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Review Article

A Comprehensive Review of Cancer: Types, Pathophysiology, Diagnosis and Treatments

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Abstract

Cancer is a complex and multifaceted disease that affects millions of people worldwide. Despite significant advances in our understanding of the biology of cancer, it remains one of the leading causes of death globally. This review aims to provide a comprehensive overview of the current state of knowledge on cancer, including its causes, diagnosis, and treatment options for various types of cancer including breast, gastric, pancreatic, oral, prostate, gallbladder, colorectal, thyroid, and ovarian cancer. The pathophysiology of cancer involves genetic and epigenetic changes, inflammation and cell adhesion. Inflammation plays a crucial role in cancer development and progression, and immunotherapy has emerged as a promising treatment approach. Furthermore, Current treatment options for cancer include surgery, chemotherapy, radiation therapy, immunotherapy, and gene therapy.

Keywords: Cancer, Breast cancer, Radiation Therapy, epigenetic Therapy, Nanotechnology.

INTRODUCTION:

Cancer is a disease of the genome that is both mysterious and terrifying. It is defined by a genomic instability in which many point mutations build up and structural changes take place during the tumor's evolution.[1,2] Cancer is a hereditary condition. One significant event in the early phases of tumor formation is the manifestation of oncogenesis.[3] Human cells that have, in a sense, gotten away with it and been recruited and partially changed into pathogenic organisms or tumor building blocks are its agents of destruction.[1] It is commonly known that inflammatory alterations and the tissue microenvironment directly affect the survival of tumor growth.[4] Over the past century, we have made remarkable progress in understanding the biology of cancer. Technological and conceptual advancements in a number of areas, such as massive next-generation sequencing, the inclusion of "omic" sciences, high-resolution microscopy, molecular immunology, flow cytometry, individual cell analysis and sequencing, new cell culture techniques, and the creation of animal models, have been particularly responsible for this progress in recent decades.[5] In oncology, personalized (or precision) medicine is based on the concept that tumors differ from one another and that an individual's response to treatment may vary depending on their lifestyle, environment, and genetic profile.[6] Chronic inflammatory reactions are essential for the development of inflammation-associated cancers, such as gastric cancer linked to Helicobacter pylori (H. pylori), hepatocellular carcinoma linked to the hepatitis virus, and colon cancer linked to colitis.[7] The therapeutic effectiveness of many medications is limited by therapy resistance, and chemoresistance in particular, which leads to relapse and metastasis, according to data from multiple studies.[8] Cancer has a significant impact on nations of all financial levels. Early detection, better treatment, and a decline in the incidence of known risk factors are all helping to lower the rates of many malignancies in Western nations.[9]

TYPES:

1. **Breast cancer:** Breast cancer is one of the many common malignant tumors that harm women. Numerous internal and external factors can contribute to the development and occurrence of breast cancer.[10] Rudolf Virchow postulated a physiological connection between inflammation and

cancer in 1863. He postulated that persistent inflammatory areas were the source of cancer. It is now clear that inflammatory cells significantly influence the growth of tumors. Leukocyte infiltration, the expression of cytokines like tumor necrosis factor (TNF) or IL-1, chemokines like CCL2 and CXCL8, active tissue remodeling, and neo-angiogenesis are some of the pro-tumor effects of inflammatory cells. Macrophages linked to tumors have a crucial role in controlling the relationship between inflammation and cancer.[11] Depending on the related class (i.e., basal-like, Luminal A, Luminal B, HER2-amplified) and the state of molecular markers, distinct breast tumor subtypes receive different treatments. HER2 negative cancers that are positive for the estrogen receptor (ER) and/or progesterone receptor (PR) are usually treated with hormonal therapy as a first line of treatment. These tumors often have a better prognosis than those that are hormone receptor-negative. The American Society for Clinical Oncology does not prescribe a specific chemotherapeutic treatment plan for hormone-positive BC; however, platinum-based medications, taxanes, and anthracyclines are effective alternatives.[11] The risk of developing breast cancer increases with age. The majority of female breast cancer cases are identified between the ages of 50 and 69.[10]

2. **Gastric cancer:** Among lymphomas, sarcomas, gastrointestinal stromal tumors, and neuroendocrine tumors, gastric cancer is the most prevalent stomach cancer. The majority of cases of this diverse disease are gastric adenocarcinomas (GC), which present with a variety of characteristics. The cardia and the non-cardia GC are the two primary GC based on topographic locations.[12] Elevated risks of gastric cancer are consistently associated with alcohol consumption and smoking.[13] Proximal gastric (cardia) and distal gastric (non-cardia) are the two primary locations of gastric cancer.[14] Surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy are all part of the treatment options for stomach cancer. Chemotherapy and radiation therapy are frequently utilized as adjuvant or neoadjuvant therapies to improve results, but surgical resection is still the major treatment choice for localized disease.[13]

3. **Pancreatic cancer:** Usually discovered at an advanced stage, pancreatic cancer is resistant to most treatments, which lowers survival rates. An aging population and rising rates of obesity and pancreatitis, two risk factors for pancreatic cancer, are associated with a steadily rising incidence of the disease.[15] The most prevalent chronic liver disease in the world is metabolic dysfunction-associated steatotic liver disease (MASLD), which affects 68% of individuals with type 2 diabetes. However, nothing is known about pancreatic inflammation and fat infiltration in MASLD patients.[16] Cigarette smoking, diabetes mellitus, body mass index, alcohol, pancreatitis, allergies, and the role of the microbiome are all known risk factors for pancreatic cancer.[17]

4. **Oral cancer:** The most common type of cancer in these regions is head and neck cancer, which includes malignancies of the paranasal sinuses, larynx, nasal cavity, pharynx, orbital cavity, and lips. Squamous cell carcinoma (SCC) and cancers of the mouth, head, and neck are closely related. Oral papillomavirus infection (HPV infection) is the term used to describe the human papillomavirus infection that causes oral carcinogenesis.[18] From the first rough descriptions of oral neoplasms by a number of significant physicians and surgeons of ancient past civilizations to the current and developing approaches for treating them, oral cancer and its symptoms and signs have been observed and described by medicine since ancient times. All subsites of the oral cavity and oropharynx, as well as malignancies of the lip, are considered oral cancer.[19] Patients who receive treatment for early-stage oral cancer have better survival and quality of life rates, as well as a favorable prognosis. However, screening offers a chance for early diagnosis because early-stage malignancies are frequently asymptomatic and mimic benign diseases, which decreases the likelihood that the public will seek care.[20] Oral cancer (OC) and other chronic illnesses can significantly affect a person's quality of life. Malignant neoplasms in the oral cavity and oncological treatment frequently lead to reduced oral functions and cosmetic deformity because oral cavity structures execute crucial tasks such communication, mastication, swallowing, and salivation.[21] Men in their sixth and seventh decades of life are typically affected by oral cancer, and they are more likely to smoke and drink heavily. However, the prevalence of oral cancer in younger patients (less than 45 years old) has increased over the past few decades, rising from 3% to 5% in the 1970s and 1980s to almost 10% currently.[22]

5. **Prostate cancer:** Beneath the bladder and encircling the urethra is the male reproductive auxiliary organ known as the prostate gland. Contributing vital secretions to semen, which produce ejaculate and preserve sperm viability, is the primary role of the prostate. Most typically in the mid-to-late stage of life, the cells in the prostate gland can develop into tumors.[23] Men of all races and ethnicities are susceptible to prostate cancer, and because the disease is often detected late, the mortality rate is higher for those from lower socioeconomic backgrounds. An individual's genetic profile may play a role in prostate cancer, according to mounting evidence.[24] Hugh Hampton Young published the first significant description of radical prostatectomy using a perineal technique in Annals of Surgery in 1905, marking the beginning of the procedure's usage to treat prostate cancer.[25] For many years, research has been conducted on hereditary prostate cancer and a genetic component propensity to prostate cancer. Family inheritance is one of the most significant genetic risk factors for prostate

cancer. The relevance of hereditary prostate cancer has been established by both epidemiological and twin investigations.[24] With a transperineal approach lowering post-procedural sepsis rates, multimodal early detection using serum prostate-specific antigen (PSA) and multi parametric magnetic resonance imaging (mpMRI) has decreased the requirement for biopsy. More precise staging using PSMA positron emission tomography/computed tomography (PET/CT) prevents unnecessary local interventions, and active surveillance is now a treatment option for localized disease, lowering risks like radiation cystitis and proctitis, erectile dysfunction, and incontinence. When choosing individualized treatment, the patient's characteristics- such as their lifestyle, comorbid illnesses, and symptom profile are the main consideration.[26]

6. **Gallbladder cancer:** A global issue, gall bladder cancer (GBC) is more common in regions of the world where cholelithiasis is prevalent. The mortality rate for GBC is considerable because it is typically discovered at an advanced stage.[27] Along with intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (eCCA), perihilar cholangiocarcinoma (pCCA or Klatskin tumor), and distal cholangiocarcinoma (dCCA), gallbladder cancer (GBC) is classified as a subgroup of biliary tract cancer (BTC).[28] A primary care physician in the present day will inevitably meet a variety of disorders that can affect proper gallbladder functioning.[29] People all throughout the world, especially those who are at high risk of GBC, now urgently need access to reliable and helpful cancer prevention information in the current environment of varied and frequently contradicting health information. Public health campaigns that educate the public about the risk factors for GBC, including obesity, gallstones, chronic gallbladder inflammation, and factors that contribute to higher mortality rates, such as eating red meat, can help lower the incidence of GBC and improve the prognosis for those who have it.[30]

7. **Colorectal cancer:** Colorectal cancer (CRC), which includes colon and/or rectum cancer, is a serious health issue as the third most common diagnosed and second most deadly cancer worldwide.[31] Colon cancer is one of the most deadly cancers, spreading to the liver, lungs, ovaries, and other parts of the gastrointestinal system.[32] Due to the anatomical difficulties and the possibility of local recurrence, a more complicated algorithm is required to treat rectal cancer than colon cancer.[33] Men have a 25% greater incidence and mortality rate than women, and their 5- and 10-year survival rates are 65% and 58%, respectively. Asian Americans and Pacific Islanders have the lowest incidence and mortality rates of colorectal cancer (CRC), while non-Hispanic Blacks have the highest rates.[34] Nowadays, the most widely used CRC serum biomarker is carcinoembryonic antigen (CEA. Both the growing fetus and several cancer cell types produce the protein CEA. CEA levels can be increased in patients with colorectal cancer (CRC), but they are normally low in healthy individuals. Since CEA can also be high in people with other conditions, such as colon inflammation, it is not a precise biomarker for colorectal cancer. Nonetheless, it is a helpful biomarker for tracking the disease's course and recurrence in CRC patients.[35]

8. **Thyroid Cancer:** Thyroid cancer is the most common endocrine cancer. Thyroid cancer is originating from follicular epithelial cells or parafollicular cells. Follicular cells derived thyroid cancers are classified into 4 histological types: papillary thyroid cancer (PTC80-85%), follicular thyroid cancer (FTC10–15%), poorly differentiated thyroid cancer (PDTC,<2%), and anaplastic thyroid cancer (ATC,<2%).[36] Over the pasts several decades, the approach to the diagnosis and management of patients with follicular cell derived thyroid cancer has evolved based on improved classification of patients better matching clinical outcomes, as well as advances in imaging, laboratory, molecular technologies, and knowledge. While thyroid surgery, radioactive iodine therapy, and TSH suppression remain the main stays of treatment, this expansion of knowledge has enabled escalation of therapy for individuals diagnosed with low risk well differentiated thyroid cancer; better definition of treatment choices for patients with more aggressive disease; and improvedability to optimize treatments for patients with persistent and/ or progressive disease.[37] There are several known modifiable risk factors for thyroid cancer, however it's not apparent which of these factors is responsible for the rise in thyroid cancer incidence. Patient age, sex, radiation exposure, nutritional status, environmental contaminants, age/ethnicity, and family history comprise the majority of known or suspected risk variables.[38]

9. **Ovarian cancer:** Uterine cancer is the most common gynecologic cancer in the United States, affecting approximately 3.1% of women in their lifetime, compared to the relatively uncommon diagnosis of ovarian cancer.[39]

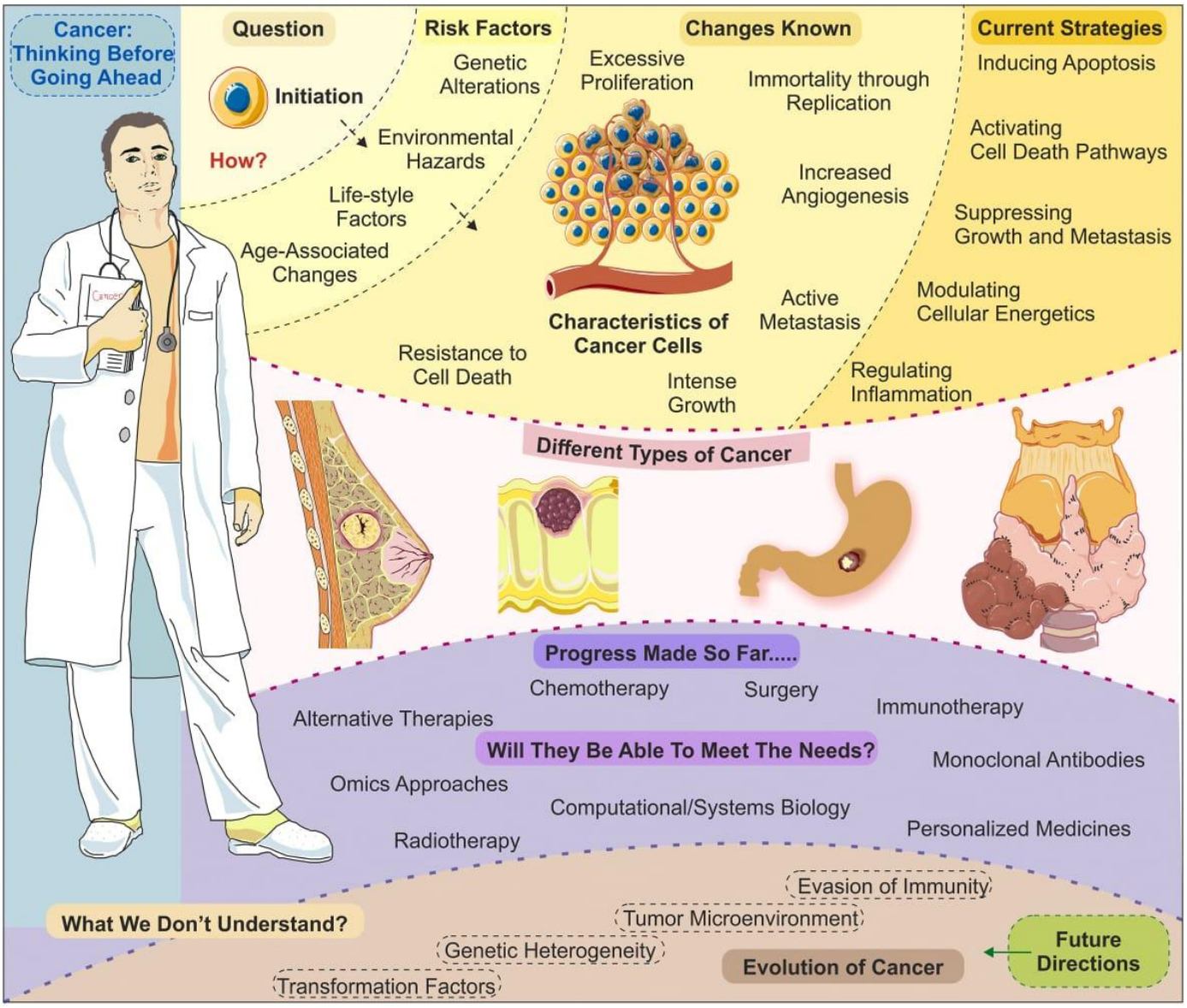

Figure 1: An overview of known, unknown, available therapeutics, and future directions of the cancer therapeutics.[4]

DESCRIPTION:

The primary underlying causes of cancer are depicted in the top panel, along with important risk factors, implicated processes, and current therapeutic and treatment development approaches. A few representative cancer forms are depicted in the center, out of the numerous that occur worldwide and cause a significant number of fatalities. The therapy approaches used globally to slow the progression of the disease are displayed in the lower subsections. On the other hand, the lowermost portion of figure number 2 indicates the few most difficult and little known aspects of tumor biology.[4]

PATHOPHYSIOLOGY OF CANCER:

Genetic and epigenetic changes in particular cells are the first signs of cancer, and some of these changes can spread and migrate to other organs.[5] Tumor virus infection of cells or modification of cellular proto-oncogenes are the two ways that oncogenes are activated.[3] An essential component of cancer pathophysiology is inflammation. Cancer can trigger an inflammatory response, and inflammation can promote the growth of cancer. In fact, innate immune cells are frequently found in tumors that are deemed immunologically cold due to the absence of an adaptive immune response.[40] Among the basic processes affecting the development of cancer, cell adhesion and metastasis are important participants. Cancer cells can attach to the extracellular matrix (ECM) more successfully because to these adhesion molecules. The dynamic interaction between the extracellular matrix and cancer cells not only promotes local invasion and tumor progression. However, it also sets up cancer cells for the later spread of the disease. When tumor cells move from the site of the tumor to other organs, this is known as metastasis.[41]

EPIDEMIOLOGY OF CANCER:

A colony of cells that proliferates more often than normal tissue, uncontrollably, and has the ability to invade and spread is referred to as a malignant tumor.[42] Evidence of cancer in early humans and hominins dating

back up to 1.8 million years has been discovered by a systematic evaluation of 154 paleopathological research.[43] Several groundbreaking articles from the early 1900s noted that particular jobs had high cancer rates. Work with infectious agents at this time yielded only modest outcomes that didn't seem to matter to people. Then, in the 1980s, groundbreaking evidence began to emerge showing that several viruses can also cause cancer in humans.[44] Multicellular organisms have had cancer for over 200 million years, and there is evidence that contemporary humans' ancestors had cancer for well over a million years.[1] According to the most recent data, cancer is still the second leading cause of death in the United States behind cardiovascular disease, despite a decline in mortality over the last ten years for both men and women.[42] Based on data released by the World Health Organization (WHO) in 2020, cancer is the second leading cause of mortality globally, accounting for 10 million fatalities.[5] Currently, one out of every six deaths is caused by a kind of cancer.[5]

CAUSES:

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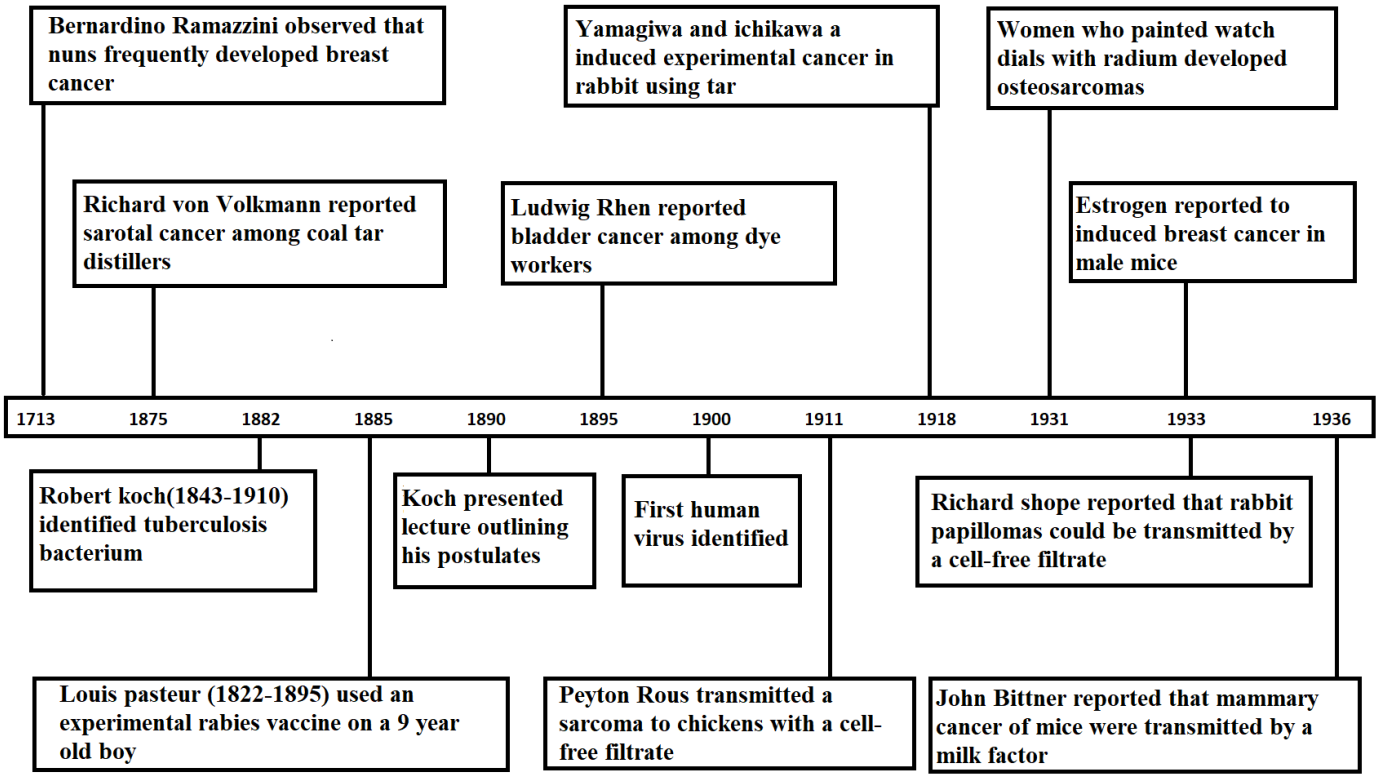

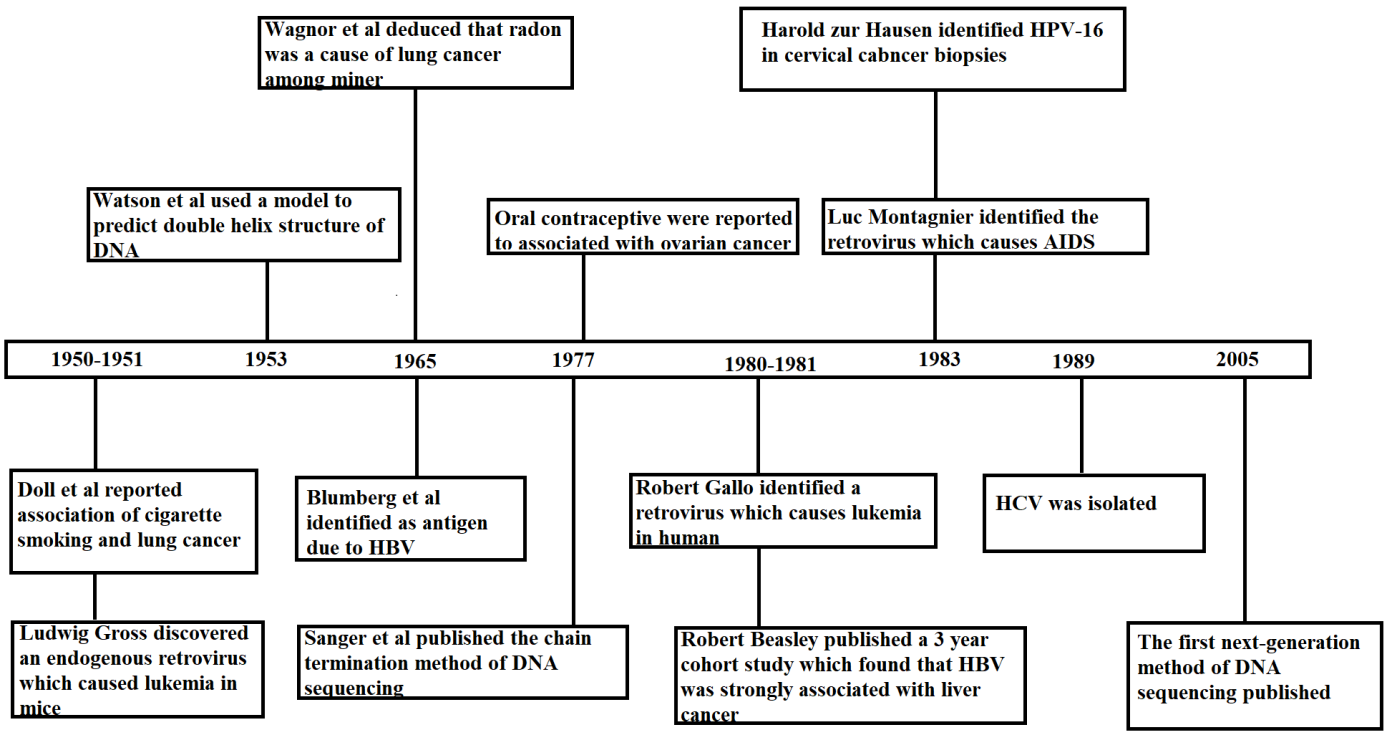

Figure 2: Some milestone publications concerning the causes of cancer, microbiology, and technology.[44]

TREATMENT:

Measures including tobacco restriction, immunization, early detection, and the encouragement of healthy lifestyles can prevent a significant percentage of malignancies.[9] The foundation of cancer treatment, and more especially the treatment of solid tumors, at the start of the 20th century was surgical tumor removal, which had been employed since antiquity in conjunction with other local control techniques like cauterization.[5] Personalized medicine has made it feasible to use quantifiable biomarkers in clinical settings. Suliman and colleagues work, which sought to correlate chemo-resistance with biological characteristics in patients with endometrial cancer (EC), is an example of individualized research.[6] The best source of anti-cancer medications is the kingdom of plants. Over 3,000 plant species have been used in cancer treatment and clinical studies to date, and about 30 distinct anti-cancer natural mixtures have been isolated from plants. [45] The development of relevant and modern cancer therapeutic approaches may help close the gaps in anticancer treatment. Meanwhile, a variety of modern medicines with intelligent features, flexible functions, and modification potential have been made available by the development of nanotechnology, material sciences, and biological sciences.[46]

IMMUNOTHERAPY:

The idea of immunotherapy is to target malignant cells specifically with one's own immune response.[47] As an alternative to targeting cancer stem cells (CSCs), immunotherapy has drawn a lot of attention due to its potential to treat and cure a variety of cancer types.[48] Traditional immunotherapy has been treating cancer for almost a century by using viral or bacterial infections to boost immune responses. When Virchow noticed that neoplastic tissues were frequently adorned with immune system leukocytes, he made the initial discovery of the link between tumors and inflammation as early as 1863.[49]

- **Multi-drug resistance:** Aldehydedehydrogenase (ALDH) could possibly be a selective marker for CSCs in lung cancer, head and neck squamous cell carcinoma, breast, bladder, and embryonal rhabdomyosarcoma.[48]
- **Gene therapy:** Using a variety of strategies that use oncolytic viruses to destroy malignant cells, boost immune responses against cancer cells, and inhibit cancer survival and supporting activities, gene therapy has enormous potential for treating cancer.[47]
- **Biopsy:** Only a biopsy can provide an accurate diagnosis of breast cancer. Removing tissues or cells from the patient's body for laboratory analysis is the aim of a biopsy. Whether or not cancer cells were found in the sample will be determined by the pathologist's report. Whether the lump is palpable that is, you can feel it or non-palpable that is, you cannot will determine the sort of biopsy that is done. The physician may utilize mammography or ultrasound to identify the area to be tested.[10]
- **The Anticancer Properties of Common Natural Flavonoids:** Derived from secondary metabolites, polyphenols are substances that are widely present in fruits, vegetables, and beverages and are known to have anticancer activities. Diphenylpropane (C6-C3-C6), the chemical structure of a natural flavonoid,

has a three-carbon ring in the middle and two aromatic rings at either corner, forming an oxygenated heterocyclic. Natural flavonoids have the most well-known biological actions, including hormone action, cardio-protection, bone resorption inhibition, and cancer prevention.[45]

- **Nanotechnology:** There are many restrictions that must be addressed in order to treat tumor tissue, which drives the growing interest in using nanomaterials.[49] Drug development and delivery have shown encouraging advances because to nanotechnology. Specifically, the use of nanoparticles in cancer treatment and diagnosis has advanced to the point where they can identify a single cancer cell and target it to deliver a treatment-related cargo. Traditional cancer treatment methods have adverse effects, and diagnostic techniques are costly and time-consuming. Because of their large surface charge, size, and shape, nanoparticles (NPs) like polymeric nanoparticles (nanogels, nanofibers, liposomes), metallic nanoparticles like goldNPs(GNPs), silver NPs (AgNP), calcium nanoparticles (CaNPs), carbon nanotubes (CNTs), graphene, and quantum dots (QDs) have transformed cancer diagnosis and treatment. Through their plasmon resonance capabilities, these nanoparticles can be functionalized with various natural molecules, such as antibodies, which aids in their targeted distribution and early cancer cell detection.[50]

- **Epigenetic Therapy:** Without altering the kind of nucleotide sequence, epigenetic therapies can cause changes in the expression of genes. New medications and treatments have been found by figuring out the epigenetic processes underlying malignancies. Histoneacetylation and DNA methylation pattern changes can be reversed by epigenetic mechanisms, which can also produce desired changes in the quantity of miRs. HDAC inhibitors and DNMT inhibitors work in concert. DNA methyltransferase inhibitors (DNMTIs), noncoding RNA-based treatments, and histonedeacetylase inhibitors (HDACIs) are examples of epigenetic medications.[51]

CONCLUSION:

Cancer is a complex and multifaceted disease that requires a comprehensive approach to prevention, diagnosis, and treatment. Recent advances in cancer research have improved our understanding of the causes and mechanisms of cancer development and progression. The development of personalized medicine, immunotherapy, and nanotechnology has opened up new avenues for cancer treatment. Natural compounds, such as flavonoids, and epigenetic therapies also hold promises for cancer prevention and treatment. However, despite these advances, cancer remains a significant challenge for global health. Further research is needed to overcome the challenges of cancer treatment, including multi-drug resistance and the need for more effective and targeted therapies. By continuing to advance our understanding of cancer biology and developing innovative approaches to cancer treatment, improving patient outcomes and ultimately reducing the burden of cancer on individuals and society.

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