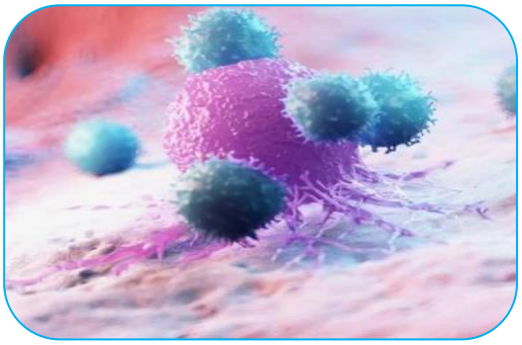
REVIEW OF RESEARCH
ISSN: 2249-894X
IMPACT FACTOR : 5.7631(UIF)
VOLUME - 14 | ISSUE - 7 | APRIL - 2025

RECENT ADVANCES IN TARGETED CANCER THERAPIES: A REVIEW

Dr. Rakesh Kumar
Associate Professor, Department of Chemistry, MMM PG College
Bhatpar Rani, Deoria, UP, INDIA.

ABSTRACT :



Over the past decades, anticancer drug development has yielded significant therapeutic breakthroughs; however, many clinically approved chemotherapeutics continue to exhibit high systemic toxicity, primarily due to poor tumor selectivity and suboptimal pharmacokinetic profiles. Key issues include low aqueous solubility, rapid systemic clearance and metabolic instability, which collectively reduce circulation time and bioavailability. Forced degradation and ICH-stability studies have demonstrated that many cytotoxic agents are highly sensitive to hydrolysis, photolysis and thermal stress, leading to the generation of reactive or inactive degradation products in both pharmaceutical formulations and environmental waste. To overcome these drawbacks, novel approaches such as prodrug design and nanoformulations have been actively explored. Prodrugs, chemically modified inactive precursors, can be selectively activated in the tumor microenvironment via enzymatic or pH-sensitive mechanisms, thereby enhancing site-specific action and minimizing off-target effects. Additionally, incorporation of active compounds into nanocarriers (e.g., polymeric micelles, liposomes, dendrimers and β-cyclodextrin inclusion complexes) or antibody-drug conjugates (ADCs) has been shown to significantly improve physicochemical stability, targeted delivery and intracellular uptake through enhanced permeability and retention (EPR) effect or receptor-mediated endocytosis. This review summarizes recent advances in the rational design of stable anticancer agents, focusing on prodrug strategies and nanotechnology-enabled delivery systems to improve therapeutic index and patient outcomes.

KEYWORDS : Anticancer drug design, systemic toxicity, pharmacokinetic, prodrug, nanotechnology, polymeric micelles, cyclodextrins, drug stability, targeted delivery, liposomes and antibody-drug conjugates (ADCs).

1. INTRODUCTION

Cancer is the second leading cause of mortality worldwide[1-2] and remains a significant public health challenge across all societies. Its onset is influenced by various lifestyle-related factors such as smoking, consumption of fried foods and red meat, alcohol intake, prolonged sun exposure, environmental pollutants, chronic infections, stress, obesity and lack of physical activity. In men, the most common cancer types include those affecting the prostate, lung and bronchus, colon, rectum and uterine corpus. Cancer arises due to both internal factors, like inherited genetic mutations, hormonal imbalances and immune dysfunctions and external or acquired influences, including exposure to tobacco, carcinogenic diets, radiation and infectious agents. Notably, heavy red meat consumption has

been strongly linked with gastrointestinal, colorectal[3-4], prostate[5-6], bladder[7], breast[8-9], gastric[10], pancreatic and oral cancers[11-12].

On the molecular level, cancer involves disruptions in genes regulating cell division and death. **Proto-oncogenes**, which normally control cell growth, may mutate into **oncogenes**, resulting in uncontrolled cellular proliferation[13]. When **tumor suppressor genes**, which serve as regulatory checkpoints, are also impaired, it leads to unchecked division of abnormal cells[14]. Cancer is thus defined as a group of diseases marked by abnormal and unregulated cell growth that can invade surrounding tissues. Tumors may be **benign**, which do not metastasize or **malignant**, which are invasive and capable of spreading to distant sites through the bloodstream or lymphatic system. Treatment primarily involves **antineoplastic agents**, though current research is increasingly focused on developing more targeted and less toxic therapies to enhance patient outcomes.

2. Classification: Cancer is a complex and heterogeneous disease marked by the uncontrolled growth and proliferation of abnormal cells, which can invade adjacent tissues and metastasize to distant organs. A widely accepted method for classifying cancers is based on the tissue or cell type from which they originate[15]. This classification system not only facilitates accurate diagnosis but also informs treatment decisions and helps predict disease prognosis. The primary categories include carcinomas, sarcomas, leukemias, lymphomas, germ cell tumors and blastomas, each originating from distinct cellular lineages and exhibiting unique pathological and clinical characteristics. The following section provides a detailed examination of these major cancer types, along with their defining features, subtypes and representative examples.

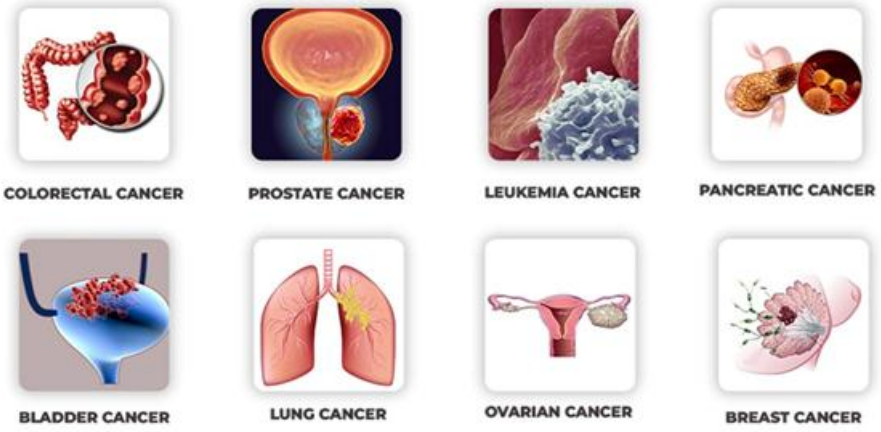


Fig 1.1 Types of Cancer on the basis of Organ effected

2.1 Carcinoma: Carcinoma is the most common type of cancer in humans originating from epithelial cells that line the inner and outer surfaces of the body. These malignancies typically affect the skin or tissues lining internal organs and can vary in growth rate from slow to rapid progression. They are capable of invading nearby tissues and metastasizing to distant sites. Carcinomas are broadly categorized into adenocarcinoma, which arises from glandular tissues (e.g., breast, colon) and squamous cell carcinoma, which develops from flat epithelial cells (e.g., skin, esophagus). Common examples include breast, lung, prostate, colon and pancreatic cancers, illustrating the breadth of diseases originating from epithelial tissues.

2.2 Sarcoma: Sarcoma is a rare but often aggressive form of cancer that originates in the connective and supportive tissues of the body, such as bones, cartilage, muscles, fat and blood vessels[16]. Unlike carcinomas, sarcomas can occur at any age, including in children and young adults. They typically present as painless, progressively enlarging masses, most commonly in the limbs or trunk. Despite their rarity, sarcomas can metastasize, with the lungs being the most common site of distant spread. Based on the tissue of origin, sarcomas are classified into subtypes such as osteosarcoma (bone), liposarcoma (fat), chondrosarcoma (cartilage) and leiomyosarcoma (smooth muscle).

Prominent examples include osteosarcoma; frequent among adolescents, Ewing sarcoma and angiosarcoma, which arises from blood vessels.

2.3 Leukemia: Leukemia is a malignancy of the bone marrow and other hematopoietic tissues, marked by uncontrolled proliferation of abnormal white blood cells that circulate in the bloodstream rather than forming a discrete solid tumour[17]. It is most frequently diagnosed at the extremes of age, being the most common cancer in children under 15 and occurring most often in adults over 55 and typically presents with anaemia, bleeding tendencies and recurrent infections. Clinically, it is divided by cell lineage (lymphoid vs myeloid) and pace of progression (acute vs chronic) into four principal entities: acute lymphoblastic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML). AML is the predominant acute leukaemia in adults, whereas ALL is the archetypal childhood leukaemia. Without treatment, malignant leukocytes infiltrate multiple organs and lead to systemic complications, but contemporary protocols combining cytotoxic, targeted and immuno-therapies have markedly improved.

2.4 Lymphoma: Lymphoma is a type of blood cancer that originates in the lymphatic system, which includes lymph nodes, spleen, thymus and bone marrow[18]. It is a common hematologic malignancy and typically presents as painless swelling of lymph nodes. Lymphomas can impair immune function and may involve bone marrow or spread to extranodal sites. The two primary subtypes are Hodgkin lymphoma, characterized by the presence of Reed–Sternberg cells and Non-Hodgkin lymphoma (NHL), a diverse group of cancers with varied behavior and prognosis. Notable examples include diffuse large B-cell lymphoma, follicular lymphoma and Hodgkin lymphoma itself.

2.5 Germ Cell Tumor: Germ cell tumors arise from germ cells, the cells responsible for producing sperm or eggs and most commonly affect young adults of both sexes[19]. These tumors are typically found in the testes or ovaries, but can also occur in extragonadal locations such as the mediastinum, brain or abdomen. Germ cell tumors may be benign or malignant and are broadly categorized into seminomas, which are slow-growing and usually testicular and non-seminomatous germ cell tumors (NSGCTs), which are more aggressive. Representative examples include testicular seminoma, ovarian dysgerminoma and embryonal carcinoma.

2.6 Blastoma: Blastomas are a group of cancers that originate from embryonic or immature precursor cells and they are most commonly diagnosed in young children, typically under the age of five[20]. These tumors closely resemble fetal or immature tissues when viewed under a microscope and are generally fast-growing and aggressive. Blastomas are often associated with specific organs and are named accordingly. Key examples include nephroblastoma (Wilms tumor) arising from the kidney, medulloblastoma from the cerebellum of the brain, retinoblastoma from the retina of the eye and hepatoblastoma from the liver. Due to their origin in developing tissues, these cancers are primarily encountered in pediatric oncology.

3. Cause of Cancer:

Cancer can arise from a complex interplay of genetic, environmental and lifestyle factors. Genetic predisposition plays a role in certain cancers, where mutations inherited from family members can significantly increase the risk, as seen in breast and colorectal cancers. Environmental exposures;such as tobacco smoke, ionizing radiation, air pollution and carcinogenic chemicals, can damage cellular DNA, triggering malignant transformations. Additionally, lifestyle choices like a poor diet, physical inactivity, obesity and excessive alcohol consumption are well-established contributors to cancer development by promoting chronic inflammation, hormonal imbalances and weakened immunity.

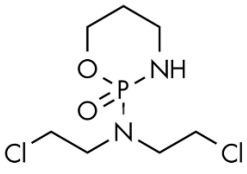
4. Medications in Cancer Therapy:

Medications play a pivotal role in the treatment of cancer, aiming to destroy cancer cells, stop their growth or prevent their spread to other parts of the body. Over the years, cancer therapy has evolved from conventional chemotherapy to more precise and personalized treatments such as

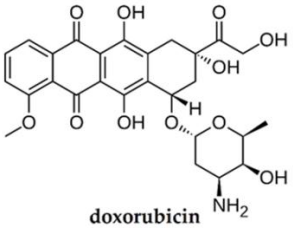
targeted therapy and immunotherapy. These therapeutic agents work through various mechanisms, either by directly killing cancer cells, interfering with their growth signals, enhancing the body's immune response or altering hormone levels in hormone-dependent cancers. The choice of medication depends on the type, location, genetic profile and stage of cancer, as well as the patient's overall health. Modern cancer treatment often involves a combination of these medications, tailored to achieve the best possible outcome with minimal side effects.

4.1 Chemotherapy:

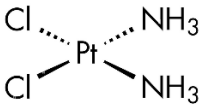
Chemotherapy is a widely used cancer treatment that involves the use of cytotoxic drugs to destroy rapidly dividing cancer cells. These drugs interfere with various stages of the cell cycle, preventing cancer cells from growing and proliferating. Chemotherapy can be administered orally or intravenously, either alone or in combination with other treatments like surgery or radiation. While effective, it may also affect healthy fast-growing cells, leading to side effects such as hair loss, fatigue and immunosuppression.



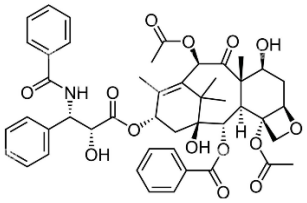
cyclophosphamide



doxorubicin



cisplatin



Paclitaxel

Common Chemotherapy Drugs and Their Uses-

4.1.1 Cyclophosphamide[21]: An alkylating agent that interferes with DNA replication. It is widely used in the treatment of breast cancer, non-Hodgkin lymphoma and chronic lymphocytic leukemia.

4.1.2 Doxorubicin[22]: An anthracycline antibiotic that inhibits topoisomerase II, leading to DNA damage. It is effective against leukemias, lymphomas and a variety of solid tumors, including breast and bladder cancers.

4.1.3 Cisplatin[23]**:** A platinum-based compound that causes DNA crosslinking, leading to apoptosis. It is commonly used in testicular, ovarian, bladder and lung cancers.

4.1.4 Paclitaxel[24]: A mitotic inhibitor that stabilizes microtubules and prevents cell division. It is used extensively in breast, lung, ovarian and pancreatic cancers.

4.2 Targeted Therapy:

Targeted therapy is a form of cancer treatment that focuses on specific molecular targets; such as proteins or genes, that are involved in the growth, progression and spread of cancer. Unlike conventional chemotherapy, which affects both cancerous and healthy rapidly dividing cells, targeted therapies are designed to be more selective, reducing damage to normal tissues and minimizing side effects. These therapies can block signals that tell cancer cells to grow, interfere with tumor blood supply or directly induce cancer cell death.

Imatinib, Trastuzumab and **Gefitinib** are key examples of targeted therapies in cancer treatment[25] that act on specific molecular pathways involved in tumor growth and progression. **Imatinib** is a tyrosine kinase inhibitor primarily used for treating chronic myeloid leukemia (CML) by inhibiting the BCR-ABL fusion protein. **Trastuzumab**, a monoclonal antibody, specifically targets the HER2 receptor and is widely used in HER2-positive breast cancer cases. **Gefitinib** inhibits the epidermal growth factor receptor (EGFR) tyrosine kinase and is effective in non-small cell lung cancer (NSCLC) patients with activating EGFR mutations. These therapies offer improved efficacy with fewer side effects compared to traditional chemotherapy by selectively targeting cancer-specific pathways.

4.3 Immunotherapy:

Immunotherapy is a cutting-edge cancer treatment that empowers the body's own immune system to recognize and destroy cancer cells more effectively. It works by stimulating or restoring immune functions to identify cancer as a threat. Major approaches include immune checkpoint inhibitors (which block proteins like PD-1, PD-L1 and CTLA-4 that inhibit immune responses) and CAR T-cell therapy (which involves genetically engineering a patient's T-cells to target cancer cells).

Nivolumab, **Pembrolizumab** and **Ipilimumab** are immunotherapeutic agents that enhance the body's immune response against cancer by targeting immune checkpoints[26]. Nivolumab and Pembrolizumab are monoclonal antibodies that block the PD-1 receptor, thereby restoring T-cell activity against tumor cells and are approved for various cancers including melanoma, non-small cell lung cancer and renal cell carcinoma. Ipilimumab works by inhibiting CTLA-4, another immune checkpoint and is primarily used in the treatment of metastatic melanoma. These agents have significantly improved survival outcomes in cancers that were previously difficult to treat.

4.4 Hormonal Therapy: Immunotherapy is a revolutionary approach in cancer treatment that enhances the body's natural defenses to identify and eliminate cancer cells. Unlike conventional therapies that directly attack tumors, immunotherapy activates the immune system to recognize cancer as a threat. Key types include immune checkpoint inhibitors (such as PD-1/PD-L1 and CTLA-4 blockers) and CAR T-cell therapy, which involves modifying a patient's T-cells to better target cancer cells.

Nivolumab and **Pembrolizumab** are PD-1 inhibitors that work by blocking the programmed cell death receptor on T cells[27], thus enhancing the immune system's ability to detect and destroy cancer cells. They are approved for use in various malignancies including melanoma, non-small cell lung cancer and renal cell carcinoma. **Ipilimumab**, a CTLA-4 inhibitor, also stimulates T-cell activation and is primarily used in the treatment of metastatic melanoma. Together, these immune checkpoint inhibitors have transformed the landscape of cancer immunotherapy by significantly improving patient survival in several hard-to-treat cancers.

4.5 Anti-angiogenic Agents: Anti-angiogenic agents are a class of cancer medications that block the formation of new blood vessels (angiogenesis), which tumors require to receive nutrients and oxygen for continued growth and metastasis. By disrupting the blood supply, these agents can slow or even shrink tumor development. This approach is often used in combination with chemotherapy or targeted therapy for enhanced effectiveness.

Bevacizumab is a monoclonal antibody that targets and inhibits vascular endothelial growth factor (VEGF)[28], a key protein involved in angiogenesis; the formation of new blood vessels that supply tumors with oxygen and nutrients. By blocking VEGF, bevacizumab restricts tumor growth and metastasis. It is commonly used in the treatment of cancers such as colorectal cancer, non-small cell lung cancer and renal cell carcinoma.

4.6 Bone-modifying Agents: Bone-modifying agents are used in cancer therapy to prevent or reduce complications related to bone metastases and cancer-induced bone loss, such as fractures, spinal cord compression and bone pain. These drugs help strengthen bones and reduce skeletal-related events, especially in cancers like breast, prostate and multiple myeloma that commonly spread to bones. Zoledronic acid – a bisphosphonate that slows bone resorption.

Denosumab is a fully human monoclonal antibody that targets and inhibits RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand)[29], a critical mediator of osteoclast formation, function and survival. By inhibiting RANKL, denosumab prevents bone resorption and destruction, making it effective in managing bone metastases and cancer-induced bone loss in conditions such as breast cancer, prostate cancer and multiple myeloma.

5. Adverse Effects of Anticancer Drugs: Anticancer drugs, particularly chemotherapy agents, are designed to kill rapidly dividing cancer cells. However, these drugs also affect normal, fast-dividing cells

in the body, such as those in the bone marrow, gastrointestinal tract, hair follicles and mucous membranes, leading to a range of adverse effects. These effects manifest as clinical signs (observable by a clinician) and symptoms (experienced by the patient).

5.1 Bone Marrow Suppression (Myelosuppression): Many anticancer drugs damage the bone marrow, where blood cells are produced. This leads to fewer red blood cells, white blood cells and platelets. As a result, patients may feel very tired (anemia), get infections easily (low white blood cells) or bleed or bruise more than usual (low platelets).

5.2 Nausea and Vomiting: Chemotherapy often causes nausea and vomiting by affecting the part of the brain that controls these functions. Some patients may feel sick right after treatment, while others may have delayed symptoms. Loss of appetite and weight loss are also common.

5.3 Fatigue (Tiredness): Fatigue is one of the most common side effects of cancer treatment. Patients may feel extremely tired even if they rest. This can happen due to low blood counts, poor nutrition or the stress of treatment.

5.4 Digestive Problems: Some drugs irritate the stomach and intestines. This may lead to diarrhea, constipation, stomach cramps or bloating. Drinking fluids and eating light foods can help manage these symptoms.

6. Evolution of Anticancer Therapies:

The development of anticancer treatments has evolved significantly over time. Initially, traditional chemotherapy was the mainstay of cancer therapy, targeting rapidly dividing cancer cells. Although effective, chemotherapy often harms healthy cells as well, leading to severe side effects. To overcome this limitation, researchers developed targeted therapies, which focus on specific molecular abnormalities present in cancer cells. A key example is imatinib, used in chronic myeloid leukemia, which marked a turning point in cancer treatment by offering precision with fewer side effects. In recent years, the field has further advanced with the introduction of immunotherapy, a revolutionary strategy that empowers the body's immune system to recognize and destroy cancer cells. Immune checkpoint inhibitors like pembrolizumab and nivolumab block proteins (such as PD-1) that prevent immune cells from attacking tumors. This approach not only improves survival rates in various cancers but also represents a deeper understanding of the dynamic interaction between cancer and the immune system. As a result, modern cancer therapy continues to move towards more personalized, effective and less toxic treatments.

7. Challenges and Limitations:

Despite remarkable progress in anticancer drug development, several challenges remain. One of the most critical issues is drug resistance, many cancers that initially respond to treatment eventually become resistant, leading to therapy failure. Understanding the biological mechanisms behind resistance is essential for designing better drugs and treatment strategies. One promising approach is the use of combination therapies, where multiple agents target different cancer pathways simultaneously, reducing the chances of resistance. Another major limitation is the side effects associated with anticancer drugs. Traditional chemotherapy, for example, is known to cause significant toxicity, including nausea, fatigue and immune suppression, which severely affect patients' quality of life. Although newer therapies are designed to be more selective and less toxic, side effects remain a major concern. Continued research is focused on developing treatments that are not only more effective but also safer and more tolerable for patients.

8. Nanotechnology in Cancer Therapy:

Nanotechnology has emerged as a transformative approach in oncology, offering new strategies for the diagnosis, treatment and monitoring of cancer. It involves the use of nanoscale materials, typically ranging from 1 to 100 nanometers, to design drug delivery systems that can overcome many limitations of conventional therapies. In cancer treatment, nanoparticles can be engineered to specifically target tumor tissues by exploiting features like the enhanced permeability and retention

(EPR) effect or by attaching ligands that recognize tumor-specific markers. This targeted delivery enhances the concentration of therapeutic agents at the tumor site, thereby increasing efficacy while reducing systemic toxicity and side effects. Examples include liposomes carrying doxorubicin (as in Doxil), gold nanoparticles used in photothermal therapy and polymeric micelles for hydrophobic drug delivery. Additionally, some nanoparticles are multifunctional, combining therapeutic and diagnostic capabilities (termed "theranostics"), allowing real-time imaging and treatment monitoring. Despite promising outcomes, challenges such as nanoparticle stability, immune response and large-scale production need to be addressed. Nevertheless, nanotechnology holds significant potential in making cancer treatment more precise, personalized and effective.

9. Conclusions:

Modern anticancer drug therapy has progressed significantly, evolving from traditional chemotherapy, which, while effective, often causes severe side effects due to its non-selective targeting of rapidly dividing cells, to more precise and personalized approaches. Targeted therapies like imatinib have improved outcomes by focusing on specific molecular pathways involved in cancer progression, while immunotherapies such as nivolumab and pembrolizumab have revolutionized treatment by activating the body's immune system to recognize and destroy cancer cells. Additionally, nanotechnology has introduced innovative drug delivery systems that enhance specificity, reduce toxicity and enable combined therapeutic and diagnostic (theranostic) capabilities. Despite these advances, challenges such as drug resistance, side effects, high costs and unequal access remain significant hurdles. Ongoing research into combination therapies, personalized medicine and novel delivery platforms holds promise for overcoming these limitations and improving patient outcomes. Thus, the evolution of anticancer therapies reflects not only technological innovation but also a deeper understanding of cancer biology, offering new hope for more effective and less toxic treatment strategies in the future.

References:

1. Siegel, R. L., Miller, K. D., & Jemal, A. (2024). *Cancer statistics, 2024*. **CA: A Cancer Journal for Clinicians, 74**(1), 7–33. https://doi.org/10.3322/caac.21763
2. World Health Organization (WHO). (2022). *Cancer Fact Sheet*. Retrieved from: https://www.who.int/news-room/fact-sheets/detail/cancer
3. Bingham SA, Hughes R, Cross AJ. Effect of white versus red meat on endogenous N-nitrosation in the human colon and further evidence of a dose response. *J Nutr.* 2002;132:3522S–3525S.
4. Hogg N. Red meat and colon cancer: heme proteins and nitrite in the gut. A commentary on diet-induced endogenous formation of nitroso compounds in the GI tract. *Free Radic Biol Med.* 2007;43(8):1037–1039. doi:10.1016/j.freeradbiomed.2007.07.006
5. Rodriguez C, McCullough ML, Mondul AM, Jacobs EJ, Chao A, Patel AV, et al. Meat consumption among Black and White men and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev.* 2006;15(2):211–216. doi:10.1158/1055-9965.EPI-05-0614
6. Capp J-P, Aliaga B, Pancaldi V. Evidence of epigenetic oncogenesis: a turning point in cancer research. *ArXiv.* 2024 Nov 21
7. Garcia-Closas R, Garcia-Closas M, Kogevinas M, Malats N, Silverman D, Serra C, et al. Food, nutrient and heterocyclic amine intake and the risk of bladder cancer. *Eur J Cancer.* 2007;43(11):1731–1740. doi:10.1016/j.ejca.2007.05.007
8. Tappel A. Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. *Med Hypotheses.* 2007;68(3):562–564. doi:10.1016/j.mehy.2006.08.025
9. O'Hanlon LH. High meat consumption linked to gastric-cancer risk. *Lancet Oncol.* 2006;7(4):287. doi:10.1016/S1470-2045(06)70638-6

10. Toporcov TN, Antunes JL, Tavares MR. Fat food habitual intake and risk of oral cancer. *Oral Oncol.* 2004;40(9):925–931. doi:10.1016/j.oraloncology.2004.04.007
11. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66(1):7–30. doi:10.3322/caac.21332
12. Ungvari Z, Fekete M, Varga P, Lehoczki A, Munkácsy G, Fekete JT, et al. Association between red and processed meat consumption and colorectal cancer risk: a comprehensive meta-analysis of prospective studies. *GeroScience.* 2025 Apr; 47: 5123–5140. doi:10.1007/s11357-025-01646-1
13. Aizawa K, Liu C, Tang S, et al. Tobacco carcinogen induces both lung cancer and non-alcoholic steatohepatitis and hepatocellular carcinomas in ferrets which can be attenuated by lycopene supplementation. *Int J Cancer.* 2016;139(6):1171–1181.
14. Matlashewski G, Lamb P, Pim D, Peacock J, Crawford L, Benchimol S. Isolation and characterization of a human p53 cDNA clone: expression of the human p53 gene. *EMBO J.* 1984;3(13):3257–3262.
15. National Cancer Institute. (2023). *Cancer Types by Body Location and System*. https://www.cancer.gov/types
16. American Cancer Society. (2023). *What Is Sarcoma?* https://www.cancer.org/cancer/sarcoma.html
17. National Cancer Institute. (2022). *Leukemia- Patient Version*. https://www.cancer.gov/types/leukemia
18. National Cancer Institute. (2022). *Lymphoma- Patient Version*. https://www.cancer.gov/types/lymphoma
19. National Cancer Institute. (2023). *Germ Cell Tumors- Patient Version*. https://www.cancer.gov/types/germ-cell
20. Pizzo, P.A., & Poplack, D.G. (2015). *Principles and Practice of Pediatric Oncology* (7th ed.). Philadelphia: Wolters Kluwer.
21. Emadi, A., Jones, R. J., & Brodsky, R. A. (2009). Cyclophosphamide and cancer: golden anniversary. *Nature Reviews Clinical Oncology*, 6(11), 638–647. https://doi.org/10.1038/nrclinonc.2009.146
22. Carvalho, C., Santos, R. X., Cardoso, S., Correia, S., Oliveira, P. J., Santos, M. S., & Moreira, P. I. (2009). Doxorubicin: The good, the bad and the ugly effect. *Current Medicinal Chemistry*, 16(25), 3267–3285.https://doi.org/10.2174/092986709788803312
23. Dasari, S., & Tchounwou, P. B. (2014). Cisplatin in cancer therapy: Molecular mechanisms of action. *European Journal of Pharmacology*, 740, 364–378. https://doi.org/10.1016/j.ejphar.2014.07.025
24. Weaver, B. A. (2014). How Taxol/paclitaxel kills cancer cells. *Molecular Biology of the Cell*, 25(18), 2677–2681. https://doi.org/10.1091/mbc.e14-04-0916
25. Zahreddine, H., & Borden, K. L. (2013). Mechanisms and insights into drug resistance in cancer. *Frontiers in Pharmacology*, 4, 28. https://doi.org/10.3389/fphar.2013.00028
26. Postow, M. A., Sidlow, R., & Hellmann, M. D. (2018). Immune-related adverse events associated with immune checkpoint blockade. *New England Journal of Medicine*, 378(2), 158–168. https://doi.org/10.1056/NEJMra1703481
27. Sharma, P., & Allison, J. P. (2015). The future of immune checkpoint therapy. *Science*, 348(6230), 56–61. https://doi.org/10.1126/science.aaa8172
28. Ferrara, N., Hillan, K. J., & Novotny, W. (2005). Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy. *Biochemical and Biophysical Research Communications*, 333(2), 328–335. https://doi.org/10.1016/j.bbrc.2005.05.132
29. Stopeck, A. T., et al. (2010). Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *Journal of Clinical Oncology*, 28(35), 5132–5139. https://doi.org/10.1200/JCO.2010.29.7101
30. Shi, J., Kantoff, P. W., Wooster, R., & Farokhzad, O. C. (2017). Cancer nanomedicine: progress, challenges and opportunities. *Nature Reviews Cancer*, 17(1), 20–37. https://doi.org/10.1038/nrc.2016.108