

# Investigating The Role Of Immune System In Cancer Development And Treatment

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**Abstract:** Cancer is a complex disease with genetic, environmental, and lifestyle aetiology. Genetic factors are the hereditary elements that influence certain traits being expressed, whereas environmental factors are due to the exposure to carcinogenic substances in our daily setting. Lifestyle factors are the behaviours the individual carries out, which increases the risk of cancer formation. The immune system plays a complicated role in development and prevention of cancer as well as its treatment. While a robust immune response can identify and eliminate malignant cells in early stages, tumour cells often evade immune detection through various mechanisms such as immune checkpoint signalling and microenvironment remodelling. Alternatively, tumour cells can evade immune detection through reducing the expression of tumour-associated antigens (TAAs) and major histocompatibility complex (MHC) class I molecules which are vital for cytotoxic T cell recognition. Advancements in cancer treatment, including gene therapy and immunotherapy, have revolutionised the treatment landscape beyond conventional methods, such as surgery, chemotherapy and radiotherapy. Improvements in surgery allow for a precise removal of tumours alongside the use of radiation allowing for an improved outcome of the removal of cancer. Furthermore, new drug regimens for combination therapy show promising outcomes as a treatment of cancer in the near future. This article investigates the dynamic interplay between the immune system and cancer, emphasising the mechanisms of immune surveillance, evasion, and suppression by tumours in hopes of improving patient care and outcome.

**Keywords:** Cancer, Immune System, Immunotherapy, Biopsychosocial.

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## 1. PURPOSE AND OBJECTIVES

The immune system attempts to protect the body's own cells through a complex network of organs, cells and proteins. Furthermore, once the microbe has entered and been destroyed, the immune system has memory to keep a record of every microbe that has been defeated in order to recognise and remove the microbe efficiently if it enters the body again.

The immune system consists of white blood cells which are made in the bone marrow and patrolling the blood and tissues in search of pathogens. White blood cells include lymphocytes such as B - cells (matured in bone marrow), T - cells (matured in thymus), and natural killer cells. As a functional system consists of various organs and tissues, the immune system also consists of antibodies, complement system, lymphatic system, spleen, bone marrow, and thymus. In particular, the lymphatic system deals with cancer cells and is made up of lymph nodes, lymph vessels, and white blood cells - especially the lymphocytes. (1)

Cancer is due to the uncontrolled division of abnormal cells caused by mutation eventually causing a tumour. (2) Cancer cells can be generally divided into two categories: benign and malignant. Benign do not spread, whereas malignant spread into other tissues. Cancer cells are different from normal cells due to them growing in the absence of signals telling them to grow whilst also ignoring signals for apoptosis to occur and they trick the immune system to help cancer cells to stay alive and grow via protecting them. There are over 100 types of cancer with different degree of malignancies. However, some cancers could begin at the lungs for example and spread to the stomach despite still being lung cancer. (3)

Between 2017 to 2019, approximately 199,000 males were diagnosed with cancer but 186,000 females were diagnosed with cancer every year. According to this, every two minutes someone in the UK is diagnosed with cancer. In 2018, almost half (45.5%) of all cancer cases were diagnosed at stage 3 and 4 - this is over 118,000 cases. A 2% rise in all cancers combined incidence rate between 2023 - 2025 and 2038 - 2040 is expected. Therefore, approximately 506,000 new cases of all cancers will occur every year in the UK between 2038 - 2040. On average, incidence rates for cancer are highest in people aged 85 to 89 years old in 2017 to 2019. Furthermore, incidence rates for all cancers combined are lower for the Asian and Black ethnic group compared to the White ethnic group. (5) On average between 2017 - 2019, there were around 167,000 cancer deaths in the UK every year, mounting up to 460 death every day: in females, there are about 78,000 cancer

deaths every year which is significantly lower than males which is about 89,200 cancer death each year. This means that every four minutes someone dies from cancer in the UK. However, since the early 1970s, mortality rates for cancer as a whole has decreased by a fifth (19%) in the UK, while rates in females have decreased by an estimate of a seventh (13%) and over a quarter (27%) in males. (6)

The financial burden of cancer is often undermined as it is continuously skyrocketing due to improved diagnosis and screening, innovation in all phases of care, longer survival and, most importantly, improved technology. It is estimated that by 2030, total oncology costs (including costs of physician services, hospitalisation and hospital services, and medication) will reach \$246 billion in the United States. Financial toxicity may be particularly acute in the USA due to higher costs of care and gaps in insurance coverage, but financial toxicity is a global issue affecting countries across health system structures and income levels. (7) The average state-level cancer care costs in the US range from approximately \$227 million to \$13.6 billion; however, medical insurance only covers 43.3% of the treatment as a whole. (8) Unfortunately, the financial toxicity of the symptoms of cancer is often overlooked.

One cancer-associated symptom is anorexia and cachexia where the costs range from \$5 US dollars (for generic olanzapine or mirtazapine tablets) to \$1,156 USD (for brand-name dronabinol solution). Another cancer-associated symptom is exocrine pancreatic insufficiency, whereby only brand-name formulations were available with the lowest cost being \$1,072 USD to the highest being \$1,514 USD. This creates a huge financial burden on the cancer patient considering insurance only covers less than half of it, adding on to the bills they have to pay for their initial cancer treatment. (9)

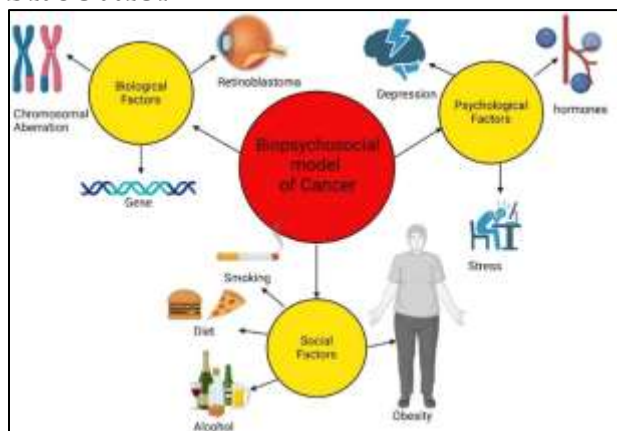
Studies have indicated that approximately 35% to 52% of cancer patients experience a high psychological burden. (10) Excessive psychological burden is detrimental because can create many additional symptoms such as difficulty breathing, insufficient rest, and dry mouth which affect the prognosis of cancer but also may lead to suicidal and self – injurious behaviours in patients. A study which investigates the psychological state of breast cancer patients during and after chemotherapy presents that approximately 44.4% of them exhibited significant levels of anxiety, 52.8% had a fear of cancer recurrence, and 41.7% presented insomnia symptoms. (11). Therefore, screening for psychological burden of cancer patients included within the routine cancer diagnosis will help improve the prognosis of cancer patients and prevent extreme behaviours. (12)

Cancer diagnosis and undergoing treatment does not only have a psychological burden on the patient but also the patient's family. Another study investigated health behaviours and psychological burdens in adolescent children of cancer parents via comparing the health behaviours and mental health outcomes between 266 adolescent children with a parent diagnosed with cancer and 3163 control adolescent children varying from ages 12 to 19 year olds. This study found adolescents with parents who had cancer has an increased alcohol use between 2 and 5 years after the diagnosis, but it decreased after 5 years. Furthermore, parental cancer was associated with increased vaccination uptake within 1 year of a diagnosis but after 2 years, no differences were observed. Some psychological effects associated with mainly maternal cancer is increased depression among adolescents including suicidal attempts or thoughts all increased within 1 year after parental diagnosis, but it reduced after 2 years of the diagnosis. (13)

## 2. METHODOLOGY

The research was conducted from scholarly sources including Google scholars, the National Center for Biotechnology Information (NCBI), the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the National Institutes of Health (NIH). The search was limited to papers published in English over the past 20 years that were focused on the following keywords for research: "Cancer", "Immune System", "Biopsychosocial model of cancer", "T cells", "Cancer treatment", "Cancer prevention". Studies were included within the following criteria: (a) focused on cancer and immune system in human, (b) were published in peer-reviewed journals. Non-English studies and studies mainly focused on animals were excluded. The figures were created using Biorender.

## DISCUSSION



**Figure 1. Biopsychosocial model of cancer.** An overview biopsychosocial factors that increase the susceptibility of cancer development. The figure was created with BioRender.com

## 3. RESULTS AND DISCUSSIONS

### 3.1 Biological factors

Inherited factors can contribute to cancer, mainly childhood cancer and cancer in early adulthood. (14) Heredity is likely to affect susceptibility to various cancers. For example, it is proven that skin colour plays a large role in sun associated cancers such as melanoma. (15) Around 5% of breast cancer cases are linked to genetics due to inheriting the BRCA1 and BRCA2 gene. (16) Furthermore, cancers due to chromosomal aberrations include chronic myeloid leukaemia (CML). A consistent chromosomal aberration was detected in CML cells. Excess neutrophils and monocytes consisting of normal form and function characterizes the early chronic phase of CML. The bone marrow precursors of the neutrophils and monocytes become gradually more immature; therefore, resulting in bone marrow failure and mortality. (17) It has been found that minute chromosome fragment was found to replace one of the four small chromosomes (19,20,21, and 22) in some cells of seven patients with CML. They decided to name the tiny fragment the Philadelphia chromosome. (18) Over 95% of patients with CML have the Philadelphia chromosome in their leukemic cells. (19) In addition, despite retinoblastoma being a relatively rare cancer, slightly over one – third of Rb cases are inherited suggesting there may be a genetic component linked to it. A mutation or a deletion in the long arm of chromosome 13 is associated with the pathogenesis of Rb. Children who have malignancy in both eyes are more likely to have inherited a mutated Rb because generally a tumour arises when cells of the retina carry mutations or deletions in the long arm of both homologues of chromosome 13. (20)

### 3.2 Social factors

Social factors include non-biological individual-level factors that influence health: for example, race, ethnicity, and socio- economic position. (21) Social determinants may contribute to up to 70% of cancer cases and significantly increase the risk of death among cancer patients and survivors.(22) For example, housing insecurity can increase the likelihood of poor health due to reduced access to healthcare which may result in a delayed diagnosis and treatment of cancer.(23) Furthermore, a recent study reported that social factors such as neighbourhood disadvantage, lack of education, poverty and social isolation play important roles in breast cancer stage and survival. (24) Lung cancer mortality has continued to increase in lower socioeconomic group but began to decrease in more socioeconomically favoured groups. The aetiology has been attributed to harmful behaviours such as smoking tobacco and alcohol consumption, which are more frequent in the lower socioeconomic demographics. (25) Additionally, a low socioeconomic status generally results in a lower intake of garden-fresh fruit and vegetables which is associated with a higher risk of gastrointestinal cancers. (26) Ethnicity can also cause cancer as African American individuals have a lower maximal capacity of aerobic metabolism and higher percentage of fast contracting (type II) skeletal muscle fibres, which overall, including a reduced energy consumption, predisposes them to obesity and other metabolic disorders. (27) Obesity can increase risk of cancer because the adipose cells release pro-mitotic signals to stimulate mitosis, which can lead to more mutations hence leading to cancer. (28)

### 3.3 Psychological factors

Psychological factors can increase the risk of cancer, which can be attributed to mental stress that can promote unhealthy behaviours, such as smoking, lack of exercise, poor diet, obesity, poor sleep, excessive alcohol consumption and lower treatment adherence. (29) Furthermore, psychological factors could impact biological mechanisms which may promote malignant growth through psycho-social processes initiating a cascade of information-processing pathways in the central nervous system and periphery, hence impacting hormonal secretion. (30) (31) Shifting hormone levels can influence how various elements within the tumour's microenvironment function. (32) (33) Additionally, psychological stress can impair the immune response, increasing the risk of cancer. (34) Chronic stress triggers the release of stress hormones such as cortisol and adrenaline, which suppress the immune system and contribute to tumour growth. The immune system is suppressed due to inflammation and reduced immune surveillance meaning that the cancer detection is not effective by the immune system. (35) Depression also plays a role in cancer because individuals with depression are more likely to experience elevated inflammatory markers which may encourage tumour growth. (36) Psychological stress can also directly alter the tumour microenvironment – including the immune cells, blood vessels, and extracellular matrix. Stress hormones increase the production of molecules including vascular endothelial growth factor (VEGF), which promotes angiogenesis to facilitate tumours growth and metastasis. (37)

### 3.4 Overview of the immune system's role in combating cancer.

The immune system consists of an immune surveillance where cell-mediated immunity can recognise and destroy proliferating cancer cells. B-cells help the body to fight cancer (and infection) via producing antibodies (which are a type of protein) that stick to cancer hence recruiting other parts of the immune system to destroy them. If a receptor on the B cell identifies a cancer cell and binds to it, it triggers the B cell to undergo change and diversify so it can be more effective at targeting those cancer cells. (38) Natural Killer (NK) cells are large, granular lymphocyte and they exhibit natural cytotoxic effects against cancer cells, despite their being no preimmunization. The most potent NK cell is CD56dim. (39) Natural Killer (NK) cells also aid antitumour immunity which can directly kill tumour cells as well as influencing antitumorigenic behaviour of other immune cells. (40) NK cells eliminate tumour cells by inducing tumour cell apoptosis through caspase-dependent and caspase-independent pathways. This process is triggered by the release of cytoplasmic granules containing perforin and granzymes, which are secreted into the intracellular space in a calcium – dependent manner. (41) Those perforins in the cytoplasmic granules induces perforations in the cell membrane, permitting granzymes to enter the tumour cells, ergo resulting in apoptosis mediated by cell death receptors. (42) In addition, cytotoxic T cells recognise specific antigens presented by tumour cells hence directly inducing cell death. In contrary, helper T cells support the activation of other immune cells, aiding the immune system's anti – tumour response. (43) A continuous process by the immune system is immune surveillance where immune cells patrol body to detect and eliminate emerging cancer cells before they become into a tumour (e.g., cancer immunoediting). Cancer immunoediting has three stages: elimination, equilibrium, and escape. Initially, immune cells can eradicate emerging tumours -which is the elimination process- but if a few cells survive, they can enter a phase in which immune pressure controls their growth without completely eradicating them (e.g., equilibrium). Over time, some cancer cells may develop mutations allowing them to evade the immune system detection and establish a detectable tumour (e.g., escape). (44)

Cancer can arise from various genetic mutations in normal cell regulation, resulting in the formation of unique antigens, for example neoantigens, differentiation antigens, and cancer testis antigens. These antigens appear on the surface of cancer cells as peptides which are bound to Major Histocompatibility Class I (MHCI) molecules, marking them as different from non-cancerous cells. CD8+ T cells in cancer patients are found to recognise those specific peptide-MHCI complexes. However, even when T cells react to them, they rarely provide the protective immunity needed.

The Cancer Immunity Cycle is a mechanism to eliminate cancer cells effectively. In the first step, oncogenesis creates neoantigens which are released and captured by dendritic cells (DCs) for processing. For an anticancer T cell response to be present, it must be accompanied by signals which specify immunity lest peripheral tolerance to the tumour antigens be induced. Some immunogenic signals may include proinflammatory cytokines and factors released by dying tumour cells. The second step is when DCs express the captured antigens on MHCI and MHCII molecules to the T cells, resulting in the priming and activation of effector T

cell responses against the cancer-specific antigens which are seen as foreign or against which central tolerance has been incomplete. During this activation, the type of immune response depends on the balance between T effector and T regulatory cells, with the ratio of these cell types influencing the effectiveness of the response. Then, activated T cells move towards and infiltrate the tumour, where they specifically recognise and bind to cancer cells via the interaction between their T cell receptor and the antigen representing cancer present on MHC I molecules. (45)

Cancer cells can evade immune detection by multiple mechanisms, including the reduction of tumour-associated antigens (TAAs) and major histocompatibility complex (MHC) class I molecules expression – which are crucial for cytotoxic T cell recognition. Therefore, immune cells fail to effectively identify or target tumours. (46) In addition, cancer cells secrete immunosuppressive molecules, for example TGF- $\beta$ , IL-10, and VEGF, which suppresses immune responses. (47) Furthermore, immune checkpoint molecules dampen T cell activity via PD-L1 and CTLA-4. PD-L1 binds to PD-1 receptors on T cells inhibiting their function, and CTLA-4 reduces T cell activation. (48) Additionally, the tumour microenvironment (TME) plays a major role in evading immune detection. Tumours recruit regulatory immune cells such as T regulatory cells and, myeloid-derived suppressor cells, which suppress cytotoxic T cells and NK cells. (49) Cancer cells further avoid detection and destruction by upregulating anti-apoptotic proteins, such as Bcl-2. Also, they express self-markers (for example CD47) to avoid phagocytosis by macrophages. (50)

Innate immunity is the first line of defence that provides rapid, nonspecific responses; however, adaptive immunity provides specific and long-term responses. Macrophages (M1 phenotype) phagocytose cancer cells and later secrete pro-inflammatory cytokines like IL-12 in order to stimulate adaptive immunity. Alternatively, many tumours polarise macrophages into the M2 phenotype, promoting tumour growth through secreting IL-10 and VEGF, enhancing angiogenesis and suppressing immune responses. (51)

Dendritic cells can present tumour antigens to T cells via MHC molecules, which eventually initiates adaptive responses. However, in the TME, dendritic cells functions are often impaired by factors like IL-10 and TGF- $\beta$ , which reduces their antigen-presentation ability. (52) NK cells are adapted to target tumour cells that contain a low MHC class I expression, via using granzymes and perforins to induce apoptosis. However, tumours can evade NK cells through upregulating inhibitory ligands, such as HLA-E, or secreting suppressive factors like TGF- $\beta$ , which reduces NK cell cytotoxicity. (53) In the adaptive immunity, CD8<sup>+</sup> cytotoxic T cells can recognise tumour antigens that are present on MHC class I molecules to kill cancer cells by releasing granzymes and perforins. In contrast, tumours may express PD-L1 which binds to PD-1 receptors on T cells resulting in their deactivation. Helper CD4<sup>+</sup> T cells secrete cytokines like IL-2 and IFN- $\gamma$  to activate cytotoxic T cells and macrophages. Alternatively, tumours can skew CD4<sup>+</sup> T cells towards an immunosuppressive Th2 phenotype, promoting tumour progression by inhibiting Th1 mediated anti-tumour response. (54) Regulatory T cells (Tregs) are recruited by tumours to suppress cytotoxic T cells and NK cells by secreting IL-10 and TGF- $\beta$ : a correlation exists between high Treg infiltration and poor prognosis for many cancers. (55) B cells secrete tumour-specific which promotes phagocytosis and complement activation; however, some B cells in the TME may produce IL-10, which suppresses T cell responses aiding tumour growth. (56)

Germline mutations alone does not always result in cancer formation but significantly increases the likelihood of additional mutations that will lead to tumour development. For example, BRCA1 and BRCA2 are tumour suppressor genes that are critical for repair of DNA. Mutations in those genes compromise homologous recombination, leading to genomic instability. Carriers of BRCA mutations have an 85% lifetime risk of breast cancer and up to a 50% risk of developing ovarian cancer in their lifetime. (57) Another example is TP53, mutations in it causes Li-Fraumeni syndrome, which is associated with a wide range of cancers: sarcomas, leukaemia, and breast cancer. (58) Another inherited cancer may be epigenetic inheritance where inherited predispositions can also involve epigenetic changes such as DNA methylation or histone modification, which silence tumour suppressor genes without altering their sequence. Aberrant methylation patterns have been found in cancers such as colorectal cancer. (59)

#### **4. Cancer Treatments**

Traditional surgery is currently the most common treatment for cancer mainly for localised cancers such as breast, colon, and lung cancer. Due to advances in surgical techniques, doctors can ensure that higher precision and fast recovery is present. Another surgical method is minimally invasive surgery which is robotic assisted offering improved outcomes with smaller incisions, less pain, and shorter hospital stays. For early-

stage cancers, a high success rate is evident and robotic assisted systems reduce recovery time and improve precision. However, surgical techniques are not suitable for metastatic cancers and it can lead to a risk of complications such as infections and long recovery times. (60)(61) Radiation therapy is another common treatment method which entails high-energy beams to induce apoptosis in cancer cells. Proton therapy is a form of radiation therapy which allows for more precise targeting of tumours while sparing healthy tissues. It is especially useful for the brain, spine and for paediatric cancers. Proton therapy minimises damage to surrounding healthy tissues however it is expensive hence not widely available. (62) Furthermore, Stereotactic Body Radiation Therapy (SBRT) is a form of radiation therapy whereby it delivers high doses of radiation to well-defined tumours, improving outcomes for early stage lung and liver cancers. SBRT allows for precise targeting of small tumours, hence improving outcome; however, there is still potential of developing secondary cancers due to radiation exposure causing multiple mutations. (63) Another treatment of cancer is the traditional chemotherapy agents which affect either macromolecular synthesis and function of neoplastic cells via interfering with RNA, DNA, or protein synthesis or affecting the appropriate functioning of the preformed molecule. When interference in macromolecular synthesis or function is sufficient, it leads to cell death either by the chemotherapeutic agent's direct effect or by triggering apoptosis. Combination therapy is an alternative chemotherapy which appear to prevent the development of resistant clones by promoting cytotoxicity in resting and dividing cells. New drug regimens, such as enfortumab vedotin and pembrolizumab (EV/pembro) for bladder cancer, are more effective and have fewer side effects. (64) Immunotherapy can include checkpoint inhibitors and CAR T-Cell therapy. Checkpoint inhibitors allow T cells to attack cancer cells effectively and Car T-Cell therapy customise T cells to become target specific markers which is useful for blood cancers such as leukemia and lymphoma. However, they have limited success in solid tumours and also may cause inflammation of healthy organs. (65) (66)

Some immune-oncology advancements are avoiding checkpoint inhibitors (such as PD-1, PD-L1, CTLA-4). A possible solution is dual checkpoint blockade regimens to enhance durability and broaden effectiveness of cells. (67) Another novel treatment may be disguising cancer as an infection to help the immune system to eliminate tumours. A study injected small viral particles directly into the tumour which activated immune cells, which resulted in apoptosis of tumour cells. The CMV-fighting T cells kill cancer cells coated with the CMV peptides because they appear to be infected. This causes the cancer fighting T cells to detect cancer cells ergo attacking it. The immune cells release signals to carry on the attack eventually creating a long-lasting protection against cancer. The potential advantages of this are the synthetic virus peptides can be rapidly produced easily in bulk. Also, there wouldn't have to be tailored to each individual patient or a particular type of cancer as opposed to CAR T-cell therapy and vaccine therapy. However, in its experimental phase the mice injected with high dose of CMV peptides became very sick possibly due to the anti-CMV T cells attacking healthy tissues which were accidentally coated with high doses of viral peptides. A possible drawback may be that it only works on people who have CMV so it cannot be used on everyone who suffers from cancer. (68)

## 5. CONCLUSION

The dynamic interplay between the immune system and cancer highlights its pivotal role in both tumour development and therapeutic intervention. While the immune system has the ability to identify and destroy aberrant cells through immune surveillance mechanisms, tumours often evade such mechanisms by inhibiting pathways, including immune checkpoint signalling, and immunosuppressive tumour microenvironment. Cancer can be caused by genetic, social, and psychological factors which are often overlooked. Furthermore, the advent of immunotherapies, for example immune checkpoint inhibitors such as PD-1, PD-L1, and CTLA-4 blockers, has transformed the treatment landscape, offering durable alternatives to cancer treatments which previously had no effect on cancers which were resistant to conventional therapies.

## REFERENCES

<https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/immune-system>

1. <https://www.cancerresearchuk.org/about-cancer/what-is-cancer>
2. <https://www.cancer.gov/about-cancer/understanding/what-is-cancer>

3. [https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2021--summary-counts-only/cancer-incidence#:~:text=In%202021%2C%20there%20was%20a,\(from%20169%2C599%20to%20167%2C918\).](https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2021--summary-counts-only/cancer-incidence#:~:text=In%202021%2C%20there%20was%20a,(from%20169%2C599%20to%20167%2C918).)
4. <https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence#heading-Four>
5. <https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality#heading-Zero>
6. Hannah R Abrams, Sienna Durbin, Cher X Huang, Shawn F Johnson, Rahul K Nayak, Greg J Zahner, Jeffrey Peppercorn, Financial toxicity in cancer care: origins, impact, and solutions, *Translational Behavioral Medicine*, Volume 11, Issue 11, November 2021, Pages 2043–2054, <https://doi.org/10.1093/tbm/ibab091>
7. Tangka, F., Trogon, J., Ekwueme, D., Guy, G., Nwaise, I. and Orenstein, D., 2013. State-level cancer treatment costs. *Cancer*, 119(12), pp.2309-2316.
8. Gupta A, Nshuti L, Grewal US, Sedhom R, Check DK, Parsons HM, Blaes AH, Virnig BA, Lustberg MB, Subbiah IM, Nipp RD, Dy SM, Dusetzina SB. Financial Burden of Drugs Prescribed for Cancer-Associated Symptoms. *JCO Oncol Pract*. 2022 Feb;18(2):140-147. doi: 10.1200/OP.21.00466. Epub 2021 Sep 24. PMID: 34558297; PMCID: PMC9213200.
9. Johannsen L, Brandt M, Frerichs W, Inhestern L, Bergelt C. The impact of cancer on the mental health of patients parenting minor children: a systematic review of quantitative evidence. *Psychooncology*. (2022) 31:869–78. doi: 10.1002/pon.5912
10. Bartmann C, Fischer LM, Hübner T, Müller-Reiter M, Wöckel A, McNeill RV, et al. The effects of the COVID-19 pandemic on psychological stress in breast cancer patients. *BMC Cancer*. (2021) 21:1–13. doi: 10.1186/s12885-021-09012-y
11. Stark DPH, House A. Anxiety in cancer patients. *Br J Cancer*. (2000) 83:1261–7. doi: 10.1054/bjoc.2000.1405
12. Kim KH, Kim MS, Choi S, Kim SM, Park SM. Health behaviors and psychological burden of adolescents after parental cancer diagnosis. *Sci Rep*. 2022 Dec 5;12(1):21018. doi: 10.1038/s41598-022-25256-5. PMID: 36471102; PMCID: PMC9722667.
13. Ponder, B. (1990) *Trends Genet*. 6, 213-218.
14. Braun, M. M., Caporaso, N. E., Page, W. F. & Hoover, R. N. (1994) *Lancet* 344, 440-443.
15. Wooster R, et al. Identification of the breast cancer susceptibility gene BRCA2. *Nature*. 1995;378:789–92
16. Book- The Biological Basis of Cancer – Author- Robert G. McKinnell, Ralph E. Parchment, Alan O. Peratoni, G. Barry Pierce. Pg 121-126
17. Goldman, J.M., & Melo, J.V. (2015). Chronic myeloid leukemia—advances in biology and new approaches to treatment. *New England Journal of Medicine*, 369(19), 1783-1796.
18. Hehlmann, R., Hochhaus, A., & Baccarani, M. (2016). Chronic myeloid leukaemia. *The Lancet*, 390(10108), 411–422.
19. Dimaras, H., Kimani, K., Dimba, E. A., Gronsdahl, P., White, A., Chan, H. S., & Gallie, B. L. (2015). Retinoblastoma. *The Lancet*, 385(9973), 1436-1446.
20. Williams DR, Mohammed SA, Shields AE. Understanding and effectively addressing breast cancer in African American women: unpacking the social context. *Cancer*. 2016;122:2138–2149.
21. Akushevich I, Kravchenko J, Akushevich L, Ukraintseva S, Arbeev K, Yashin A. Cancer Risk Behavioral Factors, Comorbidities, Functional Status in the US Elderly Population. *ISRN Oncol* (2011) 2011.
22. Banegas MP, Dickerson JF, Zheng Z, et al. Association of Social Risk Factors with Mortality Among US Adults with a New Cancer Diagnosis. *JAMA Netw Open*. 2022; 5(9):e2233009. doi:10.1001/jamanetworkopen.2022.33009
23. Coughlin SS. Social determinants of breast cancer risk, stage, and survival. *Breast Cancer Res Treat*. (2019) 177:537–48. doi: 10.1007/s10549-019-05340-7
24. Smith GD, Leon D, Shipley MJ, Rose G. Socioeconomic differentials in cancer among men. *Int J Epidemiol*. 1991 Jun;20(2):339–45.
25. Kamangar F, Malekzadeh R, Dawsey SM, Saidi F. Esophageal cancer in northeastern Iran. *Arch Iran Med*. 2007;10(1):70–82
26. Ceaser T, Hunter G. Black and White race differences in aerobic capacity, muscle fiber type, and their influence on metabolic processes. *Sports Med*. 2015;45(5):615–23.
27. <https://www.cancerresearchuk.org/about-cancer/causes-of-cancer/bodyweight-and-cancer/how-does-obesity-cause-cancer>
28. VAN Tuijl, L. A., et al. 2021. Psychosocial factors and cancer incidence (PSY-CA): Protocol for individual participant data meta-analyses. *Brain and Behavior*, 11 (10), e2340.
29. Glaser, R. and Kiecolt-Glaser, J. K., 2005. Stress-induced immune dysfunction: implications for health. *Nature Reviews. Immunology*, 5 (3), 243–251.
30. Charmandari, E., Tsigos, C. and Chrousos, G., 2005. Endocrinology of the stress response. *Annual Review of Physiology*, 67, 259–284.
31. Antoni, M. H., et al., 2006. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. *Nature Reviews. Cancer*, 6 (3), 240–248.
32. Chida, Y., et al., 2008. Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nature Clinical Practice. Oncology*, 5 (8), 466–475.
33. Reiche, E. M., Nunes, S. O. and Morimoto, H. K., 2004. Stress, depression, the immune system, and cancer. *Lancet Oncology*, 5 (10), 617–625.
34. Antoni, M. H., et al., 2006. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. *Nature Reviews. Cancer*, 6 (3), 240–248.
35. Walker, J., et al. (2014). Depression and Cancer: Risk, Mechanisms and Treatment Implications. *The Lancet Psychiatry*, 1(4), 320–327.
36. Lutgendorf, S.K., et al. (2013). Stress Influences Tumor Progression and Metastasis. *Nature Communications*, 4, Article 2166.

37. Predictability of B cell clonal persistence and immunosurveillance in breast cancer – published by Nature Immunology.
38. Cheng M., Chen Y., Xiao W., Sun R., Tian Z. NK cell-based immunotherapy for malignant diseases. *Cell. Mol. Immunol.* 2013;10:230–252. doi: 10.1038/cmi.2013.10.
39. Shimasaki, N., Jain, A. & Campana, D. NK cells for cancer immunotherapy. *Nat. Rev. Drug Discov.* **19**, 200–218 (2020).
40. Sordo-Bahamonde C., Lorenzo-Herrero S., Payer Á.R., Gonzalez S., López-Soto A. Mechanisms of apoptosis resistance to NK cell-mediated cytotoxicity in cancer. *Int. J. Mol. Sci.* 2020;21:3726. doi: 10.3390/ijms21103726.
41. Tuomela K., Ambrose A.R., Davis D.M. Escaping death: How cancer cells and infected cells resist cell-mediated cytotoxicity. *Front. Immunol.* 2022;13:867098. doi: 10.3389/fimmu.2022.867098.
42. Chen, D. S., & Mellman, I. (2017). Elements of cancer immunity and the cancer-immune set point. *Nature*, 541(7637), 321–330.
43. Schreiber, R. D., Old, L. J., & Smyth, M. J. (2015). Cancer immunoediting: Integrating immunity's roles in cancer suppression and promotion. *Science*, 331(6024), 1565–1570.
44. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013 Jul 25;39(1):1–10. doi: 10.1016/j.immuni.2013.07.012. PMID: 23890059.
45. Garrido, F., et al. (2016). MHC class I molecules in cancer cells: selective losses and their epigenetic regulation. *Oncogene*, 35(19), 2499–2510.
46. Batlle, E., & Massagué, J. (2019). Transforming Growth Factor- $\beta$  Signaling in Immunity and Cancer. *Immunity*, 50(4), 924–940.
47. Chen, D. S., & Mellman, I. (2017). Elements of cancer immunity and the cancer-immune set point. *Nature*, 541(7637), 321–330.
48. Gabrilovich, D. I., et al. (2012). Myeloid-derived suppressor cells as regulators of the immune system. *Nature Reviews Immunology*, 12(12), 862–874.
49. Chao, M. P., et al. (2012). Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate non-Hodgkin lymphoma. *Cell*, 142(5), 699–713.
50. Mantovani, A., et al. (2008). Macrophage plasticity and polarization in tissue repair and remodelling. *Journal of Pathology*, 214(2), 153–165.
51. Gardner, A., & Ruffell, B. (2016). Dendritic Cells and Cancer Immunity. *Trends in Immunology*, 37(12), 855–865.
52. Vivier, E., et al. (2012). Innate or adaptive immunity? The example of natural killer cells. *Science*, 331(6013), 44–49.
53. Chen, D. S., & Mellman, I. (2017). Elements of cancer immunity and the cancer-immune set point. *Nature*, 541(7637), 321–330.
54. Sharma, P., et al. (2017). Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell*, 168(4), 707–723.
55. Shalapour, S., & Karin, M. (2015). Immunity, inflammation, and cancer: An eternal fight between good and evil. *Journal of Clinical Investigation*, 125(9), 3347–3355.
56. King, M. C., et al. (2003). Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science*, 302(5645), 643–646.
57. Bouaoun, L., et al. (2016). TP53 mutations in human cancers: database reassessment and prospects for the next decade. *Human Mutation*, 37(9), 865–876.
58. Feinberg, A. P., & Tycko, B. (2004). The history of cancer epigenetics. *Nature Reviews Cancer*, 4(2), 143–153.
59. Bruni, S.G., et al. (2021). Advances in robotic-assisted surgery for cancer treatment. *Journal of Surgical Oncology*, 123(4), 567–573.
60. Desai, S.V., et al. (2020). Single-incision robotic cystectomy: Early outcomes. *Urologic Oncology*, 38(5), 411.e9–411.e15.
61. Durante, M., and Loeffler, J.S. (2010). Charged particles in radiation oncology. *Nature Reviews Clinical Oncology*, 7(1), 37–43.
62. Timmerman, R., et al. (2018). Stereotactic body radiation therapy for early-stage lung cancer. *Journal of Clinical Oncology*, 26(1), 1537–1541.
63. Amjad MT, Chidharla A, Kasi A. Cancer Chemotherapy. [Updated 2023 Feb 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.
64. Farkona, S., et al. (2016). Cancer immunotherapy: The beginning of the end of cancer? *BMC Medicine*, 14(1), 73.
65. June, C.H., et al. (2018). CAR T-cell immunotherapy for human cancer. *Science*, 359(6382), 1361–1365.
66. Xie N, et al. Neoantigens: promising targets for cancer therapy. *Signal Transduct Target Ther.* 2023;8(1):9.
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