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CANCER: A BLACK SPOT TO HUMAN RACE

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ABSTRACT

Cancer is a class of disease in which a group of cells display uncontrolled growth, invading adjacent tissues and sometimes metastasis or spreading to other locations in the body via lymph or blood. Cancer is a disease characterized by a shift in the control mechanisms that governs cell survival, proliferation and differentiation. The word cancer came from a Greek words karkinos to describe carcinoma tumors by a physician Hippocrates (460-370 B.C), but he was not the first to discover this disease. Some of the earliest evidence of human bone cancer was found in mummies in ancient Egypt and in ancient manuscripts dates about 1600 B.C. The world's oldest recorded case of breast cancer hails from ancient Egypt in 1500 BC and it was recorded that there was no treatment for the cancer, only palliative treatment. According to inscriptions, surface tumors were surgically removed in a similar manner as they are removed today.

KEYWORD: Cancer, metastasis, karkinos, treatment, physician.

INTRODUCTION

Cancer develops when normal cells in a particular part of the body begin to grow out of control. There are different types of cancers; all types of cancer cells continue to grow, divide and re-divide instead of dying and form new abnormal cells. Some types of cancer cells often travel to other parts of the body through blood circulation or lymph vessels (metastasis), where they begin to grow. For example when a breast cancer cell spread to liver through blood circulation, the cancer is still called as breast cancer, not a liver cancer. Generally cancer cells develop from normal cells due to damage of DNA. Most of the time when ever DNA was damaged, the body is able to repair it, unfortunately in cancer cells, damaged DNA is not repaired. People can also inherit damaged DNA from parents, which accounts for inherited cancers. Many times though, a person's DNA becomes damaged by exposure to something in the environment, like smoking. There also have been numerous developments regarding possible external factors influencing cancer in parallel with the research and experiences focusing on clinical diagnosis and treatment of patients. In a book published in 1700, Bernardino Ramazzini(1633–1714) listed a series of possible occupation-related diseases, including a virtual absence of cervical cancer, but relatively high incidence of breast cancer, among nuns. In 1761, John Hill (1716–1775) published "Cautions against the Immoderate Use of Snuff." Percivall Pott (1714–1788) described in 1775 how chimney sweeps suffered illness caused by soot, and Katsusaburo Yamagiwa (1863–1930) and Koichi Ichikawa (1888–1948) published in 1915 how they induced cancer in laboratory animals by applying tar to rabbit skin.[1]

During the 1930s, clinicians began to suspect in earnest that there was a linkage between smoking and several types of cancer, and this was subsequently confirmed in 1950. Thereafter, other substances added to the list of carcinogenic substances included asbestos. Its use started to become banned in an increasing number of settings starting in the 1980s. Benzene, a chemical widely used as a solvent and once an ingredient in an aftershave lotion, was discovered to be carcinogenic and became classified as such in 1987. In addition, a growing number of studies indicated a link between melanoma and excessive sun exposure (1970s–1990s), and a 2000 study linked excessive household radon exposure to lung cancer. Starting in 1998, the National Health Institute issued treatment guidelines highlighting the obesity–cancer link.[2]

Cancer generally forms as a solid tumor. Some cancers like leukemia (blood cancer) do not form tumors. Instead, leukemia cells involve the blood and blood forming organs and circulate through other tissues where they grow. Not all tumors are cancerous, some tumors are benign (non-cancerous). Benign tumors do not grow and are not life threatening. Different types of cancer cells can behave differently. The risk of developing many types of cancers can be reduced by changes in

lifestyle by quitting smoking and eating low fat diet. If cancer is identified in early stage it is easy to treat and may have better chances for living many years.

Cancer is not confined to humans; animals and other living organisms can get cancer. Below is a schematic that shows normal cell division and how when a cell is damaged or altered without repair to its system, the cell usually dies. Also shown is what occurs when such damaged or unrepaired cells do not die and become cancer cells and show uncontrolled division and growth -- a mass of cancer cells develop. Frequently, cancer cells can break away from this original mass of cells, travel through the blood and lymph systems, and lodge in other organs where they can again repeat the uncontrolled growth cycle. This process of cancer cells leaving an area and growing in another body area is termed metastatic spread. For example if breast cancer cells spread to a bone, it means that the individual has metastatic breast cancer to bone.[3]

The incidence of cancer and cancer types are influenced by many factors such as age, gender, diet, race, local environmental factors and genetics. Consequently, the incidence of cancer and cancer types vary depending on these variable factors. For example, the World Health Organization (WHO) provides the following general information about cancer worldwide.

- Cancer is a leading cause of death worldwide. It accounted for 8.2 million deaths (around 22% of all deaths not related to communicable diseases; most recent data from WHO).
- Lung, Liver, stomach, colon, and breast cancer cause the most cancer deaths each year.
- Deaths from cancer worldwide are projected to continue rising, with an estimated 13.1 million deaths in 2030 (about a 70% increase).[4]

TYPES OF CANCER

1) Carcinoma- It is a type of cancer that begins in skin and tissues that lines and covers internal organs such as skin, lung, and colon.
2) Sarcoma- It is a type that begins in bone, cartilage, fat, muscles, blood vessels and other connective tissues.
3) Leukemia- It is a cancer that starts in blood forming tissues such as bone marrow and causes large number of abnormal blood cells to be produced and enter in blood.
4) Lymphoma and Myeloma- It is a cancer that begins in cells of immune system that is T-cell and B-cell Lymphoma.
5) Central Nervous system cancers- Cancers that begins in tissues of brain and spinal cord. For example brain and spinal cord tumors, primitive neuroectodermal tumors.[5]

HISTORY OF CANCER

Cancer has been recorded in history since the Greco-Roman and Egyptian civilizations, with the evidence of skin, nose and breast cancers being recorded as long ago as 370 BC. The oldest known description and surgical treatment of cancer was discovered in Egypt and dates back to approximately 1600 BC. Archaeologists have found human remains dating several thousand years back from which specimens have been interpreted as consistent with cancer. Such is the case of a female skull from the Bronze Age (1900–1600) and Peruvian Inca skeletons from ca. 2,400 years ago. When it comes to written evidence, however, the oldest existing cases date from Egyptian papyri, such as the so-called Edwin Smith Papyrus from the 16th century or even earlier. In the 16th and 17th centuries, it became more acceptable for doctors to dissect bodies to discover the cause of death. With the widespread use of the microscope in the 18th century, it was discovered that the 'cancer poison' spread from the primary tumor through the lymph nodes to other sites ("metastasis"). This view of the disease was first formulated between 1871 and 1874.[6]

The use of surgery to treat cancer had poor results due to problems with hygiene. In the 19th century, asepsis improved surgical hygiene and the survival statistics went up. Hippocrates is also credited with the word cancer because he used the term karkinoma to describe ulcers or growths that appeared to be malignant tumors. The word means crab in the Greek language, and one interpretation is that Hippocrates might have associated the spreading forms of cancers with the shape of crab claws. Hippocrates's theory about cancer was to persist for more than 1,300 years and was based on his overall theory of the four types of body fluid, or humors, that a human body had. These were blood, phlegm, yellow bile, and black bile. A person was healthy when the humors were balanced. An excess of the black bile humor, however, was the cause of cancer. The surgical removal of the tumor became the primary treatment for cancer. The genetic basis of cancer was recognized in 1902.[7]

The Roman doctor Aulus Cornelius Celsus elaborated on the Hippocrates theory and divided cancers into different stages. He called the first stage cacoethes (malignant), and only this stage was receptive to treatment. The doctor and philosopher Claudius Galenus (130–200) introduced the Greek word onkos, meaning a bulk or a mass, for referring to a growth or a tumor that appeared to be malignant, and is thus credited as the originator of the term oncology. Within Arab medicine, there were also a series of doctors who made observations and recommendations regarding cancer, including Avicenna of Baghdad (980–1037), who observed that cancer, may destroy neighboring tissues.[8]

When Marie Curie and Pierre Curie discovered radiation at the end of the 19th century, they stumbled upon the first effective non-surgical cancer treatment. Approaching the 17th century, there were a number of theories contesting the humor theory, including hypotheses proposed by Zacutus Lusitani (1575–1642) and Nicholas Tulp (1593–1674), who published their

hypotheses in 1649 and 1652, respectively, that cancer was contagious based on observations of breast cancer cases within the same household. John Hunter (1728–1793) was the first to suggest possible predispositions to cancer like, for example, age, heredity, and even perhaps the climate.[9]

Xavier Bichat (1771–1802) contributed to scientific progress in a number of ways but is also known for his misleading theory published in 1800 proposing that blastema, a substance that he thought was formed from blood and lymphatic fluid, was the primary source of all cellular tissues. His view persevered as a universal theory on cancer during several subsequent decades.

One probable cause behind the lack of any significant progress regarding the treatment of cancer during especially the medieval period was that postmortem autopsies had been practiced on a very limited scale, mainly due to religious obstacles.[10]

Autopsies were, however, becoming more frequent by the 16th century and were part of the basis for the William Harvey (1578–1657) epoch-making treatise on blood circulation (1628). Later, the doctor and professor Giovanni Morgagni (1682–1771) focused for the first time in his 1769 treatise on the potential of systematic approaches toward pathology. During the 19th century, research took advantage of the findings made possible through the use of the modern microscope. Rudolf Virchow (1821–1902) has often been called the founder of cellular pathology and contributed to the understanding of tumors through a work titled Cellular Pathology(1858) as well as three comprehensive, albeit unfinished, illustrated volumes published between 1863 and 1867.[11]

According to Virchow's method, tissues that were removed by the surgeon could be examined thoroughly and a precise diagnosis of the cancer could be made. The pathological method thus provided a scientific basis for the study of cancer, and hospital staff and researchers could understand in a better way the damage that had happened to the patient as well as the options for more precise cancer surgery. This breakthrough meant in addition that a pathologist by way of using a microscope could inform about whether an operation had completely removed the tumor or not. Virchow's cellular theory is the basis of how cancer overall is understood today, but he built his treatise in part upon some of his immediate predecessors, such as Johannes Müller. Müller developed the blastema theory regarding the origin of cancer in 1838 by way of arguing that blastemas were budding cells and not lymph. He thus showed in part the way toward the understanding that cancer is made up of cells.[12]

Incidentally, significant progress occurred within the field of general surgery techniques from about the same time as these new cellular insights became widely known. Removal of tumors had been an option from ancient times, and continued to be so, but this approach faced a crucial dilemma. During surgery, the patient might die due to loss of blood or of excruciating pain, and the simple means of anesthesia that had been available, such as opium, were of limited reliability.[13] In 1846, John Collins Warren (1778–1856) and William T. G. Morton (1819–1868) used ether as a general anesthetic and performed a public demonstration of its effects when they removed a tumor from the jaw of a patient. Incidentally, the Japanese doctor Seishū Hanaoka (1760–1835) had performed more than 150 breast cancer operations from 1804 onward using a general anesthetic based on herbs, but this was unknown to the West due to Japan's closure policy of the times. The Warren and Morton operation, however, became quickly known and heralded the age of modern anesthetic techniques.[14] Furthermore, Joseph Lister (1827–1912) in Scotland applied the theories regarding germs proposed by Louis Pasteur (1822–1895) and announced in 1867 the practice of using disinfection during operations. One of the legendary surgeons of the times was William Stewart Halsted, who started to perform a radical form of operation for breast cancer in 1891.[15]

Attempting to remove all tracks of the cancer in order to avoid recurrence, Halsted removed the breast and its underlying muscles as well as the lymph nodes under the arm during his operations. Sometime after Virchow's publications, Stephen Paget (1814–1899) proposed in 1889 a new theory, called the seed and soil theory, regarding the spreading of cancer. It was similar to theories proposed by Karl Thiersch (1822–1895), showing that cancer spreading is due to the spread of the malignant cells and not the work of some kind of unidentified fluid, and by Ernst Fuchs (1851–1930) in 1882, regarding the predisposition of an organ to be the recipient of specific growths. Paget, however, constructed a more comprehensive theory, and it eventually turned out to constitute the foundation for theories regarding how cancers spread from one organ to another, the process of metastasis. Paget thought that metastatic tumor cells were like a kind of seed that spread throughout the body by way of the bloodstream but settled only in a "soil," an organ, which it finds compatible. Virchow himself incidentally thought, incorrectly, that some kind of chronic irritation was the cause of cancer and that cancers spread like a liquid.[16]

The late 19th and early 20th centuries were also a period of several technological breakthroughs regarding the diagnosis and treatment of cancers. In 1895, the physicist Wilhelm Conrad Röntgen (1845–1923) discovered electromagnetic rays later known as X-rays or Röntgen rays. The first technical manual of X-ray radiology was published, and the first diagnostic radiology units were installed in European and U.S. hospitals already in 1896. Shortly thereafter, two different research groups, including Marie Sklodowska Curie (1867–1934), Pierre

Curie (1859–1906), and Antoine H. Becquerel (1852–1908) discovered the radioactivity of uranium.[17]

Marie Sklodowska Curie is credited with the isolation of the highly potent radioactive substance that got the name radium, and the Curies used the term radio-active for the first time in a paper published in 1898. Radium was thereafter introduced as a treatment for cancers, with skin cancer being the first type. In the first years and decades of therapeutic radiation, the approach was referred to as brachytherapy, meaning that radioactive material was implanted inside or next to tumors. Cancer cells thereby received radiation from a very close range. Later, the approach became refined in a number of ways, including the first electron linear accelerator designed for radiation therapy in 1943, capable of more precise targeting of tumor cells at the same time, so healthy tissue had a better chance of being left unharmed.[18]

The era of cancer chemotherapy began in the 1940s with the first use of nitrogen mustards and folic acid antagonist drugs. With the success of combination chemotherapy and the discovery of many new agents, all cancers could be treated, if only one could administer the correct combination of drugs, at the correct doses and at the correct intervals. The first experimental usage of chemicals within cancer treatment used nitrogen mustard, based on wartime observations of the potential effects of the gas.[19]

Nitrogen mustard was approved by the Food and Drug Administration (FDA) on March 15, 1949, as the first chemotherapy drug approved for cancer because it was found that it kills cancer cells. It was temporarily effective in managing some cancers, but another avenue of research from about the same time proved to be a broader venture into chemotherapy. Sidney Farber (1903–1973), who was a pediatric doctor, used the substance aminopterin, based on folic acid, a kind of vitamin B. As vividly described in Siddhartha Mukherjee's 2010 book, aminopterin was synthesized by Farber and Yellapragada Subbarow (1895–1948), and Farber subsequently used it from 1947 onward for children with leukemia with remarkable results.[20]

From the 1960s onward, it became common to combine two or more drugs within a combination chemotherapy approach. Furthermore, so-called adjuvant therapy, in which both chemotherapy and surgery were used in treatment, was gradually being developed as chemotherapy was expected to function in the most effective way in the cases where tumors were small. Most commonly, surgery would occur first and chemotherapy second, but chemotherapy given before surgery could also be an option in order to shrink down the tumor and allow for easier surgical removal. During the 1980s, several new types of antinausea drugs were marketed in order to alleviate the side effects of chemotherapy.[21]

When it comes to diagnosis, Otto H. Warburg (1883–1970) had discovered already in 1929 that cancer cells use glucose at a higher rate than normal tissues. This principle lies behind the positron emission tomography (PET) scanning technique developed from the 1950s onward. The first and relatively simple version of a PET scanning device was invented in 1950, whereas the first complete scanner was invented as recently as 2001.[22]

Building on ultrasound technology developed during World War II, the University of Minnesota reported in 1952 that ultrasonic echography made it possible to distinguish between benign and malignant breast tumors. The first scanner for routine usage started operation in 1958. Geoffrey N. Hounsfield (1919–2004) developed during the 1960s several prototypes of the computed tomography (CT) scanner. CT scanning made it possible to differentiate very subtle differences in tissue densities.[23] The publication of the structure of DNA in 1953 had a profound impact on both the treatment and diagnosis of cancer. Renato Dulbecco (1914–2012) discovered the interaction between tumor viruses and the genetic material of cells, and he received the 1975 Nobel Prize together with Howard M. Temin (1934–1994), David Baltimore (1938), who had shown that information in the synthesis of proteins essential to such oncogenesis could be transmitted from RNA, the nucleic acid synthesizing protein within a cell, to DNA. During the 1970s, methods for sequencing DNA were developed and laid the foundation for identifying and targeting mutated genes and DNA damage that causes cancer. Subsequently, in 1976, Michael Bishop and Harold E. Varmus discovered that different forms of cancer all arise from a common genetic mechanism involving specific genes present in normal cells, the cellular origin of the retroviral oncogenes mechanism.[24]

A series of discoveries followed, including the discovery of p53, the most frequently mutated gene in connection with cancer, in 1979, and the discovery of the C-erbB2 cancer-causing gene in mice in 1981, followed by discovery of HER2, the human version of this gene, in 1985.In 1975, Georges J. F. Köhler (1946–1995) and César Milstein (1927–2002) discovered a technique for producing monoclonal antibodies for use against defined proteins. The first commercially available such monoclonal antibody drug was approved by the FDA in 1997 (rituximab, for treating non-Hodgkin's lymphoma). The following year, the first humanized antibody targeting a cancer-related molecular marker received FDA approval. This antibody was for the treatment of HER2-positive metastatic breast cancer. Shortly thereafter, the first drug specifically developed to target the molecular problem that causes a particular type of cancer was approved by the FDA: the 2001 approval of imatinib used in treatment of chronic myeloid leukemia. Still another important event was the 2004 approval of bevacizumab, used for the treatment of metastatic colorectal cancer. Bevacizumab is unique in that it targets the vascular endothelial growth factor (VEGF).

VEGF is a factor that causes the growth or proliferation of blood vessels. The drug thereby became the first antiangiogenic agent ever approved by the FDA and is also counted as the first of a new generation of targeted drugs. It was later approved for use in the treatment of, for example, non–small cell lung cancer and breast cancer.[25]

There are some cases where there may be a known genetic predisposition toward certain types of cancer. These include the 1990s discovery of the BRCA1 and BRCA2 genes, genes that cause some breast cancers. The first evidence that the BRCA1 gene existed was provided by the University of California Berkeley in 1990, and it was cloned by scientists at the University of Utah in 1994. The BRCA2 gene was discovered in 1994 at the Institute of Cancer Research in the UK. Other genes linked to cancers that run in families include genes related to cancers of the colon, rectum, kidney, ovary, thyroid, and pancreas and skin melanoma. Such familial cancers are far less common than spontaneous cancers, but the knowledge may be used to identify, through genetic screening, people who have a higher risk of developing particular forms of cancer.[26]

CAUSES OF CANCER

Tobacco: Use of tobacco has been identified by WHO as the major preventable cause of death of humankind. Tobacco smoking causes cancer of the lung and other organs and is the most intensively investigated environmental cause of cancer. Most information available involves the burden of smoking-related disease in more developed countries. The people most immediately exposed to the products of tobacco combustion are the users, that is, active smokers. The prevalence of smoking varies throughout the world and is subject to change. More than 70% of men born in Europe and North America during the first decades of the 20th century smoked during some time of their life, but this proportion has decreased in more recent times. A different pattern is seen in women. In contrast to male smoking rates, smoking by women only became prevalent in the second half of the 20th century. While in some countries, such as the United Kingdom, the proportion of women who smoke has started to decrease in recent years, in most industrialized countries this proportion is still increasing.[27] Tobacco smoking is the main known cause of human cancer-related death worldwide. Smoking most commonly causes lung cancer. Intensity of exposure to tobacco smoke is determined by the smoking device used (cigarette, cigar, pipe, hookah, etc.) and, for any one method, may be determined by the "depth" of inhalation. Smoking of black tobacco cigarettes represents a greater risk for most tobacco-related cancers than smoking of blond cigarettes. Similarly, filtered and low-tar cigarettes entail a lower risk for most tobacco-related cancers than unfiltered and high-tar cigarettes. In addition to lung cancer, smoking causes cancers of the larynx, oral cavity, pharynx, oesophagus, pancreas, kidney and bladder.[28]

Alcohol consumption, exposure to asbestos and exposure to ionizing radiation interact with smoking in determining risk of some cancers. For alcohol drinking and smoking, risks for cancer of the larynx, oesophagus and oral cavity increase multiplicatively in relation to the respective risks generated by either exposure in the absence of the other. For individuals exposed to both asbestos and tobacco smoke (for example, insulation workers who smoke), risk of lung cancer is also increased multiplicatively. As tobacco is the most important human carcinogen, elucidation of mechanisms which result in cancer among humans exposed to tobacco smoke provides an important means for assessing some preventive options, and may be relevant to the prevention of other environmentally induced cancer.[29]

Mainstream smoke (the material inhaled by smokers) is an aerosol including approximately 4,000 specific chemicals and containing 1010 particles per ml. The particulate matter (tar) is made up of some 3,500 compounds, the most abundant being nicotine (0.1-2.0 mg per cigarette) and also including most of the polycyclic aromatic hydrocarbons occurring in the smoke.[30] Another class of carcinogens represented in tobacco smoke is N-nitroso compounds, particularly including the nitroso derivatives of nicotine and nornicotine.[31] Chemicals such as aromatic amines, benzene and heavy metals, independently established as carcinogenic for humans, are present in tobacco smoke. The molecular genetics of tobacco smoke induced lung and other cancers are being progressively elucidated. An increasing number of genes are implicated as being relevant to a carcinogenic outcome.[32] The degree of current understanding is exemplified by studies of the pattern of mutation in the p53 gene. When comparison is made of particular mutation frequencies in lung cancers from smokers and non-smokers, differences are evident. Using relevant experimental systems, mutations evident in smokers are attributable, at least in part, to the miscoding caused by the binding of some polycyclic aromatic hydrocarbons to DNA.[33]

Occupational Exposure: The first reports of associations between risk of cancer and employment in particular occupations appeared during the 18th century (scrotal cancer among chimney sweeps. The IARC Monographs on the Evaluation of Carcinogenic Risks to Humans evaluate data relevant to the carcinogenic hazard to humans as a consequence of exposure to particular chemical, physical and biological agents and mixtures.[34]

Accordingly, evidence of carcinogenicity for most known or suspected occupational carcinogens has been evaluated in the IARC Monographs programme. At present, 25 chemicals, groups of chemicals or mixtures for which exposures are mostly occupational, have been established as human carcinogens.[35],[36]

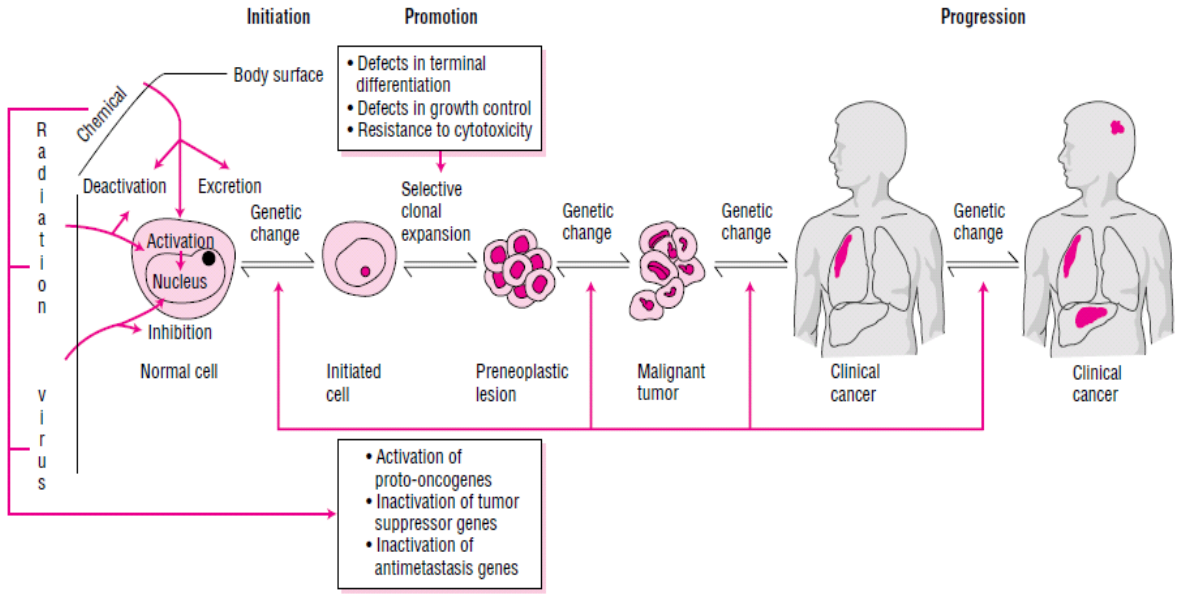
Environmental Pollutant: The present context, "environmental pollution" refers to a specific subset of cancer-causing environmental factors; namely, contaminants of air water and soil. One characteristic of environmental pollutants is that individuals lack control over their level of exposure. The carcinogenic pollutants for which most information is available include asbestos, toxic agents in urban air, indoor air pollutants and chlorination by-products and other contaminants of drinking water. Asbestos is one of the best characterized causes of human cancer in an occupational context. The carcinogenic hazard associated with inhalation of asbestos dust has been recognized since the 1950s.[36] Non-occupational exposure to asbestos may occur domestically and as a consequence of localized pollution. Cohabitants of asbestos workers may be exposed to dust brought home on clothes. The installation, degradation, removal and repair of asbestos-containing products in the context of household maintenance represent another mode of domestic exposure.[37]

Medicinal Drugs: Modern medicine has at its disposal hundreds of drugs, many of which are essential for the effective treatment of an enormous range of human diseases. A small fraction of such drugs has been found to have carcinogenicity to humans as a side-effect. This is most likely for some drugs that must be given at high doses or for prolonged periods. Drugs that have been found to be carcinogenic to humans include some antineoplastic drugs and drug combinations[38], certain hormones and hormone antagonists[39, 40], some immune suppressants and a small number of miscellaneous agents. Some antineoplastic agents and combined drug therapies have caused secondary cancer in patients.[41]

Radiation: Exposure to ionizing radiation is unavoidable. Humans are exposed both to Xrays and γ rays from natural sources (including cosmic radiation and radioactivity present in rocks and soil) and, typically to a much lower extent, from man-made sources. On average, for a member of the general public, the greatest contribution comes from medical X-rays and the use of radiopharmaceuticals, with lower doses from fallout from weapons testing, nuclear accidents (such as Chernobyl), and accidental and routine releases from nuclear installations. Medical exposures occur both in the diagnosis (e.g. radiography) of diseases and injuries and in the treatment (e.g. radiotherapy) of cancer and of some benign diseases. Occupational exposure to ionizing radiation occurs in a number of jobs, including the nuclear industry and medicine. Airline pilots and crew are exposed to cosmic radiation.[42], [43]

Pathogenesis of Cancer

Cancer pathogenesis is traceable back to DNA mutations that impact cell growth and metastasis. Substances that cause DNA mutations are known as mutagens, and mutagens that cause cancers are known as carcinogens. The mechanism by which cancers occur is incompletely understood. Cancer or neoplasm is thought to develop from a cell in which the normal mechanism for control of growth and proliferation are altered. The concept of carcinogenesis is a multistage process that is genetically regulated as shown in figure. The first step in this process is *initiation*, which requires exposure of normal cells to carcinogenic substances. These carcinogens produce genetic damage, if not repaired results in irreversible cellular mutations. This mutated cell has an altered response to its environment giving it the potential to develop into a clonal population of neoplastic cells. During the second phase, known as *promotion*, carcinogens or other factors alter the environment to favor growth of the mutated cell population over normal cells. The primary difference between initiation and promotion is that promotion is a reversible process. At some point, the mutated cell becomes cancerous (*conversion* or *transformation*). The final stage of neoplastic growth, called *progression*, involves further genetic changes leading to increased cell proliferation. The critical elements of this phase include tumor invasion into local tissues and the development of metastasis. Substances that may act as carcinogens or initiators include chemical, physical and biologic agents. Exposure to chemicals may occur by virtue of occupational and environmental means, as well as lifestyle habits. Physical agents that act as carcinogens include ionizing radiation and ultraviolet light. These types of radiation induce mutations by forming free radicals that damage DNA and other cellular components. Viruses are biologic agents that are associated with certain cancers.



Pathogenesis of Cancer[44]

Genetic Bases of Cancer

There are two major classes of genes involved in carcinogenesis: Oncogenes and Tumor-suppressor genes. Oncogenes develop from normal genes, called protooncogenes. Proto oncogenes are present in all cells and are essential regulators of normal cellular function including the cell cycle. Genetic alteration of the proto-oncogene through point mutation, chromosomal rearrangement or gene amplification activates the oncogene. These genetic alterations may be caused by carcinogenic agents such as radiation, chemicals, or viruses (somatic mutations) or they may be inherited (germ-line mutations). Once activated, the oncogene produces either excessive amounts of the normal gene product or an abnormal gene product. The result is dysregulation of normal cell growth and proliferation, which imparts a distinct growth advantage to the cell and increases the probability of neoplastic transformation.

In contrast, tumor-suppressor genes regulate and inhibit inappropriate cellular growth and proliferation. Gene loss or mutation results in loss of control over normal cell growth.[45] Two common examples of tumor-suppressor genes are the retinoblastoma and *p53* genes. Mutation of *p53* is one of the most common genetic changes associated with cancer. The normal gene product of *p53* is responsible for negative regulation of the cell cycle, allowing the cell cycle to halt for repairs, corrections and responses to other external signals. Inactivation of *p53* removes this checkpoint, allowing mutations to occur. Another group of genes important in carcinogenesis is the DNA repair genes. The normal function of these genes is to repair DNA that is damaged by environmental factors or errors in DNA that occur during replication. If not corrected, these errors can result in mutations that activate oncogenes or inactivate tumor suppressor genes. As more mutations in the genome occur, the risk for malignant transformation increases. The DNA repair genes have been classified as tumor suppressor genes, because a loss in their function results in increased risk for carcinogenesis. Oncogenes and tumor-suppressor genes provide the stimulatory and inhibitory signals that ultimately regulate the cell cycle.[46]

TREATMENT OF CANCER

There are many types of cancer treatment. The types of treatment that you receive will depend on the type of cancer you have and how advanced it is.

1. **SURGERY-** When used to treat cancer, surgery is a procedure in which a surgeon removes cancer from your body. Surgeons often use small, thin knives, called scalpels, and other sharp tools to cut your body during surgery.

Cryosurgery

Cryosurgery is a type of treatment in which extreme cold produced by liquid nitrogen or argon gas is used to destroy abnormal tissue. Cryosurgery may be used to treat early-stage skin cancer, retinoblastoma, and precancerous growths on the skin and cervix. Cryosurgery is also called cryotherapy.[47]

2. **RADIATION THERAPY-** Radiation therapy is a type of cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumors. There are two main types of radiation therapy, external beam and internal.

External Beam Radiation Therapy

External beam radiation therapy comes from a machine that aims radiation at your cancer. The machine is large and may be noisy. It does not touch you, but can move around you, sending radiation to a part of your body from many directions.

Internal Radiation Therapy
Internal radiation therapy is a treatment in which a source of radiation is put inside your body. The radiation source can be solid or liquid.

Internal radiation therapy with a solid source is called brachy therapy. In this type of treatment, seeds, ribbons, or capsules that contain a radiation source are placed in your body, in or near the tumor.[48]

3. CHEMOTHERAPY- Chemotherapy is a type of cancer treatment that uses drugs to kill cancer cells. Chemotherapy may be given in many ways. Some common ways include.

Oral: The chemotherapy comes in pills, capsules, or liquids that you swallow.

Intravenous(IV):The chemotherapy goes directly into a vein.

Injection: The chemotherapy is given by a shot in a muscle in your arm, thigh, or hip, or right under the skin in the fatty part of your arm, leg, or belly.

Intrathecal: The chemotherapy is injected into the space between the layers of tissue that cover the brain and spinal cord.

Intraperitoneal (IP): The chemotherapy goes directly into the peritoneal cavity, which is the area in your body that contains organs such as your intestines, stomach, and liver.

Intra-arterial (IA): The chemotherapy is injected directly into the artery that leads to the cancer.

Topical: The chemotherapy comes in a cream that you rub onto your skin.[49]

4. IMMUNOTHERAPY- Immunotherapy is a type of treatment that helps your immune system fight cancer. Several types of immunotherapy are used to treat cancer. These treatments can either help the immune system attack the cancer directly or stimulate the immune system in a more general way. Types of immunotherapy that help the immune system act directly against the cancer include.

Checkpoint inhibitors, which are drugs that help the immune system, respond more strongly to a tumor.

Adoptive cell transfer, which is a treatment that attempts to boost the natural ability of your T cells to fight cancer.[50]

5. **TARGETED THERAPY-** Targeted therapy is a type of cancer treatment that targets the changes in cancer cells that help them grow, divide, and spread. Most targeted therapies help treat cancer by interfering with specific proteins that help tumors grow and spread throughout the body. They treat cancer in many different ways. They can: help the immune system destroy cancer cells, stop cancer cells from growing, stop signals that help form blood vessels, deliver cell-killing substances to cancer cells, cause cancer cell death.[51]
6. **HORMONE THERAPY-** Hormone therapy is a treatment that slows or stops the growth of breast and prostate cancers that use hormones to grow.[52]
7. **STEM CELL TRANSPLANT-** Stem cell transplants are procedures that restore blood-forming stem cells in cancer patients who have had their destroyed by very high doses of chemotherapy or radiation therapy.[53]
8. **PRECISION MEDICINES-** Precision medicine helps doctors select treatments that are most likely to help patients based on a genetic understanding of their disease.[54]

CONCLUSION

In the present review article, it can be concluded that with the advancement of technology, newer and efficient methods and instruments has been developed to cure or inhibit cancer of all forms, but still a lot of research work and effort has to be made to irradicate cancer from its roots. Newer techniques and chemotherapeutic methodologies are not able to completely treat cancer of all forms.

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