

Overview of Pathophysiology of Cancer, Types, Causes, Treatment



P-ISSN: 1680-9300
E-ISSN: 2790-2129
Vol. (24), No. (4)
pp. 17-24

Riam S. abbood¹
Rusul A. Alshammary²
Marwa M. Al-Attar³

^{1,3}Department of Biology, College of Science, Mustansiriyah University, Baghdad, Iraq

²Department of Microbiology, College of Science, Mustansiriyah University, Baghdad, Iraq

Abstract:

Cancer is a disease characterized by abnormal cell growth that can invade other parts of the body, forming tumors. While some tumors are benign and do not spread, malignant ones can metastasize. Cancer can develop in nearly any body part and exists in various forms, including lymphoma, sarcoma, leukemia, and carcinoma. Symptoms may include weight loss, persistent cough, lumps, unusual bleeding, and altered bowel movements, though these symptoms can have other causes. Over 100 types of cancer exist, often linked to prolonged exposure to carcinogens and the immune system's reparative response. Understanding cancer pathology is vital for its diagnosis, treatment, and prevention.

Keywords: Pathophysiology, Types, Signs, Diagnosis, Treatment

1. Introduction:

Cancer is an abnormal cell development condition that results in the invasion and destruction of healthy tissues by aberrant cells. Although cancer has affected humans from the dawn of time, until the nineteenth century, it was an uncommon disease (Wang et al., 2016) heart disease is the leading cause of death, with cancer coming in second. One of the main causes of mortality worldwide, cancer claimed over 10 million lives in 2020 alone. For those under 70, it was either the primary or the secondary cause of death (Sung et al., 2021). Consequently,

accurate cancer detection and treatment are becoming more and more necessary, and a significant amount of effort and resource have been invested by scientists in determining the biological processes that underlie the disease's origin and progression. Studying cancer is challenging, though, because there is a considerable deal of heterogeneity among human cancers. This implies that patients with different cancer kinds may occasionally differ more from one another than from those with the same cancer type (Uhlen et al., 2017). Because of this, the majority of cancer medications on the market today are only successful in a small subset of patients, and our knowledge of alternative treatment modalities and the pathophysiology of cancer remains severely limited (Anand et al., 2023).

Drawing on the tumor's multi-omics molecular profile, Creighton et al. classified clear cell renal cell carcinoma into

four distinct subtypes (Creighton et al., 2013). Previous study categorized Hepatocellular carcinoma using a metabolic network (Bidkhorji et al., 2018). Three molecular categories that utilize distinct enzymes to catalyze the same metabolic activities were found as a result of this categorization. Additionally, study conducted a meta-analysis on long non-coding RNA HOX transcript antisense RNA using data that made available to the public, and they found potential prognostic indicators for the prediction of the survival of different malignancies (Xu et al., 2022).

2. Pathophysiology of Cancer:

Multiple organs are often affected by cancer because of unchecked cell invasion, migration, and division. Given the growing number of cases and the shortcomings of conventional treatment choices, which lead to low overall and disease-free survival rates for many patients, it is imperative to comprehend its pathophysiology. The multistep theory, which describes the genetic and epigenetic processes that turn a single cell into several cancerous cells with the ability to spread, is currently the most frequently recognized explanation (Režen et al., 2022). Cancer's pathogenesis occurs in multiple stages. The first stage is called initiation, during which a mutation in a cell's DNA causes oncogenes—genes that stimulate cell growth—to become active, or tumor suppressor genes—genes that limit cell growth—to become inactive. During the second step, known as promotion, a small cluster of aberrant cells is formed by the mutant cells being encouraged to divide and grow quickly. The abnormal cells continue to divide and expand in the third stage, which is referred to as progression, until they form a tumor that can infiltrate surrounding tissues and spread to other parts of the body through the lymphatic or circulatory systems (Jones, 2023).

Based on our research's findings and the examination of a plethora of scientific data, it is possible to conclude that malignant tumor formation involves both the necessary and true inhibition of anti-tumor immunity in addition to damage to the genetic machinery of the cell. It should be mentioned that one of the body's normal physiological reactions is the suppression of anti-tumor immunity, and that when this reaction turns into a pathologic condition in the body, cancer

develops. For this reason, one of the mechanisms in the natural healing process under physiological settings is the immune system's brief local inhibition of antitumor activity, which is always evident when chemical, physical, or biological effects damage the organism's local tissues (Martinez and Gordon, 2014).

To success restore injured tissue, the transient local reduction of anti-tumor immunity serves a physiological purpose. Study demonstrated that growing tumor cells and tissue cells have comparable features and structures. Therefore, the removal of proliferating cells would prevent active anti-tumor immunity from repairing injured tissue (Zhao et al., 2021). Accordingly, a localized, transient reduction of anti-tumor immunity and the activation of immunological responses that promote healing are essential to the outcome of tissue healing (Zhao et al., 2021).

Immunological responses are creating in hearth lesions with established cellular, cytokine, and vascular reactions, which facilitate the inflammatory process and cellular proliferation for efficient tissue regeneration. Resuming antitumor immunity or more accurately, causing CD8+ cells to accumulate at the location of injury following healing, to shield the organism against malignantly altered cells, which almost invariably surface in the inflammatory region (Al-Qahtani et al., 2024).

3. Signs and Symptoms of Cancer:

The cancer warning indicators that are the subject of this study have been utilized in various combinations in a number of prior research as well as in educational campaigns run by the cancer society (Shapley et al., 2010.), (Jones et al., 2007).

Table 1. Signs and Symptoms of Cancer

| Symptoms Studied | Abbreviations | |
|------------------|--------------------------------------|-------------------|
| Focal Symptoms: | Non-healing skin lesion | Skin lesion |
| | Lump/nodule | Lump |
| | Unusual bleeding | Bleeding |
| | Pigmented skin lesion | Mole |
| | Persistent digestive problem | Digestive problem |
| | Cough/hoarseness of uncertain origin | Cough |
| | Other symptom suspicious of | Other |

| | | |
|-------------------|---------------------------|-------------|
| | cancer | |
| General Symptoms: | Unintentional weight loss | Weight loss |
| | Unusual fatigue | Fatigue |
| | Unusual pain | Pain |

4. Carcinogenesis:

Carcinogenesis, sometimes referred to as tumorigenesis or oncogenesis, is a process that involves interactions between an organism's genes and environment. These multistep, multifactorial molecular events are what cause cancer. The so-called process is a multistep process that results in dysregulated hedonic homeostasis and unchecked cell proliferation. It involves successive mutations and/or epimutations. Cancer-causing changes gradually alter the metabolism and behavior of cells. They modify the control over their multiplication, give them an endless lifespan, change how they communicate with nearby cells, and finally give them the capacity to evade the immune system. In summary, despite being damage genetically and/or epigenetically, they have the ability to split and multiply on their own (Hong, 2018).

Even while multicellular organisms undergo differentiation, which results in widespread cellular variety, cells share basic mechanisms for carrying out essential functions that control cell division and proliferation. The intracellular corporation required for homeostasis in a multicellular organism is governed by laws and regulations that cancer cells do not abide by. As a result, cancer cells work hard to adapt, multiply so they may invade surrounding tissues, and use their invasive aggression to fend off the immune system. The dense complexity of cellular changes frequently observed in cancer cells (six) was attempt to shown by Hanahan and Weinberg in 2000 as what they named cancer hallmarks (Hanahan & Weinberg, 2000). Since then, the idea has continued to develop and has given cancer biologists new motivation. The proliferative signal is permanently activated, growth suppressors are evaded, immortality and resistance to apoptosis are displayed, continuous replication is carried out, angiogenesis is induced, invasion and metastasis occur, dysregulation of cellular metabolism is triggered, immune assault is overwhelming, genomic instability and mutations are present, and tumor-promoting inflammation and

immuno-evasion are among them. (Moses et al., 2018), (Böttcher et al., 2020). Numerous instances of genetic DNA damage (mutations) and epigenetic changes in gene expression that build up over time are part of the carcinogenesis process. These alterations aid in the slow development of cancer's characteristic features, which eventually lead to fully-grown, metastasized malignancy (Režen et al., 2022). Carcinogenesis is significantly influence by DNA damage. DNA replication and repair are among the many biological functions that must be precisely regulate for proper cell function. Repair mechanisms are usually trigger when DNA is broken. Damage to DNA can have a major effect on the cell and its offspring because DNA is the genetic code for all living things. Cells have extremely effective DNA repair systems that guard against damaging mutations in order to combat this (Huang & Zhou, 2021).

DNA damage can result from prolonged disruption of cellular function. Repair processes include base excision repair, nucleotide excision repair, mismatch repair, homologous recombination, and nonhomologous end joining are start by damaged cells. Apoptosis destroys the damaged cell in the case that healing is unsuccessful, stopping further carcinogenesis. The beginning stage is characterize by apoptosis and defective DNA repair (Lewis & Dimri, 2020). The started cell proliferates uncontrollably while avoiding tumor suppressor genes. The cell avoids immunological checkpoints and becomes immortal with further mutations. The cell creates a self-sustaining food supply as mutations mount, which promotes growth and causes distant tissue invasion. Show figure 1 (Režen et al., 2022).

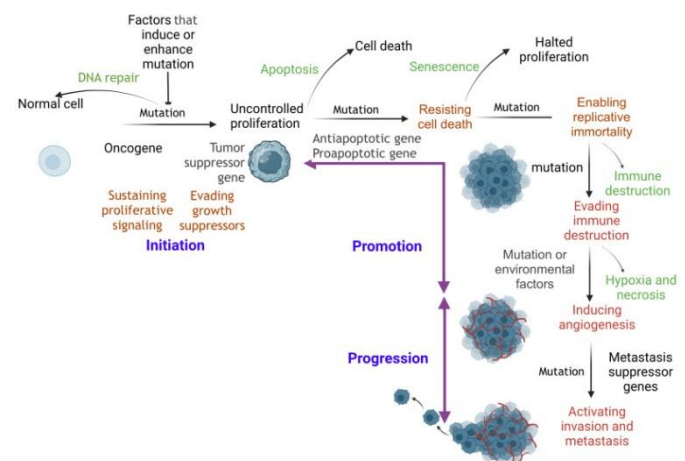


Fig. 1. The Stage of Cancer Cell Development

5. Causes of Cancer:

Many variables can cause cancer in various body areas. For instance, tobacco use accounts for 22% of fatalities, while poor diet, obesity, inactivity, and excessive alcohol use account for 10% of deaths. Other factors that may contribute to cancer deaths include specific exposure to ionizing radiation, environmental pollutants, and infections. Three types of external agents that we consume interact with genetic variables to cause cancer. These substances include (Saini et al., 2020):

5.1 Physical Agents of Carcinogenesis:

Ionizing radiation is emitted by sources of beta, gamma, alpha, and X radiation, uranium, sunlight's UV rays, and radon (Das et al., 2020).

5.2 Chemical Agents of Carcinogenesis:

Materials such as vinyl chloride, nickel, benzidine, asbestos, cadmium, and n-nitrosamines; it also includes approximately sixty substances that are known to be highly carcinogenic, such as tobacco use or smoking cigarettes, drinking water contaminated with arsenic, and food contaminated with aflatoxin (Das et al., 2020).

5.3 Genetics:

The most prevalent cause of cancer or tumor-like conditions, including skin, colorectal, breast, prostate, and ovarian cancer, is genetic. Consuming large amounts of cooked meat can further raise danger because of materials that are created at high temperatures. It is a challenge to prove that a chemical is not linked to or causes an increased risk of cancer (Saletta et al., 2015).

5.4 Biological Carcinogens:

5.4.1 The Bacterial Infection

Fusobacterium nucleatum recent study have found that can change the prognosis of the disease and speed up the growth of gastrointestinal tumors (Liu et al., 2019). In patients with Lauren's diffuse type gastric cancer; positive is linked to a worse prognosis (Boehm et al., 2020).

Streptococcus bovis: Since then, a number of investigations have verified the connection between *S. bovis* in the bloodstream and colorectal cancer. Many have also connected to hepatobiliary abnormalities and a range of other gastrointestinal disorders, such as diverticular disease, inflammatory bowel disease, and gastrointestinal bleeding (Thind et al., 2021).

Porphyromonas gingivalis; is one of the bacteria that causes periodontal disease the most aggressively (Aleksijević et al., 2022), and there has been a lot of recent discussion on the connection between *P. gingivalis* and malignancies of the mouth and upper digestive system. Due to the abundance of blood and the lack or presence of oral and mandibular vein valves, pathogenic bacteria can readily spread throughout the body (Fiorillo et al., 2019).

Helicobacter pylori, even in the absence of symptoms, can result in stomach cancer and peptic ulcers (Khan & Howden, 2019). While *H. pylori* gastritis is silent in the chronic stage, it can cause acute gastritis with hypochlorhydria, which can cause short-term symptoms such as nausea, vomiting, and stomach pain (Liao et al., 2021).

5.4.2 Viral Infections

Human papillomavirus (HPV): Known to be a highly contagious sexually transmitted infection (STD), HPV was linked to several types of cancer (Schiffman et al., 2016). Premalignant and malignant lesions can develop from persistent infections (Van Dyne, 2018).

Epstein-Barr virus (EBV): the initial human oncovirus discovered. The adult population is commonly infected with this gamma-herpes virus, primarily through salivary transmission. Six According to estimates, more than 90% of people appear to have EBV infection by the age of 35 (Shechter et al., 2022). Overall, EBV causes gastric carcinogenesis by means of direct and indirect mechanisms, such as infecting epithelial cells. Creating a latent program that results in the expression of a restricted profile of latent proteins and/or transcripts, and/or by aiding in the induction of a chronic inflammatory response, that advances tissue necrosis and cancer (Torne, 2024).

Human Polyomaviruses: PyVs are extremely carcinogenic in heterologous animal models, suggesting that non-human polyomaviruses may contribute to human cancers in addition to human polyomaviruses (Moens et al., 2022). Large tumor antigen (T-Ag) is the main oncogenic viral protein. It binds to factors including p53 and Retinoblastoma protein (pRb) to disrupt the cell cycle. On the other hand, early proteins such as Agnoprotein and tiny tumor antigen (t-Ag) seem to have a role in the cell transformation process (Delbue et al., 2017).

5.5 Types of Cancer:

Several types of cancer are (Saini et al., 2020):

5.5.1 Carcinomas

It starts with the tissue or skin that covers the interior organs and glands. It becomes a solid tumor. Carcinoma of the prostate, Breast cancer, colon cancer, and lung cancer (Cserni, 2020).

5.5.2 Sarcomas

The tissues that bind and support the body are where it begins. Blood arteries, bone, muscles, cartilage, joints, tendons, nerves, or lymph vessels can all develop it (Damerell et al., 2021).

5.5.3 Leukemia's

One kind of blood cancer is leukemia. It begins when healthy blood cells change and proliferate uncontrollably. Its four subtypes are chronic myeloid leukemia, chronic lymphocytic leukemia, acute lymphocytic leukemia, and acute myeloid leukemia (Bispo et al., 2020).

5.5.4 Lymphomas

Lymphatic cancer originates in the lymphatic system, a network of glands and tubes that supports the body's defense against infection. Hodgkin and non-Hodgkin lymphomas (Bispo et al., 2020).

Central Nervous System Cancers

The term "brain and spinal cord tumors" refers to

malignancies that start in the brain or spinal cord; further disorders include meningiomas, vestibular schwannomas, gliomas, pituitary adenomas, primitive neuro-ectodermal tumors, and primary CNS lymphomas (Nabors et al., 2020).

5.5.5 Multiple Myeloma

Multiple myelomas are cancers that originate in plasma cells, which are an additional kind of immune cell. In the bone marrow, myeloma cells, also known as plasma cells, build up and result in bone malignancies. It's referred to as Kahler disease and plasma cell myeloma. (Cowan et al., 2022).

5.5.6 Melanoma

It starts in the melanocyte progenitor cells. These are specialized cells that generate the pigment known as melanin, which gives skin its color. Although they usually appear on the skin, melanomas can also develop in other pigmented tissues, such the eye (Saginala et al., 2021).

5.5.7 Other Tumor Types

- Germ cell tumor: This type of tumor starts in the cells that develop into sperm or eggs in the end. This might occur anywhere in the body and could be benign or malignant (Torner and Robertson., 2024).
- Neuroendocrine Tumors: Neuroendocrine tumors arise from cells that respond to signals from the nervous system by releasing hormones into the bloodstream. It made up of cells that respond to signals from the nervous system by releasing hormones into the blood. These tumors can produce hormone levels that are higher than usual, which can result in a wide range of symptoms. It could be benign or cancerous (Kulke et al., 2012).

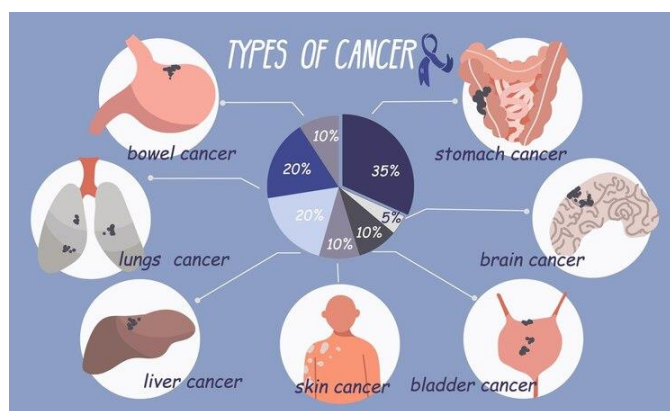


Fig. 2. Show the Different Type of Cancer

6. Diagnosis of Cancer:

A number of tests are used to diagnose cancer, including laboratory testing like blood tests and biopsies as well as imaging tests like MRI, CT, and X-rays. A biopsy determines whether a tumor is malignant or benign (non-cancerous) by removing a small sample of the tumor's tissue and examining it under a microscope. Tumor markers, for example, are chemicals that can be found in the blood that are linked to a cancer (Jones, 2023).

7. Treatment of Cancer:

Nowadays, oncology procedures are centered on developing safe and efficient cancer nanomedicines. The use of stem cells to treat primary and metastatic cancer foci has demonstrated promising results in terms of healing and restoring diseased or damaged tissues (Boehm et al., 2020). One traditional or conventional method of treating cancer is chemotherapy or cytotoxic therapy. Chemotherapy is no longer considered a necessary treatment choice for a number of cancers, nevertheless. Additionally, chemotherapy causes collateral harm to healthy cells. (Dailah et al., 2024). In addition, nanoparticles introduced fresh possibilities for treatment and diagnosis. Targeted treatment has the potential to be a game-changer since it may minimize damage to healthy cells while inhibiting the development and spread of certain cancer cells (Wang and He 2018). Two potential treatment options for cancer patients are immunotherapy and targeted therapy. Targeted therapies inhibit molecular processes crucial to tumor development and maintenance, whereas immunotherapies

trigger a host immune response that mediates long-lasting tumor elimination (Dailah et al., 2024). Furthermore, the regulation of immune responses by cytotoxic drugs and targeted therapies raises the possibility that these therapeutic modalities could be effectively paired with immunotherapy to improve clinical results (Liu et al., 2024). Also, Hyperthermic treatment was used by raising the temperature of tumor cells to between 40 and 45 °C, apoptosis and other thermally induced metabolic processes are triggered, ultimately leading to the destruction of the tumor cells (Jose et al., 2020). As well, as use the hormonal therapy to treat the breast and prostate cancer that either directly inhibits the androgen receptor or prevents the production of androgens (Desai et al., 2021)

A common less invasive technique for burning or freezing malignancies is ablation treatment, which has replaced open surgery (Bansal et al., 2019). Natural antioxidants may be able to detect free radicals and lessen the harm they do, which might aid in the treatment or prevention of cancer (Vaiserman et al., 2020).

8. Conclusion:

Millions of individuals worldwide are impacted by the complicated disease known as cancer. The development of cancer is not always caused by gene damage, and only a few other well-known cellular-molecular cancer illnesses share this pathogenic mechanism. Only when a certain pathophysiological condition known as the "cancer reparative trap" forms in the body can the cancer process begin and continue. Even though receiving a cancer diagnosis can be heartbreaking, advancements in technology and medical research have significantly improved the course of treatment and prognosis for cancer patients. This development aims to offer more precise and efficient therapeutic approaches to curtail the growth and spread of tumors. It is necessary to continue looking for the best ways to provide high-quality cancer rehabilitation and post-treatment cancer care. We may lower our risk of getting cancer and improve our chances of early detection and effective treatment by leading a healthy lifestyle, avoiding exposure to carcinogens, and getting frequent cancer screenings. Future studies should also concentrate on determining the most effective ways to

encourage cancer survivors to embrace and sustain a healthy lifestyle at the levels of individual patients, the health care system, and policy.

References

- Aleksijević, L., Aleksijević, M., Škrlec, I., Šram, M., Šram, M., and Talapko, J. (2022). Porphyromonas Gingivalis Virulence Factors and Clinical Significance in Periodontal Disease and Coronary Artery Diseases, *Pathogens*, 11(10), pp. 1173.
- Al-Qahtani, A., Alhamlan, F., and Al-Qahtani, A. (2024). Pro-inflammatory and Anti-inflammatory Interleukins in Infectious Diseases: A Comprehensive Review, *Tropical Medicine and Infectious Disease*, 9(1), pp. 13.
- Anand, U., Dey, A., Chandel, A., Sanyal, R., Mishra, A., Pandey, D. K., and de la Lastra, J. (2023). Cancer Chemotherapy and Beyond: Current Status, Drug Candidates, Associated Risks and Progress in Targeted Therapeutics, *Genes & Diseases*, 10(4), pp. 1367-1401.
- Bansal, S., Gui, J., Merrill, C., Wong, J., Burak, K., and Wilson, S. (2019). Contrast-Enhanced US in Local Ablative Therapy and Secondary Surveillance for Hepatocellular Carcinoma, *Radiographics*, 39(5), pp. 1302-1322.
- Bidkhorji, G., Benfeitas, R., Klevstig, M., Zhang, C., Nielsen, J., Uhlen, M., and Mardinoglu, A. (2018). Metabolic Network-Based Stratification of Hepatocellular Carcinoma Reveals Three Distinct Tumor Subtypes, *Proceedings of the National Academy of Sciences*, 115(50), E11874-E11883.
- Bispo, J., Pinheiro, P., and Kobetz, E. (2020). Epidemiology and Etiology of Leukemia and Lymphoma, *Cold Spring Harbor Perspectives in Medicine*, 10(6), pp. 1-22.
- Boehm, E., Thon, C., Kupcinskas, J., Steponaitiene, R., Skieceviciene, J., Canbay, A., and Link, A. (2020). Fusobacterium Nucleatum Is Associated with Worse Prognosis in Lauren's Diffuse Type Gastric Cancer Patients, *Scientific Reports*, 10(1), 16240.
- Böttcher, M., Baur, R., Stoll, A., Mackensen, A., and Mougiakakos, D. (2020). Linking Immuno-evasion and Metabolic Reprogramming in B-Cell-Derived Lymphomas, *Frontiers in Oncology*, 10, 594782.
- Cowan, A., Green, D., Kwok, M., Lee, S., Coffey, D., Holmberg, L., and Libby, E. (2022). Diagnosis and Management of Multiple Myeloma: A Review, *Jama*, 327(5), pp. 464-477.
- Creighton, C., Morgan, M., Gunaratne, P., Wheeler, D., Gibbs, R., Muzny, D. (2013). Comprehensive Molecular Characterization of Clear Cell Renal Cell Carcinoma, The Cancer Genome Atlas Research Network, Analysis Working Group: Baylor College of Medicine. *Nature* 499, pp. 43-49.
- Cserni, G. (2020). Histological Type and Typing of Breast Carcinomas and the WHO Classification Changes over Time, *Pathologica*, 112(1), pp. 25.
- Dailah, H., Hommdi, A., Koriri, M., Alqathlan, E., and Mohan, S. (2024). Potential Role of Immunotherapy and Targeted Therapy in the Treatment of Cancer: A Contemporary Nursing Practice, *Heliyon*.
- Damerell, V., Pepper, M., and Prince, S. (2021). Molecular Mechanisms Underpinning Sarcomas and Implications for Current and Future Therapy, *Signal Transduction and Targeted Therapy*, 6(1), pp. 246.
- Das, S., Kundu, M., Jena, B., and Mandal, M. (2020). Causes of Cancer: Physical, Chemical, Biological Carcinogens, and Viruses, In: *Biomaterials for 3D Tumor Modeling* (pp. 607-641), Elsevier.
- Delbue, S., Comar, M., and Ferrante, P. (2017). Review on the Role of the Human Polyomavirus JC in the Development of Tumors, *Infectious Agents and Cancer*, 12(1), pp. 1-14.
- Desai, K., McManus, J., and Sharifi, N. (2021). Hormonal Therapy for Prostate Cancer, *Endocrine Reviews*, 42(3), pp. 354-373.
- Fiorillo, L., Cervino, G., Laino, L., D'Amico, C., Mauceri, R., Tozum, T., and Ciccù, M. (2019). Porphyromonas Gingivalis, Periodontal and Systemic Implications: A Systematic Review, *Dentistry Journal*, 7(4), pp. 114.
- Göbel, U., Schneider, D., Calaminus, G., Haas, R. J., Schmidt, P., Harms, D., and Makei, G. (2000). Germ-cell Tumors in Childhood and Adolescence, *Annals of Oncology*, 11(3), pp. 263-272.
- Hanahan, D., and Weinberg, R. (2000). The Hallmarks of Cancer, *Cell*, 100(1), pp. 57-70.
- Hong, S. (2018). Genetic and Epigenetic Alterations of Colorectal Cancer, *Intestinal research*, 16(3), pp. 327-337.
- Huang, R., and Zhou, P. (2021). DNA Damage Repair: Historical Perspectives, Mechanistic Pathways and Clinical Translation for Targeted Cancer Therapy, *Signal Transduction and Targeted Therapy*, 6(1), pp. 254.
- Jones, A. (2023). Pathology of Cancer: Causes, Pathophysiology, Diagnosis, Prevention and Treatment, *J Med Surg Pathol*, 8, pp. 267.
- Jones, R., Latinovic, R., Charlton, J., and Gulliford, M. (2007). Alarm Symptoms in Early Diagnosis of Cancer in Primary Care: Cohort Study Using General Practice Research Database, *Bmj*, 334(7602), 1040.
- Jose, J., Kumar, R., Harilal, S., Mathew, G., Parambi, D., Prabhu, A., and Mathew, B. (2020). Magnetic Nanoparticles for Hyperthermia in Cancer Treatment: An Emerging Tool, *Environmental Science and Pollution Research*, 27, pp. 19214-19225.
- Khan, M., and Howden, C. (2019). Helicobacter Pylori and Related Diseases, In: *Essential Medical Disorders of the Stomach and Small Intestine* (pp. 141-154), Springer, Cham.
- Kulke, M., Benson, A., Bergsland, E., Berlin, J., Blaszkowsky, L., Choti, M. A., and Dwyer, M. (2012). Neuroendocrine Tumors, *Journal of the National Comprehensive Cancer Network*, 10(6), pp. 724-764.
- Lewis, T., and Dimri, M. (2020). Biochemistry, DNA Repair.
- Liao, Y., Hong, X., Wu, A., Jiang, Y., Liang, Y., Gao, J., and Kou, X. (2021). Global Prevalence of Norovirus in Cases of Acute

- Gastroenteritis from 1997 to 2021: An Updated Systematic Review and Meta-Analysis, *Microbial Pathogenesis*, 161, 105259.
- Liu, B., Zhou, H., Tan, L., Siu, K., and Guan, X. (2024). Exploring Treatment Options in Cancer: Tumor Treatment Strategies, Signal Transduction and Targeted Therapy, 9(1), pp. 175.
- Liu, Y., Baba, Y., Ishimoto, T., Iwatsuki, M., Hiyoshi, Y., Miyamoto, Y., and Baba, H. (2019). Progress in Characterizing the Linkage between *Fusobacterium Nucleatum* and Gastrointestinal Cancer, *Journal of Gastroenterology*, 54, pp. 33-41.
- Martinez, F., and Gordon, S. (2014). The M1 and M2 Paradigm of Macrophage Activation: Time for Reassessment, *F1000prime Reports*, 6.
- Moens, U., Prezioso, C., and Pietropaolo, V. (2022). Functional Domains of the Early Proteins and Experimental and Epidemiological Studies Suggest a Role for the Novel Human Polyomaviruses in Cancer, *Frontiers in Microbiology*, 13, 834368.
- Moses, C., Garcia-Bloj, B., Harvey, A., and Blancafort, P. (2018). Hallmarks of Cancer: The CRISPR Generation, *European Journal of Cancer*, 93, pp. 10-18.
- Nabors, L., Portnow, J., Ahluwalia, M., Baehring, J., Brem, H., Brem, S., and Darlow, S. (2020). Central Nervous System Cancers, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology, *Journal of the National Comprehensive Cancer Network*, 18(11), pp. 1537-1570.
- Režen, T., Rozman, D., Kovács, T., Kovács, P., Sipos, A., Bai, P., and Mikó, E. (2022). The Role of Bile Acids in Carcinogenesis, *Cellular and Molecular Life Sciences*, 79(5), pp. 243.
- Saginala, K., Barsouk, A., Aluru, J., Rawla, P., and Barsouk, A. (2021). Epidemiology of Melanoma, *Medical Sciences*, 9(4), pp. 63.
- Saini, A., Kumar, M., Bhatt, S., Saini, V., and Malik, A. (2020). Cancer Causes and Treatments, *Int. J. Pharm. Sci. Res.*, 11(7), pp. 3121-3134.
- Saletta, F., Dalla Pozza, L., and Byrne, J. (2015). Genetic Causes of Cancer Predisposition in Children and Adolescents, *Translational pediatrics*, 4(2), pp. 67.
- Schiffman, M., Doorbar, J., Wentzensen, N., De Sanjosé, S., Fakhry, C., Monk, B., and Franceschi, S. (2016). Carcinogenic Human Papillomavirus Infection, *Nature Reviews Disease Primers*, 2(1), pp. 1-20.
- Shapley, M., Mansell, G., Jordan, J., and Jordan, K. (2010). Positive Predictive Values of $\geq 5\%$ in Primary Care for Cancer: Systematic Review, *British Journal of General Practice*, 60(578), pp. e366-e377.
- Shechter, O., Sausen, D., Gallo, E., Dahari, H., and Borenstein, R. (2022). Epstein-Barr Virus (EBV) Epithelial Associated Malignancies: Exploring Pathologies and Current Treatments, *International Journal of Molecular Sciences*, 23(22), 14389.
- Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., and Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, *CA: A Cancer Journal for Clinicians*, 71(3), pp. 209-249.
- Thind, S., Shibib, D., and Gentry, C. (2021). The Effect of Nomenclature Revision of *Streptococcus Bovis* to *Streptococcus Gallolyticus* on Subsequent Colon Cancer Screening, In: *Open Forum Infectious Diseases* (Vol. 8, No. 9, p. ofab426). US: Oxford University Press.
- Torne, A., and Robertson, E. (2024). Epigenetic Mechanisms in Latent Epstein-Barr Virus Infection and Associated Cancers, *Cancers*, 16(5), pp. 991.
- Uhlen, M., Zhang, C., Lee, S., Sjöstedt, E., Fagerberg, L., Bidkhor, G., and Ponten, F. (2017). A Pathology Atlas of the Human Cancer Transcriptome, *Science*, 357(6352), ean2507.
- Vaiserman, A., Koliada, A., Zayachkivska, A., and Lushchak, O. (2020). Nanodelivery of Natural Antioxidants: An Anti-Aging Perspective, *Frontiers in Bioengineering and Biotechnology*, 7, pp. 447.
- Van Dyne, E. (2018). Trends in Human Papillomavirus-Associated Cancers—United States, 1999–2015, *MMWR. Morbidity and Mortality Weekly Report*, 67.
- Wang, H., and He, X. (2018). Nanoparticles for Targeted Drug Delivery to Cancer Stem Cells and Tumor, *Targeted Drug Delivery: Methods and Protocols*, pp. 59-67.
- Wang, H., Naghavi, M., Allen, C., Barber, R., Carter, A., Casey, D., and Liang, X. (2016). Global, Regional, and National Life Expectancy, All-Cause Mortality, and Cause-Specific Mortality for 249 Causes of Death, 1980 - 2015: A Systematic Analysis for the Global Burden of Disease Study 2015, *The Lancet*, 388(10053), pp. 1459-1544.
- Xu, X., Duan, F., Ng, S., Wang, H., Wang, K., Li, Y., and Xu, E. (2022). Clinicopathological and Prognostic Value of lncRNAs Expression in Gastric Cancer: A Field Synopsis of Observational Studies and Databases Validation, *Medicine*, 101(40), e30817.
- Zhao, H., Wu, L., Yan, G., Chen, Y., Zhou, M., Wu, Y., and Li, Y. (2021). Inflammation and Tumor Progression: Signaling Pathways and Targeted Intervention, *Signal Transduction and Targeted Therapy*, 6(1), pp. 263.