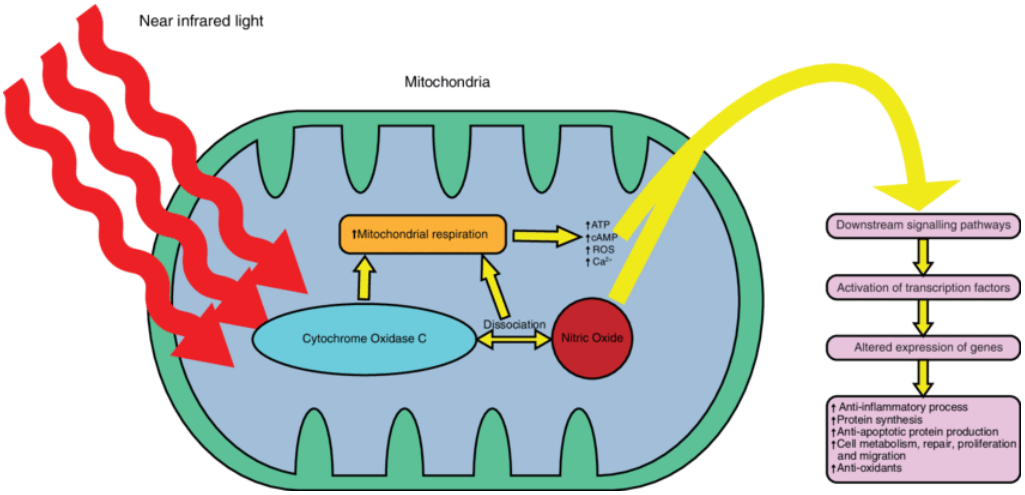


Figure 28: Mechanisms of PBM (near infrared light) on mitochondrial function and gene expression.[473]

PBM has sound evidence of benefit in cancer patients and is endorsed and accepted by the International Society of Oral Oncology as a primary and standard practice in the prevention and/or treatment of OM,[474] a common and debilitating side effect of chemo- and radiotherapy for head and neck cancer.

Figure 29 outlines the numerous other side effects of cancer therapy, which could benefit from PBM.

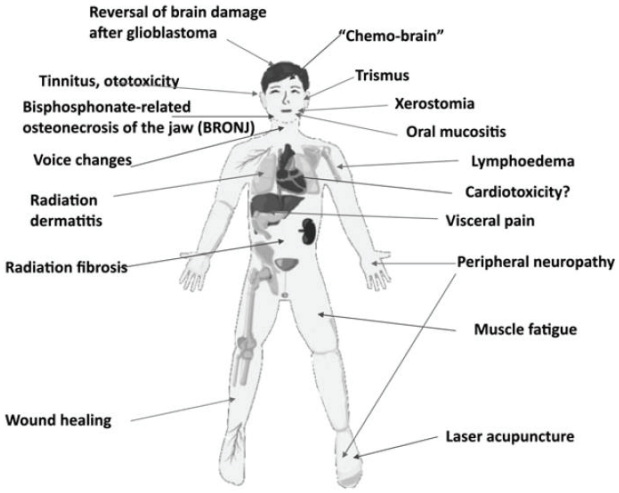


Figure 29: Cancer therapy side effects that could potentially be treated with PBM.[475]

Combining PBM with Cytotoxic Anticancer Therapies

One of the benefits of PBM in cancer is that malignant cells and normal/healthy cells respond very differently to this therapy. In healthy cells, the impact of PBM initially increases ROS which can in turn elicit protective mechanisms and defend healthy tissue from the damaging effects of cancer therapy. In contrast, when cancer cells are exposed to PBM they become more responsive to cytotoxic stimuli and apoptosis is accelerated.[476]

One study demonstrated that PBM improved treatment outcomes and progression-free survival in patients with varying types of head and neck cancers. With the aim of preventing OM during radiotherapy and chemotherapy, PBM was administered to nine points on the oral mucosa five days per week, and continued on average for 45.7 days. The parameters for PBM, based on guidelines recommended by the International Dose Response Society,[477] were 660 nanometres (Nm), 100 megawatts (mW), 4 J/cm2, and spot size 0.24 cm2.[478] The patients were followed up for 41 months, with those receiving PBM displaying a statistically significant better complete response to treatment than those in the placebo group, measured as progression-free survival (Figure 30) and a tendency to better overall survival. They also demonstrated lesser incidence of OM, reduced need for opioid medication and less requirement for gastrostomy.[479] Therefore, PBM offers a safe, effective and low cost treatment.

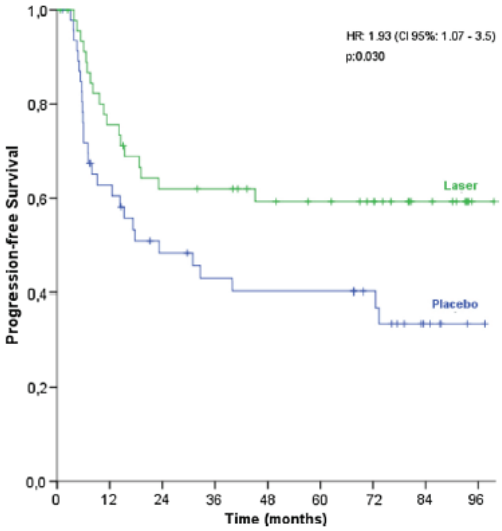


Figure 30: Progression-free survival in patients receiving PBM compared with placebo.[480]

Photodynamic therapy refers to the administration of PBM alongside cytotoxic or chemotherapeutic agents, an example demonstrated in the above study with patients with head and neck cancer. In another model, PBM was compared alone, and in combination with curcumin, for treatment of OM in cancer patients. Fifty-six patients were assigned to receive either PBM alone or PBM plus photodynamic therapy. In this instance, the photodynamic therapy required patients to rinse with 20 ml of a photosensitising mouthwash containing curcumin, and receive blue LED therapy in their oral cavity for five minutes. Significant reduction in severity of OM was seen in both groups; however, those who received the PBM plus photodynamic therapy had a reduced time to lesion remission from 15 to 11 days compared to those who received PBM alone.[481]

Hyperthermia

Hyperthermia, a therapy utilising heat to aid in the treatment against cancer, was first reported on papyrus scrolls around 5000 BC. Today, this ancient therapy is still an important adjunct therapy for many cancer patients.[482]

Temperatures induced by hyperthermia treatment range from 39 to 45 degrees Celsius and can be delivered via radiofrequency, ultrasound, microwave, laser and magnetic nanoparticles.[483] The benefits of hyperthermia for cancer include:

- Reduced cancer cell membrane integrity;
- Increased cancer cell apoptosis; and
- Enhanced immune responses, dependent upon temperature achieved (Figure 31).[484]

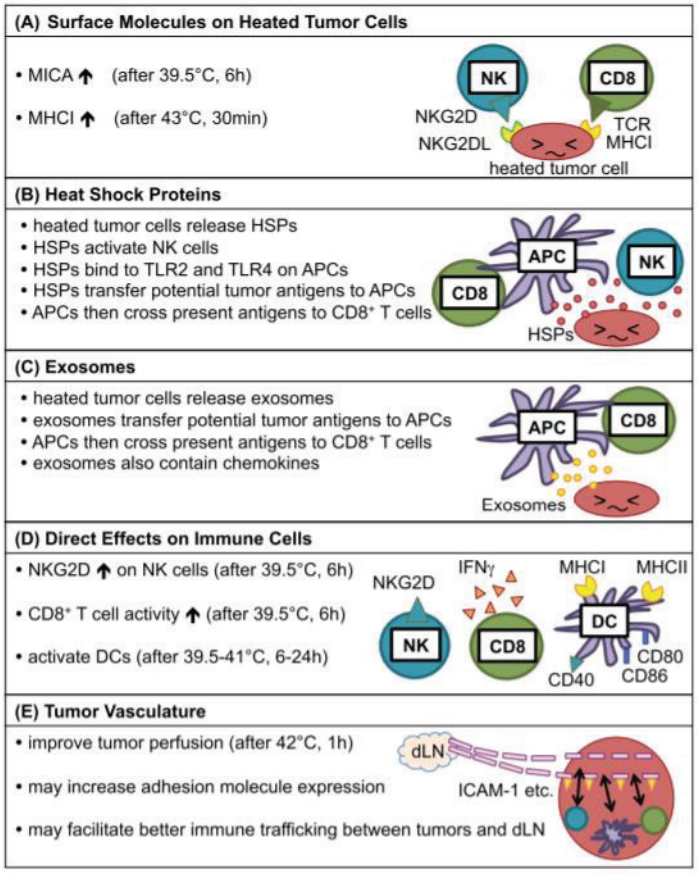


Figure 31: Effect of hyperthermia on immunity.[485]

Hyperthermia is classified as either local, regional or whole-body. Local hyperthermia is typically used for solid tumours, regional for a larger area such as a limb, and whole body is applied in the case of widespread metastatic cancer.[486] Hyperthermia is often combined with chemo- or radiotherapy, having demonstrated to enhance both therapies efficacy.[487] When local hyperthermia was added to radiotherapy in the treatment of a range of cancers the overall response rate was 54.9% compared with 39.8% in those receiving only radiotherapy.[488]

In the case of metastatic stage IV gastric cancer, a trial identified the combination of whole body hyperthermia with intravenous (IV) intraperitoneal chemotherapy improved outcomes for patients when compared with chemotherapy as a standalone. Results demonstrated:

- Complete and partial remission rate at 61.5% combined therapy vs 23.8% chemotherapy alone;
- Stable disease rate at 19.2% combined therapy vs 28.5% chemotherapy alone;
- Survival rate at one year post treatment was 38.5% for combined therapy vs 19% for chemotherapy alone; and
- Additionally, the combined group experienced improvements in QOL as indicated by their Karnofsky score (measures ability of cancer patients to perform everyday tasks).[489]

However, this therapy is not without its limitations as current challenges include accurately identifying the temperature within the tumour mass. Poor precision, with temperatures too high, can result in the damage of healthy tissue, and a temperature too low can result in inadequate treatment.[490] Hyperthermia can also have a double edged sword effect on tumour immunity. Although it has been demonstrated to increase the expression of certain heat shock proteins (Hsp) which enhance anti-tumour immunity, it can also increase Hsp which block apoptotic pathways, offering protection to cancer cells. Further, hyperthermia has been shown to have immunosuppressive effects with reduced cytotoxic activity of NK cells and T lymphocytes observed after hyperthermia treatment at 42 degree Celsius. Thus to improve patient outcomes the benefits of this therapy are experienced when combined with other anticancer treatments rather than as a standalone.[491]

Hyperbaric Oxygen: an Adjunctive Therapy in Cancer

Best known for its use in pathological conditions with hypoxic or ischaemic states, hyperbaric oxygen (HBO) therapy has also been explored as an adjuvant treatment to enhance the efficacy of chemo- and radiotherapy. HBO assists in reducing tumour hypoxia by increasing the concentration of oxygen in the plasma, and importantly, radiation treatment is found to be most effective in well-oxygenated tumour tissue. The combination of HBO and radiation appears to reduce tumour growth, improve local tumour control and subsequently increase survival time.[492]

Another safe and effective therapy with rare side effects, HBO has been used prior to and during irradiation, and has been found to improve the effectiveness of this therapy. HBO can also work as a chemotherapy adjuvant by enhancing the efficacy of certain cytostatic drugs such as cisplatin. Again, as with radiation, HBO alongside chemotherapy achieved better results than chemotherapy alone, by rendering tumour cells more sensitive to chemotherapeutic treatments.[493]

Protective Role of Vagal Nerve Stimulation in Cancer

Vagal nerve stimulation also has therapeutic potential as an adjuvant therapy for cancer patients.[494] As previously mentioned, the TME is inflammatory and the nervous system and immune system continually seek to reduce the inflammation and return the body to homeostasis. Importantly, the vagal nerve carries the 'off switch' for inflammatory cytokine production. Vagal nerve activation transmits electrical signals to the spleen, triggering the chemical activation of WBC which, in turn, release acetylcholine (ACh). This serves as the specific signal for macrophages to cease production of TNF-α and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), thereby reducing inflammation.

Heart rate variability (HRV) is intimately linked with vagal tone, and is therefore widely used to assess vagal activity. Higher HRV was predictive of improved survival rates and lower tumour markers in patients with colon cancer, non-small cell lung cancer as well as prostate and breast cancer, illustrating the potential influence of the vagus nerve to modulate immunological responses relevant to anticancer immunity.[495]

Further evidence for the protective effect of the vagus nerve in cancer is provided from patients who have undergone vagotomy to treat peptic ulcers. This was associated with an increased risk of gastric, colorectal, biliary tract and lung cancers as well as increased mortality in pulmonary carcinoma.[496]

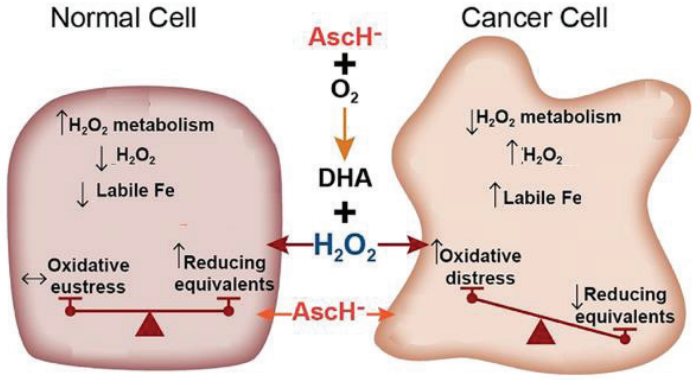
Besides electrical stimulation, several other therapies can be employed to activate the vagus nerve to 'turn down' inflammation. These include polyphenol compounds such as curcumin in turmeric; nutrients such as fish oil and magnesium; and therapeutic modalities such as acupuncture, rhythmic breathing, exercise and postural techniques.

Interestingly, the human vagus nerve produces SPMs (see page 23 for more information about SPMs), which was observed in a study after electrical vagal stimulation.[497] Therefore, restoring vagal tone offers the additional advantage of supporting the resolution of the inflammatory process locally and systemically.

Intravenous Vitamin C

The use of intravenous vitamin C (IVC) to treat cancer, dates back to the 1970s work of Nobel Laureate Linus Pauling, who treated patients with advanced cancer with high doses of vitamin C and reported a positive effect on survival.[498] Whilst there are numerous hypotheses about the anticancer mechanisms of vitamin C, the most widely accepted is based on its pro-oxidant capacity against tumour cells, while simultaneously acting as an antioxidant in normal tissue.

Figure 32 illustrates how ascorbic acid (AscH-) displays selective toxicity to cancer cells. As AscH- undergoes oxidation, hydrogen peroxide (H_2O_2) is produced which cancer cells are unable to remove, thus generating high levels of oxidative stress (OS). In addition, AscH- disrupts iron metabolism within cancer cells leading to increased levels of labile iron and further OS. This also makes the cancer cells more sensitive to the effects of chemoradiation. By contrast, H_2O_2 is nontoxic to normal cells, which have a high capability to metabolise H_2O_2 along with highly regulated iron metabolism.[499]



AscH-: Ascorbic acid; DHA: Dehydroascorbic acid; H_2O_2: Hydrogen peroxide

Figure 32: Pro-oxidant and anticancer effect of IV vitamin C.[500]

The upper oral limit of supplemental vitamin C is constrained as intestinal uptake is regulated by the sodium-dependant vitamin C transporter-1. This is bypassed with IVC administration, achieving considerably higher plasma concentrations, up to 20 mmol/L. It is generally understood that plasma vitamin C concentrations >20 mmol/L are required for generation of H_2O_2.[501] Therefore, the supraphysiological doses required to increase plasma concentrations to these levels can only be achieved with IVC (Figure 33).

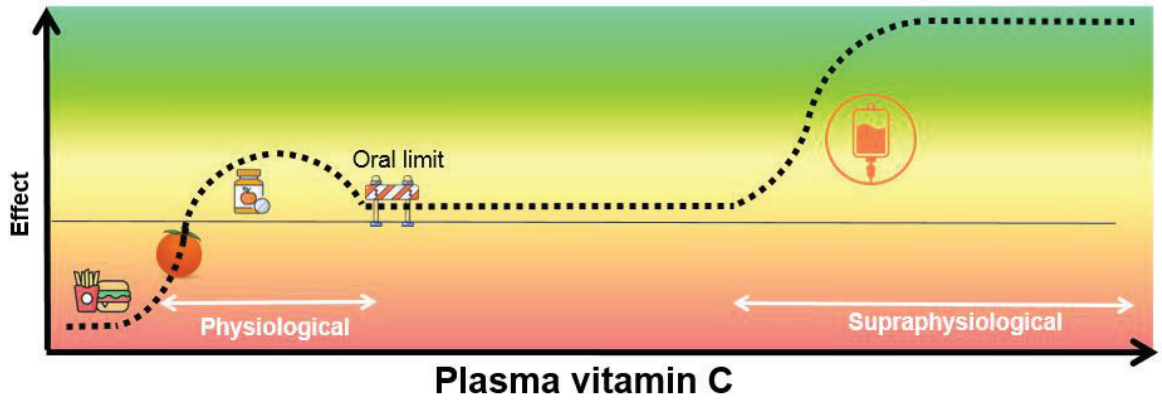
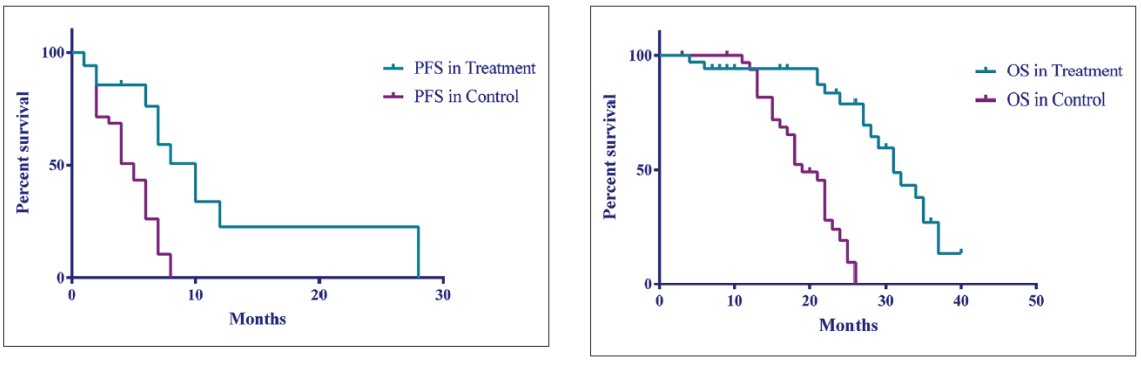


Figure 33: Oral versus IV vitamin C.

A systematic review concluded that treatment with vitamin C in cancer patients is safe and has minimal side effects, even with high doses of IVC. Further, IVC has been studied in numerous types of cancer, both alone and alongside chemotherapy, where it has been found beneficial to reduce the side effects of cytotoxic chemotherapeutic agents and prolong survival in cancer patients.[502]

A retrospective study investigated the impact of chemotherapy with or without IVC on seventy women with advanced TNBC. Those women who received chemotherapy and IVC had a median progression-free survival time and median overall survival time of seven months and 27 months respectively, compared with four and a half months and 18 months in the control group (Figure 34).



PFS: progression free survival; OS: overall survival

Figure 34: IV vitamin C prolongs survival in patients with advanced triple negative breast cancer.[503]

Screening Tools for Early Detection and Surveillance

Given the enormous impact of cancer on society, cancer screening and surveillance may offer hope in gaining earlier detection, improved prognosis and even personalised intervention. Table 11 highlights the evidence for, and limitations of a selection of novel and emerging screening tools.[504]

Table 11: Evidence and limitations of existing and emerging screening tools.[505]

Test	Background	Evidence	Limitations
Digital thermography	Used since the 1960s to detect temperature variation on the surface of the skin. Most of the literature describing the use of thermography in cancer is based on breast cancer.[506]	Demonstrated differentiation of: • Malignant from benign lesions in women (pre- and post-menopausal) with an identified breast tissue mass. • Fibroadenoma/cysts and malignant lesions in females with palpable breast mass.[507]	• Not appropriate for evaluation of granulomatous mastitis.[508] • Does not provide information on structural characteristics of tissue/organ.[509] • Research has demonstrated false positive cases, with 68% false positives in one study and 27% in another study.[510] • Its role is considered complementary to other techniques as alone it does not provide sufficient information for screening or for diagnostic confirmation in breast cancer.[511] Mammographic screening is still gold standard for early breast cancer detection[512] and thermography cannot be substituted for mammography in early breast cancer diagnosis.[513]
Circulating Tumour Cell (CTC) test	CTCs are cells that shed from the tumour and enter into circulation. CTCs can also enter the bone marrow and stay dormant for differing time periods. CTCs are proposed as being the primary cause of cancer metastasis.[514]	CTC molecular analysis provides information about the tumour including cell morphology, immunological phenotype and establishment of multiple mutations within the cell, revealing tumour heterogeneity. Using enumeration methods (biological cell features) CTC sensitivity is approx. 65% in metastatic breast cancer.[515] Prognostic marker: • Use of epithelial cell surface marker identified for breast,[516] prostate and non-small cell lung cancer, five CTCs in 7.5 ml of blood is associated with lower survival rate.	• Detection is challenging due to small numbers in samples and large numbers of other cells in samples e.g. one CTC per 10,000,000 WBC/mm of blood.[518,519] • Detection methods rely on physical properties of cells. More successful and widely accepted approach, known as enumeration, uses specific biological features such as cell surface markers.[520]

Test	Background	Evidence	Limitations
		Biomarker of treatment efficacy: • A decrease in either total CTC number or in a subgroup exhibiting a specific biomarker (e.g. epithelial growth derived receptor) is observed in response to therapy. • Conversely, an increase in CTC after treatment is associated with reduced survival. Predictive biomarker: • Provides more personalised therapy as CTCs can identify the expression of specific markers which may be resistance mutations or mutations specific to certain cancers, allowing for appropriate therapy to be utilised, increasing survival chances.[517]	
Circulating tumour derived DNA (ctDNA)	Low levels of ctDNA found in healthy individuals. However, under circumstances including but not limited to cancer, levels of ctDNA increase. ctDNA is used for: • Early cancer detection • To monitor tumour progression • To identify mutations, thereby personalising treatment.[521]	Greater accuracy in comparable studies with CTCs. • Comparison with CTC carried out in 30 breast cancer patients with PIK3CA and p53 mutations. Detectable ctDNA levels found in 97% of patients compared with 87% identified by CTCs.[522] Offers a greater efficacy and personalisation with pharmacological therapies. • An acquired epithelial growth factor (EGFR) resistance mutation was identified by ctDNA following treatment with an EGFR inhibitor. This identification allows for more appropriate treatment to be introduced.[523]	Greater accuracy in comparable studies with CTCs. • Comparison with CTC carried out in 30 breast cancer patients with PIK3CA and p53 mutations. Detectable ctDNA levels found in 97% of patients compared with 87% identified by CTCs.[524] Offers a greater efficacy and personalisation with pharmacological therapies. • An acquired epithelial growth factor (EGFR) resistance mutation was identified by ctDNA following treatment with an EGFR inhibitor. This identification allows for more appropriate treatment to be introduced.[525]

Conclusion

Natural health care Practitioners have a huge role to play in a cancer patient's journey. Putting the patient first, right at the centre of care, means considering their priorities, addressing the side effects of treatment and improving quality of life. This approach can utilise safe and effective ingredients as well as lifestyle interventions such as diet, sleep and physical activity. Furthermore, psycho-oncology is a major pillar of patient centred care, not only helping patients live well through their journey, but also improving their outcomes (Figure 35). Together, this offers a comprehensive strategy to integrative, patient centred oncology.

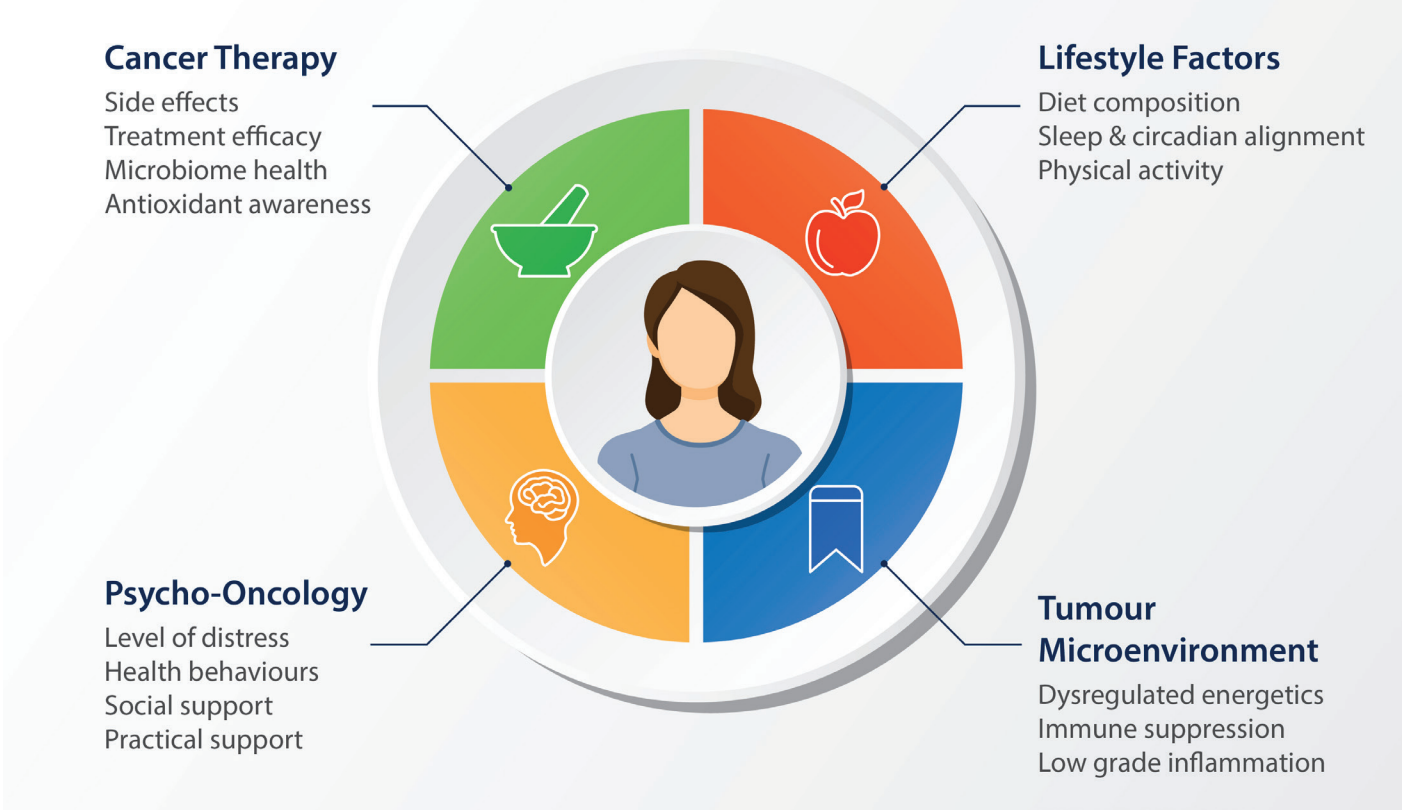


Figure 35: Patient centred care, with in the context of integrative oncology.

REFERENCES

[1] Oneview [Internet]. Chicago, IL: Oneview Ltd; 2020. The eight principles of patient-centred care; 2015 May 15 [cited 2020 Apr 4]. Available from: https://www.oneviewhealthcare.com/

[2] Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000 Jan 7;100(1):57-70. doi: 10.1016/s0092-8674(00)81683-9.

[3] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144(5):646-74. doi: 10.1016/j.cell.2011.02.013.

[4] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144(5):646-74. doi: 10.1016/j.cell.2011.02.013.

[5] Martin GS. The road to Src. Oncogene. 2004 Oct 18;23(48):7910-7. doi: 10.1038/sj.onc.1208077.

[6] Bagci O, Kurtgöz S. Amplification of cellular oncogenes in solid tumors. N Am J Med Sci. 2015 Aug;7(8):341-6. doi: 10.4103/1947-2714.163641.

[7] Takashima A, Faller DV. Targeting the RAS oncogene. Expert Opin Ther Targets. 2013 May;17(5):507-31. doi: 10.1517/14728222.2013.764990.

[8] Takashima A, Faller DV. Targeting the RAS oncogene. Expert Opin Ther Targets. 2013 May;17(5):507-31. doi: 10.1517/14728222.2013.764990.

[9] Bagci O, Kurtgöz S. Amplification of cellular oncogenes in solid tumors. N Am J Med Sci. 2015 Aug;7(8):341-6. doi: 10.4103/1947-2714.163641.

[10] Vicario R, Peg V, Morancho B, Zacarias-Fluck M, Zhang J, Martínez-Barriocanal Á, et al. Patterns of HER2 gene amplification and response to anti-HER2 therapies. PLoS One. 2015 Jun 15;10(6):e0129876. doi: 10.1371/journal.pone.0129876.

[11] Zheng J. Oncogenic chromosomal translocations and human cancer (review). Oncol Rep. 2013 Nov;30(5):2011-9. doi: 10.3892/or.2013.2677.

[12] World Health Organization. Human papillomavirus (HPV) and cervical cancer [Internet]. Who.int. 2020 [cited 14 Apr 2020]. Available from: https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer

[13] Stein Y, Rotter V, Aloni-Grinstein R. Gain-of-function mutant p53: all the roads lead to tumorigenesis. Int J Mol Sci. 2019 Dec 8;20(24). pii: E6197. doi: 10.3390/ijms20246197.

[14] Stein Y, Rotter V, Aloni-Grinstein R. Gain-of-function mutant p53: all the roads lead to tumorigenesis. Int J Mol Sci. 2019 Dec 8;20(24). pii: E6197. doi: 10.3390/ijms20246197.

[15] Mendoza PR, Grossniklaus HE. The biology of retinoblastoma. Prog Mol Biol Transl Sci. 2015;134:503-16. doi: 10.1016/bs.pmbts.2015.06.012.

[16] Mendoza PR, Grossniklaus HE. The biology of retinoblastoma. Prog Mol Biol Transl Sci. 2015;134:503-16. doi: 10.1016/bs.pmbts.2015.06.012.

[17] Wang LH, Wu CF, Rajasekaran N, Shin YK. Loss of tumor suppressor gene function in human cancer: an overview. Cell Physiol Biochem. 2018;51(6):2647-93. doi: 10.1159/000495956.

[18] Brücher BL, Jamall IS. Somatic mutation theory - why it's wrong for most cancers. Cell Physiol Biochem. 2016;38(5):1663-80. doi: 10.1159/000443106.

[19] Baker SG. A cancer theory kerfuffle can lead to new lines of research. J Natl Cancer Inst. 2014 Dec 20;107(2). pii: dju405. doi: 10.1093/jnci/dju405.

[20] Risques RA, Kennedy SR. Aging and the rise of somatic cancer-associated mutations in normal tissues. PLoS Genet. 2018 Jan 4;14(1):e1007108. doi: 10.1371/journal.pgen.1007108.

[21] Baker SG. A cancer theory kerfuffle can lead to new lines of research. J Natl Cancer Inst. 2014 Dec 20;107(2). pii: dju405. doi: 10.1093/jnci/dju405.

[22] Mukherjee S. The emperor of all maladies: a biography of cancer. New York: Scribner; 2010.

[23] Pray LA. Gleevec: the breakthrough in cancer treatment. Nature Education. 2008;1(1):37.

[24] Lipson EJ, Forde PM, Hammers HJ, Emens LA, Taube JM, Topalian SL. Antagonists of PD-1 and PD-L1 in cancer treatment. Semin Oncol. 2015 Aug;42(4):587-600. doi: 10.1053/j.seminoncol.2015.05.013.

[25] Australian Institute of Health and Welfare. Cancer in Australia 2019. Cancer series no.119. Cat. no. CAN 123 [Internet]. Canberra: AIHW. Available from: https://www.aihw.gov.au/getmedia/8c9fcf52-0055-41a0-96d9-f81b0feb98cf/aihw-can-123.pdf.aspx?inline=true

[26] Australian Institute of Health and Welfare. Cancer in Australia 2019. Cancer series no.119. Cat. no. CAN 123 [Internet]. Canberra: AIHW. Available from: https://www.aihw.gov.au/getmedia/8c9fcf52-0055-41a0-96d9-f81b0feb98cf/aihw-can-123.pdf.aspx?inline=true

REFERENCES

[27] Ilghami R, Barzegari A, Mashayekhi MR, Letourneur D, Crepin M, Pavon-Djavid G. The conundrum of dietary antioxidants in cancer chemotherapy. Nutr Rev. 2020 Jan 1;78(1):65-76. doi: 10.1093/nutrit/nuz027.

[28] Ilghami R, Barzegari A, Mashayekhi MR, Letourneur D, Crepin M, Pavon-Djavid G. The conundrum of dietary antioxidants in cancer chemotherapy. Nutr Rev. 2020 Jan 1;78(1):65-76. doi: 10.1093/nutrit/nuz027.

[29] Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity. 2019 Jul 16;51(1):27-41. doi: 10.1016/j.immuni.2019.06.025.

[30] Panigrahy D, Gartung A, Yang J, Yang H, Gilligan MM, Sulciner ML, et al. Preoperative stimulation of resolution and inflammation blockade eradicates micrometastases. J Clin Invest. 2019 Jun 17;129(7):2964-2979. doi: 10.1172/JCI127282.

[31] Abrams DI, Weil AT. Integrative oncology. 2nd ed. New York: Oxford University Press; 2014. p.169-175.

[32] Parida DK, Wakame K, Nomura T. Integrating complementary and alternative medicine in form of active hexose co-related compound (AHCC) in the management of head and neck cancer patients. Int J Clin Med. 2011 Nov;2(588-592):20. doi:10.4236/ijcm.2011.25097.

[33] Hirose A, Sato E, Fujii H, Sun B, Nishioka H, Aruoma OI. The influence of active hexose correlated compound (AHCC) on cisplatin-evoked chemotherapeutic and side effects in tumour-bearing mice. Toxicol Appl Pharmacol. 2007 Jul;222(2):152-8. PMID: 17555784.

[34] Ito T, Urushima H, Sakaue M, Yukawa S, Honda H, Hirai K, et al. Reduction of adverse effects by a mushroom product, active hexose correlated compound (AHCC) in patients with advanced cancer during chemotherapy--the significance of the levels of HHV-6 DNA in saliva as a surrogate biomarker during chemotherapy. Nutr Cancer. 2014;66(3):377-82. doi:10.1080/01635581.2014.884232.

[35] Parida DK, Wakame K, Nomura T. Integrating complementary and alternative medicine in form of active hexose co-related compound (AHCC) in the management of head and neck cancer patients. Int J Clin Med. 2011 Nov;2(588-592):20. doi:10.4236/ijcm.2011.25097.

[36] Cowawintaweewat S, Manoromana S, Sriplung H, Khuhaprema T, Tongtawe P, Tapchaisri P, et al. Prognostic improvement of patients with advanced liver cancer after active hexose correlated compound (AHCC) treatment. Asian Pac J Allergy Immunol. 2006 Mar;24(1):33-45. PMID: 16913187.

[37] Parida DK, Wakame K, Nomura T. Integrating complementary and alternative medicine in form of active hexose co-related compound (AHCC) in the management of head and neck cancer patients. Int J Clin Med. 2011 Nov;2(588-592):20. doi:10.4236/ijcm.2011.25097.

[38] Ito T, Urushima H, Sakaue M, Yukawa S, Honda H, Hirai K, et al. Reduction of adverse effects by a mushroom product, active hexose correlated compound (AHCC) in patients with advanced cancer during chemotherapy--the significance of the levels of HHV-6 DNA in saliva as a surrogate biomarker during chemotherapy. Nutr Cancer. 2014;66(3):377-82. doi:10.1080/01635581.2014.884232.

[39] Hangai S, Iwase S, Kawaguchi T, Kogure Y, Miyaji T, Matsunaga T, et al. Effect of active hexose-correlated compound in women receiving adjuvant chemotherapy for breast cancer: a retrospective study. J Altern Complement Med. 2013 Nov;19(11):905-10. doi: 10.1089/acm.2012.0914.

[40] Ito T, Urushima H, Sakaue M, Yukawa S, Honda H, Hirai K, et al. Reduction of adverse effects by a mushroom product, active hexose correlated compound (AHCC) in patients with advanced cancer during chemotherapy--the significance of the levels of HHV-6 DNA in saliva as a surrogate biomarker during chemotherapy. Nutr Cancer. 2014;66(3):377-82. doi:10.1080/01635581.2014.884232.

[41] Ryan JL, Heckler CE, Roscoe JA, Dakhil SR, Kirshner J, Flynn PJ, et al. Ginger (*Zingiber officinale*) reduces acute chemotherapy-induced nausea: a URCC CCOP study of 576 patients. Support Care Cancer. 2012 Jul;20(7):1479-89. doi: 10.1007/s00520-011-1236-3.

[42] Marx W, McCarthy AL, Ried K, McKavanagh D, Vitetta L, Sali A, et al. The effect of a standardized ginger extract on chemotherapy-induced nausea-related quality of life in patients undergoing moderately or highly emetogenic chemotherapy: a double blind, randomized, placebo controlled trial. Nutrients. 2017 Aug;9(8). pii: E867. doi: 10.3390/nu9080867.

[43] Yekta ZP, Ebrahimi SM, Hosseini M, Nasrabadi AN, Sedighi S, Surmaghi MH, et al. Ginger as a miracle against chemotherapy-induced vomiting. Iran J Nurs Midwifery Res. 2012 Jul;17(5):325-9. PMID: 23853643.

[44] Marx W, McCarthy AL, Ried K, McKavanagh D, Vitetta L, Sali A, et al. The effect of a standardized ginger extract on chemotherapy-induced nausea-related quality of life in patients undergoing moderately or highly emetogenic chemotherapy: a double blind, randomized, placebo controlled trial. Nutrients. 2017 Aug;9(8). pii: E867. doi: 10.3390/nu9080867.

[45] Hangai S, Iwase S, Kawaguchi T, Kogure Y, Miyaji T, Matsunaga T, et al. Effect of active hexose-correlated compound in women receiving adjuvant chemotherapy for breast cancer: a retrospective study. J Altern Complement Med. 2013 Nov;19(11):905-10. doi: 10.1089/acm.2012.0914.

REFERENCES

[46] Lussier DM, Schreiber RD. Cancer immunosurveillance: immunoediting. Encyclopedia of Immunobiology. 2016 4:396–405. doi: 10.1016/b978-0-12-374279-7.17001-8.

[47] Kucerova P, Vlasakova J, Cervinkova M. Coley's toxin and BCG vaccine in prevention and treatment of malignant melanoma in humans. Rev Med Microbiol. 2017 Jul 1;28(3):124-8. doi:10.1097/MRM.0000000000000108.

[48] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.

[49] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.

[50] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.

[51] Lussier DM, Schreiber RD. Cancer immunosurveillance: immunoediting. Encyclopedia of Immunobiology. 2016 4:396–405. doi: 10.1016/b978-0-12-374279-7.17001-8.

[52] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.

[53] Muenst S, Läubli H, Soysal SD, Zippelius A, Tzankov A, Hoeller S. The immune system and cancer evasion strategies: therapeutic concepts. J Intern Med. 2016 Jun;279(6):541-62. doi: 10.1111/joim.12470.

[54] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.

[55] Sharma P, Kumar P, Sharma R. Natural killer cells - their role in tumour immunosurveillance. J Clin Diagn Res. 2017 Aug;11(8):BE01-BE05. doi: 10.7860/JCDR/2017/26748.10469.

[56] Böttcher JP, Bonavita E, Chakravarty P, Blees H, Cabeza-Cabrerizo M, Sammicheli S, et al. NK cells stimulate recruitment of cDC1 into the tumor microenvironment promoting cancer immune control. Cell. 2018 Feb 22;172(5):1022-1037.e14. doi: 10.1016/j.cell.2018.01.004.

[57] Böttcher JP, Reis E, Sousa C. The role of type 1 conventional dendritic cells in cancer immunity. Trends Cancer. 2018 Nov;4(11):784-792. doi: 10.1016/j.trecan.2018.09.001.

[58] Böttcher JP, Bonavita E, Chakravarty P, Blees H, Cabeza-Cabrerizo M, Sammicheli S, et al. NK cells stimulate recruitment of cDC1 into the tumor microenvironment promoting cancer immune control. Cell. 2018 Feb 22;172(5):1022-1037.e14. doi: 10.1016/j.cell.2018.01.004.

[59] Sharma P, Kumar P, Sharma R. Natural killer cells - their role in tumour immunosurveillance. J Clin Diagn Res. 2017 Aug;11(8):BE01-BE05. doi: 10.7860/JCDR/2017/26748.10469.

[60] Morvan MG, Lanier LL. NK cells and cancer: you can teach innate cells new tricks. Nat Rev Cancer. 2016 Jan;16(1):7-19. doi: 10.1038/nrc.2015.5.

[61] Sharma P, Kumar P, Sharma R. Natural killer cells - their role in tumour immunosurveillance. J Clin Diagn Res. 2017 Aug;11(8):BE01-BE05. doi: 10.7860/JCDR/2017/26748.10469.

[62] Sharma P, Kumar P, Sharma R. Natural killer cells - their role in tumour immunosurveillance. J Clin Diagn Res. 2017 Aug;11(8):BE01-BE05. doi: 10.7860/JCDR/2017/26748.10469.

[63] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.

[64] Sharma P, Kumar P, Sharma R. Natural killer cells - their role in tumour immunosurveillance. J Clin Diagn Res. 2017 Aug;11(8):BE01-BE05. doi: 10.7860/JCDR/2017/26748.10469.

[65] Morvan MG, Lanier LL. NK cells and cancer: you can teach innate cells new tricks. Nat Rev Cancer. 2016 Jan;16(1):7-19. doi: 10.1038/nrc.2015.5.

[66] Morvan MG, Lanier LL. NK cells and cancer: you can teach innate cells new tricks. Nat Rev Cancer. 2016 Jan;16(1):7-19. doi: 10.1038/nrc.2015.5.

[67] Morvan MG, Lanier LL. NK cells and cancer: you can teach innate cells new tricks. Nat Rev Cancer. 2016 Jan;16(1):7-19. doi: 10.1038/nrc.2015.5.

[68] Böttcher JP, Bonavita E, Chakravarty P, Blees H, Cabeza-Cabrerizo M, Sammicheli S, et al. NK cells stimulate recruitment of cDC1 into the tumor microenvironment promoting cancer immune control. Cell. 2018 Feb 22;172(5):1022-1037.e14. doi: 10.1016/j.cell.2018.01.004.

[69] Böttcher JP, Reis E Sousa C. The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. Trends Cancer. 2018 Nov;4(11):784-792. doi: 10.1016/j.trecan.2018.09.001.

REFERENCES

[70] Böttcher JP, Reis E Sousa C. The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. Trends Cancer. 2018 Nov;4(11):784-792. doi: 10.1016/j.trecan.2018.09.001.
[71] Sharma P, Kumar P, Sharma R. Natural killer cells - their role in tumour immunosurveillance. J Clin Diagn Res. 2017 Aug;11(8):BE01-BE05. doi: 10.7860/JCDR/2017/26748.10469.
[72] Böttcher JP, Reis E Sousa C. The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. Trends Cancer. 2018 Nov;4(11):784-792. doi: 10.1016/j.trecan.2018.09.001.
[73] Lussier DM, Schreiber RD. Cancer immunosurveillance: immunoediting. Encyclopedia of Immunobiology. 2016 4:396–405. doi: 10.1016/b978-0-12-374279-7.17001-8.
[74] Böttcher JP, Reis E Sousa C. The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. Trends Cancer. 2018 Nov;4(11):784-792. doi: 10.1016/j.trecan.2018.09.001.
[75] Böttcher JP, Reis E Sousa C. The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. Trends Cancer. 2018 Nov;4(11):784-792. doi: 10.1016/j.trecan.2018.09.001.
[76] Haabeth OA, Tveita AA, Fauskanger M, Schjesvold F, Lorvik KB, Hofgaard PO,
et al. How do CD4(+) T cells detect and eliminate tumor cells that either lack or express MHC class II molecules? Front Immunol. 2014 Apr 15;5:174. doi: 10.3389/fimmu.2014.00174.
[77] Haabeth OA, Tveita AA, Fauskanger M, Schjesvold F, Lorvik KB, Hofgaard PO,
et al. How do CD4(+) T cells detect and eliminate tumor cells that either lack or express MHC class II molecules? Front Immunol. 2014 Apr 15;5:174. doi: 10.3389/fimmu.2014.00174.
[78] Lussier DM, Schreiber RD. Cancer immunosurveillance: immunoediting. Encyclopedia of Immunobiology. 2016 4:396–405. doi: 10.1016/b978-0-12-374279-7.17001-8.
[79] Muenst S, Läubli H, Soysal SD, Zippelius A, Tzankov A, Hoeller S. The immune system and cancer evasion strategies: therapeutic concepts. J Intern Med. 2016 Jun;279(6):541-62. doi: 10.1111/joim.12470.
[80] Lussier DM, Schreiber RD. Cancer immunosurveillance: immunoediting. Encyclopedia of Immunobiology. 2016 4:396–405. doi: 10.1016/b978-0-12-374279-7.17001-8.
[81] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.
[82] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.
[83] Lussier DM, Schreiber RD. Cancer immunosurveillance: immunoediting. Encyclopedia of Immunobiology. 2016 4:396–405. doi: 10.1016/b978-0-12-374279-7.17001-8.
[84] Lussier DM, Schreiber RD. Cancer immunosurveillance: immunoediting. Encyclopedia of Immunobiology. 2016 4:396–405. doi: 10.1016/b978-0-12-374279-7.17001-8.
[85] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.
[86] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.
[87] Lussier DM, Schreiber RD. Cancer immunosurveillance: immunoediting. Encyclopedia of Immunobiology. 2016 4:396–405. doi: 10.1016/b978-0-12-374279-7.17001-8.
[88] Muenst S, Läubli H, Soysal SD, Zippelius A, Tzankov A, Hoeller S. The immune system and cancer evasion strategies: therapeutic concepts. J Intern Med. 2016 Jun;279(6):541-62. doi: 10.1111/joim.12470.
[89] Narita Y, Kitamura H, Wakita D, Sumida K, Masuko K, Terada S, et al. The key role of IL-6-arginase cascade for inducing dendritic cell-dependent CD4(+) T cell dysfunction in tumor-bearing mice. J Immunol. 2013 Jan 15;190(2):812-20. doi: 10.4049/jimmunol.1103797.
[90] Narita Y, Kitamura H, Wakita D, Sumida K, Masuko K, Terada S, et al. The key role of IL-6-arginase cascade for inducing dendritic cell-dependent CD4(+) T cell dysfunction in tumor-bearing mice. J Immunol. 2013 Jan 15;190(2):812-20. doi: 10.4049/jimmunol.1103797.
[91] Narita Y, Kitamura H, Wakita D, Sumida K, Masuko K, Terada S, et al. The key role of IL-6-arginase cascade for inducing dendritic cell-dependent CD4(+) T cell dysfunction in tumor-bearing mice. J Immunol. 2013 Jan 15;190(2):812-20. doi: 10.4049/jimmunol.1103797.
[92] Lussier DM, Schreiber RD. Cancer immunosurveillance: immunoediting. Encyclopedia of Immunobiology. 2016 4:396–405. doi: 10.1016/b978-0-12-374279-7.17001-8.
[93] Narita Y, Kitamura H, Wakita D, Sumida K, Masuko K, Terada S, et al. The key role of IL-6-arginase cascade for inducing dendritic cell-dependent CD4(+) T cell dysfunction in tumor-bearing mice. J Immunol. 2013 Jan 15;190(2):812-20. doi: 10.4049/jimmunol.1103797.

REFERENCES

[94] Böttcher JP, Bonavita E, Chakravarty P, Blees H, Cabeza-Cabrerizo M, Sammicheli S, et al. NK cells stimulate recruitment of cDC1 into the tumor microenvironment promoting cancer immune control. Cell. 2018 Feb 22;172(5):1022-1037.e14. doi: 10.1016/j.cell.2018.01.004.

[95] Böttcher JP, Reis E Sousa C. The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. Trends Cancer. 2018 Nov;4(11):784-792. doi: 10.1016/j.trecan.2018.09.001.

[96] Vitale M, Cantoni C, Pietra G, Mingari MC, Moretta L. Effect of tumor cells and tumor microenvironment on NK-cell function. Eur J Immunol. 2014 Jun;44(6):1582-92. doi: 10.1002/eji.201344272.

[97] Böttcher JP, Reis E Sousa C. The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. Trends Cancer. 2018 Nov;4(11):784-792. doi: 10.1016/j.trecan.2018.09.001.

[98] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.

[99] Vitale M, Cantoni C, Pietra G, Mingari MC, Moretta L. Effect of tumor cells and tumor microenvironment on NK-cell function. Eur J Immunol. 2014 Jun;44(6):1582-92. doi: 10.1002/eji.201344272.

[100] Zhang Q, Zhu B, Li Y. Resolution of cancer-promoting inflammation: a new approach for anticancer therapy. Front Immunol. 2017 Feb 2;8:71. doi: 10.3389/fimmu.2017.00071.

[101] Muenst S, Läubli H, Soysal SD, Zippelius A, Tzankov A, Hoeller S. The immune system and cancer evasion strategies: therapeutic concepts. J Intern Med. 2016 Jun;279(6):541-62. doi: 10.1111/joim.12470.

[102] Ando M, Ito M, Srirat T, Kondo T, Yoshimura A. Memory T cell, exhaustion, and tumor immunity. Immunol Med. 2019 Dec 10:1-9. doi: 10.1080/25785826.201 9.1698261.

[103] Noguchi T, Ward JP, Gubin MM, Arthur CD, Lee SH, Hundal J, et al. Temporally distinct PD-L1 expression by tumor and host cells contributes to immune escape. Cancer Immunol Res. 2017 Feb;5(2):106-117. doi: 10.1158/2326-6066.CIR-16-0391.

[104] Lussier DM, Schreiber RD. Cancer immunosurveillance: immunoediting. Encyclopedia of Immunobiology. 2016 4:396–405. doi:10.1016/b978-0-12-374279-7.17001-8.

[105] Ando M, Ito M, Srirat T, Kondo T, Yoshimura A. Memory T cell, exhaustion, and tumor immunity. Immunol Med. 2019 Dec 10:1-9. doi: 10.1080/25785826.201 9.1698261.

[106] Lussier DM, Schreiber RD. Cancer immunosurveillance: immunoediting. Encyclopedia of Immunobiology. 2016 4:396–405. doi:10.1016/b978-0-12-374279-7.17001-8.

[107] Ando M, Ito M, Srirat T, Kondo T, Yoshimura A. Memory T cell, exhaustion, and tumor immunity. Immunol Med. 2019 Dec 10:1-9. doi: 10.1080/25785826.201 9.1698261.

[108] Vitale M, Cantoni C, Pietra G, Mingari MC, Moretta L. Effect of tumor cells and tumor microenvironment on NK-cell function. Eur J Immunol. 2014 Jun;44(6):1582-92. doi: 10.1002/eji.201344272.

[109] Vitale M, Cantoni C, Pietra G, Mingari MC, Moretta L. Effect of tumor cells and tumor microenvironment on NK-cell function. Eur J Immunol. 2014 Jun;44(6):1582-92. doi: 10.1002/eji.201344272.

[110] Vitale M, Cantoni C, Pietra G, Mingari MC, Moretta L. Effect of tumor cells and tumor microenvironment on NK-cell function. Eur J Immunol. 2014 Jun;44(6):1582-92. doi: 10.1002/eji.201344272.

[111] Zhang Q, Zhu B, Li Y. Resolution of cancer-promoting inflammation: a new approach for anticancer therapy. Front Immunol. 2017 Feb 2;8:71. doi: 10.3389/fimmu.2017.00071.

[112] Lussier DM, Schreiber RD. Cancer immunosurveillance: immunoediting. Encyclopedia of Immunobiology. 2016 4:396–405. doi:10.1016/b978-0-12-374279-7.17001-8.

[113] Vitale M, Cantoni C, Pietra G, Mingari MC, Moretta L. Effect of tumor cells and tumor microenvironment on NK-cell function. Eur J Immunol. 2014 Jun;44(6):1582-92. doi: 10.1002/eji.201344272.

[114] Bos PD. T(reg) cells in cancer: beyond classical immunological control. Immunol Invest. 2016 Nov;45(8):721-728. doi: 10.1080/08820139.2016.1222206.

[115] Vitale M, Cantoni C, Pietra G, Mingari MC, Moretta L. Effect of tumor cells and tumor microenvironment on NK-cell function. Eur J Immunol. 2014 Jun;44(6):1582-92. doi: 10.1002/eji.201344272.

[116] Bos PD. T(reg) cells in cancer: beyond classical immunological control. Immunol Invest. 2016 Nov;45(8):721-728. doi: 10.1080/08820139.2016.1222206.

[117] Vitale M, Cantoni C, Pietra G, Mingari MC, Moretta L. Effect of tumor cells and tumor microenvironment on NK-cell function. Eur J Immunol. 2014 Jun;44(6):1582-92. doi: 10.1002/eji.201344272.

[118] Bos PD. T(Reg) cells in cancer: beyond classical immunological control. Immunol Invest. 2016 Nov;45(8):721-728. doi: 10.1080/08820139.2016.1222206.

[119] Bos PD. T(Reg) cells in cancer: beyond classical immunological control. Immunol Invest. 2016 Nov;45(8):721-728. doi: 10.1080/08820139.2016.1222206.

[120] Hanahan D, Weinberg RA. Biological hallmarks of cancer. In: Khuri FR. Holland-Frei Cancer Medicine Cloth. 9th ed [Internet]. New Jersey: John Wiley & Sons; 2017 [cited 2020 Jan 8]. p. 255-264. Available from:

REFERENCES

https://www.epfl.ch/labs/hanahan-lab/wp-content/uploads/2019/02/HanahanWeinberg-HoC_Holland-Frei-Ch-2-2017.pdf
[121] Ishii G, Ochiai A, Neri S. Phenotypic and functional heterogeneity of cancer-associated fibroblast within the tumor microenvironment. Adv Drug Deliv Rev. 2016;99(Pt B):186–196. doi:10.1016/j.addr.2015.07.007.
[122] Hanahan D, Weinberg RA. Biological hallmarks of cancer. In: Khuri FR. Holland-Frei Cancer Medicine Cloth. 9th ed [Internet]. New Jersey: John Wiley & Sons; 2017 [cited 2020 Jan 8]. p. 255-264. Available from: https://www.epfl.ch/labs/hanahan-lab/wp-content/uploads/2019/02/HanahanWeinberg-HoC_Holland-Frei-Ch-2-2017.pdf
[123] Ishii G, Ochiai A, Neri S. Phenotypic and functional heterogeneity of cancer-associated fibroblast within the tumor microenvironment. Adv Drug Deliv Rev. 2016;99(Pt B):186–196. doi:10.1016/j.addr.2015.07.007.
[124] Hanahan D, Weinberg RA. Biological hallmarks of cancer. In: Khuri FR. Holland-Frei Cancer Medicine Cloth. 9th ed [Internet]. New Jersey: John Wiley & Sons; 2017 [cited 2020 Jan 8]. p. 255-264. Available from: https://www.epfl.ch/labs/hanahan-lab/wp-content/uploads/2019/02/HanahanWeinberg-HoC_Holland-Frei-Ch-2-2017.pdf
[125] Fujita M, Matsumoto T, Hirano R, Ishii K, Hiromatsu K, Uchino J, et al. Attenuation of pulmonary *Mycobacterium avium* disease by active hexose correlated compound (AHCC) in mice. J Nutr Disorders Ther. 2015;5(174):2161-0509. doi: 10.4172/2161-0509.1000174.
[126] Belay T, Fu CL, Woart A. Active hexose correlated compound activates immune function to decrease *Chlamydia trachomatis* shedding in a murine stress model. J Nutr Med Diet Care. 2015;1(1). pii: JNMDC-1-006. PMID:27790645.
[127] Yin Z, Fujii H, Walshe T. Effects of active hexose correlated compound on frequency of CD4+ and CD8+ T cells producing interferon-γ and/or tumour necrosis factor-α in healthy adults. Hum Immunol. 2010 Dec;71(12):1187-90. doi: 10.1016/j.humimm.2010.08.006.
[128] Mallet JF, Graham É, Ritz BW, Homma K, Matar C. Active hexose correlated compound (AHCC) promotes an intestinal immune response in BALB/c mice and in primary intestinal epithelial cell culture involving toll-like receptors TLR-2 and TLR-4. Eur J Nutr. 2016 Feb;55(1):139-46. doi: 10.1007/s00394-015-0832-2.
[129] Ritz BW, Nogusa S, Ackerman EA, Gardner EM. Supplementation with active hexose correlated compound increases the innate immune response of young mice to primary influenza infection. J Nutr. 2006 Nov;136(11):2868-73. PMID: 17056815.
[130] Roman BE, Beli E, Duriancik DM, Gardner EM. Short-term supplementation with active hexose correlated compound improves the antibody response to influenza B vaccine. Nutr Res. 2013 Jan;33(1):12-7. doi: 10.1016/j.nutres.2012.11.001.
[131] Nogusa S, Gerbino J, Ritz BW. Low-dose supplementation with active hexose correlated compound improves the immune response to acute influenza infection in C57BL/6 mice. Nutr Res. 2009 Feb;29(2):139-43. doi: 10.1016/j.nutres.2009.01.005.
[132] Wang S, Welte T, Fang H, Chang GJ, Born WK, O'Brien RL, et al. Oral administration of active hexose correlated compound enhances host resistance to West Nile encephalitis in mice. J Nutr. 2009 Mar;139(3):598-602. doi: 10.3945/jn.108.100297.
[133] Cowawintaweewat S, Manoromana S, Sriplung H, Khuhaprema T, Tongtawe P, Tapchaisri P, et al. Prognostic improvement of patients with advanced liver cancer after active hexose correlated compound (AHCC) treatment. Asian Pac J Allergy Immunol. 2006 Mar;24(1):33-45. PMID: 16913187.
[134] Smith JA, Mathew L, Gaikwad A, Rech B, Burney MN, Faro JP, et al. From bench to bedside: Evaluation of AHCC supplementation to modulate the host immunity to clear high-risk human papillomavirus infections. Front Oncol. 2019 Mar 20;9:173. doi: 10.3389/fonc.2019.00173.
[135] Aviles H, Belay T, Fountain K, Vance M, Sun B, Sonnenfeld G. Active hexose correlated compound enhances resistance to *Klebsiella pneumoniae* infection in mice in the hindlimb-unloading model of spaceflight conditions. J Appl Physiol (1985). 2003 Aug;95(2):491-6. PMID: 12692142.
[136] Terakawa N, Matsui Y, Satoi S, Yanagimoto H, Takahashi K, Yamamoto T, et al. Immunological effect of active hexose correlated compound (AHCC) in healthy volunteers: a double-blind, placebo-controlled trial. Nutr Cancer. 2008;60(5):643-51. doi: 10.1080/01635580801993280.
[137] Ritz BW, Nogusa S, Ackerman EA, Gardner EM. Supplementation with active hexose correlated compound increases the innate immune response of young mice to primary influenza infection. J Nutr. 2006 Nov;136(11):2868-73. PMID: 17056815.
[138] Terakawa N, Matsui Y, Satoi S, Yanagimoto H, Takahashi K, Yamamoto T, et al. Immunological effect of active hexose correlated compound (AHCC) in healthy volunteers: a double-blind, placebo-controlled trial. Nutr Cancer. 2008;60(5):643-51. doi: 10.1080/01635580801993280.

REFERENCES

[139] Cao Z, Chen X, Lan L, Zhang Z, Du J, Liao L. Active hexose correlated compound potentiates the antitumour effects of low-dose 5-fluorouracil through modulation of immune function in hepatoma 22 tumour-bearing mice. Nutr Res Pract. 2015 Apr;9(2):129-36. doi: 10.4162/nrp.2015.9.2.129.

[140] Cao Z, Chen X, Lan L, Zhang Z, Du J, Liao L. Active hexose correlated compound potentiates the antitumour effects of low-dose 5-fluorouracil through modulation of immune function in hepatoma 22 tumour-bearing mice. Nutr Res Pract. 2015 Apr;9(2):129-36. doi: 10.4162/nrp.2015.9.2.129.

[141] Roman BE, Beli E, Duriancik DM, Gardner EM. Short-term supplementation with active hexose correlated compound improves the antibody response to influenza B vaccine. Nutr Res. 2013 Jan;33(1):12-7. doi: 10.1016/j.nutres.2012.11.001.

[142] Yin Z, Fujii H, Walshe T. Effects of active hexose correlated compound on frequency of CD4+ and CD8+ T cells producing interferon-γ and/or tumour necrosis factor-α in healthy adults. Hum Immunol. 2010 Dec;71(12):1187-90. doi: 10.1016/j.humimm.2010.08.006.

[143] Cowawintaweewat S, Manoromana S, Sriplung H, Khuhaprema T, Tongtawe P, Tapchaisri P, et al. Prognostic improvement of patients with advanced liver cancer after active hexose correlated compound (AHCC) treatment. Asian Pac J Allergy Immunol. 2006 Mar;24(1):33-45. PMID: 16913187.

[144] Cowawintaweewat S, Manoromana S, Sriplung H, Khuhaprema T, Tongtawe P, Tapchaisri P, et al. Prognostic improvement of patients with advanced liver cancer after active hexose correlated compound (AHCC) treatment. Asian Pac J Allergy Immunol. 2006 Mar;24(1):33-45. PMID: 16913187.

[145] Matsui Y, Uhara J, Satoi S, Kaibori M, Yamada H, Kitade H, et al. Improved prognosis of postoperative hepatocellular carcinoma patients when treated with functional foods: a prospective cohort study. J Hepatol. 2002 Jul;37(1):78-86. PMID: 12076865.

[146] Kawaguchi Y. Improved survival of patients with gastric cancer or colon cancer when treated with active hexose correlated compound (AHCC): effect of AHCC on digestive system cancer. Nat Med J. 2009;1(1):1-6.

[147] Yanagimoto H, Satoi S, Yamamoto T, Hirooka S, Yamaki S, Kotsuka M, et al. Alleviating effect of active hexose correlated compound (AHCC) on chemotherapy-related adverse events in patients with unresectable pancreatic ductal adenocarcinoma. Nutr Cancer. 2016;68(2):234-40. doi: 10.1080/01635581.2016.1134597.

[148] Parida DK, Wakame K, Nomura T. Integrating complementary and alternative medicine in form of active hexose co-related compound (AHCC) in the management of head and neck cancer patients. Int J Clin Med. 2011 Nov;2(588-592):20. doi:10.4236/ijcm.2011.25097.

[149] Hirose A, Sato E, Fujii H, Sun B, Nishioka H, Aruoma OI. The influence of active hexose correlated compound (AHCC) on cisplatin-evoked chemotherapeutic and side effects in tumour-bearing mice. Toxicol Appl Pharmacol. 2007 Jul;222(2):152-8. PMID: 17555784.

[150] Shigama K, Nakaya A, Wakame K, Nishioka H, Fujii H. Alleviating effect of active hexose correlated compound (AHCC) for anticancer drug-induced side effects in non-tumour-bearing mice. J Exp Ther Oncol. 2009;8(1):43-51. PMID: 19827270.

[151] Cowawintaweewat S, Manoromana S, Sriplung H, Khuhaprema T, Tongtawe P, Tapchaisri P, et al. Prognostic improvement of patients with advanced liver cancer after active hexose correlated compound (AHCC) treatment. Asian Pac J Allergy Immunol. 2006 Mar;24(1):33-45. PMID: 16913187.

[152] Matsui Y, Uhara J, Satoi S, Kaibori M, Yamada H, Kitade H, et al. Improved prognosis of postoperative hepatocellular carcinoma patients when treated with functional foods: a prospective cohort study. J Hepatol. 2002 Jul;37(1):78-86. PMID: 12076865.

[153] Matsui Y, Uhara J, Satoi S, Kaibori M, Yamada H, Kitade H, et al. Improved prognosis of postoperative hepatocellular carcinoma patients when treated with functional foods: a prospective cohort study. J Hepatol. 2002 Jul;37(1):78-86. PMID: 12076865.

[154] Kawaguchi Y. Improved survival of patients with gastric cancer or colon cancer when treated with active hexose correlated compound (AHCC): effect of AHCC on digestive system cancer. Nat Med J. 2009;1(1):1-6.

[155] Matsui Y, Uhara J, Satoi S, Kaibori M, Yamada H, Kitade H, et al. Improved prognosis of postoperative hepatocellular carcinoma patients when treated with functional foods: a prospective cohort study. J Hepatol. 2002 Jul;37(1):78-86. PMID: 12076865.

[156] Zhang Q, Zhu B, Li Y. Resolution of cancer-promoting inflammation: A new approach for anticancer therapy. Front Immunol. 2017 Feb 2;8:71. doi: 10.3389/fimmu.2017.00071.

[157] Yang L, Lin PC. Mechanisms that drive inflammatory tumor microenvironment, tumor heterogeneity, and metastatic progression. Semin Cancer Biol. 2017 Dec;47:185-195. doi: 10.1016/j.semcancer.2017.08.001.

REFERENCES

[158] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010 Mar 19;140(6):883-99. doi: 10.1016/j.cell.2010.01.025.

[159] Aggarwal BB, Vijayalekshmi RV, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. Clin Cancer Res. 2009 Jan 15;15(2):425-30. doi: 10.1158/1078-0432.CCR-08-0149.

[160] Wroblewski LE, Peek RM Jr. Helicobacter pylori, cancer, and the gastric microbiota. Adv Exp Med Biol. 2016;908:393-408. doi: 10.1007/978-3-319-41388-4_19.

[161] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010 Mar 19;140(6):883-99. doi: 10.1016/j.cell.2010.01.025.

[162] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010 Mar 19;140(6):883-99. doi: 10.1016/j.cell.2010.01.025.

[163] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010 Mar 19;140(6):883-99. doi: 10.1016/j.cell.2010.01.025.

[164] Wilson LF, Baade PD, Green AC, Jordan SJ, Kendall BJ, Neale RE, et al. The impact of changing the prevalence of overweight/obesity and physical inactivity in Australia: An estimate of the proportion of potentially avoidable cancers 2013-2037. Int J Cancer. 2019 May 1;144(9):2088-2098. doi: 10.1002/ijc.31943.

[165] Deng T, Lyon CJ, Bergin S, Caligiuri MA, Hsueh WA. Obesity, Inflammation, and Cancer. Annu Rev Pathol. 2016 May 23;11:421-49. doi: 10.1146/annurev-pathol-012615-044359.

[166] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010 Mar 19;140(6):883-99. doi: 10.1016/j.cell.2010.01.025.

[167] Kim R, Emi M, Tanabe K. Cancer immunoediting from immune surveillance to immune escape. Immunology. 2007 May;121(1):1-14. Epub 2007 Mar 26. Review. PMID: 17386080.

[168] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.

[169] Hinshaw DC, Shevde LA. The tumor microenvironment innately modulates cancer progression. Cancer Res. 2019 Sep 15;79(18):4557-4566. doi: 10.1158/0008-5472.CAN-18-3962.

[170] Saqib U, Sarkar S, Suk K, Mohammad O, Baig MS, Savai R. Phytochemicals as modulators of M1-M2 macrophages in inflammation. Oncotarget. 2018 9(25), 17937–17950. doi:org/10.18632/oncotarget.24788.

[171] Saqib U, Sarkar S, Suk K, Mohammad O, Baig MS, Savai R. Phytochemicals as modulators of M1-M2 macrophages in inflammation. Oncotarget. 2018 9(25), 17937–17950. doi:org/10.18632/oncotarget.24788.

[172] Liguori M, Solinas G, Germano G, Mantovani A, Allavena P. Tumor-associated macrophages as incessant builders and destroyers of the cancer stroma. Cancers (Basel). 2011 Sep 28;3(4):3740-61. doi: 10.3390/cancers3043740.

[173] Xiong H, Mittman S, Rodriguez R, Moskalenko M, Pacheco-Sanchez P, Yang Y, et al. Anti-PD-L1 treatment results in functional remodeling of the macrophage compartment. Cancer Res. 2019 Apr 1;79(7):1493-1506. doi: 10.1158/0008-5472.CAN-18-3208.

[174] Xiong H, Mittman S, Rodriguez R, Moskalenko M, Pacheco-Sanchez P, Yang Y, et al. Anti-PD-L1 treatment results in functional remodeling of the macrophage compartment. Cancer Res. 2019 Apr 1;79(7):1493-1506. doi: 10.1158/0008-5472.CAN-18-3208.

[175] Sainz B Jr, Carron E, Vallespinós M, Machado HL. Cancer stem cells and macrophages: Implications in tumor biology and therapeutic strategies. Mediators Inflamm. 2016;2016:9012369. doi: 10.1155/2016/9012369.

[176] Liguori M, Solinas G, Germano G, Mantovani A, Allavena P. Tumor-associated macrophages as incessant builders and destroyers of the cancer stroma. Cancers (Basel). 2011 Sep 28;3(4):3740-61. doi: 10.3390/cancers3043740.

[177] Sainz B Jr, Carron E, Vallespinós M, Machado HL. Cancer stem cells and macrophages: Implications in tumor biology and therapeutic strategies. Mediators Inflamm. 2016;2016:9012369. doi: 10.1155/2016/9012369.

[178] Liguori M, Solinas G, Germano G, Mantovani A, Allavena P. Tumor-associated macrophages as incessant builders and destroyers of the cancer stroma. Cancers (Basel). 2011 Sep 28;3(4):3740-61. doi: 10.3390/cancers3043740.

[179] Wanderley CW, Colón DF, Luiz JPM, Oliveira FF, Viacava PR, Leite CA, et al. Paclitaxel reduces tumor growth by reprogramming tumor-associated macrophages to an M1 profile in a TLR4-dependent manner. Cancer Res. 2018 Oct 15;78(20):5891-5900. doi: 10.1158/0008-5472.CAN-17-3480.

REFERENCES

[180] Zhang Q, Zhu B, Li Y. Resolution of cancer-promoting inflammation: a new approach for anticancer therapy. Front Immunol. 2017 Feb 2;8:71. doi: 10.3389/fimmu.2017.00071.

[181] Panigrahy D, Gartung A, Yang J, Yang H, Gilligan MM, Sulciner ML, et al. Preoperative stimulation of resolution and inflammation blockade eradicates micrometastases. J Clin Invest. 2019 Jun 17;129(7):2964-2979. doi: 10.1172/JCI127282.

[182] Chiang N, Schwab JM, Fredman G, Kasuga K, Gelman S, Serhan CN. Anesthetics impact the resolution of inflammation. PLoS One. 2008 Apr 2;3(4):e1879. doi: 10.1371/journal.pone.0001879.

[183] Chang J, Bhasin SS, Bielenberg DR, Sukhatme VP, Bhasin M, Huang S, et al. Chemotherapy-generated cell debris stimulates colon carcinoma tumor growth via osteopontin. FASEB J. 2019 Jan;33(1):114-125. doi: 10.1096/fj.201800019RR.

[184] Lee Y, Kollara A, May T, Brown TJ. Wounding promotes ovarian cancer progression and decreases efficacy of cisplatin in a syngeneic mouse model. J Ovarian Res. 2018 Jul 4;11(1):56. doi: 10.1186/s13048-018-0428-6.

[185] Panigrahy D, Gartung A, Yang J, Yang H, Gilligan MM, Sulciner ML, et al. Preoperative stimulation of resolution and inflammation blockade eradicates micrometastases. J Clin Invest. 2019 Jun 17;129(7):2964-2979. doi: 10.1172/JCI127282.

[186] Hayashi T, Fujita K, Matsushita M, Nonomura N. Main inflammatory cells and potentials of anti-inflammatory agents in prostate cancer. Cancers (Basel). 2019 Aug 12;11(8). pii: E1153. doi: 10.3390/cancers11081153.

[187] Panigrahy D, Gartung A, Yang J, Yang H, Gilligan MM, Sulciner ML, et al. Preoperative stimulation of resolution and inflammation blockade eradicates micrometastases. J Clin Invest. 2019 Jun 17;129(7):2964-2979. doi: 10.1172/JCI127282.

[188] Zhang Q, Zhu B, Li Y. Resolution of cancer-promoting inflammation: a new approach for anticancer therapy. Front Immunol. 2017 Feb 2;8:71. doi: 10.3389/fimmu.2017.00071.

[189] Barden AE, Moghaddami M, Mas E, Phillips M, Cleland LG, Mori TA. Specialised pro-resolving mediators of inflammation in inflammatory arthritis. Prostaglandins Leukot Essent Fatty Acids. 2016 Apr;107:24-9. doi: 10.1016/j.plefa.2016.03.004.

[190] Zhang Q, Zhu B, Li Y. Resolution of Cancer-Promoting Inflammation: a New Approach for Anticancer Therapy. Front Immunol. 2017 Feb 2;8:71. doi: 10.3389/fimmu.2017.00071.

[191] Zhang Q, Zhu B, Li Y. Resolution of Cancer-Promoting Inflammation: a New Approach for Anticancer Therapy. Front Immunol. 2017 Feb 2;8:71. doi: 10.3389/fimmu.2017.00071.

[192] Zhang Q, Zhu B, Li Y. Resolution of Cancer-Promoting Inflammation: a New Approach for Anticancer Therapy. Front Immunol. 2017 Feb 2;8:71. doi: 10.3389/fimmu.2017.00071.

[193] Nabavi SF, Bilotto S, Russo GL, Orhan IE, Habtemariam S, Daglia M, et al. Omega-3 polyunsaturated fatty acids and cancer: lessons learned from clinical trials. Cancer Metastasis Rev. 2015 Sep;34(3):359-80. doi: 10.1007/s10555-015-9572-2.

[194] Zhang Q, Zhu B, Li Y. Resolution of cancer-promoting inflammation: a new approach for anticancer therapy. Front Immunol. 2017 Feb 2;8:71. doi: 10.3389/fimmu.2017.00071.

[195] Panigrahy D, Gartung A, Yang J, Yang H, Gilligan MM, Sulciner ML, et al. Preoperative stimulation of resolution and inflammation blockade eradicates micrometastases. J Clin Invest. 2019 Jun 17;129(7):2964-2979. doi: 10.1172/JCI127282.

[196] Zhang Q, Zhu B, Li Y. Resolution of cancer-promoting inflammation: a new approach for anticancer therapy. Front Immunol. 2017 Feb 2;8:71. doi: 10.3389/fimmu.2017.00071.

[197] Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: a current review. Ann Neurol. 2017;81(6):772–81. doi:10.1002/ana.24951.

[198] Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res. 2015 Oct 23;8:729-34. doi: 10.2147/JPR.S93106.

[199] Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S. Palmitoylethanolamide in fibromyalgia: results from prospective and retrospective observational studies. Pain Ther. 2015 Dec;4(2):169-78. doi:10.1007/s40122-015-0038-6.

[200] Skaper SD, Facci L, Fusco M, Della Valle MF, Zusso M, Costa B, et al. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology. 2014 Apr;22(2):79-94. doi:10.1007/s10787-013-0191-7.

[201] Passavanti MB, Fiore M, Sansone P, Aurilio C, Pota V, Barbarisi M, et al. The beneficial use of ultramicronized palmitoylethanolamide as add-on therapy to tapentadol in the treatment of low back pain: a pilot study comparing prospective and retrospective observational arms. BMC Anesthesiol. 2017 Dec 19;17(1):171. doi: 10.1186/s12871-017-0461-9.

REFERENCES

[202] Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res. 2015 Oct 23;8:729-34. doi: 10.2147/JPR.S93106.

[203] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-13. doi: 10.2174/1871527316666170321124949.

[204] Marini I, Lavinia Bartolucci M, Bortolotti F, Rosaria Gatto M, Alessandri Bonetti G. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. J Orofac Pain. 2012 Apr 1;26(2):99.

[205] Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. Neurotherapeutics. 2016 Apr;13(2):428-38. doi: 10.1007/s13311-016-0420-z.

[206] Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. Br J Clin Pharmacol. 2016 Oct;82(4):932-42. doi: 10.1111/bcp.13020.

[207] Truini A, Biasiotta A, Di Stefano G, La Cesa S, Leone C, Cartoni C. Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. CNS Neurol Disord Drug Targets. 2011 Dec;10(8):916-20. PMID: 22229320.

[208] Hesselink JM, Hekker TA. Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series. J Pain Res. 2012;5:437-42. doi: 10.2147/JPR.S32143.

[209] Hesselink JM, Hekker TA. Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series. J Pain Res. 2012;5:437-42. doi: 10.2147/JPR.S32143.

[210] The ASCO Post [Internet]. Huntington, NY: HSP News Service, L.L.C.; 2020. The microbiome: the next target in cancer therapy; 2019 Apr 25 [cited 2020 Apr 24]. Available from: https://ascopost.com/issues/april-25-2019/the-microbiome-the-next-target-in-cancer-therapy/

[211] Whisner CM, Athena Aktipis C. The role of the microbiome in cancer initiation and progression: how microbes and cancer cells utilize excess energy and promote one another's growth. Curr Nutr Rep. 2019 Mar;8(1):42-51. doi:10.1007/s13668-019-0257-2.

[212] van Vliet MJ, Tissing WJ, Dun CA, Meessen NE, Kamps WA, de Bont ES, et al. Chemotherapy treatment in pediatric patients with acute myeloid leukemia receiving antimicrobial prophylaxis leads to a relative increase of colonization with potentially pathogenic bacteria in the gut. Clin Infect Dis. 2009 Jul 15;49(2):262-70. doi: 10.1086/599346.

[213] Montassier E, Gastinne T, Vangay P, Al-Ghalith GA, Bruley des Varannes S, Massart S, et al. Chemotherapy-driven dysbiosis in the intestinal microbiome. Aliment Pharmacol Ther. 2015 Sep;42(5):515-28. doi: 10.1111/apt.13302.

[214] Dubin K, Callahan MK, Ren B, Khanin R, Viale A, Ling L, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun. 2016 Feb 2;7:10391. doi: 10.1038/ncomms10391.

[215] Herremans KM, Riner AN, Cameron ME, Trevino JG. The microbiota and cancer cachexia. Int J Mol Sci. 2019 Dec 12;20(24). pii: E6267. doi: 10.3390/ijms20246267.

[216] Bajic JE, Johnston IN, Howarth GS, Hutchinson MR. From the bottom-up: chemotherapy and gut-brain axis dysregulation. Front Behav Neurosci. 2018 May 22;12:104. doi: 10.3389/fnbeh.2018.00104.

[217] Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018 Jan 5;359(6371):97-103. doi: 10.1126/science.aan4236.

[218] Lalani AA, Xie W, Braun DA, Kaymakcalan M, Bossé D, Steinharter JA, et al. Effect of antibiotic use on outcomes with systemic therapies in metastatic renal cell carcinoma. Eur Urol Oncol. 2019 Sep 24. pii: S2588-9311(19)30142-7. doi: 10.1016/j.euo.2019.09.001.

[219] Osterlund P, Ruotsalainen T, Korpela R, Saxelin M, Ollus A, Valta P, et al. Lactobacillus supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. Br J Cancer. 2007 Oct 22;97(8):1028-34. doi: 10.1038/sj.bjc.6603990.

[220] Gorshein E, Wei C, Ambrosy S, Budney S, Vivas J, Shenkerman A, et al. *Lactobacillus rhamnosus* GG probiotic enteric regimen does not appreciably alter the gut microbiome or provide protection against GVHD after allogeneic hematopoietic stem cell transplantation. Clin Transplant. 2017 May;31(5). doi: 10.1111/ctr.12947.

REFERENCES

[221] Gorshein E, Wei C, Ambrosy S, Budney S, Vivas J, Shenkerman A, et al. *Lactobacillus rhamnosus* GG probiotic enteric regimen does not appreciably alter the gut microbiome or provide protection against GVHD after allogeneic hematopoietic stem cell transplantation. Clin Transplant. 2017 May;31(5). doi: 10.1111/ctr.12947.

[222] Doron S, Snydman DR. Risk and safety of probiotics. Clin Infect Dis. 2015 May 15;60 Suppl 2:S129-34. doi: 10.1093/cid/civ085.

[223] Doron S, Snydman DR. Risk and safety of probiotics. Clin Infect Dis. 2015 May 15;60 Suppl 2:S129-34. doi: 10.1093/cid/civ085.

[224] Doron S, Snydman DR. Risk and safety of probiotics. Clin Infect Dis. 2015 May 15;60 Suppl 2:S129-34. doi: 10.1093/cid/civ085.

[225] Blumberg J. The alpha-tocopherol, beta-carotene cancer prevention study in Finland. Nutrition reviews. 1994 Jul 1;52(7):242-5. doi: 10.1111/j.1753-4887.1994.tb01430.x

[226] The ATBC cancer prevention study group. The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. Ann Epidemiol. 1994 Jan;4(1):1-10. doi: 10.1016/1047-2797(94)90036-1.

[227] Omenn GS, Goodman G, Grizzle J, Thornquist M, Rosenstock L, Barnhart S, et al. CARET, the beta-carotene and retinol efficacy trial to prevent lung cancer in asbestos-exposed workers and in smokers. Anticancer Drugs. 1991 Feb;2(1):79-86. PMID: 1958856.

[228] Omenn GS, Goodman G, Thornquist M, Grizzle J, Rosenstock L, Barnhart S, et al. The beta-carotene and retinol efficacy trial (CARET) for chemoprevention of lung cancer in high risk populations: smokers and asbestos-exposed workers. Cancer Res. 1994 Apr 1;54(7 Suppl):2038s-2043s. PMID: 8137335.

[229] Goralczyk R. Beta-carotene and lung cancer in smokers: review of hypotheses and status of research. Nutr Cancer. 2009;61(6):767-74. doi: 10.1080/01635580903285155.

[230] Goralczyk R. Beta-carotene and lung cancer in smokers: review of hypotheses and status of research. Nutr Cancer. 2009;61(6):767-74. doi: 10.1080/01635580903285155.

[231] Ozben T. Antioxidant supplementation on cancer risk and during cancer therapy: an update. Curr Top Med Chem. 2015;15(2):170-8. Review. PMID: 25496272.

[232] Stone WL, Krishnan K, Campbell SE, Palau VE. The role of antioxidants and pro-oxidants in colon cancer. World J Gastrointest Oncol. 2014 Mar 15;6(3):55-66. doi: 10.4251/wjgo.v6.i3.55. Review. PMID: 24653795.

[233] Yokoyama C, Sueyoshi Y, Ema M, Mori Y, Takaishi K, Hisatomi H. Induction of oxidative stress by anticancer drugs in the presence and absence of cells. Oncol Lett. 2017 Nov;14(5):6066-6070. doi: 10.3892/ol.2017.6931.

[234] Mut-Salud N, Álvarez PJ, Garrido JM, Carrasco E, Aránega A, Rodríguez-Serrano F. Antioxidant intake and antitumor therapy: toward nutritional recommendations for optimal results. Oxid Med Cell Longev. 2016;2016:6719534. doi: 10.1155/2016/6719534.

[235] Block KI, Koch AC, Mead MN, Tothy PK, Newman RA, Gyllenhaal C. Impact of antioxidant supplementation on chemotherapeutic toxicity: a systematic review of the evidence from randomized controlled trials. *Int J Cancer*. 2008;123(6):1227–1239. doi:10.1002/ijc.23754.

[236] Labriola D, Livingston R. Avoiding antioxidant-drug interactions during cancer treatment. ASCO Post 2014 July 25. Huntington, NY: Harborside; 2014 July 25 [cited 2020 Feb 18]. Available from: https://www.ascopost.com/issues/july-25-2014/avoiding-antioxidant-drug-interactions-during-cancer-treatment/

[237] Stone WL, Krishnan K, Campbell SE, Palau VE. The role of antioxidants and pro-oxidants in colon cancer. World J Gastrointest Oncol. 2014 Mar 15;6(3):55-66. doi: 10.4251/wjgo.v6.i3.55. Review. PMID: 24653795.

[238] Ozben T. Antioxidant supplementation on cancer risk and during cancer therapy: an update. Curr Top Med Chem. 2015;15(2):170-8. Review. PMID: 25496272.

[239] Ozben T. Antioxidant supplementation on cancer risk and during cancer therapy: an update. Curr Top Med Chem. 2015;15(2):170-8. Review. PMID: 25496272.

[240] Bairati I, Meyer F, Jobin E, Gélinas M, Fortin A, Nabid A, et al. Antioxidant vitamins supplementation and mortality: a randomized trial in head and neck cancer patients. Int J Cancer. 2006 Nov 1;119(9):2221-4. PMID: 16841333.

[241] Ferreira PR, Fleck JF, Diehl A, Barletta D, Braga-Filho A, Barletta A, et al. Protective effect of alpha-tocopherol in head and neck cancer radiation-induced mucositis: a double-blind randomized trial. Head Neck. 2004 Apr;26(4):313-21.
PubMed PMID: 15054734.

REFERENCES

[242] Ozben T. Antioxidant supplementation on cancer risk and during cancer therapy: an update. Curr Top Med Chem. 2015;15(2):170-8. Review. PMID: 25496272.

[243] Bairati I, Meyer F, Jobin E, Gélinas M, Fortin A, Nabid A, et al. Antioxidant vitamins supplementation and mortality: a randomized trial in head and neck cancer patients. Int J Cancer. 2006 Nov 1;119(9):2221-4. PMID: 16841333.

[244] Singh K, Bhori M, Kasu YA, Bhat G, Marar T. Antioxidants as precision weapons in war against cancer chemotherapy induced toxicity - exploring the armoury of obscurity. Saudi Pharm J. 2018 Feb;26(2):177-190. doi: 10.1016/j.jsps.2017.12.013.

[245] Singh K, Bhori M, Kasu YA, Bhat G, Marar T. Antioxidants as precision weapons in war against cancer chemotherapy induced toxicity - Exploring the armoury of obscurity. Saudi Pharm J. 2018 Feb;26(2):177-190. doi: 10.1016/j.jsps.2017.12.013.

[246] Ilghami R, Barzegari A, Mashayekhi MR, Letourneur D, Crepin M, Pavon-Djavid G. The conundrum of dietary antioxidants in cancer chemotherapy. Nutr Rev. 2020 Jan 1;78(1):65-76. doi: 10.1093/nutrit/nuz027.

[247] Cockfield JA, Schafer ZT. Antioxidant defenses: a context-specific vulnerability of cancer cells. Cancers (Basel). 2019 Aug 20;11(8). pii: E1208. doi: 10.3390/cancers11081208.

[248] Singh K, Bhori M, Kasu YA, Bhat G, Marar T. Antioxidants as precision weapons in war against cancer chemotherapy induced toxicity - Exploring the armoury of obscurity. Saudi Pharm J. 2018 Feb;26(2):177-190. doi: 10.1016/j.jsps.2017.12.013.

[249] Gedlicka C, Scheithauer W, Schüll B, Kornek GV. Effective treatment of oxaliplatin-induced cumulative polyneuropathy with alpha-lipoic acid. *J* Clin Oncol. 2002;20(15):3359–3361. doi:10.1200/JCO.2002.99.502.

[250] Ozben T. Antioxidant supplementation on cancer risk and during cancer therapy: an update. Curr Top Med Chem. 2015;15(2):170-8. Review. PMID: 25496272.

[251] Bott AJ, Maimouni S, Zong WX. The pleiotropic effects of glutamine metabolism in cancer. Cancers (Basel). 2019 Jun 4;11(6). pii: E770. doi: 10.3390/cancers11060770.

[252] San-Millán I, Brooks GA. Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg Effect. Carcinogenesis. 2017 Feb 1;38(2):119-133. doi: 10.1093/carcin/bgw127.

[253] Schwartz L, Seyfried T, Alfarouk KO, Da Veiga Moreira J, Fais S. Out of Warburg effect: an effective cancer treatment targeting the tumor specific metabolism and dysregulated pH. Semin Cancer Biol. 2017 Apr;43:134-138. doi: 10.1016/j.semcancer.2017.01.005.

[254] Bott AJ, Maimouni S, Zong WX. The pleiotropic effects of glutamine metabolism in cancer. Cancers (Basel). 2019 Jun 4;11(6). pii: E770. doi: 10.3390/cancers11060770.

[255] Oliveira CLP, Mattingly S, Schirrmacher R, Sawyer MB, Fine EJ, Prado CM. A nutritional perspective of ketogenic diet in cancer: A narrative review. J Acad Nutr Diet. 2018 Apr;118(4):668-688. doi: 10.1016/j.jand.2017.02.003.

[256] Seyfried TN, Flores RE, Poff AM, D'Agostino DP. Cancer as a metabolic disease: implications for novel therapeutics. Carcinogenesis. 2014 Mar;35(3):515-27. doi: 10.1093/carcin/bgt480.

[257] Seyfried TN, Flores RE, Poff AM, D'Agostino DP. Cancer as a metabolic disease: implications for novel therapeutics. Carcinogenesis. 2014 Mar;35(3):515-27. doi: 10.1093/carcin/bgt480.

[258] Schwartz L, Seyfried T, Alfarouk KO, Da Veiga Moreira J, Fais S. Out of Warburg effect: an effective cancer treatment targeting the tumour specific metabolism and dysregulated pH. Semin Cancer Biol. 2017 Apr;43:134-138. doi: 10.1016/j.semcancer.2017.01.005.

[259] Li Z, Zhang H. Reprogramming of glucose, fatty acid and amino acid metabolism for cancer progression. Cell Mol Life Sci. 2016 Jan;73(2):377-92. doi:10.1007/s00018-015-2070-4.

[260] Li Z, Zhang H. Reprogramming of glucose, fatty acid and amino acid metabolism for cancer progression. Cell Mol Life Sci. 2016 Jan;73(2):377-92. doi:10.1007/s00018-015-2070-4.

[261] Li Z, Zhang H. Reprogramming of glucose, fatty acid and amino acid metabolism for cancer progression. Cell Mol Life Sci. 2016 Jan;73(2):377-92. doi:10.1007/s00018-015-2070-4.

[262] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 2009 May 22;324(5930):1029-33. doi: 10.1126/science.1160809.

[263] Lee M, Yoon JH. Metabolic interplay between glycolysis and mitochondrial oxidation: the reverse Warburg effect and its therapeutic implication. World J Biol Chem. 2015 Aug 26;6(3):148-61. doi: 10.4331/wjbc.v6.i3.148.

[264] Chen XS, Li LY, Guan YD, Yang JM, Cheng Y. Anticancer strategies based on the metabolic profile of tumour cells: therapeutic targeting of the Warburg effect. Acta Pharmacol Sin. 2016 Aug;37(8):1013-9. doi: 10.1038/aps.2016.47.

REFERENCES

[265] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 2009 May 22;324(5930):1029-33. doi: 10.1126/science.1160809.

[266] Fu Y, Liu S, Yin S, Niu W, Xiong W, Tan M, et al. The reverse Warburg effect is likely to be an Achilles' heel of cancer that can be exploited for cancer therapy. Oncotarget. 2017 May 25;8(34):57813-57825. doi: 10.18632/oncotarget.18175.

[267] Li Z, Zhang H. Reprogramming of glucose, fatty acid and amino acid metabolism for cancer progression. Cell Mol Life Sci. 2016 Jan;73(2):377-92. doi:10.1007/s00018-015-2070-4.

[268] Cutruzzolà F, Giardina G, Marani M, Macone A, Paiardini A, Rinaldo S, et al. Glucose metabolism in the progression of prostate cancer. Front Physiol. 2017 Feb 21;8:97. doi: 10.3389/fphys.2017.00097.

[269] Zhu A, Lee D, Shim H. Metabolic positron emission tomography imaging in cancer detection and therapy response. Semin Oncol. 2011 Feb;38(1):55-69. doi: 10.1053/j.seminoncol.2010.11.012.

[270] Chen XS, Li LY, Guan YD, Yang JM, Cheng Y. Anticancer strategies based on the metabolic profile of tumor cells: therapeutic targeting of the Warburg effect. Acta Pharmacol Sin. 2016 Aug;37(8):1013-9. doi: 10.1038/aps.2016.47.

[271] Chen XS, Li LY, Guan YD, Yang JM, Cheng Y. Anticancer strategies based on the metabolic profile of tumor cells: therapeutic targeting of the Warburg effect. Acta Pharmacol Sin. 2016 Aug;37(8):1013-9. doi: 10.1038/aps.2016.47.

[272] San-Millán I, Brooks GA. Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg Effect. Carcinogenesis. 2017 Feb 1;38(2):119-133. doi: 10.1093/carcin/bgw127.

[273] San-Millán I, Brooks GA. Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg Effect. Carcinogenesis. 2017 Feb 1;38(2):119-133. doi: 10.1093/carcin/bgw127.

[274] San-Millán I, Brooks GA. Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg Effect. Carcinogenesis. 2017 Feb 1;38(2):119-133. doi: 10.1093/carcin/bgw127.

[275] Fu Y, Liu S, Yin S, Niu W, Xiong W, Tan M, et al. The reverse Warburg effect is likely to be an Achilles' heel of cancer that can be exploited for cancer therapy. Oncotarget. 2017 May 25;8(34):57813-57825. doi: 10.18632/oncotarget.18175.

[276] Zhao L, Mao Y, Zhao Y, Cao Y, Chen X. Role of multifaceted regulators in cancer glucose metabolism and their clinical significance. Oncotarget. 2016 May 24;7(21):31572-85. doi: 10.18632/oncotarget.7765.

[277] San-Millán I, Brooks GA. Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg Effect. Carcinogenesis. 2017 Feb 1;38(2):119-133. doi: 10.1093/carcin/bgw127.

[278] San-Millán I, Brooks GA. Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg Effect. Carcinogenesis. 2017 Feb 1;38(2):119-133. doi: 10.1093/carcin/bgw127.

[279] Zhao L, Mao Y, Zhao Y, Cao Y, Chen X. Role of multifaceted regulators in cancer glucose metabolism and their clinical significance. Oncotarget. 2016 May 24;7(21):31572-85. doi: 10.18632/oncotarget.7765.

[280] Pavlides S, Whitaker-Menezes D, Castello-Cros R, Flomenberg N, Witkiewicz AK, Frank PG, et al. The reverse Warburg effect: aerobic glycolysis in cancer associated fibroblasts and the tumor stroma. Cell Cycle. 2009 Dec;8(23):3984-4001. Epub 2009 Dec 5. PMID: 19923890.

[281] Fu Y, Liu S, Yin S, Niu W, Xiong W, Tan M, et al. The reverse Warburg effect is likely to be an Achilles' heel of cancer that can be exploited for cancer therapy. Oncotarget. 2017 May 25;8(34):57813-57825. doi: 10.18632/oncotarget.18175.

[282] Chen XS, Li LY, Guan YD, Yang JM, Cheng Y. Anticancer strategies based on the metabolic profile of tumor cells: therapeutic targeting of the Warburg effect. Acta Pharmacol Sin. 2016 Aug;37(8):1013-9. doi: 10.1038/aps.2016.47.

[283] Potter M, Newport E, Morten KJ. The Warburg effect: 80 years on. Biochem Soc Trans. 2016 Oct 15;44(5):1499-1505. Review. PMID: 27911732.

[284] Chen XS, Li LY, Guan YD, Yang JM, Cheng Y. Anticancer strategies based on the metabolic profile of tumor cells: therapeutic targeting of the Warburg effect. Acta Pharmacol Sin. 2016 Aug;37(8):1013-9. doi: 10.1038/aps.2016.47.

[285] Olson KA, Schell JC, Rutter J. Pyruvate and metabolic flexibility: illuminating a path toward selective cancer therapies. Trends Biochem Sci. 2016 Mar;41(3):219-230. doi: 10.1016/j.tibs.2016.01.002.

REFERENCES

[286] Chen XS, Li LY, Guan YD, Yang JM, Cheng Y. Anticancer strategies based on the metabolic profile of tumor cells: therapeutic targeting of the Warburg effect. Acta Pharmacol Sin. 2016 Aug;37(8):1013-9. doi: 10.1038/aps.2016.47.

[287] Chen XS, Li LY, Guan YD, Yang JM, Cheng Y. Anticancer strategies based on the metabolic profile of tumor cells: therapeutic targeting of the Warburg effect. Acta Pharmacol Sin. 2016 Aug;37(8):1013-9. doi: 10.1038/aps.2016.47.

[288] Michalopoulou E, Bulusu V, Kamphorst JJ. Metabolic scavenging by cancer cells: when the going gets tough, the tough keep eating. Br J Cancer. 2016 Sep 6;115(6):635-40. doi: 10.1038/bjc.2016.256.

[289] Cutruzzolà F, Giardina G, Marani M, Macone A, Paiardini A, Rinaldo S, Paone A. Glucose metabolism in the progression of prostate cancer. Front Physiol. 2017 Feb 21;8:97. doi: 10.3389/fphys.2017.00097.

[290] Michalopoulou E, Bulusu V, Kamphorst JJ. Metabolic scavenging by cancer cells: when the going gets tough, the tough keep eating. Br J Cancer. 2016 Sep 6;115(6):635-40. doi: 10.1038/bjc.2016.256.

[291] Hoerner CR, Chen VJ, Fan AC. The 'Achilles heel' of metabolism in renal cell carcinoma: glutaminase inhibition as a rational treatment strategy. Kidney Cancer. 2019 Feb 5;3(1):15-29. doi: 10.3233/KCA-180043.

[292] Bott AJ, Maimouni S, Zong WX. The pleiotropic effects of glutamine metabolism in cancer. Cancers (Basel). 2019 Jun 4;11(6). pii: E770. doi: 10.3390/cancers11060770.

[293] Bott AJ, Maimouni S, Zong WX. The pleiotropic effects of glutamine metabolism in cancer. Cancers (Basel). 2019 Jun 4;11(6). pii: E770. doi: 10.3390/cancers11060770.

[294] Jolfaie NR, Mirzaie S, Ghiasvand R, Askari G, Miraghajani M. The effect of glutamine intake on complications of colorectal and colon cancer treatment: A systematic review. J Res Med Sci. 2015 Sep;20(9):910-8. doi:10.4103/1735-1995.170634.

[295] Sayles C, Hickerson SC, Bhat RR, Hall J, Garey KW, Trivedi MV. Oral glutamine in preventing treatment-related mucositis in adult patients with cancer: a systematic review. Nutr Clin Pract. 2016 Apr;31(2):171-9. doi: 10.1177/0884533615611857.

[296] Amara S. Oral glutamine for the prevention of chemotherapy-induced peripheral neuropathy. Ann Pharmacother. 2008 Oct;42(10):1481-5. doi: 10.1345/aph.1L179.

[297] Jolfaie NR, Mirzaie S, Ghiasvand R, Askari G, Miraghajani M. The effect of glutamine intake on complications of colorectal and colon cancer treatment: A systematic review. J Res Med Sci. 2015 Sep;20(9):910-8. doi:10.4103/1735-1995.170634.

[298] Jolfaie NR, Mirzaie S, Ghiasvand R, Askari G, Miraghajani M. The effect of glutamine intake on complications of colorectal and colon cancer treatment: A systematic review. J Res Med Sci. 2015 Sep;20(9):910-8. doi:10.4103/1735-1995.170634.

[299] Sayles C, Hickerson SC, Bhat RR, Hall J, Garey KW, Trivedi MV. Oral glutamine in preventing treatment-related mucositis in adult patients with cancer: a systematic review. Nutr Clin Pract. 2016 Apr;31(2):171-9. doi: 10.1177/0884533615611857.

[300] Amara S. Oral glutamine for the prevention of chemotherapy-induced peripheral neuropathy. Ann Pharmacother. 2008 Oct;42(10):1481-5. doi: 10.1345/aph.1L179.

[301] Teixeira FJ, Santos HO, Howell SL, Pimentel GD. Whey protein in cancer therapy: A narrative review. Pharmacol Res. 2019 Jun;144:245-256. doi: 10.1016/j.phrs.2019.04.019.

[302] Zhang M, Di Martino JS, Bowman RL, Campbell NR, Baksh SC, Simon-Vermot T, et al. Adipocyte-derived lipids mediate melanoma progression via FATP proteins. Cancer Discov. 2018 Aug;8(8):1006-1025. doi: 10.1158/2159-8290.CD-17-1371.

[303] Jones CL, Stevens BM, D'Alessandro A, Reisz JA, Culp-Hill R, Nemkov T, et al. Inhibition of amino acid metabolism selectively targets human leukemia stem cells. Cancer Cell. 2018 Nov 12;34(5):724-740.e4. doi: 10.1016/j.ccell.2018.10.005.

[304] Reczek CR, Chandel NS. ROS promotes cancer cell survival through calcium signaling. Cancer Cell. 2018 Jun 11;33(6):949-951. doi: 10.1016/j.ccell.2018.05.010.

[305] Liou GY, Storz P. Reactive oxygen species in cancer. Free Radic Res. 2010 May;44(5):479-96. doi: 10.3109/10715761003667554.

[306] Cockfield JA, Schafer ZT. Antioxidant defenses: a context-specific vulnerability of cancer cells. Cancers (Basel). 2019 Aug 20;11(8). pii: E1208. doi: 10.3390/cancers11081208.

[307] Liou GY, Storz P. Reactive oxygen species in cancer. Free Radic Res. 2010 May;44(5):479-96. doi: 10.3109/10715761003667554.

[308] Liou GY, Storz P. Reactive oxygen species in cancer. Free Radic Res. 2010 May;44(5):479-96. doi: 10.3109/10715761003667554.

REFERENCES

[309] Cancer Council Australia. Nutrition and cancer [Internet]. Cancer Council Australia; Sydney, NSW: 2019 Jun [cited 2020 Mar 23]. Available from: https://www.cancerwa.asn.au/resources/2019-03-19-Nutrition-and-Cancer.pdf

[310] Cancer Council Australia. Nutrition and cancer [Internet]. Cancer Council Australia; Sydney, NSW: 2019 Jun [cited 2020 Mar 23]. Available from: https://www.cancerwa.asn.au/resources/2019-03-19-Nutrition-and-Cancer.pdf

[311] Klement RJ, Brehm N, Sweeney RA. Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes. Med Oncol. 2020 Jan 11;37(2):14. doi: 10.1007/s12032-020-1337-2.

[312] Klement RJ. Beneficial effects of ketogenic diets for cancer patients: a realist review with focus on evidence and confirmation. Med Oncol. 2017 Aug;34(8):132. doi: 10.1007/s12032-017-0991-5.

[313] Klement RJ, Brehm N, Sweeney RA. Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes. Med Oncol. 2020 Jan 11;37(2):14. doi: 10.1007/s12032-020-1337-2.

[314] Klement RJ. Beneficial effects of ketogenic diets for cancer patients: a realist review with focus on evidence and confirmation. Med Oncol. 2017 Aug;34(8):132. doi: 10.1007/s12032-017-0991-5.

[315] Klement RJ. Beneficial effects of ketogenic diets for cancer patients: a realist review with focus on evidence and confirmation. Med Oncol. 2017 Aug;34(8):132. doi: 10.1007/s12032-017-0991-5.

[316] Klement RJ, Brehm N, Sweeney RA. Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes. Med Oncol. 2020 Jan 11;37(2):14. doi: 10.1007/s12032-020-1337-2.

[317] Klement RJ. Beneficial effects of ketogenic diets for cancer patients: a realist review with focus on evidence and confirmation. Med Oncol. 2017 Aug;34(8):132. doi: 10.1007/s12032-017-0991-5.

[318] Klement RJ, Brehm N, Sweeney RA. Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes. Med Oncol. 2020 Jan 11;37(2):14. doi: 10.1007/s12032-020-1337-2.

[319] Klement RJ, Brehm N, Sweeney RA. Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes. Med Oncol. 2020 Jan 11;37(2):14. doi: 10.1007/s12032-020-1337-2.

[320] Klement RJ, Brehm N, Sweeney RA. Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes. Med Oncol. 2020 Jan 11;37(2):14. doi: 10.1007/s12032-020-1337-2.

[321] Klement RJ, Brehm N, Sweeney RA. Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes. Med Oncol. 2020 Jan 11;37(2):14. doi: 10.1007/s12032-020-1337-2.

[322] van der Louw EJTM, Olieman JF, van den Bemt PMLA, Bromberg JEC, Oomen-de Hoop E, Neuteboom RF, Catsman-Berrevoets CE, et al. Ketogenic diet treatment as adjuvant to standard treatment of glioblastoma multiforme: a feasibility and safety study. Ther Adv Med Oncol. 2019 Jun 21;11:1758835919853958. doi: 10.1177/1758835919853958.

[323] Elsakka AMA, Bary MA, Abdelzaher E, Elnaggar M, Kalamian M, Mukherjee P, et al. Management of glioblastoma multiforme in a patient treated with ketogenic metabolic therapy and modified standard of care: a 24-month follow-up. Front Nutr. 2018 Mar 29;5:20. doi: 10.3389/fnut.2018.00020.

[324] Seyfried TN, Shelton L, Arismendi-Morillo G, Kalamian M, Elsakka A, Maroon J, et al. Provocative question: should ketogenic metabolic therapy become the standard of care for glioblastoma? Neurochem Res. 2019 Oct;44(10):2392-2404. doi: 10.1007/s11064-019-02795-4.

[325] Seyfried TN, Flores RE, Poff AM, D'Agostino DP. Cancer as a metabolic disease: implications for novel therapeutics. Carcinogenesis. 2014 Mar;35(3):515-27. doi: 10.1093/carcin/bgt480.

[326] Seyfried TN, Flores RE, Poff AM, D'Agostino DP. Cancer as a metabolic disease: implications for novel therapeutics. Carcinogenesis. 2014 Mar;35(3):515-27. doi: 10.1093/carcin/bgt480.

[327] Tantamango-Bartley Y, Jaceldo-Siegl K, Fan J, Fraser G. Vegetarian diets and the incidence of cancer in a low-risk population. Cancer Epidemiol Biomarkers Prev. 2013 Feb;22(2):286-94. doi: 10.1158/1055-9965.EPI-12-1060.

[328] Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74. doi: 10.1073/pnas.0803080105.

[329] Orlich MJ, Singh PN, Sabaté J, Fan J, Sveen L, Bennett H, et al. Vegetarian dietary patterns and the risk of colorectal cancers. JAMA Intern Med. 2015 May;175(5):767-76. doi: 10.1001/jamainternmed.2015.59.

[330] Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74. doi: 10.1073/pnas.0803080105.

[331] Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: A systematic review with meta-analysis of observational studies. Crit Rev Food Sci Nutr. 2017 Nov 22;57(17):3640-3649. doi: 10.1080/10408398.2016.1138447.

[332] Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74. doi: 10.1073/pnas.0803080105.

REFERENCES

[333] McCarty MF. Plant-based diets relatively low in bioavailable phosphate and calcium may aid prevention and control of prostate cancer by lessening production of fibroblast growth factor 23. Med Hypotheses. 2017 Feb;99:68-72. doi: 10.1016/j.mehy.2017.01.001.
[334] McCarty MF. GCN2 and FGF21 are likely mediators of the protection from cancer, autoimmunity, obesity, and diabetes afforded by vegan diets. Med Hypotheses. 2014 Sep;83(3):365-71. doi: 10.1016/j.mehy.2014.06.014.
[335] Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: A systematic review with meta-analysis of observational studies. Crit Rev Food Sci Nutr. 2017 Nov 22;57(17):3640-3649. doi: 10.1080/10408398.2016.1138447.
[336] Key TJ, Appleby PN, Crowe FL, Bradbury KE, Schmidt JA, Travis RC. Cancer in British vegetarians: updated analyses of 4998 incident cancers in a cohort of 32,491 meat eaters, 8612 fish eaters, 18,298 vegetarians, and 2246 vegans. Am J Clin Nutr. 2014 Jul;100 Suppl 1:378S-85S. doi: 10.3945/ajcn.113.071266.
[337] Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74. doi: 10.1073/pnas.0803080105.
[338] Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74. doi: 10.1073/pnas.0803080105.
[339] Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74. doi: 10.1073/pnas.0803080105.
[340] Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74. doi: 10.1073/pnas.0803080105.
[341] Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74. doi: 10.1073/pnas.0803080105.
[342] Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74. doi: 10.1073/pnas.0803080105.
[343] Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74. doi: 10.1073/pnas.0803080105.
[344] Orlich MJ, Singh PN, Sabaté J, Fan J, Sveen L, Bennett H, et al. Vegetarian dietary patterns and the risk of colorectal cancers. JAMA Intern Med. 2015 May;175(5):767-76. doi: 10.1001/jamainternmed.2015.59.
[345] Sanderson SM, Gao X, Dai Z, Locasale JW. Methionine metabolism in health and cancer: a nexus of diet and precision medicine. Nat Rev Cancer. 2019 Nov;19(11):625-637. doi: 10.1038/s41568-019-0187-8.
[346] Sanderson SM, Gao X, Dai Z, Locasale JW. Methionine metabolism in health and cancer: a nexus of diet and precision medicine. Nat Rev Cancer. 2019 Nov;19(11):625-637. doi: 10.1038/s41568-019-0187-8.
[347] Sanderson SM, Gao X, Dai Z, Locasale JW. Methionine metabolism in health and cancer: a nexus of diet and precision medicine. Nat Rev Cancer. 2019 Nov;19(11):625-637. doi: 10.1038/s41568-019-0187-8.
[348] Sanderson SM, Gao X, Dai Z, Locasale JW. Methionine metabolism in health and cancer: a nexus of diet and precision medicine. Nat Rev Cancer. 2019 Nov;19(11):625-637. doi: 10.1038/s41568-019-0187-8.
[349] Sanderson SM, Gao X, Dai Z, Locasale JW. Methionine metabolism in health and cancer: a nexus of diet and precision medicine. Nat Rev Cancer. 2019 Nov;19(11):625-637. doi: 10.1038/s41568-019-0187-8.
[350] Sanderson SM, Gao X, Dai Z, Locasale JW. Methionine metabolism in health and cancer: a nexus of diet and precision medicine. Nat Rev Cancer. 2019 Nov;19(11):625-637. doi: 10.1038/s41568-019-0187-8.
[351] Halpern BC, Clark BR, Hardy DN, Halpern RM, Smith RA. The effect of replacement of methionine by homocysteine on survival of malignant and normal adult mammalian cells in culture. Proc Natl Acad Sci U S A. 1974 Apr;71(4):1133-6. PubMed PMID: 4524624.
[352] Halpern BC, Clark BR, Hardy DN, Halpern RM, Smith RA. The effect of replacement of methionine by homocysteine on survival of malignant and normal adult mammalian cells in culture. Proc Natl Acad Sci U S A. 1974 Apr;71(4):1133-6. PubMed PMID: 4524624.
[353] Sanderson SM, Gao X, Dai Z, Locasale JW. Methionine metabolism in health and cancer: a nexus of diet and precision medicine. Nat Rev Cancer. 2019 Nov;19(11):625-637. doi: 10.1038/s41568-019-0187-8.
[354] Sanderson SM, Gao X, Dai Z, Locasale JW. Methionine metabolism in health and cancer: a nexus of diet and precision medicine. Nat Rev Cancer. 2019 Nov;19(11):625-637. doi: 10.1038/s41568-019-0187-8.

REFERENCES

[355] Strekalova E, Malin D, Rajanala H, Cryns VL. Preclinical breast cancer models to investigate metabolic priming by methionine restriction. Methods Mol Biol. 2019;1866:61-73. doi: 10.1007/978-1-4939-8796-2_6.

[356] Strekalova E, Malin D, Rajanala H, Cryns VL. Preclinical breast cancer models to investigate metabolic priming by methionine restriction. Methods Mol Biol. 2019;1866:61-73. doi: 10.1007/978-1-4939-8796-2_6.

[357] Strekalova E, Malin D, Rajanala H, Cryns VL. Preclinical breast cancer models to investigate metabolic priming by methionine restriction. Methods Mol Biol. 2019;1866:61-73. doi: 10.1007/978-1-4939-8796-2_6.

[358] Strekalova E, Malin D, Rajanala H, Cryns VL. Preclinical breast cancer models to investigate metabolic priming by methionine restriction. Methods Mol Biol. 2019;1866:61-73. doi: 10.1007/978-1-4939-8796-2_6.

[359] Strekalova E, Malin D, Rajanala H, Cryns VL. Preclinical breast cancer models to investigate metabolic priming by methionine restriction. Methods Mol Biol. 2019;1866:61-73. doi: 10.1007/978-1-4939-8796-2_6.

[360] Strekalova E, Malin D, Rajanala H, Cryns VL. Preclinical breast cancer models to investigate metabolic priming by methionine restriction. Methods Mol Biol. 2019;1866:61-73. doi: 10.1007/978-1-4939-8796-2_6.

[361] Epner DE, Morrow S, Wilcox M, Houghton JL. Nutrient intake and nutritional indexes in adults with metastatic cancer on a phase I clinical trial of dietary methionine restriction. Nutr Cancer. 2002;42(2):158-66. PMID: 12416254.

[362] Epner DE, Morrow S, Wilcox M, Houghton JL. Nutrient intake and nutritional indexes in adults with metastatic cancer on a phase I clinical trial of dietary methionine restriction. Nutr Cancer. 2002;42(2):158-66. PMID: 12416254.

[363] Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. Nat Rev Cancer. 2018 Nov;18(11):707-719. doi: 10.1038/s41568-018-0061-0.

[364] Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. Nat Rev Cancer. 2018 Nov;18(11):707-719. doi: 10.1038/s41568-018-0061-0.

[365] Buono R, Longo VD. Starvation, stress resistance, and cancer. Trends Endocrinol Metab. 2018 Apr;29(4):271-280. doi: 10.1016/j.tem.2018.01.008.

[366] Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. Nat Rev Cancer. 2018 Nov;18(11):707-719. doi: 10.1038/s41568-018-0061-0.

[367] Buono R, Longo VD. Starvation, stress resistance, and cancer. Trends Endocrinol Metab. 2018 Apr;29(4):271-280. doi: 10.1016/j.tem.2018.01.008.

[368] de Groot S, Pijl H, van der Hoeven JJM, Kroep JR. Effects of short-term fasting on cancer treatment. J Exp Clin Cancer Res. 2019 May 22;38(1):209. doi: 10.1186/s13046-019-1189-9.

[369] Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. Nat Rev Cancer. 2018 Nov;18(11):707-719. doi: 10.1038/s41568-018-0061-0.

[370] Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. Nat Rev Cancer. 2018 Nov;18(11):707-719. doi: 10.1038/s41568-018-0061-0.

[371] Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. Nat Rev Cancer. 2018 Nov;18(11):707-719. doi: 10.1038/s41568-018-0061-0.

[372] Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. Nat Rev Cancer. 2018 Nov;18(11):707-719. doi: 10.1038/s41568-018-0061-0.

[373] Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, Cohen P, Longo VD. Fasting and cancer treatment in humans: A case series report. Aging (Albany NY). 2009 Dec 31;1(12):988-1007. PubMed PMID: 20157582; PubMed Central PMCID: PMC2815756.

[374] Bauersfeld SP, Kessler CS, Wischnewsky M, Jaensch A, Steckhan N, Stange R, et al. The effects of short-term fasting on quality of life and tolerance to chemotherapy in patients with breast and ovarian cancer: a randomized cross-over pilot study. BMC Cancer. 2018 Apr 27;18(1):476. doi: 10.1186/s12885-018-4353-2.

[375] de Groot S, Pijl H, van der Hoeven JJM, Kroep JR. Effects of short-term fasting on cancer treatment. J Exp Clin Cancer Res. 2019 May 22;38(1):209. doi: 10.1186/s13046-019-1189-9.

[376] Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, Cohen P, Longo VD. Fasting and cancer treatment in humans: A case series report. Aging (Albany NY). 2009 Dec 31;1(12):988-1007. PubMed PMID: 20157582; PubMed Central PMCID: PMC2815756.

[377] Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, Cohen P, Longo VD. Fasting and cancer treatment in humans: A case series report. Aging (Albany NY). 2009 Dec 31;1(12):988-1007. PubMed PMID: 20157582; PubMed Central PMCID: PMC2815756.

REFERENCES

[378] Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, Cohen P, Longo VD. Fasting and cancer treatment in humans: A case series report. Aging (Albany NY). 2009 Dec 31;1(12):988-1007. PubMed PMID: 20157582; PubMed Central PMCID: PMC2815756.
[379] Bauersfeld SP, Kessler CS, Wischnewsky M, Jaensch A, Steckhan N, Stange R, et al. The effects of short-term fasting on quality of life and tolerance to chemotherapy in patients with breast and ovarian cancer: a randomized cross-over pilot study. BMC Cancer. 2018 Apr 27;18(1):476. doi: 10.1186/s12885-018-4353-2.
[380] Bauersfeld SP, Kessler CS, Wischnewsky M, Jaensch A, Steckhan N, Stange R, et al. The effects of short-term fasting on quality of life and tolerance to chemotherapy in patients with breast and ovarian cancer: a randomized cross-over pilot study. BMC Cancer. 2018 Apr 27;18(1):476. doi: 10.1186/s12885-018-4353-2.
[381] Bauersfeld SP, Kessler CS, Wischnewsky M, Jaensch A, Steckhan N, Stange R, et al. The effects of short-term fasting on quality of life and tolerance to chemotherapy in patients with breast and ovarian cancer: a randomized cross-over pilot study. BMC Cancer. 2018 Apr 27;18(1):476. doi: 10.1186/s12885-018-4353-2.
[382] Clinical Trials.org. Fasting mimicking diet, cancer [Internet]. National Institute of Health: Bethesda; 2020 Mar 1 [cited 2020 Feb 1]. Available from: https://clinicaltrials.gov/ct2/results?cond=Cancer&term=fasting+mimicking+diet&cntry=&state=&city=&dist=
[383] McLelland J. How to starve cancer. United Kingdom: Agenor Publishing; Nov 10 2018. p. 317.
[384] Xu J, Long Y, Ni L, Yuan X, Yu N, Wu R, et al. Anticancer effect of berberine based on experimental animal models of various cancers: a systematic review and meta-analysis. BMC Cancer. 2019 Jun 17;19(1):589. doi: 10.1186/s12885-019-5791-1.
[385] Ortiz LM, Lombardi P, Tillhon M, Scovassi AI. Berberine, an epiphany against cancer. Molecules. 2014 Aug 15;19(8):12349-67. doi: 10.3390/molecules190812349.
[386] Mortazavi H, Nikfar B, Esmaeili SA, Rafieenia F, Saburi E, Chaichian S, et al. Potential cytotoxic and anti-metastatic effects of berberine on gynaecological cancers with drug-associated resistance. Eur J Med Chem. 2020 Feb 1;187:111951. doi: 10.1016/j.ejmech.2019.111951.
[387] Zhang C, Sheng J, Li G, Zhao L, Wang Y, Yang W, et al. Effects of berberine and its derivatives on cancer: a systems pharmacology review. Front Pharmacol. 2020 Jan 15;10:1461. doi: 10.3389/fphar.2019.01461.
[388] Wang Y, Liu Y, Du X, Ma H, Yao J. The anti-cancer mechanisms of berberine: a review. Cancer Manag Res. 2020 Jan 30;12:695-702. doi: 10.2147/CMAR.S242329.
[389] Habtemariam S. Recent advances in berberine inspired anticancer approaches: from drug combination to novel formulation technology and derivatization. Molecules. 2020 Mar 20;25(6). pii: E1426. doi: 10.3390/molecules25061426.
[390] Hallajzadeh J, Maleki Dana P, Mobini M, Asemi Z, Mansournia MA, Sharifi M, et al. Targeting of oncogenic signaling pathways by berberine for treatment of colorectal cancer. Med Oncol. 2020 Apr 17;37(6):49. doi: 10.1007/s12032-020-01367-9.
[391] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F,et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017 Feb;36(1):11-48. doi: 10.1016/j.clnu.2016.07.015.
[392] Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. Nat Rev Cancer. 2017 Sep 25;17(10):620-632. doi: 10.1038/nrc.2017.78.
[393] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[394] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[395] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular ,echanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[396] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[397] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[398] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[399] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[400] Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. Nat Rev Cancer. 2017 Sep 25;17(10):620-632. doi: 10.1038/nrc.2017.78.

REFERENCES

[401] Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. Nat Rev Cancer. 2017 Sep 25;17(10):620-632. doi: 10.1038/nrc.2017.78.
[402] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[403] Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. Nat Rev Cancer. 2017 Sep 25;17(10):620-32. doi: 10.1038/nrc.2017.78.
[404] Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. Nat Rev Cancer. 2017 Sep 25;17(10):620-32. doi: 10.1038/nrc.2017.78.
[405] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[406] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[407] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[408] Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. Nat Rev Cancer. 2017 Sep25;17(10):620-32. doi: 10.1038/nrc.2017.78.
[409] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[410] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018 Jan 9;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
[411] Breastcancer.org. Experts update exercise guidelines for people treated for cancer [internet]. Ardmore, PA: Breastcancer.org; 2020 [updated 2019 October 23; cited 2020 April 28]. Available from: https://www.breastcancer.org/research-news/updated-exercise-guidelines-for-cancer
[412] COSA Exercise and Cancer Group Executive Committee. Clinical Oncology Society of Australia position statement on exercise in cancer care. Med J Aust. 2019 Jan;210(1):54.e1. doi: 10.5694/mja2.12039.
[413] Liu L, Ancoli-Israel S. Sleep disturbances in cancer. Psychiatr Ann. 2008 Sep 1;38(9):627-34. doi: 10.3928/00485713-20080901-01.
[414] Fu L, Kettner NM. The circadian clock in cancer development and therapy. Prog Mol Biol Transl Sci. 2013;119:221-82. doi: 10.1016/B978-0-12-396971-2.00009-9.
[415] Menegaux F, Truong T, Anger A, Cordina-Duverger E, Lamkarkach F, Arveux P, et al. Night work and breast cancer: a population-based case-control study in France (the CECILE study). Int J Cancer. 2013 Feb 15;132(4):924-31. doi: 10.1002/ijc.27669.
[416] Erren TC, Morfeld P, Foster RG, Reiter RJ, Groß JV, Westermann IK. Sleep and cancer: synthesis of experimental data and meta-analyses of cancer incidence among some 1,500,000 study individuals in 13 countries. Chronobiol Int. 2016;33(4):325-50. doi: 10.3109/07420528.2016.1149486.
[417] Menegaux F, Truong T, Anger A, Cordina-Duverger E, Lamkarkach F, Arveux P, et al. Night work and breast cancer: a population-based case-control study in France (the CECILE study). Int J Cancer. 2013 Feb 15;132(4):924-31. doi: 10.1002/ijc.27669.
[418] Menegaux F, Truong T, Anger A, Cordina-Duverger E, Lamkarkach F, Arveux P, et al. Night work and breast cancer: a population-based case-control study in France (the CECILE study). Int J Cancer. 2013 Feb 15;132(4):924-31. doi: 10.1002/ijc.27669.
[419] Behrens T, Rabstein S, Wichert K, Erbel R, Eisele L, Arendt M, et al. Shift work and the incidence of prostate cancer: a 10-year follow-up of a German population-based cohort study. Scand J Work Environ Health. 2017 Nov 1;43(6):560-68. doi: 10.5271/sjweh.3666.
[420] Erren TC, Morfeld P, Foster RG, Reiter RJ, Groß JV, Westermann IK. Sleep and cancer: synthesis of experimental data and meta-analyses of cancer incidence among some 1,500,000 study individuals in 13 countries. Chronobiol Int. 2016;33(4):325-50. doi: 10.3109/07420528.2016.1149486.
[421] Kaczor T. An overview of melatonin and breast cancer. Nat Med J. 2010;2(2).
[422] Lee Y, Lahens NF, Zhang S, Bedont J, Field JM, Sehgal A. G1/S cell cycle regulators mediate effects of circadian dysregulation on tumor growth and provide targets for timed anticancer treatment. PLoS Biol. 2019 Apr 30;17(4):e3000228. doi: 10.1371/journal.pbio.3000228.
[423] Lee Y, Lahens NF, Zhang S, Bedont J, Field JM, Sehgal A. G1/S cell cycle regulators mediate effects of circadian dysregulation on tumor growth and provide targets for timed anticancer treatment. PLoS Biol. 2019 Apr 30;17(4):e3000228. doi: 10.1371/journal.pbio.3000228.
[424] Erren TC, Morfeld P, Foster RG, Reiter RJ, Groß JV, Westermann IK. Sleep and cancer: synthesis of experimental data and meta-analyses of cancer incidence among some 1,500,000 study individuals in 13 countries. Chronobiol Int. 2016;33(4):325-50. doi: 10.3109/07420528.2016.1149486.

REFERENCES

[425] Fu L, Kettner NM. The circadian clock in cancer development and therapy. Prog Mol Biol Transl Sci. 2013;119:221-82. doi: 10.1016/B978-0-12-396971-2.00009-9.
[426] Fu L, Kettner NM. The circadian clock in cancer development and therapy. Prog Mol Biol Transl Sci. 2013;119:221-82. doi: 10.1016/B978-0-12-396971-2.00009-9.
[427] Fu L, Kettner NM. The circadian clock in cancer development and therapy. Prog Mol Biol Transl Sci. 2013;119:221-82. doi: 10.1016/B978-0-12-396971-2.00009-9.
[428] Garcia-Prieto P. Pyscho-oncology: A patient's view. Recent Results Cancer Res. 2018;210:57-66. doi: 10.1007/978-3-319-643010-6_4.
[429] Lang-Rollin I, Berberich G. Pyscho-oncology. Dialogues Clin Neurosci. 2018 Mar;20(1):13-22. PMID: 29946207.
[430] Lang-Rollin I, Berberich G. Pyscho-oncology. Dialogues Clin Neurosci. 2018 Mar;20(1):13-22. PMID: 29946207.
[431] NIH National Cancer Institute [Internet]. Bethesda MD: National Cancer Institute; 2019. Adjustment to cancer: anxiety and distress (PDQ®) – health professional version. 2019 Mar 6 [cited 2020 Mar 12]. Available from: https://www.cancer.gov/about-cancer/coping/feelings/anxiety-distress-hp-pdq
[432] Garcia-Prieto P. Pyscho-oncology: A patient's view. Recent Results Cancer Res. 2018;210:57-66. doi: 10.1007/978-3-319-643010-6_4.
[433] Garcia-Prieto P. Pyscho-oncology: A patient's view. Recent Results Cancer Res. 2018;210:57-66. doi: 10.1007/978-3-319-643010-6_4.
[434] Schwarz R. Pyschosocial factors in carcinogenesis: on the problem of the so-called cancer-prone personality. Psychother Psychosom Med Psychol. 1993 Jan;43(1):1-9. PMID: 8441795.
[435] Schwarz R. Pyschosocial factors in carcinogenesis: on the problem of the so-called cancer-prone personality. Psychother Psychosom Med Psychol. 1993 Jan;43(1):1-9. PMID: 8441795.

[436] Lang-Rollin I, Berberich G. Pyscho-oncology. Dialogues Clin Neurosci. 2018 Mar;20(1):13-22. PMID: 29946207.
[437] Kubler-Ross E. On death and dying. New York, NY: Simon & Schuster; 1969.
[438] Renz M, Koeberle D, Cerny T, Strasser F. Between utter despair and essential hope. J Clin Oncol. 2009 Jan 1;27(1):146-9. doi: 10.1200/JCO.2008.19.2203.
[439] Kubler-Ross E. On death and dying. New York, NY: Simon & Schuster; 1969.
[440] Renz M, Koeberle D, Cerny T, Strasser F. Between utter despair and essential hope. J Clin Oncol. 2009 Jan 1;27(1):146-9. doi: 10.1200/JCO.2008.19.2203.
[441] Renz M, Koeberle D, Cerny T, Strasser F. Between utter despair and essential hope. J Clin Oncol. 2009 Jan 1;27(1):146-9. doi: 10.1200/JCO.2008.19.2203.
[442] Renz M, Koeberle D, Cerny T, Strasser F. Between utter despair and essential hope. J Clin Oncol. 2009 Jan 1;27(1):146-9. doi: 10.1200/JCO.2008.19.2203.
[443] NIH National Cancer Institute [Internet]. Bethesda MD: National Cancer Institute; 2019. Adjustment to cancer: anxiety and distress (PDQ®) – health professional version. 2019 Mar 6 [cited 2020 Mar 12]. Available from: https://www.cancer.gov/about-cancer/coping/feelings/anxiety-distress-hp-pdq
[444] NIH National Cancer Institute [Internet]. Bethesda MD: National Cancer Institute; 2019. Adjustment to cancer: anxiety and distress (PDQ®) – health professional version. 2019 Mar 6 [cited 2020 Mar 12]. Available from: https://www.cancer.gov/about-cancer/coping/feelings/anxiety-distress-hp-pdq
[445] Lang-Rollin I, Berberich G. Pyscho-oncology. Dialogues Clin Neurosci. 2018 Mar;20(1):13-22. PMID: 29946207.
[446] Riba MB, Donovan KA, Andersen B, Braun I, Breitbart WS, Brewer BW, et al. Distress management, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw.2019 Oct 1;17(10):1229-49. doi: 10.6004/jnccn.2019.0048.
[447] NIH National Cancer Institute [Internet]. Bethesda MD: National Cancer Institute; 2019. Adjustment to cancer: anxiety and distress (PDQ®) – health professional version. 2019 Mar 6 [cited 2020 Mar 12]. Available from: https://www.cancer.gov/about-cancer/coping/feelings/anxiety-distress-hp-pdq
[448] Lynch J, Goodhart F, Saunders Y, O'Connor SJ. Screening for psychological distress in patients with lung cancer: results of a clinical audit evaluating the use of the patient Distress Thermometer. Support Care Cancer. 2010 Feb;19(2):193-202. doi: 10.1007/s00520-009-0799-8.
[449] Suvarna B, Suvarna A, Phillips R, Juster RP, McDermott B, Samyai Z. Health risk behaviours and allostatic load: A systematic review. Neurosci Biobehah Rev. 2020 Jan;108;694-711. doi: 10.1016/j.neurobiorev.2019.12.020.

REFERENCES

[450] Antoni MH, Lutgendorf SK, Blomberg B, Carver CS, Lechner S, Diaz A, et al. Cognitive-behavioural stress management reverses anxiety-related leukocyte transcriptional dynamics. Biol Psychiatry. 2012 Feb 15;71(4):366-72. doi: 10.1016/j.biopsych.2011.10.007.

[451] Stagl JM, Lechner SC, Carver CS, Bouchard LC, Gudenkauf LM, Jutagir DR, et al. A randomised controlled trial of cognitive behavioural stress management in cancer: survival and recurrence at 11-year follow up. Breast Cancer Res Treat. 2015 Nov;154(2):319-28. doi: 10.1007/s10549-015-3626-6.

[452] Stagl JM, Lechner SC, Carver CS, Bouchard LC, Gudenkauf LM, Jutagir DR, et al. A randomised controlled trial of cognitive behavioural stress management in cancer: survival and recurrence at 11-year follow up. Breast Cancer Res Treat. 2015 Nov;154(2):319-28. doi: 10.1007/s10549-015-3626-6.

[453] Stagl JM, Lechner SC, Carver CS, Bouchard LC, Gudenkauf LM, Jutagir DR, et al. A randomised controlled trial of cognitive behavioural stress management in cancer: survival and recurrence at 11-year follow up. Breast Cancer Res Treat. 2015 Nov;154(2):319-28. doi: 10.1007/s10549-015-3626-6.

[454] Stagl JM, Lechner SC, Carver CS, Bouchard LC, Gudenkauf LM, Jutagir DR, et al. A randomised controlled trial of cognitive behavioural stress management in cancer: survival and recurrence at 11-year follow up. Breast Cancer Res Treat. 2015 Nov;154(2):319-28. doi: 10.1007/s10549-015-3626-6.

[455] Stagl JM, Lechner SC, Carver CS, Bouchard LC, Gudenkauf LM, Jutagir DR, et al. A randomised controlled trial of cognitive behavioural stress management in cancer: survival and recurrence at 11-year follow up. Breast Cancer Res Treat. 2015 Nov;154(2):319-28. doi: 10.1007/s10549-015-3626-6.

[456] Antoni MH, Dhabhar FS. The impact of psychosocial stress and stress management on immune responses in patients with cancer. Cancer. 2019 May 1;125(9):1417-31. doi: 10.1002/cncr.31943.

[457] Hiller JG, Cole SW, Crone EM, Byrne DJ, Shackleford DM, Pang JB, et al. Preoperative β-blockade with propranolol reduces biomarkers of metastasis in breast cancer: A phase II randomised trial. Clin Cancer Res. 2019 Nov 21. doi: 10.1158/1078-0432.CCR-19-2641.

[458] Barre PV, Padmaja G, Rana S, Tiamongla. Stress and quality of life in cancer patients: medical and psychological intervention. Indian J Psychol Med. 2018 May-Jun;40(3):232-238. doi: 10.4103/ijpsym_512_17.

[459] Hiller JG, Cole SW, Crone EM, Byrne DJ, Shackleford DM, Pang JB, et al. Preoperative β-blockade with propranolol reduces biomarkers of metastasis in breast cancer: A phase II randomised trial. Clin Cancer Res. 2019 Nov 21. doi: 10.1158/1078-0432.CCR-19-2641.

[460] Watkins JL, Thaker PH, Nick AM, Ramondetta LM, Kumar S, Urbauer DL, et al. Clinical impact of selective and nonselective beta blockers on survival in patients with ovarian cancer. Cancer. 2015 Oct 1;121:(19):3444-51. doi: 10.1002/cncr.29392.

[461] Watkins JL, Thaker PH, Nick AM, Ramondetta LM, Kumar S, Urbauer DL, et al. Clinical impact of selective and nonselective beta blockers on survival in patients with ovarian cancer. Cancer. 2015 Oct 1;121:(19):3444-51. doi: 10.1002/cncr.29392.

[462] Garcia-Prieto P. Pyscho-oncology: A patient's view. Recent Results Cancer Res. 2018;210:57-66. doi: 10.1007/978-3-319-643010-6_4.

[463] Carlson Le, Speca M, Faris P, Patel KD. One year pre-post intervention follow up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. Brain Behav Immun. 2007 Nov;21(8):1038-49. doi: 10.1016/j.bbi.2007.04.002.

[464] Carlson Le, Speca M, Faris P, Patel KD. One year pre-post intervention follow up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. Brain Behav Immun. 2007 Nov;21(8):1038-49. doi: 10.1016/j.bbi.2007.04.002.

[465] Carlson Le, Speca M, Faris P, Patel KD. One year pre-post intervention follow up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. Brain Behav Immun. 2007 Nov;21(8):1038-49. doi: 10.1016/j.bbi.2007.04.002.

[466] Van de Wal M, Thewes B, Gielissen M, Speckens A, Prins J. Efficacy of blended cognitive behaviour therapy for high fear of recurrence in breast, prostate, and colorectal cancer survivors: The SWORD study, a randomised controlled trial. J Clin Oncol. 2017 Jul 1;35(19):2173-2183. doi: 10.1200/JCO.2016.70.5301.

[467] Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv. 2013 Sep;7(3):300-22. doi: 10.1007/s11764-013-0272-z.

[468] Van de Wal M, Thewes B, Gielissen M, Speckens A, Prins J. Efficacy of blended cognitive behaviour therapy for high fear of recurrence in breast, prostate, and colorectal cancer survivors: The SWORD study, a randomised controlled trial. J Clin Oncol. 2017 Jul 1;35(19):2173-83. doi: 10.1200/JCO.2016.70.5301.

[469] Gil KM, Mishel MH, Germino B, Porter LS, Carlton-LaNey I, Belyea M. Uncertainty management intervention for older African American and Caucasian long-term breast cancer survivors. J Psychosoc Oncol. 2005;23(2-3):3-21. doi: 10.1300/j077v23n02 02.

REFERENCES

[470] Hamblin MR, Nelson ST, Strahan JR. Photobiomodulation and cancer: what is the truth? Photomed Laser Surg. 2018 May;36(5):241-45. doi: 10.1089/pho.2017.4401.
[471] Ao J, Wood JP, Chidlow G, Gillies MC, Casson RJ. Retinal pigment epithelium in the pathogenesis of age-related macular degeneration and photobiomodulation as a potential therapy? Clin Exp Ophthalmol. 2018 Aug;46(6):670-86. doi: 10.1111/ceo.13121.
[472] Ao J, Wood JP, Chidlow G, Gillies MC, Casson RJ. Retinal pigment epithelium in the pathogenesis of age-related macular degeneration and photobiomodulation as a potential therapy? Clin Exp Ophthalmol. 2018 Aug;46(6):670-86. doi: 10.1111/ceo.13121.
[473] Ao J, Wood JP, Chidlow G, Gillies MC, Casson RJ. Retinal pigment epithelium in the pathogenesis of age-related macular degeneration and photobiomodulation as a potential therapy? Clin Exp Ophthalmol. 2018 Aug;46(6):670-86. doi: 10.1111/ceo.13121.
[474] Zadik Y, Arany PR, Fregnani ER, Bossi P, Antunes HS, Bensadoun RJ, et al. Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer. 2019 Oct;27(10):3969-83. doi: 10.1007/s00520-019-04890-2.
[475] Hamblin MR, Nelson ST, Strahan JR. Photobiomodulation and cancer: what is the truth? Photomed Laser Surg. 2018 May;36(5):241-45. doi: 10.1089/pho.2017.4401.
[476] Hamblin MR, Nelson ST, Strahan JR. Photobiomodulation and cancer: what is the truth? Photomed Laser Surg. 2018 May;36(5):241-45. doi: 10.1089/pho.2017.4401.
[477] Huang YY, Sharma SK, Carroll J, Hamblin MR. Biphasic dose response in low level light therapy – an update. Dose Response. 2011;9(4):602-18. doi: 10.2203/dose-response.11-009.
[478] Antunes HS, Herchenhorn D, Small IA, Araujo CMM, Viegas CMP, de Assis Ramos G, et al. Long-term survival of a randomised phase III trial of head and neck cancer patients receiving concurrent chemoradiation therapy with or without low-level laser therapy (LLLT) to prevent oral mucositis. Oral Oncol. 2017 Aug;71:11-15. doi: 10.1016/j.oraloncology.2017.05.018.
[479] Antunes HS, Herchenhorn D, Small IA, Araujo CMM, Viegas CMP, de Assis Ramos G, et al. Long-term survival of a randomised phase III trial of head and neck cancer patients receiving concurrent chemoradiation therapy with or without low-level laser therapy (LLLT) to prevent oral mucositis. Oral Oncol. 2017 Aug;71:11-15. doi: 10.1016/j.oraloncology.2017.05.018.
[480] Antunes HS, Herchenhorn D, Small IA, Araujo CMM, Viegas CMP, de Assis Ramos G, et al. Long-term survival of a randomised phase III trial of head and neck cancer patients receiving concurrent chemoradiation therapy with or without low-level laser therapy (LLLT) to prevent oral mucositis. Oral Oncol. 2017 Aug;71:11-15. doi: 10.1016/j.oraloncology.2017.05.018.
[481] Pires Marques EC, Lopes FP, Nascimento IC, Morelli J, Pereira MV, Meiken VMM, et al. Photobiomodulation and photodynamic therapy for the treatment of oral mucositis in patients with cancer. Photodiagnosis Photodyn Ther. 2020 Mar;29:101621. doi: 10.1016/j.pdpdt.2019.101621.
[482] Datta NR, Ordóñez SG, Gaipl US, Paulides MM, Crezee H, Gellermann J, et al. Local hyperthermia combined with radiotherapy and/or chemotherapy: recent advances and promises for the future. Cancer Treat Rev. 2015;41(9):742-53. doi:10.1016/j.ctrv.2015.05.009.
[483] Datta NR, Ordóñez SG, Gaipl US, Paulides MM, Crezee H, Gellermann J, et al. Local hyperthermia combined with radiotherapy and/or chemotherapy: recent advances and promises for the future. Cancer Treat Rev. 2015;41(9):742-53. doi:10.1016/j.ctrv.2015.05.009.
[484] Toraya-Brown S, Fiering S. Local tumour hyperthermia as immunotherapy for metastatic cancer. Int J Hyperthermia. 2014;30(8):531-39. doi:10.3109/02656736.2014.968640.
[485] Toraya-Brown S, Fiering S. Local tumour hyperthermia as immunotherapy for metastatic cancer. Int J Hyperthermia. 2014;30(8):531-39. doi:10.3109/02656736.2014.968640.
[486] Toraya-Brown S, Fiering S. Local tumour hyperthermia as immunotherapy for metastatic cancer. Int J Hyperthermia. 2014;30(8):531-39. doi:10.3109/02656736.2014.968640.
[487] Mahmoudi K, Bouras A, Bozec D, Ivkov R, Hadjipanayis C. Magnetic hyperthermia therapy for the treatment of glioblastoma: a review of the therapy's history, efficacy and application in humans. Int J Hyperthermia. 2018;34(8):1316-28. doi:10.1080/02656736.2018.1430867.
[488] Datta NR, Ordóñez SG, Gaipl US, Paulides MM, Crezee H, Gellermann J, et al. Local hyperthermia combined with radiotherapy and/or chemotherapy: recent advances and promises for the future. Cancer Treat Rev. 2015;41(9):742-53. doi:10.1016/j.ctrv.2015.05.009.
[489] Zhao C, Dai C, Chen X. Whole-body hyperthermia combined with hyperthermic intraperitoneal chemotherapy for the treatment of stage IV advanced gastric cancer. Int J Hyperthermia. 2012;28(8):735-41. doi:10.3109/02656736.2012.734894.
[490] Mahmoudi K, Bouras A, Bozec D, Ivkov R, Hadjipanayis C. Magnetic hyperthermia therapy for the treatment of glioblastoma: a review of the therapy's history, efficacy and application in humans. Int J Hyperthermia. 2018;34(8):1316-28. doi:10.1080/02656736.2018.1430867.

REFERENCES

[491] Kang CD, Kim SH. Effects of regional hyperthermia with moderate temperature on cancer treatment. J Life Sci. 2016 Sep;26(9):1088-96. doi: 10.5352/JLS.2016.26.9.1088.

[492] Stępień K, Ostrowski RP, Matyja E. Hyperbaric oxygen as an adjunctive therapy in treatment of malignancies, including brain tumours. Med Oncol. 2016 Sep;33(9):101. doi: 10.1007/s12032-016-0814-0.

[493] Stępień K, Ostrowski RP, Matyja E. Hyperbaric oxygen as an adjunctive therapy in treatment of malignancies, including brain tumours. Med Oncol. 2016 Sep;33(9):101. doi: 10.1007/s12032-016-0814-0.

[494] Reijmen E, Vannucci L, De Couck M, De Grève J, Gidron Y. Therapeutic potential of the vagus nerve in cancer. Immunol Lett. 2018 Oct;202:38-43. doi: 10.1016/j.imlet.2018.07.006.

[495] Reijmen E, Vannucci L, De Couck M, De Grève J, Gidron Y. Therapeutic potential of the vagus nerve in cancer. Immunol Lett. 2018 Oct;202:38-43. doi: 10.1016/j.imlet.2018.07.006.

[496] Reijmen E, Vannucci L, De Couck M, De Grève J, Gidron Y. Therapeutic potential of the vagus nerve in cancer. Immunol Lett. 2018 Oct;202:38-43. doi: 10.1016/j.imlet.2018.07.006.

[497] Serhan CN, de la Rosa X, Jouvene CC. Cutting Edge: Human vagus produces specialised proresolving mediators of inflammation with electrical stimulation reducing proinflammatory eicosanoids. J Immunol. 2018 Dec 1;201(11):3161-65. doi: 10.4049/jimmunol.1800806.

[498] van Gorkom GNY, Lookermans EL, Van Elssen CHMJ, Bos GMJ. The effect of vitamin C (ascorbic acid) in the treatment of patients with cancer: a systematic review. Nutrients. 2019 Apr 28;11(5). pii: E977. doi: 10.3390/nu11050977.

[499] Schoenfeld JD, Alexander MS, Waldron TJ, Sibenaller ZA, Spitz DR, Buettner GR, et al. Pharmacological ascorbate as a means of sensitizing cancer cells to radio-chemotherapy While Protecting Normal Tissue. Semin Radiat Oncol. 2019 Jan;29(1):25-32. doi: 10.1016/j.semradonc.2018.10.006.

[500] Schoenfeld JD, Alexander MS, Waldron TJ, Sibenaller ZA, Spitz DR, Buettner GR, et al. Pharmacological ascorbate as a means of sensitizing cancer cells to radio-chemotherapy While Protecting Normal Tissue. Semin Radiat Oncol. 2019 Jan;29(1):25-32. doi: 10.1016/j.semradonc.2018.10.006.

[501] Carr AC, Cook J. Intravenous vitamin C for cancer therapy – identifying the current gaps in our knowledge. Front Physiol. 2018 Aug 23;9:1182. doi: 10.3389/fphys.2018.01182.

[502] van Gorkom GNY, Lookermans EL, Van Elssen CHMJ, Bos GMJ. The effect of vitamin C (ascorbic acid) in the treatment of patients with cancer: a systematic review. Nutrients. 2019 Apr 28;11(5). pii: E977. doi: 10.3390/nu11050977.

[503] Ou J, Zhu X, Zhang H, Du Y, Chen P, Wang J, et al. A retrospective study of gemcitabine and carboplatin with or without intravenous vitamin C on patients with advanced triple-negative breast cancer. Integr Cancer Ther. 2020 Jan-Dec;19:1534735419895591. doi: 10.1177/1534735419895591.

[504] Schiffman JD, Fisher PG, Gibbs P. Early detection of cancer: past, present, and future. Am Soc Clin Oncol Educ Book. 2015;57-65. doi:10.14694/EdBook_AM.2015.35.57.

[505] Schiffman JD, Fisher PG, Gibbs P. Early detection of cancer: past, present, and future. Am Soc Clin Oncol Educ Book. 2015;57-65. doi:10.14694/EdBook_AM.2015.35.57.

[506] Fitzgerald A, Berentson-Shaw J. Thermography as a screening and diagnostic tool: a systematic review. N Z Med J. 2012 Mar 9;125(1351):80-91. PMID: 22426613.

[507] Sarigoz T, Ertan T, Topuz O, Sevim Y, Cihan Y. Role of digital infrared thermal imaging in the diagnosis of breast mass: a pilot study: diagnosis of breast mass by thermography. Infrared Phys Techn. 2018 Jun 1;91:214-9. doi: 10.1016/j.infrared.2018.04.019.

[508] Sarigoz T, Ertan T, Topuz O, Sevim Y, Cihan Y. Role of digital infrared thermal imaging in the diagnosis of breast mass: a pilot study: diagnosis of breast mass by thermography. Infrared Phys Techn. 2018 Jun 1;91:214-9. doi: 10.1016/j.infrared.2018.04.019.

[509] Fitzgerald A, Berentson-Shaw J. Thermography as a screening and diagnostic tool: a systematic review. N Z Med J. 2012 Mar 9;125(1351):80-91. PMID: 22426613.

[510] Fitzgerald A, Berentson-Shaw J. Thermography as a screening and diagnostic tool: a systematic review. N Z Med J. 2012 Mar 9;125(1351):80-91. PMID: 22426613.

[511] Fitzgerald A, Berentson-Shaw J. Thermography as a screening and diagnostic tool: a systematic review. N Z Med J. 2012 Mar 9;125(1351):80-91. PMID: 22426613.

[512] Sarigoz T, Ertan T, Topuz O, Sevim Y, Cihan Y. Role of digital infrared thermal imaging in the diagnosis of breast mass: a pilot study: diagnosis of breast mass by thermography. Infrared Phys Techn. 2018 Jun 1;91:214-9. doi: 10.1016/j.infrared.2018.04.019.

[513] Omranipour R, Kazemian A, Alipour S, Najafi M, Alidoosti M, Navid M, et al. Comparison of the accuracy of thermography and mammography in the detection of breast cancer. Breast Care (Basel). 2016;11(4):260-264. doi:10.1159/000448347.

REFERENCES

[514] Lozar T, Gersak K, Cemazar M, Kuhar CG, Jesenko T. The biology and clinical potential of circulating tumor cells. Radiol Oncol. 2019 May 8;53(2):131-47. doi:10.2478/raon-2019-0024.
[515] Dawson SJ, Tsui DW, Murtaza M, Biggs H, Rueda OM, Chin SF, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. N Engl J Med. 2013;368(13):1199-1209. doi:10.1056/NEJMoa1213261.
[516] Dawson SJ, Tsui DW, Murtaza M, Biggs H, Rueda OM, Chin SF, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. N Engl J Med. 2013;368(13):1199-1209. doi:10.1056/NEJMoa1213261.
[517] Krebs MG, Metcalf RL, Carter L, Brady G, Blackhall FH, Dive C. Molecular analysis of circulating tumour cells-biology and biomarkers. Nat Rev Clin Oncol. 2014;11(3):129-44. doi:10.1038/nrclinonc.2013.253.
[518] Lozar T, Gersak K, Cemazar M, Kuhar CG, Jesenko T. The biology and clinical potential of circulating tumor cells. Radiol Oncol. 2019 May 8;53(2):131-47. doi:10.2478/raon-2019-0024.
[519] Krebs MG, Metcalf RL, Carter L, Brady G, Blackhall FH, Dive C. Molecular analysis of circulating tumour cells-biology and biomarkers. Nat Rev Clin Oncol. 2014;11(3):129-44. doi:10.1038/nrclinonc.2013.253.
[520] Krebs MG, Metcalf RL, Carter L, Brady G, Blackhall FH, Dive C. Molecular analysis of circulating tumour cells-biology and biomarkers. Nat Rev Clin Oncol. 2014;11(3):129-44. doi:10.1038/nrclinonc.2013.253.
[521] Cree IA, Uttley L, Buckley Woods H, Kikiuchi H, Reiman A, Harnan S, et al. The evidence base for circulating tumour DNA blood-based biomarkers for the early detection of cancer: a systematic mapping review. BMC Cancer. 2017 Oct 23;17(1):697. doi:10.1186/s12885-017-3693-7.
[522] Dawson SJ, Tsui DW, Murtaza M, Biggs H, Rueda OM, Chin SF, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. N Engl J Med. 2013;368(13):1199-1209. doi:10.1056/NEJMoa1213261.
[523] Krebs MG, Metcalf RL, Carter L, Brady G, Blackhall FH, Dive C. Molecular analysis of circulating tumour cells-biology and biomarkers. Nat Rev Clin Oncol. 2014;11(3):129-44. doi:10.1038/nrclinonc.2013.253.
[524] Dawson SJ, Tsui DW, Murtaza M, Biggs H, Rueda OM, Chin SF, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. N Engl J Med. 2013;368(13):1199-1209. doi:10.1056/NEJMoa1213261.
[525] Krebs MG, Metcalf RL, Carter L, Brady G, Blackhall FH, Dive C. Molecular analysis of circulating tumour cells-biology and biomarkers. Nat Rev Clin Oncol. 2014;11(3):129-44. doi:10.1038/nrclinonc.2013.253.

ABBREVIATIONS

5-FU – 5-flurorouracil
α7 nAChR – α7 subunit of the nicotinic AChR
ACh – Acetylcholine
ADRB1 – Adrenergic beta-1 receptor
AHCC™ – Active hexose correlated compound
AO – Antioxidants
ALT – Alanine transferase
AscH – Ascorbic acid
AST – Aspartate aminotransferase
ATP – Adenosine triphosphate
bCBT – Blended cognitive behavioural therapy
BP – Blood pressure
CAF – Cancer associated fibroblasts
CAU – Care as usual
CBSM – Cognitive behavioural stress management
CBT – Cognitive behavioural therapy
CFU – Colony forming units
CIPN – Chemotherapy induced peripheral neuropathy
CML – Chronic myeloid leukaemia
CSC – Cancer stem cells
CTC – Circulating tumour cell
ctDNA – Circulating tumour derived DNA
CTLA-4 – Cytotoxic T-lymphocyte-associated protein 4
DC – Dendritic cells
DC1 – Type one dendritic cells
DNA – Deoxyribonucleic acid
ECM – Extracellular matrix
EGCG – Epigallocatechin gallate
EGFR – Epithelial growth factor receptor
EOC – Epithelial ovarian, primary peritoneal or fallopian tube cancers
FCR – Fear of cancer recurrence
FMD – Fasting mimicking diet
G-CSF – Granulocyte colony-stimulating factor
GI – Gastrointestinal
H2O2 – Hydrogen peroxide
HBO – Hyperbaric oxygen
HER2 – Human epidermal growth factor receptor 2
HIF – Hypoxia inducible factor
HPV – Human papilloma virus
HR – Heart rate
HRV – Heart rate variability
HSCT – Haematopoietic stem cell transplants
Hsp – Heat shock protein
IGF – Insulin-like growth factor
IgG – Immunoglobulin G
IL – Interleukin
INF – Interferon
IV – Intravenous
IVC – Intravenous vitamin C
KD – Ketogenic diets
LGG® – *Lactobacillus rhamnosus* (LGG®)
LLLT – Low-level laser therapy
LSC – Leukaemia stem cells
MBSR – Mindfulness-based stress reduction
MCP – Meaning centred psychotherapy
MCT – Monocarboxylate transporter
MHC I – Major histocompatibility complex
MR – Methionine restriction
NF-κB – Nuclear factor kappa-light-chain-enhancer of activated B cells
NIR – Near-infrared light
NK – Natural killer
NO – Nitric oxide
NSAIDs – Non-steroidal anti-inflammatory drugs
OM – Oral mucositis
OS – Overall survival
OS – Oxidative stress
PBM – Photobiomodulation
PD-1 – Programmed death-1
PD-L1 – Programmed death ligand-1
PEA – Palmitoylethanolamide
PFS – Progression-free survival
PG – Prostaglandin
QOL – Quality of life
ROS – Reactive oxygen species
RNA – Ribonucleic acid
RSV – Rous sarcoma virus
SBP – Systolic blood pressure
SNS – Sympathetic nervous system
SOSI – Symptoms of stress inventory
SPMs – Specialised pro-resolving mediators
STF – Short-term fasting
SVCT1– Sodium-dependant vitamin C transporter-1

ABBREVIATIONS

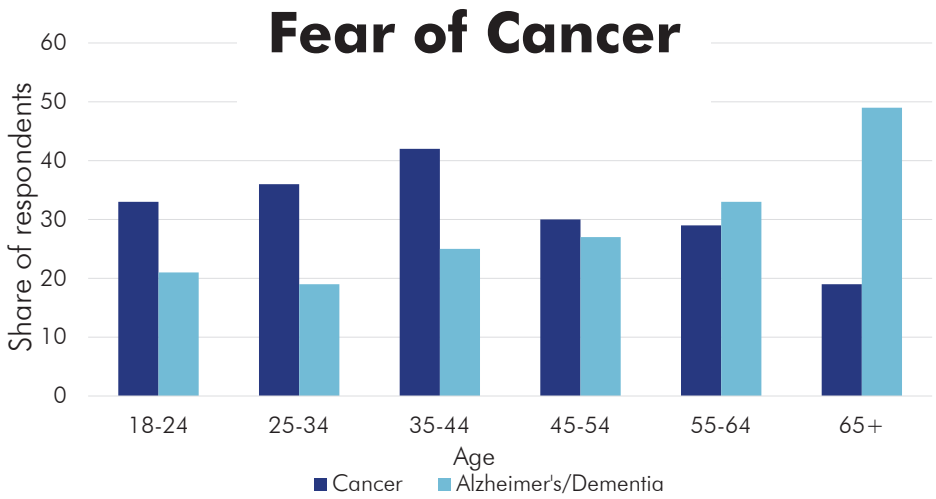
TAMs – Tumour associated macrophages
TCA – Tricarboxylic acid
TCR – T cell receptor
TGF-β – Transforming growth factor-β
Th1 – T helper 1
Th2 – T helper 2
TLR – Toll-like receptor
TME – Tumour microenvironment
TNBC – Triple-negative breast cancer
TNF-α – Tumour necrosis factor-α
TRAIL-R2 – TNF-related apoptosis-inducing ligand-receptor 2
VEGF – Vascular endothelial growth factor
WBC – White blood cell

INTEGRATIVE ONCOLOGY

Learning Objectives – Part 1

- Understand the unique characteristics of cancer.
- Learn to support patients undergoing cancer treatments, such as managing the side effects of chemotherapy.
- Safety with antioxidants and what this means in patient management.
- Protecting and supporting cancer patients gut microbiome.
- Learn the metabolic characteristics of cancer, and how diets can nourish patients whilst starving cancer.
- The importance of prescribing diet, sleep and exercise for cancer patients.

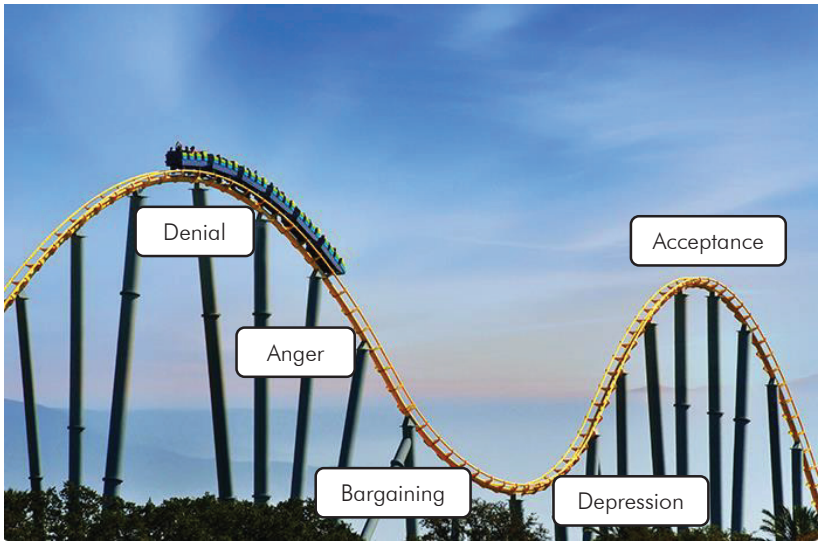
INTEGRATIVE ONCOLOGY



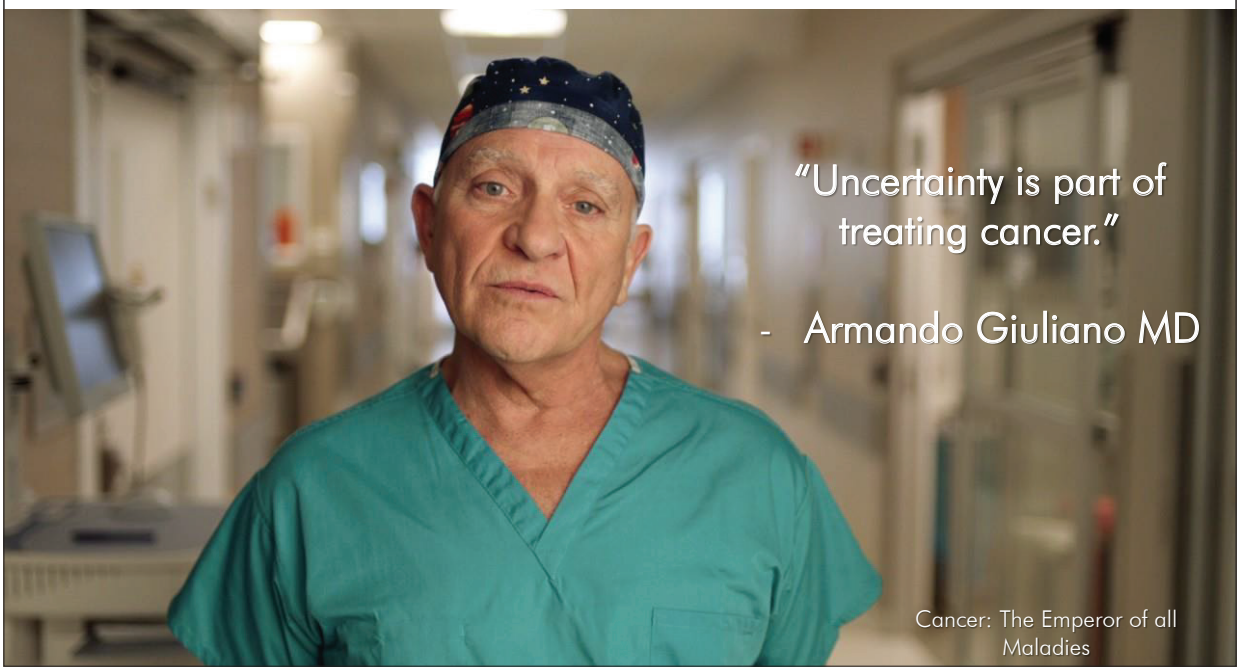
Statista [Internet]. Share of individuals that fear being diagnosed with cancer and Alzheimer's disease in England in 2018. Available from: https://www.statista.com/statistics/921479/fear-of-cancer-and-alzheimer-s-disease-in-england-by-age/

INTEGRATIVE ONCOLOGY

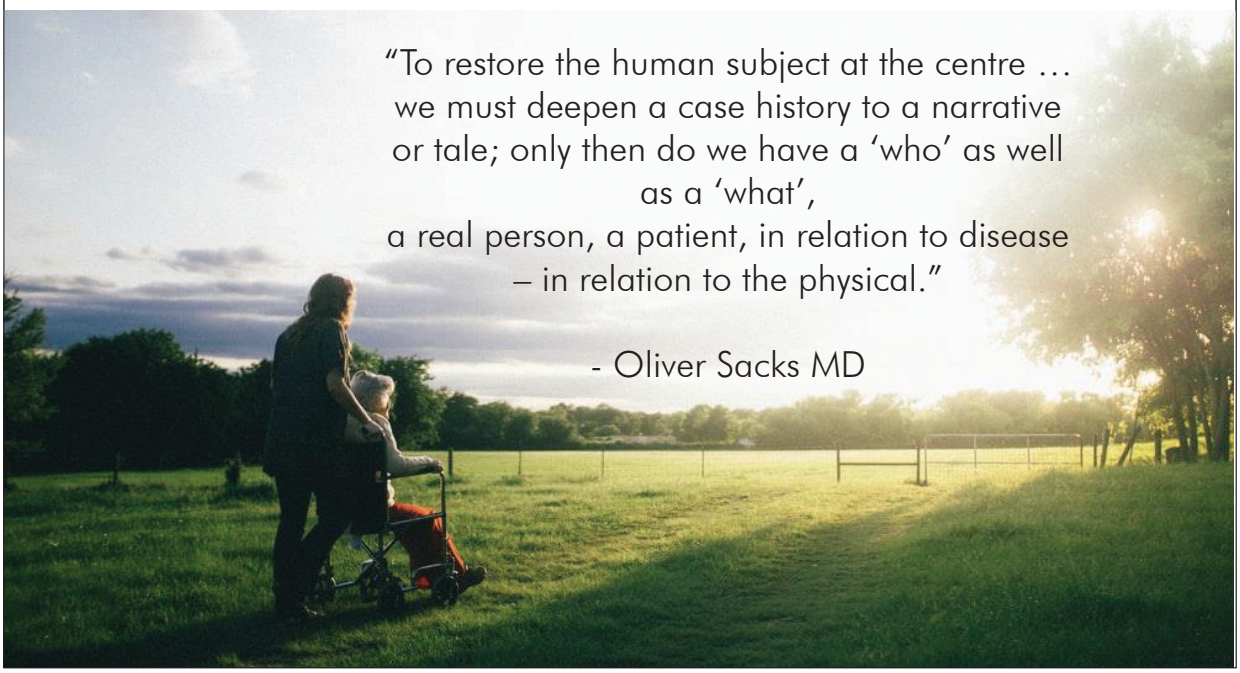
The Patient Journey

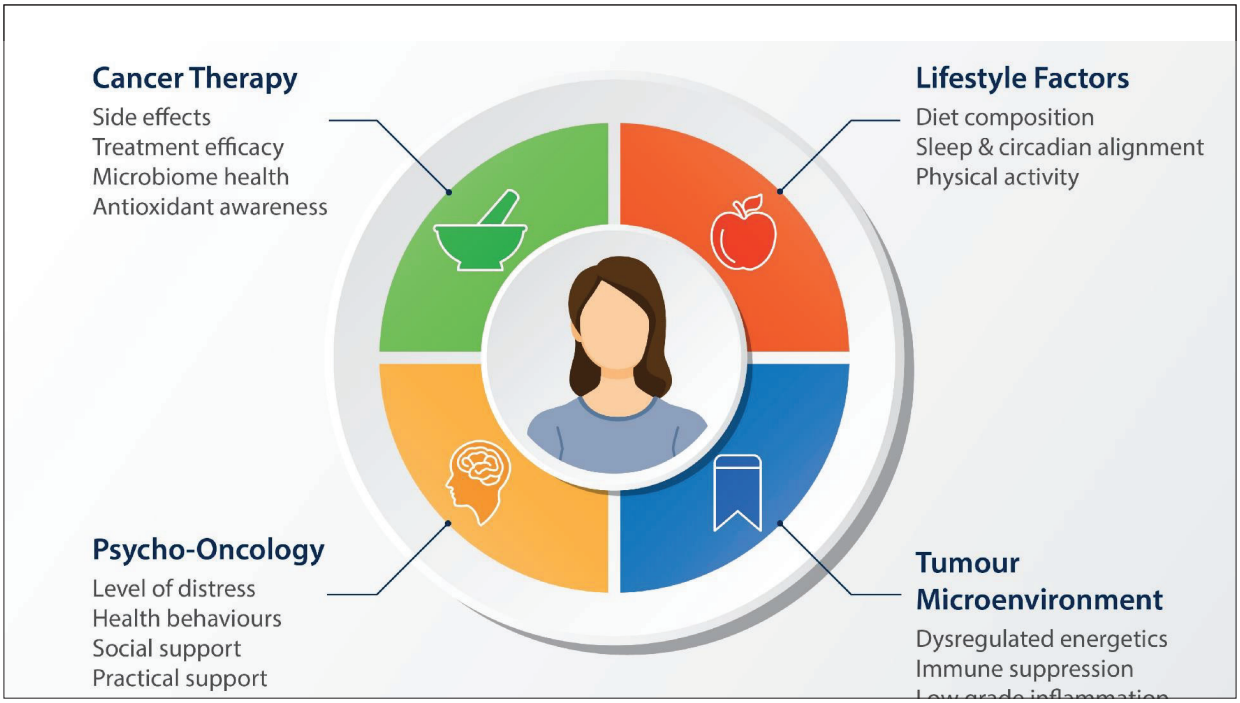


Adapted from Renz M, et al. J Clin Oncol. 2009 Jan 1;27(1):146-9. doi: 10.1200/JCO.2008.19.2203; Kubler-Ross E. New York, NY, Simon & Schuster, 1969.

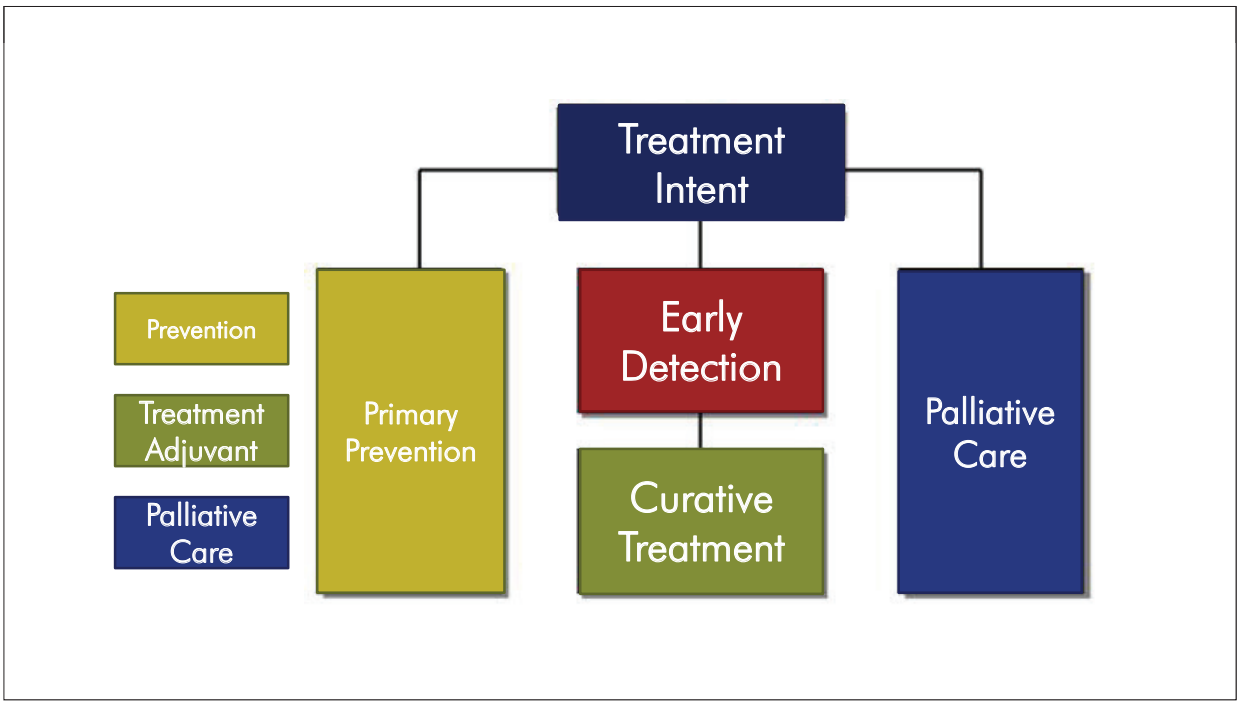


INTEGRATIVE ONCOLOGY



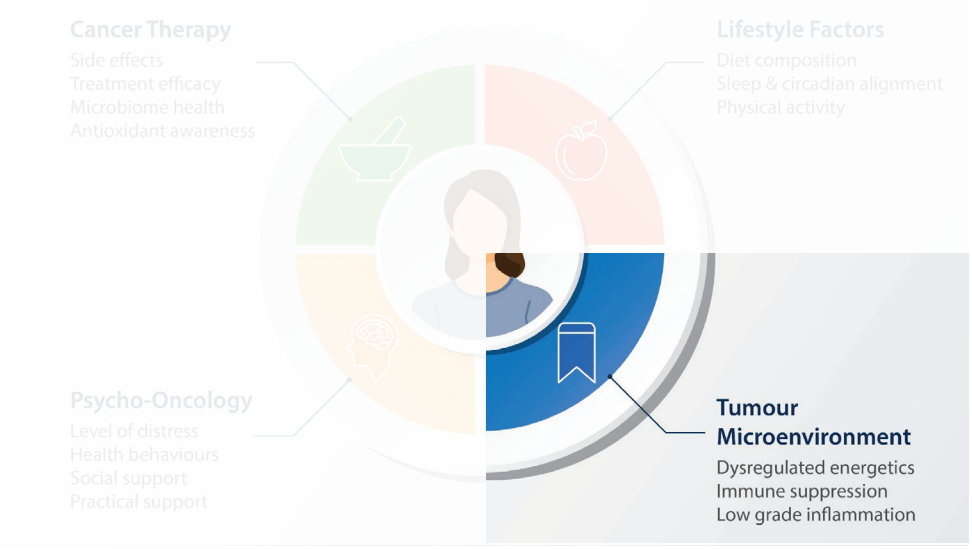


INTEGRATIVE ONCOLOGY

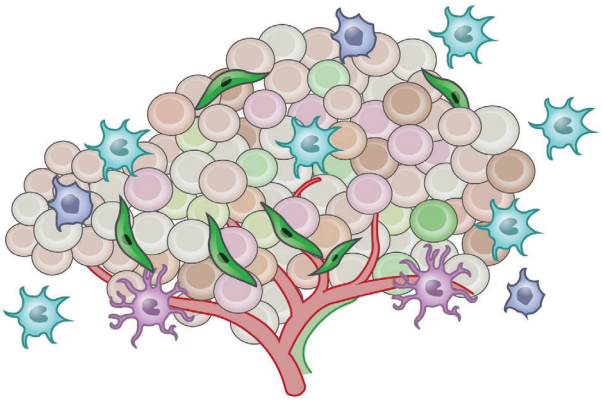


TUMOUR MICROENVIRONMENT AND THE HALLMARKS OF CANCER

Tumour Microenvironment

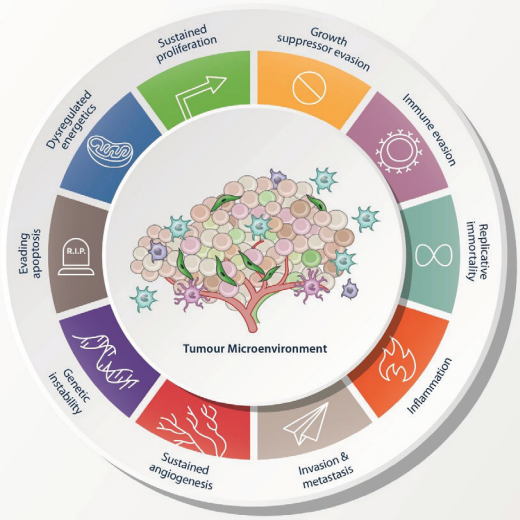


The Tumour Microenvironment

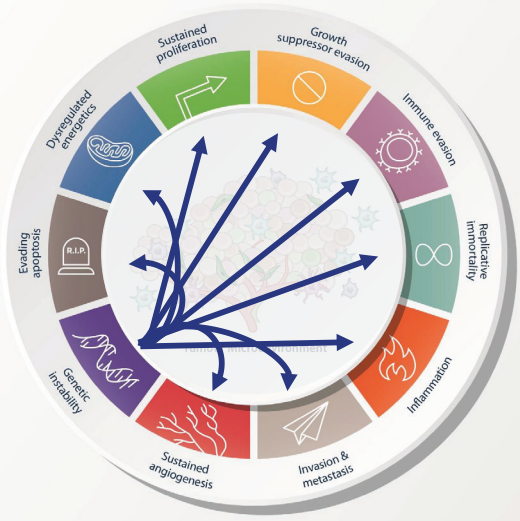


TUMOUR MICROENVIRONMENT AND THE HALLMARKS OF CANCER

Hallmarks of Cancer



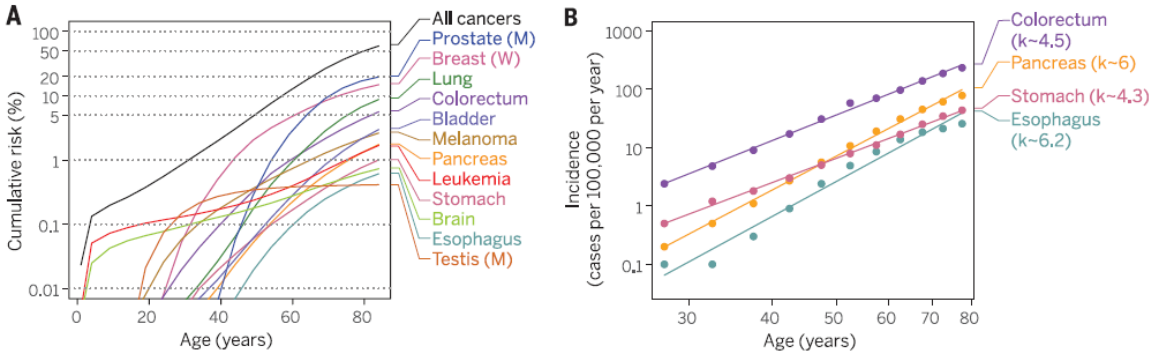
Genomic Instability Enables Cancer Hallmarks



Yang L, et al. Semin Cancer Biol. 2017 Dec;47:185-195. doi: 10.1016/j.semcancer.2017.08.001.

TUMOUR MICROENVIRONMENT AND THE HALLMARKS OF CANCER

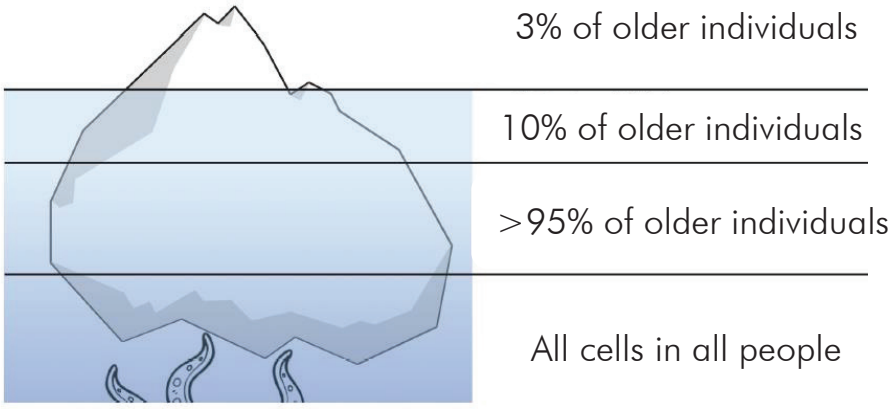
Age is the Biggest Risk Factor



"Cancer is virtually inevitable in complex, long-lived, multicellular organisms"

Martincorena I, et al. Science. 2015 Sep 25;349(6255):1483-9. doi: 10.1126/science.aab4082.

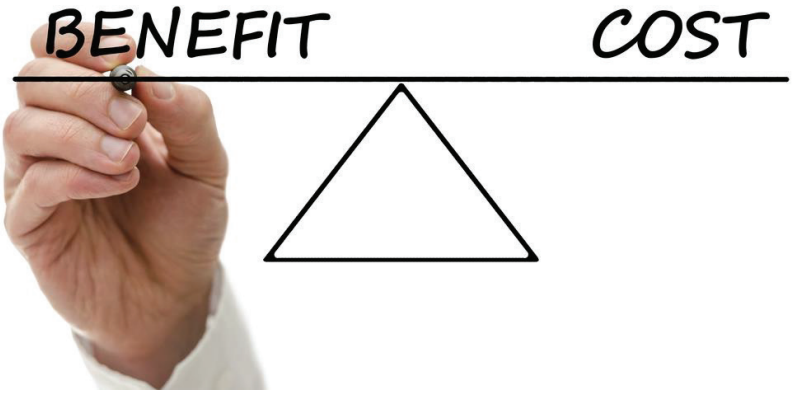
We Are All Mutants



Risques RA, et al. PLoS Genet. 2018 Jan 4;14(1):e1007108. doi: 10.1371/journal.pgen.1007108.

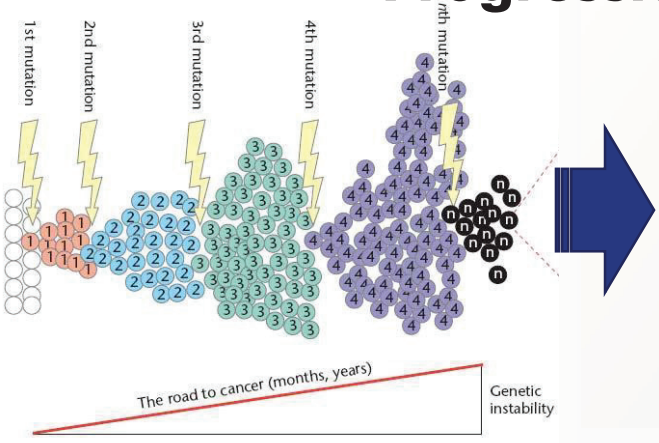
TUMOUR MICROENVIRONMENT AND THE HALLMARKS OF CANCER

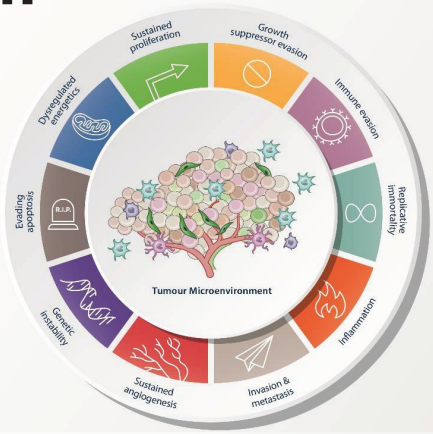
The Benefit vs Cost of DNA Repair



Nik-Zainal S, et al. Science. 2019 Nov 15;366(6467):802-803. doi: 10.1126/science.aax8046.

Genetic Instability Enables Tumour Progression



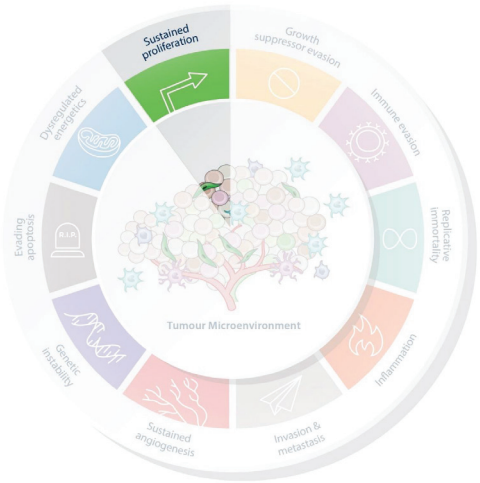


Sarah.ip. Overview of the road to cancer [Image on Internet]. Available from: https://wiki.cancer.org.au/oncologyformedicalstudents/File:Overview_of_the_road_to_cancer.jpg

ONCOGENES

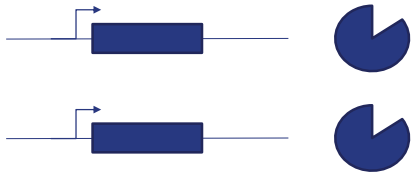
Oncogenes

- Originate from proto-oncogenes which promote cell cycle
- Gain of function mutation
- E.g. RAS, C-MYC



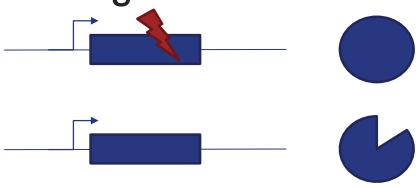
Missense Mutation

Proto-oncogene



Missense mutation

Oncogene

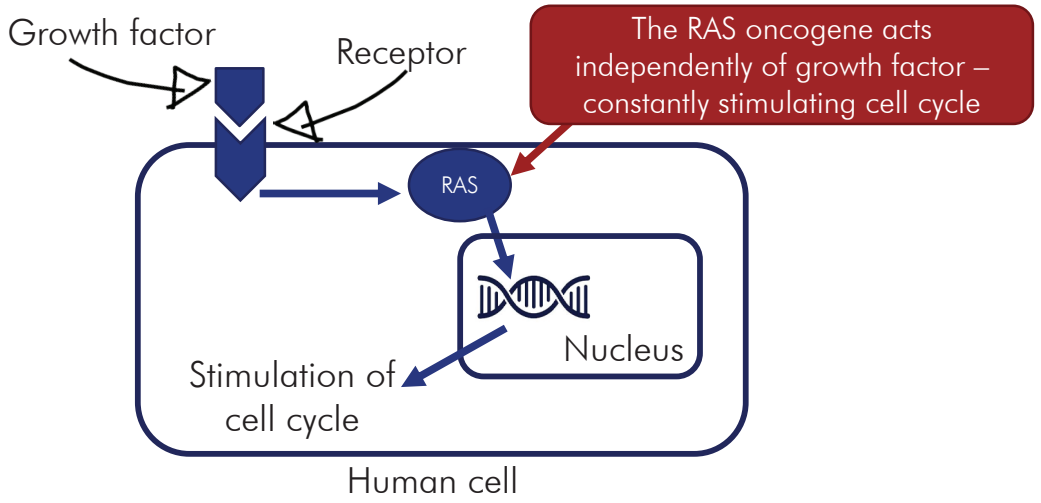


Produces a protein that is active only with stimulus

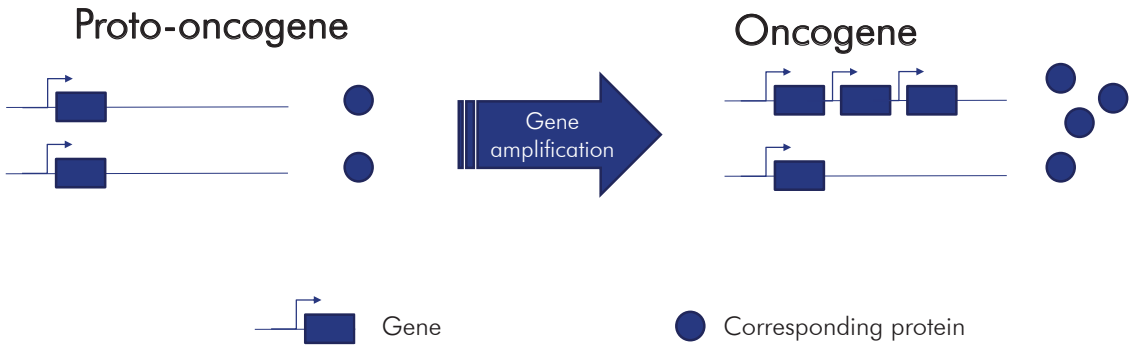
Produces a protein that is *always* active
Will drive cell proliferation with one mutation

ONCOGENES

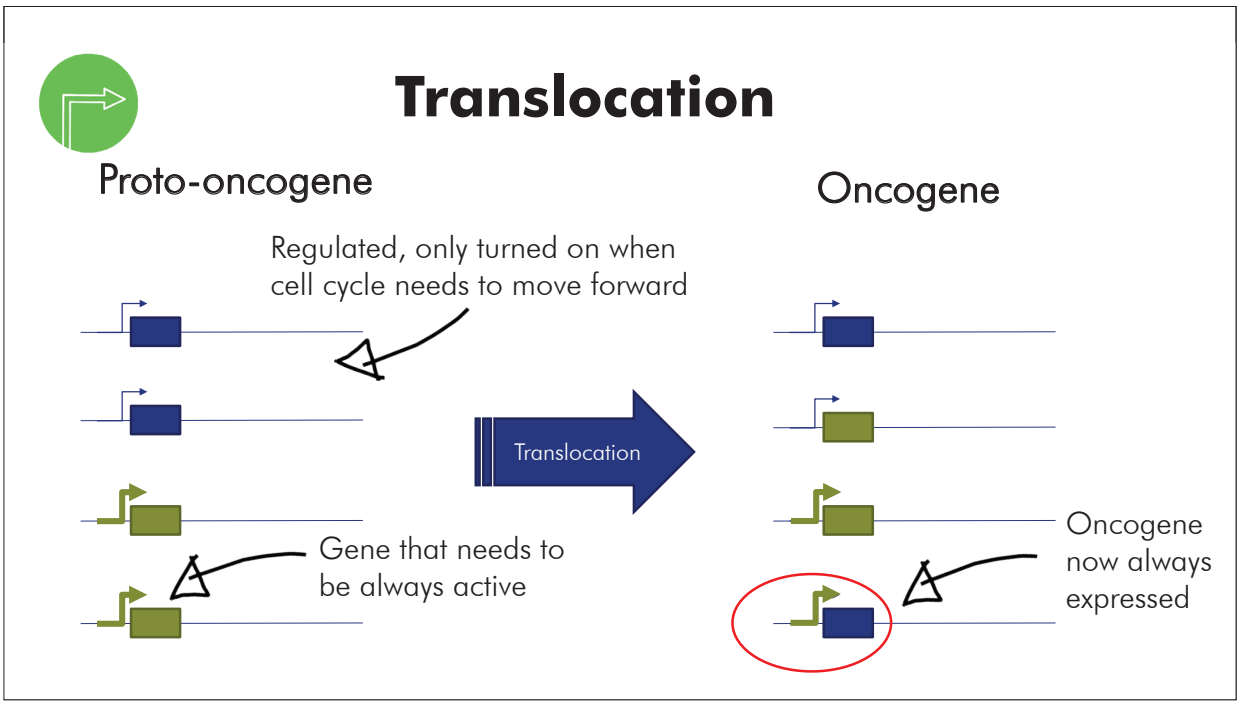
Missense Mutation: RAS

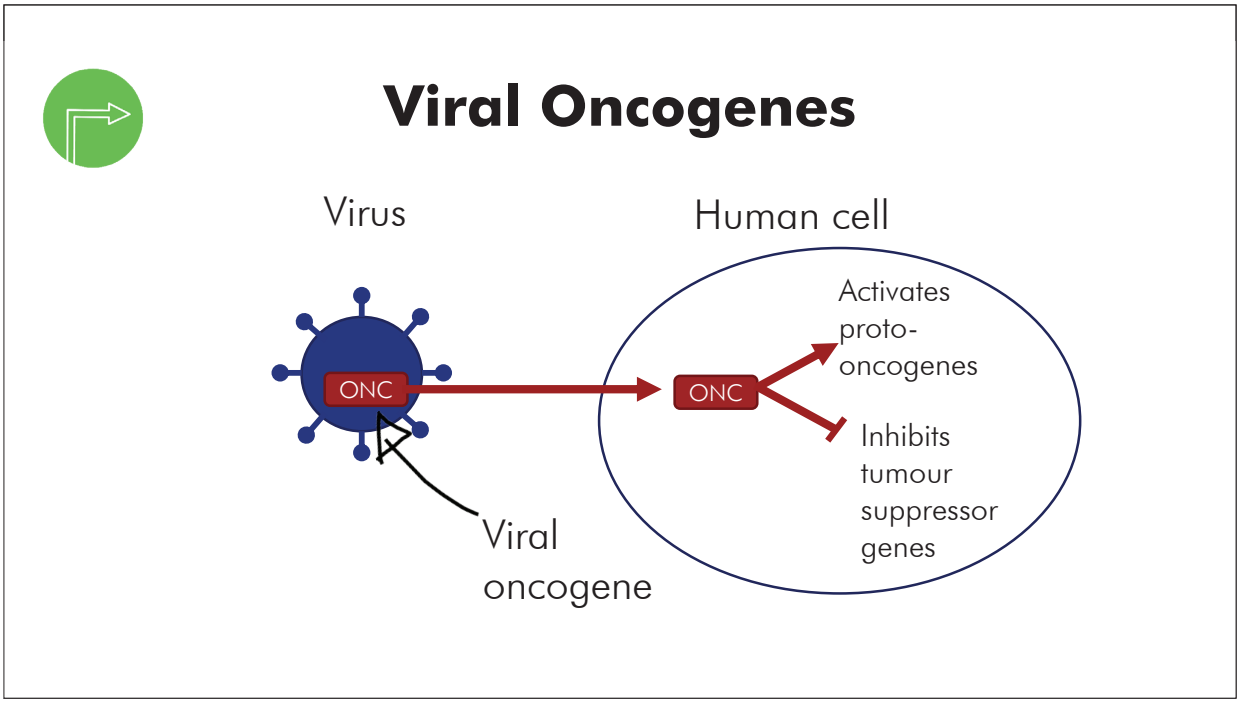


Gene Amplification



ONCOGENES

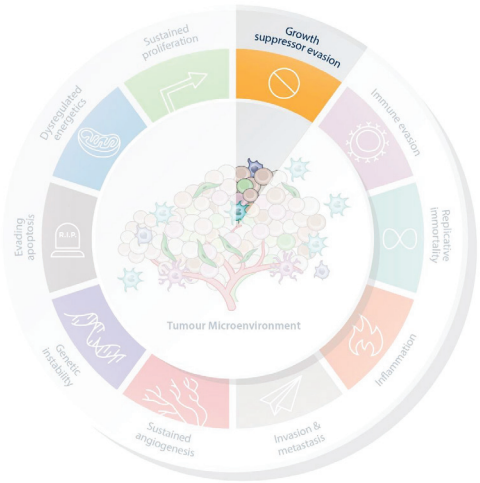

Translocation
Proto-oncogene
Oncogene
Regulated, only turned on when cell cycle needs to move forward
Translocation
Gene that needs to be always active
Oncogene now always expressed


Viral Oncogenes
Virus
Human cell
ONC
ONC
Activates proto-oncogenes
Inhibits tumour suppressor genes
Viral oncogene

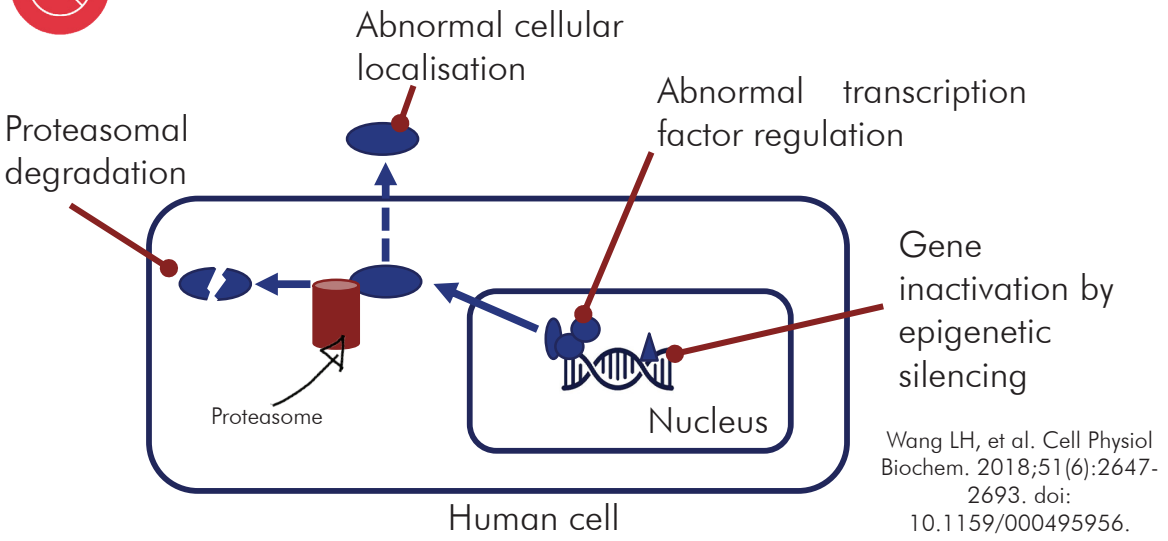
TUMOUR SUPPRESSOR GENES

Tumour suppressor genes

- Originate from genes that slow down cell cycle
- **Loss of function mutation**
- E.g. TP53, BRAC1&2, pRb



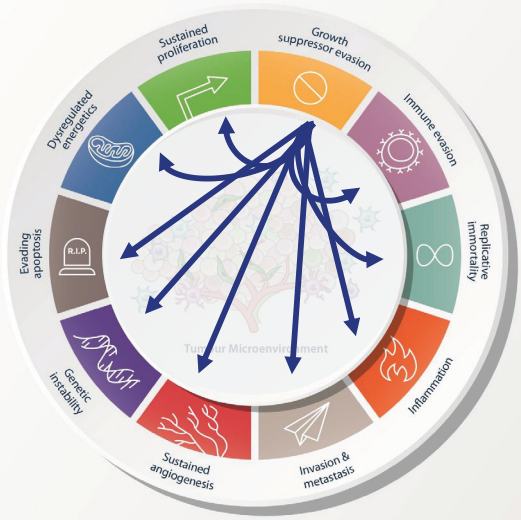
Loss of Function Beyond Mutation



Wang LH, et al. Cell Physiol Biochem. 2018;51(6):2647-2693. doi: 10.1159/000495956.

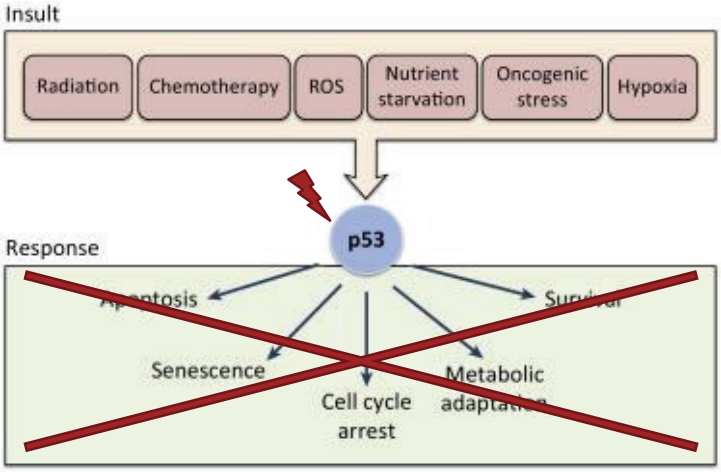
TUMOUR SUPPRESSOR GENES

Growth Suppressor Evasion Drives Cancer Hallmarks



Yang L, et al. Semin Cancer Biol. 2017 Dec;47:185-195. doi: 10.1016/j.semcancer.2017.08.001.

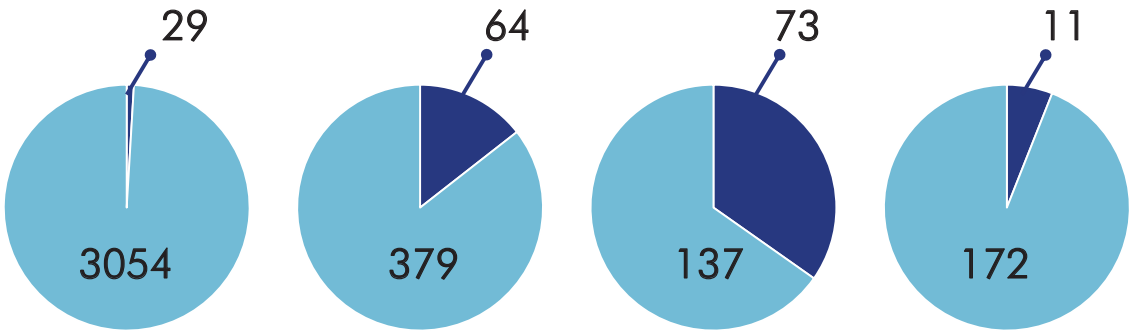
p53 the Guardian of the Genome



Gurpinar E, et al. Trends Cell Biol. 2015 Aug;25(8):486-95. doi: 10.1016/j.tcb.2015.04.001.

TUMOUR SUPPRESSOR GENES

Cancers With No Genetic Mutations



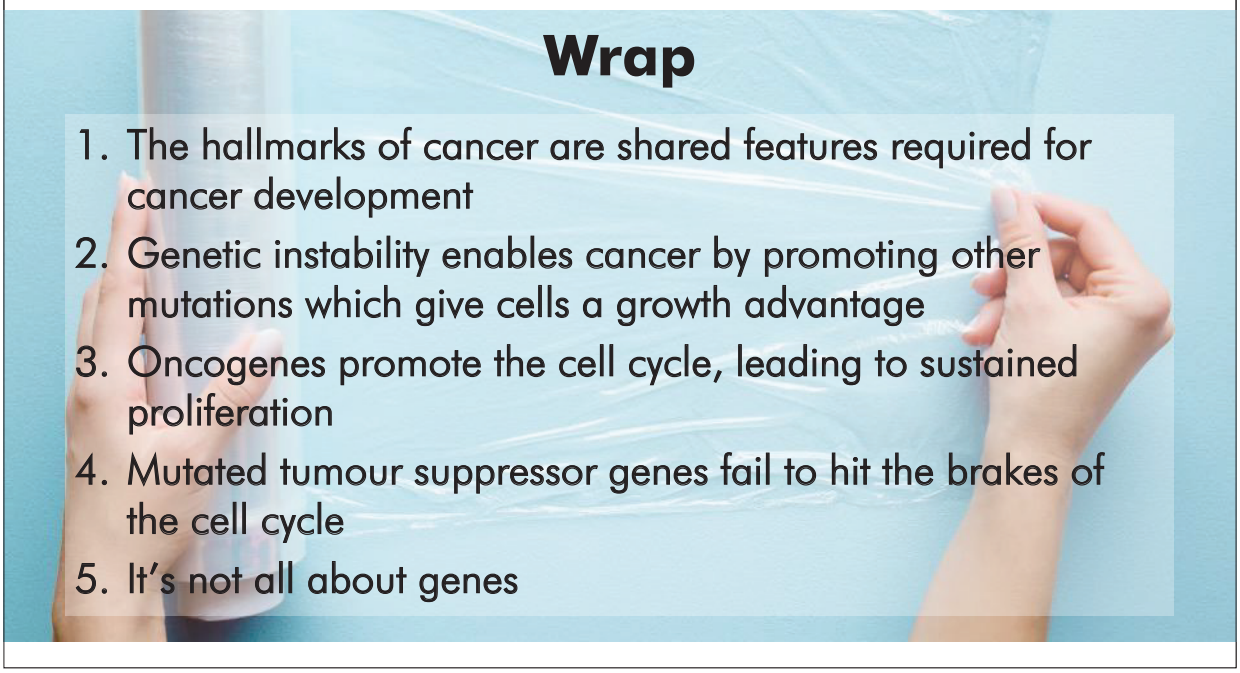
Baker SG. J Natl Cancer Inst. 2014 Dec 20;107(2). pii: dju405. doi: 10.1093/jnci/dju405.

Maybe it's *Not* in Your Genes...

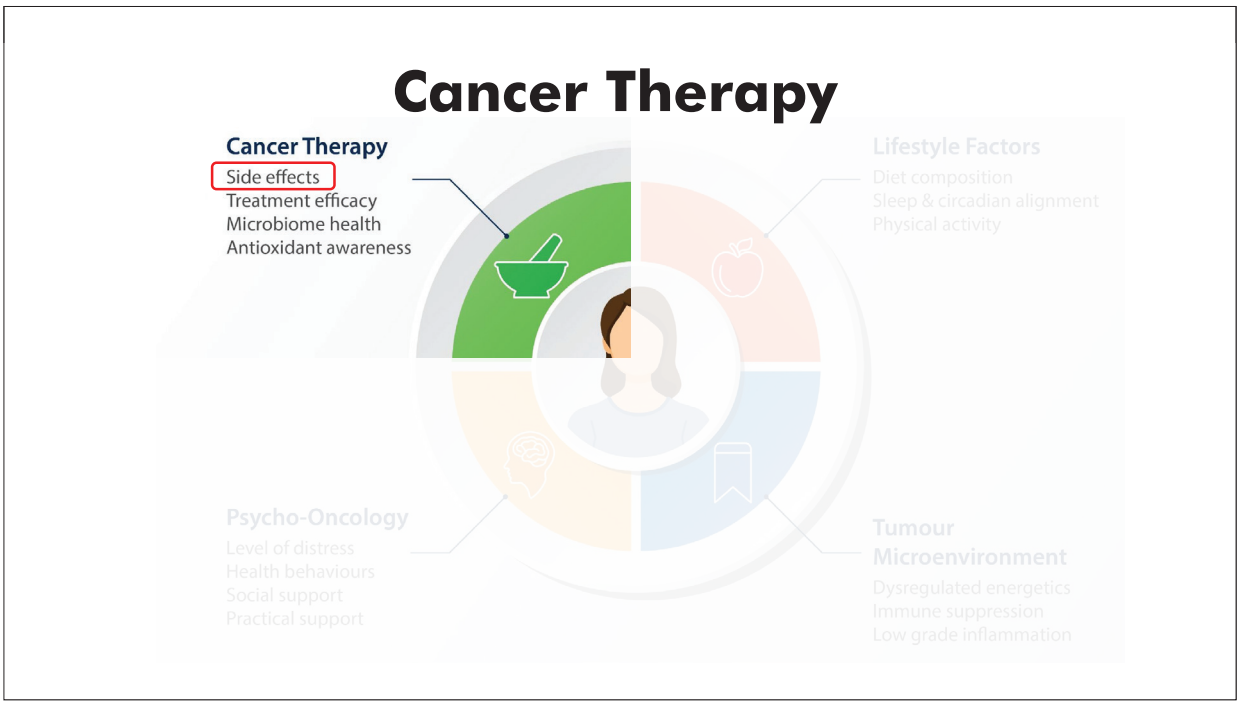
	Somatic mutation theory	Tissue organisation theory
Summary	Genetic disease Focus on cancer cell	Development gone awry Focus on tissue interactions
Mutations	Causative	Epiphenomenon
Adjacent tissue	Supporting role	Key role
Location relative to exposure	Cancer can only arise in tissue exposed to carcinogen	Cancer can arise in tissue not exposed to carcinogen

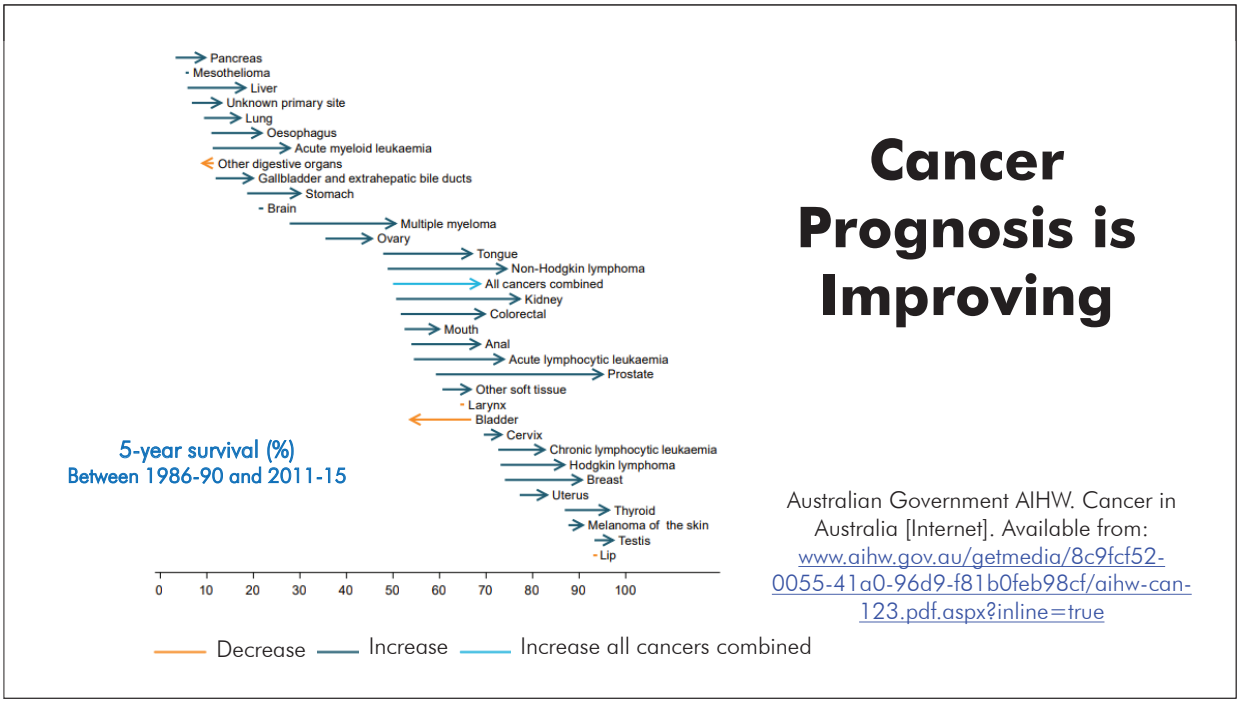
Baker SG. J Natl Cancer Inst. 2014 Dec 20;107(2). pii: dju405. doi: 10.1093/jnci/dju405.

TUMOUR SUPPRESSOR GENES



CANCER THERAPY MECHANISMS AND SIDE EFFECTS



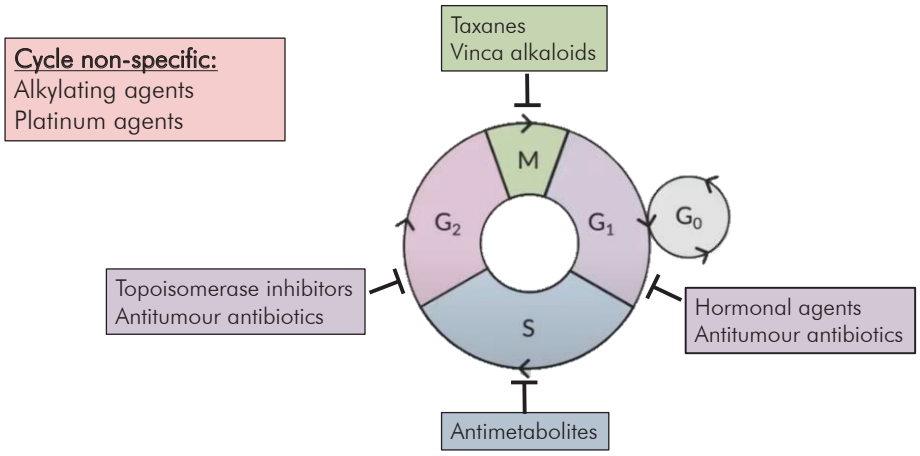


Cancer Prognosis is Improving

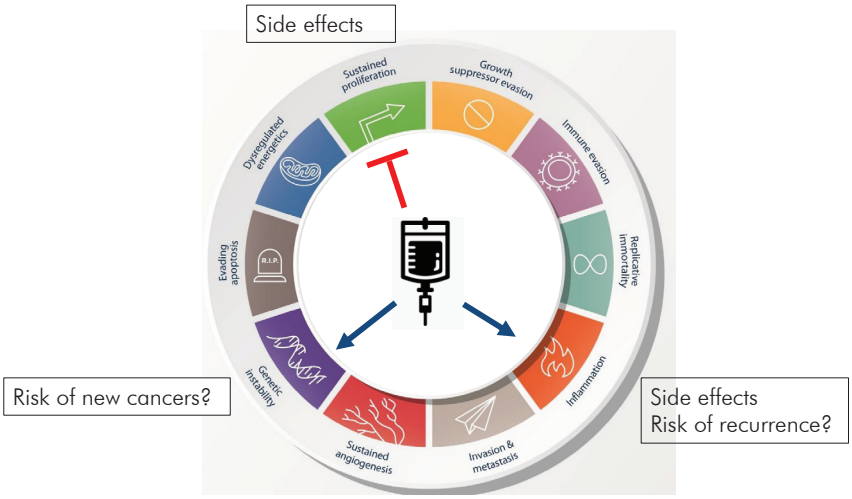
Australian Government AIHW. Cancer in Australia [Internet]. Available from: www.aihw.gov.au/getmedia/8c9fcf52-0055-41a0-96d9-f81b0feb98cf/aihw-can-123.pdf.aspx?inline=true

CANCER THERAPY MECHANISMS AND SIDE EFFECTS

Chemotherapeutics Inhibit the Cell Cycle



Chemotherapy side effects



CANCER THERAPY MECHANISMS AND SIDE EFFECTS

CHEMOTHERAPY SIDE EFFECTS

CHEMOTHERAPY IS A SYSTEMIC THERAPY

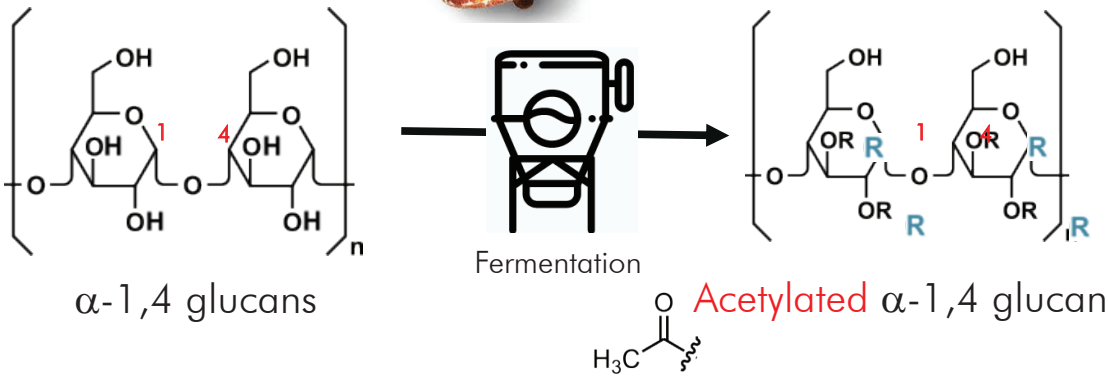
meaning that the drugs travel in the bloodstream throughout the entire body

AHCC™ AND GINGER

What is AHCC™?

Shiitake *(Lentinula edodes)*

AHCC™
Active Hexose Correlated Compound



α-1,4 glucans

Acetylated α-1,4 glucans

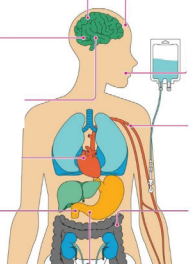
AHCC™ and Cancer Summary

- Improves survival rate in cancer patients both as single treatment and alongside chemotherapy.
  - Improved survival time by average of 9 months longer in conjunction with chemo compared with chemo only.
- Enhances chemotherapy efficacy:
  - Tumor regression experienced by 44% of advanced cancer patients combining AHCC and chemo. 32% of patients had reduced disease progression.

AHCC™ AND GINGER

AHCC™ and Ginger Reduces Chemotherapy Side Effects

↓Fatigue
↓ Stress and anxiety
↓ Nausea and vomiting



↑ Quality of life
↑ Appetite
↓ Neutropenia
↓ Hepatotoxicity

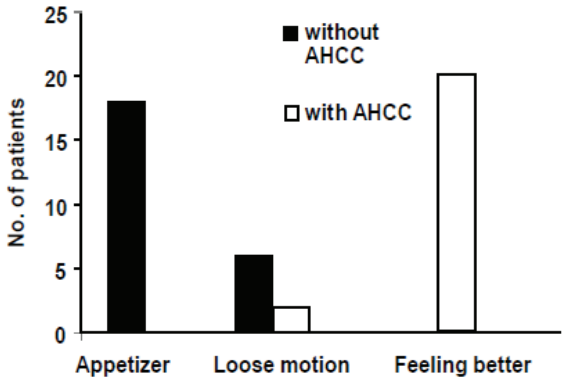
AHCC™ Improves QOL Post Cancer Treatment

	Without AHCC	With AHCC
Confinement to bed	14 - 16 hr/day	8 - 10 h/d
Talking to people	not	yes
Sleep pattern	irregular	regular
Required antiemetic for Chemo related Nausea/vomiting	7 - 14 Days	3 - 5 Days

Parida DK. Int J Clin Med. 2011 Nov 1;2(588-592):20. doi:10.4236/ijcm.2011.25097.

AHCC™ AND GINGER

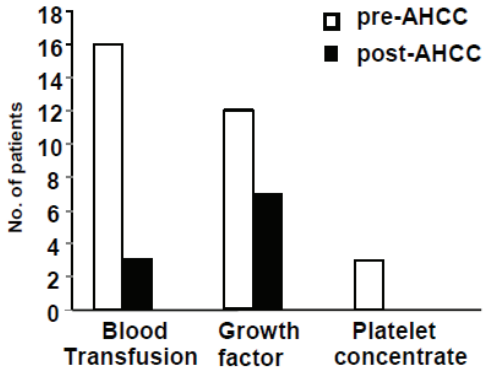
AHCC™ Supports Appetite During Cancer Treatment



The requirement for an anti-emetic dropped from 7-14 days pre AHCC™ treatment to 3-5 days post AHCC™ treatment.

Parida DK. Int J Clin Med. 2011 Nov 1;2(588-592):20. doi:10.4236/ijcm.2011.25097.

AHCC™ Improves Hematological Parameters



Treatment with AHCC™ lowered the need for blood transfusions by 81%.

Parida DK. Int J Clin Med. 2011 Nov 1;2(588-592):20. doi:10.4236/ijcm.2011.25097.

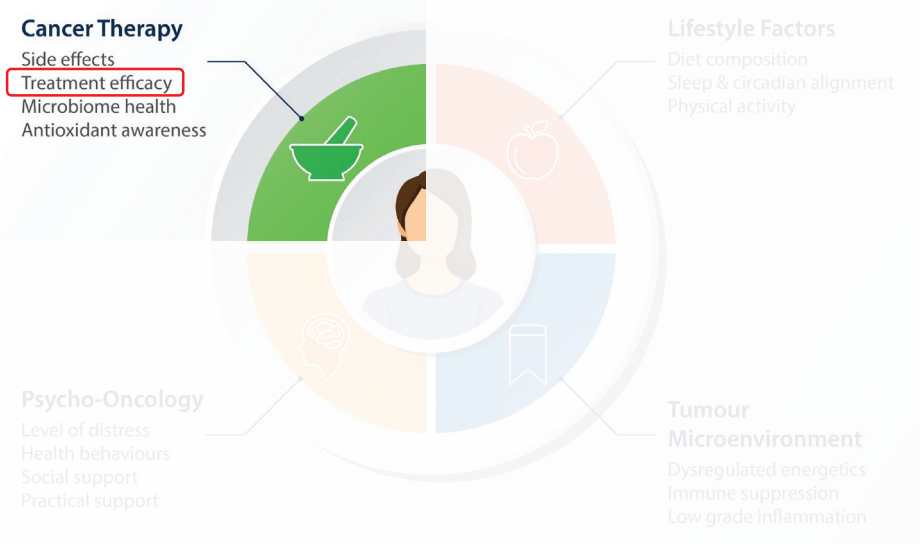
AHCC™ AND GINGER

Ginger Helps Chemotherapy Nausea and Fatigue

Adjuvant ginger supplementation with 60 mg per day of gingerols is associated with better chemotherapy-induced nausea-related quality of life and less cancer-related fatigue.

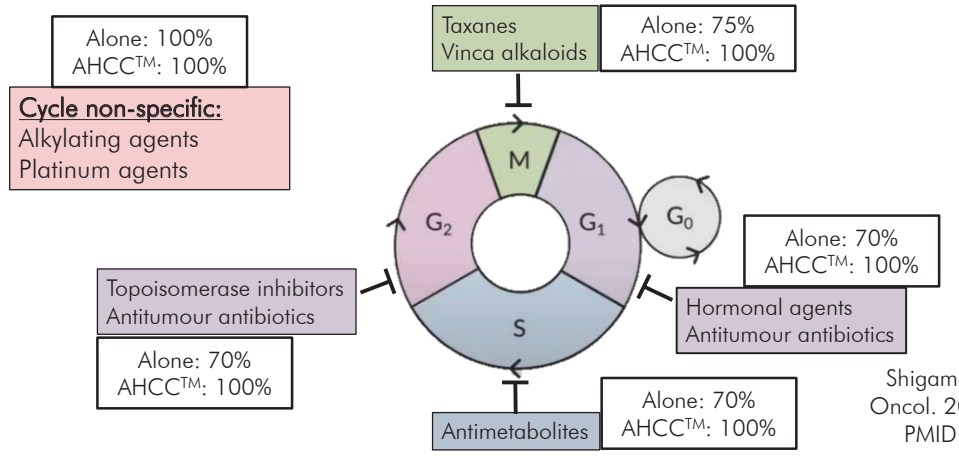
Marx W. Nutrients. 2017 Aug;9(8). pii: E867. doi: 10.3390/nu9080867.

Cancer Therapy



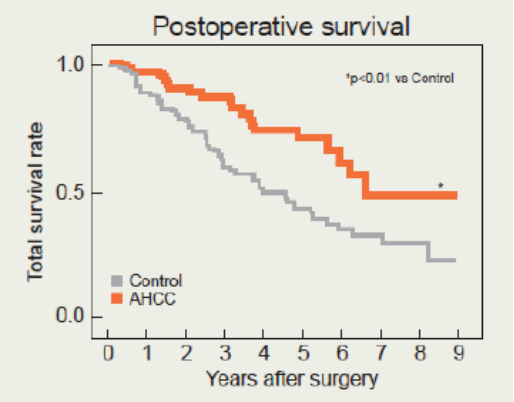
AHCC™ AND GINGER

Chemotherapeutics Inhibit the Cell Cycle



Shigama K. J Exp Ther Oncol. 2009;8(1):43-51. PMID: 19827270.

AHCC™ Improves Survival in Liver Cancer Patients



Compared to the control group, the AHCC™ group achieved:

- Lower recurrence of malignancy.
- 50% less deaths.
- Average life span extended by nine months.

Matsui Y. J Hepatol. 2002 Jul;37(1):78-86. PMID: 12076865.

AHCC™ AND GINGER

AHCC™ Improves Survival in GI Cancer Patients

Survival % for Gastric Cancer

	AHCC Study	Japanese Gastric Cancer Association	Other Japanese Institutions
Stage IA	100 %	93.4 %	91.5 – 93.4 %
Stage IB	100 %	87.0 %	85.5 – 88.7 %
Stage II	92.3 %	68.3 %	74.9 – 75.9 %
Stage IIIA	82.8 %	50.1 %	53.6 – 61.7 %
Stage IIIB	35.7 %	30.8 %	40.4 – 42.4 %
Stage IV	14.3 %	16.6 %	Stage IVA: 14.3 – 19.7 % Stage IVB: 4 %

Survival % for Colon Cancer

	AHCC Study	Other Japanese Institutions
Stage 0	100 %	100 %
Stage I	100 %	93 – 100 %
Stage II	100 %	81 – 88 %
Stage IIIA	95.2 %	73 – 76 %
Stage IIIB	73.3 %	63 – 78 %
Stage IV	7.1 %	0 – 17 %

Kawaguchi Y. Improved survival of patients with gastric cancer or colon cancer when treated with active hexose correlated compound (AHCC): effect of AHCC on digestive system cancer. Nat Med J. 2009;1(1):1-6.

AHCC™ and Ginger

Key Actions:

- Immune enhancement, surveillance and modulation
- Gastrointestinal support
- Anti-inflammatory
- Anti-emetic
- Autonomic nervous system modulation

Clinical Applications:

- Cancer support
  - Improves survival rate, enhances chemotherapy efficacy
  - Reduce anticancer drug treatment side effects
- Chronic and critical infections

CASE STUDY: LOBULAR BREAST CANCER

Case Study: GC – Stage IV Lobular Breast Cancer

- 61 year old female with stage IV (metastatic) lobular breast cancer.
- Inoperable metastasis affecting bowel; has had surgery (stent) to prevent obstruction.
- Referred from naturopath for intravenous (IV) nutritional support.

Symptoms

- Underweight: 41.0 kg
- Nausea and poor appetite
- Lack of energy and fatigue

PROFESSIONAL INTEGRATIVE MEDICINE

Case kindly provided by Dr Timothy Hall, Clinic: Professional Integrative Medicine. Cumberland Park, SA

GC – Medications and Supplements

Medication

- Chemotherapy (Doxorubicin IV once per week)

Current supplements

- CoQ10 100 mg per day
- R-lipoic acid 200 mg per day
- Nutrient and herbal formulation to support phase II liver detox
- Calcium ascorbate (oral) 2-5 g per day
- Fish oil 1000 mg per day
- Vitamin D3/K2 spray once per day
- Vitamin D3 5000IU per day

CASE STUDY: LOBULAR BREAST CANCER

Case Study: GC – Screening and Initial Prescription

Screening
- Patient Reported Outcome Measurement Information System (PROMIS)

Initial score: 25

Prescription (added to supplements)
- IV vitamin C 30 grams, once every two weeks
- *AHCC™ and Ginger* – 2 capsules twice daily

Case Study: GC – Results

Initial first week
- Patient hospitalised with abdominal pain and bloating – *AHCC™ and Ginger* discontinued.
- Investigations revealed abdominal pain was attributed to chemotherapy and intestinal stent.
- Patient recommenced *AHCC™ and Ginger.*

8 weeks
- Decreased Cancer antigen 15-3: Dec 2019 (873) to Jan 2020 (655)

12 weeks
- PROMIS questionnaire: reduced nausea and vomiting.

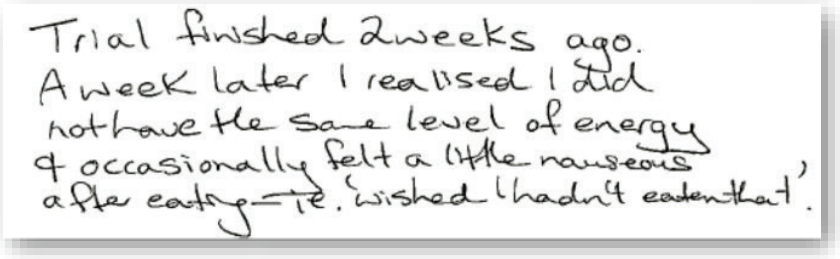
"The Metagenics supplement has stopped me from vomiting"

CASE STUDY: LOBULAR BREAST CANCER

Case Study: GC – Results

14 weeks:

- Patient report after *AHCC™ and Ginger* trial:


Trial finished 2 weeks ago.
A week later I realised I did
not have the same level of energy
& occasionally felt a little nauseous
after eating – I'd 'wished I hadn't eaten that'.

- Continues *AHCC™ and Ginger* for ongoing support.
- Elevated liver enzymes, cause not determined.

Case Study: GC – Update

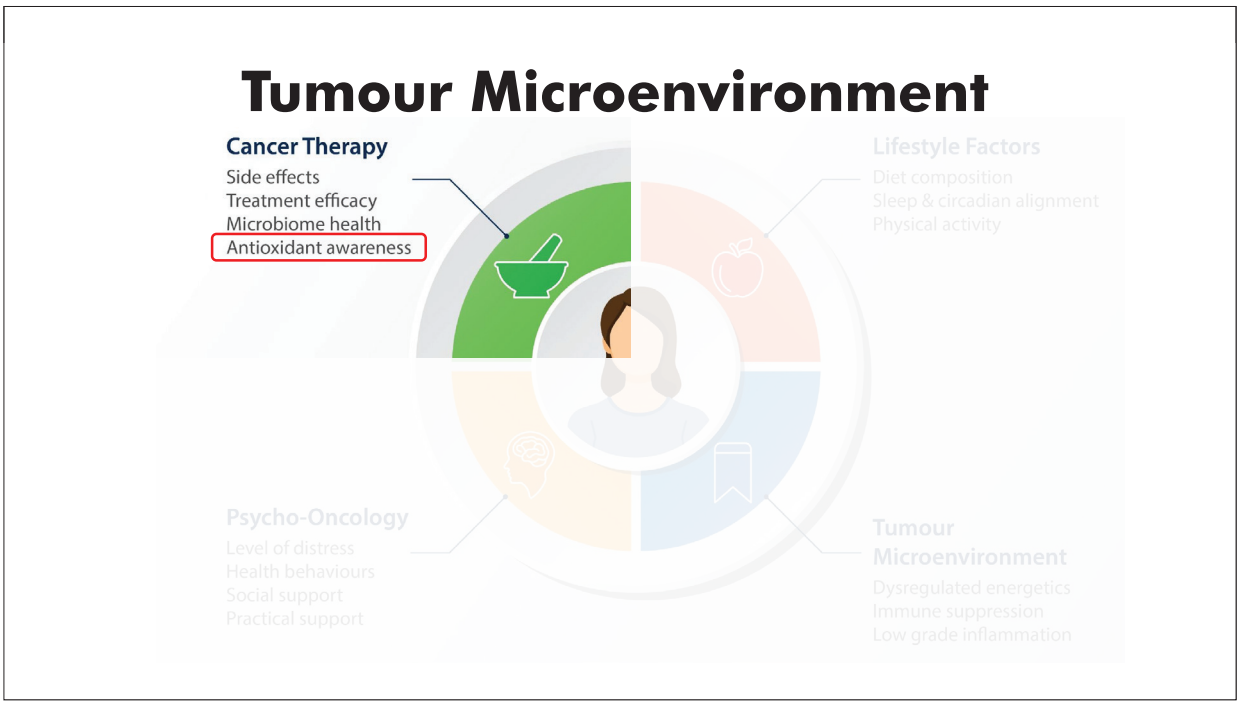
18 weeks

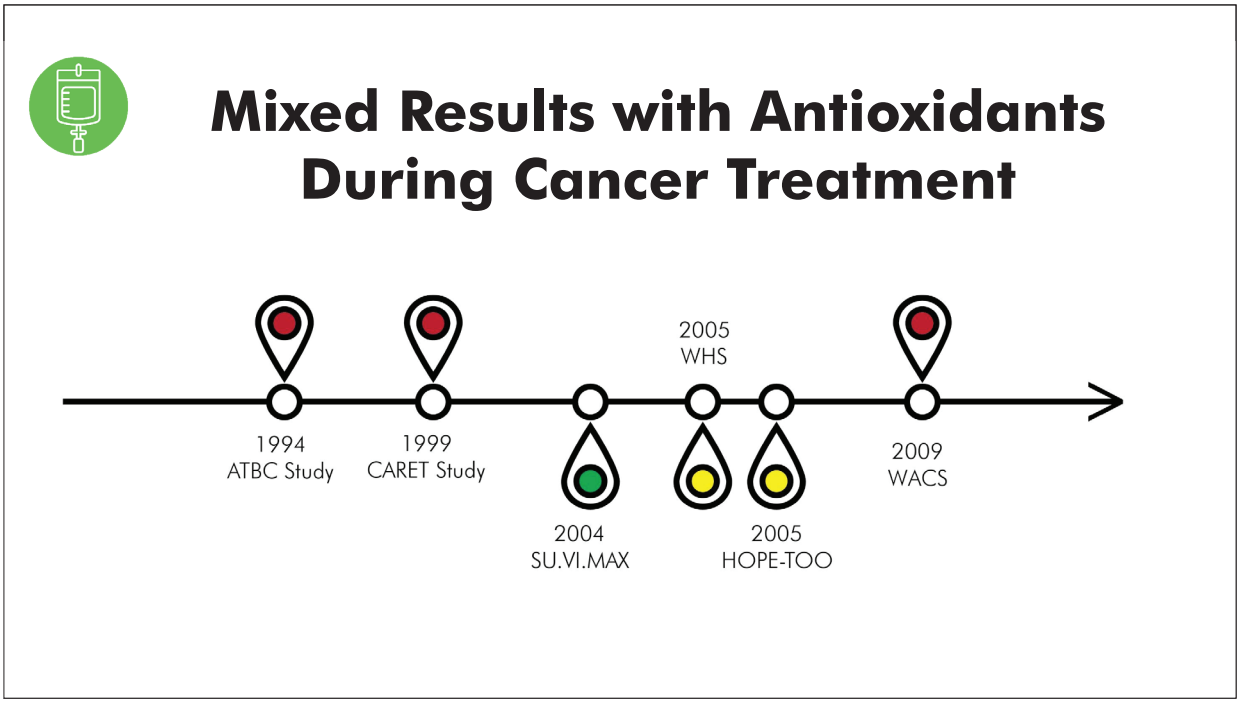
- Patient reports significantly improved energy and less nausea after recommencing *AHCC™ and Ginger*.
- Continues *AHCC™ and Ginger* for ongoing support.

Marker	Dec 2019	8 weeks	14 weeks	18 weeks	Ref Range
Alanine transferase (ALT) (U/L)	431	288	–	–	7–55
Aspartate transferase (ALP) (U/L)	71	55	349	266	6-34
Gamma glutamyl transferase (GGT) (U/L)	826	497	649	393	9–48
PROMIS Score	25	–	–	16	

Case kindly provided by Dr Timothy Hall, Clinic: Professional Integrative Medicine. Cumberland Park, SA

ANTIOXIDANT AWARENESS

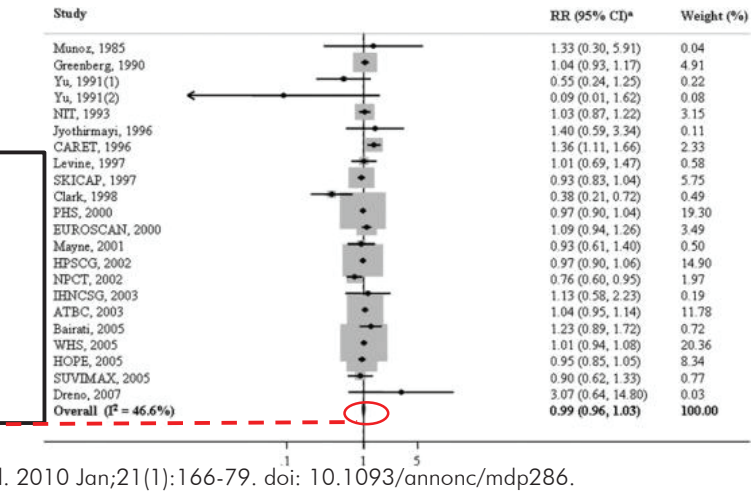




ANTIOXIDANT AWARENESS

Antioxidants Fail to *Prevent* Cancer

Supplements:
- Vitamin A
- Vitamin C
- Vitamin E
- Beta-carotene
- Selenium



Myung SK, et al. Ann Oncol. 2010 Jan;21(1):166-79. doi: 10.1093/annonc/mdp286.

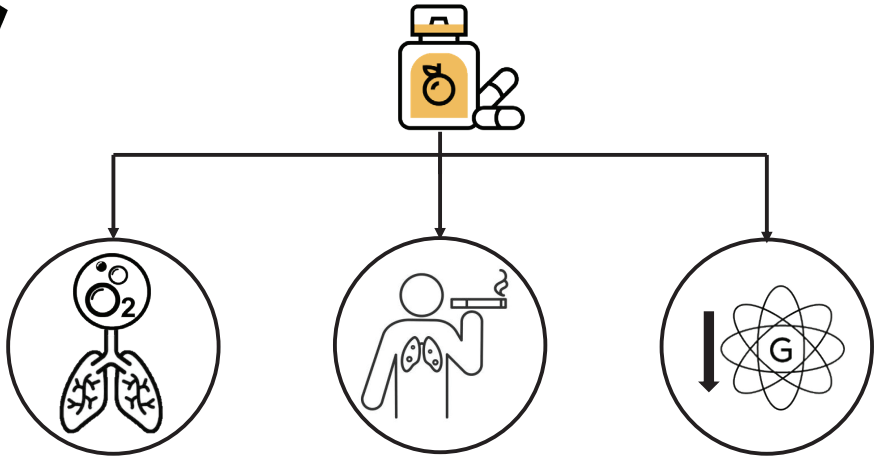
Antioxidants and Cancer

- May protect cellular structure and DNA
- May off-set side effects of chemotherapy and radiation
- No clear evidence of therapeutic efficiency

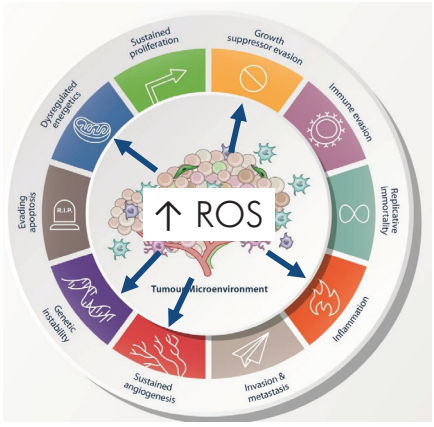
- May influence the efficiency of treatment
- May repair damage to cancer cells and inhibit apoptosis
- May influence long term remission / survival

ANTIOXIDANT AWARENESS

Mechanisms of Beta-Carotene



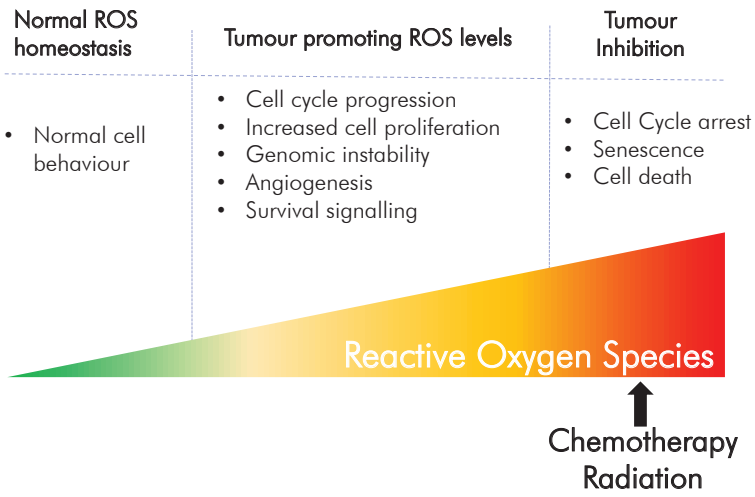
Cancer Cells Generate Oxidation for Survival



Kumari S, et al. Biomark Insights. 2018 Feb 6;13:1177271918755391. doi: 10.1177/1177271918755391.

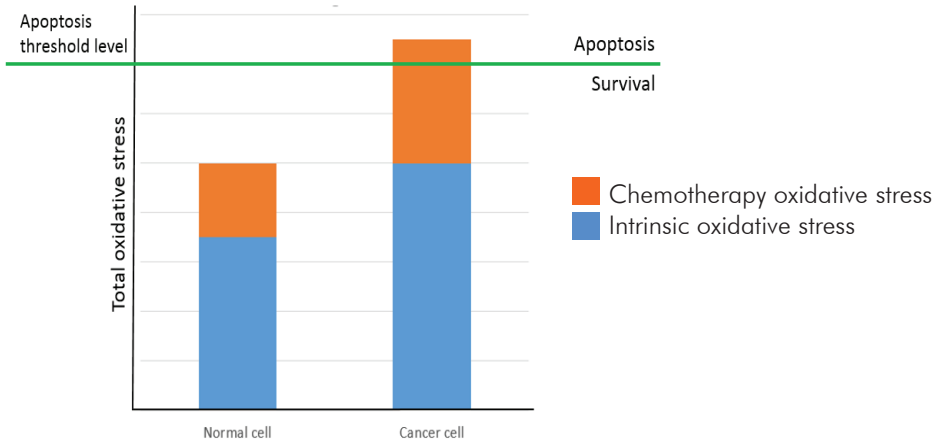
ANTIOXIDANT AWARENESS

Oxidative Stress and Cancer Cell Survival



Liou GY, et al. Free Radic Res. 2010 May;44(5):479-96. doi: 10.3109/10715761003667554.

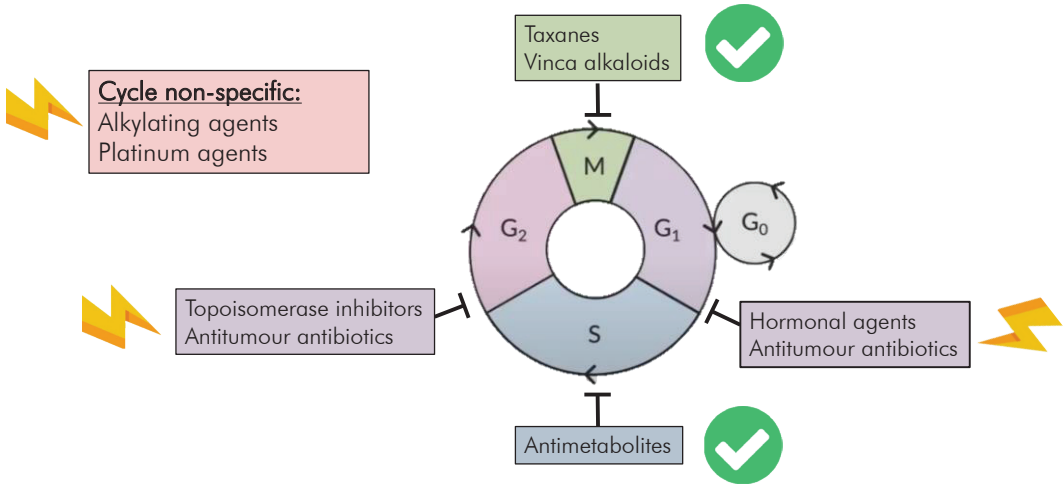
Oxidative Stress as Therapy



Stone WL, et al. World J Gastrointest Oncol. 2014 Mar 15;6(3):55-66. doi: 10.4251/wjgo.v6.i3.55.

ANTIOXIDANT AWARENESS

Chemotherapy and Oxidative Stress



Uncertainty About Antioxidants *During* Chemotherapy

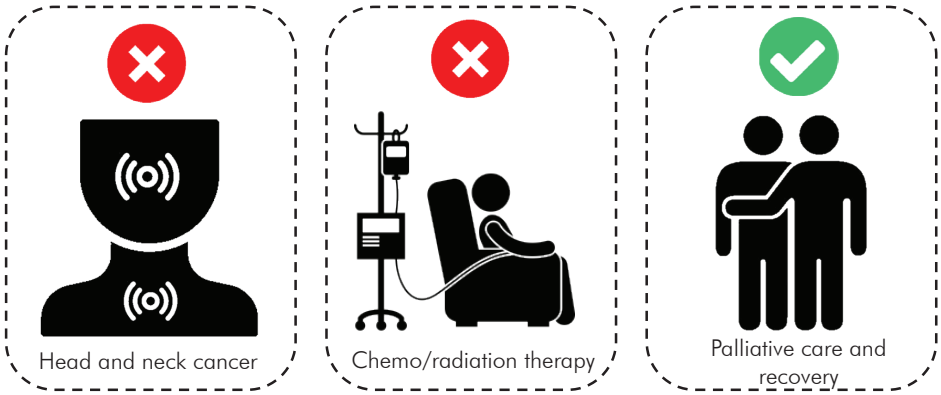
49 RCTs investigated:

"It was difficult to determine whether antioxidants affect treatment outcomes or whether antioxidants ameliorate adverse effects induced by chemotherapy and radiotherapy"

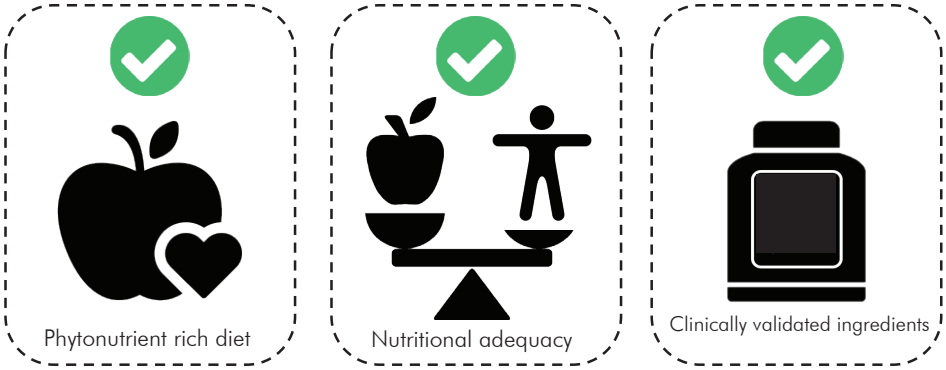
Yasueda A, et al. Integr Cancer Ther. 2016 Mar;15(1):17-39. doi: 10.1177/1534735415610427.

ANTIOXIDANT AWARENESS

Antioxidant Awareness - First do no Harm



Antioxidant Awareness - Alternatives



ANTIOXIDANT AWARENESS

High Absorption Multi Mineral with Apple Cider Vinegar

- Calcium phosphate dihydrate
- Potassium citrate
- Meta Mag® - Magnesium bisglycinate
- Meta Fe® - Iron bisglycinate
- Meta Zn® - Zinc bisglycinate
- Manganese
- Boron
- Iodine
- Molybdenum
- Selenium
- Chromium

Road to Recovery Smoothie

Undenatured Whey Protein Isolate

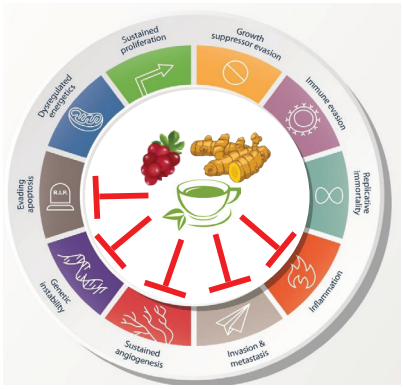
– Anabolic muscle growth

High Absorption Multi Mineral with Apple Cider Vinegar

– Bioavailable minerals to support immune system function, musculoskeletal strength and metabolic health.

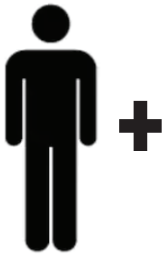
ANTIOXIDANT AWARENESS

Anti-Cancer Properties of Green Tea, Resveratrol and Curcumin



Abrams DI, Weil AT. Integrative Oncology. 2nd ed. New York: Oxford University Press; 2014. p.169-175.

4-8 g/day of Curcumin Reduces Myeloma Progression



+

4-8 g/d

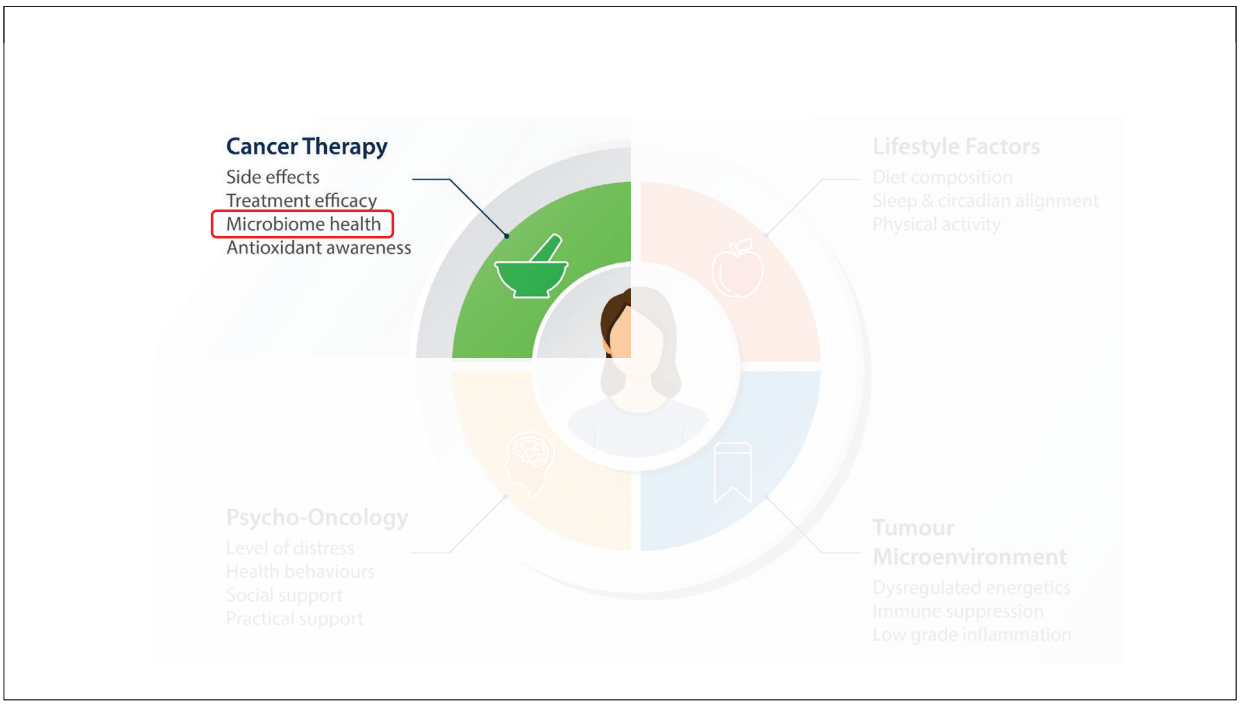
3-9 yrs

1 participant developed progressive myeloma

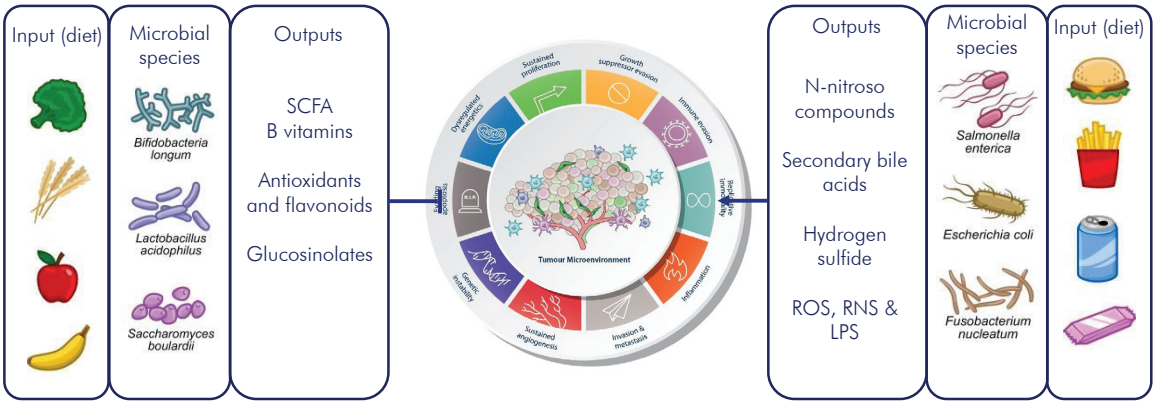
12 participants status remained stable

Golombick T. Hematol Med Oncol. 2017 Apr 29;2(2):1-2. doi: 10.15761/HMO.1000125.

MICROBIOME HEALTH



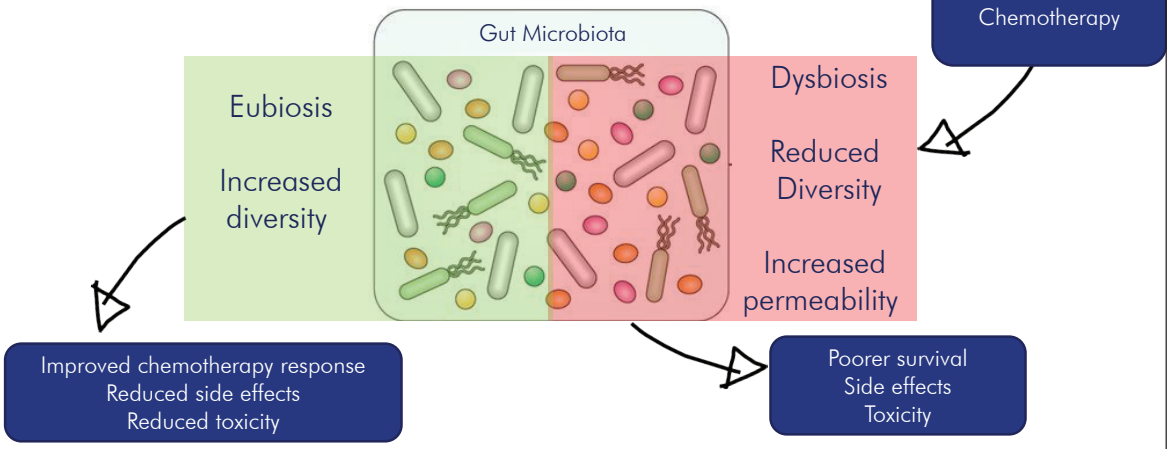
Microbiome and Cancer Risk



Whisner CM, et al. Curr Nutr Rep. 2019 Mar;8(1):42-51. doi: 10.1007/s13668-019-0257-2.

MICROBIOME HEALTH

Microbiome Health Associated with Better Outcomes



LGG® Reduces Chemotherapy Side Effects

Reduced abdominal discomfort and diarrhoea

Fewer chemotherapy dose reductions

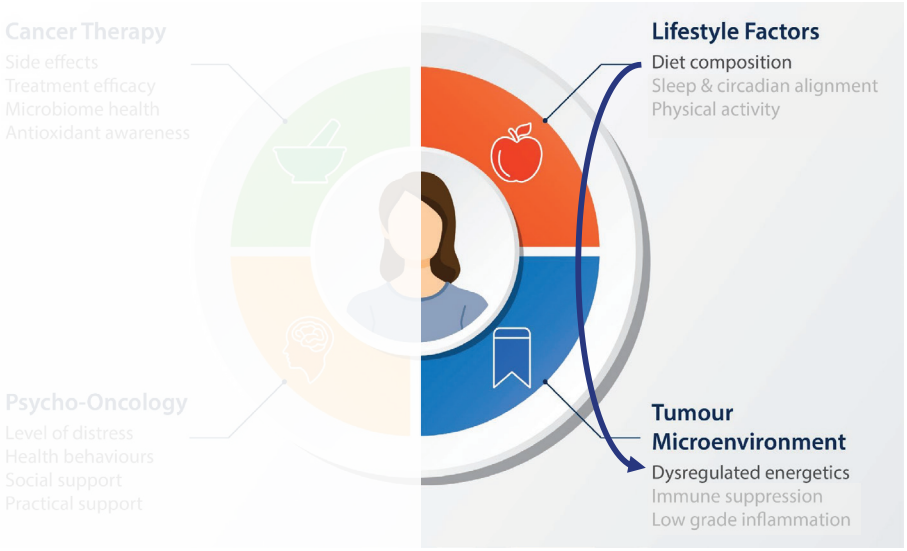
Osterlund P, et al. Br J Cancer. 2007 Oct 22;97(8):1028-34. doi: 10.1038/sj.bjc.6603990.

MICROBIOME HEALTH

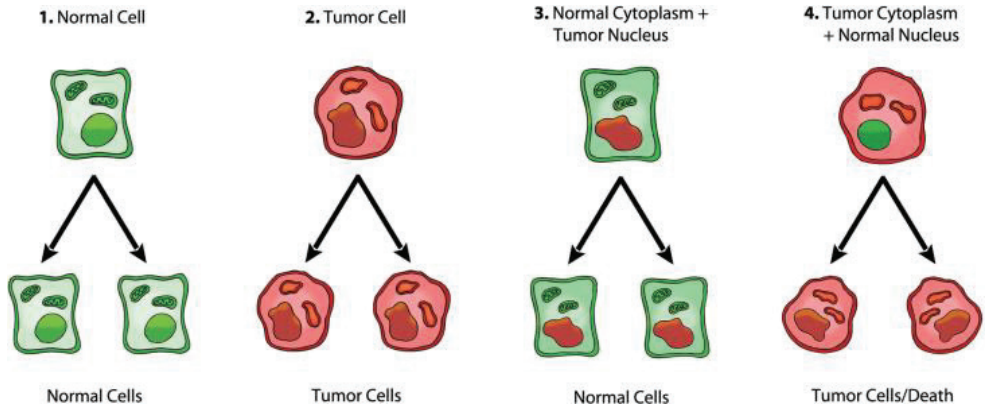
Neutrophil count	Probiotic safety considerations
Normal neutrophil count 2,500 to 6,000	Strain specific, quality probiotics generally regarded as safe Consider *Strain Specific Probiotics for Gut Microbiota Restoration and Support* post cancer therapy to rebuild Avoid probiotics if undergoing haematopoietic stem cell transplants
Low neutrophil count 500 to 2,500	Consider strain specific, quality probiotics with considerable safety profile, such as *Double Strength, Researched, Authentic LGG®* Avoid use of *S. boulardii* Avoid probiotics if undergoing haematopoietic stem cell transplants
Neutropaenia <500	Avoid probiotic use until neutropaenia is resolved

DYSREGULATED ENERGETICS

What Should Cancer Patients Eat?



Cancer as a Metabolic Disease

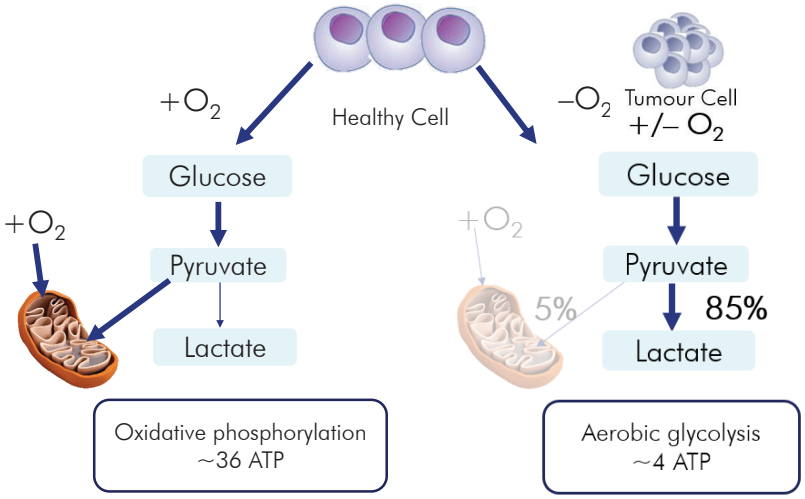


Seyfried TN, et al. Carcinogenesis. 2014 Mar;35(3):515-27. doi: 10.1093/carcin/bgt480.

DYSREGULATED ENERGETICS

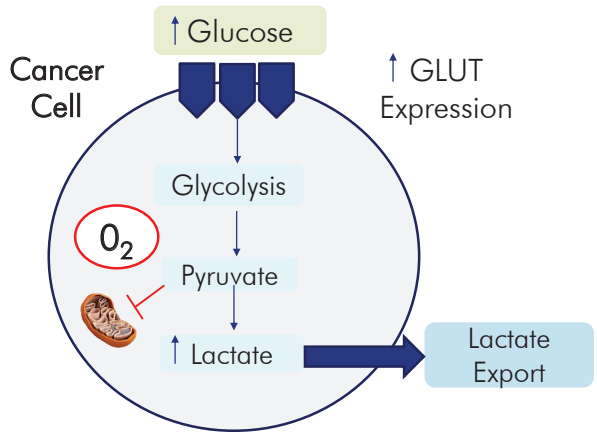
The Warburg Effect

Otto Warburg



Vander Heiden MG, et al. Science. 2009 May 22;324(5930):1029-33. doi: 10.1126/science.1160809.

Lactate a Key Player in Tumourigenesis

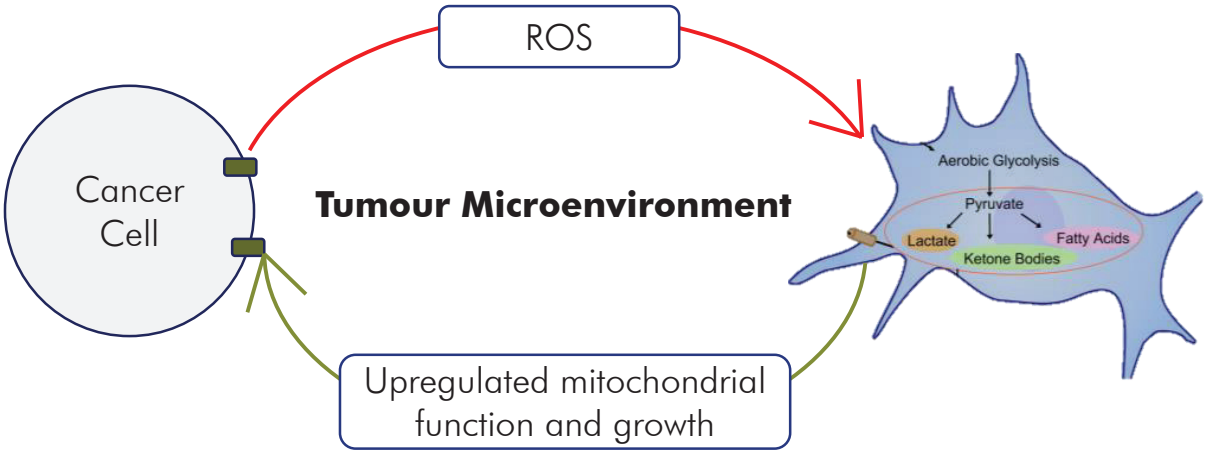


- ↓ extracellular pH
- ↓ immune surveillance
- ↑ angiogenesis
- ↑ tumour cell migration

San-Millán I, et al. Carcinogenesis. 2017 Feb 1;38(2):119-133. doi: 10.1093/carcin/bgw127.

DYSREGULATED ENERGETICS

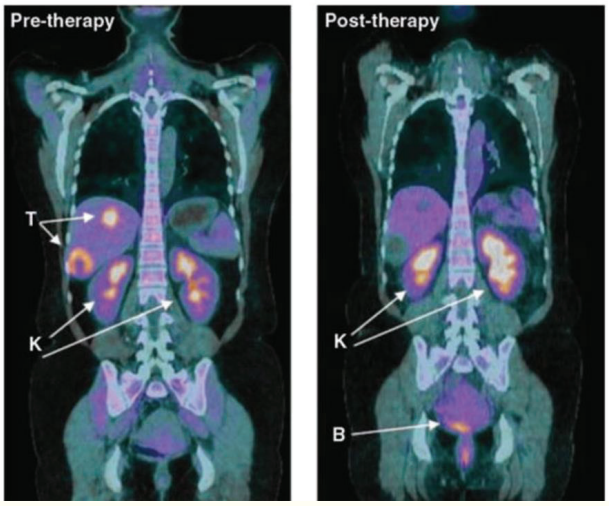
Metabolic Coupling and the Reverse Warburg Effect



Tumours Consume High Amounts of Glucose

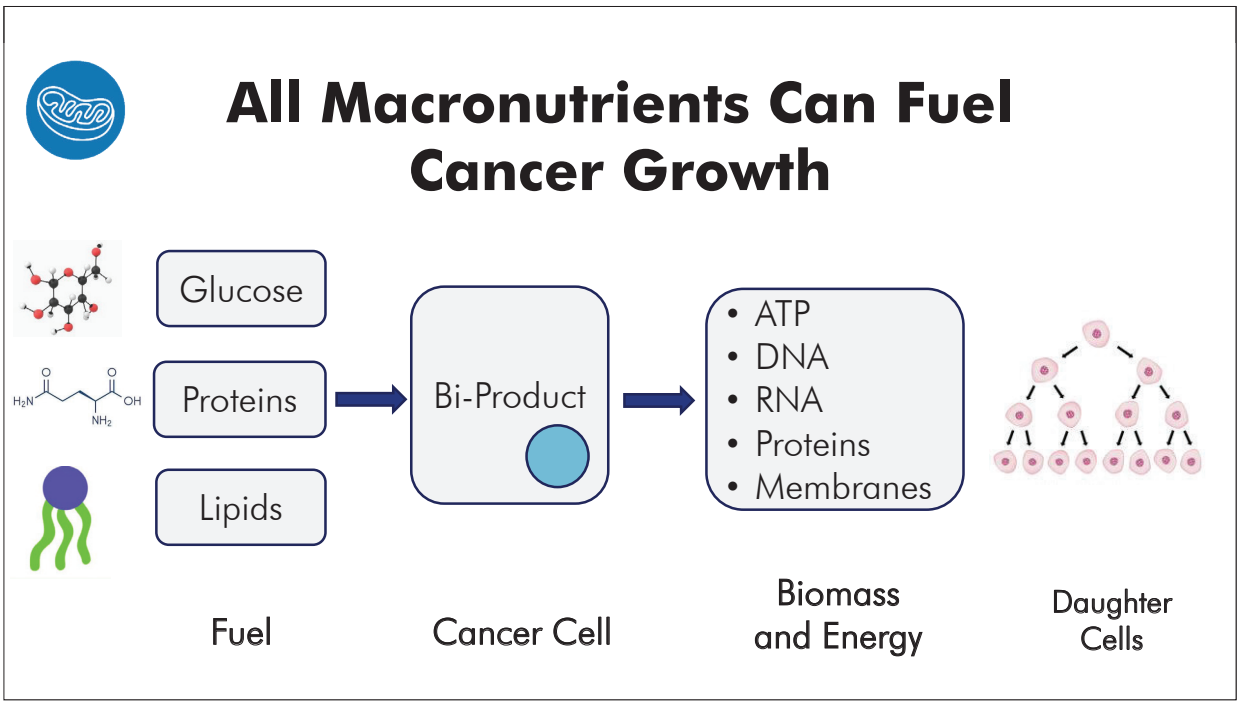
80-90% of cancers have an increased glucose metabolism

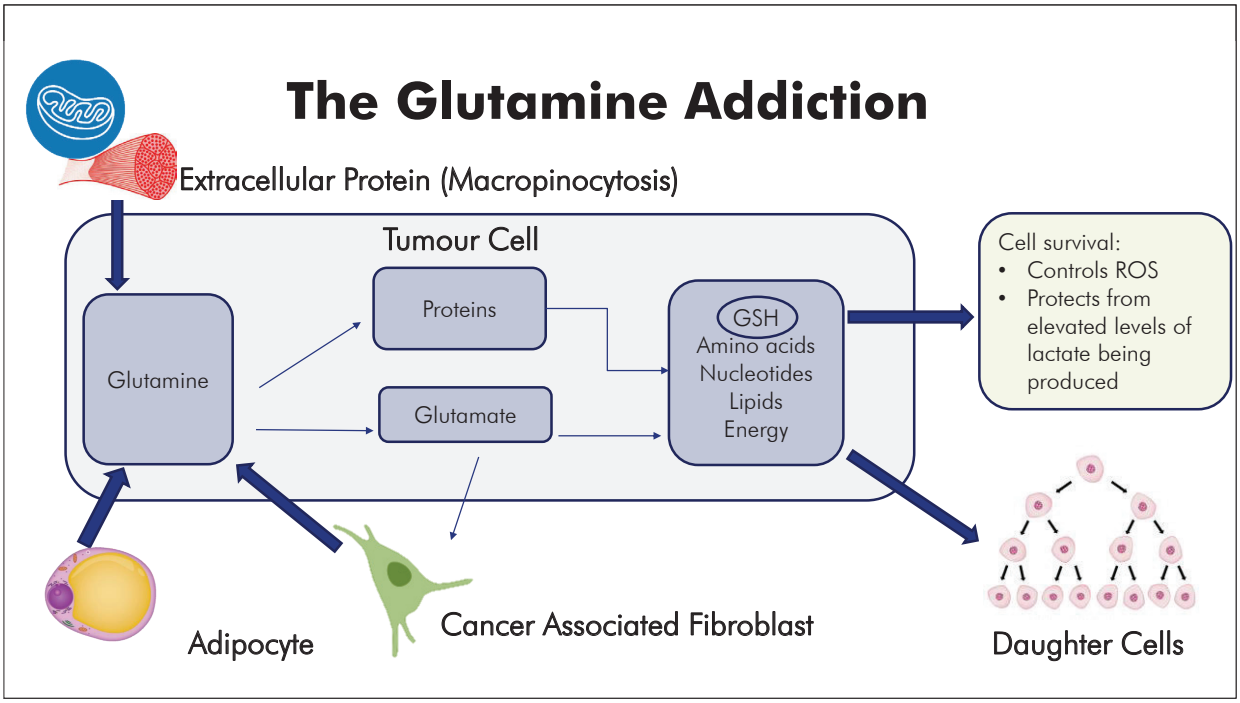
Key:
T = Tumour
K = Kidney
B = Bladder



Vander Heiden MG, et al. Science. 2009 May 22;324(5930):1029-33. doi: 10.1126/science.1160809;
Zhu A, et al. Semin Oncol. 2011 Feb;38(1):55-69. doi: 10.1053/j.seminoncol.2010.11.012.

DYSREGULATED ENERGETICS



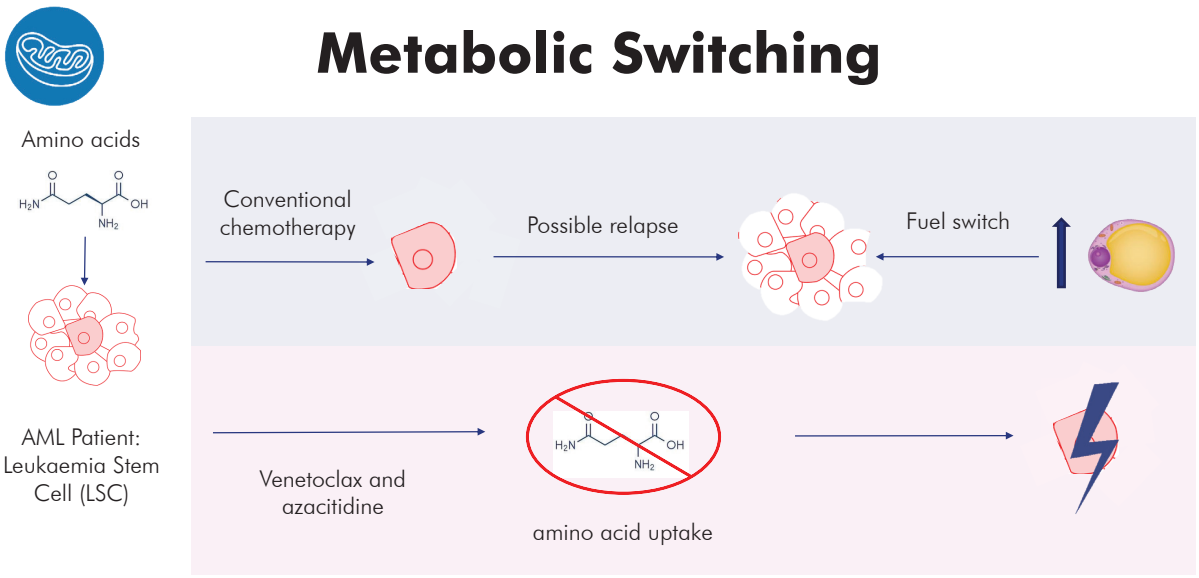


DYSREGULATED ENERGETICS

References: The Glutamine Addiction: Glutaminolysis

- Hoerner CR, Chen VJ, Fan AC. The 'Achilles Heel' of Metabolism in Renal Cell Carcinoma: Glutaminase Inhibition as a Rational Treatment Strategy. Kidney Cancer. 2019 Feb 5;3(1):15-29. doi: 10.3233/KCA-180043.
- Bott AJ, Maimouni S, Zong WX. The Pleiotropic Effects of Glutamine Metabolism in Cancer. Cancers (Basel). 2019 Jun 4;11(6). pii: E770. doi: 10.3390/cancers11060770.

Metabolic Switching



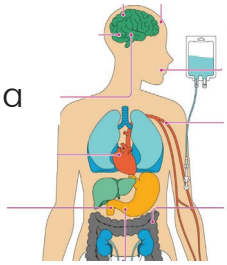
Jones CL, et al. Cancer Cell. 2018 Nov 12;34(5):724-740.e4. doi: 10.1016/j.ccell.2018.10.005.

DYSREGULATED ENERGETICS

Can we Supplement Glutamine?

↓ Cachexia

↓ Peripheral neuropathy



↓ Mucositis

↑ Immunity

↓ Diarrhoea

30 g/day of oral glutamine is safe

References: Can we Supplement with Glutamine?

- Sayles C, Hickerson SC, Bhat RR, Hall J, Garey KW, Trivedi MV. Oral Glutamine in Preventing Treatment-Related Mucositis in Adult Patients With Cancer: A Systematic Review. Nutr Clin Pract. 2016 Apr;31(2):171-9. doi: 10.1177/0884533615611857.
- Amara S. Oral glutamine for the prevention of chemotherapy-induced peripheral neuropathy. Ann Pharmacother. 2008 Oct;42(10):1481-5. doi: 10.1345/aph.1L179.
- Jolfaie NR, Mirzaie S, Ghiasvand R, Askari G, Miraghajani M. The effect of glutamine intake on complications of colorectal and colon cancer treatment: A systematic review. J Res Med Sci. 2015 Sep;20(9):910-8. doi:10.4103/1735-1995.170634.

DYSREGULATED ENERGETICS

Whey Protein Anti-Cancer Effects

30-40 g/day

- Positive clinical data
- Whey protein sub-fractions have specific anti-cancer effects
- Reduces cachexia & anorexia
- Practical, feasible, and cost-effective
- Easy to digest

?

- May increase systemic glutathione
- Mixed results regarding influence upon IGF-1

Teixeira FJ, et al. Pharmacol Res. 2019 Jun;144:245-256. doi: 10.1016/j.phrs.2019.04.019.

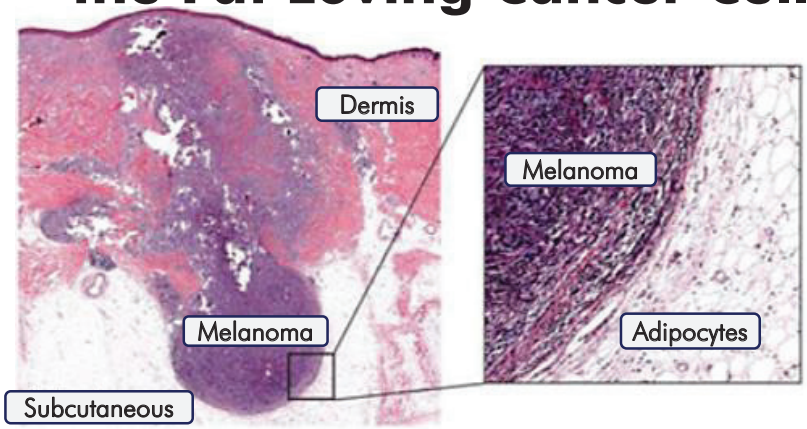
Positive Effects of Whey Protein in Cancer

Study	Cancer Type	Whey Type administration	Effect
Kennedy et al. (1995)	Breast, pancreatic, liver	WPC, 30 g/day	Mixed
See et al. (2002)	Bladder, breast, prostate, neuroblastoma, lung, colon, ovarian, gastric, lymphoma, osteosarcoma	WPI, 40 g/day	Positive
Gillis et al. (2016)	Colon		Positive
Madzima et al. (2017)	Breast	Whey & casein 40 g/day	Positive
Bumrungpert et al. (2018)	Breast, colon, lung, rectum, stomach, cholangiocarcinoma, pancreatic	WPI 40 g/day	Positive

Teixeira FJ, et al. Pharmacol Res. 2019 Jun;144:245-256. doi: 10.1016/j.phrs.2019.04.019.

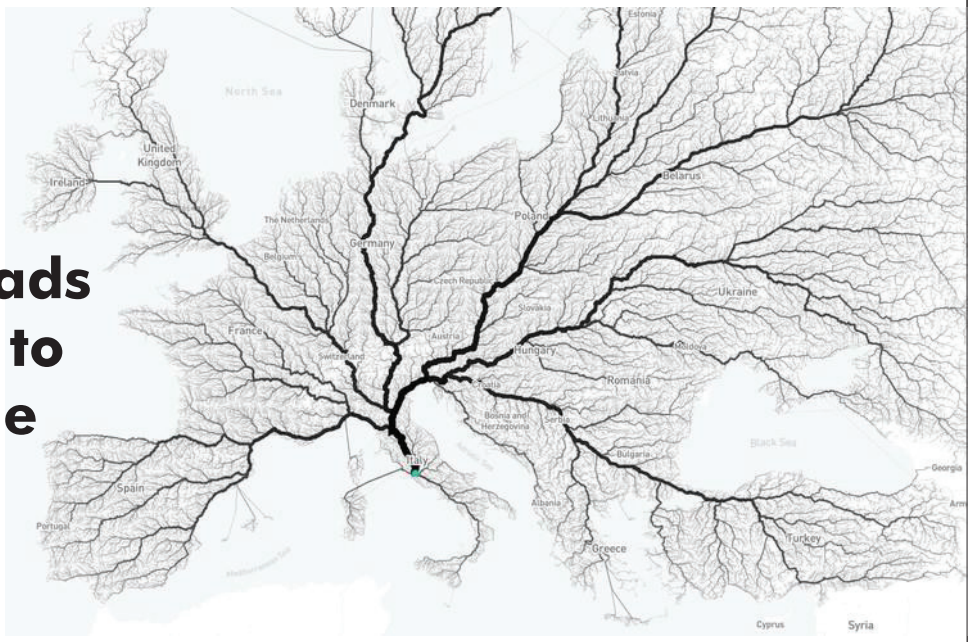
DYSREGULATED ENERGETICS

Melanoma: the Fat Loving Cancer Cell



Zhang M, et al. Cancer Discov. 2018 Aug;8(8):1006-1025. doi: 10.1158/2159-8290.CD-17-1371.

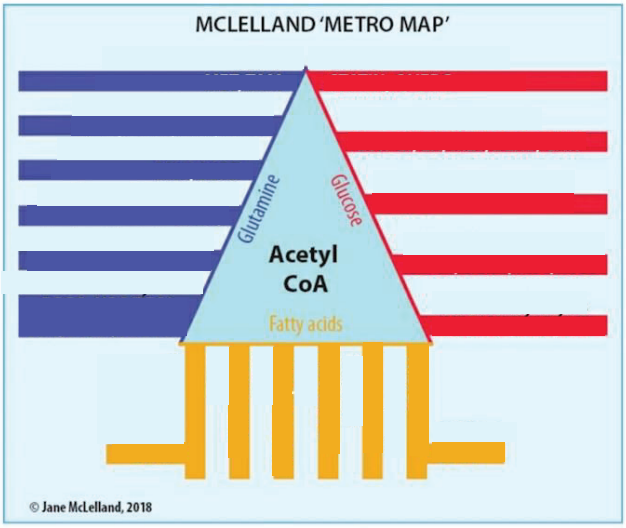
All Roads Lead to Rome



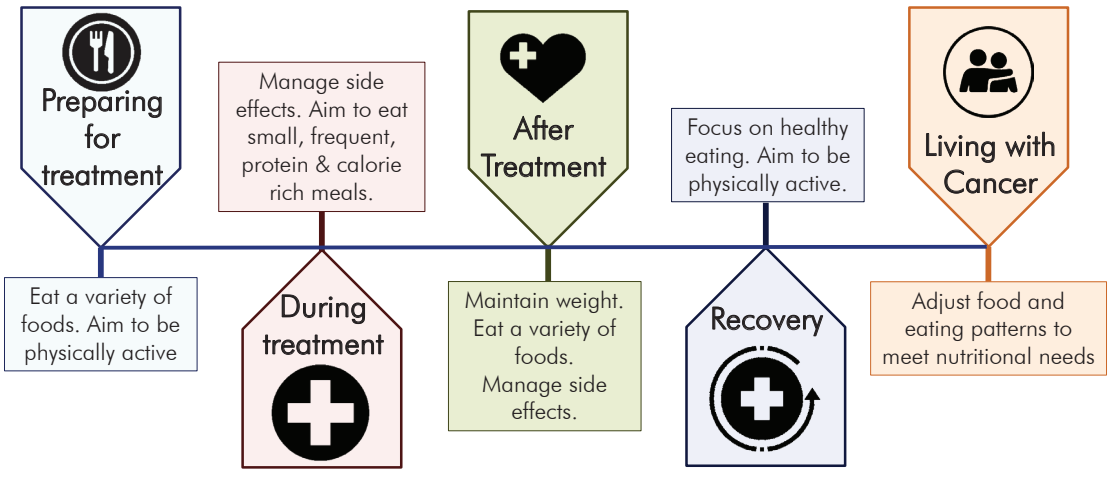
DYSREGULATED ENERGETICS

Metabolically Flexible Cancer Cell

McLelland J. How to Starve Cancer. United Kingdom: Agenor Publishing; Nov 10 2018. Page 317.



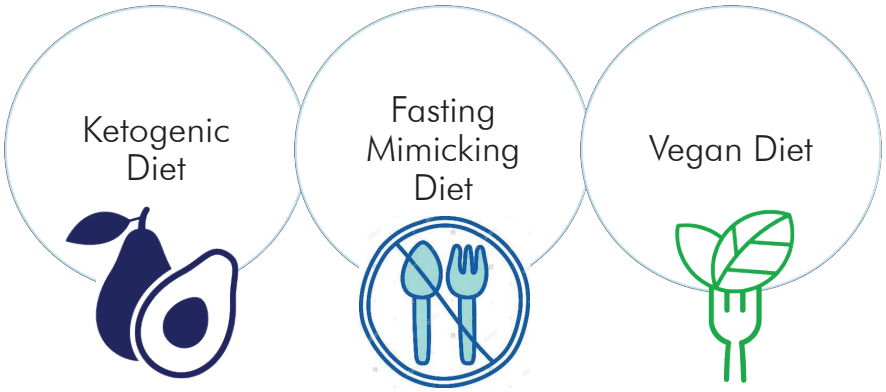
Eating Well After A Cancer Diagnosis



Cancer Council Australia. Nutrition and cancer [Internet]. Available from: https://www.cancerwa.asn.au/resources/2019-03-19-Nutrition-and-Cancer.pdf

DYSREGULATED ENERGETICS

Using Diet to Influence Cancer Metabolism



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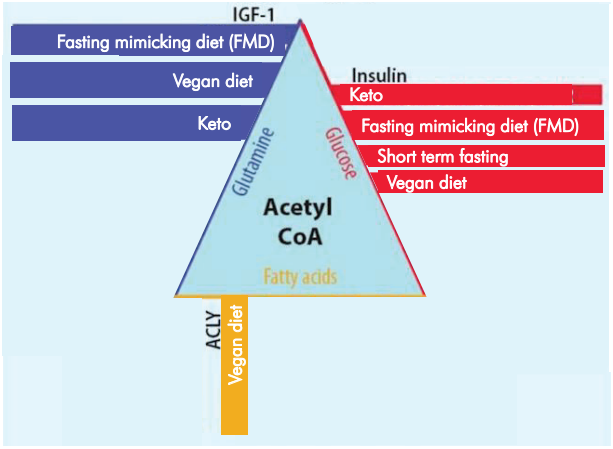
Fasting Mimicking Diet (FMD)



Dr Dominic D'Agostino

Ketogenic Diet

Dr Dean Ornish

Vegan Diet

DYSREGULATED ENERGETICS

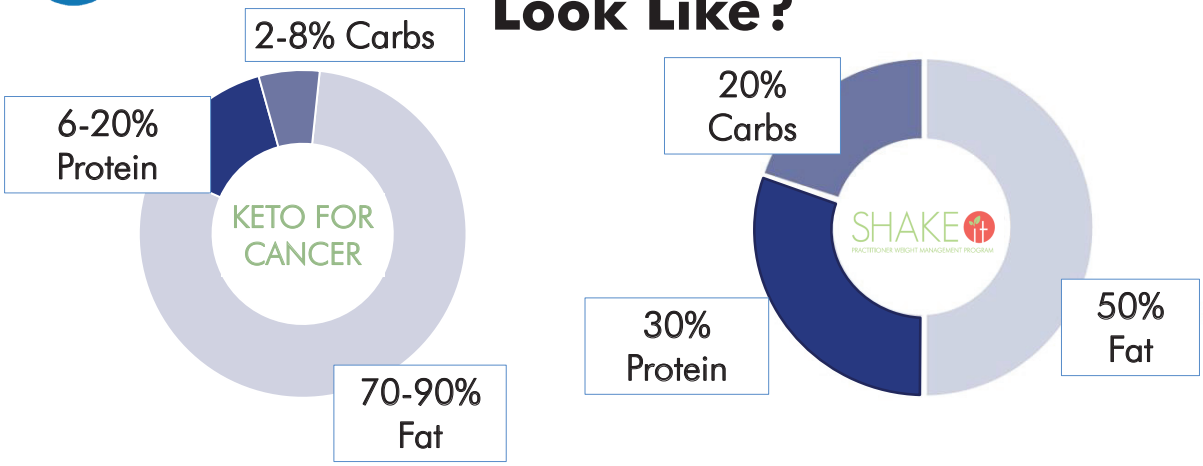
Ketogenic Diet Benefits for Cancer Patients

Beneficial effects on body composition – for both overweight and frail patient populations.

Beneficial effects on overall survival and/or progression free survival

Klement RJ, et al. Med Oncol. 2020 Jan 11;37(2):14. doi: 10.1007/s12032-020-1337-2.

What Does a Cancer Keto Diet Look Like?



Klement RJ, et al. Med Oncol. 2020 Jan 11;37(2):14. doi: 10.1007/s12032-020-1337-2.

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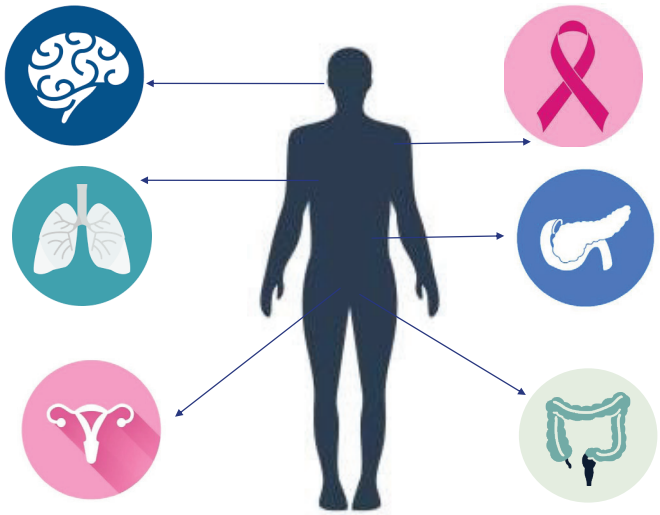
Keto Research on Specific Cancers



Klement RJ, et al. Med Oncol. 2020 Jan 11;37(2):14. doi: 10.1007/s12032-020-1337-2.

Review on Keto and Cancer

Cancer	Controlled	Randomised	Keto	Duration	Outcome	Simultaneous Therapies
Glioma 2014	Yes	No	60 g carbs/day	12 weeks	Increased progression free survival	Targeted therapy and chemo – 3 patients
Glioma 2018	No	No	70% fat, 20g carbs/day	12 weeks	Improved body composition	Chemo and radiotherapy – 3 patients
Glioma 2019	No	No	84.4-88.8% fat	14 weeks	Increased overall survival	Chemo and radiotherapy
Glioma 2019	No	No	Modified Atkins	6 weeks	Increased overall survival, progression free survival	Chemo and radiotherapy
Pancreas 2018	Yes	No	70-80% fat	NA	Improved body composition	NA
Pancreas 2019	No	No	Low carb high fat	NA	Increased overall survival, progression free survival	Chemo
Pancreas and lung 2017	No	No	4:1 ratio - 90% fat	5 and 6 weeks	Increased overall survival, progression free survival	Chemo and radiotherapy
Lung 2019	No	No	Low carb high fat	NA	Increased overall survival, progression free survival	Chemo and hyperbaric oxygen
Breast 2019	Yes	Yes	55% fat, 20% MCT	3 months	Increased overall survival, improved body composition	Chemo
Breast, HNSCC, Rectal 2019	Yes	No	75-80% fat	4-6 weeks	Improved body composition	Radiotherapy
Rectal 2018	Yes	No	1.4:1 ratio	1 year	Increased progression free survival	Chemo
Ovarian/Endomentrial 2018	Yes	Yes	70% fat	12 weeks	Improved body composition	Chemo

DYSREGULATED ENERGETICS

Additional References: Ketogenic Diet and Cancer

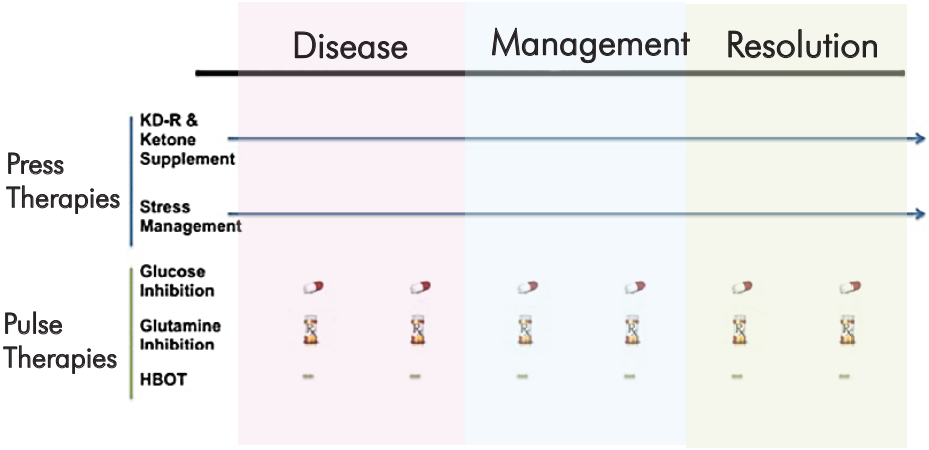
- Kang CM, Yun B, Kim M, Song M, Kim YH, Lee SH, et al. Postoperative serum metabolites of patients on a low carbohydrate ketogenic diet after pancreatectomy for pancreatobiliary cancer: a nontargeted metabolomics pilot study. Sci Rep. 2019 Nov 14;9(1):16820. doi: 10.1038/s41598-019-53287-y.
- Branca JJ, Pacini S, Ruggiero M. Effects of Pre-surgical Vitamin D Supplementation and Ketogenic Diet in a Patient with Recurrent Breast Cancer. Anticancer Res. 2015 Oct;35(10):5525-32. PubMed PMID: 26408720.
- İyikesici MS, Slocum AK, Slocum A, Berkarda FB, Kalamian M, Seyfried TN. Efficacy of Metabolically Supported Chemotherapy Combined with Ketogenic Diet, Hyperthermia, and Hyperbaric Oxygen Therapy for Stage IV Triple-Negative Breast Cancer. Cureus. 2017 Jul 7;9(7):e1445. doi: 10.7759/cureus.1445.
- Cohen CW, Fontaine KR, Arend RC, Soleymani T, Gower BA. Favorable Effects of a Ketogenic Diet on Physical Function, Perceived Energy, and Food Cravings in Women with Ovarian or Endometrial Cancer: A Randomized, Controlled Trial. Nutrients. 2018 Aug 30;10(9). pii: E1187. doi: 10.3390/nu10091187.
- Cohen CW, Fontaine KR, Arend RC, Alvarez RD, Leath CA III, Huh WK, et al. A Ketogenic Diet Reduces Central Obesity and Serum Insulin in Women with Ovarian or Endometrial Cancer. J Nutr. 2018 Aug 1;148(8):1253-1260. doi: 10.1093/jn/nxy119.

Additional References: Ketogenic Diet and Cancer

- Martin-McGill KJ, Srikandarajah N, Marson AG, Tudur Smith C, Jenkinson MD. The role of ketogenic diets in the therapeutic management of adult and paediatric gliomas: a systematic review. CNS Oncol. 2018 Apr;7(2):CNS17. doi: 10.2217/cns-2017-0030.
- Mukherjee P, Augur ZM, Li M, Hill C, Greenwood B, Domin MA, et al. Therapeutic benefit of combining calorie-restricted ketogenic diet and glutamine targeting in late-stage experimental glioblastoma. Commun Biol. 2019 May 29;2:200. doi: 10.1038/s42003-019-0455-x.
- Winter SF, Loebel F, Dietrich J. Role of ketogenic metabolic therapy in malignant glioma: A systematic review. Crit Rev Oncol Hematol. 2017 Apr;112:41-58. doi: 10.1016/j.critrevonc.2017.02.016.
- Artzi M, Liberman G, Vaisman N, Bokstein F, Vitinshtein F, Aizenstein O, et al. Changes in cerebral metabolism during ketogenic diet in patients with primary brain tumors: (1)H-MRS study. J Neurooncol. 2017 Apr;132(2):267-275. doi: 10.1007/s11060-016-2364-x.
- Martuscello RT, Vedam-Mai V, McCarthy DJ, Schmoll ME, Jundi MA, Louviere CD, et al. A supplemented high-fat low-carbohydrate diet for the treatment of glioblastoma. Clin Cancer Res. 2016 May 15;22(10):2482-95. doi: 10.1158/1078-0432.CCR-15-0916.

DYSREGULATED ENERGETICS

Novel Press-Pulse Theory



Key:
KD-R: calorie restricted ketogenic diet
HBOT: hyperbaric oxygen therapy

Seyfried TN, et al. Nutr Metab (Lond). 2017 Feb 23;14:19. doi: 10.1186/s12986-017-0178-2.

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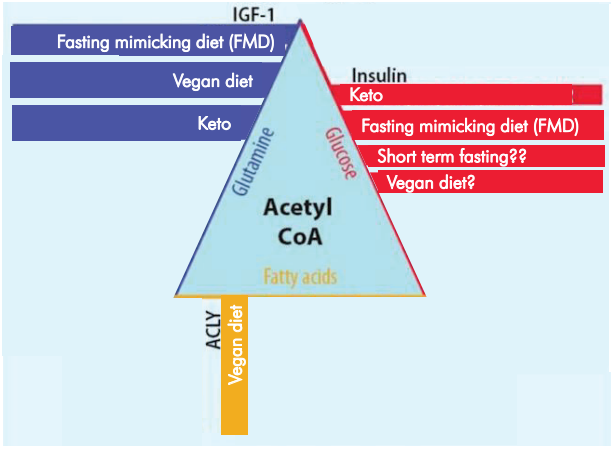
Fasting Mimicking Diet (FMD)



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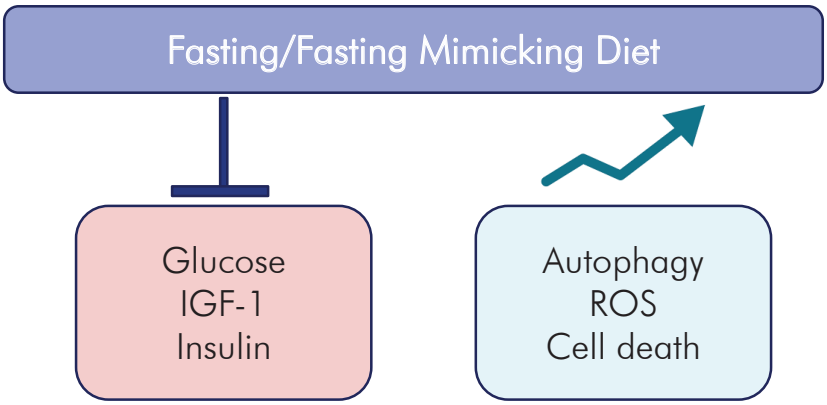
Ketogenic Diet

Dr Dean Ornish

Vegan Diet

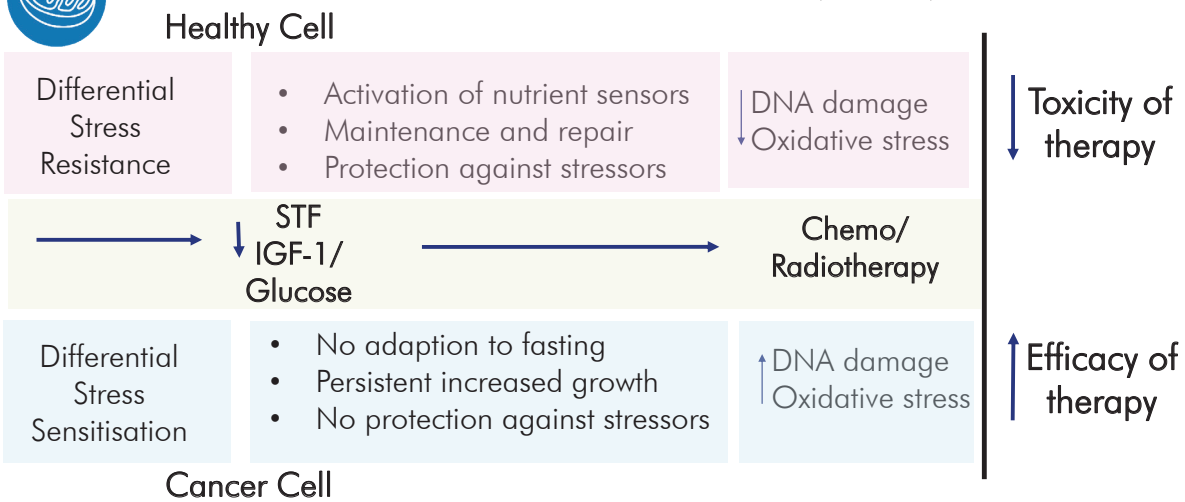
DYSREGULATED ENERGETICS

Cellular Response to Fasting



Adapted from: Nencioni A, et al. Nat Rev Cancer. 2018 Nov;18(11):707-719. doi: 10.1038/s41568-018-0061-0.

Short Term Fasting (STF)



DYSREGULATED ENERGETICS

Reference: Short Term Fasting

- Adapted: de Groot S, et al. J Exp Clin Cancer Res. 2019 May 22;38(1):209. doi: 10.1186/s13046-019-1189-9.

Animal Data on STF

- Increased efficacy of chemotherapy (CT) and radiation therapy
- Decreased chemo-toxicity
- Increased survival and decreased metastasis
- STF alone was as effective as CT in some cases
- Colon cancer no effect on efficacy of CT but decreased toxicity

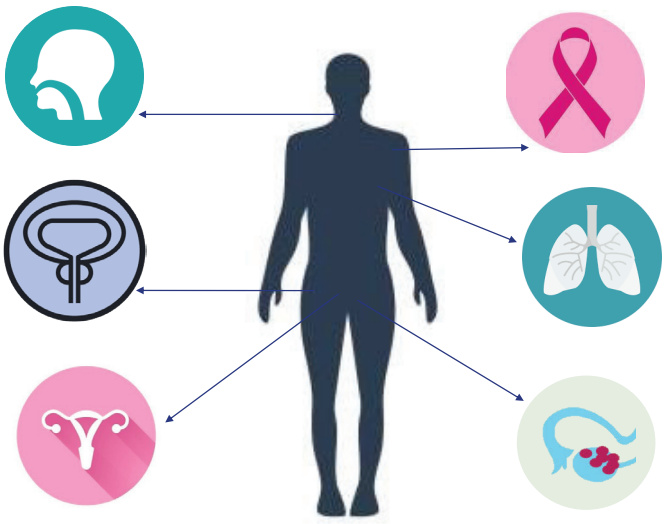
- STF safe and feasible reduction in vomiting with CT
- No reduction in IGF-1

de Groot S, et al. J Exp Clin Cancer Res. 2019 May 22;38(1):209. doi: 10.1186/s13046-019-1189-9.

DYSREGULATED ENERGETICS

STF With Chemotherapy

Less fatigue, weakness and gastrointestinal side effects during chemotherapy alongside fasting



Safdie FM, et al. Aging (Albany NY). 2009 Dec 31;1(12):988-1007. PubMed PMID: 20157582.

STF During Chemotherapy

RESEARCH ARTICLE — Open Access

The effects of short-term fasting on quality of life and tolerance to chemotherapy in patients with breast and ovarian cancer: a randomized cross-over pilot study

Stephan P. Bauersfeld[1], Christian S. Kessler[1,2], Manfred Wischnewsky[3], Annette Jaensch[3], Nico Steckhan[1], Rainer Stange[1,2], Barbara Kunz[3], Barbara Brückner[4], Jalid Sehouli[4] and Andreas Michalsen[1,2*]

Abstract

Background: This pilot trial aimed to study the feasibility and effects on quality of life (QOL) and well-being of short-term fasting (STF) during chemotherapy in patients with gynecological cancer.

Methods: In an individually-randomized cross-over trial patients with gynecological cancer, 4 to 6 planned chemotherapies followed by normocaloric diet (group A;n = 18) or vice versa (group B;n = 16). Fasting started 36 h before and ended 24 h after chemotherapy (60 h-fasting period). QOL was assessed by the FACIT-measurement system.

Results: The chemotherapy-induced reduction of QOL was less than the Minimally Important Difference (MID; FACT-G = 5) with STF but greater than the MID for non-fasted periods. The mean chemotherapy-induced deterioration of total FACIT-F was 10.4 ± 5.3 for fasted and 27.0 ± 6.3 for non-fasted cycles in group A and 14.1 ± 5.6 for non-fasted and 11.0 ± 5.6 for fasted cycles in group B. There were no serious adverse effects.

Conclusion: STF during chemotherapy is well tolerated and appears to improve QOL and fatigue during chemotherapy. Larger studies should prove the effect of STF as an adjunct to chemotherapy.

Trial registration: This trial was registered at clinicaltrials.gov: NCT01954836.

Keywords: Breast cancer, Chemotherapy, Fasting, Pilot study, Quality of life, Ovarian cancer

Short term fasting during chemotherapy is well tolerated and appears to improve QOL and fatigue

Bauersfeld SP, et al. BMC Cancer. 2018 Apr 27;18(1):476. doi: 10.1186/s12885-018-4353-2.

DYSREGULATED ENERGETICS

Fasting Mimicking Diet (FMD) for Cancer

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	Day 1 4600 kJ	Days 2–5 3000 kJ/day
Protein	11%	9%
Fat	46%	44%
CHO	43%	47%

- Targets IGF-1 and glucose
- Several ongoing clinical trials for FMD and cancer
- FMD: 3 days before and continues for 1 day after chemotherapy

Buono R, et al. Trends Endocrinol Metab. 2018 Apr;29(4):271-280. doi: 10.1016/j.tem.2018.01.008.

Current Research on FMD and Cancer

Study Title	Study Status	Conditions	Interventions
Safety, feasibility and metabolic effects of the fasting mimicking diet (FMD) in cancer patients	Recruiting	• Malignant neoplasm • Cancer	• FMD
Fasting mimicking diet with chemo-immunotherapy in non-small cell lung cancer (NSCLC)	Recruiting	• NSCLC	• FMD • Regular diet
Fasting mimicking diet in patients undergoing active cancer treatment	Recruiting	• Cancer • Beast cancer • Colorectal cancer	• Prolon
Fasting mimicking diet in prostate cancer and metabolic syndrome	Active	• Prostate cancer • Metabolic syndrome • Intermittent fasting	• FMD
Calorie restriction with or without metformin in triple negative breast cancer	Not yet recruiting	• Triple negative breast cancer	• FMD • Metformin • Preoperative chemo
Dietary restriction as an adjunct to neoadjuvant chemotherapy for HER2 negative breast cancer	Completed	• Fasting mimicking diet • Breast cancer • Neoadjuvant chemotherapy • Pathological complete response	• FMD
Impact of dietary intervention on tumour immunity: the digesT trial	Recruiting	• Breast cancer • Melanoma, Malignant	• FMD
Fasting and nutritional therapy in patients with advanced metastatic prostate cancer	Recruiting	• Fasting • Prostatic neoplasms	• Fasting • Control
Metformin plus/minus fasting mimicking diet To target the metabolic vulnerabilities of LKB1-inactive lung adenocarcinoma	Not yet recruiting	• Advanced LKB1-inactive lung adenocarcinoma	• Metformin Hydrochloride • Cisplatin

Clinical Trials.org. Fasting mimicking diet, cancer. [Internet]. National Institute of Health: Bethesda. 2020 Mar 1. Available from:

DYSREGULATED ENERGETICS

Caution for STF/FMD in Cancer Patients

- Not recommended for frail or malnourished patients.
- Manage nutritional deficiencies resulting from fasting and/or FMDs.
- Periodic anorexia and nutritional status assessments should be an integral part of studies of fasting and/or FMDs in cancer.
- Without current firm evidence of a benefit, *fasting during chemotherapy cannot be recommended.*

References: Caution for STF/FMD in Cancer Patients

- de Groot S, Pijl H, van der Hoeven JJM, Kroep JR. Effects of short-term fasting on cancer treatment. J Exp Clin Cancer Res. 2019 May 22;38(1):209. doi: 10.1186/s13046-019-1189-9.
- Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017 Feb;36(1):11-48. doi: 10.1016/j.clnu.2016.07.015.
- Caccialanza R, Aprile G, Cereda E, Pedrazzoli P. Fasting in oncology: a word of caution. Nat Rev Cancer. 2019 Mar;19(3):177. doi: 10.1038/s41568-018-0098-0.
- Nencioni A, Caffa I, Cortellino S, Longo VD. Reply to 'Fasting in oncology: a word of caution'. Nat Rev Cancer. 2019 Mar;19(3):178. doi: 10.1038/s41568-018-0100-x.

DYSREGULATED ENERGETICS

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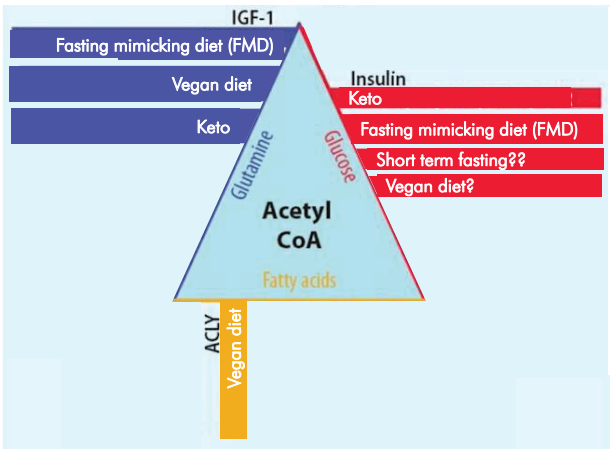
Fasting Mimicking Diet (FMD)



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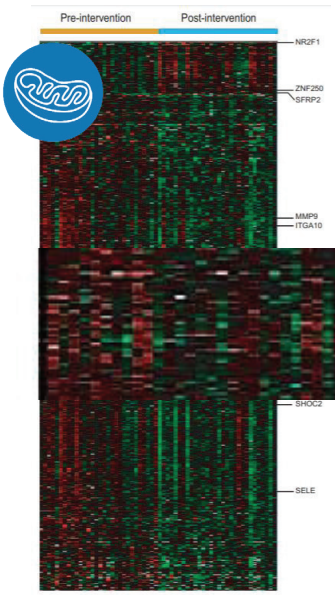
Ketogenic Diet

Dr Dean Ornish

Vegan Diet



Vegan Diet and Lifestyle Intervention Block All Roads to Rome

We found down-regulation of IGF pathway genes [*IGF1 receptor (IGF1R)*, fat metabolism genes and carbohydrate metabolism genes

Ornish D, et al. Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74. doi: 10.1073/pnas.0803080105.

DYSREGULATED ENERGETICS

Vegan Diet Reduces Total Cancer Risk

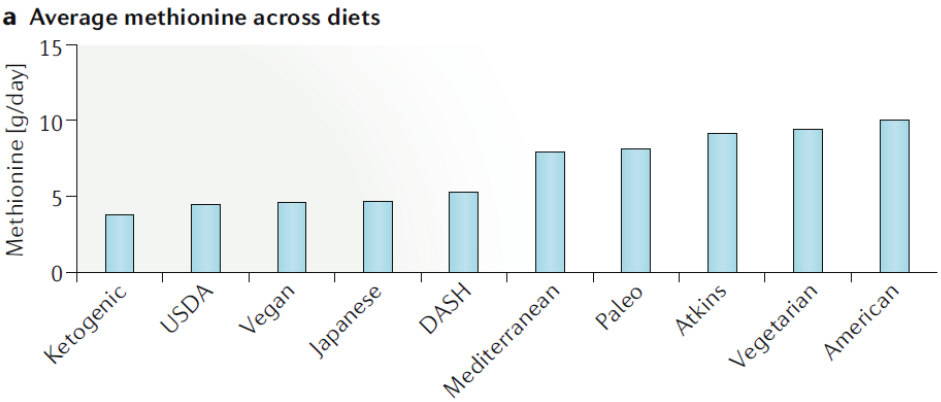
61,647 Participants
14.9 year follow-up
4998 incident of cancer

Total cancer incidence compared to meat eaters:

- 19% lower in vegans
- 12% lower in fish eaters
- 11% lower in vegetarians

Key TJ, et al. Am J Clin Nutr. 2014 Jul;100 Suppl 1:378S-85S. doi: 10.3945/ajcn.113.071266.

Which Diets Low in Methionine?



Sanderson SM, et al. Nat Rev Cancer. 2019 Nov;19(11):625-637. doi: 10.1038/s41568-019-0187-8.

DYSREGULATED ENERGETICS

Dietary Guidelines for Cancer

- Maintain a healthy weight
- Encourage physical activity
- Eat a wide variety of foods
- Limit alcohol, saturated fat, salt, sugar
- Prepare and store food correctly

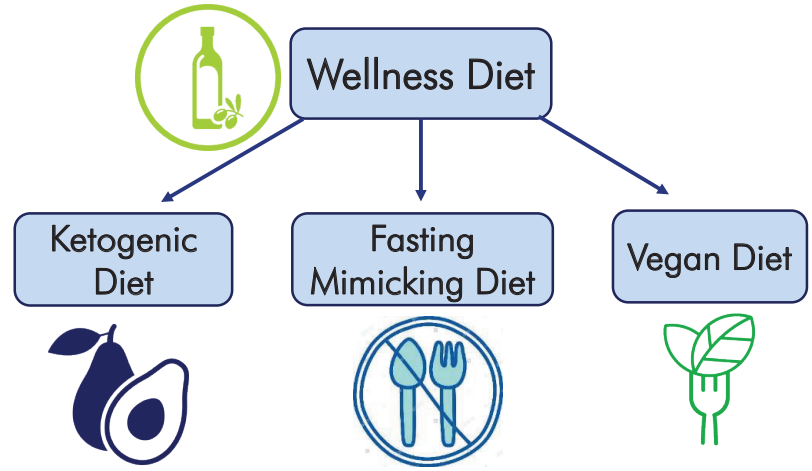
Cancer Council Australia. Nutrition and cancer [Internet].
Available from: https://www.cancerwa.asn.au/resources/2019-03-19-Nutrition-and-Cancer.pdf

Dietary Guidelines

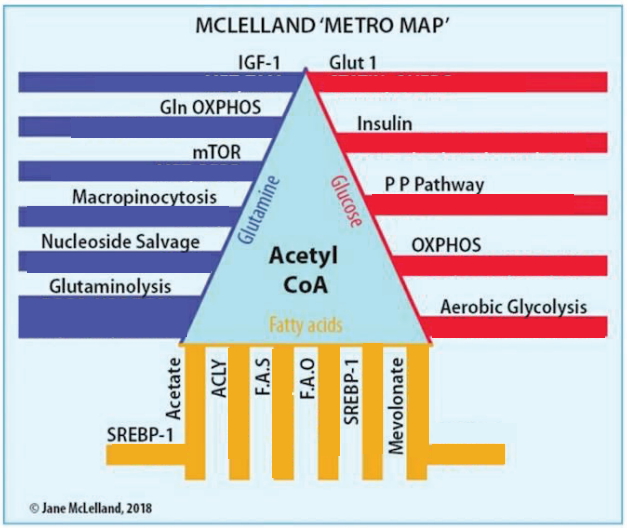
- Wholefood diet, unprocessed foods
- Ensure maintenance of muscle mass
- Meet the patient where they are at. Is the patient able or prepared to implement new dietary changes?

DYSREGULATED ENERGETICS

A Hierarchy of Diets for Cancer



Beyond Diet for Cancer Metabolism

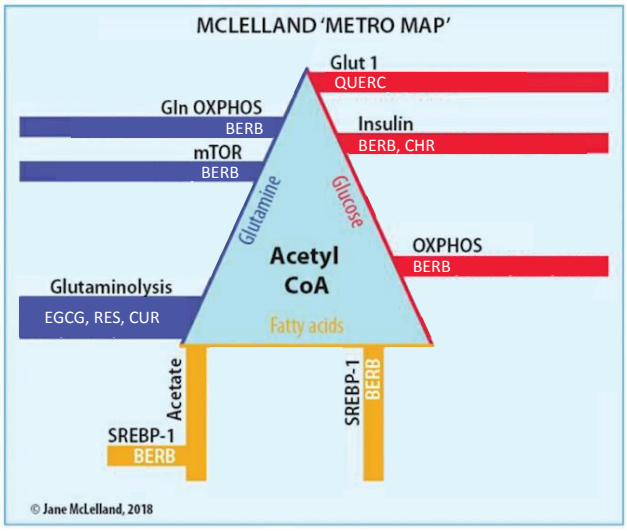


McLelland J. How to Starve Cancer. United Kingdom: Agenor Publishing; Nov 10 2018. page 317.

DYSREGULATED ENERGETICS

Natural Ingredients that Block Roads to Rome

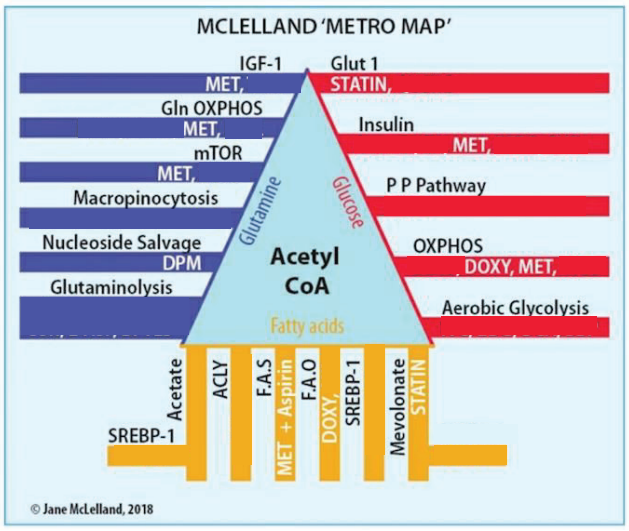
- Berberine (BERB)
- Quercetin (QUERC)
- Chromium (CHR)
- Epigallocatechin gallate (EGCG)
- Resveratrol (RES)
- Curcumin (CUR)



McLelland J. How to Starve Cancer. United Kingdom: Agenor Publishing; Nov 10 2018. page 317.

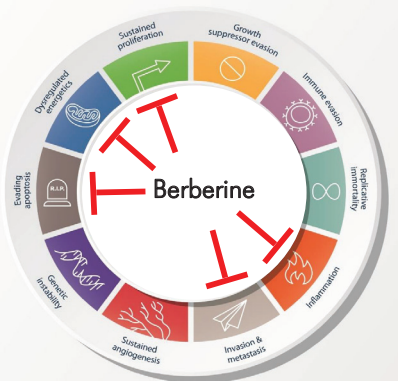
McLelland's Off-Label Blockbusters Drugs

- Aspirin
- Metformin
- Statin
- Dipyridamole
- Doxycyline



DYSREGULATED ENERGETICS

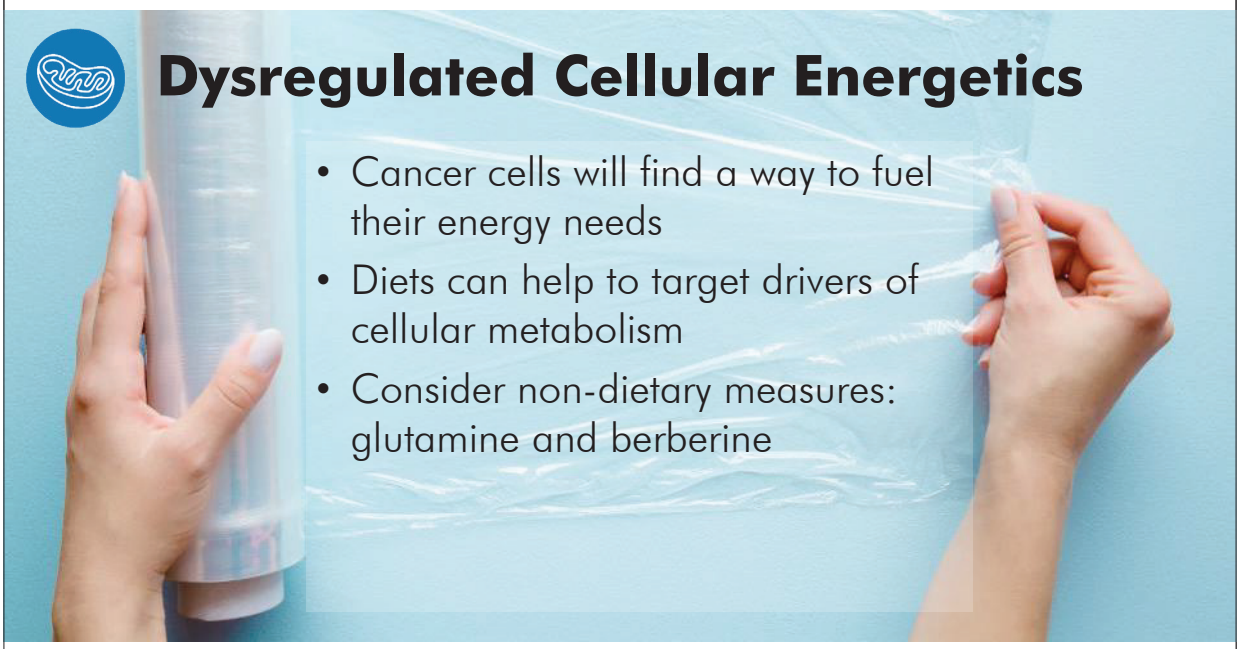
Berberine Shows Promise on the Road to Rome



References: Berberine Shows Promise, Blocking All Roads to Rome

- Xu J, et al. Anticancer effect of berberine based on experimental animal models of various cancers: a systematic review and meta-analysis. BMC Cancer. 2019 Jun 17;19(1):589. doi: 10.1186/s12885-019-5791-1.
- Ortiz LM, et al. Berberine, an epiphany against cancer. Molecules. 2014 Aug 15;19(8):12349-67. doi: 10.3390/molecules190812349.
- Mortazavi H, et al. Potential cytotoxic and anti-metastatic effects of berberine on gynaecological cancers with drug-associated resistance. Eur J Med Chem. 2020 Feb 1;187:111951. doi: 10.1016/j.ejmech.2019.111951.
- Zhang C, et al. Effects of Berberine and Its Derivatives on Cancer: A Systems Pharmacology Review. Front Pharmacol. 2020 Jan 15;10:1461. doi: 10.3389/fphar.2019.01461.
- Wang Y, et al. The Anti-Cancer Mechanisms of Berberine: A Review. Cancer Manag Res. 2020 Jan 30;12:695-702. doi: 10.2147/CMAR.S242329.
- Habtemariam S. Recent Advances in Berberine Inspired Anticancer Approaches: From Drug Combination to Novel Formulation Technology and Derivatization. Molecules. 2020 Mar 20;25(6). pii: E1426. doi: 10.3390/molecules25061426.
- Hallajzadeh J, et al. Targeting of oncogenic signaling pathways by berberine for treatment of colorectal cancer. Med Oncol. 2020 Apr 17;37(6):49. doi: 10.1007/s12032-020-01367-9.

DYSREGULATED ENERGETICS



SLEEP AND EXERCISE

Epidemiology of Sleep

Short sleep associated with breast cancer *in Asia* (RR 1.53 to 1.62)

Long sleep associated with colorectal cancer (RR 1.20)

Sleep-disordered breathing associated with cancer (RR 1.40)

Erren TC, et al. Chronobiol Int. 2016;33(4):325-350. doi:10.3109/07420528.2016.1149486.

Palamaner Subath Shanther et al, 2012. Sleep Med, 16(10) – See notes below

SLEEP AND EXERCISE

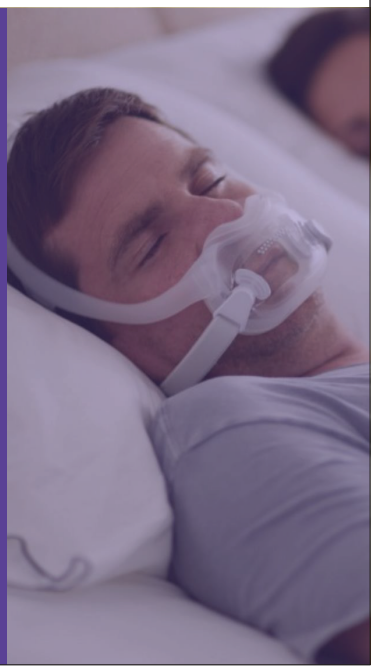
Hypothesis: sleep apnoea *strongly* increases the risk of developing cancer

✓ Polysomnography

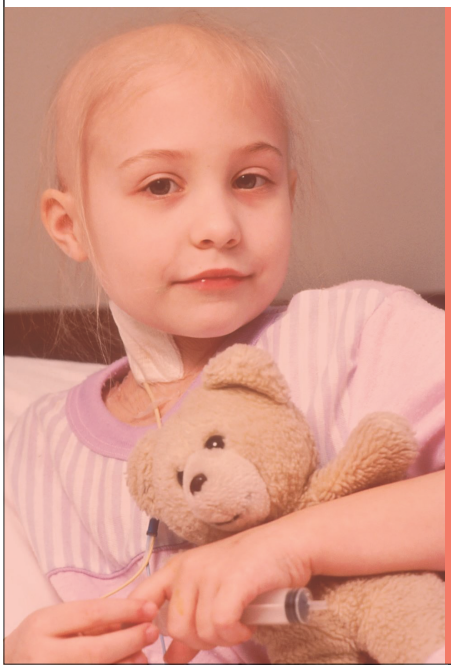
Dose-response: severe OSA (hypoxaemia index ≥ 11.2%): *8.6 times* as likely to die of cancer

Apnoea-hypopnea index > 30: *4.8 times* as likely to die of cancer

Hypoxaemia index also associated with cancer mortality in patients



Nieto FJ, et al. Am J Respir Crit Care Med. 2012;186(2):190-194. doi:10.1164/rccm.201201-0130OC.; Martínez-García MA, et al. Sleep Med. 2014;15(7):742-748. doi:10.1016/j.sleep.2014.01.020.



Insomnia is rife in cancer patients

Treatment may exacerbate insomnia

Direct effects

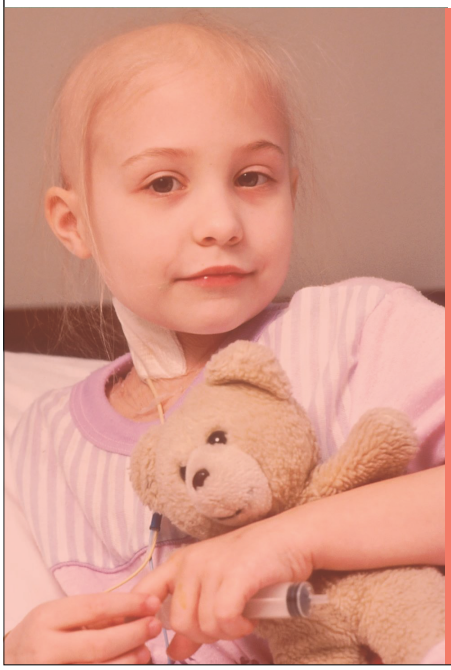
Chemotherapy

40% report moderate or severe insomnia after first treatment…
… and sleep problems may persist

Radiotherapy and steroids

Palesh OG, et al. J Clin Oncol. 2010;28(2):292-298. doi: 10.1200/JCO.2009.22.5011.
Kotronoulas G, et al. Breast. 2012;21(2):128-141. doi:

SLEEP AND EXERCISE



Insomnia is rife in cancer patients

Treatment may exacerbate insomnia

Indirect effects

Treatment-induced nausea

Hormone therapy-induced hot flashes

Urinary incontinence
(e.g., after prostatectomy)

Anti-Cancer Properties of Sleep

Abrams DI, Weil AT. Integrative Oncology. 2nd ed. New York: Oxford University Press; 2014. p.169-175;
Betof AS,. Brain Behav Immun. 2013;30 Suppl(0):S75-S87. doi:10.1016/j.bbi.2012.05.001.

SLEEP AND EXERCISE

Circadian system disruption: artificial light at night

Light at night increased therapy resistance in a rat model of breast cancer

Some epidemiological study authors have reported associations between light at night and risk of breast cancer. Others have not

Dauchy et al, 2014. Cancer Res, 74(15)
Hurley et al, 2014. Epidemiology, 25(5)
Johns et al, 2018. Br J Cancer, 118(4)

Circadian system disruption: mistimed nutrition

Women who fast for ≥ 13 h each day have a lower risk of breast cancer

Eating dinner before 9:30 PM associated with reduced risk of prostate cancer and breast cancer

In mice, time-restricted feeding alters diurnal changes in skin sensitivity to UVB-induced DNA damage

Marinac et al, 2016. JAMA Oncol, 2(8)
Srour et al, 2018. Int J Cancer, 143(10)
Andersen et al, 2017. Cell Rep, 20(5)

SLEEP AND EXERCISE

Timely chemotherapy

✓ Reduced side effects in breast, colorectal, and endometrial cancer treatment

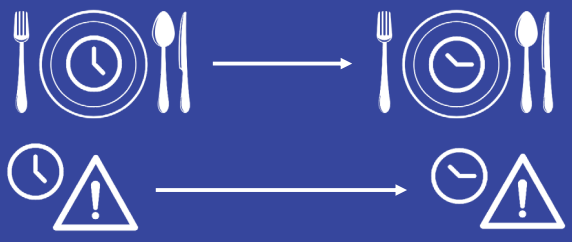
Clinical trials: administering drugs at optimal circadian times can nearly *double* antitumour efficacy and reduce toxicity *up to five-fold*

Coudert et al, 2008. Chronobiol Int, 25(5)
Lévi et al, 1994. J Natl Cancer Inst, 86(21)
Gallion et al, 2003. J Clin Oncol, 21(20)
Dallman et al, 2016. Trends Mol Med, 22(5)

Table 2. Recent Clinical Chronotherapy Studies[a]

Disease	Drug(s) (Dose, Route)	Study Design	Dosing Schedule	/V	Main Findings	Ref.
Breast cancer (hormone receptor receptive)	Tamoxifen (20 or 40 mg p.o.)	PK crossover	8:00 vs 13:00 vs 20:00 (4 weeks on each dosing-time)	27 F	Mean C_{max} and $AUC_{0-8\ h}$ of tamoxifen and endoxifen (bioactive metabolite) 8:00>>20:00 (by ≈20%) Mean t_{max} 8:00<20:00 High CYP2D6 metabolism may enhance circadian effect	[146]
Renal cell cancer, gastrointestinal stromal, or pancreatic neuroendocrine tumours	Sunitinib (stable once daily dose for >2 weeks before entry)	PK randomised crossover	8:00 vs 18:00 (3 weeks on each dosing-time) Additional testing of 13:00 for pt subset	27 pts (22 M, 5 F) 12 pts: three dosing-times	Mean concentration at time of subsequent dose intake (C_{trough}): (13:00 = 18:00) > 8:00 No difference in AUC	[142]
Non-small cell lung cancer (advanced)	Cisplatin (20 mg/m²/day × 4 days, combined with docetaxel or gemcitabine)	Randomised Phase II with minimisation	6:00 vs 18:00	41 pts (28 M, 13 F)	Neutropenia gr 3–4: 12% at 18:00 vs 33% at 6:00 Nausea gr 1–2: 18:00 < 6:00 Total and unbound cisplatin clearance 18:00 > 6:00	[152]
Metastatic colorectal cancer	5-FU–LV and L-OHP (5-FU 3000–3600 mg/m², LV 1200 mg/m², L-OHP 100 mg/m², q 2 weeks	International randomised Phase III (post hoc analysis)	Fixed chronomodulated delivery (chronoFLO4) vs conventional delivery (FOLFOX2)	556 pts (331 M, 225 F)	Neutropenia – All grades: chronoFLO4, 33%, FOLFOX2, 61% – Grade 3–4: chronoFLO4, 7% FOLFOX2, 25% – More frequent in women – Predictive of a better survival for FOLFOX2, not chronoFLO4	[153]
Metastatic colorectal cancer	5-FU–LV and L-OHP (5-FU 3000–3600 mg/m², LV 1200 mg/m², L-OHP 100 mg/m², q 2 weeks	International randomised Phase III (post hoc analysis)	Fixed chronomodulated delivery (chronoFLO4) vs conventional delivery (FOLFOX2)	556 pts (331 M, 225 F)	Neutropenia – All grades: chronoFLO4, 33%, FOLFOX2, 61% – Grade 3–4: chronoFLO4, 7% FOLFOX2, 25% – More frequent in women – Predictive of a better survival for FOLFOX2, not chronoFLO4	[153]
	5-FU–LV and L-OHP (5-FU 3000–3600 mg/m², LV 1200–1500 mg/m², L-OHP, 100–125 mg/m², q 2–3 weeks)	Meta-analysis of three international randomised Phase III	ChronoFLO vs Conv (FOLFOX2 or constant rate infusion)	842 pts (497 M, 345 F)	Sex-dependent efficacy of optimal fixed schedule: – Median survival Male: ChronoFLO: 20.8 months Conv: 17.5 months – Median survival Female: ChronoFLO: 16.6 months Conv: 18.4 months – Same sex-schedule interaction for progression-free survival and tumour response rate in pooled analysis and for each randomised trial	[154]

Chrononutrition in the prevention and treatment of cancer



Scheduled food access enhances circadian system function and slows tumor growth in mice

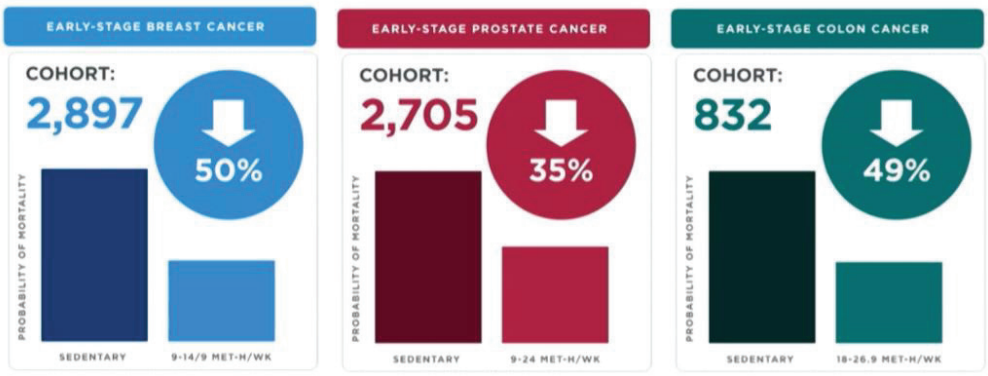
Matsunaga et al, 2004. J Pharmacol Exp Ther, 311(2)
Li et al, 2010. Cancer Res, 70(8)

SLEEP AND EXERCISE

Chrononutrition in the prevention and treatment of cancer

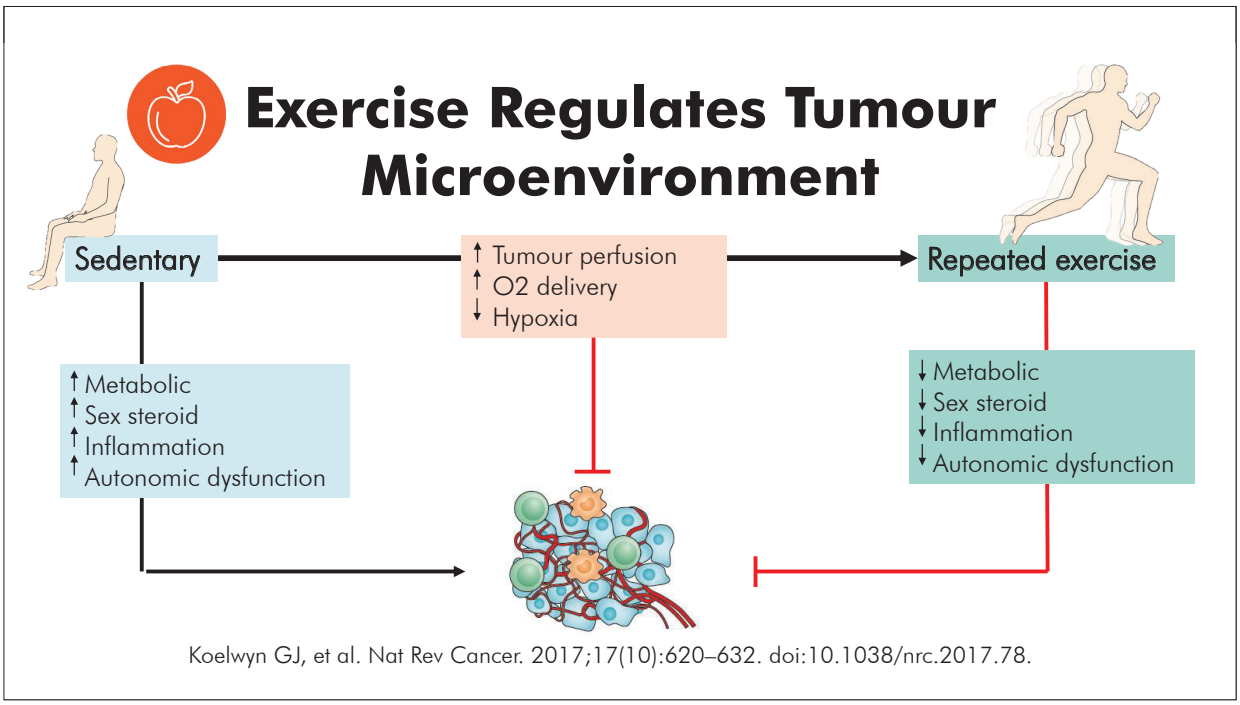
- Caloric period of 6 to 12 h each day (upper end of range if bodyweight loss is a problem)
- Breakfast ≥ 30 mins after natural wake time
- Finish final meal ≥ 2 h before bedtime
- 3 to 6 h between meals
- Consume the majority of calorie, carbohydrate, and fat intakes in the first half of the caloric period
- At caloric events, consume carbohydrate-rich items last
- Regularity is key

Exercise and Cancer Outcomes

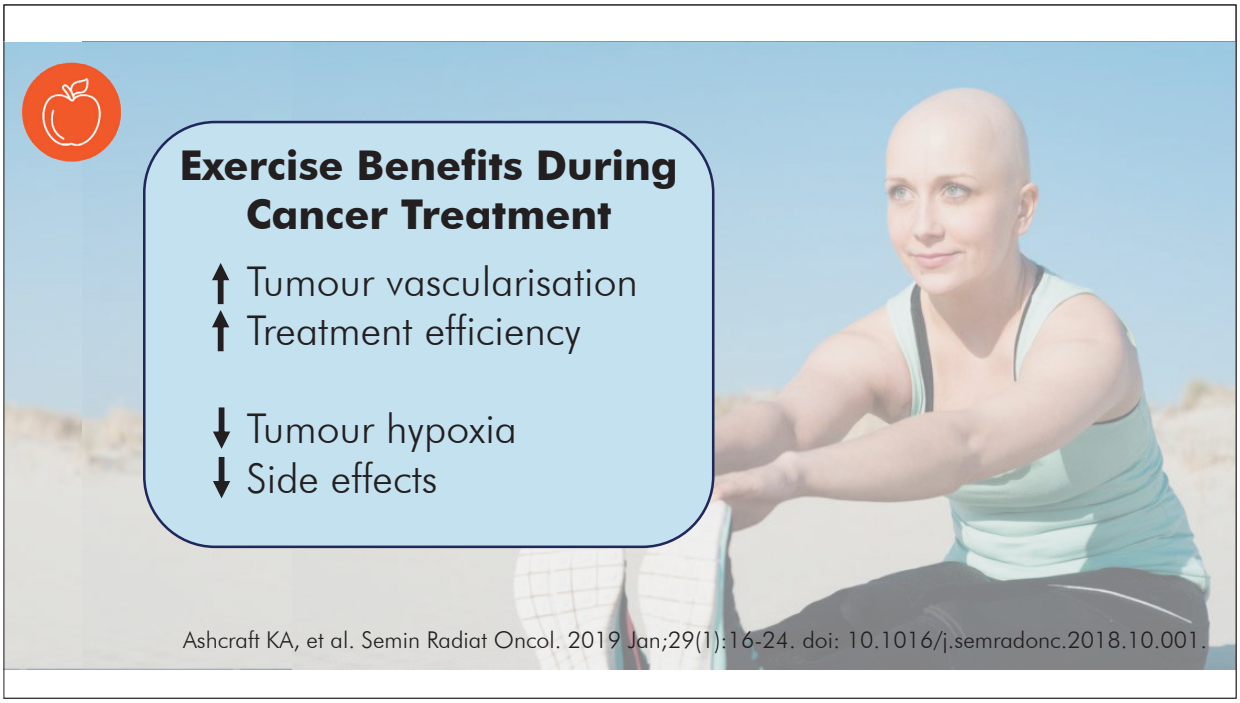


Holmes MD, et al. *JAMA*. 2005;293(20):2479–2486. doi:10.1001/jama.293.20.2479;
Kenfield SA, et al. *J Clin Oncol*. 2011;29(6):726–732. doi:10.1200/JCO.2010.31.5226;
Meyerhardt JA, et al. *J Clin Oncol*. 2006;24(22):3527–3534. doi:10.1200/JCO.2006.06.0855.

SLEEP AND EXERCISE



Koelwyn GJ, et al. Nat Rev Cancer. 2017;17(10):620–632. doi:10.1038/nrc.2017.78.



Ashcraft KA, et al. Semin Radiat Oncol. 2019 Jan;29(1):16-24. doi: 10.1016/j.semradonc.2018.10.001.

SLEEP AND EXERCISE

Anti-Cancer Properties of Exercise

Ashcraft KA, et al. Semin Radiat Oncol. 2019 Jan;29(1):16-24. doi: 10.1016/j.semradonc.2018.10.001.

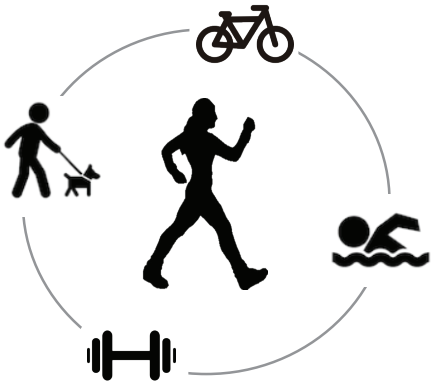
Exercise Recommendations

150 minutes

of moderate intensity aerobic exercise per week

including

2-3 resistance exercise sessions per week



Cancer Council Australia. [Internet]. Available from: https://www.cancer.org.au/news/blog/treatment/every-cancer-patient-should-be-prescribed-exercise-medicine.html

SLEEP AND EXERCISE

Goals Of Exercise In Cancer

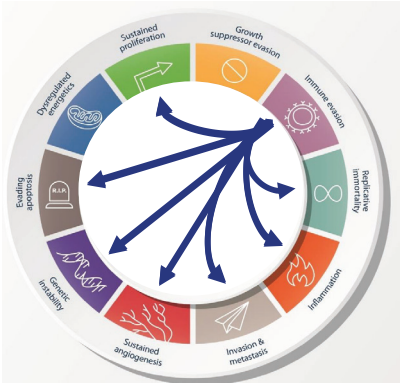
- Restore and improve physical function, strength and flexibility
- Improve function: cardiorespiratory, endocrine, neurological, muscular, cognitive
- Improve treatment tolerance and reduce risk of reoccurrence
- Improve quality of life

Schwartz AL, et al. Oncology (Williston Park). 2017 Oct 15;31(10):711-7. PMID: 29083464.

IMMUNE SUPPRESSION

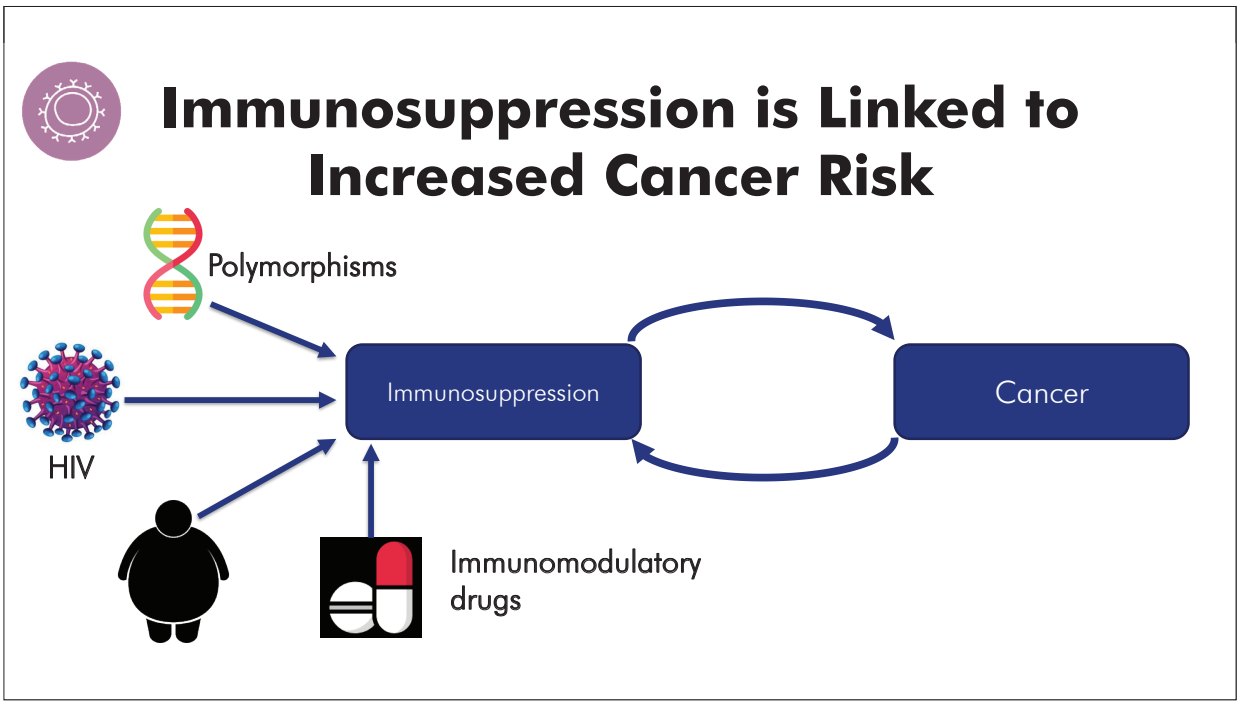
Immune Suppression

Immune Evasion Promotes Additional Hallmarks of Cancer



Yang L, et al. Semin Cancer Biol. 2017 Dec;47:185-195. doi: 10.1016/j.semcancer.2017.08.001.

IMMUNE SUPPRESSION

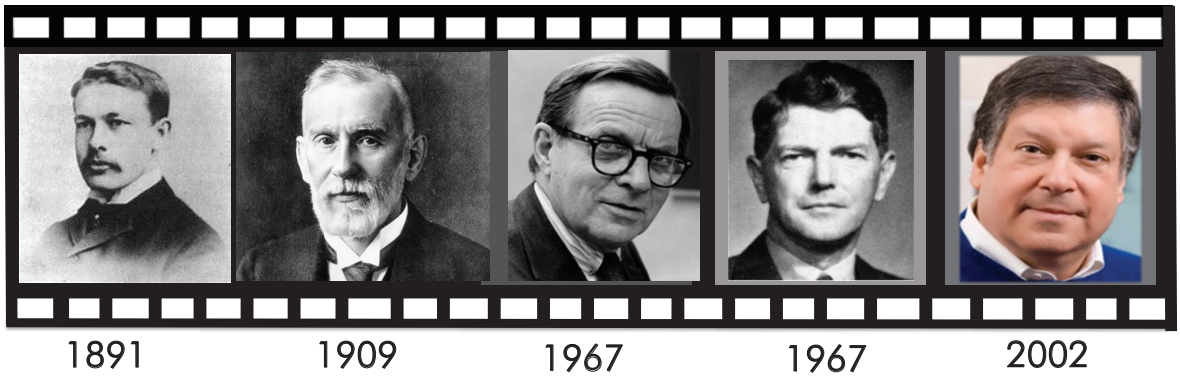


Immunosupression causes cancer references

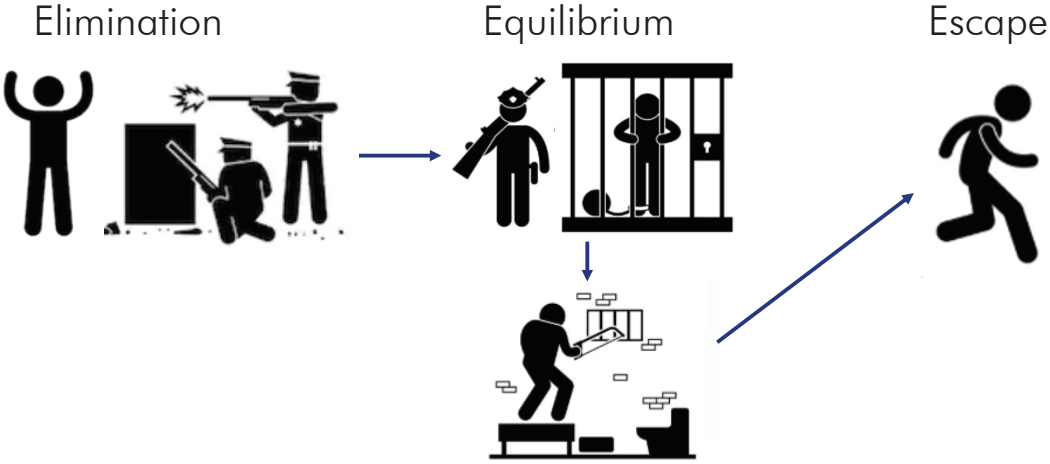
- Morvan MG, Lanier LL. NK cells and cancer: you can teach innate cells new tricks. Nat Rev Cancer. 2016;16(1):7–19. doi:10.1038/nrc.2015.5.
- Silverberg MJ, Chao C, Leyden WA, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. *Cancer Epidemiol Biomarkers Prev*. 2011;20(12):2551–2559. doi:10.1158/1055-9965.EPI-11-0777.
  Tobin LM, Mavinkurve M, Carolan E, et al. NK cells in childhood obesity are activated, metabolically stressed, and functionally deficient. *JCI Insight*. 2017;2(24):e94939. Published 2017 Dec 21. doi:10.1172/jci.insight.94939.
- Axelrad JE, Lichtiger S, Yajnik V. Inflammatory bowel disease and cancer: The role of inflammation, immunosuppression, and cancer treatment. *World J Gastroenterol*. 2016;22(20):4794–4801. doi:10.3748/wjg.v22.i20.4794.

IMMUNE SUPPRESSION

The Concept of Immune Surveillance in Cancer



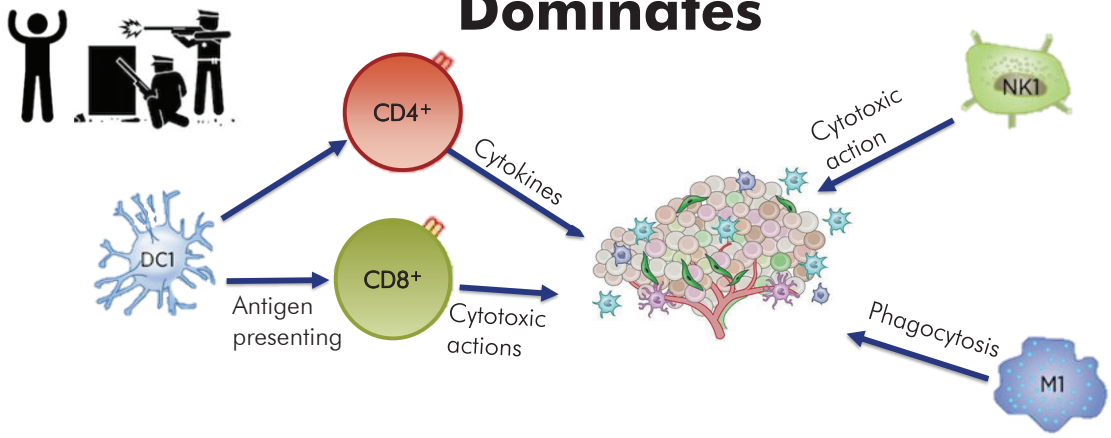
The Three E's of Immunoediting



Adapted from Muenst S. J Intern Med. 2016 Jun;279(6):541-62. doi: 10.1111/joim.12470.

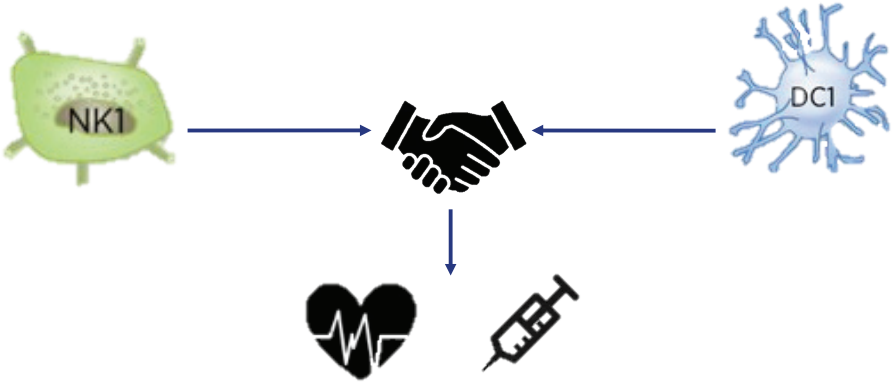
IMMUNE SUPPRESSION

When Anti-Tumour Immunity Dominates



Adapted from: Mittal D. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.

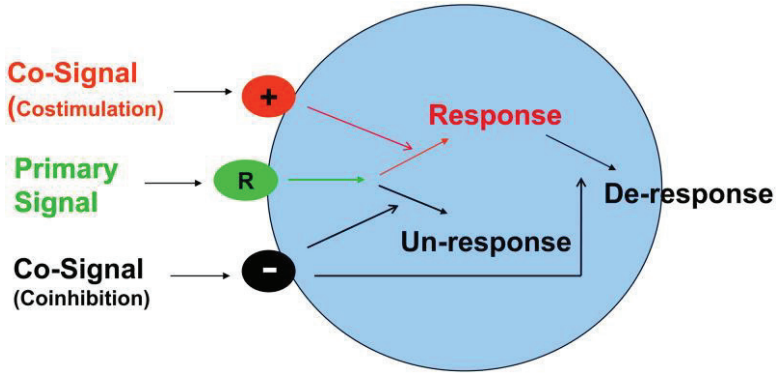
NK-DC1 Clusters Associated With Better Outcomes



Barry KC. Nat Med. 2018;24(8):1178–1191. doi:10.1038/s41591-018-0085-8;
Böttcher JP. Trends Cancer. 2018;4(11):784–792. doi:10.1016/j.trecan.2018.09.001;
Böttcher JP. Cell. 2018;172(5):1022–1037.e14. doi:10.1016/j.cell.2018.01.004.

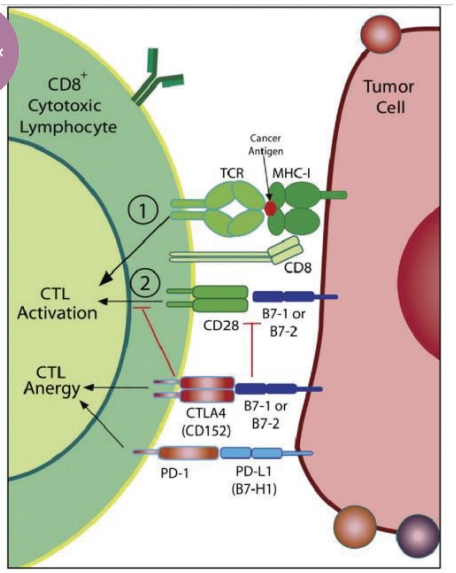
IMMUNE SUPPRESSION

Co-Stimulation Model of Cytotoxic Immune Control



Zhu Y, et al. 2011 Apr 22;34(4):466-78. doi: 10.1016/j.immuni.2011.04.008.

Tumour Elimination Depends on T Cell Activation

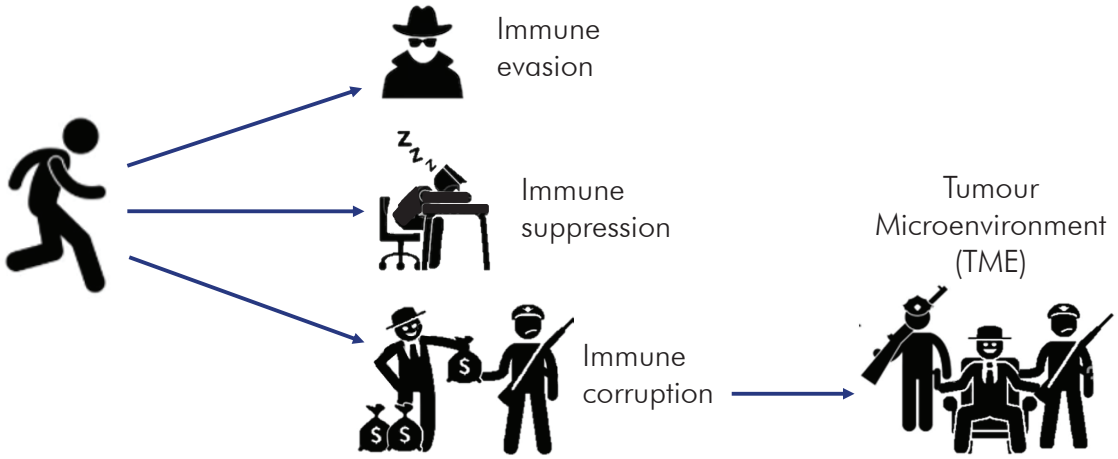


Infiltration of T cells in the tumour microenvironment is a critical factor in prognosis for many cancers.

Burkholder B. Biochim Biophys Acta. 2014;1845(2):182–201. doi:10.1016/j.bbcan.2014.01.004.

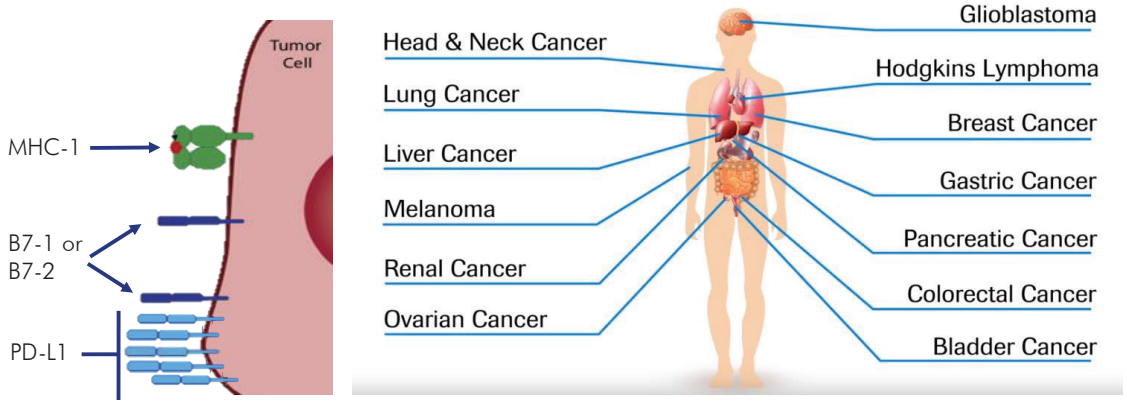
IMMUNE SUPPRESSION

The Great Escape



Adapted from: Mittal D. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004.

Overexpression of PD-L1 Confers a Poorer Prognosis



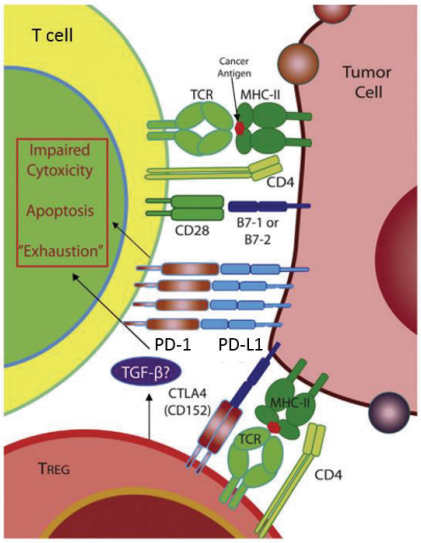
Patel SP. Mol Cancer Ther. 2015;14(4):847–856. doi:10.1158/1535-7163.MCT-14-0983.

IMMUNE SUPPRESSION

Tumours and the TME Exhaust T cells

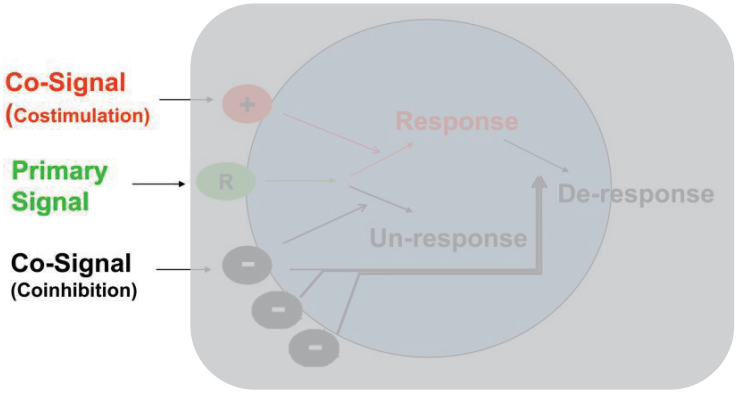
Exhausted T cells:

- ↑ Inhibitory receptors
- ↓ IFN-γ and TNF-α
- ↓ Proliferation
- Poor killing ability



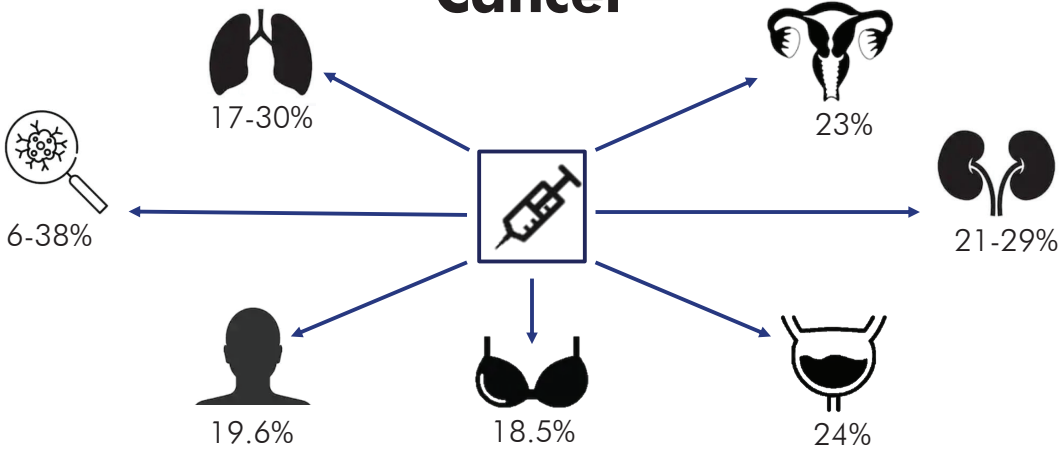
Ando M. Immunol Med. 2019 Dec 10:1-9. doi: 10.1080/25785826.2019.1698261;
Burkholder B. Biochim Biophys Acta. 2014;1845(2):182–201. doi:10.1016/j.bbcan.2014.01.004.

T Cell Exhaustion



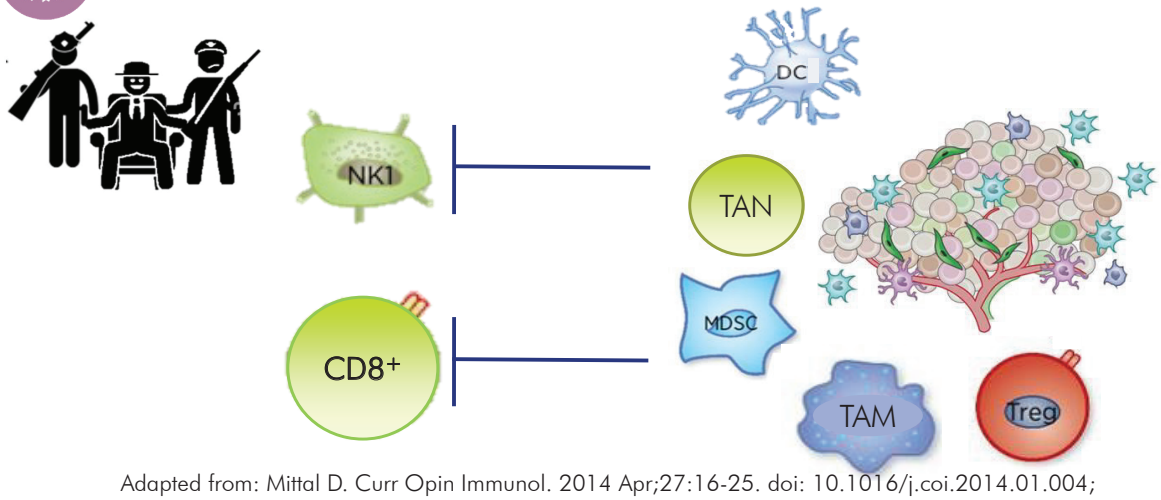
IMMUNE SUPPRESSION

PD-1 Immunotherapy Response in Cancer



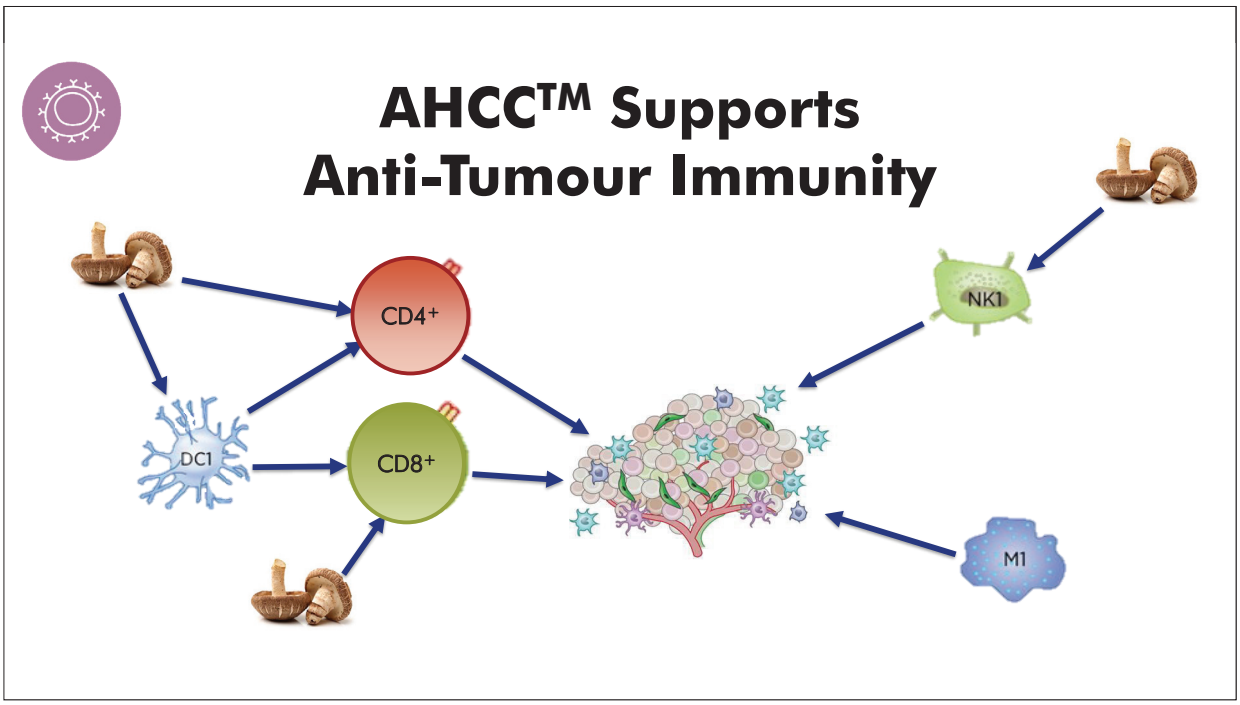
Adapted from:Lipson EJ. Semin Oncol. 2015;42(4):587–600. doi:10.1053/j.seminoncol.2015.05.013.

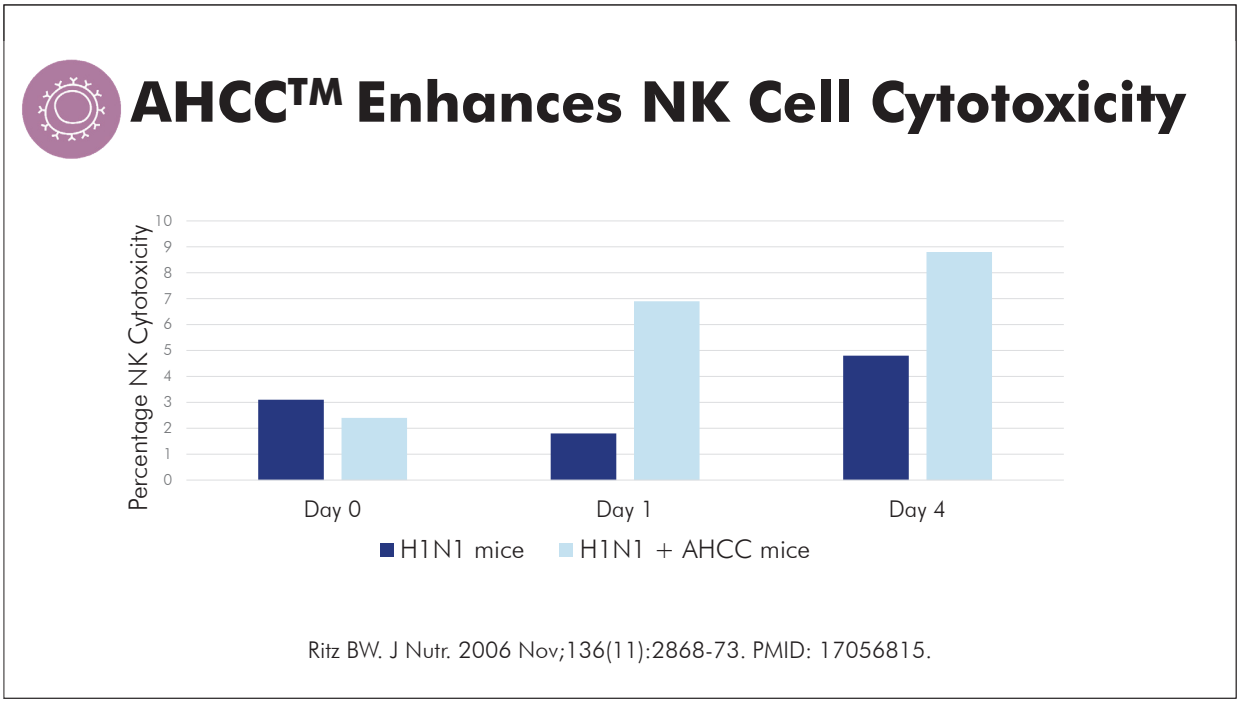
The Tumour Mafia Boss



Adapted from: Mittal D. Curr Opin Immunol. 2014 Apr;27:16-25. doi: 10.1016/j.coi.2014.01.004; Vitale M. Eur J Immunol. 2014 Jun;44(6):1582-92. doi: 10.1002/eji.201344272.

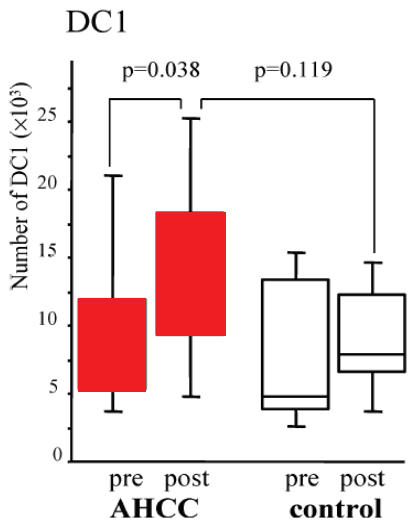
IMMUNE SUPPRESSION





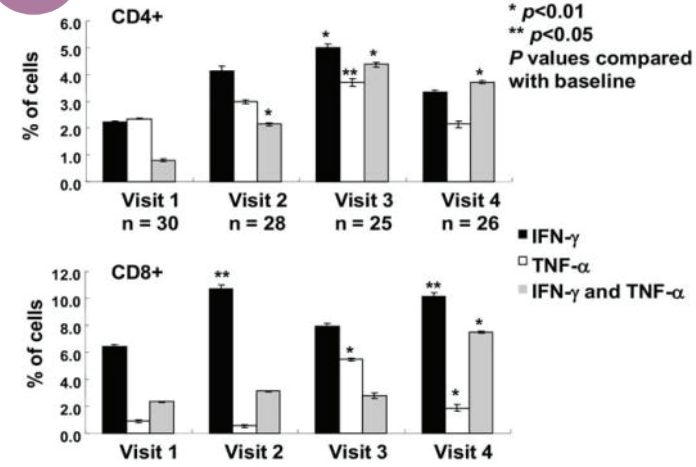
Ritz BW. J Nutr. 2006 Nov;136(11):2868-73. PMID: 17056815.

IMMUNE SUPPRESSION



AHCC™ Boosts Dendritic Type 1 Cells

Terakawa N. Nutr Cancer. 2008;60(5):643-51. doi: 10.1080/01635580801993280.



AHCC™ Boosts T Cell Function

The effects of AHCC™ are more evident in hosts with the **impaired** immune function.

Yin Z.Hum Immunol. 2010 Dec;71(12):1187-90. doi: 10.1016/j.humimm.2010.08.006.

IMMUNE SUPPRESSION

AHCC™ Enhances Immunity with Chemotherapy

Group	CD8+ (%)	NK (%)	CD4+/CD8+ (%)
Control	8.7	6.7	2.5
5-fluorouracil (5-FU)	9.6	5.0	2.8
5-FU + AHCC™	10.3	10.7 - ↑ 50%	3.9

Higher CD4+/CD8+ ratio associated with stronger immunological response

Cao Z. Nutr Res Pract. 2015 Apr;9(2):129-36. doi: 10.4162/nrp.2015.9.2.129.

Anti-Cancer Properties of AHCC™

IMMUNE SUPPRESSION

AHCC™ and Ginger

Key Actions:

- Immune enhancement, surveillance and modulation
- Gastrointestinal support
- Anti-inflammatory
- Anti-emetic
- Autonomic nervous system modulation

Clinical Applications:

- Cancer support
  - Improves survival rate, enhances chemotherapy efficacy
  - Reduce anticancer drug treatment side effects
- Chronic and critical infections

CASE STUDY: BREAST CANCER

Case Study: Mrs S – Breast Cancer

- 62 year old female presented with breast cancer (oestrogen positive, HER2 negative) – diagnosed December 2019.
- PET Scan showed no lymph or metastatic involvement.
  - Clip placed for future monitoring.
- History of hyperinsulinaemia managed by paleo diet and exercise.

Symptoms:

- Stress, fatigue, recent liver function elevation, reflux, constipation and weight gain.

Case kindly provided by Carla Wrenn. Peninsula Herbal Dispensary, Mornington, VIC

Case Study – Mrs S

- Patient sought assistance for complementary medicine support to:
  - Minimise chemotherapy side effects.
  - Nutritional advice to assist with past pre-diabetic elevated blood sugar levels.
  - Achieving the best outcome possible providing simple integrative naturopathic support.

Screening

- Patient Reported Outcome Measurement Information System (PROMIS) score 52

CASE STUDY: BREAST CANCER

Case Study: Mrs S – Medications

Oncology treatment plan

- AC-T – chemotherapy combination specific for breast cancer:
  - Initial doxorubicin and cyclophosphamide - 21 day cycle for 4 cycles followed by 12 weekly paclitaxel sessions.
- Pegfilgrastim and dexamethasone will also be used throughout the treatment cycles.
- Surgery will follow chemotherapy.
- 4 weeks of daily radiation will follow surgery.

After first full round of chemotherapy, nausea, poor energy and hot flushes were having a very significant impact on Mrs S quality of life. Treatment tailored to reduce these effects.

Case Study: Mrs S – Initial Prescription

Supplement Prescription (prior to second chemotherapy cycle)

- *AHCC™ and Ginger* – 2 capsules twice per day – avoided the day of and day after chemotherapy infusion (for 8 weeks).
- *Bovine Protein for Good Health* – 1-2 tablespoons daily
- Nausea and hot flush herbal homeopathic drops

Dietary Prescription (prior to second chemotherapy cycle)

- Whole food, blood glucose balancing, low carbohydrate, quality protein, anti-inflammatory diet
- Time Restricted Feeding -16:8 schedule of fasting.
- Fast around chemotherapy infusion to minimise side effects.

CASE STUDY: BREAST CANCER

Case Study: Mrs S – Results

Week 4

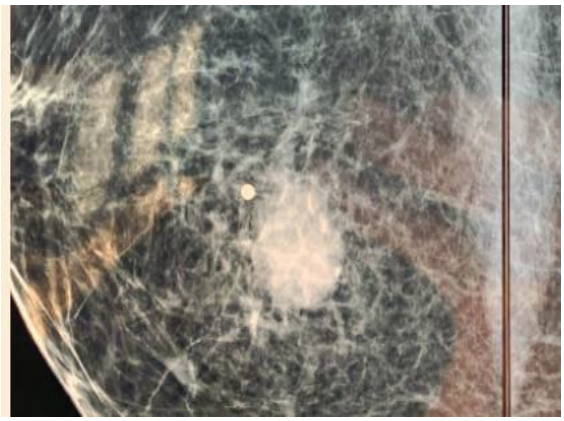
- Patient completed third cycle of chemotherapy. Oncologist advised tumour is now more palpable.
- Hot flushes have settled.
- PROMIS questionnaire shows improvements in fatigue and nausea.

Week 8

- Mammogram and CT scan showed complete metabolic response to chemotherapy.
- Natural treatment suspended in preparation for surgery.

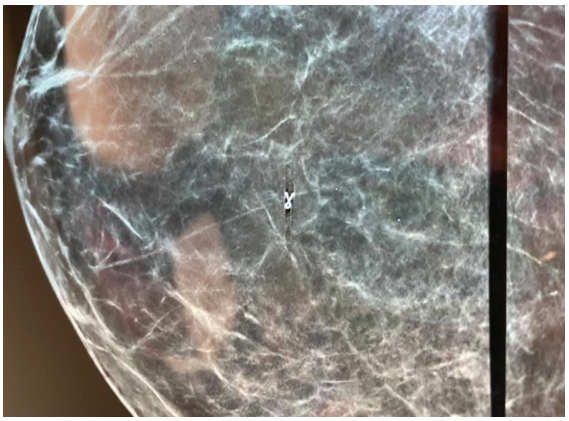
Case kindly provided by Carla Wrenn, Clinic: Peninsula Herbal Dispensary, Mornington, VIC

Initial Mammogram



Baseline

Post-Chemotherapy Treatment Mammogram



8 weeks

CASE STUDY: BREAST CANCER

AHCC™ and Ginger

Key Actions:

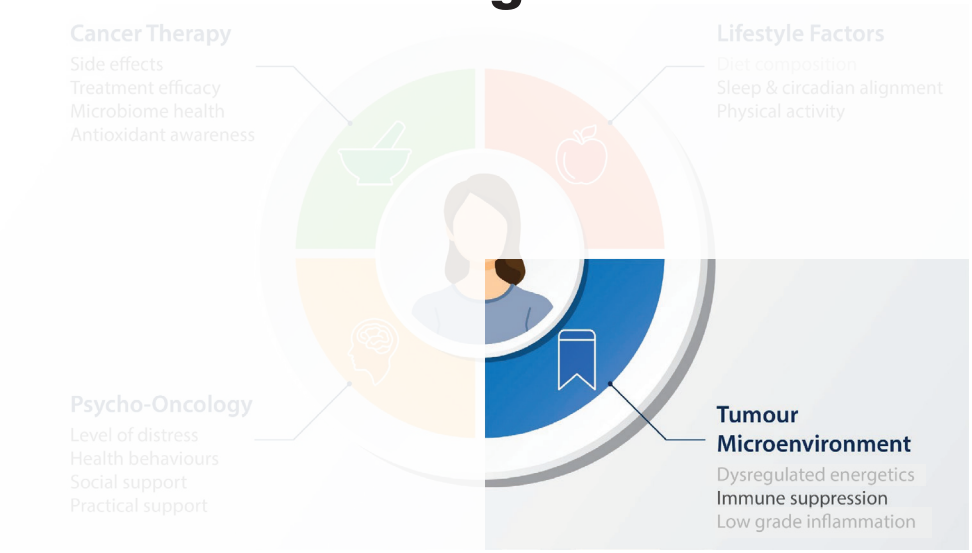
- Immune enhancement, surveillance and modulation
- Gastrointestinal support
- Anti-inflammatory
- Anti-emetic
- Autonomic nervous system modulation

Clinical Applications:

- Chronic and critical infections
- Cancer support
  - Improves survival rate, enhances chemotherapy efficacy
  - Reduce anticancer drug treatment side effects

LOW GRADE INFLAMMATION

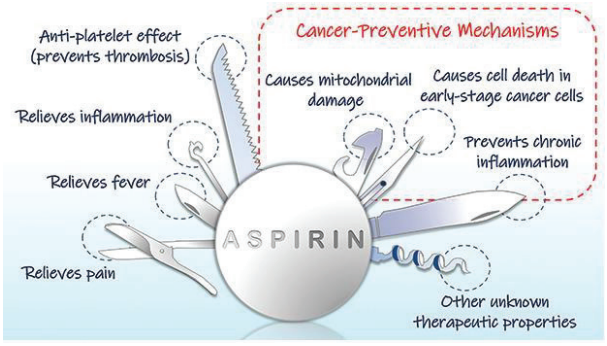
Tumour Promoting Inflammation



Aspirin Linked to Reduced Incidence of Cancer

Reduce incidence of:

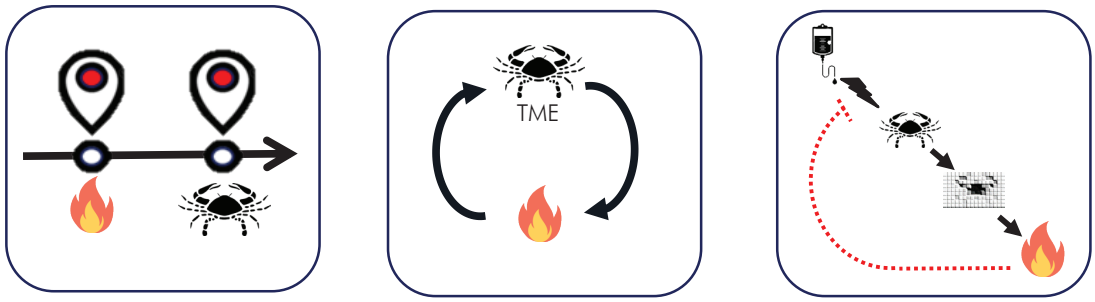
- Colorectal cancer
- Prostate cancer
- Ovarian cancer
- Liver cancer
- Cancer recurrence



Campi R, et al. Eur Urol Focus. 2019 Nov;5(6):1029-1057. doi: 10.1016/j.euf.2018.04.001.

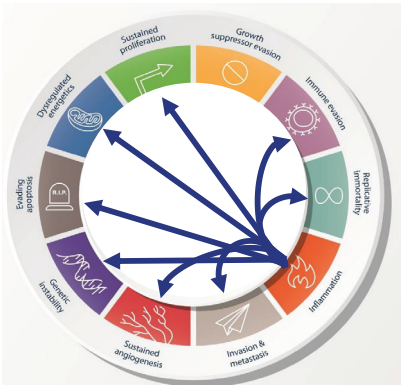
LOW GRADE INFLAMMATION

Inflammation Intimately Connected to Cancer



Greten FR, et al. Immunity. 2019 Jul 16;51(1):27-41. doi: 10.1016/j.immuni.2019.06.025. R.

Inflammation Drives Cancer Hallmarks



Yang L, et al. Semin Cancer Biol. 2017 Dec;47:185-195. doi: 10.1016/j.semcancer.2017.08.001.

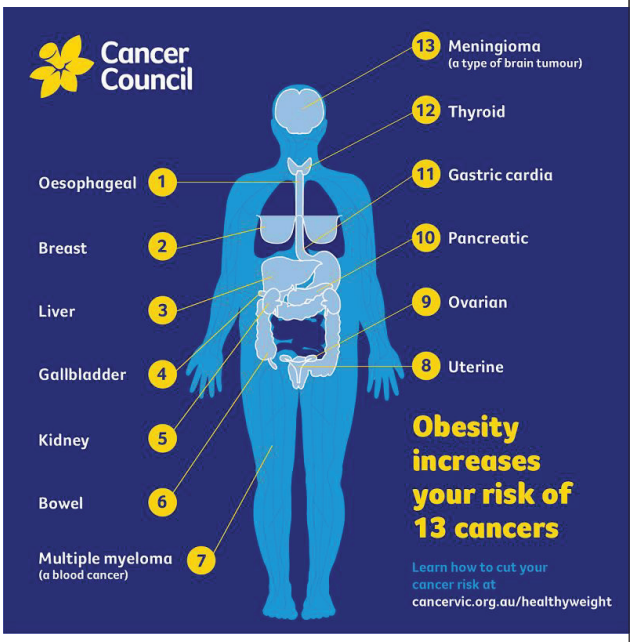
LOW GRADE INFLAMMATION

Obesity Risks 13 Cancers

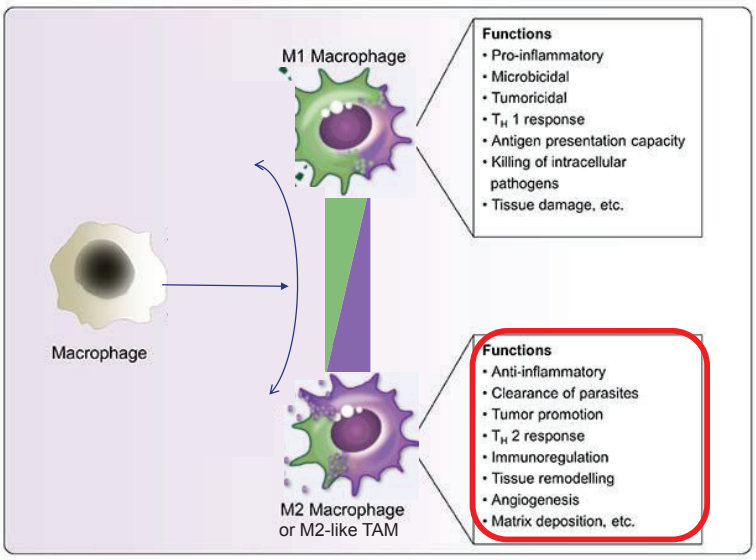
AWARENESS OF CANCER LINKED TO OVERWEIGHT AND OBESITY

Around 3 in 4 people did not think cancer could result from being overweight or obese.*

*When asked "Which, if any, health conditions do you think can result from being obese/overweight?"



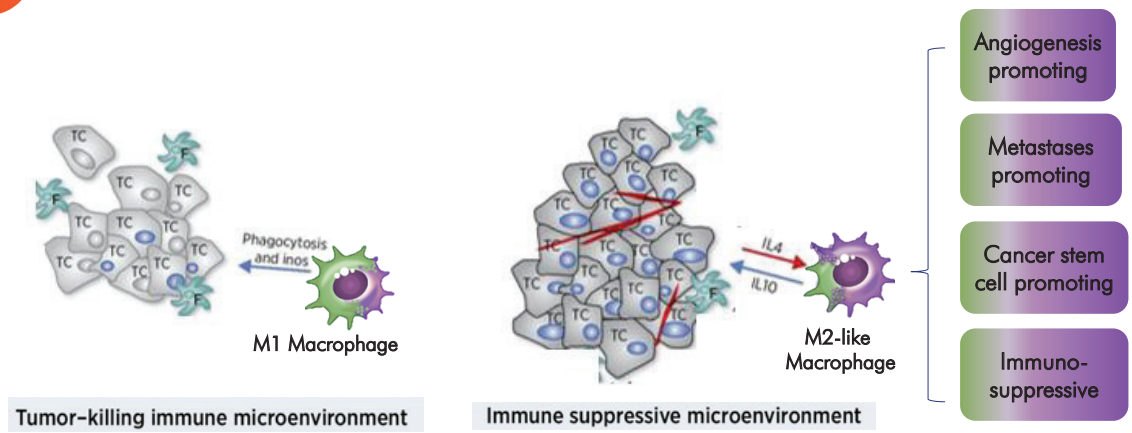
Macrophages Polarise For Different Functions



Adapted from: Saqib U, et al. Oncotarget. 2018 Apr 3;9(25):17937-17950. doi: 10.18632/oncotarget.24788.

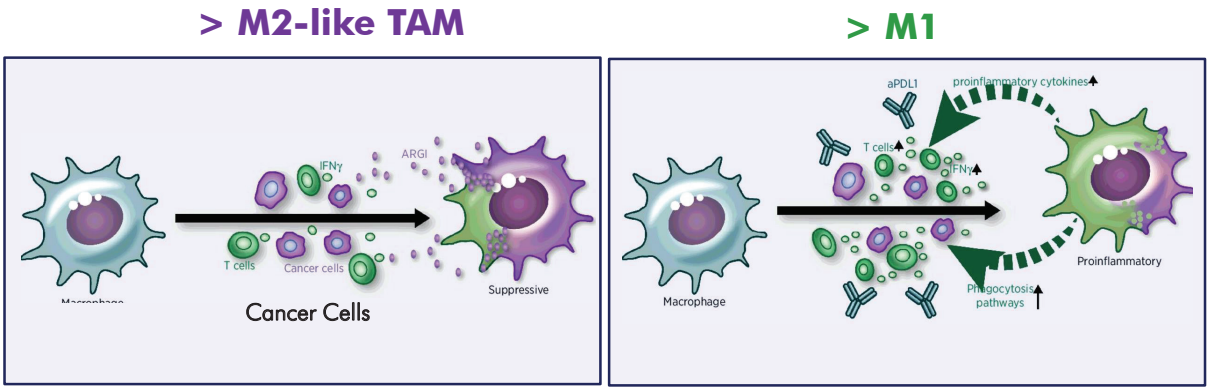
LOW GRADE INFLAMMATION

TME Suppresses Marcophages



Hinshaw DC, et al. Cancer Res. 2019;79(18):4557-4566. doi: 10.1158/0008-5472.CAN-18-3962;
Sainz B Jr, et al. Mediators Inflamm. 2016;2016:9012369. doi: 10.1155/2016/9012369.

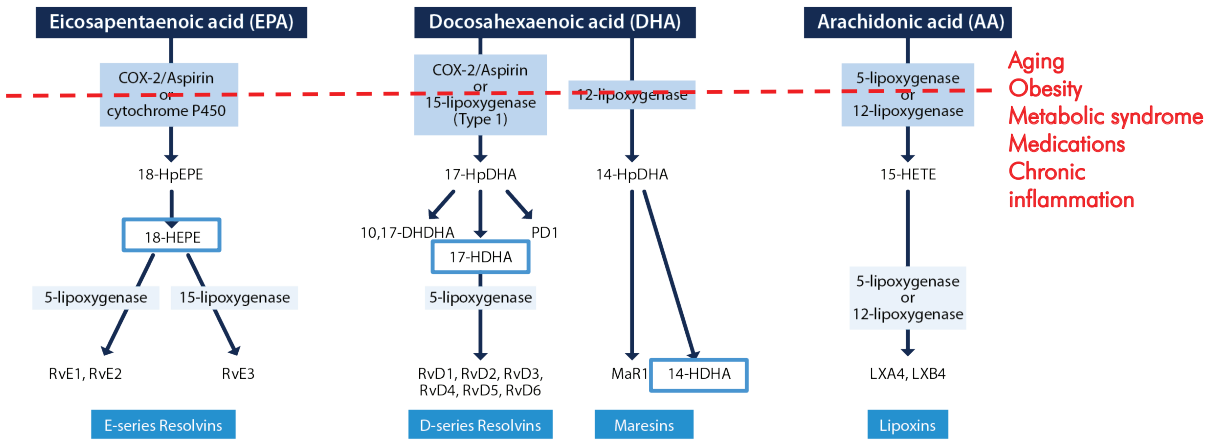
Chemo Reverses Immune Suppression



Xiong H, et al. Cancer Res. 2019;79(7):1493-1506. doi: 10.1158/0008-5472.CAN-18-3208.

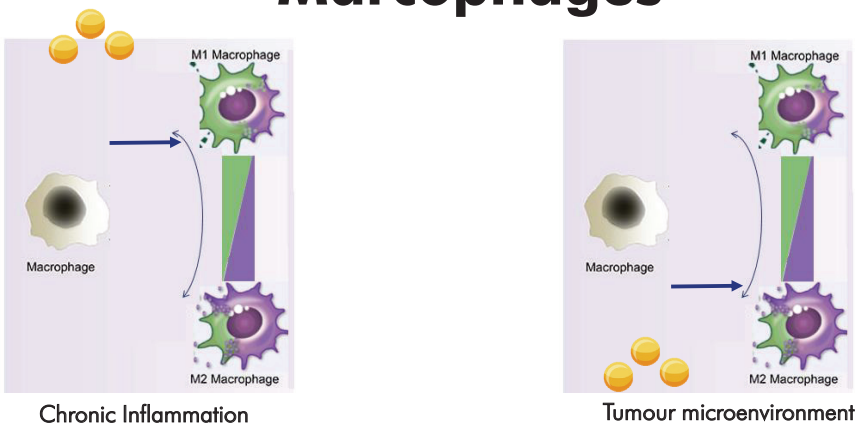
SPECIALISED PRO-RESOLVING MEDIATORS

SPMs – The Lipid Mediator Switch



Barden AE, et al. Prostaglandins Leukot Essent Fatty Acids. 2016 Apr;107:24-9. doi: 10.1016/j.plefa.2016.03.004.

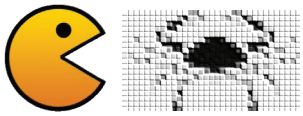
SPMs are Adaptogens for Marcophages



Adapted from: Zhang Q. Front Immunol. 2017 Feb 2;8:71. doi: 10.3389/fimmu.2017.00071

SPECIALISED PRO-RESOLVING MEDIATORS

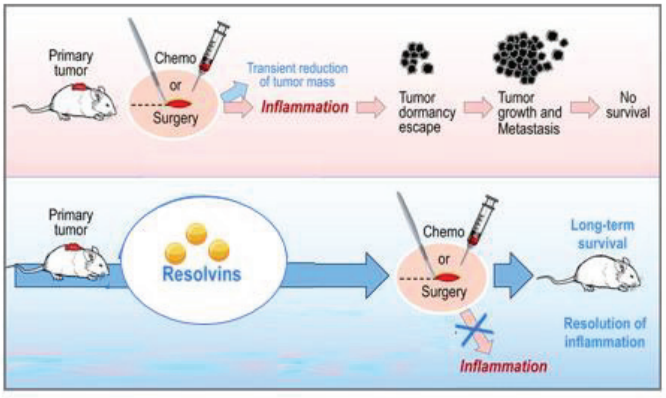
SPMs Resolve Inflammatory Cancer Biology



Increase phagocytosis of debris

Sulciner ML, et al. Cancer Metastasis Rev. 2018;37(2-3):557-572. doi: 10.1007/s10555-018-9754-9.

SPMs Promote Resolution Without Suppressing Immunity



Panigrahy D, et al. J Clin Invest. 2019 Jun 17;129(7):2964-2979. doi: 10.1172/JCI127282.

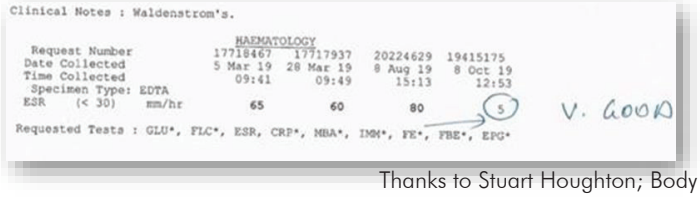
SPECIALISED PRO-RESOLVING MEDIATORS

Specialised Pro-Resolving Mediators – Feedback

The results I'm seeing on ESR is incredible, such as two recent patients:

- *The* **ESR went from 59 to 10**, *after being elevated for 2.5 years. She has previously been on pregnisone with no change. She could only afford one product and SPM was used.*

- *The second patient the* **ESR went from 65 to 5**, *after being elevated for over 10 years. This patient has managed Waldenström. Since treating her for the past 3 years she has not required any chemotherapy which she was on a 6 monthly cycle for 7 years to control. After starting SPM mid Aug 2019 the ESR has returned to normal. Today this patient turns 81.*



Clinical Notes : Waldenstrom's.

	HAEMATOLOGY			
Request Number	17718467	17717937	20224629	19415175
Date Collected	5 Mar 19	28 Mar 19	8 Aug 19	8 Oct 19
Time Collected	09:41	09:49	15:13	12:53
Specimen Type: EDTA				
ESR (< 30) mm/hr	65	60	80	5

V. GOOD

Requested Tests : GLU*, FLC*, ESR, CRP*, MBA*, IMM*, FE*, FBE*, EPG*

Thanks to Stuart Houghton; Body Belief Therpaies – SYD, NSW

PERIPHERAL NEUROPATHY AND PEA

Chemotherapy-Induced Peripheral Neuropathy

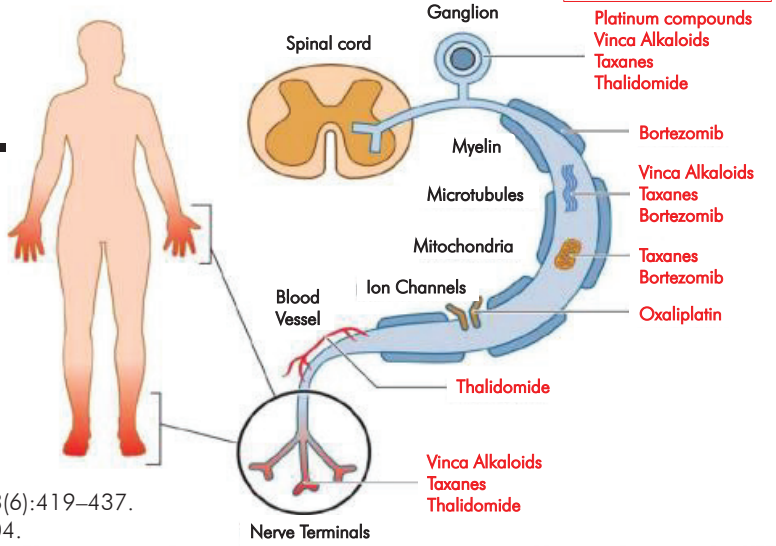
Affects 60-75% of chemotherapy patients

Walking ability hindered in 66% of patients

Side effect with most impact on QOL

Persistent tingling and numbness in 81% of patients

Chemotherapy-Induced Peripheral Neuropathy

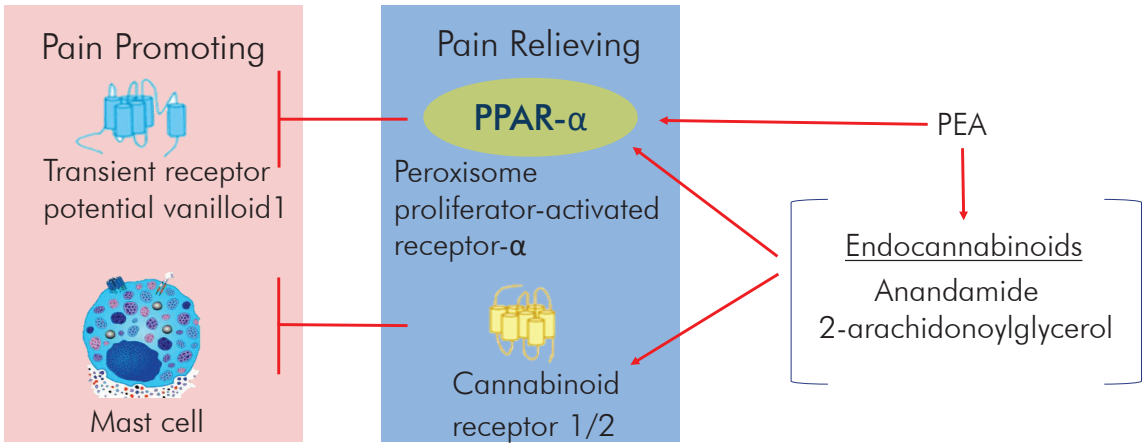


Park SB. CA Cancer J Clin. 2013;63(6):419–437. doi:10.3322/caac.21204.

PERIPHERAL NEUROPATHY AND PEA

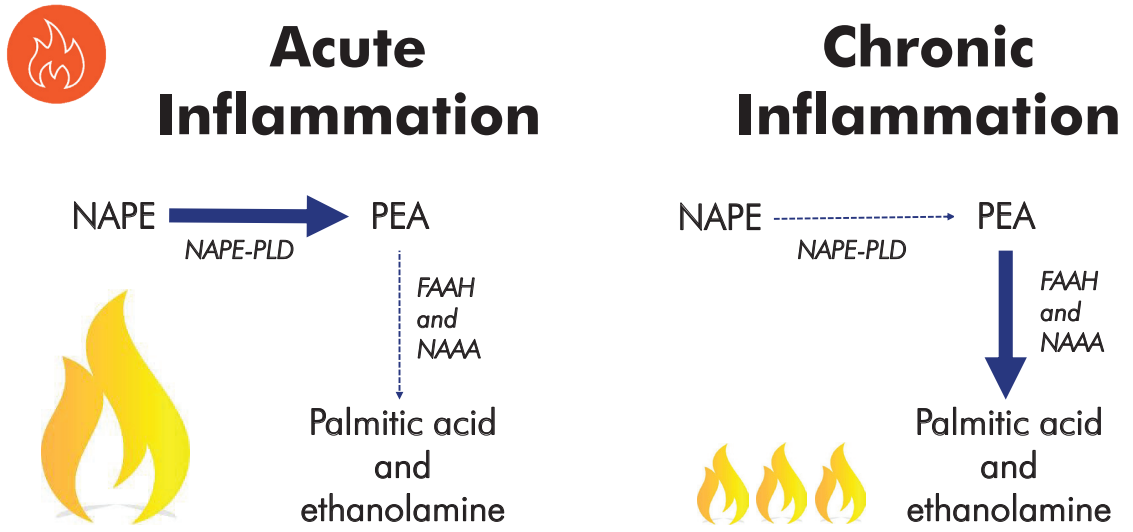
P for Pain; PEA for Pain Relief

PEA Indirectly Lowers Pain



Barrie N. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025;
Petrosino S. Br J Pharmacol. 2017 Jun;174(11):1349-1365. doi: 10.1111/bph.13580.

PERIPHERAL NEUROPATHY AND PEA



Alhouayek M. Drug Discov Today. 2014 Oct;19(10):1632-9. doi: 10.1016/j.drudis.2014.06.007;
Skaper SD. Inflammopharmacology. 2014 Apr;22(2):79-94. doi:0.1007/s10787-013-0191-7.

PEA Lowered Peripheral Neuropathy in Myeloma Patients

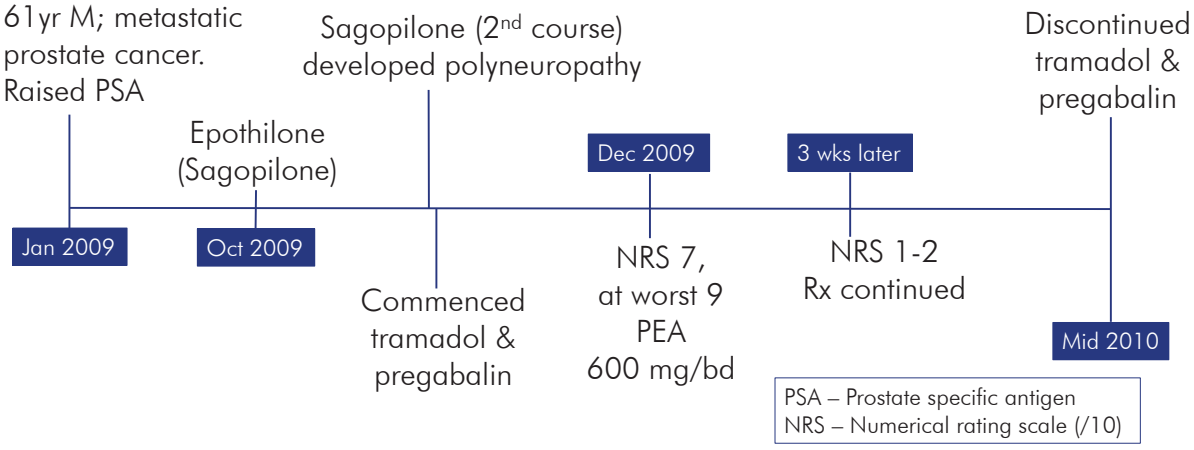
	Pre-treatment Mean +/- SD	Post-treatment Mean +/- SD
Pain (Numerical Rating Scale)	4.5 +/- 1.2	3.4 +/- 1.0

24% Reduction in pain compared with baseline

Truini A. CNS Neurol Disord Drug Targets. 2011 Dec;10(8):916-20. PMID: 22229320.

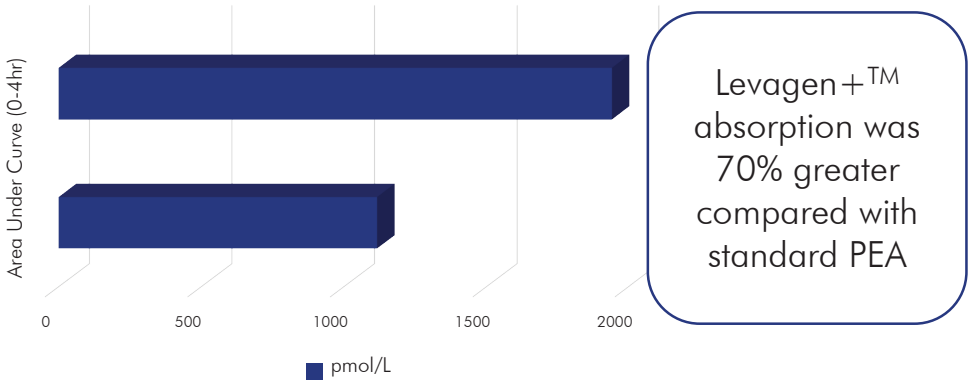
PERIPHERAL NEUROPATHY AND PEA

Polyneuropathy + PEA: Case Study



Hesselink JM. J Pain Res. 2012;5:437–442. doi:10.2147/JPR.S32143.

PEA Absorption Enhanced With Lipisperse®



Briskey D. Increased absorption of palmitoylethanolamide using a novel dispersion technology system (LipiSperse®).

PERIPHERAL NEUROPATHY AND PEA

Highly Bioavailable Palmitoylethanolamide (PEA) With Endocannabinoid Action

Key Actions:

- ECS Modulation
- Analgesic
- Anti-inflammatory
- Neuroprotective

Clinical Applications:

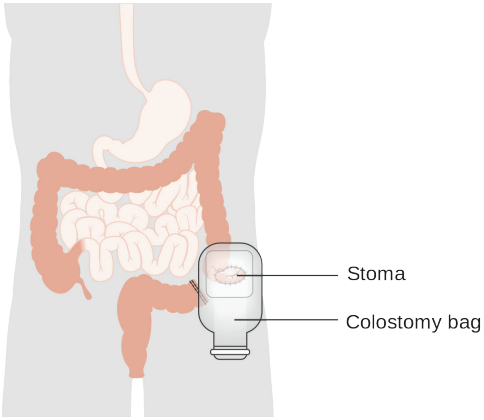
- Chronic and neuropathic pain
- Neurodegenerative conditions

CASE STUDY: POST OPERATIVE PAIN

Case Study: Jim - Post Operative Pain

- Male 63yrs – post-op ileostomy for colorectal cancer.
- Experiencing pain from surgical stitches and port insertion (from surgical recovery).
- Grey pallor, irritable and 8/10 pain.
- Diagnosed Sept 2019, followed by 5 weeks chemo- and radiotherapy.

" I'm irritable because of the pain.
I can't do the things I usually do.
Physically I'm struggling."



Jim – Initial Treatment

Initial post-op prescription:

- *AHCC™ and Ginger* – 2 capsules twice daily
- *Specialised Pro-Resolving Mediators* – 2 capsules twice daily
- *BCM-95™ Turmeric and Devil's Claw to Treat Chronic Inflammation*– 3 capsules twice daily
- *Meta Mag® Magnesium and Electrolytes to Rehydrate Without Carbs*– 3-4 serves per day

CASE STUDY: POST OPERATIVE PAIN

Jim – Prescription Update

Week 2:

- Added: *Highly Bioavailable Palmitoylethanolamide (PEA) With Endocannabinoid Action* – 1 capsule three times daily

Week 10:

- Reduced (*PEA*) to – 1 capsule twice daily

	Baseline (week 2)	Week 8	Week 14
Pain (10 is worst)	8/10	4/10	1/10
Energy (10 is best)	3/10	5/10	7/10
Fatigue (10 is worst)	7/10	5/10	3/10
# Oxycodone/day	4	1	0
# Paracetomol/day	2 to 3	1	0

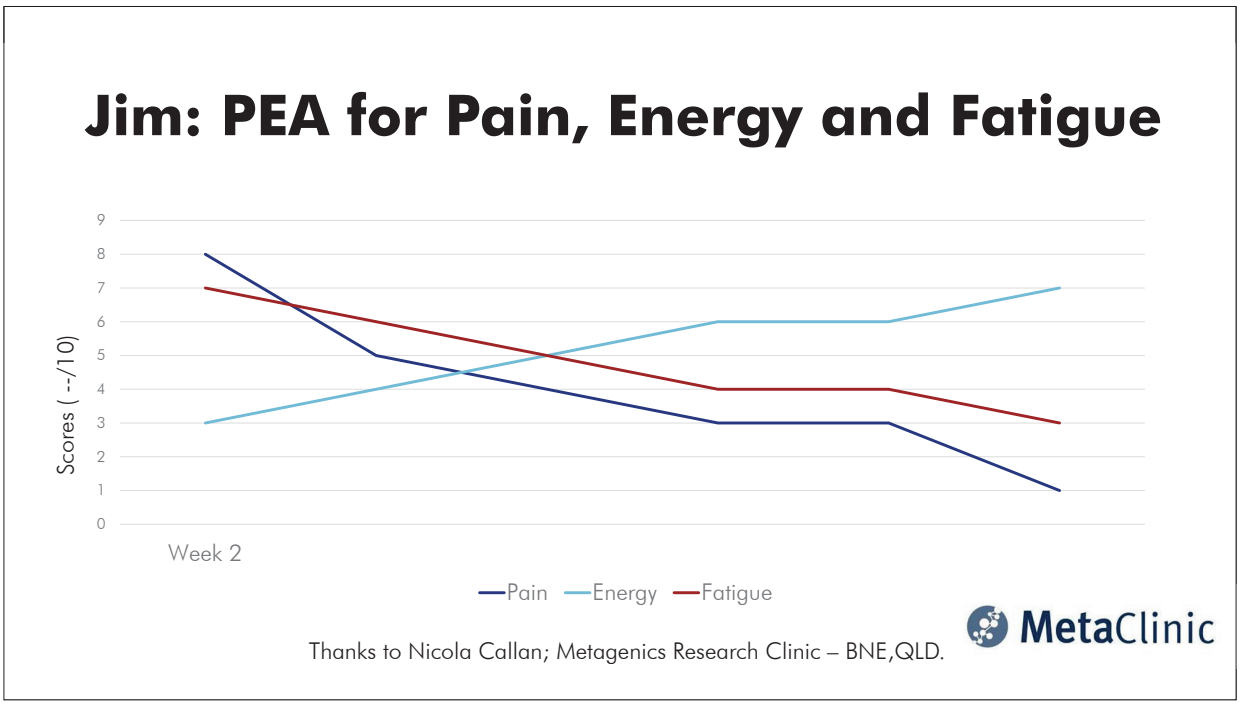
Jim - Outcomes

Four days after starting PEA, noticeable colour returning in cheeks.

"My stoma and stitches are not really painful now, the pain comes and goes but nothing I can't handle.

I'm able to walk the dog everyday and I'm moving better."

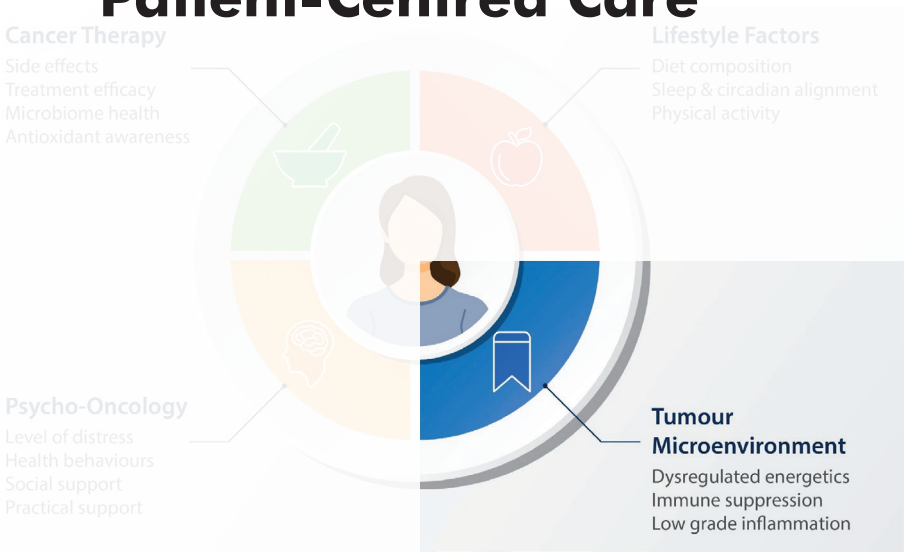
CASE STUDY: POST OPERATIVE PAIN



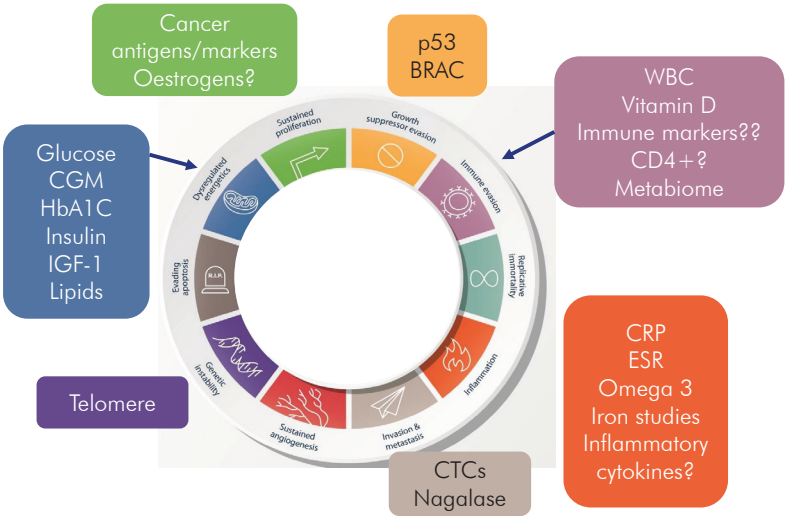
Thanks to Nicola Callan; Metagenics Research Clinic – BNE,QLD.

NOVEL AND EMERGING THERAPIES AND SCREENING

Patient-Centred Care

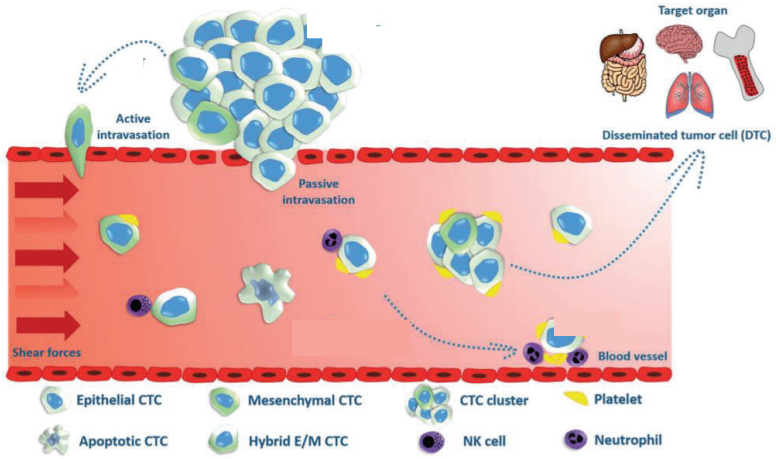


Possible Screening Tests



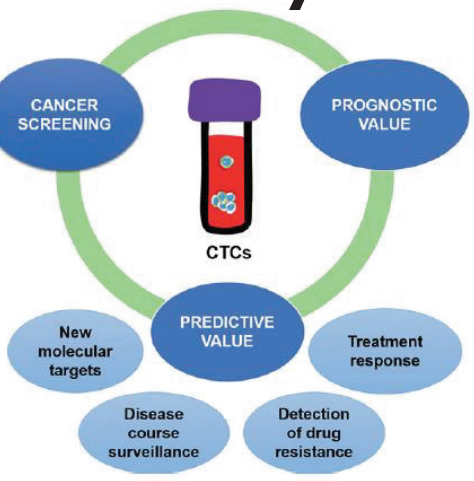
NOVEL AND EMERGING THERAPIES AND SCREENING

Circulating Tumour Cells



Lozar T, et al. Radiol Oncol. 2019 May 8;53(2):131-147. doi: 10.2478/raon-2019-0024.

Clinical Utility of CTCs

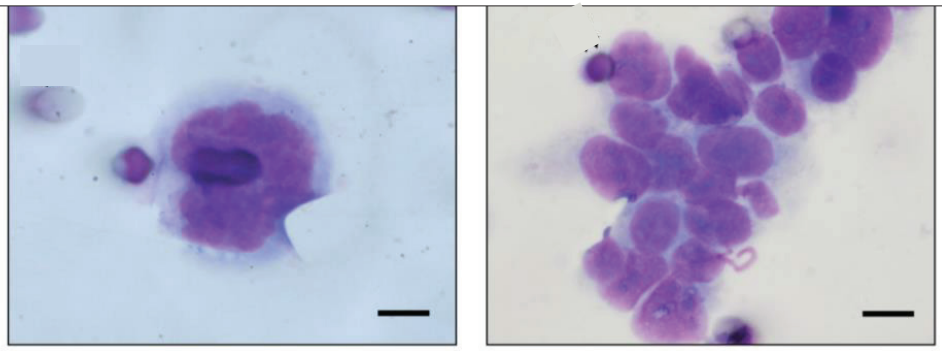


Lozar T, et al. Radiol Oncol. 2019 May 8;53(2):131-147. doi: 10.2478/raon-2019-0024.

NOVEL AND EMERGING THERAPIES AND SCREENING

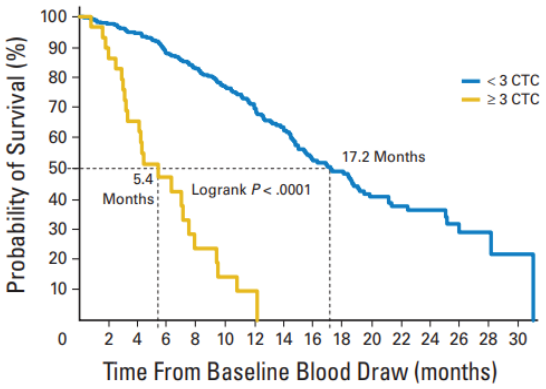
CTCs Detect Early Tumourogenesis

In patients with COPD, CTCs were detected 1to 4 years earlier than radiologic signs of malignancy.



Ilie M, et al. PLoS One. 2014 Oct 31;9(10):e111597. doi: 10.1371/journal.pone.0111597.

CTCs are Prognostic in Cancer

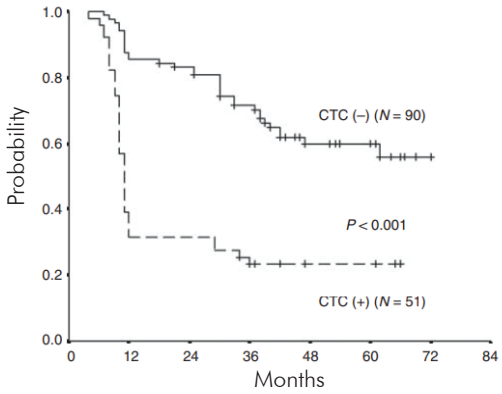


Metastatic patients with high baseline CTC counts that decrease after one cycle of chemotherapy have better prognosis.

Cohen SJ, et al. J Clin Oncol. 2008;26(19):3213-3221. doi:10.1200/JCO.2007.15.8923.

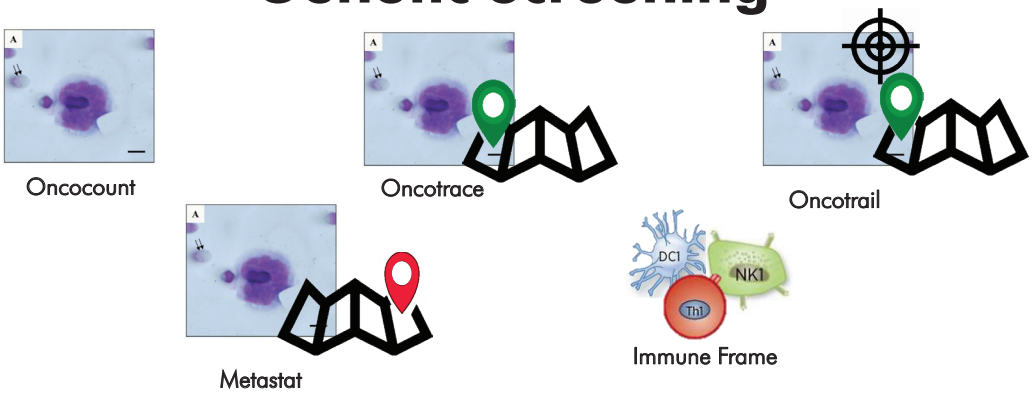
NOVEL AND EMERGING THERAPIES AND SCREENING

CTCs are Predictive of Cancer Recurrence



Lu CY, et al. Br J Cancer 2011; 104: 1178-84. doi: 10.1038/bjc.2011.40.

CTC Add-on Tests and Genetic Screening

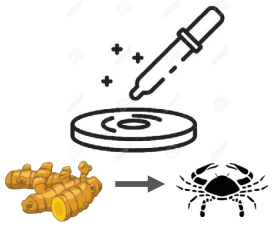


Lozar T, et al. Radiol Oncol. 2019 May 8;53(2):131-147. doi: 10.2478/raon-2019-0024.

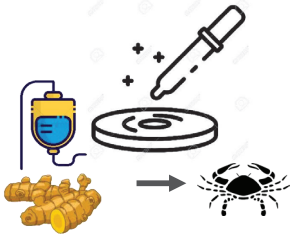
NOVEL AND EMERGING THERAPIES AND SCREENING

Therapeutics Screening

Onconomics



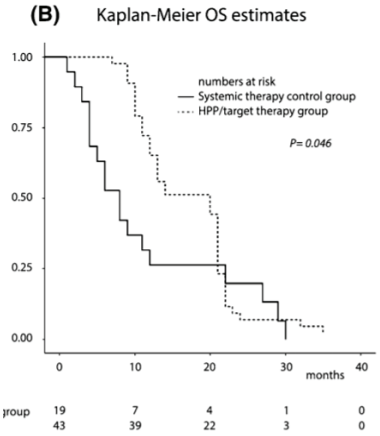
Onconomics Extracts



Onconomics Plus

Emerging Evidence on Onconomics

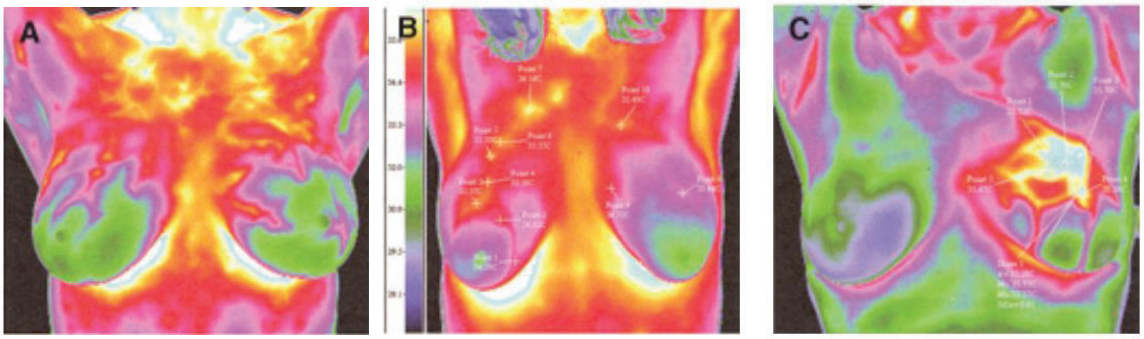
Onconomics



Guadagni S, et al. J Cancer Res Clin Oncol. 2020;146(1):205-219. doi: 10.1007/s00432-019-03046-3.

NOVEL AND EMERGING THERAPIES AND SCREENING

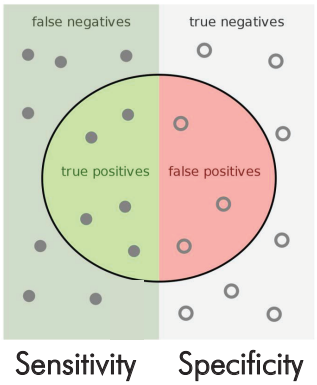
Breast Thermography



Normal. Early stage cancer in R. breast. Advanced cancer in L breast.

Kennedy DA, et al. Integr Cancer Ther. 2009 Mar;8(1):9-16. doi: 10.1177/1534735408326171.

Thermography Adds But *Does Not* Replace Mammography

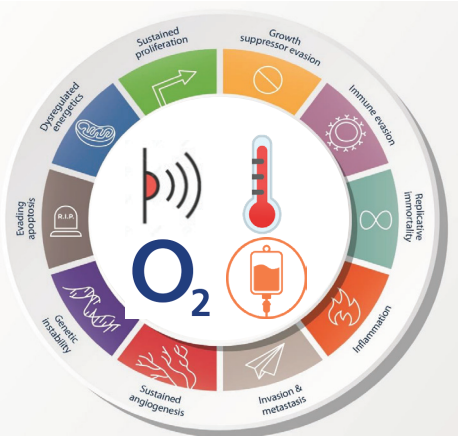


Thermography alone had a sensitivity of 83% in detecting breast cancer, while the combination of mammography and thermography had a 95% sensitivity

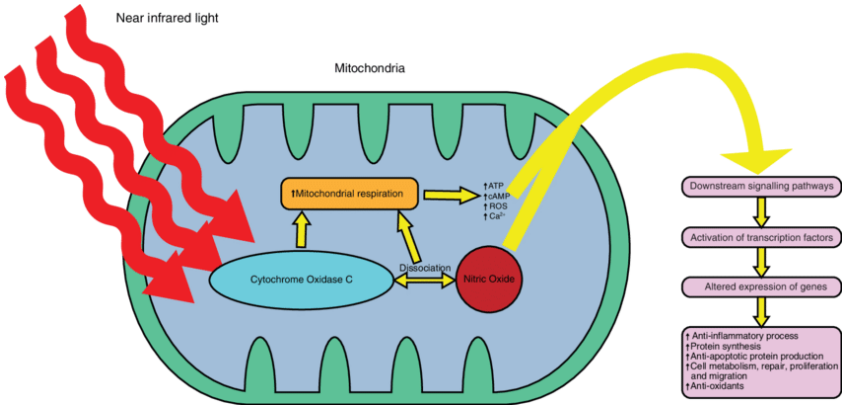
Kennedy DA, et al. Integr Cancer Ther. 2009 Mar;8(1):9-16. doi: 10.1177/1534735408326171.

NOVEL AND EMERGING THERAPIES AND SCREENING

Potential Adjuvant Therapeutics



Photobiomodulation Stimulates Mitochondria

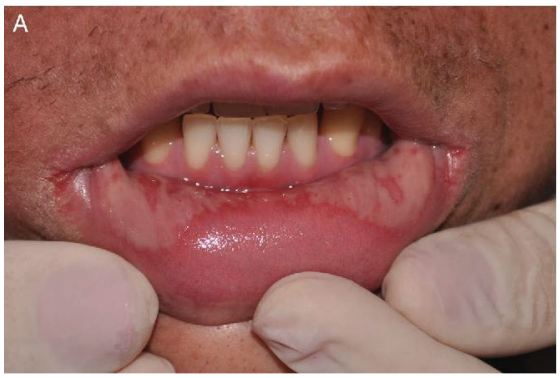


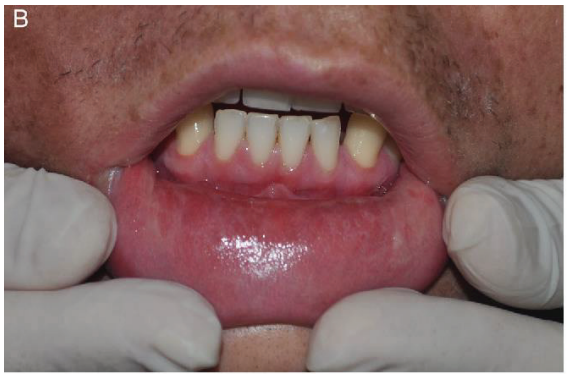
Ao J, et al. Clin Exp Ophthalmol. 2018 Aug;46(6):670-686. doi: 10.1111/ceo.13121.

NOVEL AND EMERGING THERAPIES AND SCREENING

NOVEL AND EMERGING THERAPIES AND SCREENING

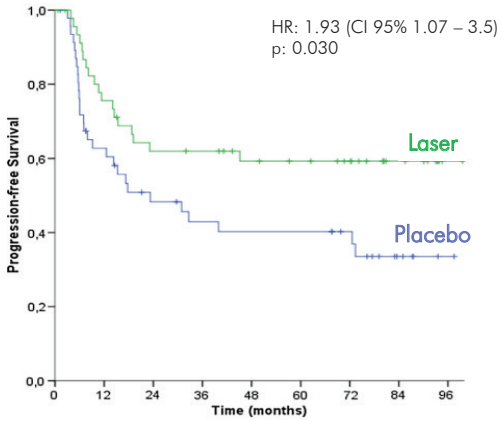
Photobiomodulation Reduces Oral Mucositis





Silva GB, et al. Lasers Med Sci. 2015 Jan;30(1):117-26. doi: 10.1007/s10103-014-1624-2.

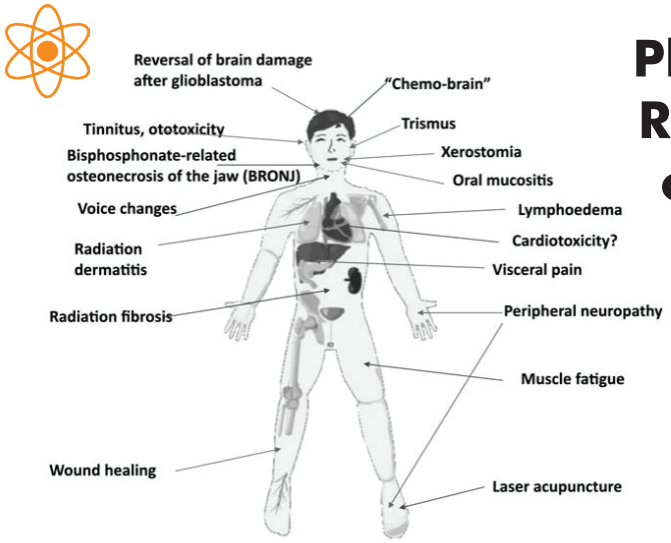
Photobiomodulation Improves Survival in Head and Neck Cancer



↓ Mucositis
↓ Opioid use
↓ Gastrostomy

Antunes HS, et al. Oral Oncol. 2017;71:11-15. doi: 10.1016/j.oraloncology.2017.05.018.

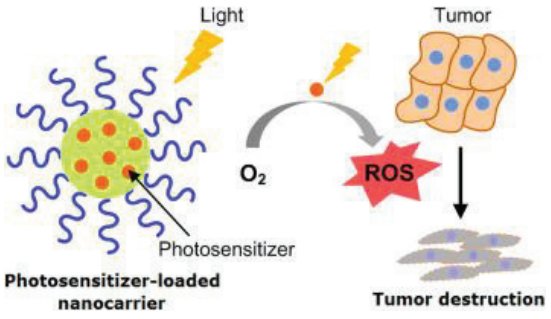
NOVEL AND EMERGING THERAPIES AND SCREENING



Photobiomodulation Reduces Side Effects of Cancer Therapy

Hamblin MR, et al. Photomed Laser Surg. 2018 May;36(5):241-245. doi: 10.1089/pho.2017.4401.

Curcumin & Photobiomodulation: Photodynamic Therapy

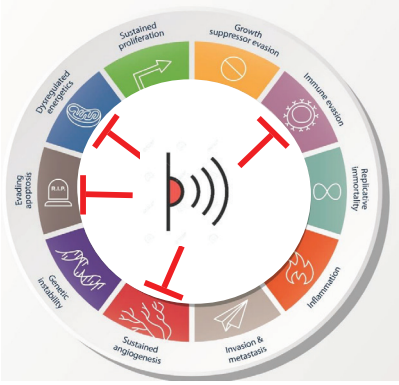


Photobiomodulation with turmeric accelerated the mucositis healing process, reducing time to lesion remission from 15 to 11 days.

Hong EJ, et al. Acta Pharm Sin B. 2016 Jul;6(4):297-307. doi: 10.1016/j.apsb.2016.01.007;
Pires Marques EC, et al. Photodiagnosis Photodyn Ther. 2020;29:101621. doi: 10.1016/j.pdpdt.2019.101621

NOVEL AND EMERGING THERAPIES AND SCREENING

Anti-Cancer Properties of Photobiomodulation



Hamblin MR, et al. Photomed Laser Surg. 2018 May;36(5):241-245. doi: 10.1089/pho.2017.4401

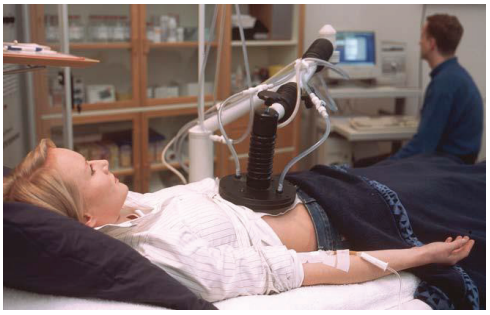
Uncertainty on Whole Body Hyperthermia

Combination of WBH with chemotherapy did give promising results, albeit at the cost of a high proportion of patients suffering from grade 3 and 4 toxicities.

Lassche G, et al. Crit Rev Oncol Hematol. 2019 Jul;139:67-74. doi: 10.1016/j.critrevonc.2019.04.023.

NOVEL AND EMERGING THERAPIES AND SCREENING

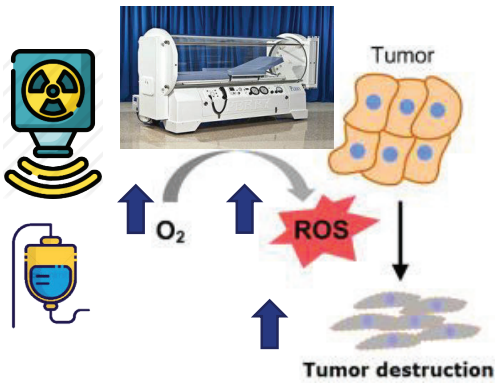
Regional Hyperthermia Provides Benefit



- Adjuvant to radiotherapy
- Breast and head and neck cancers
- Improves survival by 2.5 – 9 times
- Good safety profile

Datta NR, et al. Int J Hyperthermia. 2016;32(1):31-40. doi: 10.3109/02656736.2015.1099746;
Datta NR, et al. Int J Radiat Oncol Biol Phys. 2016.1;94(5):1073-87. doi: 10.1016/j.ijrobp.2015.12.361;
Hu Y, et als. J Clin Pharm Ther. 2017 Apr;42(2):155-164. doi: 10.1111/jcpt.12498.

Hyperbaric Oxygen Helps in Cancer



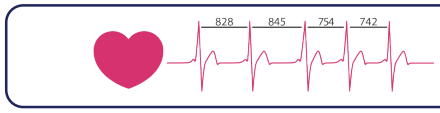
Clinical benefits in the treatment of tumours:

- Enhances efficacy of chemo- and radiotherapy
- Safe and well tolerated

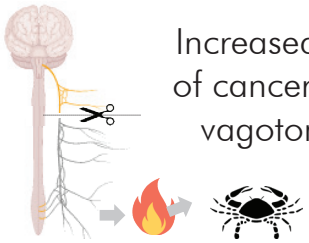
Stępień K, et al. Med Oncol. 2016 Sep;33(9):101. doi: 10.1007/s12032-016-0814-0.

NOVEL AND EMERGING THERAPIES AND SCREENING

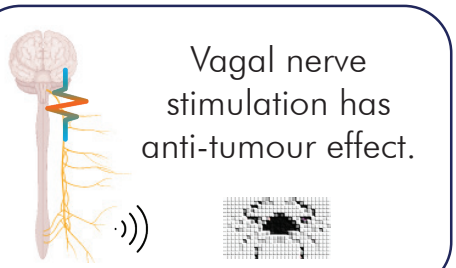
Vagal Nerve Function Integral to Cancer Care



Better prognosis with high HRV



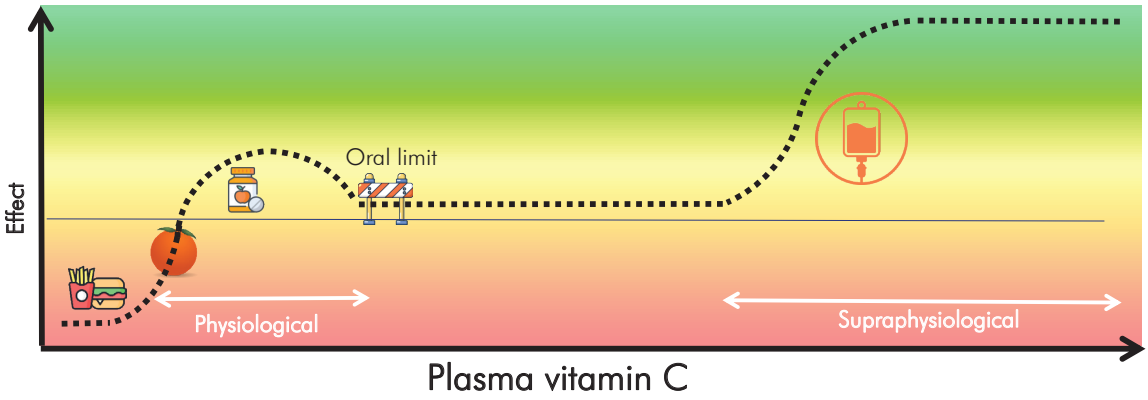
Increased risk of cancer with vagotomy.



Vagal nerve stimulation has anti-tumour effect.

Reijmen E, et al. Immunol Lett. 2018 Oct;202:38-43. doi: 10.1016/j.imlet.2018.07.006.

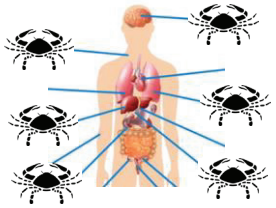
The Apples and Oranges of Oral vs IV Vitamin C



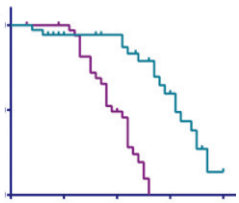
Carr AC, et al. Front Physiol. 2018;9:1182. 2018 Aug. doi:10.3389/fphys.2018.01182.

NOVEL AND EMERGING THERAPIES AND SCREENING

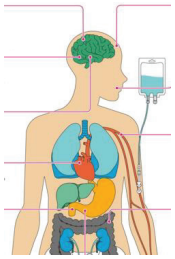
IV Vitamin C
Safe and Effective in Cancer



Used in many cancers



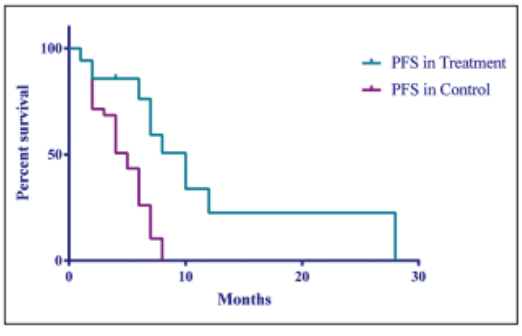
Extends survival

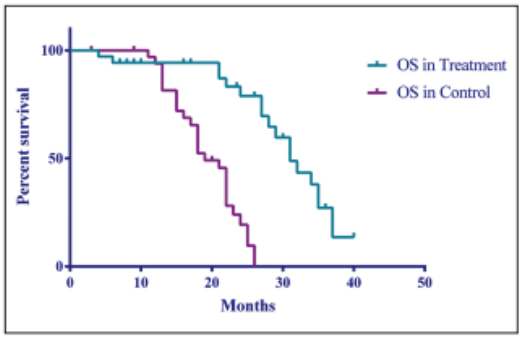


Reduces side effects

van Gorkom et al. Nutrients. 2019 Apr 28;11(5). pii: E977. doi: 10.3390/nu11050977.

IV Vitamin C Prolongs Survival in Triple Negative Breast Cancer

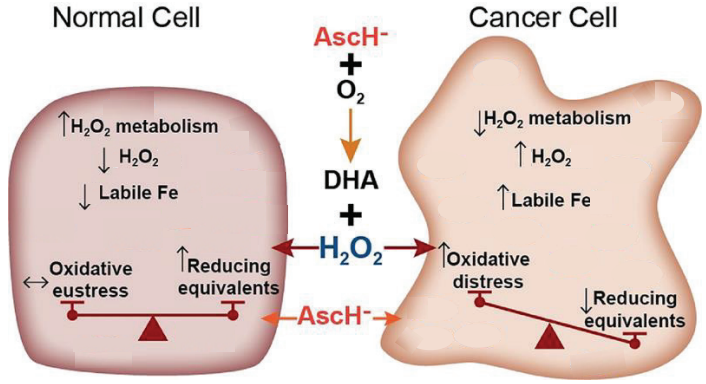




Ou J, et al. Integr Cancer Ther. 2020 Jan-Dec;19:1534735419895591. doi: 10.1177/1534735419895591.

NOVEL AND EMERGING THERAPIES AND SCREENING

IV Vitamin C
Pro-Oxidant and Anti-Cancer

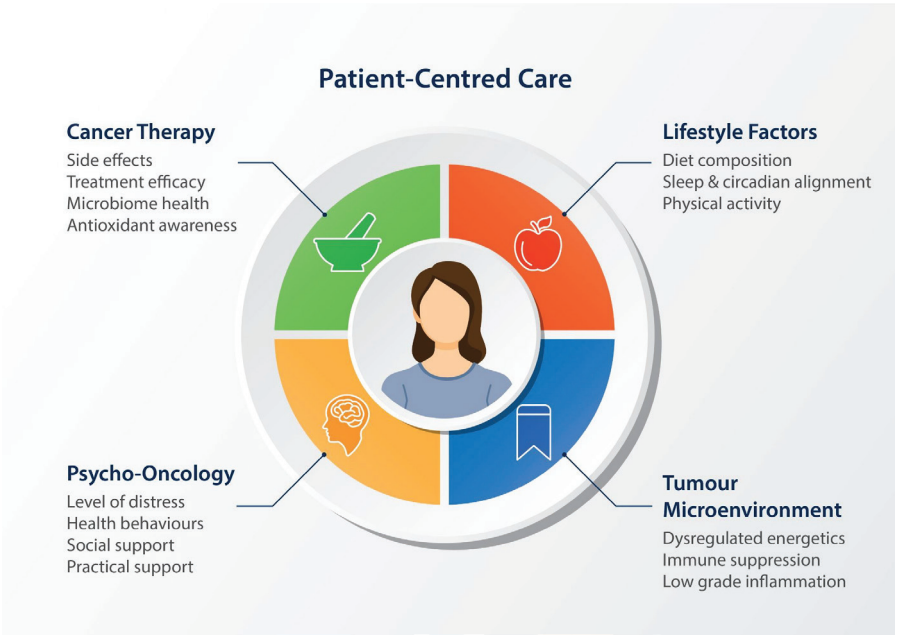


Schoenfeld JD, et al. Semin Radiat Oncol. 2019 Jan;29(1):25-32. doi: 10.1016/j.semradonc.2018.10.006.

Pro-Oxidant and Anti-Cancer Effects of IV Vitamin C

Carr AC, et al Front Physiol. 2018 Aug 23;9:1182. doi: 10.3389/fphys.2018.01182.

PSYCHO-ONCOLOGY



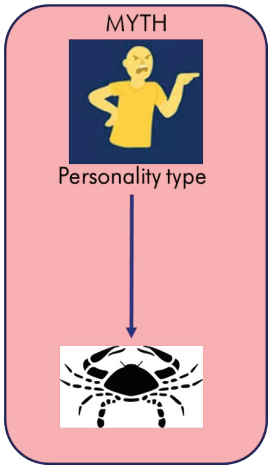
"Psycho-oncological care needs to be fully acknowledged as a central part of cancer treatment."

- Patricia Garcia-Prieto.

Garcia-Prieto P. Recent Results Cancer Res. 2018;210:57-66. doi: 10.1007/978-3-319-643010-6_4.

PSYCHO-ONCOLOGY

Myth: The "Cancer Personality"



Historically, concepts like the "cancer personality" have had detrimental effects leading, for example, to dysfunctional self-attribution of guilt in cancer patients.

Lang-Rollin I, et al. Dialogues Clin Neurosci. 2018 Mar;20(1):13-22. PMID: 29946207.

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PSYCHO-ONCOLOGY

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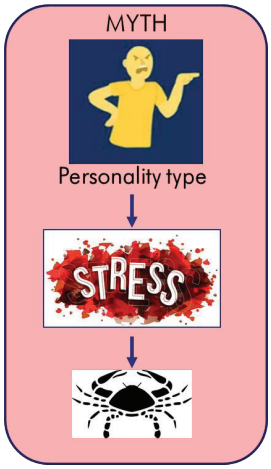

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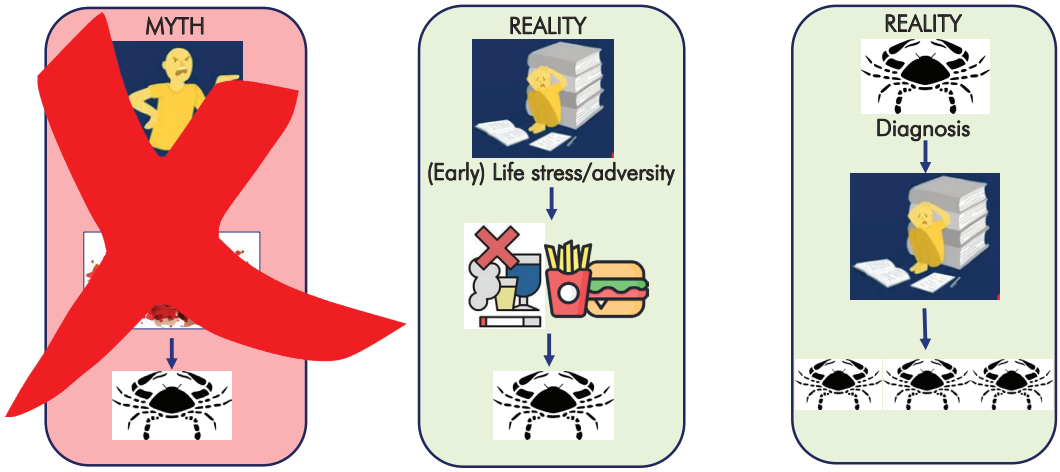
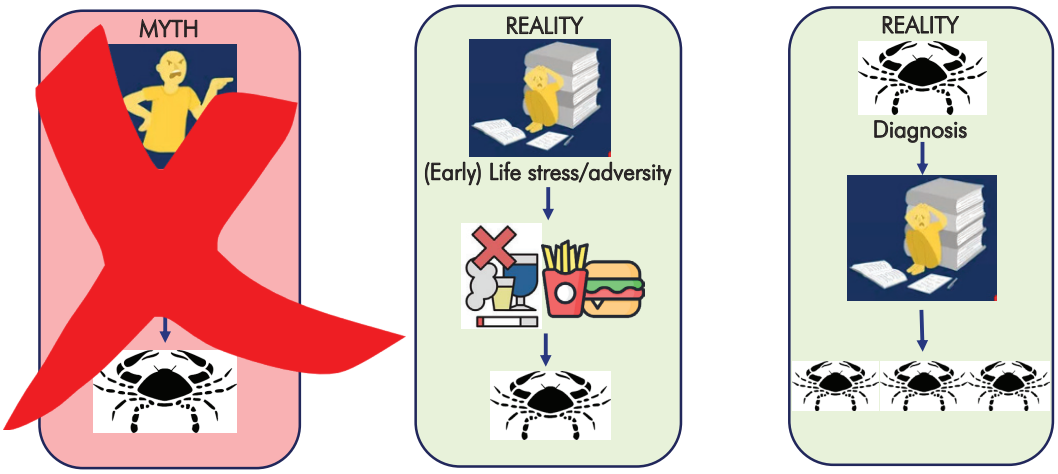
Lang-Rollin I, et al. Dialogues Clin Neurosci. 2018 Mar;20(1):13-22. PMID: 29946207.

The True Stress Connection

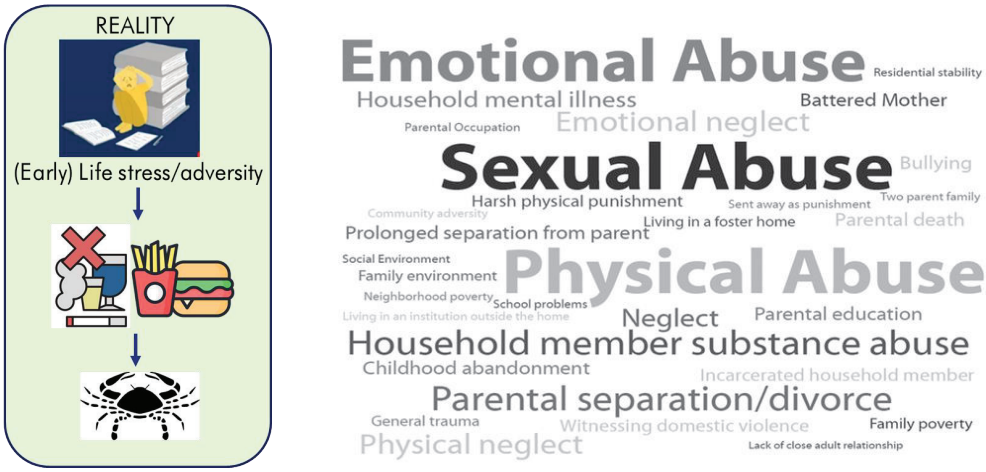


PSYCHO-ONCOLOGY

Reality: The True Stress Connection



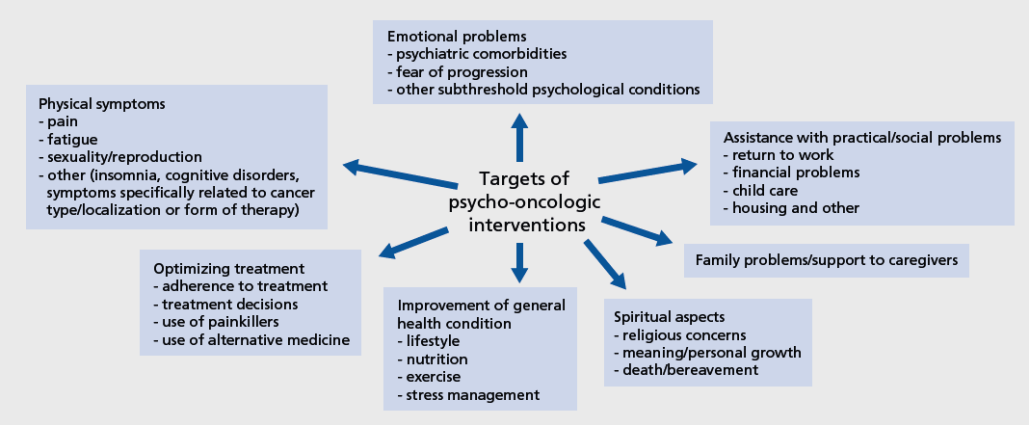
Early Life Adversity Linked to Cancer



Ports KA, et al. J Pediatr Nurs. 2019 Jan - Feb;44:81-96. doi: 10.1016/j.pedn.2018.10.009.

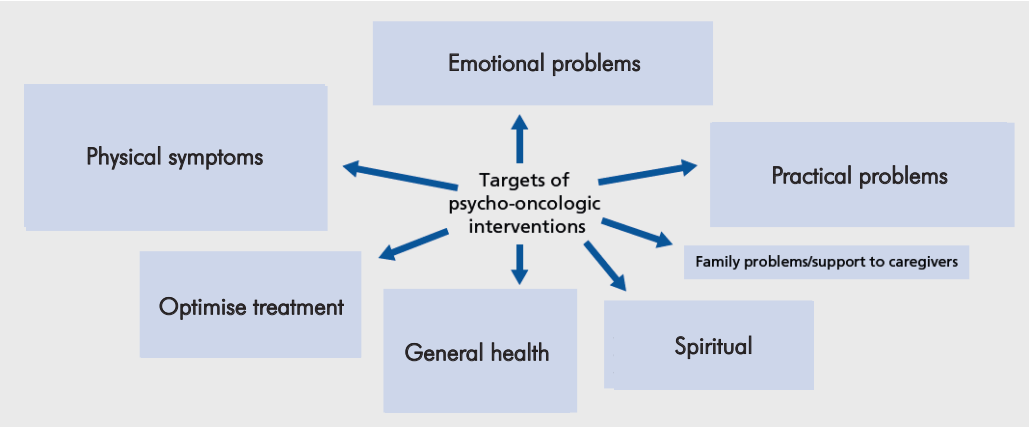
PSYCHO-ONCOLOGY

Targets of Psycho-Oncology



Lang-Rollin I, Berberich G. Dialogues Clin Neurosci. 2018 Mar;20(1):13-22. PMID: 29946207.

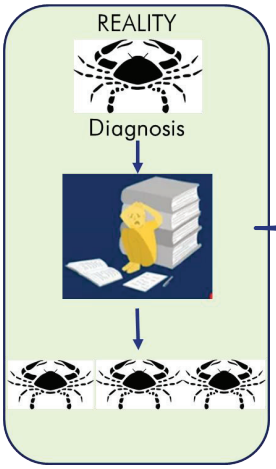
Targets of Psycho-Oncology



Lang-Rollin I, Berberich G. Dialogues Clin Neurosci. 2018 Mar;20(1):13-22. PMID: 29946207.

PSYCHO-ONCOLOGY

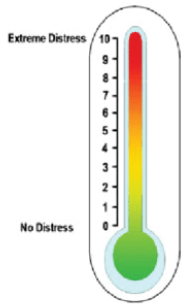
Key Elements of Psycho-oncology



- Support and connection
- Adjustment and adaptive skills
- Manage stressors of disease and treatment
- Mitigate effects of stress on tumour progression

The Distress Thermometer

First please circle the number (0-10) that best describes how much distress you have been experiencing in the past week including today.



Second, please indicate if any of the following has been a problem for you in the past week including today. Be sure to check YES or NO for each.

YES NO Practical Problems
- ☐ ☐ Child Care
- ☐ ☐ Housing
- ☐ ☐ Insurance/financial
- ☐ ☐ Transportation
- ☐ ☐ Work/school

Family Problems
- ☐ ☐ Dealing with children
- ☐ ☐ Dealing with partner
- ☐ ☐ Dealing with close Friend/relative

Emotional Problems
- ☐ ☐ Depression
- ☐ ☐ Fears
- ☐ ☐ Nervousness
- ☐ ☐ Sadness
- ☐ ☐ Worry
- ☐ ☐ Loss of interest in usual activities
- ☐ ☐ Spiritual/religious concerns

YES NO Physical Problems
- ☐ ☐ Appearance
- ☐ ☐ Bathing/dressing
- ☐ ☐ Breathing
- ☐ ☐ Changes in urination
- ☐ ☐ Constipation
- ☐ ☐ Diarrhoea
- ☐ ☐ Eating
- ☐ ☐ Fatigue
- ☐ ☐ Feeling Swollen
- ☐ ☐ Fevers
- ☐ ☐ Getting around
- ☐ ☐ Indigestion
- ☐ ☐ Memory/concentration
- ☐ ☐ Mouth sores
- ☐ ☐ Nausea
- ☐ ☐ Nose dry/congested
- ☐ ☐ Pain
- ☐ ☐ Sexual
- ☐ ☐ Skin dry itchy
- ☐ ☐ Sleep
- ☐ ☐ Tingling in hands/feet

Other problems

Lynch J et al, Support Care Cancer. 2010 Feb;19(2):193-202. doi: 10.1007/s00520-009-0799-8.

PSYCHO-ONCOLOGY

The Patient Journey

Adapted from Renz M, et al. J Clin Oncol. 2009 Jan 1;27(1):146-9. doi: 10.1200/JCO.2008.19.2203; Kubler-Ross E. New York, NY, Simon & Schuster, 1969.

How can we help?

- Provide space and time
- Listen
- Support wellbeing
- Reduce distress
- Be there
- REFER!

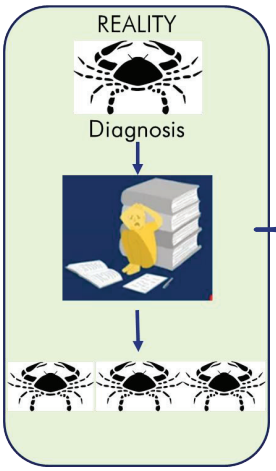
PSYCHO-ONCOLOGY

The Power of Social Support

A prospective study of >700 men followed over 7 years found that the presence of stressful events predicted increased risk of mortality only among participants reporting low emotional support. Those with high levels of support were protected.

Cohen S, et al. Annu Rev Psychol.2019 Jan 4;70:577-597. doi: 10.1146/annurev-psych-010418-102857;
Rosengren A, et al. BMJ. 1993 Oct 30;307(6912):1102-5. doi: 10.1136/bmj.307.6912.1102.

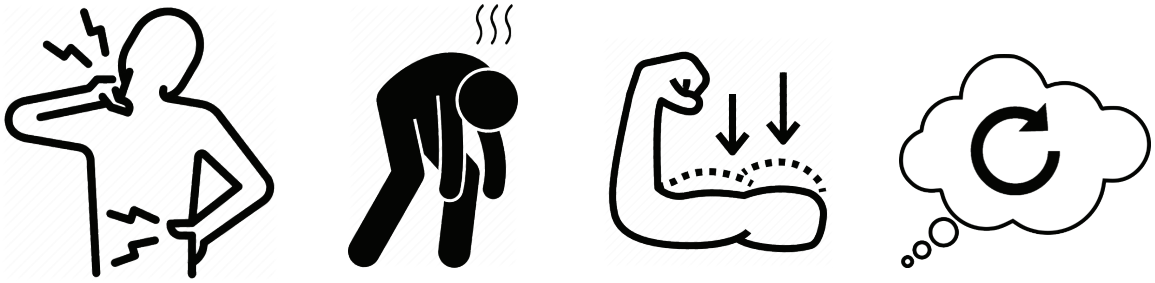
Key Elements of Psycho-oncology



- Support and connection
- Adjustment and adaptive skills
- Manage stressors of disease and treatment
- Mitigate effects of stress on tumour progression

PSYCHO-ONCOLOGY

Causes of Distress in Cancer Patients



Pain | Fatigue | Physical Weakness / Cachexia | Distress

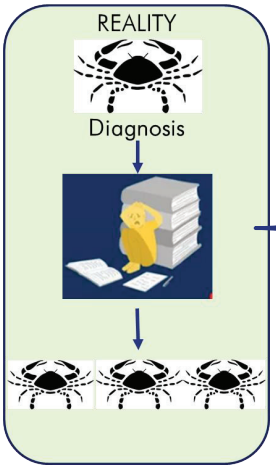
Causes of Distress in Cancer Patients

- **Pain** – most common form of physical distress. Emotional distress, depression, anxiety, uncertainty and hopelessness interact with pain (Lang-Rollin 2018).
- **Fatigue** – cancer-related fatigue less often addressed and recognised but at least as common and as significant a cause of distress and reduced function throughout different stages of the disease (Lang-Rollin 2018).
- **Cachexia** – severely impacts QOL & reduces survival
- **Fear of recurrence** – one of most commonly cited concerns of cancer survivors (Lang-Rollin 2018).

- Almost all cancer patients have symptoms of anorexia, fatigue and emaciation (Lai 2019)

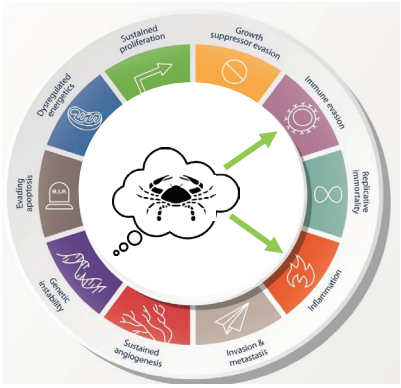
PSYCHO-ONCOLOGY

Key Elements of Psycho-oncology



- Support and connection
- Adjustment and adaptive skills
- Manage stressors of disease and treatment
- Mitigate effects of stress on tumour progression

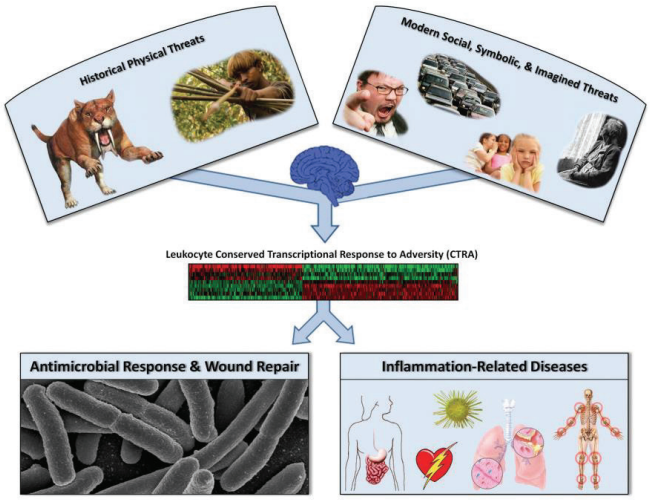
The Carcinogenic Effects of Chronic Stress



Antoni MH, Dhabhar FS. Cancer. 2019 May 1;125(9):1417-1431. doi: 10.1002/cncr.31943.

PSYCHO-ONCOLOGY

The Stress – Cancer Connection



Slavich GM, Cole SW. Clin Psychol Sci. 2013 Jul;1(3):331-348. doi: 10.1177/2167702613478594.

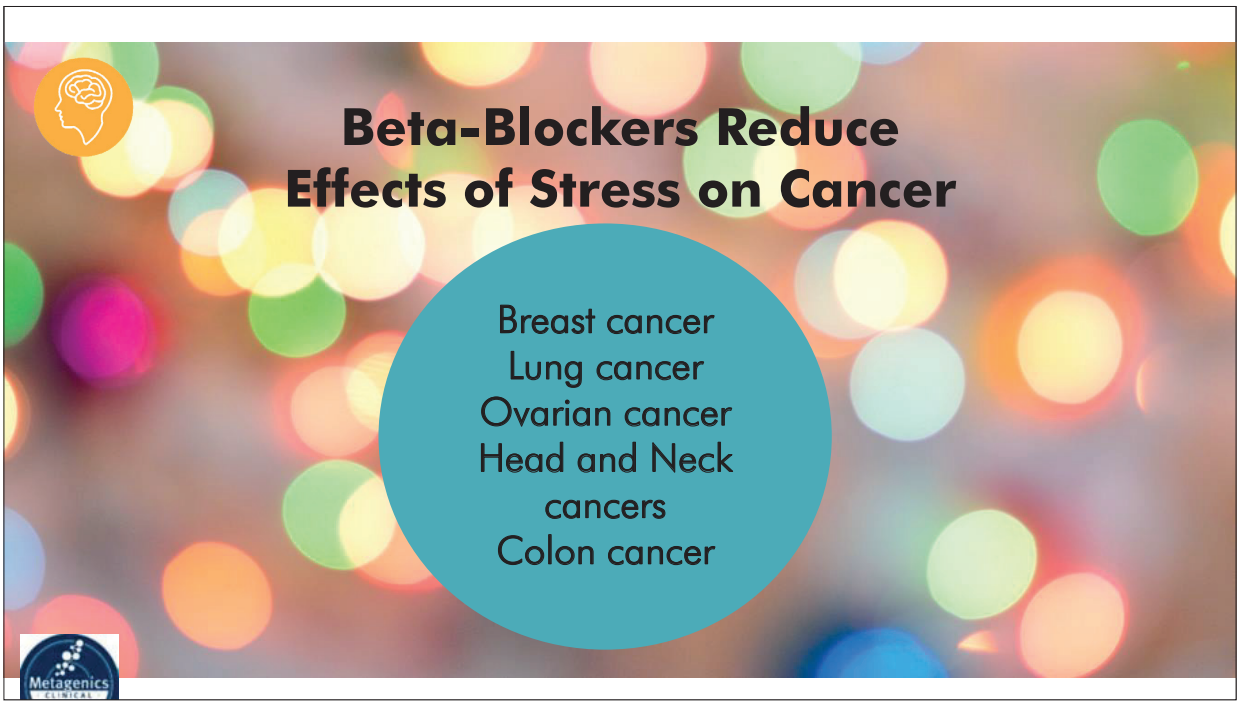
Common drug could be used to slow the spread of breast cancer

By Raffaella Ciccarelli | A month ago

Australian study finds Beta blockers can stop the spread of cancer cells by reducing the impact of stress.

Hiller JG, et al. Clin Cancer Res. 2019 Nov 21. doi: 10.1158/1078-0432.CCR-19-2641.

PSYCHO-ONCOLOGY



Beta-Blockers Reduce Effects of Stress on Cancer

- Hiller JG, Cole SW, Crone EM, Byrne DJ, Shackleford DM, Pang JB, et al. Preoperative β-blockade with propranolol reduces biomarkers of metastasis in breast cancer: A phase II randomised trial. Clin Cancer Res. 2019 Nov 21. doi: 10.1158/1078-0432.CCR-19-2641.
- Armaiz-Pena GN, Allen JK, Cruz A, Stone RL, Nick AM, Lin YG, et al. Src activation by β-adrenoreceptors is a key switch for tumour metastasis. Nat Commun 2013;4:1403. doi: 10.1038/ncomms2413.
- Wang HM, Liao ZX, Komaki R, Welsh JW, O'Reilly MS, Chang JY, et al. Improved survival outcomes with the incidental use of beta-blockers among patients with non-small-cell lung cancer treated with definitive radiation therapy. Ann Onocl. 2013 May;24(5):1312-9. doi: 10.1093/annonc/mds616.
- Watkins JL, et al. Clinical impact of selective and nonselective beta blockers on survival in patients with ovarian cancer. Cancer. 2015 Oct 1;121:(19):3444-51. doi: 10.1002/cncr.29392.

PSYCHO-ONCOLOGY

Ann Oncol. 2013 May;24(5):1312-9. doi: 10.1093/annonc/mds616. Epub 2013 Jan 8.

Improved survival outcomes with the incidental use of beta-blockers among patients with non-small-cell lung cancer treated with definitive radiation therapy.

Wang HM[1], Liao ZX, Komaki R, Welsh JW, O'Reilly MS, Chang JY, Zhuang Y, Levy LB, Lu C, Gomez DR.

Author information

Abstract

BACKGROUND: Preclinical studies have shown that norepinephrine can directly stimulate tumor cell migration and that this effect is mediated by the beta-adrenergic receptor.

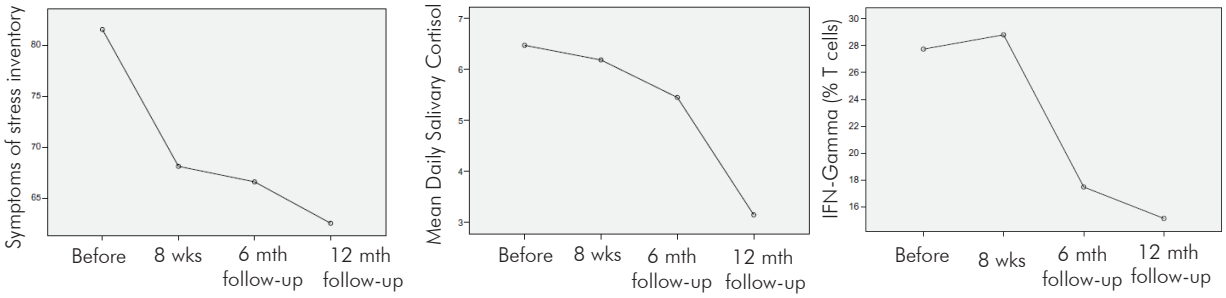
PATIENTS AND METHODS: We retrospectively reviewed 722 patients with non-small-cell lung cancer (NSCLC) who received definitive radiotherapy (RT). A Cox proportional hazard model was utilized to determine the association between beta-blocker intake and locoregional progression-free survival (LRPFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS).

RESULTS: In univariate analysis, patients taking beta-blockers (n = 155) had improved DMFS (P < 0.01), DFS (P < 0.01), and OS (P = 0.01), but not LRPFS (P = 0.33) compared with patients not taking beta-blockers (n = 567). In multivariate analysis, beta-blocker intake was associated with a significantly better DMFS [hazard ratio (HR), 0.67; P = 0.01], DFS (HR, 0.74; P = 0.02), and OS (HR, 0.78; P = 0.02) with adjustment for age, Karnofsky performance score, stage, histology type, concurrent chemotherapy, radiation dose, gross tumor volume, hypertension, chronic obstructive pulmonary disease and the use of aspirin. There was no association of beta-blocker use with LRPFS (HR = 0.91, P = 0.63).

CONCLUSION: Beta-blocker use is associated with improved DMFS, DFS, and OS in this large cohort of NSCLC patients. Future prospective trials can validate these retrospective findings and determine whether the length and timing of beta-blocker use influence survival outcomes.

PMID: 23300016 PMCID: PMC3629895 DOI: 10.1093/annonc/mds616

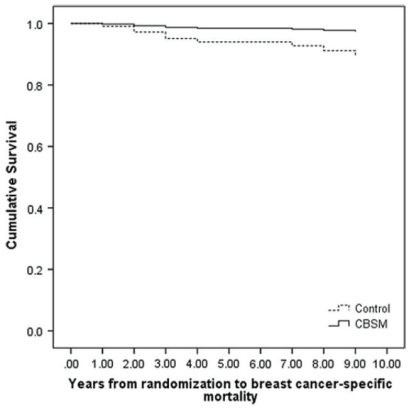
Mindfulness Practice in Breast And Prostate Cancer Patients

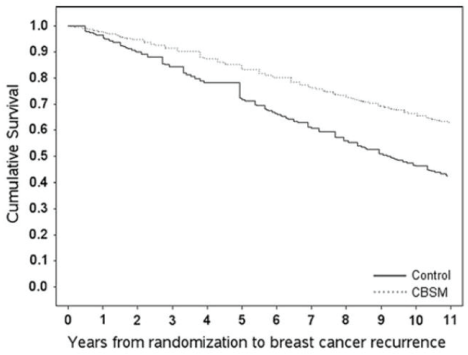


Carlson LE, et al. Brain Behav Immun. 2007 Nov;21(8):1038-49. doi: 10.1016/j.bbi.2007.04.002.

PSYCHO-ONCOLOGY

CBT Reduces Breast Cancer Mortality and Recurrence





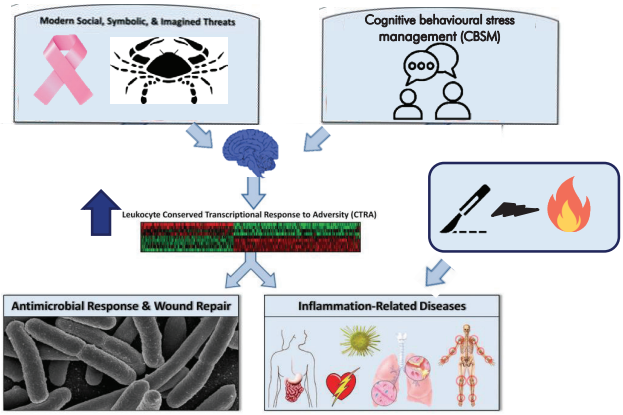
Stagl JM, et al. Breast Cancer Res Treat. 2015 Nov;154(2):319-28. doi: 10.1007/s10549-015-3626-6.

App-Based Cognitive Therapy On Demand

https://www.sciencedaily.com/releases/2019/05/190529180230.htm

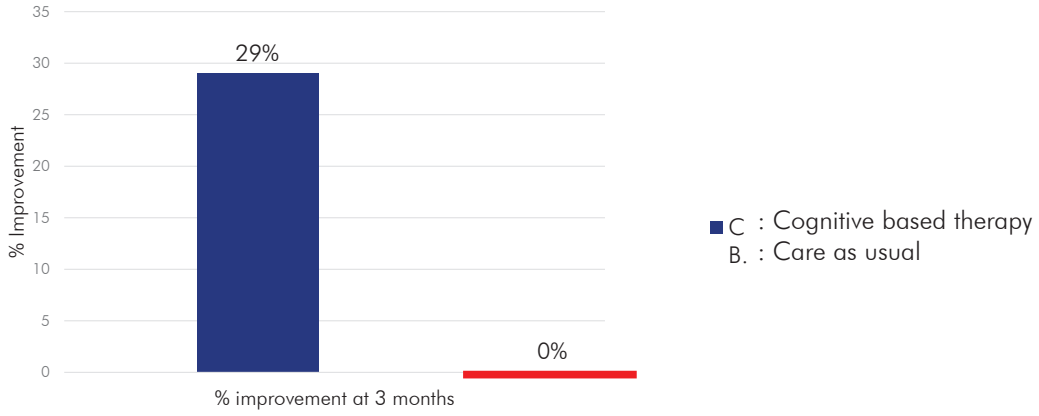
PSYCHO-ONCOLOGY

CBSM Improves Survival Rates in Breast Cancer Patients



Antoni MH, et al. Psychoneuroendocrinology. 2016 Dec;74:269-277. doi: 10.1016/j.psyneuen.2016.09.012;
Slavich GM, Cole SW. Clin Psychol Sci. 2013 Jul;1(3):331-348. doi: 10.1177/2167702613478594.

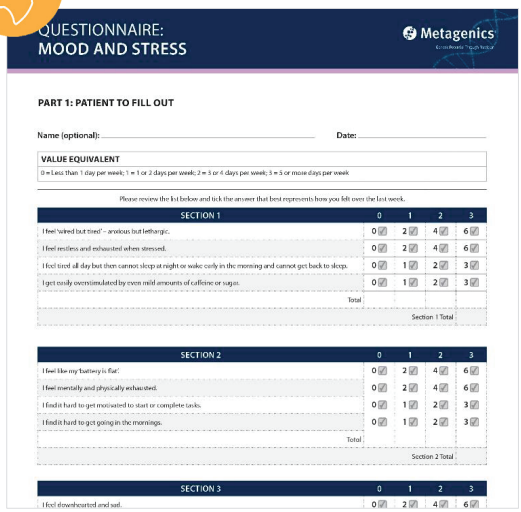
CBT Reduces Fear of Cancer Recurrence



Van de Wal M, et al. J Clin Oncol. 2017 Jul 1;35(19):2173-2183. doi: 10.1200/JCO.2016.70.5301.

PSYCHO-ONCOLOGY

Stress Less Program


QUESTIONNAIRE:
MOOD AND STRESS

Metagenics

PART 1: PATIENT TO FILL OUT

Name (optional): _____ Date: _____

VALUE EQUIVALENT

0 = Less than 1 day per week; 1 = 1 or 2 days per week; 2 = 3 or 4 days per week; 3 = 5 or more days per week

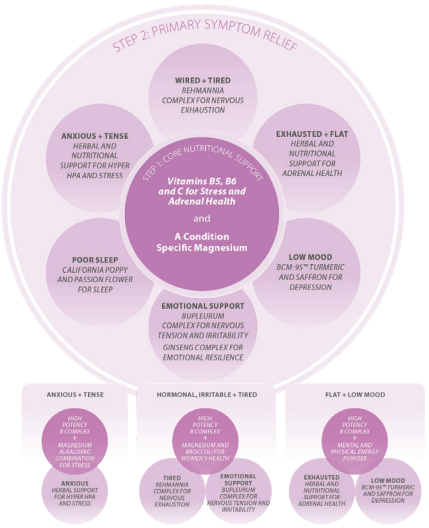
Please review the list below and tick the answer that best represents how you felt over the last week.

SECTION 1	0	1	2	3
I feel 'wired but tired' – anxious but lethargic.	0	2	4	6
I feel restless and exhausted when stressed.	0	2	4	6
I feel tired all day but then cannot sleep at night or wake early in the morning and cannot get back to sleep.	0	1	2	3
I get easily overstimulated by even mild amounts of caffeine or sugar.	0	1	2	3
Total				
Section 1 Total				

SECTION 2	0	1	2	3
I feel like my 'battery is flat'.	0	2	4	6
I feel mentally and physically exhausted.	0	2	4	6
I find it hard to get motivated to start or complete tasks.	0	1	2	3
I find it hard to get going in the mornings.	0	1	2	3
Total				
Section 2 Total				

SECTION 3	0	1	2	3
I feel downhearted and sad.	0	2	4	6

+



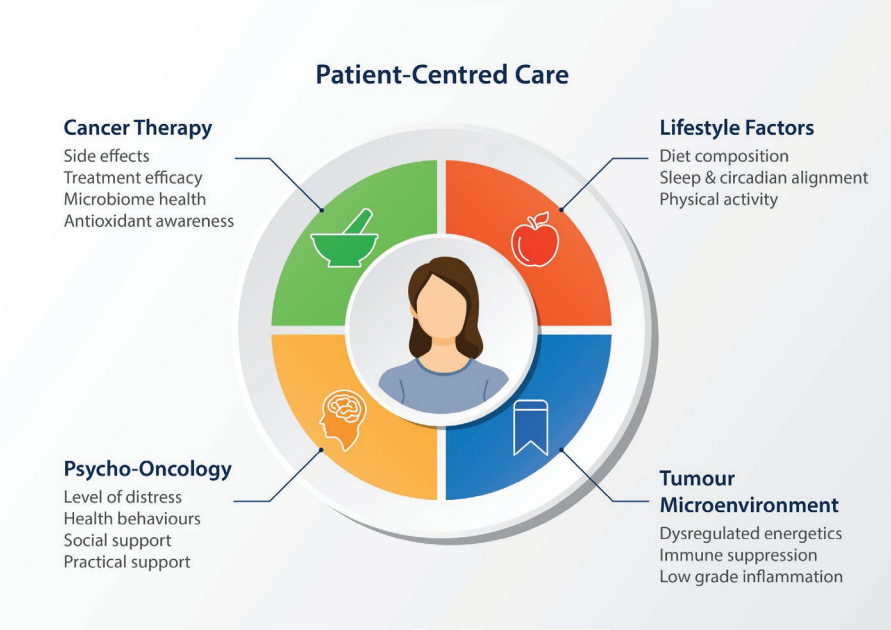
Safety of Nervine Herbs

Rehmannia	✓
Magnolia	✓
Zizyphus	✓
Lavender	✓
Passion flower	✓
Wild oats	✓
American ginseng	✓
Dong quai	⚠
Kudzu	⚠

PSYCHO-ONCOLOGY

Nervous System Support for Cancer Patients

	Treatment consideration
Stress Management	*Meta Mag® Magnesium, Taurine and Glutamine for Stress* *Vitamins B5, B6 and C for Stress and Adrenal Health*
Depression	*BCM-95™ Turmeric and Saffron for Depression*
Anxiety	*Herbal Support for Hyper HPA and Stress*
Chemotherapy "brain fog"	*Lipid and Tocotrienols for Healthy Cell Membranes and Cognition* *Choline* *Bacopa/Gingko Complex*
Metagenics Stress Less Program	



Metagenics®
Genetic Potential Through Nutrition

Technical Data Sheet

Highly Bioavailable Palmitoylethanolamide (PEA) With Endocannabinoid Action

Chronic pain affects 38% of the global population,[1] having detrimental effects on physical and emotional health, lowering quality of life (QOL)[2] and contributing to individual and societal economic burden.[3] Chronic pain is driven by multiple complex mechanisms[4,5,6] resulting in a hyperinflammatory-nociception cascade, with chronic immune cell activity. Pain and inflammation are mitigated by the endocannabinoid system (ECS) from the actions of endogenous cannabinoids, N-arachidonoylethanolamine (anandamide) and 2-arachidonylgylcerol (2-AG),[7,8] and lipid-like mediators such as palmitoylethanolamide (PEA).[9,10] Disruption or dysfunction in the synthesis of these endogenous compounds, leads to heightened and/or chronic pain and inflammation[11] which is often challenging to treat.[12] Current pharmaceutical therapies are either ineffective or offer partial resolution[13,14,15,16,17,18] with common and/or numerous adverse effects.[19,20] Multiple studies have demonstrated the efficacy of supplemental PEA in lowering chronic pain[21,22,23,24,25,26,27,28,29,30,31] and promoting the resolution of inflammation (Figure 1).[32,33,34,35,36] Without the potential for addiction and central nervous system (CNS) side effects[37,38,39,40,41] PEA dosing ranges from 300 mg/d to 2,400 mg/d condition dependant. Additionally, it has been safely used alongside a range of medications including analgesics, anti-inflammatories, antidepressants and dopamine agonists.[42,43,44,45] Absorption of standard supplemental PEA is hindered due to its lipophilic nature,[46] however the use of LipiSperse®, a patented technology, significantly enhances absorption compared with standard forms of PEA.*

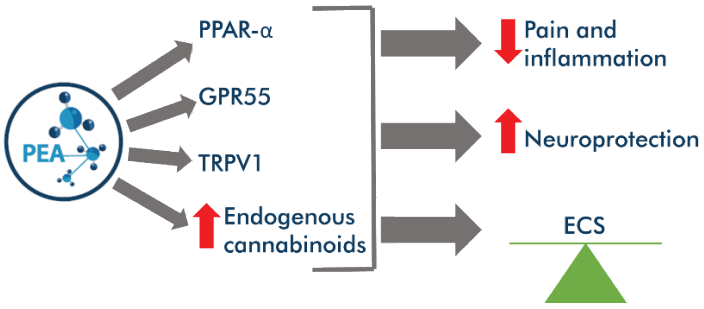


Figure 1: PEA actions.[47,48,49,50,51,52,53]

Nutrients That May Assist
Palmitoylethanolamide (PEA)

Actions

- Endocannabinoid system modulation
- Analgesic
- Anti-inflammatory
- Neuroprotective

Clinical Applications

- Chronic pain
  - Neuropathic pain
  - Compression neuropathy
  - Chronic pain syndromes
  - Arthritic pain
  - Endometrial pain
- Neurodegenerative conditions
  - Parkinson's disease
  - Multiple sclerosis
  - Mild cognitive impairment and Alzheimer's disease

Dosing Considerations*

Co-prescribing considerations: refer to page 8 and 9.

Pregnancy ✗

Breastfeeding ✓

*Dosing regimens should be determined by appropriate assessment and monitoring.

* Levagen+™ combines LipiSperse® with PEA for enhanced absorption.

Background Technical Information

Palmitoylethanolamide (PEA)

PEA is a member of the family of bioactive lipids known at N-acylethanolamines (NAEs), which regulate the ECS.[54] PEA was isolated and identified as the anti-inflammatory component in egg yolks in 1957.[55] In 1970 its efficacy against the common cold and influenza was observed, thereafter it was sold in Europe for immune support.[56] In current years the focus has been on its analgesic, anti-inflammatory and neuroprotective properties.[57,58] In addition to being endogenously produced,[59] PEA is found in several foods including eggs, soy oil, peanut oil and human milk.[60]

PEA, classified as an autacoid†, is produced on demand from plasma membrane phospholipids in response to tissue damage and inflammation.[61] Its synthesis is highly regulated by the enzymes N-acyltransferase and N-acylphosphatidylethanolamine-preferring phospholipase D (NAPE-PLD).[62,63] The degradation of PEA occurs via fatty acid amide hydrolase (FAAH)[64] and N-acylethanolamine-hydrolysing acid amidase (NAAA) (Figure 2).[65]

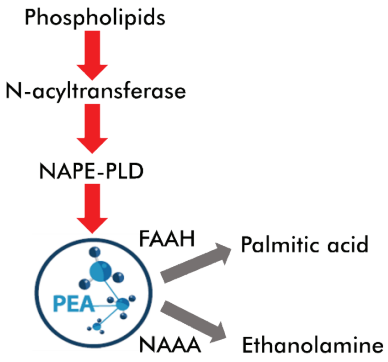


Figure 2: Synthesis and degradation of PEA.[66]

Chronic Inflammation Reduces PEA Synthesis

Chronic inflammation influences endogenous levels of PEA, suppressing synthesis and elevating degradation,[67,68] and low PEA levels hinder the resolution of inflammation.[69] Further, an inverse relationship exists between PEA levels in the CNS and pain threshold.[70] Thus, PEA supplementation may be therapeutically beneficial in chronic pain and inflammatory conditions.[71]

PEA Absorption Is Limited

PEA has poor water solubility[72] limiting its absorption and bioavailability.[73] Micronisation of PEA improved bioavailability compared with nonmicronised PEA in animals.[74] Yet, even with micronisation, PEA remains lipophilic resulting in aggregation and lower absorption at the hydrophilic gastrointestinal mucosal layer. These limitations are overcome with the addition of LipiSperse®, a patented technology which lowers surface tension, prevents aggregation and increases the hydrophilic qualities of the PEA molecule.

A randomised, double-blind study comparing absorption capacity of PEA to PEA + LipiSperse® (Levagen+™) revealed absorption was 70% greater with the addition of LipiSperse®.[75]

Actions

Endocannabinoid System (ECS) Modulation

As a lipid messenger with cannabimimetic properties, PEA does not bind to the cannabinoid receptors 1 (CB1) and 2 (CB2), but instead increases their expression and/or activity indirectly.[76,77] CB1 is densely expressed throughout the nervous system and plays an important role modulating pain pathways.[78,79,80] CB2 receptors modulate inflammatory cytokine release[81] and are predominantly expressed on immune cells,[82] including mast cells, microglial cells[83,84] and astrocytes.[85] The anti-inflammatory, analgesic and neuroprotective actions of PEA result from its effects on:

- Peroxisome proliferator-activated receptor alpha (PPAR-α) (Figure 3a)
- Orphan G-protein coupled receptor (GPR55) (Figure 3a)
- Transient receptor potential vanilloid type 1 (TRPV1) (Figure 3b, c, d)[86]
- The 'entourage effect' whereby PEA raises tissue levels of anandamide and 2-AG, which act on TRPV1 in addition to CB1 and CB2 (Figure 3d)[87,88,89,90]

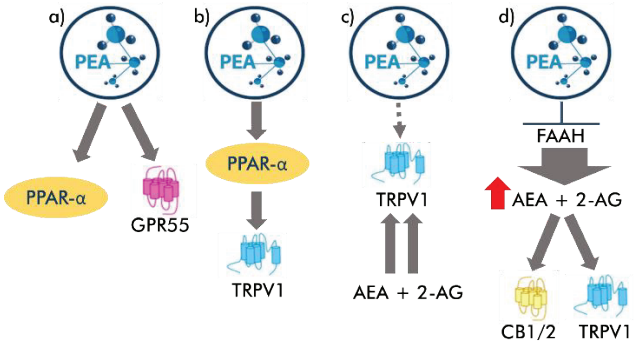


Figure 3: PEA targets.[91]

† An autocoid is a physiologically active substance that has a localised effect for a brief duration.

Analgesic

The analgesic effects of PEA are partly achieved through the entourage effect.[92,93,94] PEA inhibits anandamide degradation (Figure 3d)[95,96] and potentiates the endocannabinoid's action at CB1 and CB2 receptors (Figure 3c).[97,98,99]

The stimulation of TRPV1 by proinflammatory cytokines results in pain sensations.[100,101] Desensitisation of TRPV1 with pharmaceutical antagonists effectively reduces pain, but not without undesirable effects.[102] PEA increased the binding of anandamide to TRPV1,[103] desensitising the receptor, lowering neuronal calcium influx and elevating pain thresholds (Figure 3c).[104,105,106]

The activation and desensitisation of TRPV1 was also increased through elevated PPAR-α activity induced by PEA (Figure 3b),[107] which diminished symptoms of allodynia in animals.[108]

Anti-Inflammatory

The anti-inflammatory effects of PEA are partly attributed to its influence on PPAR-α (Figure 3a).[109 110,111,112,113,114]

PPAR-α activation inhibits the nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), which represses the synthesis of the proinflammatory cytokine tumour necrosis factor-alpha (TNF-α), and further limits the recruitment of immune cells.[115,116] Reduced expression of PPAR-α, as observed in inflammatory conditions, is reversed with PEA supplementation.[117]

Anandamide has been shown to inhibit the translocation of NFκB and the subsequent release of TNF-α.[118] By way of the entourage effect (Figure 3d), PEA supplementation lead to a reduction in inflammatory cytokines and elevated plasma anandamide levels in patients with relapsing remitting multiple sclerosis (RRMS).[119]

'Reduced expression of PPAR-α as observed in inflammatory conditions is reversed with PEA supplementation.'

Another mechanism providing anti-inflammatory effects may be from PEA stimulation of GPR55[120] (Figure 3a) as proposed in a colitis model[121] where high expression of GPR55 occurs in the gastrointestinal tract.[122] However, the role of this receptor and its activation by PEA in the inflammatory response requires further clarification.[123]

From indirect actions on CB2 receptors, PEA regulates mast cell activity. Mast cells are widely distributed throughout the body, including in the CNS,[124] peripheral nervous system,[125] synovium[126] and endometrial tissues,[127] and play a key role in both systemic and neuro-inflammation.[128,129,130] PEA was discovered in 1993 to modulate mast cells,[131,132,133,134] shifting their phenotype from activated to resting,[135] and inhibiting their migration and degranulation, blocking the release of histamine, prostaglandin (PG) and TNF-α.[136]

Neuroprotective

Following tissue damage or neuro-inflammation, neurons and microglial cells synthesise and release PEA[137,138,139] and microglia migrate to the site of injury.[140] Supplemental PEA increased microglial migration by elevating PPAR-α activity.[141] Further, PEA significantly raised microglial phagocytosis by 60%, mediated through heightened PPAR-α function.[142] An impairment in microglial phagocytic clearance is associated with neurodegenerative diseases and cognitive decline.[143]

'PEA treatment shifted the microglia back towards an anti-inflammatory phenotype through increased CB2 receptor activity.'

Additionally, repeated insults to the CNS shifts microglia towards a sustained proinflammatory M1 phenotype.[144] PEA treatment shifted the microglia back towards an anti-inflammatory phenotype[145] by indirectly increasing CB2 receptor activity.[146]

M1 microglia support astrocytes transformation towards a proinflammatory state.[147,148] Chronic astrocytosis is linked with allodynia and hyperalgesia[149] and, in conjunction with blunted PPAR-α activity, is a feature of Alzheimer's disease (AD).[150] An AD model revealed PEA treatment increased the function of PPAR-α and converted astrocytes back to a resting phase.[151]

Raised PPAR-α activity lead to a greater synthesis of the intracellular neurosteroid, allopregnanolone, which increased GABA signalling[152] and resistance to reactive oxygen species.[153] Further neuronal protection with supplemental PEA was provided via binding to GPR55 which:

- Reduced glutamate neurotransmission
- Enhanced GABA synaptic transmission
- Indirectly lowered GABAergic tone[154] which is increased with neuro-inflammation.[155]

Clinical Applications

Chronic Pain

Neuropathic Pain

Peripheral neuropathic pain can be induced by diabetes[156] or develop as a side effect from some anticancer treatments.[157,158] Table 1 provides a summary of research demonstrating PEA efficacy in neuropathic pain.

Table 1: PEA use in neuropathic pain studies.

Study type	Dose of PEA	Duration	Outcome
Open label study - 30 participants with diabetic-induced peripheral neuropathy.[159]	600 mg/d	8 weeks	Significant reduction in intensity and presence of pain, paraesthesia, burning and numbness from baseline ($p < 0.0001$).
Cohort - 30 participants with either diabetic induced or traumatic neuropathic pain.[160]	1,200 mg/d	6 weeks	Lower pain scores and neuropathic symptoms compared with baseline.
Case study – male with diabetic induced neuropathic pain.[161]	1,200 mg/d (combined with 300 mg/d of R-alpha lipoic acid)	16 weeks	Numerical rating score (NRS) for pain (scored out of 10, 10 being the most pain) dropped from 7 at baseline to 3 post treatment.
Case study – male with diabetic induced neuropathic pain.[162]	1,200 mg/d (combined with 300 mg/d of R-alpha lipoic acid and 2000IU of vitamin D)	12 weeks	NRS value dropped from 6 to 1.5 post treatment.
Single-blind controlled trial - 20 patients undergoing thalidomide and bortezomib treatment for multiple myeloma with concomitant neuropathic pain.[163]	600 mg/d	8 weeks	Patients reported a 24% reduction in pain scores from baseline to treatment conclusion.
Case study - male with prostate cancer who developed neuropathic pain after the second course of antineoplasm agent.[164]	1,200 mg/d	3 weeks	NRS for pain reduced from 7 to 1-2 post PEA treatment. Approximately six months later the patient was able to discontinue the use of his analgesics, using paracetamol occasionally.

Compression Neuropathy

Pain resulting from nerve compression, as in the case of carpal tunnel syndrome (CTS) or sciatica, is common and challenging to treat when severity is low and surgery is not indicated.[165] Table 2 highlights the benefits of administering PEA in CTS and lumbosciatica.

Table 2: PEA in compression neuropathic conditions.

Study type	Dose of PEA	Duration	Outcome
Single-blind randomised placebo controlled trial – 50 participants with mild to moderate CTS.[166]	1,200 mg/d	8 weeks	The PEA group experienced a decrease in pain intensity, by 17.87% at treatment conclusion compared with the control group whose pain intensity increased by 14.43%.

A large scale pivotal randomised double-blind placebo controlled trial – 636 participants with lumbosciatica pain.[167]	300 mg/d or 600 mg/d	3 weeks	The group receiving 600 mg/d of PEA reported a significant improvement in QOL ($p < 0.001$). Pain was reduced by greater than 50% compared with the 300 mg/d and placebo group.
Prospective randomise controlled trial – 118 participants with lumbosciatica.[168]	600 mg/d	4 weeks	PEA supplementation alongside standard treatments significantly decreased the visual analogue scale (VAS) pain score ($p < 0.000$) in patients compared with the standard treatments alone.

Chronic Pain Syndromes

At present, treatment of the wide spread pain associated with fibromyalgia favours anti-epileptics, which provide on average a 30% reduction in pain intensity in approximately half of patients.[169]

A study with two arms evaluated the efficacy of duloxetine and pregabalin together, or with the inclusion of PEA in reducing fibromyalgic pain in eighty participants over a six month period

The first arm was a retrospective study with 45 participants who received duloxetine and pregabalin for six months. The group experienced a reduction in tender points, evoked pain and VAS pain scores post treatment.

The second arm was a prospective observational study with 35 participants prescribed duloxetine and pregabalin for three months. At the end of the third month 600 mg/d of PEA was added to the regime for a further three months. The addition of PEA reduced the number of tender points from 8 down to 1 at treatment conclusion and the VAS pain score from 3.7 to 1.9 out of 10, 10 being worst pain. The addition of PEA gave better results over a three month period compared with duloxetine and pregabalin combination over six months (Figure 4).[170]

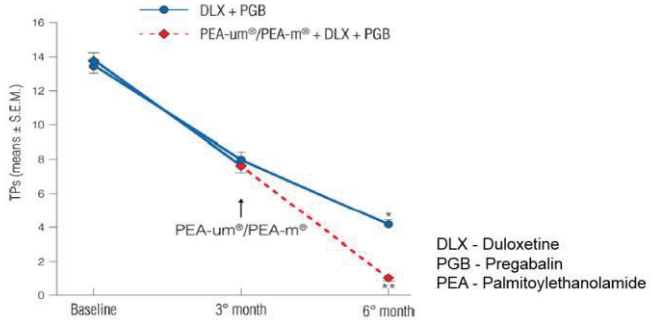


Figure 4: Addition of PEA to duloxetine and pregabalin offered better results than duloxetine and pregabalin alone.[171]

The benefits of using PEA for pain reduction in multiple conditions was established in a study with 564 participants with different pathologies. Participants received 600 mg/d of PEA for three weeks followed by 300 mg/d for four weeks concomitant with existing analgesics. PEA treatment markedly decreased pain intensity for all participants, with an average decrease from 6.4 out of 10 to 2.5 at treatment conclusion.[172]

Within this study a group of participants were able to discontinue existing analgesic therapy experiencing benefit with the use of PEA as standalone treatment.[173]

Arthritic Pain

Arthritic pain results from the collaboration of inflammatory mediators, TRPV1 receptor expression,[174] and mast cell activation and degranulation.[175]

The analgesic and anti-inflammatory effects of PEA was assessed in mild to moderate knee osteoarthritis (OA). A double-blind randomised placebo controlled trial with 111 participants received either placebo, 300 mg/d of PEA or 600 mg/d of PEA for eight weeks. At treatment conclusion pain and stiffness decreased by 53.7% in the 600 mg/d group and by 42% in the 300 mg/d group (Figure 5). At week four, total pain in the placebo group dropped by 25% with no further change.[176]

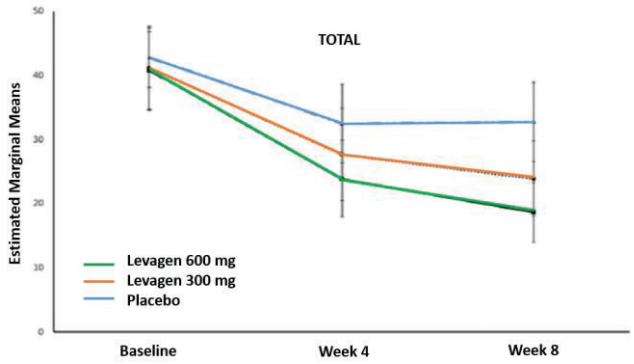


Figure 5: Total decrease in The Western Ontario and McMaster Universities Osteoarthritis Index score with PEA supplementation in knee OA participants.[177]

Treatment with PEA, at 900 mg/d for seven days and then 600 mg/d for a further seven days, was compared with 1,800 mg/d of ibuprofen in participants with temporomandibular joint (TMJ) pain. Pain intensity was similar between groups at baseline however, PEA group experienced a significant reduction at treatment conclusion ($p<0.0001$) compared with the ibuprofen group (Figure 6).[178]

Table 1 Pain Intensity in Patients at Baseline and After Treatment with Ibuprofen or PEA

Treatment	Baseline VAS (mm)	Final VAS (mm)
Ibuprofen (n = 12)	68.42 ± 0.15	37.42 ± 0.36
PEA (n = 12)	69.96 ± 0.22	7.69 ± 0.19

Visual analogue scale (VAS) out of 100 (100 represented 'worst pain imaginable')

Figure 6: Reduction in pain intensity with PEA treatment compared to ibuprofen in patients with TMJ pain.[179]

Endometrial Pain

The aetiology of endometriosis is still largely undefined but it is understood that mast cells in endometriotic lesions and in deep infiltrating lesions proximal to the nerves contribute to the pain and inflammation associated with the condition.[180]

PEA, in combination with polydatin, a natural glucoside of resveratrol, reduced pelvic pain associated with endometriosis in a double-blind randomised placebo controlled trial. Sixty one participants received either 800 mg/d of PEA and 80 mg/d of polydatin (group A), placebo (group B) or 400 mg/d of a cyclo-oxygenase-2 inhibitor (group C). The combination of PEA and polydatin (group A) produced a greater reduction in pelvic pain compared with the placebo (group B) (Figure 7).[181]

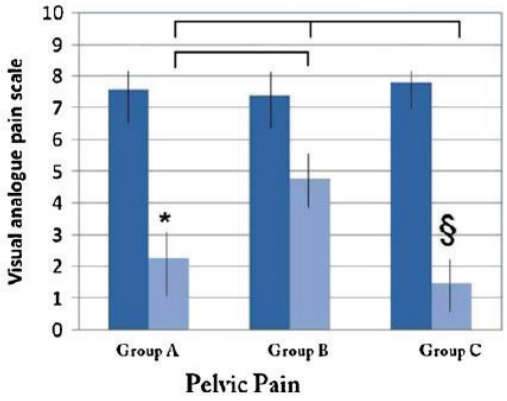


Figure 7: The combination of PEA at 800 mg/d and polydatin at 80 mg/d (group A) reduced pelvic pain compared with placebo (group B).[182]

The significant reduction in chronic pelvic pain ($p<0.05$) with the combination of PEA and polydatin was observed in another study with participants with endometrial pain. Further to the large reduction in pain was the significant improvement in psychological wellbeing ($p<0.0005$).[183]

Neurodegenerative Conditions

Parkinson's Disease

Oxidative stress and neuro-inflammation play a role in the pathogenesis and progression of PD, as demonstrated in animal models. Treatment with PEA in humans with PD and animal PD models has reduced disease severity[184] which may be attributed to its neuroprotective effects.

A prospective observational study revealed the benefits of adding PEA to levodopa in PD patients. At 600 mg/d for three months followed by 300 mg/d for a further 12 months, participants experienced significant reductions in symptoms of dyskinesia (Figure 8). Participants reported mood, sleep, fatigue and pain were significantly improved. Further, QOL was enhanced, with improvements in speech, tremors, getting out of bed, walking and balance.[185]

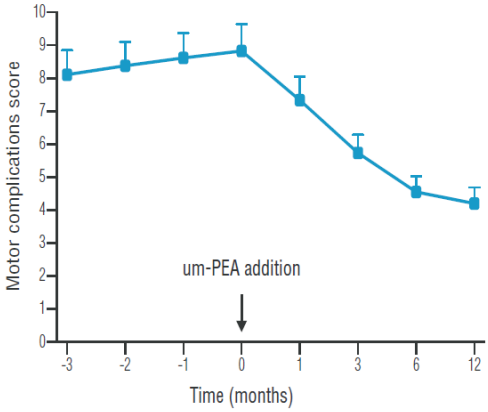


Figure 8: The addition of PEA to levodopa treatment lowers motor complications in PD patients.[186]

In animal PD models, PEA dampened microglial and astroglial activation, protected dopaminergic neurons, improved motor responses and increased tyrosine hydroxylase expression, the enzyme that converts tyrosine to L-DOPA.[187]

Multiple Sclerosis

First line therapy for treatment of relapsing remitting multiple sclerosis (RRMS) is interferon (IFN)-β1a, yet pain and myalgia are commonly reported adverse effects, reducing patient compliance and thus affecting QOL.[188]

PEA reduced adverse effects associated with IFN-β1a treatment in a double-blind randomised placebo controlled trial. Twenty nine participants with RRMS received either 600 mg/d of PEA or placebo alongside IFN-β1a therapy for 12

months. The addition of PEA significantly improved perceived pain at the site of injection, cognitive function and emotional wellbeing ($p<0.05$). Further, there were significant reductions in proinflammatory cytokine serum levels, IFN-γ (Figure 9), interleukin-17 and TNF-α levels ($p<0.05$).[189]

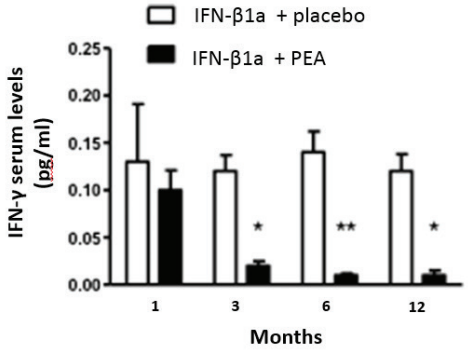


Figure 9: PEA supplementation combined with IFN-β1a therapy significantly reduced IFN-γ levels in participants with RRMS.[190]

Mild Cognitive Impairment and Alzheimer's Disease

Neuro-inflammation and microglial activation play a prominent role in the progression of mild cognitive impairment and AD. As the neuroprotective and anti-inflammatory effects of PEA have been established in animal models it was combined with the antioxidant luteolin and prescribed to a patient with mild cognitive impairment. Over a nine month period the patient received 700 mg/d of PEA in combination with 70 mg/d of luteolin. At the end of treatment significant improvements in cognitive function and short-term memory were observed with the patient gaining more independence with daily living tasks. In addition, this duo of nutrients improved cerebrovascular health, as indicated by the patient's single photon emission computed tomography (SPECT)‡ scan, where signs of significant bilateral hypoperfusion prior to treatment had normalised.[191]

In animal AD models PEA administration:

- Reduced astrocytosis
- Lowered glial fibrillary acidic protein and S100B protein (associated with neuro-inflammation)
- Inhibited tau hyperphosphorylation.[192]

The application of PEA in conditions which prominently feature chronic pain and inflammation extends far beyond this discussion. Table 3 lists the versatility of PEA applications and Table 4 highlights its safety profile in combination with a range of medications. Further, due to the lack of adverse effects and its safety profile, the dosing for PEA has a large range, between 300 and 2,400 mg/d, as presented under dosing considerations.

Table 3: Use of supplemental PEA in other health conditions.

Condition	Study Type	Dose of PEA	Duration	Outcome
Acute respiratory tract infection[193]	Randomised double-blind placebo controlled study (n=444)	1,800 mg/d	2 weeks	PEA treatment markedly reduced incidence of fever, headaches and sore throats.
Autism[194]	Case study (n=2)	600 mg/d 1,200 mg/d 600 mg/d	1 week 3 weeks 12 weeks	Patient one experienced remarkable improvements in behaviour, expressive language and atopic presentations. Patient two showed improvements in aggression, cognitive and behavioural skills.
Cerebral ischemia[195]	Observational study(n=250)	700 mg/d alongside 70 mg/d of luteolin bid	8 weeks	Significant improvement in cognitive function ($p<0.0001$), severity of muscle spasticity ($p<0.0015$), pain intensity ($p<0.0001$) and participants' independence and mobility ($p<0.0001$) in daily living activities.
Exercise recovery[196]	Randomised double-blind placebo controlled study (n=28)	600 mg/d (Levagen+™)	1 day	PEA lowered blood lactate concentrations, linked with anaerobic glucose metabolism, and myoglobin concentrations, associated with skeletal muscle damage.

‡ Single photon emission computed tomography (SPECT) is an imaging test to identify blood flow to tissues and organs.

Idiopathic occipital neuralgia[197]	Case study (n=1)	1,200 mg/d	2 weeks	Patient, after experiencing adverse effects from gabapentin medication, experienced gradual and significant reduction in occipital pain over period of supplementation.
Lower back pain[198]	Pilot observational study with prospective and retrospective arms (n=55)	1,200 mg/d alongside Tapentadol	24 weeks	PEA plus tapentadol experienced a significantly greater reduction in intensity of pain and neuropathy in addition to reduced disability ($p<0.0001$). Further, the required dose of tapentadol was lowered by 40%.
Major depressive disorder[199]	Randomised double-blind placebo controlled study (n=54)	1,200 mg/d alongside citalopram	6 weeks	Significantly greater improvement in depressive symptoms in PEA combined with citalopram group ($p<0.004$) compared with placebo combined with citalopram.
Ocular hypertension[200]	Randomised double-blind placebo controlled crossover study (n=40)	600 mg/d Two month wash out 600 mg/d	12 weeks 12 weeks	Supplementation with PEA resulted in an improvement in arterial blood flow and reduced intraocular pressure compared to both placebo and baseline values. Further, arterial blood flow readings continued to remain improved two months after discontinuation of PEA.
Post-surgery[201]	Randomised single-blind study (n=30)	300 mg/d	2 weeks	Post-operative pain significantly milder with PEA treatment ($p<0.0001$).
Vestibulodynia[202]	Randomised double-blind placebo controlled study (n=20)	800 mg/d alongside 80 mg/d of transpolydatin and transcutaneous electrical nerve stimulation (TENS) therapy	8 weeks	PEA and transpolydatin with TENS therapy had a greater effect on symptom regression compared with TENS therapy alone.

Table 4: Studies demonstrating PEA safety when combined with existing medications.

Condition	Medication	Dose PEA	Duration
Anticancer drug-induced neuropathic pain[203]	Methotrexate, tramadol and pregabalin	1,200 mg/d	15+ weeks
Burning mouth syndrome[204]	Gabapentin	1,200 mg/d	12 weeks
Fibromyalgia[205]	Duloxetine and gabapentin	600 mg/d	12 weeks
Lower back pain[206]	Oxycodone	1,200 mg/d	4 weeks
Lower back pain[207]	Tapentadol	1,200 mg/d	24 weeks
Major depressive disorder[208]	Citalopram	1,200 mg/d	6 weeks
Migraine with aura[209]	NSAIDs	1,200 mg/d	12 weeks
Multiple sclerosis[210]	IFN-β1	600 mg/d	52 weeks
Parkinson's disease[211]	Levodopa	600 mg/d 300 mg/d	12 weeks 52 weeks
Prophylaxis treatment for nummular headache[212]	Topiramate	600 mg/d	16 weeks
Trigeminal neuralgia[213]	Carbamazepine	1,200 mg/d	6 weeks

Dosing Considerations

Condition	Dose Range	Duration
Common cold / influenza[214]	600 – 1,800 mg/d	2 – 9 weeks
Carpel tunnel syndrome[215,216,217,218]	600- 1,200 mg/d	4 – 8 weeks
Cognitive impairment – with luteolin[219]	700 mg/d + 70 mg Luteolin	36 weeks
Depression – with citalopram[220]	1,200 mg/d	6 weeks
Dysmenorrhea with transpolydatin[221]	400 mg/d	
Neuropathic pain – including diabetic and traumatic[222,223]	600 – 1,200 mg/d	6 – 9 weeks
Endometriosis pain[224,225,226]	800 mg/d	12 – 26 weeks
Fibromyalgia[227,228]	1,800 mg/d 1,200 mg/d 600 mg/d	First 2 weeks Next 3 weeks Up to 60 weeks
Glaucoma[229]	600 mg/d	2 – 26 weeks
Lumbosciatica / lower back pain[230,231,232]	600 – 1,200 mg/d	4 – 24 weeks
Neuropathy Chemotherapy induced)[233]	600 mg/d	8 weeks
Osteoarthritis pain[234,235]	300 mg – 600 mg/d	8 weeks
Pain relief (general) [236,237]	300 mg – 1,200 mg/d	2 – 25 weeks
Parkinson's disease[238]	1,200 – 2,400 mg	12 – 52 weeks
Radiculopathy (compressed nerve pain)	600 mg	17 weeks
Sciatica pain (chronic) – see also lower back pain[239,240.241,242]	300 mg – 600 mg/d ** up to 1,200 mg/d	3 weeks
Stroke – with luteolin[243]	1,400 mg/d	8 weeks
Molar surgery[244]	600 mg/d	2 weeks
Multiple sclerosis[245,246]	600 – 1,200 mg/d	32 – 52 weeks
Vestibulodynia (with transcranial magnetic stimulation therapy)[247]	800 mg/d	8 weeks

Cautions and Contraindications

Cautions - Low Level

- None of note

Cautions – Moderate Level

- None of note

Cautions – High Level

- **Prescription analgesic medications:** PEA exerts an analgesic effect.[248] Use of PEA alongside analgesics may theoretically lead to an additive or synergistic analgesic effect. When taken alongside prescription pharmaceutical analgesics, PEA has been shown to exert an additive analgesic effect in human studies,[249,250,251,252] and a synergistic analgesic effect in murine studies.[253,254] It should be noted that minimal adverse side effects have been reported with use of PEA alongside pharmaceutical analgesics in humans to date.[255,256] Monitor in those patients taking PEA alongside prescription analgesic medications as dosage may need adjusting.

Pregnancy and Breastfeeding

Pregnancy

- Limited/unavailable research. A review did not identify any concerns for use during pregnancy, however safety has not been conclusively established in humans.

Breastfeeding

- A review did not identify any concerns for use during breastfeeding, however safety has not been conclusively established in humans.

Children

- No information available.

References

[1] Wang J. Glial endocannabinoid system in pain modulation. Int J Neurosci. 2019 Jan;129(1):94-100. doi: 10.1080/00207454.2018.1503178.
[2] Steels E, Venkatesh R, Steels E, Vitetta G, Vitetta L. A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis. Inflammopharmacology. 2019 Jun;27(3):475-485. doi: 10.1007/s10787-019-00582-9.
[3] Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Med. 2012 Sep;13(9):1121-30. doi:10.1111/j.1526-4637.2012.01432.x.
[4] Wang J. Glial endocannabinoid system in pain modulation. Int J Neurosci. 2019 Jan;129(1):94-100. doi: 10.1080/00207454.2018.1503178.
[5] Skaper SD, Facci L, Fusco M, Della Valle MF, Zusso M, Costa B, et al. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology. 2014 Apr;22(2):79-94. doi:10.1007/s10787-013-0191-7.
[6] Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: its relevance to rheumatic disease. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025.
[7] Grotenhermen F. Cannabinoids and the endocannabinoid system. Cannabinoids. 2006;1(1):10-4.
[8] Wang J. Glial endocannabinoid system in pain modulation. Int J Neurosci. 2019 Jan;129(1):94-100. doi: 10.1080/00207454.2018.1503178.
[9] Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: its relevance to rheumatic disease. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025.
[10] Lu HC, Mackie K. An introduction to the endogenous cannabinoid system. Biol Psychiatry. 2016 Apr 1;79(7):516-25. doi: 10.1016/j.biopsych.2015.07.028.
[11] Wang J. Glial endocannabinoid system in pain modulation. Int J Neurosci. 2019 Jan;129(1):94-100. doi: 10.1080/00207454.2018.1503178.
[12] Wang J. Glial endocannabinoid system in pain modulation. Int J Neurosci. 2019 Jan;129(1):94-100. doi: 10.1080/00207454.2018.1503178.
[13] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015 Feb;14(2):162-73. doi: 10.1016/S1474-4422(14)70251-0.
[14] Schifilliti C, Cucinotta L, Fedele V, Ingegnosi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat. 2014;2014:849623. doi: 10.1155/2014/849623.
[15] Skaper SD, Facci L, Fusco M, Della Valle MF, Zusso M, Costa B, et al. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology. 2014 Apr;22(2):79-94. doi:10.1007/s10787-013-0191-7.
[16] Steels E, Venkatesh R, Steels E, Vitetta G, Vitetta L. A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis. Inflammopharmacology. 2019 Jun;27(3):475-485. doi: 10.1007/s10787-019-00582-9.
[17] Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S. Palmitoylethanolamide in fibromyalgia: results from prospective and retrospective observational studies. Pain Ther. 2015 Dec;4(2):169-78. doi:10.1007/s40122-015-0038-6.
[18] Marcucci M, Germini F, Coerezza A, Andreinetti L, Bellintani L, Nobili A, et al. Efficacy of ultra-micronized palmitoylethanolamide (um-PEA) in geriatric patients with chronic pain: study protocol for a series of N-of-1randomized trials. Trials. 2016 Jul 29;17:369. doi: 10.1186/s13063-016-1496-9.
[19] Donvito G, Wilkerson JL, Damaj MI, Lichtman AH. Palmitoylethanolamide reverses paclitaxel-induced allodynia in mice. J Pharmacol Exp Ther. 2016 Nov;359(2):310-318. PMID: 27608657.
[20] Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Med. 2012 Sep;13(9):1121-30. doi:10.1111/j.1526-4637.2012.01432.x.
[21] Schifilliti C, Cucinotta L, Fedele V, Ingegnosi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat. 2014;2014:849623. doi: 10.1155/2014/849623.
[22] Cocito D, Peci E, Ciaramitaro P, Merola A, Lopiano L. Short-term efficacy of ultramicronized palmitoylethanolamide in peripheral neuropathic pain. Pain Res Treat. 2014;2014:854560. doi: 10.1155/2014/854560.
[23] Truini A, Biasiotta A, Di Stefano G, La Cesa S, Leone C, Cartoni C. Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. CNS Neurol Disord Drug Targets. 2011 Dec;10(8):916-20. PMID: 22229320.
[24] Hesselink JM, Hekker TA. Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series. J Pain Res. 2012;5:437-42. doi: 10.2147/JPR.S32143.
[25] Assini A, Laricchia D, Pizzo R, Pandolfini L, Belletti M, Colucci M, et al. The carpal tunnel syndrome in diabetes: clinical and electrophysiological improvement after treatment with palmitoylethanolamide: P1577. Eur J Neurol. 2010 Sep 17;12(3):295-295.
[26] Guida G, De Martino M, De Fabiani A, Canterieri L, Alexandre A, Vassallo GM, et al. Palmitoylethanolamide (Normast®) in chronic neuropathic pain due to compression lumbociatalgia: a multicenter clinical study. DOLOR. 2010:25(1):35-42.
[27] Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S. Palmitoylethanolamide in fibromyalgia: results from prospective and retrospective observational studies. Pain Ther. 2015 Dec;4(2):169-78. doi:10.1007/s40122-015-0038-6.

[28] Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Med. 2012 Sep;13(9):1121-30. doi:10.1111/j.1526-4637.2012.01432.x.
[29] Steels E, Venkatesh R, Steels E, Vitetta G, Vitetta L. A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis. Inflammopharmacology. 2019 Jun;27(3):475-485. doi: 10.1007/s10787-019-00582-9.
[30] Marini I, Lavinia Bartolucci M, Bortolotti F, Rosaria Gatto M, Alessandri Bonetti G. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. J Orofac Pain. 2012 Apr 1;26(2):99.
[31] Cobellis L, Castaldi MA, Giordano V, Trabucco E, De Franciscis P, Torella M, et al. Effectiveness of the association micronized N-palmitoylethanolamine (PEA)-transpolydatin in the treatment of chronic pelvic pain related to endometriosis after laparoscopic assessment: a pilot study. Eur J Obstet Gynecol Reprod Biol. 2011 Sep;158(1):82-6. doi: 10.1016/j.ejogrb.2011.04.011.
[32] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949.
[33] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949.
[34] Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. Neurotherapeutics. 2016 Apr;13(2):428-38. doi: 10.1007/s13311-016-0420-z.
[35] Scuderi C, Stecca C, Valenza M, Ratano P, Bronzuoli MR, Bartoli S, et al. Palmitoylethanolamide controls reactive gliosis and exerts neuroprotective functions in a rat model of Alzheimer's disease. Cell Death Dis. 2014 Sep 11;5:e1419. doi: 10.1038/cddis.2014.376.
[36] Peritore AF, Siracusa R, Crupi R, Cuzzocrea S. Therapeutic efficacy of palmitoylethanolamide and its new formulations in synergy with different antioxidant molecules present in diets. Nutrients. 2019 Sep 11;11(9).e2175. doi: 10.3390/nu11092175.
[37] Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res. 2015 Oct 23;8:729-34. doi: 10.2147/JPR.S93106.
[38] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949.
[39] Marini I, Lavinia Bartolucci M, Bortolotti F, Rosaria Gatto M, Alessandri Bonetti G. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. J Orofac Pain. 2012 Apr 1;26(2):99.
[40] Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. Neurotherapeutics. 2016 Apr;13(2):428-38. doi: 10.1007/s13311-016-0420-z.
[41] Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. Br J Clin Pharmacol. 2016 Oct;82(4):932-42. doi: 10.1111/bcp.13020.
[42] Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res. 2015 Oct 23;8:729-34. doi: 10.2147/JPR.S93106.
[43] Marini I, Lavinia Bartolucci M, Bortolotti F, Rosaria Gatto M, Alessandri Bonetti G. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. J Orofac Pain. 2012 Apr 1;26(2):99.
[44] Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. Neurotherapeutics. 2016 Apr;13(2):428-38. doi: 10.1007/s13311-016-0420-z.
[45] Domínguez CM, Martín AD, Ferrer FG, Puertas MI, Muro AL, González JM, et al. N-palmitoylethanolamide in the treatment of neuropathic pain associated with lumbosciatica. Pain Manag. 2012 Mar;2(2):119-24. doi:10.2217/pmt.12.5.
[46] Impellizzeri D, Bruschetta G, Cordaro M, Crupi R, Siracusa R, Esposito E, et al. Micronized/ultramicronized palmitoylethanolamide displays superior oral efficacy compared to nonmicronized palmitoylethanolamide in a rat model of inflammatory pain. J Neuroinflammation. 2014 Aug 28;11:136. doi: 10.1186/s12974-014-0136-0.
[47] Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res. 2015 Oct 23;8:729-34. doi: 10.2147/JPR.S93106.
[48] Petrosino S, Schiano Moriello A, Cerrato S, Fusco M, Puigdemont A, De Petrocellis L, et al. The anti-inflammatory mediator palmitoylethanolamide enhances the levels of 2-arachidonoyl-glycerol and potentiates its actions at TRPV1 cation channels. Br J Pharmacol. 2016 Apr;173(7):1154-62. doi: 10.1111/bph.13084.
[49] Artukoglu BB, Beyer C, Zuloff-Shani A, Brener E, Bloch MH. Efficacy of palmitoylethanolamide for pain: a meta-analysis. Pain Physician. 2017 Jul;20(5):353-362. PMID: 28727699.
[50] Guida F, Luongo L, Boccella S, Giordano ME, Romano R, Bellini G. Palmitoylethanolamide induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor. Sci Rep. 2017 Mar 23;7(1):375. doi: 10.1038/s41598-017-00342-1.
[51] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[52] Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. Neurotherapeutics. 2016 Apr;13(2):428-38. doi: 10.1007/s13311-016-0420-z.
[53] Ambrosino P, Soldovieri MV, Russo C, Taglialatela M. Activation and desensitization of TRPV1 channels in sensory neurons by the PPARα agonist palmitoylethanolamide. Br J Pharmacol. 2013 Mar;168(6):1430-44. doi:10.1111/bph.12029.
[54] Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: its relevance to rheumatic disease. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025.
[55] Peritore AF, Siracusa R, Crupi R, Cuzzocrea S. Therapeutic efficacy of palmitoylethanolamide and its new formulations in synergy with different antioxidant molecules present in diets. Nutrients. 2019 Sep 11;11(9).e2175. doi: 10.3390/nu11092175.
[56] Keppel Hesselink JM, de Boer T, Witkamp RF. Palmitoylethanolamide: a natural body-own anti-inflammatory agent, effective and safe against influenza and common cold. Int J Inflam. 2013;2013:151028. doi: 10.1155/2013/151028.
[57] Peritore AF, Siracusa R, Crupi R, Cuzzocrea S. Therapeutic efficacy of palmitoylethanolamide and its new formulations in synergy with different antioxidant molecules present in diets. Nutrients. 2019 Sep 11;11(9).e2175. doi: 10.3390/nu11092175.
[58] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[59] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.

[60] Peritore AF, Siracusa R, Crupi R, Cuzzocrea S. Therapeutic efficacy of palmitoylethanolamide and its new formulations in synergy with different antioxidant molecules present in diets. Nutrients. 2019 Sep 11;11(9).e2175. doi: 10.3390/nu11092175.
[61] Alhouayek M, Muccioli GG. Harnessing the anti-inflammatory potential of palmitoylethanolamide. Drug Discov Today. 2014 Oct;19(10):1632-9. doi: 10.1016/j.drudis.2014.06.007.
[62] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[63] Alhouayek M, Muccioli GG. Harnessing the anti-inflammatory potential of palmitoylethanolamide. Drug Discov Today. 2014 Oct;19(10):1632-9. doi: 10.1016/j.drudis.2014.06.007.
[64] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[65] Alhouayek M, Muccioli GG. Harnessing the anti-inflammatory potential of palmitoylethanolamide. Drug Discov Today. 2014 Oct;19(10):1632-9. doi: 10.1016/j.drudis.2014.06.007.
[66] Petrosino S, Di Marzo V. The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations. Br J Pharmacol. 2017 Jun;174(11):1349-1365. doi: 10.1111/bph.13580.
[67] Alhouayek M, Muccioli GG. Harnessing the anti-inflammatory potential of palmitoylethanolamide. Drug Discov Today. 2014 Oct;19(10):1632-9. doi: 10.1016/j.drudis.2014.06.007.
[68] Peritore AF, Siracusa R, Crupi R, Cuzzocrea S. Therapeutic efficacy of palmitoylethanolamide and its new formulations in synergy with different antioxidant molecules present in diets. Nutrients. 2019 Sep 11;11(9).e2175. doi: 10.3390/nu11092175.
[69] Skaper SD, Facci L, Fusco M, Della Valle MF, Zusso M, Costa B, et al. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology. 2014 Apr;22(2):79-94. doi:0.1007/s10787-013-0191-7.
[70] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[71] Skaper SD, Facci L, Fusco M, Della Valle MF, Zusso M, Costa B, et al. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology. 2014 Apr;22(2):79-94. doi:10.1007/s10787-013-0191-7.
[72] Beggiato S, Tomasini MC, Ferraro L. Palmitoylethanolamide (PEA) as a potential therapeutic agent in Alzheimer's disease. Front Pharmacol. 2019 Jul 24;10:821. doi: 10.3389/fphar.2019.00821.
[73] Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. Br J Clin Pharmacol. 2016 Oct;82(4):932-42. doi: 10.1111/bcp.13020.
[74] Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. Br J Clin Pharmacol. 2016 Oct;82(4):932-42. doi: 10.1111/bcp.13020.
[75] Briskey D, Mallard AR, Rao A. Increased absorption of palmitoylethanolamide using a novel dispersion technology system (LipiSperse®). [cited 2020 2 25].
[76] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[77] Guida F, Luongo L, Boccella S, Giordano ME, Romano R, Bellini G. Palmitoylethanolamide induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor. Sci Rep. 2017 Mar 23;7(1):375. doi: 10.1038/s41598-017-00342-1.
[78] Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: its relevance to rheumatic disease. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025.
[79] Donvito G, Wilkerson JL, Damaj MI, Lichtman AH. Palmitoylethanolamide reverses paclitaxel-induced allodynia in mice. J Pharmacol Exp Ther. 2016 Nov;359(2):310-318. PMID: 27608657.
[80] Grotenhermen F. Cannabinoids and the endocannabinoid system. Cannabinoids. 2006;1(1):10-4.
[81] Grotenhermen F. Cannabinoids and the endocannabinoid system. Cannabinoids. 2006;1(1):10-4.
[82] Wang J. Glial endocannabinoid system in pain modulation. Int J Neurosci. 2019 Jan;129(1):94-100. doi: 10.1080/00207454.2018.1503178.
[83] Guindon J, Hohmann AG. The endocannabinoid system and pain. CNS Neurol Disord Drug Targets. 2009 Dec;8(6):403-21. PMID: 19839937.
[84] Cassano T, Calcagnini S, Pace L, De Marco F, Romano A, Gaetani S. Cannabinoid receptor 2 signalling in neurodegenerative disorders: from pathogenesis to a promising therapeutic target. Front Neurosci. 2017 Feb 2;11:30. doi:10.3389/fnins.2017.00030.
[85] Cassano T, Calcagnini S, Pace L, De Marco F, Romano A, Gaetani S. Cannabinoid receptor 2 signalling in neurodegenerative disorders: from pathogenesis to a promising therapeutic target. Front Neurosci. 2017 Feb 2;11:30. doi:10.3389/fnins.2017.00030.
[86] Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res. 2015 Oct 23;8:729-34. doi: 10.2147/JPR.S93106.
[87] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[88] Schifilliti C, Cucinotta L, Fedele V, Ingegnosi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat. 2014;2014:849623. doi: 10.1155/2014/849623.
[89] Peritore AF, Siracusa R, Crupi R, Cuzzocrea S. Therapeutic efficacy of palmitoylethanolamide and its new formulations in synergy with different antioxidant molecules present in diets. Nutrients. 2019 Sep 11;11(9).e2175. doi: 10.3390/nu11092175.
[90] Petrosino S, Schiano Moriello A, Cerrato S, Fusco M, Puigdemont A, De Petrocellis L, et al. The anti-inflammatory mediator palmitoylethanolamide enhances the levels of 2-arachidonoyl-glycerol and potentiates its actions at TRPV1 cation channels. Br J Pharmacol. 2016 Apr;173(7):1154-62. doi: 10.1111/bph.13084.
[91] Petrosino S, Di Marzo V. The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations. Br J Pharmacol. 2017 Jun;174(11):1349-1365. doi: 10.1111/bph.13580.
[92] Schifilliti C, Cucinotta L, Fedele V, Ingegnosi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat. 2014;2014:849623. doi: 10.1155/2014/849623.
[93] Peritore AF, Siracusa R, Crupi R, Cuzzocrea S. Therapeutic efficacy of palmitoylethanolamide and its new formulations in synergy with different antioxidant molecules present in diets. Nutrients. 2019 Sep 11;11(9).e2175. doi: 10.3390/nu11092175.
[94] Petrosino S, Schiano Moriello A, Cerrato S, Fusco M, Puigdemont A, De Petrocellis L, et al. The anti-inflammatory mediator palmitoylethanolamide enhances the levels of 2-arachidonoyl-glycerol and potentiates its actions at TRPV1 cation channels. Br J Pharmacol. 2016 Apr;173(7):1154-62. doi: 10.1111/bph.13084.
[95] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[96] Donvito G, Wilkerson JL, Damaj MI, Lichtman AH. Palmitoylethanolamide reverses paclitaxel-induced allodynia in mice. J Pharmacol Exp Ther. 2016 Nov;359(2):310-318. PMID: 27608657.
[97] Schifilliti C, Cucinotta L, Fedele V, Ingegnosi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat. 2014;2014:849623. doi: 10.1155/2014/849623.

[98] Alhouayek M, Muccioli GG. Harnessing the anti-inflammatory potential of palmitoylethanolamide. Drug Discov Today. 2014 Oct;19(10):1632-9. doi: 10.1016/j.drudis.2014.06.007.
[99] Peritore AF, Siracusa R, Crupi R, Cuzzocrea S. Therapeutic efficacy of palmitoylethanolamide and its new formulations in synergy with different antioxidant molecules present in diets. Nutrients. 2019 Sep 11;11(9).e2175. doi: 10.3390/nu11092175.
[100] Donvito G, Wilkerson JL, Damaj MI, Lichtman AH. Palmitoylethanolamide reverses paclitaxel-induced allodynia in mice. J Pharmacol Exp Ther. 2016 Nov;359(2):310-318. PMID: 27608657.
[101] Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: its relevance to rheumatic disease. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025.
[102] Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: its relevance to rheumatic disease. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025.
[103] Ambrosino P, Soldovieri MV, Russo C, Taglialatela M. Activation and desensitization of TRPV1 channels in sensory neurons by the PPARα agonist palmitoylethanolamide. Br J Pharmacol. 2013 Mar;168(6):1430-44. doi: 10.1111/bph.12029.
[104] Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: its relevance to rheumatic disease. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025.
[105] Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res. 2015 Oct 23;8:729-34. doi: 10.2147/JPR.S93106.
[106] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[107] Petrosino S, Schiano Moriello A, Cerrato S, Fusco M, Puigdemont A, De Petrocellis L, et al. The anti-inflammatory mediator palmitoylethanolamide enhances the levels of 2-arachidonoyl-glycerol and potentiates its actions at TRPV1 cation channels. Br J Pharmacol. 2016 Apr;173(7):1154-62. doi: 10.1111/bph.13084.
[108] Donvito G, Wilkerson JL, Damaj MI, Lichtman AH. Palmitoylethanolamide reverses paclitaxel-induced allodynia in mice. J Pharmacol Exp Ther. 2016 Nov;359(2):310-318. PMID: 27608657.
[109] Alhouayek M, Muccioli GG. Harnessing the anti-inflammatory potential of palmitoylethanolamide. Drug Discov Today. 2014 Oct;19(10):1632-9. doi: 10.1016/j.drudis.2014.06.007.
[110] Schifilliti C, Cucinotta L, Fedele V, Ingegnosi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat. 2014;2014:849623. doi: 10.1155/2014/849623.
[111] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[112] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[113] Guida F, Luongo L, Boccella S, Giordano ME, Romano R, Bellini G. Palmitoylethanolamide induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor. Sci Rep. 2017 Mar 23;7(1):375. doi: 10.1038/s41598-017-00342-1.
[114] Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. Neurotherapeutics. 2016 Apr;13(2):428-38. doi: 10.1007/s13311-016-0420-z.
[115] Alhouayek M, Muccioli GG. Harnessing the anti-inflammatory potential of palmitoylethanolamide. Drug Discov Today. 2014 Oct;19(10):1632-9. doi: 10.1016/j.drudis.2014.06.007.
[116] Donvito G, Wilkerson JL, Damaj MI, Lichtman AH. Palmitoylethanolamide reverses paclitaxel-induced allodynia in mice. J Pharmacol Exp Ther. 2016 Nov;359(2):310-318. PMID: 27608657.
[117] Alhouayek M, Muccioli GG. Harnessing the anti-inflammatory potential of palmitoylethanolamide. Drug Discov Today. 2014 Oct;19(10):1632-9. doi: 10.1016/j.drudis.2014.06.007.
[118] Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: its relevance to rheumatic disease. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025.
[119] Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. Neurotherapeutics. 2016 Apr;13(2):428-38. doi: 10.1007/s13311-016-0420-z.
[120] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[121] Beggiato S, Tomasini MC, Ferraro L. Palmitoylethanolamide (PEA) as a potential therapeutic agent in Alzheimer's disease. Front Pharmacol. 2019 Jul 24;10:821. doi: 10.3389/fphar.2019.00821.
[122] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[123] Beggiato S, Tomasini MC, Ferraro L. Palmitoylethanolamide (PEA) as a potential therapeutic agent in Alzheimer's disease. Front Pharmacol. 2019 Jul 24;10:821. doi: 10.3389/fphar.2019.00821.
[124] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949.
[125] Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Med. 2012 Sep;13(9):1121-30. doi:10.1111/j.1526-4637.2012.01432.x.
[126] Marini I, Lavinia Bartolucci M, Bortolotti F, Rosaria Gatto M, Alessandri Bonetti G. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. J Orofac Pain. 2012 Apr 1;26(2):99.
[127] Stochino Loi E, Pontis A, Cofelice V, Pirarba S, Fais MF, Daniilidis A, et al. Effect of ultramicronized-palmitoylethanolamide and co-micronized palmitoylethanolamide/polydatin on chronic pelvic pain and quality of life in endometriosis patients: an open-label pilot study. Int J Womens Health. 2019 Aug 12;11:443-449. doi: 10.2147/IJWH.S204275.
[128] Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res. 2015 Oct 23;8:729-34. doi: 10.2147/JPR.S93106.
[129] Marini I, Lavinia Bartolucci M, Bortolotti F, Rosaria Gatto M, Alessandri Bonetti G. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. J Orofac Pain. 2012 Apr 1;26(2):99.
[130] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949.
[131] Artukoglu BB, Beyer C, Zuloff-Shani A, Brener E, Bloch MH. Efficacy of palmitoylethanolamide for pain: a meta-analysis. Pain Physician. 2017 Jul;20(5):353-362. PMID: 28727699.

[132] Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res. 2015 Oct 23;8:729-34. doi: 10.2147/JPR.S93106.
[133] Schifilliti C, Cucinotta L, Fedele V, Ingegnosi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat. 2014;2014:849623. doi: 10.1155/2014/849623.
[134] Truini A, Biasiotta A, Di Stefano G, La Cesa S, Leone C, Cartoni C, et al. Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. CNS Neurol Disord Drug Targets. 2011 Dec;10(8):916-20. PMID: 22229320.
[135] Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res. 2015 Oct 23;8:729-34. doi: 10.2147/JPR.S93106.
[136] Steels E, Venkatesh R, Steels E, Vitetta G, Vitetta L. A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis. Inflammopharmacology. 2019 Jun;27(3):475-485. doi: 10.1007/s10787-019-00582-9.
[137] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[138] Guida F, Luongo L, Boccella S, Giordano ME, Romano R, Bellini G. Palmitoylethanolamide induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor. Sci Rep. 2017 Mar 23;7(1):375. doi: 10.1038/s41598-017-00342-1.
[139] Guida F, Luongo L, Boccella S, Giordano ME, Romano R, Bellini G. Palmitoylethanolamide induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor. Sci Rep. 2017 Mar 23;7(1):375. doi: 10.1038/s41598-017-00342-1.
[140] Zhang F, Nance E, Alnasser Y, Kannan R, Kannan S. Microglial migration and interactions with dendrimer nanoparticles are altered in the presence of neuroinflammation. J Neuroinflammation. 2016 Mar 22;13(1):65. doi: 10.1186/s12974-016-0529-3.
[141] Guida F, Luongo L, Boccella S, Giordano ME, Romano R, Bellini G. Palmitoylethanolamide induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor. Sci Rep. 2017 Mar 23;7(1):375. doi: 10.1038/s41598-017-00342-1.
[142] Guida F, Luongo L, Boccella S, Giordano ME, Romano R, Bellini G. Palmitoylethanolamide induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor. Sci Rep. 2017 Mar 23;7(1):375. doi: 10.1038/s41598-017-00342-1.
[143] Pluvinage JV, Haney MS, Smith BAH, Sun J, Iram T, Bonanno L, et al. CD22 blockade restores homeostatic microglial phagocytosis in ageing brains. Nature. 2019 Apr;568(7751):187-192. doi: 10.1038/s41586-019-1088-4.
[144] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949.
[145] Artukoglu BB, Beyer C, Zuloff-Shani A, Brener E, Bloch MH. Efficacy of palmitoylethanolamide for pain: a meta-analysis. Pain Physician. 2017 Jul;20(5):353-362. PMID: 28727699.
[146] Guida F, Luongo L, Boccella S, Giordano ME, Romano R, Bellini G. Palmitoylethanolamide induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor. Sci Rep. 2017 Mar 23;7(1):375. doi: 10.1038/s41598-017-00342-1.
[147] Skaper SD, Facci L, Fusco M, Della Valle MF, Zusso M, Costa B, et al. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology. 2014 Apr;22(2):79-94. doi:10.1007/s10787-013-0191-7.
[148] Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Med. 2012 Sep;13(9):1121-30. doi:10.1111/j.1526-4637.2012.01432.x.
[149] Alshelh Z, Mills EP, Kosanovic D, Di Pietro F, Macey PM, Vickers ER, et al. Effects of the glial modulator palmitoylethanolamide on chronic pain intensity and brain function. J Pain Res. 2019 Aug 2;12:2427-2439. doi: 10.2147/JPR.S209657.
[150] Scuderi C, Stecca C, Valenza M, Ratano P, Bronzuoli MR, Bartoli S, et al. Palmitoylethanolamide controls reactive gliosis and exerts neuroprotective functions in a rat model of Alzheimer's disease. Cell Death Dis. 2014 Sep 11;5:e1419. doi: 10.1038/cddis.2014.376.
[151] Scuderi C, Stecca C, Valenza M, Ratano P, Bronzuoli MR, Bartoli S, et al. Palmitoylethanolamide controls reactive gliosis and exerts neuroprotective functions in a rat model of Alzheimer's disease. Cell Death Dis. 2014 Sep 11;5:e1419. doi: 10.1038/cddis.2014.376.
[152] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[153] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[154] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[155] Hernandez-Rabaza V, Cabrera-Pastor A, Taoro-Gonzalez L, Gonzalez-Usano A, Agusti A, Balzano T, et al. Neuroinflammation increases GABAergic tone and impairs cognitive and motor function in hyperammonemia by increasing GAT-3 membrane expression. Reversal by sulforaphane by promoting M2 polarization of microglia. J Neuroinflammation. 2016;13(1):83. Published 2016 Apr 18. doi:10.1186/s12974-016-0549-z.
[156] Schifilliti C, Cucinotta L, Fedele V, Ingegnosi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat. 2014;2014:849623. doi: 10.1155/2014/849623.
[157] Truini A, Biasiotta A, Di Stefano G, La Cesa S, Leone C, Cartoni C. Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. CNS Neurol Disord Drug Targets. 2011 Dec;10(8):916-20. PMID: 22229320.
[158] Donvito G, Wilkerson JL, Damaj MI, Lichtman AH. Palmitoylethanolamide reverses paclitaxel-induced allodynia in mice. J Pharmacol Exp Ther. 2016 Nov;359(2):310-318. PMID: 27608657.
[159] Schifilliti C, Cucinotta L, Fedele V, Ingegnosi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat. 2014;2014:849623. doi: 10.1155/2014/849623.
[160] Cocito D, Peci E, Ciaramitaro P, Merola A, Lopiano L. Short-term efficacy of ultramicronized palmitoylethanolamide in peripheral neuropathic pain. Pain Res Treat. 2014;2014:854560. doi: 10.1155/2014/854560.
[161] Hesselink JM, Hekker TA. Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series. J Pain Res. 2012;5:437-42. doi: 10.2147/JPR.S32143.
[162] Hesselink JM, Hekker TA. Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series. J Pain Res. 2012;5:437-42. doi: 10.2147/JPR.S32143.
[163] Truini A, Biasiotta A, Di Stefano G, La Cesa S, Leone C, Cartoni C. Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. CNS Neurol Disord Drug Targets. 2011 Dec;10(8):916-20. PMID: 22229320.
[164] Hesselink JM, Hekker TA. Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series. J Pain Res. 2012;5:437-42. doi: 10.2147/JPR.S32143.
[165] Faig-Martí J, Martínez-Catassús A. Use of palmitoylethanolamide in carpal tunnel syndrome: a prospective randomized study. J Orthop Traumatol. 2017 Dec;18(4):451-455. doi: 10.1007/s10195-017-0453-z.
[166] Assini A, Laricchia D, Pizzo R, Pandolfini L, Belletti M, Colucci M, et al. The carpal tunnel syndrome in diabetes: clinical and electrophysiological improvement after treatment with palmitoylethanolamide: P1577. Eur J Neurol. 2010 Sep 17;12(3):295-295.

[167] Guida G, De Martino M, De Fabiani A, Canterieri L, Alexandre A, Vassallo GM, et al. Palmitoylethanolamide (Normast®) in chronic neuropathic pain due to compression lumbociatalgia: a multicenter clinical study. DOLOR. 2010:25(1):35-42.
[168] Domínguez CM, Martín AD, Ferrer FG, Puertas MI, Muro AL, González JM, et al. N-palmitoylethanolamide in the treatment of neuropathic pain associated with lumbosciatica. Pain Manag. 2012 Mar;2(2):119-24. doi:10.2217/pmt.12.5.
[169] Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S. Palmitoylethanolamide in fibromyalgia: results from prospective and retrospective observational studies. Pain Ther. 2015 Dec;4(2):169-78. doi:10.1007/s40122-015-0038-6.
[170] Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S. Palmitoylethanolamide in fibromyalgia: results from prospective and retrospective observational studies. Pain Ther. 2015 Dec;4(2):169-78. doi:10.1007/s40122-015-0038-6.
[171] Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S. Palmitoylethanolamide in fibromyalgia: results from prospective and retrospective observational studies. Pain Ther. 2015 Dec;4(2):169-78. doi:10.1007/s40122-015-0038-6.
[172] Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Med. 2012 Sep;13(9):1121-30. doi: 10.1111/j.1526-4637.2012.01432.x.
[173] Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Med. 2012 Sep;13(9):1121-30. doi: 10.1111/j.1526-4637.2012.01432.x.
[174] Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: its relevance to rheumatic disease. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025.
[175] Marini I, Lavinia Bartolucci M, Bortolotti F, Rosaria Gatto M, Alessandri Bonetti G. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. J Orofac Pain. 2012 Apr 1;26(2):99.
[176] Steels E, Venkatesh R, Steels E, Vitetta G, Vitetta L. A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis. Inflammopharmacology. 2019 Jun;27(3):475-485. doi: 10.1007/s10787-019-00582-9.
[177] Steels E, Venkatesh R, Steels E, Vitetta G, Vitetta L. A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis. Inflammopharmacology. 2019 Jun;27(3):475-485. doi: 10.1007/s10787-019-00582-9.
[178] Marini I, Lavinia Bartolucci M, Bortolotti F, Rosaria Gatto M, Alessandri Bonetti G. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. J Orofac Pain. 2012 Apr 1;26(2):99.
[179] Marini I, Lavinia Bartolucci M, Bortolotti F, Rosaria Gatto M, Alessandri Bonetti G. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. J Orofac Pain. 2012 Apr 1;26(2):99.
[180] Stochino Loi E, Pontis A, Cofelice V, Pirarba S, Fais MF, Daniilidis A, et al. Effect of ultramicronized-palmitoylethanolamide and co-micronized palmitoylethanolamide/polydatin on chronic pelvic pain and quality of life in endometriosis patients: an open-label pilot study. Int J Womens Health. 2019 Aug 12;11:443-449. doi: 10.2147/IJWH.S204275.
[181] Cobellis L, Castaldi MA, Giordano V, Trabucco E, De Franciscis P, Torella M, et al. Effectiveness of the association micronized N-palmitoylethanolamine (PEA)-transpolydatin in the treatment of chronic pelvic pain related to endometriosis after laparoscopic assessment: a pilot study. Eur J Obstet Gynecol Reprod Biol. 2011 Sep;158(1):82-6. doi: 10.1016/j.ejogrb.2011.04.011.
[182] Cobellis L, Castaldi MA, Giordano V, Trabucco E, De Franciscis P, Torella M, et al. Effectiveness of the association micronized N-palmitoylethanolamine (PEA)-transpolydatin in the treatment of chronic pelvic pain related to endometriosis after laparoscopic assessment: a pilot study. Eur J Obstet Gynecol Reprod Biol. 2011 Sep;158(1):82-6. doi: 10.1016/j.ejogrb.2011.04.011.
[183] Stochino Loi E, Pontis A, Cofelice V, Pirarba S, Fais MF, Daniilidis A, et al. Effect of ultramicronized-palmitoylethanolamide and co-micronized palmitoylethanolamide/polydatin on chronic pelvic pain and quality of life in endometriosis patients: an open-label pilot study. Int J Womens Health. 2019 Aug 12;11:443-449. doi: 10.2147/IJWH.S204275.
[184] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949.
[185] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949.
[186] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949.
[187] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949.
[188] Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. Neurotherapeutics. 2016 Apr;13(2):428-38. doi: 10.1007/s13311-016-0420-z.
[189] Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. Neurotherapeutics. 2016 Apr;13(2):428-38. doi: 10.1007/s13311-016-0420-z.
[190] Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. Neurotherapeutics. 2016 Apr;13(2):428-38. doi: 10.1007/s13311-016-0420-z.
[191] Calabrò RS, Naro A, De Luca R, Leonardi S, Russo M, Marra A, et al. PEALut efficacy in mild cognitive impairment: evidence from a SPECT case study. Aging Clin Exp Res. 2016 Dec;28(6):1279-1282. 2016 Jan 28. PMID: 26820462.
[192] Scuderi C, Stecca C, Valenza M, Ratano P, Bronzuoli MR, Bartoli S, et al. Palmitoylethanolamide controls reactive gliosis and exerts neuroprotective functions in a rat model of Alzheimer's disease. Cell Death Dis. 2014 Sep 11;5:e1419. doi: 10.1038/cddis.2014.376.
[193] Masek K, Perlík F, Klíma J, Kahlich R. Prophylactic efficacy of N-2-hydroxyethyl palmitamide (impulsin) in acute respiratory tract infections. Eur J Clin Pharmacol. 1974;7(6):415–419. doi:10.1007/bf00560353.
[194] Antonucci N, Cirillo A, Siniscalco D. Beneficial effects of palmitoylethanolamide on expressive language, cognition, and behaviors in autism: a report of two cases. Case Rep Psychiatry. 2015;2015:325061. doi:10.1155/2015/325061.
[195] Caltagirone C, Cisari C, Schievano C, Di Paola R, Cordaro M, Bruschetta G et al. Co-ultramicronized palmitoylethanolamide/luteolin in the treatment of cerebral ischemia: from rodent to man. Transl Stroke Res. 2016 Feb;7(1):54-69. doi: 10.1007/s12975-015-0440-8.
[196] Mallard A, Briskey D, Richards A, Mills D, Rao A. The effect of orally dosed Levagen+™ (palmitoylethanolamide) on exercise recovery in healthy males—a double-blind, randomized, placebo-controlled study. Nutrients. 2020 Mar;12(3):596.
[197] Calabrò RS, Bramanti P. Occipital neuralgia responding to palmitoylethanolamide. Headache. 2017 Nov;57(10):E23-E24. doi: 10.1111/head.12136.
[198] Passavanti MB, Fiore M, Sansone P, Aurilio C, Pota V, Barbarisi M, et al. The beneficial use of ultramicronized palmitoylethanolamide as add-on therapy to tapentadol in the treatment of low back pain: a pilot study comparing prospective and retrospective observational arms. BMC Anesthesiol. 2017 Dec 19;17(1):171. doi: 10.1186/s12871-017-0461-9.

[199] Ghazizadeh-Hashemi M, Ghajar A, Shalbafan MR, Ghazizadeh-Hashemi F, Afarideh M, Malekpour F, et al. Palmitoylethanolamide as adjunctive therapy in major depressive disorder: A double-blind, randomized and placebo-controlled trial. J Affect Disord. 2018 May;232:127-133. doi:10.1016/j.jad.2018.02.057.
[200] Strobbe E, Cellini M, Campos EC. Effectiveness of palmitoylethanolamide on endothelial dysfunction in ocular hypertensive patients: a randomized, placebo-controlled cross-over study. Invest Ophthalmol. 2013 Feb 1;54(2):968-73.
[201] Bacci C, Cassetta G, Emanuele B, Berengo M. Randomized split-mouth study on postoperative effects of palmitoylethanolamide for impacted lower third molar surgery. ISRN Surg. 2011;2011:917350. doi: 10.5402/2011/917350.
[202] Murina F, Graziottin A, Felice R, Radici G, Tognocchi C. Vestibulodynia: synergy between palmitoylethanolamide + transpolydatin and transcutaneous electrical nerve stimulation. J Low Genit Tract Dis. 2013 Apr;17(2):111-6. doi: 10.1097/LGT.0b013e3182652316.
[203] Hesselink JM, Hekker TA. Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series. J Pain Res. 2012;5:437–442. doi:10.2147/JPR.S32143.
[204] Chirchiglia D, Chirchiglia P, Marotta R, Gallelli L. Add-on administration of ultramicronized palmitoylethanolamide in the treatment of new-onset burning mouth syndrome. Int Med Case Rep J. 2019 Feb 15;12:39–42. doi:10.2147/IMCRJ.S194403.
[205] Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S. Palmitoylethanolamide in fibromyalgia: results from prospective and retrospective observational studies. Pain Ther. 2015 Dec;4(2):169-78. doi:10.1007/s40122-015-0038-6.
[206] Skaper SD, Facci L, Fusco M, Della Valle MF, Zusso M, Costa B, et al. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology. 2014 Apr;22(2):79-94. doi:10.1007/s10787-013-0191-7.
[207] Passavanti MB, Fiore M, Sansone P, Aurilio C, Pota V, Barbarisi M, et al. The beneficial use of ultramicronized palmitoylethanolamide as add-on therapy to tapentadol in the treatment of low back pain: a pilot study comparing prospective and retrospective observational arms. BMC Anesthesiol. 2017 Dec 19;17(1):171. doi: 10.1186/s12871-017-0461-9.
[208] Ghazizadeh-Hashemi M, Ghajar A, Shalbafan MR, Ghazizadeh-Hashemi F, Afarideh M, Malekpour F, et al. Palmitoylethanolamide as adjunctive therapy in major depressive disorder: A double-blind, randomized and placebo-controlled trial. J Affect Disord. 2018 May;232:127-133. doi:10.1016/j.jad.2018.02.057.
[209] Chirchiglia D, Cione E, Caroleo MC, Wang M, Di Mizio G, Faedda N, et al. Effects of add-on ultramicronized N-palmitolethanolamide in patients suffering of migraine with aura: a pilot study. Front Neurol. 2018 Aug 17;9:674. doi:10.3389/fneur.2018.00674.
[210] Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. Neurotherapeutics. 2016 Apr;13(2):428-38. doi: 10.1007/s13311-016-0420-z.
[211] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949.
[212] Chirchiglia D, Della Torre A, Signorelli F, Volpentesta G, Guzzi G, Stroscio CA, et al. Administration of palmitoylethanolamide in combination with topiramate in the preventive treatment of nummular headache. Int Med Case Rep J. 2016 Jul 18;9:193–195. doi:10.2147/IMCRJ.S106323.
[213] Skaper SD, Facci L, Fusco M, Della Valle MF, Zusso M, Costa B, et al. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology. 2014 Apr;22(2):79-94. doi:10.1007/s10787-013-0191-7.
[214] Keppel Hesselink JM, de Boer T, Witkamp RF. Palmitoylethanolamide: a natural body-own anti-inflammatory agent, effective and safe against influenza and common Cold. Int J Inflam. 2013;2013:151028. doi: 10.1155/2013/151028.
[215] Assini A, Laricchia D, Pizzo R, Pandolfini L, Belletti M, Colucci M, et al. The carpal tunnel syndrome in diabetes: clinical and electrophysiological improvement after treatment with palmitoylethanolamide: P1577. Eur J Neurol. 2010 Sep 17;12(3):295-295.
[216] Coraci D, Loreti C, Granata G, Arezzo MF, Padua L. Carpal tunnel syndrome treatment with palmitoylethanolamide: neurophysiology and ultrasound show small changes in the median nerve. Rheumatol Int. 2018 Jul;38(7):1307-1309. doi:10.1007/s00296-018-4064-7.
[217] Faig-Martí J, Martínez-Catassús A. Use of palmitoylethanolamide in carpal tunnel syndrome: a prospective randomized study. J Orthop Traumatol. 2017 Dec;18(4):451-455. doi: 10.1007/s10195-017-0453-z.
[218] Conigliaro R, Drago V, Foster PS, Schievano C, Di Marzo V. Use of palmitoylethanolamide in the entrapment neuropathy of the median in the wrist. Minerva Med. 2011 Apr;102(2):141-7. PMID: 21483401.
[219] Calabrò RS, Naro A, De Luca R, Leonardi S, Russo M, Marra A, et al. PEALut efficacy in mild cognitive impairment: evidence from a SPECT case study. Aging Clin Exp Res. 2016 Dec;28(6):1279-1282. 2016 Jan 28. PMID: 26820462.
[220] Ghazizadeh-Hashemi M, Ghajar A, Shalbafan MR, Ghazizadeh-Hashemi F, Afarideh M, Malekpour F, et al. Palmitoylethanolamide as adjunctive therapy in major depressive disorder: A double-blind, randomized and placebo-controlled trial. J Affect Disord. 2018 May;232:127-133. doi:10.1016/j.jad.2018.02.057.
[221] Tartaglia E, Armentano M, Giugliano B, Sena T, Giuliano P, Loffredo C, et al. Effectiveness of the association N-palmitoylethanolamine and transpolydatin in the treatment of primary dysmenorrhea. J Pediatr Adolesc Gynecol. 2015 Dec;28(6):447-50. doi: 10.1016/j.jpag.2014.12.011.
[222] Schifilliti C, Cucinotta L, Fedele V, Ingegnosi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat. 2014;2014:849623. doi: 10.1155/2014/849623.
[223] Cocito D, Peci E, Ciaramitaro P, Merola A, Lopiano L. Short-term efficacy of ultramicronized palmitoylethanolamide in peripheral neuropathic pain. Pain Res Treat. 2014;2014:854560. doi: 10.1155/2014/854560.
[224] Cobellis L, Castaldi MA, Giordano V, Trabucco E, De Franciscis P, Torella M, et al. Effectiveness of the association micronized N-palmitoylethanolamine (PEA)-transpolydatin in the treatment of chronic pelvic pain related to endometriosis after laparoscopic assessment: a pilot study. Eur J Obstet Gynecol Reprod Biol. 2011 Sep;158(1):82-6. doi: 10.1016/j.ejogrb.2011.04.011.
[225] Giugliano E, Cagnazzo E, Soave I, Lo Monte G, Wenger JM, Marci R. The adjuvant use of N-palmitoylethanolamine and transpolydatin in the treatment of endometriotic pain. Eur J Obstet Gynecol Reprod Biol. 2013 Jun;168(2):209-13. doi: 10.1016/j.ejogrb.2013.01.009.
[226] Di Francesco A, Pizzigallo D. Use of micronized palmitoylethanolamide and trans-polydatin in chronic pelvic pain associated with endometriosis: an open-label study. Giornale Italiano di Ostetricia e Ginecologia CIC Edizioni Internazionali.2014 May 30;36(2):353-358.
[227] Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S. Palmitoylethanolamide in fibromyalgia: results from prospective and retrospective observational studies. Pain Ther. 2015 Dec;4(2):169-78. doi:10.1007/s40122-015-0038-6.
[228] Schweiger V, Martini A, Bellamoli P, Donadello K, Schievano C, Balzo GD, et al. Ultramicronized palmitoylethanolamide(um-PEA) as add-on treatment in fibromyalgia syndrome (FMS): retrospective observational study on 407 patients. CNS Neurol Disord Drug Targets. 2019;18(4):326-333. doi: 10.2174/1871527318666190227205359.
[229] Keppel Hesselink JM, Costagliola C, Fakhry J, Kopsky DJ. Palmitoylethanolamide, a natural retinoprotectant: its putative relevance for the treatment of glaucoma and diabetic retinopathy. J Ophthalmol. 2015;2015:430596. doi: 10.1155/2015/430596.
[230] Domínguez CM, Martín AD, Ferrer FG, Puertas MI, Muro AL, González JM, et al. N-palmitoylethanolamide in the treatment of neuropathic pain associated with lumbosciatica. Pain Manag. 2012 Mar;2(2):119-24. doi:10.2217/pmt.12.5.
[231] Passavanti MB, Fiore M, Sansone P, Aurilio C, Pota V, Barbarisi M, et al. The beneficial use of ultramicronized palmitoylethanolamide as add-on therapy to tapentadol in the treatment of low back pain: a pilot study comparing prospective and retrospective observational arms. BMC Anesthesiol. 2017 Dec 19;17(1):171. doi: 10.1186/s12871-017-0461-9.

[232] Desio P. Combination of oxycodone and palmitoylethanolamide for low back pain treatment. AMC. 2011;1(2):62–71.
[233] Truini A, Biasiotta A, Di Stefano G, La Cesa S, Leone C, Cartoni C. Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. CNS Neurol Disord Drug Targets. 2011 Dec;10(8):916-20. PMID: 22229320.
[234] Steels E, Venkatesh R, Steels E, Vitetta G, Vitetta L. A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis. Inflammopharmacology. 2019 Jun;27(3):475-485. doi: 10.1007/s10787-019-00582-9.
[235] Marini I, Lavinia Bartolucci M, Bortolotti F, Rosaria Gatto M, Alessandri Bonetti G. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. J Orofac Pain. 2012 Apr 1;26(2):99.
[236] Artukoglu BB, Beyer C, Zuloff-Shani A, Brener E, Bloch MH. Efficacy of palmitoylethanolamide for pain: a meta-analysis. Pain Physician. 2017 Jul;20(5):353-362. PMID: 28727699.
[237] Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Med. 2012 Sep;13(9):1121-30. doi:10.1111/j.1526-4637.2012.01432.x.
[238] Brotini S, Schievano C, Guidi L. Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. CNS Neurol Disord Drug Targets. 2017;16(6):705-713. doi: 10.2174/1871527316666170321124949.
[239] Domínguez CM, Martín AD, Ferrer FG, Puertas MI, Muro AL, González JM, et al. N-palmitoylethanolamide in the treatment of neuropathic pain associated with lumbosciatica. Pain Manag. 2012 Mar;2(2):119-24. doi:10.2217/pmt.12.5.
[240] Guida G, De Martino M, De Fabiani A, Canterieri L, Alexandre A, Vassallo GM, et al. Palmitoylethanolamide (Normast®) in chronic neuropathic pain due to compression lumbociatalgia: a multicenter clinical study. DOLOR. 2010:25(1):35-42.
[241] Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. J Pain Res. 2015;8:729-734. doi:10.2147/JPR.S93106.
[242] Guida G, Cantieri L, Petrosino S. Reduction of the consumption of anti-inflammatory drugs and analgesics in the treatment of chronic neuropathic pain in patients affected by compressive lumbociatalgia and in treatment with Normast® 300 mg. Pain. Clin & Thera Res 2010; 25(4):227-234.
[243] Caltagirone C, Cisari C, Schievano C, Di Paola R, Cordaro M, Bruschetta G, et al. Co-ultramicronized palmitoylethanolamide/luteolin in the treatment of cerebral ischemia: from rodent to man. Transl Stroke Res. 2016 Feb;7(1):54-69. doi: 10.1007/s12975-015-0440-8.
[244] Bacci C, Cassetta G, Emanuele B, Berengo M. Randomized split-mouth study on postoperative effects of palmitoylethanolamide for impacted lower third molar surgery. ISRN Surg. 2011;2011:917350. doi: 10.5402/2011/917350.
[245] Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral palmitoylethanolamide treatment is associated with reduced cutaneous adverse effects of interferon-β1a and circulating proinflammatory cytokines in relapsing-remitting multiple sclerosis. Neurotherapeutics. 2016 Apr;13(2):428-38. doi: 10.1007/s13311-016-0420-z.
[246] Kopsky DJ, Hesselink JM. Multimodal stepped care approach with acupuncture and PPAR-α agonist palmitoylethanolamide in the treatment of a patient with multiple sclerosis and central neuropathic pain. Acupunct Med. 2012 Mar;30(1):53-5. doi: 10.1136/acupmed-2011-010119.
[247] Murina F, Graziottin A, Felice R, Radici G, Tognocchi C. Vestibulodynia: synergy between palmitoylethanolamide + transpolydatin and transcutaneous electrical nerve stimulation. J Low Genit Tract Dis. 2013 Apr;17(2):111-6. doi: 10.1097/LGT.0b013e3182652316.
[248] Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. Br J Clin Pharmacol. 2016 Oct;82(4):932-42. doi: 10.1111/bcp.13020.
[249] Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. Am J Hosp Palliat Care. 2019 Dec;36(12):1134-1154. doi: 10.1177/1049909119850807.
[250] Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Med. 2012;13(9):1121–30. doi:10.1111/j.1526-4637.2012.01432.x.
[251] Artukoglu BB, Beyer C, Zuloff-Shani A, Brener E, Bloch MH. Efficacy of palmitoylethanolamide for pain: a meta-analysis. Pain Physician. 2017 Jul;20(5):353-362. PMID: 28727699.
[252] Paladini A, Fusco M, Cenacchi T, Schievano C, Piroli A, Varrassi G. Palmitoylethanolamide, a special food for medical purposes, in the treatment of chronic pain: a pooled data meta-analysis. Pain Physician. 2016;19(2):11–24.
[253] Déciga-Campos M, Ramírez-Marín PM, López-Muñoz FJ. Synergistic antinociceptive interaction between palmitoylethanolamide and tramadol in the mouse formalin test. Eur J Pharmacol. 2015;765:68–74. doi:10.1016/j.ejphar.2015.08.025.
[254] Russo R, LoVerme J, La Rana G, D'Agostinoa G, Sassoa O, Calignano A, et al. Synergistic antinociception by the cannabinoid receptor agonist anandamide and the PPAR-alpha receptor agonist GW7647. Eur J Pharmacol. 2007;566(1-3):117–9. doi:10.1016/j.ejphar.2007.03.007.
[255] Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. Br J Clin Pharmacol. 2016 Oct;82(4):932-42. doi: 10.1111/bcp.13020.
[256] Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Med. 2012;13(9):1121–30. doi:10.1111/j.1526-4637.2012.01432.x.