CHAPTER

3 The Etiology and Prevention of Cancer

The different etiologic factors responsible for human cancer are generally classified into three main groups: extrinsic, intrinsic and unknown. Extrinsic factors include: chemical, physical factors (radiation) and infections (mainly oncogenic viruses). Intrinsic factors refer to genetic, hormonal and immune causes. It is apparent from (Table 3-1) that extrinsic factors predominate as etiologic agents of human cancer with a total estimate of about 85% of cases. Extrinsic factors are particularly important in cancers of adults, whereas, intrinsic genetic factors are the main contributing agents in pediatric malignancy (Fig 3-1).

The etiology of cancer is commonly multifactorial. Interaction of multiple factors occurs to determine the overall susceptibility and risk. This interaction is illustrated by the following examples:

1. Multiple extrinsic factors: Interaction of chemical and viral factors, such as, in hepatocellular carcinoma and nasopharyngeal carcinoma. Also, virus, smoking and contraceptive pills cooperate in producing carcinoma of the uterine cervix.

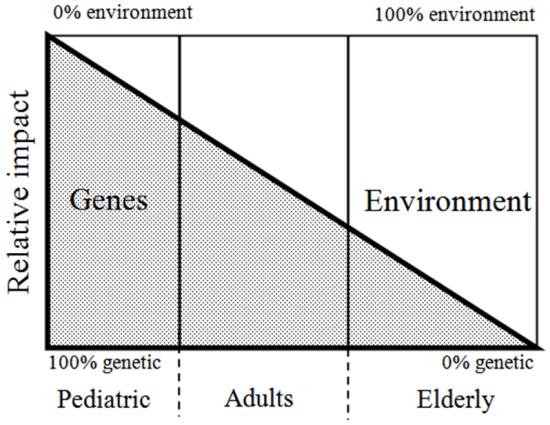

Fig 3-1 *The relative contribution of genetic and environmental factors in cancers of different age groups.*

Table 3-1 Proportions of Cancers Attributed to Various Etiologic Factors (USA)

Factor	Percent
Diet	35
Tobacco	30
Virus	5
Genetic predisposition	5
Occupational hazards	4
Alcohol	3
Radiations	3
Medications	2
Pollution*	2
Unknown	**11**

(Data from Doll 1981 and DeVita 1989)

* Mainly polycyclic hydrocarbons from fuel combustion.

2. Multiple intrinsic factors: Familial breast and prostatic cancer are the result of interaction of genetic and hormonal factors.

3. Extrinsic and intrinsic factors: In cutaneous cancers that develop in patients with xeroderma pigmentosum, there is interaction of a genetic factor (defect in DNA repair) with an extrinsic physical factor (ultraviolet radiation). Similarly, squamous carcinoma that develops in the skin of patients with epidermodysplasia verruciformis is the result of interaction of four factors, namely: genetic defect, immune deficiency, a virus and ultraviolet radiation.

Inference about whether an observed epidemiologic association is causal can be supported by the following logical criteria: (1) strong association (high risk ratio), (2) specificity (a single type of exposure leading to a single disease), (3) gradient effect (there is a dose-response relationship), (4) temporal relation (the cause must precede the effect), (5) consistency (reproducibility of results by others), and (6) biological plausibility (presence of a biologic mechanism to explain the etiologic relation).

EXTRINSIC FACTORS

Chemical Carcinogens

Chemicals that cause cancer generally have electron-deficient atoms (reactive electrophilic centers) that combine with electron-rich atoms in nucleic acids and proteins. Such highly-reactive electron-deficient compounds are called electrophiles. A key mechanism involved in carcinogenesis at the atomic level, therefore, is the reaction of electrophiles with biologically important molecules, especially DNA, resulting into gene mutation. Chemical carcinogens are classified according to their metabolic activation in the body, organ specificity and the degree of evidence of carcinogenicity (IARC categories).

1. Metabolic activation: Carcinogens fall into one of two categories: (a) direct acting carcinogens which are intrinsically electrophilic, hence they do not require metabolic activation in the body for their carcinogenicity, or (b) indirect-acting or procarcinogens which require metabolic conversion in the liver to produce ultimate active carcinogens capable of transforming cells.

Direct-acting carcinogens are activation independent, and in general are weak carcinogens. This group of compounds is important because it includes many therapeutic alkylating agents used as anticancer drugs (e.g. Cyclophosphamide, Chlorambucil, Melphalan, Thiotepa, Busulfan, BCNU and Cisplatin).

Indirect-acting carcinogens includes most of the known potent carcinogens (e.g. benzo (a) pyrene, vinyl-chloride, 2-naphthylamine, nitrosamine and aflatoxin). These are activated in the liver by the enzyme cytochrome P450 oxidase into active carcinogens (Fig 3-2). An example is the polycyclic aromatic hydrocarbon (PAH) Benzo (a)pyrene. It is first oxidized into a carcinogenic epoxide, then further oxidation will produce the highly carcinogenic dihydrodiol epoxide. It will attach to DNA bases by covalent bonds forming a carcinogen-DNA adduct. This causes point mutation as a result of rotation of DNA bases which no longer pair with other bases. The carcinogen may also cause cross-link between DNA strands thus arresting DNA replication and transcription. Most of DNA damage produced by carcinogens is enzymatically repaired, but some damage is lethal to the cell.

The detoxication system of carcinogens works by combining these poorly-soluble compounds to hydrophilic groups (e.g. glucuronic acid or glutathione) producing water soluble products which are readily excreted in urine. At present, sensitive biochemical tests are readily available to measure carcinogen-DNA adducts, as well as, carcinogen metabolites in blood and urine samples (bio markers of exposure).

In conclusion, the ultimate carcinogenic effect of the chemical will depend upon the balance of three activities, namely: activation, detoxication and repair of DNA damage (Fig 3.3). Cancer will only develop as a result of sublethal DNA damage which is not repaired and the cell is viable enough to undergo mitosis.

2. Organ-specificity: Another way of classifying chemical carcinogens is according to their organ tropism, which is largely determined by the sites of activation or excretion of the chemical. Accordingly, carcinogens may be grouped into two main categories, namely: (a) those which affect single organs such as aflatoxin, vinyl chloride and butter yellow producing liver cancer (their site of activation), and naphthylamine producing bladder cancer (their site of excretion), and (b) those which affect multiple organs such as nitrosamine and polycyclic aromatic hydrocarbons (according to the route of administration).

3. IARC Categories: The International Agency for Cancer Research (IARC) classified human carcinogens into three categories according to the degree of evidence of carcinogenicity from epidemiologic studies: (a) sufficient evidence of carcinogenicity to indicate causal relation, (b) limited evidence of carcinogenicity and indefinite causal relation, and (c) inadequate evidence of carcino-

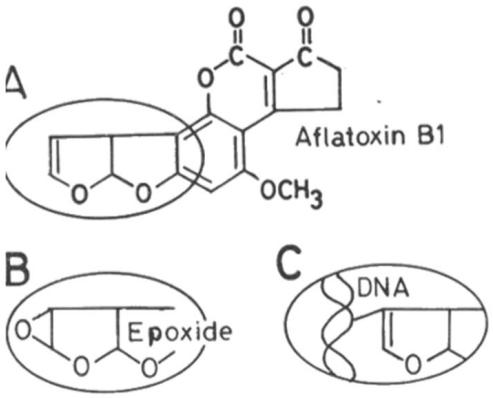

Fig 3-2 *Metabolic activation of aflatoxin B1. The unreactive procarcinogen (A) is metabolized by hepatic oxidase to yield a highly reactive electrophilic epoxide (B) which covalently binds to DNA (C).*

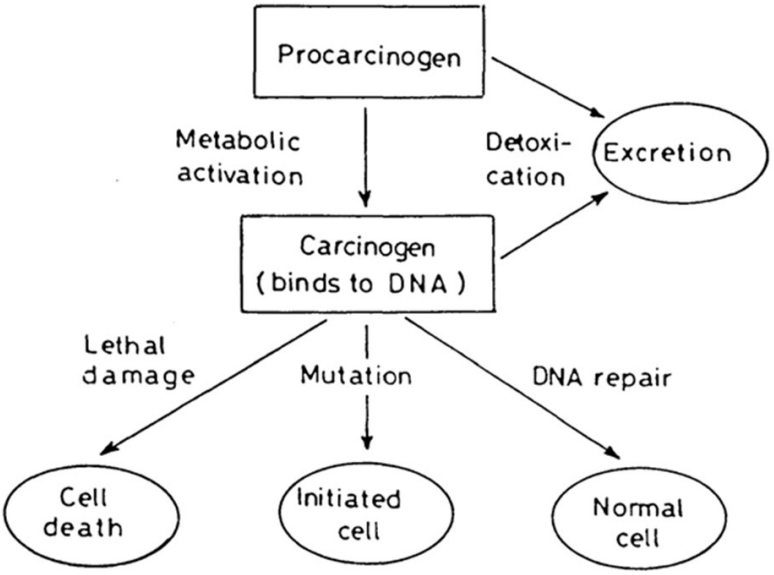

Fig 3-3 *Events in chemical carcinogenesis. The outcome depends on the balance between metabolic activation, detoxication and DNA repair.*

genicity as a result of few studies, inconclusive studies or investigations showing no evidence of carcinogenicity. The major classes of chemicals which have been definitely proven to be cancer causative agents (IARC category as are shown in (Table 3-2). Examples of industrial carcinogens are listed in (Table 3-3). Medication belonging to category a and leading to iatrogenic cancer are presented in (Table 3-4).

Table 3-2 Major Classes of Human Chemical Carcinogens

Class	Example
Polycyclic aromatic hydrocarbon	Benzo (a) pyrene
Aromatic amines	2- Napthylamine
Nitrosoamines and nitrosoureas	Dimethylnitrosoamine
Alkylating agents	Nitrogen mustard
	Cyclophosphamide
Alkyl and aryl halides	Polychlorinated biphenyls
Natural products	Aflatoxin
Metals	Arsenic, nickel, Cadmium and chromates
Fibers and dusts	Asbestos, silica and wood dust

Tobacco

About 30% of all cancer deaths in the USA is attributed to tobacco smoking. It has been firmly linked to cancers not only of the lung, but also of oral cavity, larynx, pharynx, esophagus, pancreas, urinary bladder and renal pelvis. For smokers of two or more packs per day, the risk of lung cancer is about 20 times that of nonsmokers. Passive smoking (exposed nonsmokers) have also an increased risk. The use of cigar and smokeless tobacco (chewing tobacco or snuff) also leads to cancer of oral cavity.

At least 30 carcinogens are present in the tobacco smoke including : the polycyclic aromatic hydrocarbon (PAH) benzo (a) pyrene, N-nitrosamine, 2-naphthylamine, formaldehyde, benzene, vinyl chloride, arsenic, nickel and chromium. Nitrosamines have been associated with esophageal and pancreatic cancers, whereas, aromatic amines are associated with kidney and bladder cancers. Moreover, the oxidants in cigarette smoke, mainly nitrogen oxides, deplete the antioxidants of the body.

Diet

Dietary factors contribute a sizable proportion of all cancers (about 35% in Western countries).

The sites of cancers involved are those of the colon, stomach, esophagus, breast, endometrium, prostate and lung. The etiologic factors may be related to excess or deficiency of dietary components, or the presence of various dietary additives or contaminants. Although the public often attributes the source of carcinogens in our food supply to food additives, synthetic pesticides and various environmental contaminants, these chemicals are estimated to represent less than 1% of the carcinogens found in food . Most dietary carcinogens comprise "natural pesticides" (toxins produced by plants for protection against fungi and insects), mycotoxins produced by molds and substances produced during food preparation or cooking such as: polycyclic aromatic hydrocarbons (PAHs), heterocyclic aromatic amines (HAAs) and N-nitroso compounds (NOCs).

In developed countries there is increased consumption of animal proteins and fat (40% of energy source is saturated fatty acids), increased consumption of free sugar and decline of fiber intake in vegetables. Conversely, the diet in developing countries is mostly vegetables. This is reflected on the cancer incidence which is at least three times in developed countries. Diets rich in oleic acid, olive oil, and fish oil are not associated with increased cancer risk.

The carcinogenic risk of high dietary fat is explained by several mechanisms. Thus, cooking fat at high temperature will produce carcinogenic products (e.g. benzo (a) pyrene). The digestive products of fat, namely: fatty acids and their associated increase in bile salts are cancer promoting agents, with high dietary calcium as a potential antidote. Fatty acids and bile acids may also be changed to carcinogenic products by anaerobic bacterial action in intestine. Finally, obesity increases the risk of breast and endometrial cancers by increasing the synthesis of estrogens in adipose tissue and decreasing the sex-hormone binding globulin.

Increased consumption of red meat also correlates with a high incidence of colonic carcinoma, mainly due to high fat content. Moreover, carcinogenic heterocyclic aromatic amines (HAA) may be formed during cooking meat at high temperature due to cyclization of amino acids. Finally, excessive iron intake from red meat is a possible, though unproven, contributor to the production of mutagenic oxygen radicals.

Diet may also contain naturally occurring carcinogens (e.g. tannins in tea, hydrazine in mushrooms and alkenyl benzenes in spices). Fungal contamination of stored food (grains) may produce aflatoxin, a potent liver carinogen.

Other notable carcinogens in the human diet are the nitrosamines which are derived from the interaction of nitrites with secondary or tertiary amines. Both sodium nitrate and its bacterial reduction product, sodium nitrite, occur naturally in plants, meats and dairy products. They are also widely used as preservatives in smoked meat and salted fish. Nitrosamines have been linked with cancer at four main sites, namely: the nasopharynx, esophagus, stomach and urinary bladder. The generation of nitrosamines, in stored food or in the gut, may be blocked by vitamin C or other antioxidants.

Evidence is accumulating that a low intake of certain food groups, particularly green vegetables and fruits, may predispose to cancer. The specific factors involved are the antioxidant micronutrients (e.g. Vit.C, E, carotinoids and selenium) and dietary fibers (cellulose, pectin and lignin). Vitamin A also acts as a potent antipromoter, and vitamin C blocks the endogenous formation of nitrosamines, Vitamin B 12 deficiency (pernicious anemia) predisposes to gastric cancer. Also, iron deficiency in females (Plummer- Vinson's syndrome) predisposes to hypopharyngeal carcinoma.

Deficiency of dietary fibers (normally present in wheat bran and vegetables) increases the risk of colonic cancer. Several mechanisms have been proposed to explain the inhibitory effect of fibers on colorectal carcinogenesis. Fibers increase fecal bulk and prevent constipation, hence, it reduce fecal carcinogen concentration, as well as, reduce the period of exposure of colonic mucosa to the carcinogens.

Cancers which are related industrial exposure or therapy are presented in (Table 3-3 and Table 3 -4)

Radiation

Radiant energy, whether in the form of ionizing electromagnetic and particulate radiation, or as ultraviolet (UV) rays from sunlight, can induce a variety of human neoplasms (Table 3-5). The contribution of radiation to the total burden of cancer is probably small (3%) and is characterized by its long latency and cumulative effect.

Ionizing radiation. Electromagnetic (x-rays, gamma rays) and particulate (alpha particles, beta particles, protons, neutrons) radiations are all

Table 3-3 Chemicals Associated with Occupational Cancer

Industry (Carcinogen)	Site of Cancer
Miners (Radon, silica)	Lung
Chromate (Chromium)	Lung
Insulators (Asbestos)	Lung, mesothelioma
Petroleum (PAH)*	Lung, skin
Ore smelters (Arsenic)	Lung, Skin
Refiners (Nickel)	Lung, nasal sinuses
Furniture (wood dust)	Nasal sinuses
Rubber (2-Naphthylamine)	Bladder
Dye (2-Naphthylamine)	Bladder
Varnish (Benzene)	Leukemia
Plastic (Vinyl chloride)	Liver, brain

*PAH - polycyclic aromatic hydrocarbons

Table 3-4 Medications which Pose a Carcinogenic Risk to Humans

Drug	Iatrogenic Neoplasm
Alkylating agents	Bladder, Leukemia
Chlornaphazine	Bladder
Phenacetin	Renal pelvis
Thorotrast	Liver (angiosarcoma)
Androgens	Liver
Inorganic arsenic	Liver, Skin
Methoxypsoralen	Skin
Diethylstilbesterol	Vagina*
Estrogen,	Endometrium
Tamoxifen	Endometrium
Immunosuppressants	Lymphoma, Kaposi, Skin squamous cancer

* In offspring affected by estrogens in uterus.

carcinogenic. Many examples can be given to support this etiologic relation. Thus, miners of radioactive elements suffered a tenfold increased incidence of lung cancer. Survivors of the atomic bombs dropped on Japan disclosed a markedly increased incidence of leukemia, thyroid, breast, lung and colonic carcinomas. Thyroid cancers have developed in about 9% of those exposed during their childhood to head and neck radiation. Young women (below the age 40) exposed to mammography may show a higher risk of developing breast cancer. Finally, a higher risk of lung cancer was also associated with indoor levels of radon gas emanating from soils containing uranium deposits.

The mechanism of radiation injury to DNA is explained by two theories, namely: a) radiation directly ionizes DNA molecules, or b) according to the indirect theory, it first interacts with water or molecular oxygen to produce free radicals that mediate the damage. Radiant energy causes chromosomal breakage, translocations and point mutations. Carcinogenicity of radiation appears to correlate best with its mutagenicity, being highest with neutrons and alpha particles. Also, children are more vulnerable than adults.

Solar radiation. Ultraviolet radiation from the sun is a major cause of skin cancer, both squamous and basal cell carcinomas, as well as, melanoma. The degree of risk depends on the intensity of exposure and the quantity of melanin pigment in the skin which plays a protective role. Also of vital importance are a group of enzymes which normally excise and repair any DNA segment containing a mutation. The high incidence of skin cancer in individuals with fair skin as well as patients with albinism is due to the deficiency of melanin pigment. Whereas, in patients with xeroderma pigmentosum the high risk of skin cancer is due to hereditary deficiency of excision-repair enzymes of DNA.

Table 3-5 Radiation-Induced Human Cancers

Exposure	Cancer Types
Nuclear weapons	
Blast	Leukemia and solid tumors
Fallout	Thyroid
Diagnostic and therapeutic	Leukemia and solid tumors
Professional exposure	
Early radiologists	Leukemia, skin
Uranium miners	Lung Cancer
Nuclear industry	Multiple myeloma
Radium dial painters	Osteosarcoma

Chronic Infections

Chronic infections, whether bacterial, viral or parasitic, are associated with increased cancer risk, contributing about one third of world's cancer. *Helicobacter pylori bacteria*, which infect the stomach of more than one-third of the world's population, are a major cause of gastric carcinoma and MALT lymphoma. *Schistosoma hematobium* infestation is associated with bladder cancer in Egypt and similarly *Chlonorchis sinensis* is associated with biliary cancer in China. The inflammatory reaction to infection involves the production of potent oxidizing agents to destroy the organisms, which are also mutagenic to DNA. Bacterial activity also contributes to the increased endogenous production of nitrosamine and also stimulates cellular hyperplasia, which is a promoting factor.

Viruses play a major role in the etiology of cancer in domestic and laboratory animals. Conversely, they are a rare cause of human cancer, contributing only 5% of all cases. Oncogenic viruses fall into two classes, namely: DNA and RNA viruses. So far, seven viruses have been definitely associated with human cancers (Table 3-6), four are DNA type (Hepatitis B virus HBV, Epstein Barr virus EBV, Human herpes virus HHV-8 and Human papilloma virus HPV) and three are RNA type (Human T-cell leukemia virus HTLV-1, Human immunodeficiency virus HIV and Hepatitis C virus HCV). Except for HTLV-1 virus, none of the other viruses is sufficient alone to induce human cancer. Associated carcinogenic agents are necessary (initiators) with viruses acting as promoting factors.

Table 3-6 Human Oncogenic Viruses

Class	Virus type	Cancer
DNA Viruses	HBV	Hepatocellular carcinoma
	EBV	Burkitt lymphoma
		Nasal type T-cell lymphoma
		Hodgkin disease
		Nasopharyngeal carcinoma
	HHV-8	Kaposi sarcoma
	HPV-5, 8, 14	Skin squamous carcinoma
	HPV-6,11	Verrucous carcinoma
	HPV-16, 18,31,33,35	Uterine carcinoma, oral cancer
	HPV-30,40	Larynx
RNA (Retro-viruses)	HTLV-1	Adult T leukemia/ lymphoma
	HIV	Kaposi sarcoma
		Non-Hodgkin lymphoma
		anal, skin squamous carcinoma
		Pediatric leiomyosarcoma
	HCV	Hepatocellular carcinoma

DNA Oncogenic Viruses

1. Hepatitis B virus (HBV) is a member of heapdenoviruses, also called Dane's particle following the name of its discoverer. The mature HBV virion is a spherical double layered structure with an outer surface envelope of protein, lipid, and carbohydrate, enclosing a slightly hexagonal core containing the DNA and polymerase. The genome of HBV is a partially double-stranded DNA molecules (Fig 3-4) and it encodes the following proteins: (a) envelope surface protein (HBsAg) (b) nucleocapsid core protein (HBcAg) (c) DNA polymerase, and (d) A protein from the X region (HBX) which is necessary for virus replication by acting as a transcriptional transactivator of both viral and cellular genes.

HBV infections pass through two phases. During the proliferative phase, viral DNA is present outside cellular DNA (episomal form) with formation of complete virions and marked cell damage (necrosis followed by cirrhosis). In the integrative phase, viral DNA is incorporated into the host genome (Fig 3-5). Only two viral genes, HBX and pre S2/S are usually retained intact after viral DNA integration, hence it is incapable of reproduction.

A close association exists between HBV infection and the incidence of hepatocelluar carcinoma. Thus, HBV infection is endemic in the Far East Asia and tropical Africa, where 10% of the population are HBV carriers. These two areas have the highest incidence of liver cancer. Viral DNA is identified in the nuclei of tumor cells. Infection

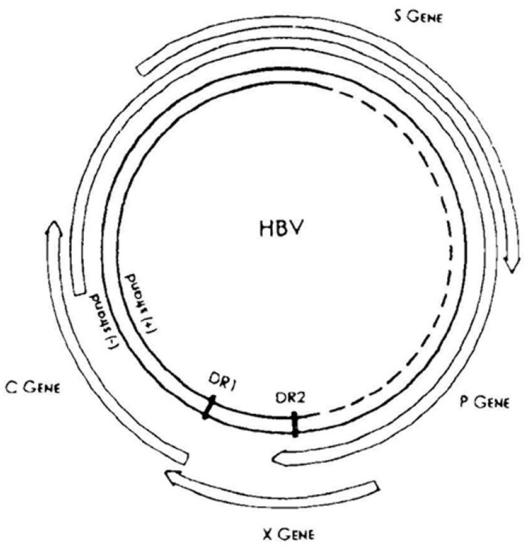

Fig 3-4 *Structure of HBV genome, dashed line represents the single-stranded region of viral genome.*

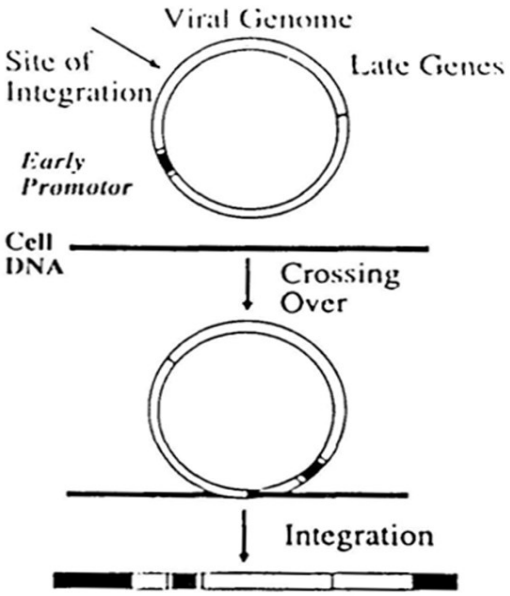

Fig 3-5 *Integration of viral DNA into the DNA of the host. Early viral genes are essential few transformations.*

occurs in children, and tumors develop in adults, with a latent period of about 35 years. This suggests that the virus is a weak transforming agent.

The role of the virus is probably indirect, by producing liver necrosis with subsequent cell regeneration and cirrhosis (promotion). Synergistic initial carcinogenic factors (e.g. aflatoxin) is necessary. Recently, however, a direct role of the virus is considered possible. Thus, the viral genome after integration into cellular DNA may encode a regulatory element (HBX protein) which transactivates cellular proto-oncogenes, and or, inhibits p53 protein product.

2. Epstein-Barr virus (EBV): This virus, a member of the herpes family, infects more than 90% of the human population by the age of 20 years, usually without any manifestation of disease. The virus exhibits a strong tropism to B lymphocytes and squamous cells of pharynx both of which express a surface receptor molecule which serves also as a receptor for EBV. Virus strains are classified into two main types: type I (common in Western countries) and type II (prevalent in central Africa and New Guinea). EBV has been implicated in the pathogenesis of 4 types of cancer, namely : Burkitt's lymphoma, nasal type T-cell lymphoma, Hodgkin's disease and nasopharyngeal carcinoma.

Burkitt's lymphoma is the most common pediatric tumor in tropical Africa. An identical lymphoma also occurs sporadically throughout the world. About 100% of the African tumors carry EBV-antigen (EBNA), whereas, in non-African Burkitt's lymphoma, only 20% of cases carry that antigen. In endemic areas such as China, 100% of the nasopharyngeal tumors carry the EBV-antigen, Within the infected cell, the linear genome of EBV circularizes to form an episome in the cell nucleus outside DNA (nonintegrated). The infection in the cells is latent, without viral replication or cell kill.

Four of the viral genes are considered most important for cellular transformation, namely: Epstein-Barr nuclear antigens EBNA-1 and EBNA-2, and the latent membrane protein LMP -1 and LMP-2. A chromosomal translocation t(8:14) is present in 80% of Burkitt lymphomas. This results in activation of c-myc proto-oncogene with immortalization and proliferation of B-lymphocytes. The role of EBV in nasopharyngeal carcinoma is probably mediated by LMP-1 which is expressed in 65% of tumors. EBNA-2 may also activate Bcl-2 and blocks apoptosis, leading to immortalization and accumulation of cells.

3. Human herpes virus (HHV-8): also known as Kaposi sarcoma herpes virus (KSHV) has recently been implicated in the pathogenesis of Kaposi sarcoma. The virus is sexually transmitted and infects B cells. The lesion is characterized by

monoclonal proliferation of perivascular mesenchymal cells. This proliferation is triggered by cytokines produced by the KSHV-infected lymphocytes. However, mitogenic cytokines liberated from mesenchymal cells or HIV-infected T-helper lymphocytes and tat protein may also play a role.

4. Human papilloma viruses (HPV) make up a large family and it is the most commonly diagnosed sexually transmitted infection in the United States. It is associated with anogenital condyloma acuminate (cervical, vaginal, vulval, penile, anal) and squamous intraepithelial lesions of head and neck cancer.

HPV is a small DNA virus of approximately 7900 base pairs. DNA sequencing techniques have facilitated HPV typing and characterization with each type formally defined as distinct by having less than 90 percent DNA base-pair homology with any another HPV type. There are over 40 HPV types that infect the anogenital area. HPV viruses show the same genome organization of at least seven genes (El to E7) and two late genes (LI and L2). The genes E6 and E7 are responsible for cell transformation (Fig 3.6). HPVs are classified into low and high-risk types according to the rate of malignant transformation (5% versus 33% respectively).

The low-risk types (6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 73 and 81) infect the genital tract and are associated with benign genital warts and mild dysplasia or low grade squamous intraepithelial lesion (LSIL), which are usually regressive lesions. The virus in these cases is maintained as an episome (nonintegrated circular form).

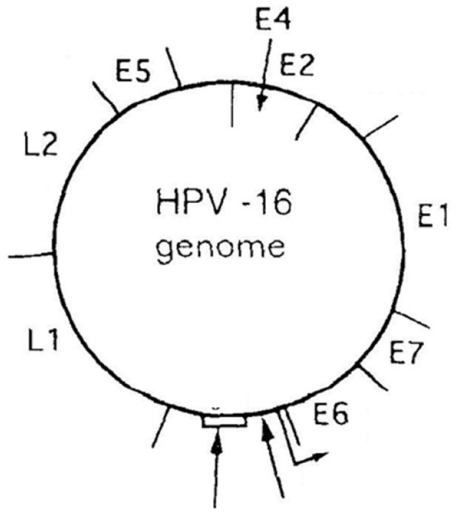

Fig 3-6 *Genomic structure of HPV16.*

The high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) are found in about 90% of all cervical uterine cancers. Types 16 and 18 are the most commonly isolated HPV types in cervical cancer with type 16 found in approximately 50 percent of patients. However, not all infections with HPV type 16 or 18 progress to cancer. Furthermore, within single oncogenic HPV types, variants exist that are associated with different oncogenic potential. In high-risk types, the virus is randomly integrated into host DNA, with expression of E6 and E7 viral proteins which bind and inhibit p53 and Rb protein products respectively, resulting in cellular transformation.

HPV is also implicated in cancer of the anus. The spectrum of HPV types in the anal canal is similar to that described in the cervix and is associated with the same risk phenotypes. HPV 16 is also the most commonly detected HPV type associated with anal cancer. Using PCR typing techniques, one group has isolated 29 individual HPV types and 10 HPV groups from the anal canal of men who have sex with men (MSM), both with and without HIV infection. The range of HPV types is similar in the HIV-positive and HIV -negative men. A few of the more commonly isolated HPV types in the anal samples have only rarely been reported in cervical samples (types 53, 58, 61, 70). HPV 32, characteristically an oral HPV type, was also isolated from anal samples and may indicate transmission by oral-anal intercourse.

HPV is also associated with squamous carcinomas in other locations especially skin (tumors with epidermodysplasia verruciformis), verrucous carcinoma, laryngeal cancer and oral carcinoma.

RNA Oncogenic Viruses

All oncogenic RNA viruses are retroviruses. They are so named because they contain the enzyme reverse transcriptase, which allows the transcription of viral RNA into viral DNA, an essential step before viral integration into cellular DNA. This is the reverse to what normally happens in the nucleus, where DNA is transcribed to RNA.

Retroviruses belong to the C type virus particles. These are characteristically extracellular particles that develop by budding from cell membrane and their envelope encloses a centrally placed dense core (capsid) containing two strands of RNA and the enzyme reverse transcriptase (Fig 3-7).

After penetrating the plasma membrane the capsid is uncoated with release of RNA. The single stranded viral RNA genome is reversely transcribed to double stranded DNA. At the ends of this double stranded DNA regulating units called the long-terminal repeats (LTR) are developed. These linear DNA molecules migrate to the nucleus and integrate into cellular DNA where it is called the provirus (Fig 3-8).

Retroviruses are classified into two main classes according to their transforming activity, namely: *acute transforming viruses* which affect lower animals and are characterized by the rapid induction of tumors in the infected hosts. They contain special transforming sequences (viral oncogenes, v -onc), which are derived from cellular DNA (proto-oncogenes), and are incorporated (transduced) into viral genome during the process of viral replication within a normal cell. The viral oncogene is inserted in place of deleted viral replicative genes (Fig 3-9). Hence, this virus type is potent in malignant transformation, but deficient in viral replication. It needs a helper virus for its replication.

Slow transforming retroviruses represent the classic types which affect human. They do not have oncogenes, hence they produce tumors after a long latent period. They are replication competent and display typical retroviral genomic organization (Fig 3-10), with 4 sets of genes gag, pol, env and TAT, bound on each side by the promoters LTR. The gag codes for viral core protein, pol encodes for reverse transcriptase, env codes for envelope protein and TAT codes for a special protein (tax) which may activate viral LTR or cellular genes.

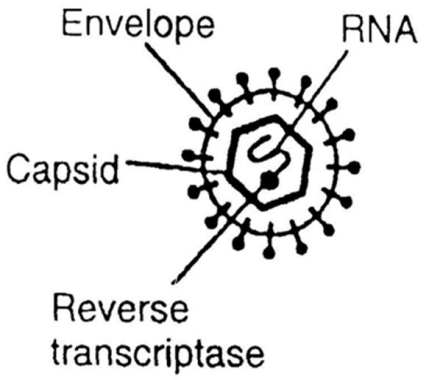

Fig 3-7 *Structure of RNA virus.*

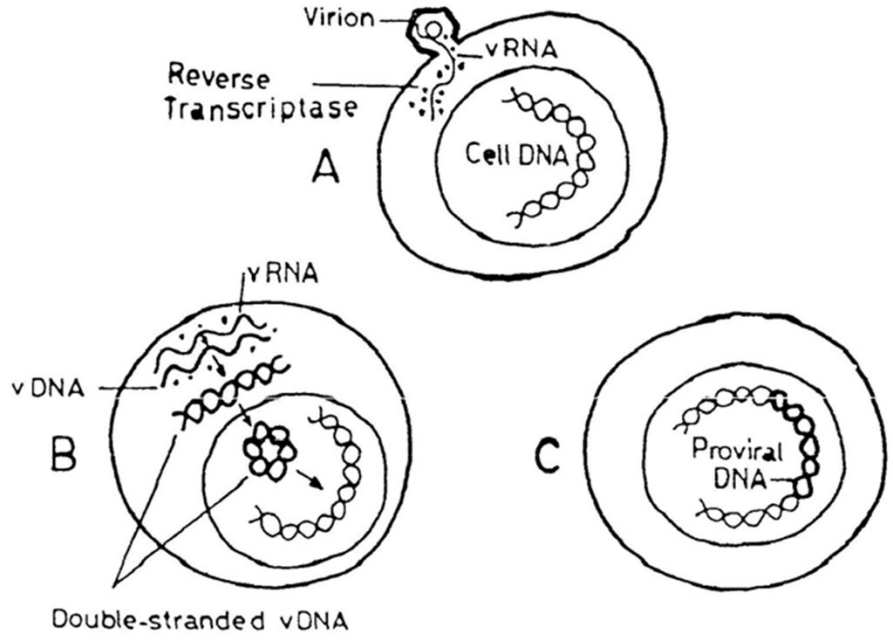

Fig 3-8 *Phases of retrovirus infection. (A) Cell penetration, (B) Reverse transcription to single stranded then double stranded DNA, (C) Integration of proviral DNA into host DNA.*

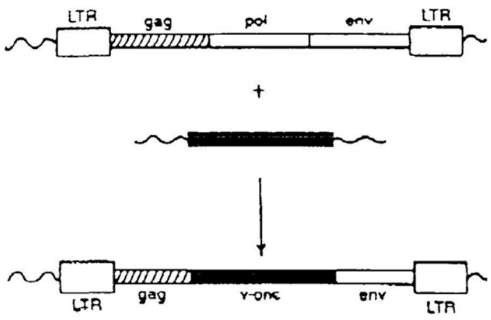

Fig 3-9 *Genomic structure of acute transforing virus. Viral oncogene (v-onc) is derived from cellular protooncogene through a process of transduction.*

Three human retroviruses which are related to human cancer are: The human T-cell leukemia virus (HTLV-1), human immunodeficiency virus (HIV) and hepatitis C virus (HCV).

1. HTLV-1. The virus is associated with a highly aggressive T-cell lymphoma/ leukemia which is endemic in Southern Japan and Caribbean. Transmission of the disease may occur through blood transfusion, breast feeding and sexual intercourse. Infection is more common than malignancy, and less than 1% of the seropositive patients ever develop the disease, with a long latent period of several years. The leukemia/ lymphoma is associated with skin manifestations and hypercalcemia and is rapidly fatal in few months.

Although the provirus integrates randomly into the DNA of infected cells, it is found preferentially close to the proto-oncogene in the tumors that develop (Fig 3-10). This indicates that HTLV-1 is involved in cell transformation and not a passenger virus The development of malignancy is explained by three mechanisms: (1) promoter insertion: the pro viral LTR acts as a promoter to activate cellular proto-oncogene into cellular oncogene (c-onc) which is responsible for transformation, (2) enhancer insertion: occurs if the provirus LTR will stimulate a cellular enhancer that controls a cellular proto-oncogene, and (3) TAT gene product (tax protein) is involved in transactivation of cellular genes involved in cell proliferation (e.g. IL-2, c-myc, c-fos, c-jun, bcl-2 and GMCSF). The virus first infects T-helper cells (CD 4) which secretes IL-2 causing T-cell expansion. The T-cell proliferation is first polyclonal then ultimately becomes monoclonal (neoplastic).

2. HCV: Hepatitis C virus is the major causative agent of HCC, mainly through indirect pathways: Chronic inflammation, cell deaths, and proliferation. There is more risk to develop hepatomas with HCV infection more than HBV infection because the former is more associated with chronic hepatitis and cirrhosis. Clinical research using transgenic mouse models, in which the core protein of HCV has an oncogenic potential, indicate that HCV is directly involved in hepatocarcinogenesis. Recent data has shown that HCV is capable of inducing this active production of free radicals per se, and it is not just through inflammation, a feature peculiar to this virus and the specific activity of its core protein. In addition, viral overproduction accumulates toxic quantities of the surface antigen within the hepatocyte. The latter develops a severe, prolonged hepatocellular injury that initiates a programmed response within the liver, characterized by inflammation, regenerative hyperplasia, transcriptional deregulation, and aneuploidy that progresses to neoplasia.

The risk of developing HCC for a patient with

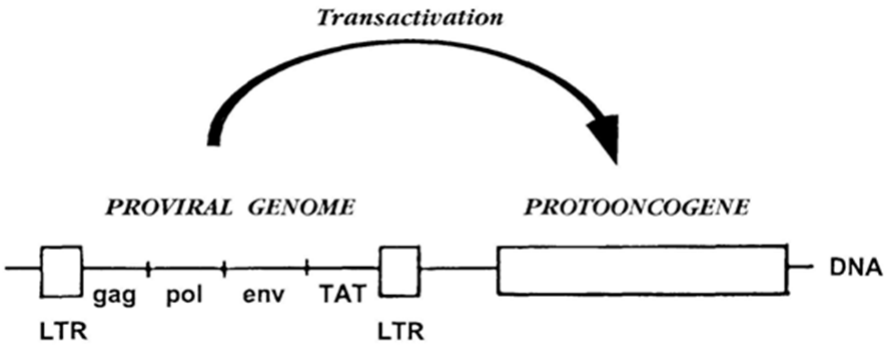

Fig 3-10 *Genomic structure of slow transforming RNA virus. Viral TAT and LTR products activates cellular protooncogenes (transactivation).*

HCV-related cirrhosis is approximately 2-6% per year. HCC risk increases to 17-fold in HCV-infected patients compared to HCV-negative subjects. In general, HCC develops only after two or more decades of HCV infection and the increased risk is restricted largely to patients with cirrhosis or advanced fibrosis. Cirrhotic patients infected with HCV type 1b carry a significantly higher risk of developing HCC than patients infected by other HCV types.

3. HIV and AIDS-Associated Malignancies: Acquired immunodeficiency syndrome (AIDS) is defined as an epidemic disease caused by the retrovirus HIV (discovered in 1983) and characterized by profound immunosuppression, associated with opportunistic infections, secondary neoplasms and neurologic manifestations. HIV is one of the world's leading infectious killers, claiming more than 25 million lives over the past three decades. There were approximately 34.2 million people living with HIV in 2011 (60% of those are living in sub-Saharan Africa and 3.4 are <15 years, WHO data 2011). HIV infection can be diagnosed through blood tests detecting presence or absence of antibodies and antigens. A cure for HIV infection has not been found but with effective treatment with antiretroviral drugs, patients can control the virus and enjoy healthy and productive lives. In 2011, more than 8 million people living with HIV were receiving antiretroviral therapy in low and middle-income countries.

In the Middle East and North Africa, the total number of those living with HIV infection by the end of 2010 was 560000 and prevalence rate for adults (15-49 years) is 0.2%. Deaths due to AIDS in the same period was 38000. Data collected from 12 Arab Countries showed that the number of those living with HIV infection by end of 2009 was 409300. From those 63.5% are present in Sudan, 8.3% in Somalia, 6.4% in Morocco (this includes data from Western Sahara), 6.1 in Eritrea, 3.4% in each of Mauritania and Djibouti. In Egypt 11000 were living with HIV by end of 2009 and less than 500 were dead from AIDS (WHO data).

Epidemiologic studies indicate that there are three basic modes of HIV transmission: (1) unprotected sexual intercourse, whether heterosexual or homosexual. When it was first recognized in the USA it was predominantly a disease of homosexuals and drug abusers, but heterosexual transmission is now common. In sub-Saharan Africa, the area of the world with the highest number of AIDS cases, it is predominantly a heterosexual disease, (2) contaminated blood and blood products, and (3) maternal-fetal transmission (during pregnancy, childbirth or during breast feeding). Epidemiologic data do not support transmission by casual contact.

The course of HIV infection can be best understood in terms of interplay between HIV and the immune system. Three phases are recognized, namely: (1) an early acute phase of viral dissemination, (2) an inter-mediate chronic phase of latent virus and (3) a final crisis phase of viremia, opportunistic infections and neoplasia (AIDS phase). It can take 10-15 years for an HIV-infected person to develop AIDS; antiretroviral drugs can slow down the process even further.

It has been estimated that up to 40% of AIDS patients will develop neoplasms as their immunodeficiency becomes more profound. The incidence of these malignancies is increasing as prolonged survival in AIDS becomes more common. The four most common tumors, with descending order of frequency, are: Kaposi's sarcoma (KS), B-cell non-Hodgkin's lymphoma (NHL), Hodgkin's disease (HD) and cervical cancer in women. Recently, two other neoplasms were reported namely: carcinoma of the anal region in homosexual AIDS patients and leiomyosarcomas in children.

Virology

HIV virion is spherical and contains an electron-dense core surrounded by a lipid envelope. The virus core contains several core proteins, two strands of genomic RNA and the enzyme reverse transcriptase which allows the virus to synthesize a DNA copy of its RNA genome. Studding the viral envelope are two viral glycoproteins gpl20 and gp41, which are critical for HIV infection of cells (Fig 3-11). The viral genome contains the tat gene which transcribes a protein that may activate other genes in the virus or host cell.

HIV virus has a selective tropism for T-helper lymphocytes (CD4). This is explained by the high affinity of gpl20 envelope protein to bind with CD4 surface lymphocyte receptors. Once internalized, the viral genome undergoes reverse transcription, leading to formation of viral DNA that is then integrated into the host genome. The virus may remain latent or undergo reproduction leading to cell death. The selective cytopathic effect of HIV on T4 lymphocytes will profoundly affect the immune system, considering the pivotal role of T4 in regulating all other cells of the immune re-

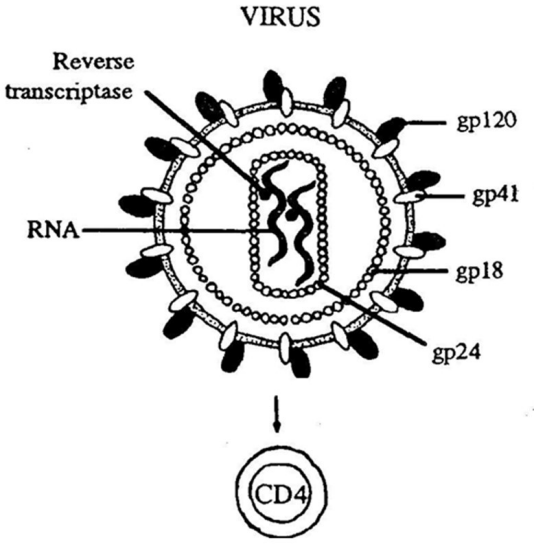

Fig 3-11 *Structure of HIV virus.*

sponse. Therefore, loss of this master cell will impair both cellular and humoral immunity.

Pathogenesis

The mechanisms involved in AIDS-associated malignancies remain poorly understood. However, both direct and indirect mechanisms are possible, with the latter probably playing a more important role. The direct mechanisms may involve the production of viral oncoproteins (tat gene products) leading to transactivation of cellular oncogenes. Disturbances of normal cytokine milieu, as a result of viral infection may possibly provide the specific signal for cancer development. Moreover, the immunodeficiency resulting from HIV infection will generally undermine the immune surveillance mechanisms against cancer.

Conversely, indirect mechanisms are related to other opportunistic oncogenic viral infections in AIDS patients, such as: EBV and the development of lymphomas, as well as, the sexually-transmitted virus (HPV) and carcinoma of the uterine cervix and carcinoma of the anal region. Accordingly, AIDS-associated malignancies, may be regarded as opportunistic neoplasms in the immunocompromized host not directly related to HIV.

EPIDEMIC KAPOSI SARCOMA

Kaposi sarcoma is the most common HIV/AIDS-related cancer, and it is more common in men than women. It is estimated that a person with an HIV infection is 20,000 times more likely to develop Kaposi sarcoma than a person without HIV. However, Kaposi sarcoma has decreased due to improved HIV treatment. It develops most commonly (70%) in homosexual men and the lesions may arise early prior to immunosuppression. This suggests a sexually-transmitted etiologic agent independent from HIV, such as the recently identified human herpes virus 8 (HHV8).

Pathogenesis

Kaposi sarcoma (KS) is a locally aggressive endothelial tumor that typically presents with cutaneous lesions in the form of multiple patches, plaques or nodules but may also involve mucosal sites, lymph nodes and visceral organs. The development of Kaposi sarcoma in AIDS patients appears to be a multifactorial event. Expression of viral oncoproteins (HIV-tat gene products) may initiate the process of cell transformation. Moreover, CD4 cells chronically infected by HIV may produce oncostatin, a cytokine which either directly or indirectly via induction of interleukin-6 (IL-6), serves as a major growth factor for Kaposi sarcoma. The most important recent development in this field has been the discovery that a new human herpes virus (HHV8) is present in almost 100% of Kaposi sarcoma lesions, whether HIV-related, classic, endemic, or iatrogenic. HHV8, also known as Kaposi sarcoma-associated herpes virus (KSHV), is a gamma-herpes virus closely related to EBV. It is believed to be necessary but not sufficient to cause the disease, with other factors (such as immunosuppression) probably playing a major contributory role. Parenthetically, HHV8 is also involved in the pathogenesis of multicentric Castleman disease and primary effusion lymphoma. DNA sequences of the virus and the protein encoded by this virus (ORF-73) have been detected in the spindle cells by in situ hybridization, PCR, and immunohistochemistry (the latter by using monoclonal antibody ORF-73).

Pathology

The histopathology of early lesions is characterized by marked vascular proliferation. Ultimately, there is perivascular infiltrate of spindle-shaped cells, extravasated erythrocytes and infiltrate of lymphocytes and plasma cells. Kaposi sarcoma spindle cells are probably endothelial in origin in view of factor VIII positivity. In more advanced lesions (nodular), the vascular component is reduced. The disseminated lesions of KS in visceral organs are closely associated with the feeding vessels.

Clinical Features

Epidemic or AIDS-associated Kaposi sarcoma differ from classic Kaposi tumor by the younger age, more widespread and multicentric skin lesions and more visceral involvement and aggressive course. Cutaneous lesions are reddish in color and appear macular, nodular or ulcerative. Mucosal involvement may occur in oral cavity or conjunctiva. Visceral involvement, of mainly the lungs and gastrointestinal tract, occur in 15% of patients with cutaneous lesions and 50% of patients with mucosal involvement. Finally, KS involves the lymph nodes and lymphatics causing marked local edema.

Staging

The most widely used staging system is that of Kriegel (1988) which is mainly based on the extent of the disease. Stage I represents cutaneous locally indolent KS, stage II is a locally-aggressive cutaneous disease, stage III defines generalized cutaneous and/or lymph node involvement and/or minimal gastrointestinal disease, and stage IV represents the presence of visceral disease. Another recent staging classification (Krown 1989) takes into consideration the presence of opportunistic infections and the severity of immunosuppression. Accordingly, unfavorable prognostic factors include: (1) visceral involvement, (2) CD4 cells below 200/microliter, (3) presence of opportunistic infections or B symptoms, and (4) performance status below 70. In most case series, the median survival of AIDS patients with KS is 18-24 months.

NON-HODGKIN LYMPHOMAS (NHL)

The estimated risk of NHL developing in a patient with symptomatic HIV infection is about 2% per year. In USA about 7% of AIDS patients have NHL.

Pathogenesis

Coinfection by a herpes virus, particularly EBV is the main etiologic factor. The EBV has been demonstrated in tumor cells in 90% of CNS lymphomas and 75% of large cell lymphomas. The virus infection causes polyclonal B-cell proliferation. In normal subjects, this lymphocytic proliferation is probably blocked by cell-mediated immunity. But, in AIDS patients with defective T-cell function, B-cell proliferation continues unchecked, with enhancement of spontaneous mutations and the development of monoclonal malignancy. Other genetic alterations include: c-myc translocation in 40% of cases, and less commonly, the abnormalities of p53 and ras oncogene.

Pathology

More than 80% of lymphomas in people with HIV/AIDS are high-grade B-cell lymphoma. About 20% of all people with both NHL and HIV/AIDS develop central nervous system lymphoma. This is compared to a low frequency (1%) in non-AIDS series. The histology of CNS lymphoma is usually large cell, immunoblastic subtype with characteristic perivascular distribution.

Clinical

NHL in AIDS patients is characterized by the high frequency of advanced stage, extranodal disease and B symptoms. Primary CNS localization is also frequent. Certain radiographic criteria help to differentiate CNS lymphoma from toxoplasmosis lesions. The former is located centrally (white matter and basal ganglia), more than 2 cm in size and may cross the middle line. The prognosis of NHL in AIDS patients is grim, and overall survival is less than one year.

HODGKIN LYMPHOMA

Hodgkin lymphoma is the third most common neoplasm associated with AIDS, after Kaposi's sarcoma and NHL. The ratio of HD to NHL in AIDS patients varies with age, with HD predominating before the age of 30 years and NHL predominating after the age of 30 years.

Pathogenesis

The immunodeficiency resulting from HIV infection could increase the susceptibility to pathogens involved in the etiology of Hodgkin disease. A probable candidate is EBV which is invariably demonstrated in Reed-Sternberg giant cells.

Pathology

The predominant histologic type in AIDS patients is mixed cellularity. Extra-nodal affection, such as skin, gastrointestinal, CNS and lung are more commonly affected (67%) than nodal disease. Lymph node spread is non-contiguous. There is also high frequency (48%) of bone marrow involvement.

Clinical

The majority of patients (85%) present in

advanced stage of the disease (III and IV) and at unusual sites. There is usually massive extranodal involvement (lung, liver, bone marrow, and intestine) with only modest lymph nodal disease. The median survival of AIDS patients with Hodgkin disease does not exceed 16 months.

CERVICAL CANCER

Because of an increased susceptibility to infection with human papilloma virus (HPV), about 11% to 29% of women with HIV/AIDS develop cervical intraepithelial neoplasia (CIN). Women with AIDS have a higher risk of developing invasive cervical cancer. A primary means by which HIV infection may influence the pathogenesis of HPV-associated cervical pathology is by molecular interaction between HIV and HPV genes. An upregulation of human papilloma virus E7 gene expression by HIV proteins (such as tat) has been postulated by some authors. Moreover, the E6 and E7 oncoproteins of HPV ultimately inactivate p53 and Rb proteins resulting in dysregulation of cell cycle and neoplastic development.

INTRINSIC FACTORS

Hereditary and Familial Cancers

In some types of cancer, there is familial clustering of the same type of cancer in the offspring who are at a higher risk than the general population. Two distinct types are recognized; namely: hereditary and familial cancers. Hereditary cancer is due to single gene affection or monogenic, with germline mutation of tumor suppressor gene. It follows Mendelian laws of inheritance with high specific risk in offspring (25% or 50%) and affection of one sex only if sex-linked. Conversely, familial cancers run in families and represent examples of multifactorial inheritance with interaction of multiple genes (polygenic) with environmental or hormonal factors. It does not follow Mendelian laws of inheritance. For first-degree relatives of affected patients, cancer risk is low (5-10%). Also, the cancers which develop in patients with inborn chromosomal abnormalities are not hereditary cancer, since the cancer risk is not transmitted to children. Examples of this group are: (a) patients with Down's syndrome or mongolism (trisomy of chromosome 21) who are predisposed to leukemia, and (b) male patients with Klinefelter's syndrome (XXY) who are predisposed to breast cancer and leukemia.

Special Features

The following are the seven cardinal features of hereditary cancer:

1. Familial clustering of the same type of cancer (site specificity).
2. Mendelian pattern of tumor transmission.
3. Identification of specific abnormal gene.
4. Early age of onset (<40 years).
5. Multicentricity and bilaterality of tumors.
6. Multiple primary cancers at different sites.
7. Associated congenital abnormalities.

Mechanisms

1. Loss of tumor suppressor genes (e.g. Rb, p53, WT1) resulting in cellular growth advantage.
2. Defective DNA repair mechanisms (e.g. xeroderma and HNPCC) or hypersensitivity to DNA damaging agents (e.g. Bloom syndrome, Fanconi anemia and ataxia telangiectasia).
3. Deranged signal transduction with upregulation of cellular proliferation (e.g. Men-2, NF-1 and APC).
4. Loss of cell adhesive molecules (E-cadherin) and cytoskeleton defect resulting in cell dissociation, loss of contact inhibition and differentiation signal (e.g. NF-2).
5. Congenital immunodeficiency with loss of tumor surveillance or opportunistic infection with oncogenic viruses.

Classification

Hereditary cancer is classified into four main groups according to the underlying hereditary defect, as well as, the type of Mendelian transmission (Table 3-7).

I-Inherited cancer risk

This group, is in a high risk disease, the appearance of disease in every generation, 50% incidence and equal sex affection (Fig 3-12). The increased cancer risk is mainly due to loss of tumor suppressor genes . The following are examples with indication of gene involved, chromosomal location and the resulting tumors.

1. Familial retinoblastoma (Rb/13q) with predisposition to retinoblastoma, as well as, brain tumors, pineoblastoma melanoma and breast carcinoma.
2. Familial Wilms tumor (WTl/llp) with increased risk of nephroblastoma.
3. Li-Fraumeni syndrome (p53/17p) a germline mutation of p53 predisposes to breast cancer and sarcomas.

Table 3-7 Classification of Hereditary Cancer

Group	Mendelian transmission
I- Inherited cancer risk	Autosomal recessive
II- Inherited precancerous lesions	Autosomal dominant
III- Inherited precancerous syndromes	Autosomal recessive
IV- Inherited immune-deficiency	X-linked

4. Von-Hippel - Lindau (VHL/3p) is associated with renal cell carcinoma and pheochromocytoma.
5. MEN-2 (Ret/ l0q) is associated with thyroid medullary carcinoma and pheochromocytoma.
6. Cancer family syndromes, including: (a) Breast cancer type 1 (BRCA-l/17q) is associated with breast and ovarian cancers. (b) Breast cancer type 2 (BRCA-/13q) with increased risk of breast cancer only, (c) HNPCC-l (Lynchl:hMLH-l/3p) hereditary nonpolyposis cancer colon is associated with increased risk of cancer colon only, (d) HNPCC-2 (Lynch 2: hMSH-2p) is associated with increased risk of cancer colon, as well as, extracolonic cancers mainly breast, endometrium and urothelial.

II- Inherited precancerous lesions

These are also autosomal dominant and the inherited precancerous lesion may turn malignant, or may be associated with malignancy. The following are examples:
Familial polyposis coli or adenomatous polyposis (APC/5q): colon cancer;
Gardner's syndrome: colon cancer; and Peutz-Jegher syndrome: small intestine
Von-Recklinghausen (NF-l/17q): Neurosarcoma and gliomas; and acoustic neuroma (Merlin/22q): gliomas
Genodermatosis: Dysplastic nevus syndrome: malignant melanoma. Basal cell nevus syndrome: basal cell carcinoma. Multiple trichoepithelioma: visceral malignancy. Porokeratosis of Mibelli: squamous carcinoma. Epidermodysplasia verruciformis: squamous carcinoma. Tylosis: esophageal cancer. Cowden's disease or multiple hamartoma syndrome. (PTEN/ chromosome 10): breast, thyroid and uterine cancers.

III-Inherited precancerous syndromes

These are autosomal recessive syndromes, characterized by skipped generations without manifest disease, affection of 25% offspring and equal sex affection. They are associated with increased cancer risk. The following are illustrative examples of this group:
1. Xeroderma pigmentosum (ERCC/8): skin cancer.
2. Bloom syndrome: leukemia and gastrointestinal cancer.
3. Fanconi anemia (FACC/4): acute myeloid

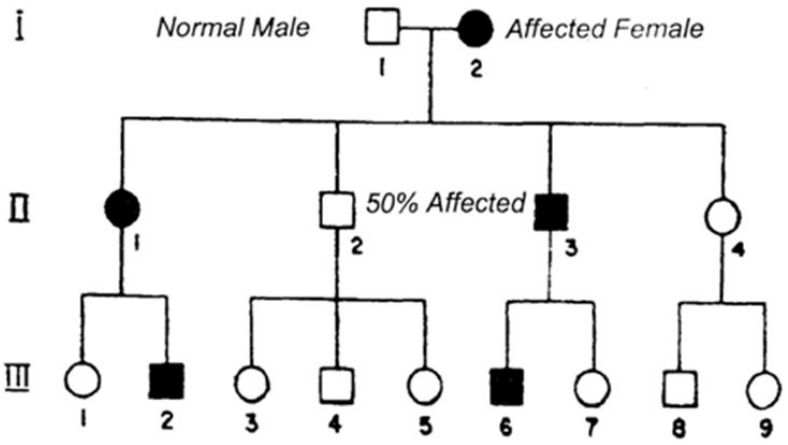

Fig 3-12 *An illustrative pedigree of autosomal dominant inheritance. Both sexes are affected in every generation with an overall frequency of 50%.*

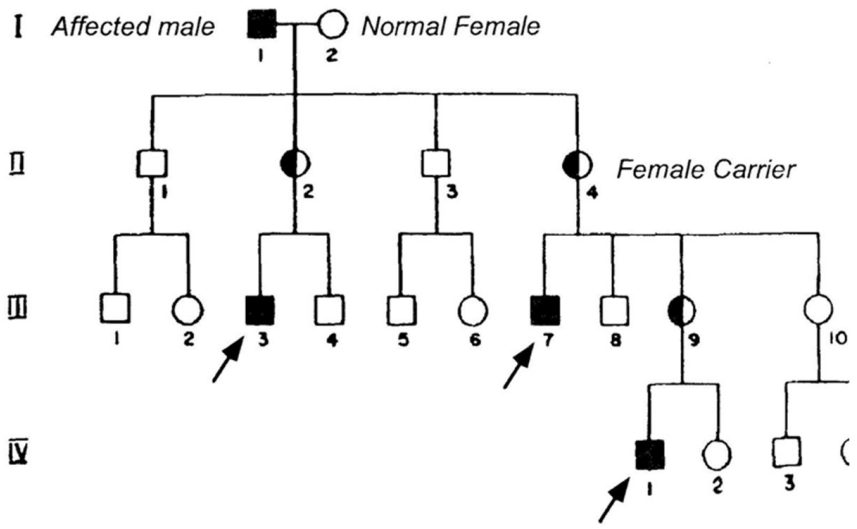

Fig 3-13 *An illustrative pedigree of X-linked recessive inheritance. Only males are affected by the disease (arrows) and females only act as carriers of the disease.*

leukemia.
4. Ataxia telangiectasia (ATM/llq): lymphoma.
5. Tuberous sclerosis: gliomas.
6. Gonadal dysgenesis: dysgerminoma and gonadoblastoma.

IV- Inherited immunodeficiency

These are inherited as x-linked (Fig 3-13) and there is increased risk of malignant lymphoma (NHL) and leukemia (e.g. Wiscott-Aldrich syndrome, infantile agammaglobulinemia and severe combined immunodeficiency).

IMMUNOSUPPRESSION AND CANCER

The WHO (2000) recognizes 4 clinical settings of immunosuppression and called it *immunodeficiency-associated lymphoproliferative disorders*: (1) Primary immunodeficiency syndromes, (2) infection with HIV virus (AIDS), (3) post transplant immunosuppression and (4) iatrogenic immunosuppression associated with methotrexate treatment (mainly rheumatoid patients).

Three main mechanisms are operable in lymphomagenesis, namely: (1) defective immune surveillance to oncogenic viruses (e.g. EBV and HHV-8) as well as chronic antigenic stimulation (in congenital immune deficiency, AIDS and organ transplant recipients), (2) defective DNA repair (as in ataxia telangiectasia). And (3) defective apoptosis, as well as inherent risk for the development of lymphoma in patients with autoimmune disease.

The histopathologic profile of lymphoprobferative disorders encountered is generally similar to those observed in sporadic patients in whom the disease passes through 3 stages: (1) early stage of plasmacytic hyperplasia with intact architecture, (2) polymorphic cell stage with loss of nodal architecture, and (3) a final monomorphic large cell lymphoma stage with lost architecture.

Congenital (Primary) Immunodeficiency

A group of genetically-determined immunodeficiency diseases are recognized (Table 3-8) which are associated with increased risk of cancer. They differ according to their underlying immune defect, extent of cancer risk and the types of evolving tumors. The highest risk of cancer is reported in X-linked lymphoproliferative syndrome. Conversely, the more severe forms of immunodeficiency (e.g. infantile sex-linked hypogammaglobulinemia) have low malignancy rates as a result of the short survival of these severely compromised individuals. Non-Hodgkin's lymphomas account for over one half of the malignancies and tend to arise at unusual extranodal sites such as the brain and gastrointestinal tract.

Table 3-8 Cancer in Congenital (Primary) Immunodeficiency

Syndrome	Cell Defect	Risk %	Tumors
X-linked lymphoproliferative syndrome	B and T	35	NHL
Wiskott-Aldrich	B and T	15-30	NHL, AML
Ataxia telangiectasia	B and T	12	NHL, ALL, NS, OV, SK, ST
Severe combined immunodeficiency	B and T	1.5	NHL, HL, ALL
Infantile sex-linked hypogammaglobulinemia	B	0.7	NHL, ALL
Thymic hypoplasia (DiGeorge)	T	unknown	NS

(Blattner and Hoover, 1985). Abbreviations: NHL Non-Hodgkin lymphoma, HL Hodgkin lymphoma, ALL acute lymphatic leukemia, NS nervous system, OV Ovarian, Sk Skin, ST Stomach, AML acute myelogenous leukemia

Acquired immunodeficiency

AIDS was previously discussed page 42-43.

Iatrogenic Immunodeficiency

Immunosuppressive therapy is usually given to patients undergoing organ transplantation. Most regimens involve a combination of drugs such as: azathioprine (Imuran), cyclosporin A, cyclophosphamide and prednisone. The increased risk to develop cancer is limited to certain tumor types, whereas, common tumors such as breast and colon cancers are not increased. The 4 tumor types which develop in these patients with increased risk and their relative frequency in a series of 1436 tumors encountered in organ allograft recipients (Penn 1982) are as follows: squamous carcinoma of skin (20%), non-Hodgkin's lymphoma (14.5%) Kaposi sarcoma (3.3%) and malignant melanoma (1.5%). The incidence of lymphoma is 50 times more than expected and characterized by frequent involvement of the central nervous system. Squamous skin cancer in the immunosuppressed (20 times more risk than normal) is also a more aggressive tumor. The average time of onset of tumors from the start of therapy is 2.4 years in case of lymphomas and 4.5 years for non-lymphomatous tumors. Female patients under immunosuppressive therapy are prone to develop dysplasia of the uterine cervix, which in some patients may progress to carcinoma.

Chemotherapy and radiotherapy given to cancer patients also have immunosuppressive effects. The treated patients who are cured of their original tumors may develop second primary cancers etiologically related to such therapy. The most common second malignancies are leukemias especially AML (50%), lymphomas (13%) and carcinomas of the urinary bladder (9%). The latent period is 2 to 7 years in case of chemotherapy and 10 to 15 years after radiotherapy.

HORMONES AND CANCER

Endogenous hormones play a major role in the etiology of several human cancers, namely : breast, endometrium, ovary, prostate, testis, thyroid and bone. Neoplasia of hormone target tissues currently accounts for more than 40% of all newly diagnosed female cancers and 35% of all male cancers. A key element in the pathogenesis of the tumors is excessive hormonal stimulation of the particular target organs (Fig 3-14) . In general, hormones act as promoting factors.

1. Breast carcinoma: The underlying hormonal imbalance is predominance of estrogen over progesterone. Thus, early menarche and late menopause are associated with increased risk of breast cancer. In obese individuals, the enzyme aromatase in adipose tissue converts androstenedione into estrone which is subsequently transformed to the more potent estradiol, thus explaining the increased risk of breast cancer in such

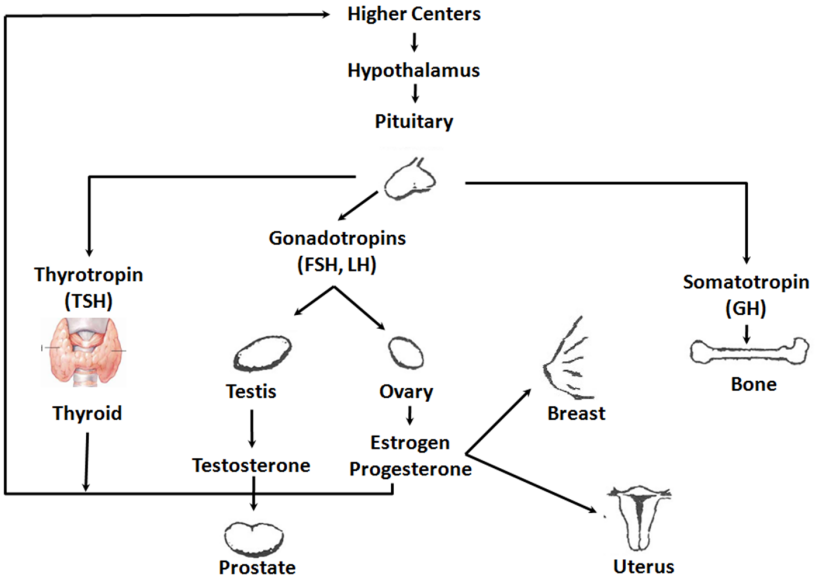

Fig 3-14 *Hypothesized relation of different hormones and human cancer.*

individuals. The production of the growth factor TGF-α , which is mediated by estrogen, is necessary for tumor promotion.

2. Endometrial carcinoma: Most cases of endometrial carcinoma (80%), especially premenopausal patients, are related to hyperestrinism. Endometrial carcinoma may also occur as a side effect of estrogen-secreting granulosa cell tumors, and because of hormone dependence the endometrial carcinoma may regress after excision of the ovarian tumor. Progesterone has an antiestrogenic activity. Thus, the use of oral contraceptive pills containing both estrogen and progesterone for at least one year decrease the risk of endometrial carcinoma by 50%. The mechanism of antiestrogenic effect of progesterone is a double-one. First, progesterone reduces the concentration of estradiol receptors, and second, it increases the activity of the enzyme system that converts estradiol to estrone which is biologically less potent.

3. Ovarian carcinoma: The hormonal basis of ovarian cancer is explained by the incessant ovulation theory. Accordingly, repeated ovulations will traumatize the surface epithelium and leads to its proliferation. Thus, the carcinogenic effect of gonadotropins is an indirect one by increasing ovulation. This theory is supported by the rare incidence of ovarian carcinoma in nulliparous women, as well as, in patients with anovulatory cycle or users of contraceptive pills which inhibit ovulation .

4. Prostatic carcinoma: The hormonal imbalance underlying prostatic carcinoma is mainly an increase of testosterone of testicular origin, and to a lesser extent due to increase of androstenedione of adrenal origin. A high dietary meat and fat leads to increase of androgen levels. In the prostate, testosterone is converted to dihydrotestosterone (DHT) through the action of the enzyme 5-α reductase. DHT is bound to the androgen receptor, and the hormone-receptor complex is translocated into the nucleus where it acts as a transcriptor factor for genes responsible for the proliferation of prostatic epithelium. This hormonal mechanism is the basis of hormone manipulation therapy for prostatic cancer (e.g. castration, antiandrogens and LHR hormone agonists).

5. Testicular cancer: The age specific incidence rates of malignant germ cell tumors of the testis peak in early adult life. This suggests that the etiology of testicular germ cell neoplasm may involve in utero abnormal hormonal exposure of the testes (estrogen excess hypothesis). Cryptorchidism is also related to high estrogen levels early in pregnancy and represents another pathway leading to germ cell tumors of testis.

6. Thyroid carcinoma: Excess of pituitary TSH is of etiologic importance in the development of thyroid carcinoma, especially follicular carcinoma. Iodine deficient diet leads to elevated TSH levels. Moreover, the predominance of thyroid carcinoma in females suggests that sex hormones may also play a role. However, another explanation for this incidence increase is the increased level of TSH induced by increased demand for thyroid hormones triggered by physiological changes of

the female child-bearing age. Suppression of TSH release by the administration of thyroxin is an effective treatment for differentiated thyroid carcinoma.

7. Osteosarcoma is probably related to the growth hormone somatotropin. Thus, osteosarcomas are most common in adolescents and commonly affecting the metaphyses of long bones, an age and site of maximal skeletal growth

PREMALIGNANCY

Premalignancy refers to a lesion or a condition (syndrome) that tends to become malignant. The cancer risk varies considerably. Thus, in few cases this risk is inevitable (100%) and urgent treatment is needed (e.g. familial polyposis of colon, xeroderma pigmentosum and Hutchinson melanotic freckle of the skin). Cancer risk is also high (50%) in villous adenomas of colon. However, fortunately, the majority of cases are of low risk (2-5%) requiring only careful follow up. Premalignancy is classified into two main groups: precancerous lesions and precancerous syndromes. Each group is subclassified into four classes, namely: precarcinomas, premelanomas, presarcomas and prelymphomas (Table 3-9).

Precarcinomas are rather commonly encountered lesions in clinical practice and fall under three subgroups: inflammatory lesions, dysplasia and benign tumors. *(1) Inflammatory lesions* notable examples are: chronic ulcers and sinuses of skin, chronic ulcerative colitis and calcular disease of gall bladder and urinary passages. Chronic inflammatory lesions induce a state of tissue destruction and regeneration allowing for genetic faults and dysplasia to occur. *(2) Dysplasia* (atypical hyperplasia) may affect different sites and can be initiated by chronic inflammatory condition, chronic exposure to physical injurious agent or infection by oncogenic virus. Examples include: skin (solar keratosis), oral cavity and larynx (leukoplakia), esophagus (Barrett's intestinal metaplasia with dysplasia), stomach (H. pylori gastritis with intestinal metaplasia and dysplasia), liver (hepatitis with cirrhosis), breast (atypical ductal hyperplasia), cervix (high-grade Squamous Intraepithelial Lesion HSIL), and urinary bladder (bilharzial-associated urothelial dysplasia). *(3) Benign epithelial tumors:* only few may turn malignant. Important examples are the villous and serrated adenomas of the colon.

Premalignant conditions refer to hereditary cancer syndromes, all are the result of germline mutation of tumor suppressor genes with one exception, namely: MEN syndrome which is the result of mutation of RET protooncogene. DNA repair defects syndromes and immunodeficiency syndromes (both congenital and acquired) are also considered premalignant conditions.

CANCER PREVENTION

A big step in the control of cancer is to prevent it. Three strategies may be adopted. In primary prevention, etiologic agents are eliminated or avoided or the carcinogenic process arrested by chemicals (chemoprevention). In secondary prevention cancer is detected by screening at an early stage which is more curable. Tertiary prevention aims at reducing the risk of development of a second malignancy resulting from therapy of the primary tumor.

Primary Prevention

Epidemiologic studies indicate that about 80% of human cancers are due to environmental factors, and hence potentially avoidable. This may be easily accomplished in some cancers, but difficult in others. Thus, although 80% of cancers are theoretically preventable, practically, only 30% are actually preventable. Primary prevention involves the removal of etiologic agents from human environment, or advising human subjects to avoid them. In case of compulsory exposure, such as industrial or bilharzial, primary prevention is easy through eradication of the etiologic agent. Conversely, in voluntary exposure, such as tobacco smoking and alcohol, primary prevention is rather difficult since these agents are habit forming. Thus, in spite of prolonged antismoking campaigns, male smokers dropped from 51% to only 34.6% with increase of female and teenager smokers (WHO report on global tobacco epidemic 2009). The situation in developed Western countries is relatively better than Egypt. In the USA current cigarette smoking prevalence among all adults aged ≥18 years has decreased 42.4% since 1965, but declines in current smoking prevalence have slowed during the past 5 years (declining from 20.9% in 2005 to 19.3% in 2010) but it didn't meet the Healthy People 2010 objective to reduce cigarette smoking among adults to ≤12%. In Britain in 1948, 82% smoked some form of tobacco. By 1970, smoking prevalence had fallen to 55%. From the 1970s onwards, smoking prevalence fell rapidly until the mid-

Table 3-9 Premalignant Lesions and Syndromes

Class	Lesions	Syndromes
Precarcinoma	Chronic ulcers Dysplasia Villous adenoma Pleomorphic adenoma	Genodermatosis: Albinism Xeroderm pigmentosum Epidermodysplasia verriciformis Basal cell nevus (Gorlin) MEN syndromes
Premelanoma	Hutchinson nevus Dysplastic nevus Congenital giant nevus	Familial dysplastic nevus
Presarcoma	Plexiform neurofibroma Osteochondroma Paget's disease of bone	Neurofibromatosis Familial neuroblastoma Li-Fraumeni
Prelymphoma	Lymphoepithelial lesion Castelman disease Progressive transformation of germinal centers (PTGC)	Primary immunodeficiency Secondary immunodeficiency (AIDS or Iatrogenic)

1990s. Since then the rate has continued to fall slowly and in 2007 around a fifth (22%) of men (aged 16 and over) were reported as cigarette smokers. The rate then slowly fell to 21% in 2010. In Egypt Ministry of Health demographic health surveys were completed in 2005 and 2008. Indicated a male smoking prevalence of 43.9%. In Egypt, use of shisha is the second most common type of tobacco consumed. Shisha smoking was generally limited to older males, usually of low socioeconomic level, in rural areas and in the older parts of cities. However, since the early 1990s there has been an increase in shisha use in cities and among new groups such as females, young people and those from high socioeconomic levels . Findings from a national survey carried out by the Egyptian Smoking Prevention Research Institute in 2005 revealed that shisha smoking among young people 18 years or older was 5.5% in rural areas and 4.3% in urban areas. In rural areas, shisha smoking among males was 15.3% and 0.1% among females, while in urban areas it was 10.9% among males and 0.2% among females. There is a current alarming growth in the number of smoking young people (13–15 year old). More than 10% of students were currently using tobacco products other than cigarettes, with a relatively narrow gap between the prevalence among boys (12.3%) and girls (6.7%) (13). Moreover, the likelihood of initiating smoking in the next year by never smokers was 18.3% (Global Youth Tobacco Survey GYTS, Egypt, 2005).

Two other approaches of primary prevention are vaccination and chemoprevention. Thus, hepatocellular carcinoma could be prevented by vaccination of children against hepatitis B virus. For several reasons, chemoprevention has received growing consideration as a means of cancer control.

Chemoprevention

Cancer chemoprevention can be defined as the prevention, inhibition or reversal of carcinogenesis by the administration of natural or synthetic

chemicals, hence, prevent progression to invasive cancer. It would appear that about 50% of human cancer could be prevented by this approach.

Our understanding of epithelial carcinogenic mechanisms provides the scientific basis of chemoprevention. Thus, epithelial carcinogenesis is a long process involving three distinct phases of molecular and cellular alterations, namely: initiation, promotion and progression (Chapter 6). Also, according to the field cancerization theory, epithelial carcinogenesis affects large areas of epithelium and this explains the high risk to develop second tumors after successful treatment of the primary ones, especially in certain organ sites as head and neck, skin, and urinary tract.

Target Populations

The projected target populations for chemopreventive interventions include the following 4 high-risk groups:

1. High exposure to carcinogens, e.g. tobacco smokers, industrial exposure and, carcinogen-contaminated food.

2. Individuals with inherited cancer risk with identifiable specific genetic defects e.g. Rb, WT-1, Li-Fraumeni p53 syndrome, VHL, Men-2, and cancer family syndromes, such as BRCA and HNPCC.

3. Individuals with precancerous lesions: These are classified into two main subgroups: (a) high-risk lesions, in which the development of carcinoma is inevitable or 100%, e.g. familial colonic polyposis, villous adenoma of colon, xeroderma pigmentosum, familial dysplastic nevus and lentigo maligna, and (b) Low-risk lesions, in which malignant profession is low (3% to 10%), e.g. leukoplakia, solar keratosis, sporadic dysplastic nevus, congenital giant nevus, Barrett's esophagus, ulcerative colitis, Paget's disease of bone and neurofibromatosis. Unfortunately, the development of malignancy in the last two mentioned lesions cannot be prevented.

4. Survivor of primary cancer who are at increased risk of a second tumor because of field cancerization, e.g. cancer of upper aerodigestive tract, skin, colon and breast.

In conclusion, chemoprevention strategies are only adopted in high-risk groups, and should not be used in the general population, other than certain dietary measures.

Classes Of Chemopreventive Agents

Wattenberg classified chemopreventive agents into three main groups according to their mechanism of action in experimental animal models, namely: anticarcinogens, blocking and suppressing agents.

1. Anticarcinogens: A classic example is ascorbic acid (vit. C) which inhibits the formation of endogenous nitrosamines from its precursors (nitrite and secondary amines). Other compounds with similar action are: caffeic acid, gallic acid, acetyl cysteine and proline.

2. Blocking agents are inhibitors of the initiation stage of carcinogenesis. Examples are: (a) inhibitors of the enzyme system (cytochrome P450) which activates the procarcinogens, e.g. ellagic acid and isothiocyanates, (b) stimulators of carcinogen-detoxication enzymes (glutathione 5-transferase), e.g. isothiocyanate, (c) antioxidants or trapping agents of activated carcinogens and free radicals, e.g. vit. E and ellagic acid, and (d) drugs which increase DNA repair, e.g. vanillin.

3. Suppressing agents: These are inhibitors of promotion and/or progression. Examples are: (a) inducers of cell differentiation (Vit. A and retinoids) which are classic examples of antipromoters, (b) inhibitors of polyamine metabolism, e.g. polyphenols, (c) modulator of signal transduction, such as flavonoids which inhibit protein kinase C (PKC), (d) modulator of hormonal/ growth factor activity, such as tamoxifen, (e) inhibitors of oncogene activity, e.g. nonsteroidal anti-inflammatory drugs NSAID, (f) promotors of intercellular communication, (g) restorers of immune response, such as retinoic acid and vit. E , (h) inducers of apoptosis, e.g. tamoxifen and the NSAID sulindac, (i) correctors of DNA methylation imbalance: thus hypomethylation which causes genetic instability is corrected by the methyl group donor methionine, (j) inhibitors of basement membrane degradation, such as protease inhibitors, and (k) inhibitors of arachidonic acid metabolism, such as polyphenols and NSAID.

Chemoprevention Applications

Chemoprevention clinical trials are usually designed in 3 phases. Phase I trials determine the dose related safety of the drugs. Phase II trials evaluate drug toxicity with prolonged use. Phase III trials involve the recruitment of a large cohort of subjects for randomized intervention studies.

Intermediate endpoints are short-term changes in the precancerous lesions (e.g. dysplasia), as well as, biochemical or molecular markers which can monitor the effect of chemopreventive agents at

an early phase. Examples of human chemopreventive trials in progress are presented in (Table 3-10). Successful chemopreventive findings are reported on the following tumor sites:

Breast: Tamoxifen is effective in the prevention of primary breast cancer in high-risk patients, as well as, prevention of a second primary tumor (contralateral breast) in patients with breast cancer. The risk reduction is about 49%. Tamoxifen acts as an estrogen antagonist by directly binding to estrogen receptors, and also by increasing the estrogen-binding globulin. In addition, tamoxifen has antiproliferative effects through inhibition of protein kinase C, increase of TGF-α and decline of IGF-1. Major concerns are the increased risk of endometrial carcinoma, liver tumors and thrombophlebitis with the use of tamoxifen.

Colon: The use of NSAID such as aspirin and sulindac are effective in causing regression of adenomas in patients with familial adenomatous polyposis. It also reduces the risk of colorectal carcinoma when taken for a long time in combination with calcium and fiber.

Head and Neck: Vitamin A analogues (retinoids) are effective in the reversal of oral leukoplakia, as well as, reducing the development of a second primary. Vit. A is not used, because of its toxicity in high doses. The compound 4HPR, is a new safe synthetic retinoid effective in chemoprevention. β-carotenes are precursors of vit. A which are metabolized in the body into active compounds. Retinoids act mainly as repressor drugs in the phases of promotion and progression.

Lung: High-risk populations (e.g. tobacco smokers and asbestos workers) may benefit from β-carotene and Vit. E.

Prostate: The conversion of testosterone to the more active dihydrotestosterone in the prostate requires the activity of the enzyme 5-α-reductase. Finasteride, is a potential chemopreventive agent of prostatic carcinoma being a 5-α- reductase inhibitor.

Endometrium: Progesterone is a potent antiestrogen. Combination oral contraceptives, which contain progesterone, are chemopreventive to both endometrial, as well as, ovarian cancer.

In conclusion, clinical chemoprevention faces the problem of recruitment and compliance of a large number of subjects. Moreover, the agents have to be administered for a long time (usually exceeding 10 years), hence the costs of chemoprevention trials are very high.

Secondary Prevention

This aims at early detection of cancer, when it is small and localized, or even at its precancerous stage, and hence more often curable. This is usually accomplished by selective screening of high-risk asymptomatic groups of the population.

Important two requirements of screening programs are: the availability of a reliable screening test, and the availability of an effective treatment associated with high curability. Thus, although there are more than 100 different cancers, only 7 cancers have widely acceptable screening interventions, namely: breast, cervix , skin, colo-

Table 3-10 Human Chemoprevention Trials

Site	Agent
Prevention of Primary cancer	
Breast (high-risk)	Tamoxifen
Colon (polyposis)	NSAID*
Lung (high risk)	Vit E, beta-carotene
Skin	Selenium
Prostate	Finasteride
Oral cavity (leukoplakia)	Retinoids
Prevention of Second Primary tumor	
Breast	Tamoxifen
Colon	NSAID, Calcium
Head and Neck	Retinoids
Lung	Vit E, beta-Carotene

NSAID nonsteroidal anti-inflammatory drugs, like aspirin and sulindac

rectal, bladder, prostate and testis (Table 3-11). It is not advisable to screen cancer lung, esophagus or pancreas, because the treatments currently available for these tumors are associated with poor prognosis. Accordingly, the most important measure of the efficacy of a screening program is a reduction in mortality observed in randomized clinical trials. However, the yield of the test (case finding) and the improvement in survival are two additional measures.

The discovery of susceptibility genes for cancer presents a new challenge to the screening programs. Thus, it is necessary to redefine the risk-groups to include these individuals and screening has to be started at an earlier age.

Evaluation of Screening Tests

A screening test must fulfill the following criteria outlined by Cochrane and Holland, namely: Simplicity, acceptability, high accuracy, low cost, high precision (consistent results when repeated), high sensitivity and high specificity.

Sensitivity of a test, means the percentage of positive reports in cancer patients, whereas, specificity means the percentage of negative reports in normal (nonmalignant) individuals (Table 3-12). Both sensitivity and specificity are a measure of the validity of the screening test. The validity refers to the ability of the test to classify persons who have the preclinical disease as test positive, and those without the disease as test negative. The accuracy of the test is a measure of validity and indicates the percentage of all correct results (both true positive and negative). Finally, the positive predictive value of the test measures the probability of the disease being present in patients with positive reports.

Table 3-11 Cancer Detection Tests

Organ	Test
Breast	Breast self examination (BSE) Breast clinical examination (BCE) Mammography
Uterine cervix	Papanicolaou test (Pap.)
Skin	Skin self examination (SSE) Skin clinical examination (SCE)
Colorectal	Digital rectal examination (DRE) Fecal occult blood test (FOBT) Sigmoidoscopy
Bladder	Urine cytology
Prostate	Digital rectal examination (DRE) Prostate specific antigen (PSA) Transrectal ultrasonography (TRUS)
Testis	Clinical testicular examination (CTE)

Screening Programs

The following is a discussion of organ sites for which screening programs are advisable:

Breast Cancer

Widely accepted techniques for breast cancer screening include: breast self-examination (BSE), clinical breast examination (CBE) and mammography. Monthly BSE is recommended from age 20 years, annual periodic physical examination from age 40 years, and annual or biannual mammography after the age 40 years. But, if there is a family history of breast cancer, mammography may be started at an earlier age.

The early treatment of screened population ultimately reduced mortality from breast cancer by 20% to 30%. This reduction was mainly observed in patients over the age of 50 years and not in younger patients.

Uterine Cervix

Pap test is the method of choice for screening the uterine cervix. It is recommended to start annual screening by age 20 years or when a woman becomes sexually active. However, when three consecutive normal tests are obtained, screening may be done every 3 years.

Cervical cytology has a sensitivity of 89% in diagnosing malignant lesions. Screening programs have a significant advantage since the disease is detected in its preinvasive stage of dysplasia or carcinoma in situ. Thus, with appropriate treatment at this stage, invasive cancer is prevented. The yield of the test in patients aged 20 to 40 years is about 4 per 1000. However, there is a reduction in the yield in older patients (a yield of one per 1000). It is estimated that regular cervical screening could reduce mortality from the disease by about 90%, the highest mortality reduction rate among screened cancers.

Table 3-12 Evaluation of a Screening Test

Screening Test Results	Truth of Cases	
	Cancer Patients	Normal Subjects
Positive	TP	FP
Negative	FN	TN
Sensitivity =	100 (TP/TP+ FN)	
Specificity =	100 (TN/TN +FP)	
PV+ =	100 (TP/TP +FP)	
Accuracy =	100 (TP + TN/TP + TN + FP + FN)	

Abbreviations: TP true positive, FP false positive, FN false negative, TN true negative, PV+ positive predictive value

Skin Cancer

In Australia, which has the highest reported incidence of skin cancer, has mounted successful population-based programs that have had dramatic effects. The available methods include skin self examination (SSE) and clinical skin examination (CSE). It is recommended to screen the population by CSE every 3 years by the age of 20 years, but annually in high-risk subjects, such as a family or personal history of skin cancer, presence of precancerous lesions or increased exposure to sunlight.

Colorectal Cancer

The screening recommendation for early detection in average-risk individuals include: annual digital rectal examination (DRE), fecal occult blood test (FOBT) from age 50 years, and flexible sigmoidoscopy every 5 years after the age of 50. However, in high-risk individuals, screening is started at an earlier age and endoscopy repeated every 3 years.

FOBT has a false positive rate of 2.5% and false negative rate of 25%. DRE detects only 15% of colorectal cancer, whereas, flexible sigmoidoscopy can detect 65% of colorectal cancer. Screening by FOBT has reduced mortality by 30%, whereas, sigmoidoscopy has shown a 70% reduction in mortality.

Bladder Cancer

In non-bilharzial series, the sensitivity of urine cytology is dependent on the grade of tumors (31% in grade 1, 44% in grade 2, and 72% in grade 3). A higher sensitivity of about 90% is reported in bilharzial bladder cancer. Urine cytology is an effective method for screening of bilharzia-infested populations with a yield of 2 per 1000 high-risk individuals (farmers aged 20 years and above). Tumors are detected at an early stage. Urine cytology is also valuable in the detection of bladder cancer in industrial workers exposed to aromatic amines with a higher yield of 7 to 70 cases per 1000 screened.

Prostate Cancer

The three main screening modalities for prostatic carcinoma include: digital rectal examination (DRE), serum prostate specific antigen (PSA) and transrectal ultrasonography (TRUS). Annual examination of males after the age of 50 years is recommended by all three methods. However, an early start at age 40 years is advisable if there is a family history of prostatic cancer.

The screening methods of prostatic cancer have fallen short of expectations. Thus, normal PSA values are observed in about one third of men with localized cancer, and elevated PSA levels are seen in patients with benign nodular hyperplasia. The sensitivity and specificity of TRUS are rather low, both ranging from 41% to 79%. Also, there is no evidence that screening improves clinical outcome.

Testicular cancer

Periodic clinical examination is the screening method of choice. Any mass within the tunica is considered malignant until proved otherwise. Additional aids are ultrasonography and tumor markers. Thus, placental alkaline phosphatase is elevated in 40% of patients with seminoma. Beta human chorionic gonadotropin (β-hCG) is in creased in choriocarcinoma and 50% of embryonal carcinoma. Alfa-fetoprotein (AFP) is elevated in yolk sac tumors.

Tertiary Prevention

The adoption of multimodality therapy for cancer in 1950 has improved patient survival, hence, increasing the risk of development of a second primary tumor. Such iatrogenic tumors are the result of the genotoxic effect of chemotherapy (especially alkylating agents) and radiotherapy. The following are three illustrative examples:

1. Children surviving Hodgkin's disease have the highest incidence of second cancers (5% in 10 years and 20% in 20 years). A lower risk is observed in children treated for lymphoblastic lymphoma/leukemia and the resulting tumors are either leukemias (ALL) or lymphomas (NHL)

developing early at about 5 years.

2. Children receiving irradiation are at increased risk to develop second cancers, usually a solid tumor in thyroid, skin and soft tissue (commonly malignant fibrous histiocytoma). Children receiving cranial irradiation for lymphoblastic lymphoma/leukemia may develop brain tumors.

3. Patients with breast cancer receiving tamoxifen are at increased risk to develop endometrial cancer at a rate of 4 cases per 1000 patients per year. Raloxifene is a recently introduced safe antiestrogen without associated risk of endometrial carcinoma.

The strategy of tertiary prevention is to reduce iatrogenic cancer through minimizing the genotoxicity of current cancer therapy. Moreover, careful long-term follow up is essential for the early detection and treatment of the second cancer.

REFERENCES

Ablashi DV, Chatlynne LG, Whitman Jr JE, Cesarman E: Spe ctrum of Kaposi's sarcoma-associated herpes virus, or human herpes virus 8, diseases. Clin Microbiol Rev 2002; 15: 439-464.

de Oliveria LJ, Carvalho Melo R, De Souza EC, et al: Association Between Hepatitis C and Hepatocellular Carcinoma. J Glob Infect Dis. 2009 Jan-Jun; 1(1): 33–37.

de Sanjose S, Quint WG, Alemany L, et al: Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010; 11(11):1048.

Hildesheim A, Schiffman M, Bromley C, et al: Human papillomavirus type 16 variants and risk of cervical cancer. J Natl Cancer Inst. 2001; 93(4):315.

Martinelli PT, Tyring SK: Human herpesvirus 8. Dermatol Clin 2002; 20:307-314.

Palefsky JM, Holly EA, Ralston ML, Jay N: Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. J Infect Dis. 1998; 177(2):361.

Sarid R, Klepfish A, Schattner A: Virology, pathogenetic mechanisms, and associated diseases of Kaposi sarcoma-associated herpes virus ('human herpes virus 8). Mayo Clin Proc 2002; 77:941-949.

The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development (1987) Combination oral contraceptive use and the risk of endometrial cancer. JAMA 257:796–800