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BASICS OF CARCINOGENESIS

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> *Normal cells may bear the seeds of their own destruction in the form of cancer genes. The activities of these genes may represent the final common pathway by which many carcinogens act. Cancer genes may not be unwanted guests but essential constituents of the cell's genetic apparatus, betraying the cell only when their structure or control is distributed by carcinogens.*
>
> *Bishop, 1982 (Nobel Prize Winner, 1989)*

I. INTRODUCTION

Cancer is the second among fatal diseases, next to cardiovascular diseases, in the industrialized countries and third fatal disease in India. It is estimated that in the next quarter of a century the number of new cancer cases globally is going to double, half of them in the developing countries (WHO 1991). World Health Organization has launched a campaign against cancer, with a three-fold strategy: prevent all the preventable cancers, cure all that can be cured, and reduce pain and discomfort where cure is not possible (WHO 1995). In this context it may be worthwhile to examine the basic cellular changes leading to cancer development and to discuss some of the areas where strategies for prevention can be implemented.

Cancer is a broad term used for identifying a large number of diseases. Perhaps the only common feature of these diseases is the ability of uncontrolled cell proliferation that cannot be checked by the normal cell kinetics regulators. A normal cell suddenly turns into a rogue cell and start dividing continuously without check, leading to the development of solid lumps (tumors) or an abnormal rise in the number of dispersed cells like the blood corpuscles. Cancer can occur in any part of the body and in any organ or tissue. Even though most of the cancers are generally associated with old age, no age group is immune to this disease. Cancer originates in our own cells, but several factors, both intrinsic and external to the body, which influence our daily life, can add to the life time cancer risk. While cancer, as such, is not infectious, some infections can act as a stimulus to induce and promote cancer development. In addition, environmental pollutants like many chemicals, industrial effluents, some therapeutic drugs, and mutagenic agents, including ionizing radiation, can increase the incidence of cancer. About 50% of all cancers are attributed to life style, eg. diet, tobacco habits and alcohol consumption, and exposure to industrial toxins.

II. PROCESS OF CARCINOGENESIS

Cancer development is understood to be a multi-step process. The concept of multi-stage carcinogenesis was first proposed by Berenblum and Schubik in 1948 and supported by later studies. Present day oncology recognizes three main phases: initiation, promotion and progression.

Initiation: Neoplasia initiation is essentially irreversible changes in appropriate target somatic cells. In the simplest terms, initiation involves one or more stable cellular changes arising spontaneously or induced by exposure to a carcinogen. This is considered to be the first step in carcinogenesis, where the cellular genome undergoes mutations, creating the potential for neoplastic development (UNSCEAR 1993, Cox 1994), which predisposes the affected cell and its progeny to subsequent neoplastic transformation. The human DNA sequences responsible for transformation are called oncogenes. Many of the active oncogenes have been isolated by molecular cloning, eg. human bladder carcinoma, Burkitt's lymphoma, lung carcinoma, carcinoma of the breast and several others. Although the activation of more than one oncogene appears to be necessary for neoplastic transformation, the data imply that initiation may be induced with one hit kinetics (Bishop 1982). For example, in the human bladder carcinoma, a single point mutation converting the Ha-ras proto-oncogene into a potent oncogene was the first identified mutation in a human oncogene (Tabin et al. 1982). Such tumor gene mutations can have profound effects on cellular behavior and response, and can lead to dysregulation

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of genes involved in biochemical signaling pathways associated with control of cell proliferation and/or disruption of the natural processes of cellular communication, development and differentiation. However, the full expression of such neoplasia initiating mutations invariably requires interaction with other later arising gene mutations and/or changes to the cellular environment, but the initiating mutation creates the stable potential for pre-neoplastic cellular development in cells with proliferative capacity (UNSCEAR 2000). The transformed cell undergoes continuous division with fidelity to the transformed karyotype and, possibly, with further mutations, before a malignant lesion is manifested.

III.MECHANISMS OF ONCOGENE ACTIVATION

Each oncogene is closely associated with a normal DNA sequence present in the cellular genome, the proto-oncogene. At least five different mechanisms are considered for the conversion of proto-oncogenes to active oncogenes (Land et al. 1983): (1) Over-expression of proto-oncogene following acquisition of a novel transcriptional promoter. The oncogene then acquires activity because their transcripts are produced at much higher levels than those of the related normal proto-oncogene. (2) Over-expression due to amplification of the proto-oncogene or oncogene. The increased gene copies cause corresponding increases in transcript and gene product. (3) Influences on the levels of transcription and, in turn, the amount of gene product. (4) Juxtaposition of the oncogene and immunoglobulin domains, following chromosomal translocations, that appears to result in deregulation of the gene. (5) Alteration in the structure of the oncogene protein. This is the most well documented mechanism in the case of the oncogene proteins encoded by the ras genes.

The fourth and fifth mechanisms seem to be inter-related.

A translocation can disturb the regulation of an oncogene (Rabbitts 1994) by:

a) providing a new promoter region or some other control element that would activate the oncogene; or
b) altering the coding sequence of a gene, changing its protein product from a benign to a malignant form.

A close association between specific chromosomal translocations and certain human neoplasms has been demonstrated (Rowley and Mitelman 1993).

Promotion: The transformed (initiated) cell can remain harmless, unless and until it is stimulated to undergo further proliferation, upsetting the cellular balance. The subsequent changes of an initiated cell leading to neoplastic transformation may involve more than one step and requires repeated and prolonged exposures to promoting stimuli (Upton et al. 1986). Thus, in contrast to initiation which is induced at a rate of 0.1-1.0 per cell/Gy of radiation, the subsequent transforming event in the initiated cells occurs at a rate of only 10-6 to 10-7 per cell generation (Kennedy and Little 1984). Neoplastic development is influenced by the intra- and extracellular environment. Expression of the initial mutation will depend not only on interaction with other oncogenic mutations but also on factors that may temporarily change the patterns of specific gene expression, eg. cytokines, lipid metabolites, and certain phorbol esters. This may result in an enhancement of cellular growth potential and/or an uncoupling of the intercellular communication processes that restrict cellular autonomy and thereby coordinate tissue maintenance and development (Trosko et al. 1992, UNSCEAR 1993).

Progression: is the process through which successive changes in the neoplasm give rise to increasingly malignant sub-populations. Molecular mechanisms of tumor progression are not fully understood, but mutations and chromosomal aberrations are thought to be involved. The process may be accelerated by repeated exposures to carcinogenic stimuli or by selection pressures favoring the autonomous clonal derivatives. The initiated cells proliferate causing a fast increase in the tumor size. As the tumor grows in size, the cells may undergo further mutations, leading to increasing heterogeneity of the cell population.

In the first phase of progression, sometimes referred to as neoplastic conversion, the pre-neoplastic cells are transformed to a state in which they are more committed to malignant development. This may involve further gene mutations accumulating within the expanding pre-neoplastic cell clone (UNSCEAR 2000). The dynamic cellular heterogeneity, a feature of malignant development, may, in many instances, be a consequence of the early acquisition of gene-specific mutations that destabilize the genome. Examples are mutations of the p53 gene (Hartwell and Kastan 1994) or DNA mismatch repair genes (Fishel and Kolodner 1995). Many tumor types develop transforming sequences in their DNA during their progression from the normal to the cancerous state. An elevated mutation rate established relatively early in tumor development may, therefore, provide for the high-frequency generation of variant cells within a pre-malignant cell population. Such variant cells, having

the capacity to evade the constraints that act to restrict proliferation of aberrant cells, will tend to be selected during tumorigenesis (UNSCEAR 2000).

Tumor metastasis: As the tumor progression advances, the cells lose their adherence property, detach from the tumor mass and invade the neighboring tissues. The detached cells also enter the circulating blood and lymph and are transported to other organs/tissues away from the site of the primary growth and develop into secondary tumors at the new sites. These form the distant metastases, resulting in widely spread cancers. Cancer metastasis consists of a number of steps; the main steps are common for all tumors. The progress of the neoplastic disease depends on metastatic changes that facilitate: (a) invasion of local normal tissues, (b) entry and transit of neoplastic cells in the blood and lymphatic systems, and (c) the subsequent establishment of secondary tumor growth at distant sites (Hart and Saini 1992, Takeichi 1993).

Many of the steps in tumor metastasis involve cell -cell and cell-matrix interactions, involving specific cell surface molecules. Malignant cells are thought to have reduced ability to adhere to each other, so that they detach from the primary tumor and invade the surrounding tissues. The behavior of tumor is influenced by the cell adhesion molecules, one of the most important of which are cadherins (Takeichi 1991). Animal studies have shown that a down-regulation of E-cadherin expression, resulting in lower levels, correlated with metastatic behavior in vivo, suggesting that cadherins function as invasion suppressor gene products (Vleminckx et al. 1991).

It is the metastatic process and tumor spreading that are mainly responsible for the lethal effects of many common human tumors. In many cases gene mutations are believed to be the driving force for tumor metastasis, with the development of tumor vasculature playing an important role in the disease progression (Folkman 1995).

Tumor angiogenesis: Tumor growth depends on the supply of growth factors and efficient removal of toxic molecules, which comes through an adequate blood supply. In solid tumors, efficient oxygen diffusion from capillaries occurs to a radius of 150-200(m, beyond which the cells become anoxic and die. Therefore, increase in tumor mass to more than 1-2 mm will depend on adequate blood supply through development of blood capillaries (angiogenesis). Schubik was the first to coin the term 'tumor angiogenesis' (Shubik 1982). But it was Judah Folkman who hypothesized the importance of tumor angiongenesis in the development and metastasis of solid tumors. His theories are widely accepted today. Folkman and colleagues established that tumor growth beyond about 2mm size could proceed only if a vascular supply is established (Folkman 1985). A number of tissue factors have been identified, which stimulate endothelial cell proliferation. These include the tumor angiogenesis factor (TAF, Folkman 1974), the vascular endothelial growth factor (VEGF, Dvorak et al 1995), angioproteins - ang-1 and ang - 2 (Davis and Yancopoulos 1999), transforming growth factors (TGFs) (Leibovich et al. 1987), interleukin - 1 ((Mahadevan et al 1989), and platelet-derived endothelial cell growth factor (PD-ECGF, Ishikawa et al. 1989).

Although the blood vessels that supply the developing tumors are derived from the host vasculature, their architecture differs considerably from that in the normal tissue. Tumor vessels are often dilated, saccular and tortuous and may contain tumor cells within the endothelial lining of the vessel (Jain 1989). Therefore, the blood flow in the tumor may be sluggish compared to that in the adjacent normal tissues and the tumor microvasculature may show hyperpermeability to plasma proteins.

IV. CANCER GENES

Somatic gene mutations are widely accepted as the basic event in the conversion of a normal cell into cancer cell. Many different genes are demonstrated to be involved in carcinogenesis. The gene mutation theory of oncogenesis maintains that carcinogens interact with DNA resulting in irreversible changes in the gene (point mutations), which predispose the cells to malignant transformation. The somatic genetic changes in cells that contribute to multistage tumor development potentially involve sequential mutation of different classes of genes, ie. Proto-oncogenes, tumor suppressor genes, genes involved in cell cycle regulation, and genes that play roles in maintaining normal genomic stability. Biochemical interactions between tumor gene mutations may destabilize the genome, compromise control of cell signaling, proliferation, and differentiation, and interfere with the normal interaction of cells in tissues (Karp and Broder 1995; Skuse and Ludlow 1995).

Two classes of regulatory genes are directly involved in carcinogenesis, the oncogenes and the anti-oncogenes (Vogelstein and Kinzler 1998).

Oncogenes: They are positive regulators of carcinogenesis. In non-transformed cells, they are inactive (proto-oncogenes). Gene mutations can activate proto-oncogenes, resulting in a gain of function.

Several proto-oncgenes were first identified through viral transformation of cellular genome, eg. c-erbB, c-mos, c-myc, c-myb, C-H-ras (reviewed by Bishop 1987). A large number of mutations in specific oncogenes - eg. ras, myc, etc. - have been found to be closely associated with different types of cancers.

Anti-oncogenes or tumor suppressor genes: They are negative growth regulators. Many human tumors, eg. retinoblastoma, Wilm's tumor, colon carcinoma, result from recessive mutation, which cause cancer when present on both homologues (Knudson 1993). These genes function as anti-oncogenes or tumor suppressor genes. In normal cells they regulate cell proliferation by checking cell cycle progression. Mutation in these genes results in a loss of gene function (the protein product will not be produced), which promotes carcinogenesis (Perkins and Stern 1997). Such gene mutations have been detected in several solid tumors, eg. cancers of breast, lung, rectum, etc., but only few such mutations have been seen in leukemias.

The two most widely studied tumor suppressor genes are the Rb gene and p53 gene. The proteins encoded by these genes inhibit cell cycle progression by blocking transcription of gene products necessary for transition from G1 to S phase. Mutation in the Rb gene could lead to loss of normal inhibitory control of cell cycle progression and, thereby, increase cell proliferation. This effect, coupled with genetic changes that cause loss of apoptotic signals, would enhance malignant transformation (Symonds 1994).

p53 has a major role in maintaining the genomic stability and cellular equilibrium. In normal cells, this gene promotes apoptosis, regulates cell cycle through G1 - S checkpoint control and induces cell differentiation. p53 participates in a cell cycle checkpoint signal transduction pathway that causes either a G1 arrest or apoptotic cell death after DNA damage (Kastan 1997). Mutations in p53, resulting in loss of function, will cause suppression of apoptosis, promote cell division by releasing the G1-S block and prevent differentiation of the cells, leading to neoplasm development (Curtis 1993). Mutations in the p53 gene are the most common genetic change observed in a large number of human malignancies; at least 50% of all human cancers have been found to contain p53 abnormality (Hollstein et al. 1991). Mutations in this gene have been observed in a wide range of human cancers like cancers of the breast, lung, colon, skin, urinary bladder, ovary and lymphoid organs. More than 500 mutations of this gene have been documented in breast cancer (Hartmann et al. 1997).

V. THEORIES OF CARCINOGENESIS

Gene mutation theory:

This theory maintains that somatic gene mutations form the basis of neoplastic transformation and their clonal expansion leading to carcinogenesis. It is the most widely accepted and is supported by a large volume of experimental data (review by Bishop 1987). However, it does not explain tumor heterogeneity and aneuploidy and also the long latent periods between exposure to carcinogens and the development of tumors.

Aneuploidy theory:

Another theory that is currently gaining momentum is the aneuploidy hypothesis. According to this hypothesis, a carcinogen initiates carcinogenesis by a preneoplastic aneuploidy, which destabilizes mitosis. This initiates an autocatalytic karyotype evolution that generates new chromosomal variants, including rare neoplastic aneuploidy (Duesberg et al. 2001). The aneuploidy hypothesis provides a plausible explanation for the long latent periods from carcinogen treatment to cancer development and the clonality.

Epigenetic theory:

It has been recognized that non-mutational stable changes occur in cellular genome, which can contribute to carcinogenesis (Feinberg 1993 Cross and Bird 1995). Such events are broadly termed epigenetic and are thought to involve DNA methylation, genome imprinting and changes in DNA - nucleoprotein structure. Increased levels of methylated cytosine (one of the pyrimidine bases in DNA) results in the elevation of spontaneous mutation rates in the affected genome (Balmain 1995).

While each theory has its own merits, it may not be possible to assign an exclusive role to a single process alone in carcinogenesis. In many cases, a combination of the two or all process may work in co-operation. An initiating somatic gene mutation can destabilize the genome and lead to aneuploidy and chromosome heterogeneity, characteristic of solid tumors, while epigenetic events can contribute to the neoplastic cell transformation and also facilitate promotional changes.

VI. FACTORS INFLUENCING CANCER DEVELOPMENT

A number of intrinsic (biological) and external factors are associated with the development of cancers. The intrinsic factors include the age and hormonal status of the individual, familial history and genetic predisposition. The extraneous factors include diet

and life style, individuals habits like smoking and alcohol use, exposure to toxic chemicals and radiation, some infections, etc. Several external factors, including asbestos, many chemicals, dyes, food additives, vehicular emissions, act as promoters in carcinogenesis.

Biological factors:

Age and hormonal status:

Cancer is considered to be an old age disease. Some types of cancers are almost entirely found in people above 50-55 years, eg. prostate cancer. Similarly cervix cancer in women are more commonly detected at the peri- or post-menopausal ages. However, no age group is immune to this disease. Hormonal factors play an important role in the development of gender-specific cancers, eg. estrogen in cancers of ovary and uterus in female (Henderson et al. 1988).

Family history:

Some cancers are indicated to have a link with familial occurrence. For example, women whose close relatives like grandmother, mother, maternal aunt or sister has suffered from breast cancer, are found to run about 3 times higher risk of developing breast cancer than those who do not have such a family history. Similarly, cancers of the uterine cervix (females) and of prostate (males) are also thought to have a familial connection.

Genetic predisposition:

Certain genetic conditions are known to predispose the individual to cancer. For example, individuals with genetic conditions like xeroderma pigmentosum, ataxia telangiectasia, Bloom's syndrome, and Fanconi's anaemia are found to be highly susceptible to different types of cancer (Bale and Li 1997).

External factors:

Diet, alcohol, and tobacco use: More than 50% of all cancers are related to the diet and individual habits like alcoholism, tobacco chewing and smoking. High fat diet and obesity are associated with breast cancer. A positive correlation has been reported between age-adjusted breast cancer mortality rates and the average per capita fat consumption in a given nation on a daily basis (Carroll et al. 1975). Similarly, deep-fried and burnt food and preserved (high salt) food are associated with increase in gastric cancer incidence. Regular consumption of food low in fibre content and rich in animal fat increased the risk of cancers of stomach and oesophagus. High intake of red meat and low fibre diet has been considered to be the cause of the high incidence of gastric cancer in the USA.

The role of cigarette smoking in lung cancer is established. Tobacco smoke contains a chemical, nitrosamine, which can induce neoplastic changes in the lung cells. Non-smoking tobacco habits, like chewing, are found to greatly increase the cancers of the upper alimentary tract and buccal mucosa. India has the highest incidence of oral cancers in the world, which is correlated with the tobacco chewing habit. Alcoholism is found to increase the risk of liver and bladder cancers. Smoking combined with alcohol consumption poses a higher risk of cancers of the breast, oesophagus, liver, stomach and urinary bladder. Alcoholism along with hepatitis B virus infection is a more serious risk factor in liver cancer.

Radiation and cancer:

Ionizing radiation is an established carcinogen, having both initiating and promoting effects. The positive correlation between ionizing radiation and carcinogenesis has been established from the studies on the early radiologists, radium dial painters and atom bomb victims of Japan. A positive association has been seen in the increase in childhood cancers and obstetric X-ray exposures of the mother (Knox et al. 1987). Tumors induced by radiation have relatively long latencies, which vary in different species as a more or less constant function. Within a given species the latency varies also with age at the time of irradiation and with the type of neoplasm induced. The age differences in latencies appear to be related to similar age differences in the rates of corresponding spontaneous leukemias (Upton et al. 1964). The risk of adult type of malignancies tend to increase progressively with time after irradiation, in parallel with the age-dependent increase in the underlying base-line incidence (UNSCEAR 1993).

Viruses and cancer:

Oncoviruses play an important role in specific human cancers, eg. human papilloma virus in cervix cancer (zur Hausen 1994), and certain skin cancers (Mc Grae et al. 1993); Epstein-Barr virus in Burkitt lymphoma (Tosato et al. 1994) and nasopharyngeal carcinoma (Fandi and Cvitkovoc 1995); hepatitis B virus in hepatocellular carcinoma (Robinson 1994); human T-cell leukemia virus in leukemia (Feuer and Chen 1992). The viruses are of two types: DNA viruses which incorporate into the cellular genome and the retroviruses (RNA viruses) which cause transformation of cellular genome, leading to malignant changes in the infected cell.

Role of free radicals:

Reactive oxygen species (ROS) and other free radicals are produced in the body, both during the normal metabolic process as well as by interaction with external toxic agents, for example, radiation and toxic chemicals. They include superoxide anions, hydroxyl radicals, peroxy radicals and hydroperoxides. These interact with DNA and produce gene mutations and chromosomal aberrations, leading to cell transformation. Free radicals are considered to have a major role in the induction of cancers by chemicals and radiation (Clayson et al. 1994). Several factors of our modern life style, eg. excess alcohol consumption, tobacco chewing and smoking habits, exposure to toxic chemicals and radiations, all add to the free radical production in the body and increase the risk of cancer.

VII. CELLULAR DEFENSE MECHANISMS IN RELATION TO CANCER PREVENTION AND CARCINOGENESIS

Normal cells are naturally equipped with efficient defense mechanisms that work at different levels.

Antioxidants:

The cells synthesize their own defense molecules, which include the non-protein thiol gluthathione, and antioxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase, reductase and S-transferases. These scavenge the ROS before they can reach the target molecules in the cell (Halliwell et al. 1992) and thus protect against their attack on the vital molecules like DNA. Thus they serve as the biological watchdogs in safeguarding against free radical induced initiating changes, mutations and chromosomal aberrations. Many dietary ingredients like green vegetables, fruits, tea, spices and some diet supplements contain antioxidants. These include the vitamins A, C, and E, beta-carotene, alpha-tocopherol, ascorbic acid, flavonoids, lycopenes, curcumins and enzymes like caspasine. They act as chemo-preventers by scavenging free radicals and enhancing cellular defense through their adaptogenic properties.

DNA repair:

Damage to cellular DNA is the crucial early event in the neoplastic transformation of a cell. The DNA lesions may include altered bases, co-valent binding of bulky adducts, inter- and intra-strand cross-links and generation of strand breaks. A range of alkylated products is formed in DNA by exposure to nitroso-compounds and other alkylating agents. Ionizing radiation and many genotoxic chemicals generate free radicals, which interact with DNA and produce different lesions ranging from base damage, deletions and complex and multiple lesions. Most normal cells possess a high capacity for repair of DNA damage. However, efficient repair depends on the type of damage, its severity and the time available for repair. The base damage and single strand breaks are repaired fast and without error, restoring the molecular structure. But double strand breaks and multiple breaks and local cluster lesions are not properly repaired and often contain errors (error-prone repair or misrepair), leading to cell death or cell survival with abnormal gene functions and chromosomal abnormalities which are associated with malignant cell transformation. DNA repair involves a number of genes, the products of which operate in a co-ordinated manner to form repair pathways that control restitution of DNA structure (reviewed by Hall 1993).

Apoptosis or programmed cell death is an important mechanism of cellular defense in reducing the risks of error-prone repair. Cells with DNA damage undergo apoptosis, thus preventing these cells from surviving and entering the proliferating cell pool and, thereby, preventing the possibility of tumor development. Apoptosis is a genetically controlled process involving p53, bcl2 and other genes. Mutations in p53 can block the tumor-suppressive effect by eliminating apoptosis (Curtis 1993), and ,thus, allowing the damaged cells to survive and undergo proliferation (UNSCEAR 2000). Some of the gene products that control cell cycle also influence apoptotic tendencies, eg. c-myc, pRb, Tp53.

VIII. ROLE OF DIET IN CANCER CONTROL

Doll and Peto (1981) were the first to point out an association between dietary constituents and cancer. A vegetarian diet is considered to be beneficial in reducing cancer incidence. Epidemiological studies have suggested that diets rich in vegetables, and fruits reduces the risk of certain cancers. For example, diets rich in fibre, vitamins A,C, and E, beta-carotene, retinols, alpha-tocopherol, polyphenols, and flavonoids, and minerals like selenium and zinc, have cancer chemopreventive effect. Fruits and vegetables are rich sources of chemopreventive chemicals. These include inhibitors of carcinogen formation, blocking agents (block conversion of procarcinogens to carcinogens), stimulators of detoxifying system, trapping agents (trap and eliminate potential carcinogens) and suppressing agents (suppress the different steps of the metabolic pathway leading to cancer) (Stavric 1994). A study in China showed a high incidence of oesophageal and gastric cancers in a population whose

diet is deficient in beta-carotene and vitamins C and E. An interventional program, where the diet was supplemented with beta-carotenes, vitamin E and selenium, produced a 20% reduction in the stomach cancer mortality over a period 5 years (Blot et al. 1993).

WHO has recommended dietary intervention in the cancer control strategy for the new millennium. Dietary intervention follows two approaches:

1. Intervention through supplementing with vitamins, antioxidants and other dietary factors.
2. Intervention through dietary modification in which target levels are established for consumption of meat, fat, fiber, fruits and vegetables (Schatzkin et al. 1995).

IX. CONCLUSIONS

Cancer is a broad term to describe a large variety of diseases, the common feature of which is uncontrolled cell division. The process of carcinogenesis consists of three major steps: initiation, where an irreversible change is affected in the cellular genes; promotion, where the initiated cells expand by self-proliferation leading to abnormal growth and further mutations; and progression, where the cells detach from the primary tumor and invade other organs and tissues, forming metastatic growths. Angiogenesis plays an important role in the tumor metastasis. Different types of cancer genes - oncogenes and anti-oncogenes (tumor suppressor genes) - are involved in cancer development. Gain of function mutations in the oncogenes, leading to abnormal cell proliferation, and loss of function mutations in the anti-oncogenes leading to suppression of cell differentiation and apoptosis, are the major events leading to cancer development. Chromosomal aneuploidy and epigenetic events are also thought to be important. Several factors like age, sex, genetic predisposition, along with extrinsic factors like diet, environmental pollutants, alcoholism and tobacco habits have a major role in determining the cancer risk. Dietary intervention as a cancer preventive measure is a primary agenda on the WHO program.

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