Even in the twenty first century, after science has conquered many frontiers and earned many laurels, the word cancer sends a chill down our spine. Despite notable advances in the therapy of specific types of cancer, the disease still comes as a messenger of death. Concerted efforts of world’s leading doctors could not prevent Steve Jobs’ death at only fifty six, and such examples are plentiful.

Though medical science is at a loss when it confronts a case of cancer with metastasis (last stage), scientists now have a reasonably clear understanding of the process through which a cancerous cell is generated. Cancer is a conglomerate of many diseases each with distinct character of its own, but all are cancers and arise from same cause. Knowing these causes and avoiding the avoidable causes can help to reduce the burden of cancer appreciably, though not fully. We try to discuss some of the known facts of cancer here.

**A Normal Cell Cycle, Interplay of Growth Factors and Growth Inhibitors**

The human body is a society of cells of many types. The individual cells grow, multiply and many also die during the life time of the individual. They interact and cooperate with each other, all with a common goal, the welfare of the person. It is a very selfless society with no struggle for existence. So cells in our body grow and multiply only when they are told to do so. Initially, after conception this occurs very fast, when cells double by thirty minutes. The rate of course slows down gradually, and in an adult, barring some specific tissues like blood or skin, most cells normally do not grow. Thus knowing when to grow and how much is a lesson that is ingrained in the eukaryotic cells.

The control is achieved through growth signals or factors, which start a series of biochemical reactions, and the signal, from its place of origin (which may be extracellular or intracellular) travels through the cytoplasm, reaches the nucleus and induces expression of genes whose products are necessary for DNA replication and cell division.

![Figure 1. The Cell Cycle (Not to scale)](image-url)

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**IS CANCER PREVENTABLE?**

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* This review article on cancer traces genesis of cancer at cellular level, then discusses causative agents of cancer in food, occupation and environment and the role of genes in cancer susceptibility. Finally it compares cancer rates in different countries to indicate the kind of lifestyle that would encourage reduction in cancer incidence. Foods that help to protect from cancer are also discussed.
Growth cycle of a eukaryotic cell can be schematically represented as in figure 1. \( G_0 \) is the resting phase where the non-growing cell stays. When a growth signal comes, the cell enters the cycle. During \( G_1 \) it synthesizes the ingredients necessary for DNA synthesis. After the preparations are complete, the cell enters S phase when DNA replicates. After replication is complete, and the DNA content of the cell has doubled, G2 phase begins and the cell prepares for cell division. Actual cell division takes place during mitosis (M), and two daughter cells separate, each to follow its own destiny.

There are also genes which serve as watchdogs and prevent untimely cell cycling when the cell is not ready with all the ingredients necessary for a successful replication or cell division cycle. If there is damage in the DNA, the DNA synthesis is immediately halted and efforts are made to repair the damage. In case such damage occurs during G2, and the situation is beyond repair, the system will induce suicide (termed apoptosis) in the cell and get rid of the cell with damaged DNA, as individual cells live only to foster the survival and well-being of the whole organism.

**Mutation May Cause Improper Cycling**

Despite the precautions, sometimes a cell becomes rogue and starts growing when it has not been asked to do so and disregards signals of the watchdogs, the process of malignancy starts in. This occurs because the DNA in which all the necessary information about the biochemical reactions that take place in the cell, what protein is to be synthesized, at which time and how much, is written in the language of deoxynucleotides, the building blocks of DNA, has changed or mutated.

Mutation in DNA can have many effects. It may decrease or increase the rate of production of a protein, may produce an altered protein or altogether stop its production. Sometimes a mutation does not have any effect at all. While the effects are definitely harmful when present in a person’s germ line (the DNA of the sperm or egg), mutations in a somatic cell (all cells of a person’s body except the germ cells) are usually inconsequential. Any tissue is made up of many cells and one going astray does not affect the function of the tissue as a whole. However if the mutation changes the growth properties of the cell, and induces inappropriate growth, trouble starts and we get tumors, which, if left untreated ultimately lead to cancer.

The cancer causing changes can be of two types, either the growth promoting genes (proto onco genes) overwork or the growth inhibiting (tumor suppressor) genes fail to do their work. Either way, the equilibrium between the growth promoters and inhibitors is tilted in favor of the promoters. It takes mutations of at least four to five genes in a single cell for malignancy to develop. Cancer tissue from experimental animals, as well as patients has been tested for presence of such mutations and many genes associated with cancer have been identified\(^1\).

**Mutagenesis and its Evaluation**

Mutations may be considered as the main cause of cancer. In fact to test the carcinogenic potential of a compound, the ability of the compound to induce mutations in bacteria is examined, and it is considered enough proof of carcinogenicity of the compound. Some compounds, known to be carcinogenic fail this test though. These compounds become active carcinogen inside the body, after the initial steps of their metabolism. So an in vitro step to mimic the metabolism is employed to make the test full-proof.

Why do mutations occur? There are many reasons behind mutagenesis, and it can never be eliminated completely. In fact such permanence in the genome content of any species is quite harmful in the long run. The species will lose its ability to evolve, change and cope with the changing environments. Hence the process of generation of a new individual or a new cell, all involve some steps to ensure diversity. So, DNA replication is associated with spontaneous mutations, and meiosis with sister chromatid exchange.

**Man-made Carcinogens**

However, along with these natural processes, civilization has produced many other avenues of exposure to mutagens/carcinogens. Radioactive materials are highly carcinogenic, though proponents of nuclear arms tried to deny it for a long time. There was a large increase in leukemia cases a few years after the atomic blasts in Japan, and the news was suppressed. Film actor John Wayne and friends attended the experimental blasts of nuclear warheads in the deserts of Nevada after the end of Second World War, to demonstrate how safe the blasts were! Each one of them developed cancer ultimately.

Fortunately world had been spared facing another nuclear warhead use till now. However the incidence of cancer increased appreciably in western countries in the years 1950-70. Certain incidences demonstrated that exposure to apparently harmless and inactive substances may lead to carcinogenesis.
A group of workers received a large exposure of Vinyl chloride monomers, the constituents of PVC or plastic and ultimately each of them developed cancer. Now we know that Vinyl chloride monomers are highly carcinogenic. This incident sensitized scientists about the carcinogenic potential of man made compounds which were being developed and used at a large scale. The (Ames’) test described earlier is one of the many tests developed at that time to test for carcinogenicity of new compounds and has been accepted widely for its simplicity and elegance.

Nevertheless, modern day people knowingly or unknowingly expose themselves to many carcinogens. A large majority of cancers are possibly caused by environmental factors. Of these pollutants like cigarette smoke, diet and occupational exposure are the main categories.

**Tobacco is Responsible for Largest Number of Cancers**

The first and foremost culprit is of course tobacco and tobacco products. Worldwide it is the most preventable cause of cancer. It produces cancer of lung, mouth, lips, nasal cavity and sinuses, larynx, pharynx, esophagus, stomach, pancreas, kidney, bladder, uterus, cervix, colon, rectum, ovary and acute myeloid leukemia. In United States, 1 in 5 deaths is due to tobacco related cancer. In India 42% of male and 18% of female cancer lethality stems from tobacco. Oral cancer incidence in India is more frequent than lung cancer due to use of Gutkha and Khaini, by twice or more. Betel quid with or without tobacco products and areca nut has also been listed as human carcinogen by the International agency for research on cancer.

Tobacco use is a dispensable habit. However, we expose ourselves to many other confirmed carcinogens through food, environmental exposure or due to occupational reasons. Our lifestyle also contributes significantly by modulating the level of hormones in the body, which play a significant role in carcinogenesis.

**Carcinogens in Our Food**

Excessive use of animal protein, particularly red meat has been linked with high incidence of colorectal cancers in Americans. Japanese people, who eat mostly fish and rice, have low colorectal cancer incidences in Japan. However, when they emigrate to US, they acquire higher cancer rate along with the meat rich diet of their adopted country. Some byproducts produced during cooking, notably burnt and brown material from heating protein during cooking of meat or fish is highly carcinogenic and such cooking though tasty should be avoided. Any charred food, from burnt popcorn to burnt toast is carcinogenic. Mutagens are more easily detectable in the urine of a smoker compared to a non smoker. Same is true for a person who has consumed a meal of fried bacon or pork. Excessive fat, particularly trans fat in fries and snack chips, excessive salt and spices in food, artificial sweetener like aspartame have been linked to carcinogenesis. Sodas for their high sugar content and harmful additives and excessive alcohol are also carcinogenic. Alcoholic beverages have acetaldehyde which is carcinogenic. Coffee in excess has been linked to cancer. From the list above it is apparent that many items in so called fast food are carcinogenic and consumption of such foods at regular basis should be avoided.

Analysis of soy sauce used in Chinese cooking detected carcinogenic chemicals 3-MPCD (3-monochloropropenal, 3-diol) and 3-MPCD 1, 3-DCP (1, 3-dichloropropane-2-ol) present at unacceptable level in more than 22% of tested samples. Chinese salted fish has also been listed. Chinese people have high rate of stomach and liver cancer. So, enjoy your Chinese, but not too often and avoid them during pregnancy.

Grains with fungal contamination are also a source of carcinogens and accounts for the high rate of liver cancer in some African and south east Asian countries, where high humidity and temperature make the grains susceptible to fungal contamination. The fungi produce a toxin Aflatoxin (Aspergillus flavus toxin) which after entering the body is metabolized in human liver into highly carcinogenic and reactive epoxide. Aflatoxin is very stable and is not destroyed even after cooking or autoclaving. So care should be taken for proper storage of food grains. Fungally contaminated peanut is another big source of Aflatoxin and should be avoided.

**The Good Foods**

Most of the mutagens act by producing DNA damaging compounds like oxygen radicals. Some foods, on the other hand act as anti mutagens or anti oxidants. They supply in ample quantity some compounds that are involved in detoxification of foreign compounds or xenobiotics in the body. Cauliflower, cabbage, broccoli, Brussels’ sprout, avocados, watermelon, peach tomato and peas are all anti mutagens. Some spices are also quite beneficial, like turmeric, cinnamon, cardamom, garlic, onion and red peppers. Low incidence of colon cancer in India and Pakistan is attributed to the regular use of turmeric in our food. These foods reduce carcinogenesis by reducing incidence of mutation in our cells\(^2\).
Lifestyle Related Causes of Cancer

Cancer is a disease of growth. So, agents that stimulate cell growth can expedite (promote) carcinogenesis in overexposed cells. Thus obesity is linked to cancer. Different hormones, which promote growth in certain tissues, promote cancer in those organs. Hormone replacement therapy for post menopausal women thus increases the risk of breast cancer. Estrogens from other sources are also harmful. Modern day dairies milk the cows even when they are heavily pregnant and the amount of estrogen in the milk is more than thirty times the normal value. A study comparing diet and cancer rates in forty two countries have shown that the rate of testicular cancer in men of age group 20 to 39 is strongly correlated to consumption of milk and cheese. As the hormone remains associated with the fat, drinking skimmed milk is an option that can be considered. Estrogen-progestogen oral contraceptives have been linked to breast cancer.

Wound healing involves cell growth and chance of mutation. So repeated wounding at one place is also a big risk factor. Such wounding in mouth caused by broken teeth leads to oral cancer.

Some microbial infections cause cancer in specific organs. Cervical cancer due to Human Papilloma virus infection, liver cancer from Hepatitis B infection and stomach cancer from H Pylori infection are well known.

Occupation Related Causes of Cancer

Persons in specific professions are exposed to specific pollutants. For example Benzene is highly toxic and is a potent carcinogen. It is said that the only safe concentration of Benzene is zero. Vapors from glue, paint, furniture wax or detergent are sources of Benzene. Those who do the polishing of furniture should use masks, though in practice they seldom do that in India.

Inhaling dust or particulate matter, which produces abrasions routinely, like asbestos or wood dust, is carcinogenic. Several professions involve exposure to carcinogenic agents and in such cases proper protections need to be taken. A painter’s job involves exposure to carcinogens. Products of, as well as many by products of coal gasification, coal-tar distillation, coal-tar pitch and coke production are carcinogenic. Soot, to which chimney sweeps are exposed, is carcinogenic. Workers of iron and steel foundries, hematite mining and those working with nickel compounds and Chromium VI are also exposed.

People working in nuclear plants or X-ray laboratories are also at a small risk compared to the normal population. However, failure to use proper safety measures in these professions can be fatal. Also, the danger of leakage from nuclear plants, which is not a distant possibility anymore, cannot be overemphasized. Investing the resource and effort involved in setting up a plant, if used in generating solar energy will be advantageous in the long run and the example of Germany in this matter should be followed. Barred from use of nuclear energy, they have excelled in development of renewable energy and 60% of their domestic needs come from renewable sources.

Environmental Exposure to Carcinogens.

Car exhausts, fumes produced during household coal combustion, strong inorganic acid mists are identified carcinogens. The amount of PAH (polyaromatic hydrocarbons) in the atmosphere of big cities reach alarming level in the evenings.

Arsenic is a very important environmental carcinogen in some places like West Bengal and Bangladesh, where overuse of underground water has caused leaching of Arsenic into the water. Prolonged use of such Arsenic contaminated subsoil water has been linked to cancer of lung, bladder, kidney, liver and skin.

International agency for research on Cancer publishes list of agents which have been accepted as human carcinogens and it is available online. It is necessary to mention that how an agent affects a person depends, in addition to the exposure dose, on the exposure route and the genetic make up of the person exposed. In many cases the cancer is detected many years after exposure, though the response may be quicker in other cases. Many carcinogens are associated with cancers of specific organs because these organs are exposed during the metabolism of the carcinogenic substance3.

Enzymes of Xenobiotic Metabolism and Their Polymorphisms

Liver is the organ where Xenobiotics, or substances foreign to the normal biochemistry of the organism are metabolized, usually by first making them soluble (by modification through oxidation/reduction/hydrolysis). This is termed as the phase I reaction. Cytochrome P450 mono oxygenases constitute a large family of enzymes operating in phase I.

In phase II the modified compounds are conjugated to polar components. Methylation, acetylation, glucoronidation, sulfation or conjugation with glutathione is some of the methods used in phase II.

In phase III the compounds are further modified and excreted.
There is an elaborate system of enzymes for this biotransformation in all major groups of organisms. The enzymes are characterized by overlapping substrate profile and polymorphisms, affecting their efficacy and inducibility.

The reactions are also called detoxification reactions. It is to be noted that some of the reactions change the character of the compounds from reactive to non reactive and in many other cases, non reactive inert compounds are metabolized to highly reactive forms in the intermediate stage.

The activity of the enzymes varies with physiological and pathologic factors. Physiological factors like age, sex, enterohepatic circulation, nutrition, intestinal flora etc affect xenobiotic metabolism. Inter-individual genetic differences (also termed polymorphism) are also a large source of variation in drug metabolism rate. As an example, N-acetyltransferase enzymes may come as fast or slow acetylators and persons with the slower variety will remove the intermediates produced in phase I slowly. This allows the toxic intermediates to damage DNA and produce mutation leading to future development of Cancer. Such slow acetylators are quite common in some populations and slow and fast acetylators split roughly 50:50 in Canadian population.

This type of polymorphism is present in most of the other phase I and phase II genes. Deficiency of some of the Cytochrome P-450 enzymes may occur in 30% of people in some ethnic backgrounds. These lead to variability in response to drugs, some food as well as other environmental pollutants. Apart from other physiological disturbances, some of these prolong the life of reactive components inside the body, leading to DNA damage and ultimately a higher susceptibility to specific kinds of cancer. Others may protect individuals from particular type of cancer. For example, polyaromatic hydrocarbons are products of incomplete combustion of hydrocarbon fuels and aryl hydrocarbon hydroxylase or CYP1A1 gene product is involved in their metabolism. In Phase I reaction, inert PAH is turned into highly reactive epoxide involved in carcinogenesis. So in a population exposed to such carcinogens, deficiency of CYP1A1 provides some protection against cancer. On the other hand slow acetylators of the NAT2 gene has been shown to have higher incidence of bladder cancer.

In this context, it is worth mentioning that a large number of persons in any population harbor such polymorphisms and the risk to them is minimal, and becomes apparent only when they are exposed to large doses of carcinogen. A person with deficiency in more than one enzyme of same pathway is at a greater risk. Simultaneous inheritance of GST M1 null allele (both copies of the gene deleted) and slow acetylator allele of NAT2 gene has been linked to higher incidence of lung and head and neck cancer in asbestos workers.

A Small Group is Genetically Susceptible to Cancer

Persons with germline mutations in cancer related genes are at a much higher risk of developing malignancy. Cancer, as we discussed before, is a disease arising out of mutations in the somatic cells (all cells of a person’s body except the germ cells). However, it is possible that a deleterious mutation in a cancer related gene like the tumor suppressor gene RB or BRCA has occurred in a person’s egg or sperm cells (though our somatic cells harbor two copies of most genes the egg or sperm has only one). All cells of his/her child who originates from the defective sperm/egg will have only one copy of this gene (that came from the other parent) as shown in Fig 2. Loss of this remaining gene in any somatic cell will push that cell towards excessive growth, which ultimately may lead to cancer. Families with such mutations have a higher cancer incidence rate than normal. The cancers are usually of specific types. RB gene mutation leads to eye tumor Retinoblastoma, or BRCA1 and 2 gene mutations produces breast cancer susceptibility. The TP53 gene has more ubiquitous role and its germline mutation produces many different type of malignancies like breast cancer, brain tumor, acute leukemia, soft tissue sarcoma, bone sarcomas and adrenal cortical carcinoma, increasing the chance of getting the disease by 25 times before a person reaches 50. Worldwide 64 affected families have been reported in scientific literature. In western countries, people (including children) with familial susceptibility to cancer are recommended to undergo annual physical examination and avoid radiation therapy. Older individuals are suggested to have organ specific surveillance like screening for breast or colorectal cancer.

![Figure 2. A susceptible parent transmits susceptibility to half of the offspring.](image)
Multiple cases of malignancies may also arise in a 
family due to environmental exposure, which needs to be 
investigated before inferring familial susceptibility. In fact 
not more than 5% of cancer cases are due to familial gene 
defect.

**TABLE I. Incidence of breast, cervix, colorectal and 
liver cancer per 100000 populations in India, US and 
China**

<table>
<thead>
<tr>
<th>Country</th>
<th>Breast</th>
<th>Cervix</th>
<th>Colorectal male</th>
<th>Liver male</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>25.8</td>
<td>28</td>
<td>&lt;4.3</td>
<td>3.0</td>
</tr>
<tr>
<td>USA</td>
<td>92.9</td>
<td>6.4</td>
<td>&gt;28.2</td>
<td>4.4</td>
</tr>
<tr>
<td>China</td>
<td>22.1</td>
<td>9.8</td>
<td>16.3-28.1</td>
<td>29.5</td>
</tr>
</tbody>
</table>

**Cancer Incidence in Different Countries**

Getting back to population at large, study of rate of 
cancer incidence in different countries, and how these are 
changing with change of lifestyle provides ample 
indications about the agents that foster cancer incidence. 
In USA the two leading causes of death are heart disease 
and cancer, both accounting for almost one fourth of total 
deaths. A study on incidence of cancer between people of 
different diet shows that meat eaters definitely have higher 
incidence of cancer than vegetarians. Vegan diet (consuming 
no animal product including milk or egg) seems to be a 
protection against breast cancer and lacto-ovo diet against 
gastro-intestinal cancer.

In India, where incidences of many types of cancer 
are quite low, people suffer from high incidence of cervical 
cancer and stomach cancer due to poor hygiene and 
infection from HPV and H Pylori respectively. Cervical 
cancer incidence in India is as high as 28 per 100000, 
whereas in US resident Asians, it becomes comparable to 
that in US whites (6.4), at 6.6 per 100000.

How the incidence of specific cancer varies with the 
lifestyle of specific countries is demonstrated in Table I.

Use of Gutkha, khaini and Jardah makes India and 
neighboring countries the capital of oral cancer, more than 
25 people per 100000 being affected.

In western countries, intense awareness program 
against smoking has reduced mortality from lung cancer 
in males. However, in developing economies like ours, 
rapid westernization without proper safeguard to check 
pollution is leading to increase in cancer cases over 
previous years.

The increase in breast cancer in India due to risk 
factors like obesity and physical inactivity, late pregnancy, 
lack of breast feeding, use of hormonal contraceptives and 
exposure to environmental xenoestrogens like that from soy 
is an example. On a shorter time scale, breast cancer made 
up 22% of all cancer incidences of India in 2008, but in 
2012 the figure is 27%. The mortality rate is very high 
compared to western countries due to late reporting. Table 
II illustrates how the incidence of breast cancer in India 
has changed with changing lifestyle of women.

In the highly industrialized societies of US and Europe 
standard of living was upgraded appreciably after 1950s. 
Looking back, we understand now that the lifestyle also 
gave the westerners a dramatic increase of cancer incidence 
rate. What we do now with our new found prosperity is 
for us to decide.

**Is Cancer Preventable?**

Scientists believe that fifty percent of cancers are 
preventable. Whereas it is impossible to predict that a 
particular person will never fall victim to the disease, 
experience shows that with changes in lifestyle and 
environment, incidences do change, and sometimes for the 
better. Experiments carried out during 1970-80s made 
people aware of the role nicotine plays in carcinogenesis. 
This led to intense awareness program in the US, and some 
legal cases against tobacco companies in which the 
companies had to pay large compensation to the patients. 
Restrictions were also imposed on smoking in public places. 
All these steps led to dramatic decrease in lung cancer in 
western countries. Mortality in males decreased from 55 
per 100000 in 1985 to 40 per 100000 in 2005 in USA. In 
UK the figures are 60 and 34 respectively. In China, after 
rapid industrialization lung cancer mortality increased from 
~20 to 30 per 100000 during the period 1990-2000.

**TABLE II. Incidence of breast cancer in younger 
patients increased compared to 25 years earlier**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Percentage of patients being affected 25 years ago</th>
<th>Percentage of patients being affected presently</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-30</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>30-40</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>40-50</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>50-60</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>60+</td>
<td>33</td>
<td>22</td>
</tr>
</tbody>
</table>
A cleaner atmosphere, a diet rich in green vegetables and fruit, avoiding too much fat and animal protein and engaging in physical activity regularly is all we need to do. With temperatures soaring above 45°C in summer and plummeting below -45°C in winter, maybe we need to deviate from the model of endless industrial expansion and slow down, for our own survival, and that of humanity as a whole.

Acknowledgement

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References

3. International Agency for research on Cancer IARC database; Globocan database