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A Review on Various Causes of Cancer

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ABSTRACT: Cancer is the abnormal proliferation of tissues of the organs of the body. It has been responsible for large number of deaths all over the world. It is the result of unwanted and non-remedial mutations caused by carcinogens in smoke or produced from alcohol intake. Improper diet and lack of physical exercise can also be the indirect causes of cancer. Some cancers are caused by improper and excessive release of hormones. The exposure to radiations and tiny particles of asbestos have been major contributors for these carcinogenic mutations and carcinomas. A few types of cancers like breast cancers, colorectal cancers are known to be hereditary. The chronic infection of the epithelial wall of the stomach with *Helicobacter pylori* and gastric cancer are interlinked. The Hepatitis viruses especially Hepatitis B and Hepatitis C infections lead to liver carcinoma.

KEYWORDS: Cancer, Carcinogenesis, infections, Mutations, Smoke, Asbestos

I. INTRODUCTION

Cancer is the irregular and uncontrolled cell division resulting in abnormal growth of tissues. Cancer is a generic term for large group of diseases or malfunctioning of tissues that can affect any part of the body. Other terms used for cancer can be malignant tumours, neoplasms, carcinogenesis, oncogenesis or tumorigenesis. Cell division is a physiological process that occurs in almost all tissues and under a variety of circumstances. Normally, the balance between proliferation and programmed cell death in the form of apoptosis is maintained to ensure the integrity of tissues and organs. According to the prevailing accepted theory of carcinogenesis (The somatic mutation theory), mutations and epimutations in DNA that lead to cancer disrupt these orderly processes by disrupting the programming of regulating the processes and upsetting the normal balance between proliferation and cell death.

Random mistakes in normal DNA replication may result in cancer causing mutations [1]. A series of several mutations to certain classes of genes is usually required before a normal cell transforms into a cancer cell [2][3][4]. Only certain mutations lead to cancer whereas majority do not. Mostly, cancers are related to environment lifestyle or behavioural exposures[5]. The term environmental refers to everything outside the human body that interacts with humans[6]. As such the environment is not limited to the biophysical environment like exposure to air pollution, but also it includes lifestyle, economic and behavioural factors[7].

II. RELATED WORK

It is probably impossible to prove the particular and specific reason being the cause of cancer in the any individual because most cancers have multiple causes. Cancer is generally not contagious in humans though it can be caused by onco-viruses and cancer bacteria. By knowing a vast number of causes of cancer potentially about 30% of cancers can be avoided. Pollution due to tobacco smoke is responsible for 20% of cancer cases. 20% of cancers are due to infections such as Hepatitis B, Hepatitis C and Papilloma virus[8]. Nearly 5-10% of cancers are due to genetic defects inherited from parents[9]. Ageing is considered a risk factor, and this is explained by the observation that many molecular and cellular changes are involved, which may accumulate during the ageing process and collectively lead to cancer. About 10% of cancer risks are due to obesity, poor diet, lack of physical activity and alcohol consumption [10]. Other factors include exposure to ionising and non-ionising radiations and environmental pollutants [11].

A. Tobacco as cause of cancer

Many forms of cancer are associated with tobacco chewing and smoking[12]. Smoking cigarettes is the cause of about 80% of lung cancer[13]. WHO estimates that each year tobacco causes 6 million deaths, (about 10 % of all deaths) 600,000 of which are the cases of passive smoking. Smoke or any other burnt organic matter may contain many

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carcinogens. The lung cancer due to carcinogens of smoke may take upto 20 years to develop. The males are predominantly at major risk as smoking habit is more prevalent in males than in females. Cigarette smoke contains about 90 known carcinogens[14]. The following are some of the most potent carcinogens:

A.1. Polycyclic Aromatic Hydrocarbons(PAH)

PAH are tar compounds, toxic in their normal form and become even more toxic in liver. These PAH are hydrophobic in nature, don't dissolve in water, thus it becomes difficult for the body metabolism to excrete them out. To make PAH water soluble, liver produces an enzyme called Cytochrome P450. This enzyme gives additional oxygen to PAH turning them into mutagenic epoxides which are more soluble but very reactive[15]. The first PAH identified as carcinogen in tobacco was Benzopyrene. The Benzopyrene gets converted into Benzopyrene diol epoxide and then gets permanently attached to nuclear DNA, which may either kill the cell or cause a genetic mutation.

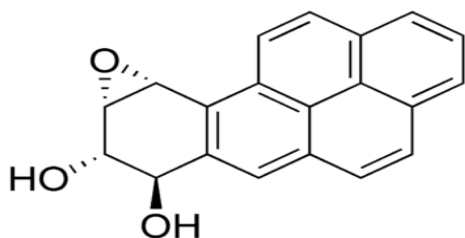


Fig. 1.1. Benzopyrene diol epoxide

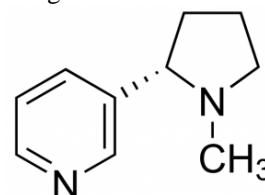


Fig. 1.2. Nicotine

A.2. Acrolein

Acrolein is abundant in smoke. It gives an acrid smell and an irritating lachrymatory effect and is a major contributor to the carcinogenicity. Acrolein is an electrophilic alkylating agent and permanently binds to DNA base guanine. The Acrolein-guanine adduct induces mutations during DNA copying and causes cancer. The carcinogenicity of acrolein has been difficult to study by animal experimentation because it has such a toxicity that it tends to kill the animals before they develop cancer[16]

A.3. Nitrosamines

Nitrosamines are a group of carcinogenic compounds found in the cigarette smoke but not in the uncured tobacco leaves. These are formed on the flue-cured tobacco leaves during the curing process by a chemical reaction between nicotine and other compounds contained in the uncured leaves and various oxides of nitrogen found in all combustion gases. Switching to indirect fire curing has been shown to reduce nitrosamine levels to less than 0.1ppm [17].

A.4. Radioactive carcinogens in tobacco smoke

Tobacco and tobacco smoke has been found to contain the radioactive carcinogens like Polonium-210 and Lead-210. The experimentally measured levels being 0.0263- 0.036PCi(0.97-1.33mBq)[18][19]. Research by NCAR radiochemist Ed Martells suggested that radioactive compounds in cigarette smoke are deposited in "hotspots" where bronchial tubes branch. The damage to the protective epithelial tissue from smoking only increases the prolonged retention of insoluble Polonium-210 compounds produced from burning tobacco. Martell estimated that a carcinogenic radiation dose of 80-100n rads is delivered to the lung tissue of most smokers who die of lung cancer[20].

A 1999 review of tobacco smoke carcinogens published in the journal of National Cancer Institute states that "levels of Polonium-210 in tobacco smoke are not believed to be great enough to significantly impact lung cancer in smokers" [21]. In 2011 Hecht has also stated that the levels of Polonium-210 in cigarette smoke are probably too low to be involved in lung cancer induction[22].

A.5. Nicotine

Nicotine present in tobacco smoke is highly addictive psychoactive chemical compound. When tobacco is smoked most of the nicotine is pyrolyzed. The amount of nicotine absorbed by the body from smoke depends upon many factors like type of smoke, pressure of smoke, temperature of smoke and concentration of smoke. There is a formation of hormone (a MAO inhibitor) from acetaldehyde in cigarette smoke which seems to play an important role in nicotine addiction probably by facilitating dopamine release in the nucleus acumbensin response to nicotine stimuli [23]. The carcinogenicity of nicotine is still not ascertained. Nicotine is however found to inhibit apoptosis, therefore accelerating existing cancers[24]. NNK, a nicotine derivative can also be carcinogenic.

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A.6. Chewing tobacco

Chewing tobacco causes cancer of mouth and throat. Oral and spit tobacco increases the risk of leukoplakia a precursor of oral cancer[25].

A.7. Dipping tobacco

Users of dipping tobacco are believed to face less risk of cancer than the smokers but are still at greater risk such as increased rate of atherosclerosis

B. Alcohol as cause of cancer

International agency for Research on Cancer (IARC) has regarded alcoholic beverages as group 1 carcinogenic agents. Alcohol is the cause of cancer of breast, Colo rectum, larynx, liver, oesophagus, oral cavity, pharynx and pancreas [26]. A study in Australia (2009) found that 2100 Australians die from alcohol related cancer[27]. In Europe, a 2011 study found that one out of ten cancers in men and one out of thirty-three cancers in women were caused by alcohol intake[28][29]. The breakdown product of alcohol is acetaldehyde which is produced in liver. The liver normally eliminates 99% of acetaldehyde but the 1% which remains in liver for longer periods is said to be the cause of cancer as a consequence of defect in the gene for alcohol dehydrogenase, liver and the upper gastrointestinal tract being more at risk[20].

B.1. Local carcinogenic effects of alcohol

The tissues in direct contact with ingested alcohol like oral cavity, pharynx, oesophagus, etc are at higher risk of cancer. Recent evidences have suggested that the cytotoxic effect of ethanol on the epithelial cells lining the oral cavity, pharynx and oesophagus activates the division of the stem cells located in deeper layers of mucosa to replace the dead cells. Everytime stem cells divide, they become exposed to unavoidable errors associated with cell division (e.g. Mutations arising during DNA replication and chromosomal alterations occurring during mitosis) and also become highly invulnerable to the genotoxic activity of DNA damaging agents (e.g. Acetaldehyde and tobacco carcinogens). The local cytotoxic effect of ethanol may also explain the known synergistic effect of alcohol use as the risk of these cancers[31].

B.2. Epithelial mesenchymal transitions

A study found that alcohol stimulates the epithelial mesenchymal transition (EMT) in which the ordinary cancer cells change into more aggressive form and begin to spread throughout the body [32].

B.3. Effect of alcohol on established cancer

It is found that alcohol intake influences more on tumour growth of hepatocellular carcinoma in patients with type C cirrhosis [33]. In a study where higher amount of alcohol was given to mice it was found that the alcohol intake accelerated the cancer growth by speeding bodyfat loss and depressing immune system[34].

C. Cancer due to diet and physical inactivity

About 14-20% of all cancer deaths are associated directly or indirectly with excess bodyweight and physical inactivity [35]. The physical inactivity contributes to cancer through its effect on body weight and negative effects on immune system and endocrine system. Diets low in vegetables fruits whole grains and high in processed or red meats are linked more with cancer. A high salt diet for prolonged periods causes gastric cancer.

D. Infections and cancer

About 18% cancer deaths are due to infectious diseases. These proportions vary in different regions of the world. African countries suffer 20% deaths. While the developed countries suffer 10% [36]. Viruses are the major contributors while bacteria and parasites may also have an effect. The virus causing cancer is called as oncovirus. These viruses are human papilloma viruses (cause cervical carcinoma), Epstein-Barr virus (β -cell lympho proliferative disease and nasopharyngeal carcinoma), Hepatitis B and Hepatitis C viruses (Hepatocellular carcinoma), Kaposi's Sarcoma, Herpe virus (Kaposi's Sarcoma and primary effusion lymphoma) and human T cell leukemia virus-I(T-Cell leukemias). Bacterial infection can also increase the risk of cancer as seen in Helicobacter pylori-induced gastric carcinoma[37].

The parasitic infections including Schistosoma haematobium (squamous cell carcinoma of the bladder), liver flukes Opisthorchis viverrini and clonorchiasis (cholangio carcinoma) are equally associated with development of cancer[38].

E. Radiation induced cancer

Both ionising and non-ionising UV radiation exposure leads to cancer[36]. The non-melanoma skin cancer is caused by non-ionizing UV radiations. The radiations can cause cancer in almost all body parts of living beings at any age and may take several years to develop. The radiation induced solid tumours may take about years and 40 years to clinically manifest. Radiation induced leukemias typically require 2-10 years to appear. Persons with nevoid basal cell carcinoma

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syndrome or retinoblastomas are more susceptible to cancer from radiation exposure. Children and adolescents are more prone to radiation induced leukemia. Low dose exposures such as living near a nuclear power plant have no or very little effects on cancer development. Radiation is a more potent source of cancer when it combines with other cancer causing agents like radon gas and tobacco smoking.

The ionising radiations hit the molecules within cells randomly. It may break down the chromosome resulting abnormal number of chromosomes, may inactivate one or more genes or the part of genes or may delete DNA sequence and may cause chromosome translocations or abnormalities. The three independent stages are the morphological changes to the cell, acquiring cellular immortality (losing normal life limiting cell regulatory processes) and adaptations that favour formation of tumour. Medical use of ionizing radiations is a growing source of radiation induced cancer. Ionizing radiations may be used to treat other cancers, but this may in some cases induce second form of cancer [39]. The most common forms of skin cancer - The melanoma and malignancies are the result of prolonged exposure to ultraviolet radiations [40]. World Health Organization's international agency for research on cancer has stated that non-ionizing radio frequency radiation from mobile phones can be carcinogenic [41]. However, recent studies have not confirmed this fact so far [42].

F. Cancer by exposure to Asbestos and other physical agents

Prolonged exposure to asbestos has been found to be the cause of mesothelioma which is a cancer of serous membrane surrounding the lungs. The other physical agents which can cause cancer when inhaled as tiny particles include wolestonides, attapulgit, glass wool, rock wool, non-fibrous particulate materials such as powdered metallic cobalt, nickel, crystalline silica (quartz), crystobalite, tridymite [43]. The long-term application of hot objects to the body, repeated burns on the same part of the body may induce skin cancer. Frequently drinking, scalding hot tea may cause oesophageal cancer. Similarly, repeated injuries to the same tissue may cause cell proliferation and carcinogenic mutation [44].

G. Hormones and cancer

Hormones are the cause of sex related cancers such as cancer of breast, endometrium, prostate, ovary and testis. It is observed that daughters of women with breast cancer have significantly higher levels of estrogen and progesterone than the daughters of women with no cancer. These higher levels of hormones are the cause of higher risk of cancer. Likewise, men of African ancestry have higher levels of testosterone than the men of European ancestry and have more chances of prostate cancer. Men of Asian ancestry have lowest levels of testosterone activating androstane-diol glucuronide and have least number of cases of prostate cancer. Women who take hormone replacement therapy are at higher risk. The people who exercise for more than the average have lower levels of these hormones and are at least risk [45].

H. Hereditary transmission of cancer

Larger proportion of cancers are not transmitted from parents to offsprings i.e. these are normally sporadic cancers. But studies have revealed that less than 0.3% population are carriers of the genetic mutations, which may be the cause of cancer. The inherited mutations in the genes BRCA-I and BRCA-II have more than 75% risk of breast cancer and ovarian cancer [46]. About 3% of the people may have hereditary non-polyposis colorectal cancer [47].

III. CONCLUSION

In this review article, an attempt has been made to give a glimpse of various causes of cancer. The cancer has been a great concern and imparts significant risk and pain to the mankind. The proper and adequate understanding of the facts about cancer causing phenomena and thereon proliferation can minimize or even undo the fatal effects of carcinogenesis. Many forms of the cancer are associated with the carcinogenic particles in tobacco smoke or chewing of tobacco. The control on tobacco use thus can prevent the carcinogenic action. The inhaling of tiny particles of asbestos, glass wool and other harmful pollutants by the industrial workers and the population living nearby the industrial area are at significant risk of developing lung and tracheal cancers. By making use of proper chimneys and condensing the smoke at outlet, the chances of harmful effects of pollutants get minimised. The exposure of body tissues to ionizing and non-ionizing radiations (radon, ultraviolet radiations, etc) for longer periods are the major cause of skin cancers. Even certain viral and bacterial infections may cause uncontrolled cell proliferations leading to carcinoma. The hereditary transmission of genetic changes especially in case of breast cancer though in less percentage is engulfing the lifespan of affected mankind. Various treatments for cancer including drugs, natural products, radiations are in operation but till date none has proven as potentially effective especially in later stages of cancer. No

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doubt as of now cancer cannot be cured effectively but it can be prevented to a greater extent. The role of various social and related organizations in making the people aware of the basic causes of cancer can definitely reduce the number of cancer patients and even can be kept away.

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