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Role of Environmental Factors in Carcinogenesis

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Abstract

Cancer is one of the most serious diseases that threaten human being today. Most cancer results from the interaction of genetic and the environment. Genetic factors by themselves are thought to explain only about 5%-10% of all cancers and the remainder can be attributed to environmental carcinogens. The involuntary or voluntary exposure to these carcinogens may account for the recent growing incidence of cancer. These agents include; microorganisms (viruses, bacteria and parasites), radiations (radioactivity, UV and pulsed electromagnetic fields), occupational exposures, tobacco smoke, sexual behavior, alcohol, dietary constituents, pollutants (in the workplace, air, water, and food supply), formaldehyde, volatile organic compounds such as benzene and 1,3 butadiene and many xenochemicals, carcinogenic metals and metalloids, pharmaceutical medicines, food additives, additive in cosmetics, etc. The industrial revolution over the second half of the last century and its consequences in domains such as energy, transport, agriculture, food and health led to synthesize, produce and introduce into the environment, millions of man-made chemicals or substances. Although environmental, occupational, and recreational exposures to carcinogens contribute to cancer risk in humans, variation in incidence and progression of cancers among individuals can be attributed to inter-individual variation in genetic makeup. The risk fraction attributable to environmental factors is still unclear. One of the hopeful messages from cancer research is that most of the cases of cancer are linked to environmental factors and, in principle, can be prevented by growing awareness about the modulating risks from environmental carcinogens.

Keywords: Carcinogenesis, Environment, Air pollution; Food additives; Pesticides
Radiations; Screening; Tobacco smoke; Virus

Introduction

Cancer is one of the most serious diseases that threaten human being today. Tumor development in humans is considered to be a multistep process analogous to Darwinian evolution, during which normal cells undergo a succession of genetic alterations that results in their acquiring various growth advantages, and ultimately their conversion into cancer cells (Hananan and Weinberg, 2000). Cancer is a group of complicated diseases and a genetic disease but environmental and other non-genetic factors directly or in-directly play a role in many stages of carcinogenesis. There are many harmful substrates around us, especially with the development of industry which are potential carcinogens. Major carcinogens, numerous and of varied natures, have been identified in the working environment (asbestos fibres, heavy metals, soot and tar, arsenic, benzene, aromatic amines, vinyl monochloride, ionizing radiation, etc.), and in the overall environment (residential radon, UV radiation, aflatoxin). Several viruses (EBV, HPV, HBV, HCV, HTLV1, HHV8, etc.) have been shown to be carcinogenic, as are some bacteria (*Helicobacter pylori*) and parasites (*Schistosoma*). Certain major carcinogens are of iatrogenic origin, in particular cancer treatments (ionizing radiations, alkylating agents, epipodophyllotoxin), as are, to a lesser degree, some hormone treatments. To date, apart from alcohol intake with respect to esophageal, upper aerodigestive tract, and liver cancer, few diet-related factors have been shown to be carcinogenic.

There are number of environmental factors which are directly or indirectly associated with cancer and are discussed here.

Radiation and cancer

Radiation-induced cancers are a stochastic late effect of ionizing or non-ionizing radiation. They include some leukemia and lymphoma, thyroid cancer, skin cancer, some sarcomas and some lung and breast carcinomas (Wakeford, 2004). The most important environmental mutagen by far is the ultraviolet (UV) component of sunlight which has been rated as carcinogenic to humans by IARC (IARC Press, 1992). Exposure to UV is a dose-dependent risk factor (Kopf *et al.*, 1984; Gallagher *et al.*, 2005), which can cause skin cancers, mostly basal cell and squamous cell carcinoma. Radiation-induced cancers are a stochastic late effect of ionizing or non-ionizing radiation. They include some leukemia and lymphoma, thyroid cancers, skin cancers, some sarcomas and some lung and breast carcinomas (Wekford, 2004). Ionizing radiation induced DNA damages produce irreversible changes during DNA replication or during the processing of the DNA damage by enzymatic repair processes. Most of these changes take place during the cell cycles immediately following exposure. However, a number of evidences have implicated that the progeny of normal cells exposed to ionizing radiation, for example, X-radiation and UV-radiation, exhibit delayed response including specific gene mutations and chromosome aberrations, termed radiation-induced genomic instability (Wright, 1999). Exposure to radon and radon decay products at home and/or at the workplace are the most widely found sources of exposure to ionizing radiation (Axelson *et al.*, 2002). Breast cancer risk is most increased among girls exposed to chest radiation around the

age at puberty, at a time of intense breast development. Different environmental agents responsible of different types of cancer are shown in Table 1.

Biological Agents (viruses, bacteria and other pathogens) and Cancer

The infection-attributable cancers are estimated to be about 17.8% of the global cancer burden in the year 2002 comprising 1.9 million total cases (Parkin *et al.*, 2006). International Agency for Research in Cancer (IARC) has identified six viruses: human papillomavirus (types 16 and 18), Epstein-Barr virus (EBV), hepatitis B virus, hepatitis C virus, human T-cell lymphotropic virus type I and human immunodeficiency virus type-1 (HIV-1) as group 1 carcinogens (IARC Monographs). In addition, bacteria *Helicobacter pylori* (*H. pylori*), parasite *Schistosoma haematobium* and liver fluke *Opisthorchis viverrini* has also been included in group 1 carcinogens. Apart from these established carcinogenic infection there are certain infection such as, polyomaviruse (SV40), *Schistosoma japonicum* and *Clonorchis sinensis*, which have only sporadically been associated with cancer development. It is estimated that oncogenic viruses are involved worldwide in about 16% of neoplasia (Pisani *et al.*, 1990), with a range from less than 10% in high-income countries to 25% in Africa (Parkin *et al.*, 2000; Talbot *et al.*, 2004). In Western developed countries, human papilloma virus (HPV), in particular HPV type 16 or 18 (HPV-16, HPV-18), and hepatitis B virus (HBV) are the most frequent oncogenic DNA viruses. These two viruses contribute differently to carcinogenesis: HPV-16 is directly mutagenic by inducing the viral genes E6 and E7 (Song *et al.*, 1999). HBV is a precursor to cirrhosis of the liver and is associated with an increased lifetime risk of developing primary hepatocarcinoma (PHC) (also called hepatocellular carcinoma, HCC), usually 20-30 years later. HBV also may synergize with environmental factors such as alcohol-associated cirrhosis in causing PHC. Besides, HBV, hepatitis C virus may be involved in PHC, too. Recently, a novel herpes virus (HHV-8) was isolated which is associated with three neoplastic disorders: Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), and diffuse Castleman's disease. HHV-8 has been found to encode several homologues of cellular genes, which may enable the virus to facilitate cell proliferation (Blaho and Anaranson, 1999). In non-Western countries, in addition to the abovementioned cancers, Burkitt's lymphoma and nasopharyngeal carcinoma have been shown to be caused by EBV, and Kaposi sarcoma (KS) to be associated with HIV and the Human herpes virus type 8 (HHV-8) (IARC monographs, 1996; IARC monographs, 1997; Griffin, 2000; Pagano *et al.*, 2004). RNA tumor viruses include the hepatitis C virus (HCV) and the unique retrovirus presently known to be oncogenic in humans, the human T-cell lymphotropic virus type 1 (HTLV-1). HTLV-1 is directly mutagenic, while HCV, as HBV, is thought to produce oxidative stress in infected cells and thus to act indirectly through chronic inflammation (de Maria *et al.*, 1996; Koike *et al.*, 2002). There are other microorganisms, including selected parasites such as *Opisthorchis viverrini* or *Schistosoma haematobium* and bacteria such as *Helicobacter pylori* may also be involved, acting as cofactors and/or carcinogens (Belpomme *et al.*, 2007). Table 2, summarizes the data related to contribution made by some other biological agents who are responsible for different cancers.

Chemical agents and cancer

There are two classic environmental carcinogens: polycyclic aromatic hydrocarbons (PAH), generated from the combustion of fossil fuels, and aromatic amines, which are present in cigarette smoke and other environmental media. Both PAH and aromatic amines are major etiologic factors in lung, bladder and possibly breast cancer. Carcinogenic residues bound to DNA or surrogate proteins (known as adducts) provide both a fingerprint of exposure and an indicator of procarcinogenic DNA damage. In general, more PAH-DNA adducts are formed in persons who smoke or are exposed to PAH in the workplace and ambient air. PAH-DNA adducts, especially those formed by the carcinogen benzopyrene diol epoxide (BPDE), have been linked to an increased risk of lung cancer. PAH-DNA adducts in human lung tissue increase sister chromatid exchange formation, and mutagenicity of lung microsomes. Trichloroethylene has been reported to be strongly associated with kidney, liver, esophageal cancers and non-Hodgkin's lymphoma (IARC, 1995; Wartenberg *et al.*, 2000; Hansen *et al.*, 2001; Wartenberg *et al.*, 2002; Raaschou-Nielsen *et al.*, 2003) and perchloroethylene with esophageal cancers (Ruder *et al.*, 1994; Weiss, 1995). Similarly, smokers have more hemoglobin adducts formed by the aromatic amine 4-aminobiphenyl (4-ABP) which is associated with an increased risk of the bladder cancer (Perera, 1997). As for the malignant disease in human hematological system, a variety of chemicals and drugs have been suggested as possible leukemogenic agents in human leukemia, but only benzol can be unequivocally implicated. Disturbances of the hematopoietic system, especially marrow aplasia with pancytopenia, in workers chronically exposed to benzol have been recognized for many years. And the overwhelming predominance of acute myelocytic leukemia (AML) or closely related syndromes, often preceded by periods of aplasia with pancytopenia, in such workers provides compelling evidence for an etiologic relationship. The documentation for a link between leukemia and other solvents is not as firm as it is for benzene. Nonetheless, evidence for a link between lymphoma and organochlorine group, such as 1,3-dichloropropene, herbicides (mostly 2,4-dichlorophenoxyacetic acid) and so on, is becoming stronger. Although some studies suggest there might be an association between exposure to pesticides and acute leukemia, MDS, lymphoma, myeloma, and myeloproliferative disorders, the risk from exposure to it appears to be greater for solid tumors than for leukemia. Exposure to chemical substances is also one of the most important conditions potentially associated with cancer development in different sites. This results from the ability of such substances to act as cancer initiators (substances able to cause DNA damage in a single cell) and/or cancer promoters (substances stimulating an altered cell to divide, thus reproducing prior DNA damage). When prevalent in the environment, such cancer promoters can cause the incipient tumor tissue to grow, making this process irreversible and enabling further clinical tumor expression (Le *et al.*, 2002).

Smoking

Smoking is the most important risk factor for cancer, with a marked role in lung cancer etiology, but also recognized as a major risk factor in other cancers also. Cigarette, cigar, and pipe smoking, chewing tobacco, snuff, and exposure to environmental tobacco

smoke (ETS or secondhand smoke) are all linked to increased cancer risks. Cigarette, cigar, and pipe smoking have been associated with cancers of the lung, mouth, bladder, colon, kidney, throat, nasal cavity, voice box, esophagus, lip, stomach, cervix, liver, and pancreas, and with leukemia; smokeless tobacco has been linked to cancers of the mouth; and ETS has been implicated in lung cancer. Cigarette smoke contains more than 100 cancer-causing substances. The risk for cancers of the mouth, voice box, and esophagus is further increased among smokers who also drink more than two drinks per day (English *et al.*, 1995; IARC Press, 2004).

Occupational Chemicals

In 1775, Sir Percival Pott reported, cancers of the scrotum which was the first recognized occupational chemically-induced cancer. Now a day, occupational cancers are reported to represent 2-10% of all cancers, but this percentage is probably underestimated and may be as high as 15-20% in men. Harvard Center for Cancer Prevention (HCCP), in 1996, classified 32 substances or industries as carcinogenic in humans (Landrigan *et al.*, 1995; HCCP, 1996). Recently, 28 agents have been considered as definite occupational carcinogens in human, 27 as probable occupational carcinogens and 113 as possible occupational carcinogens (Siemiatycki *et al.*, 2004; Clapp *et al.*, 2005). Among carcinogenic substances, asbestos is a classical example. There is no doubt that asbestos is carcinogenic and induces occupational cancers, including mesothelioma and approximately 10% of lung cancer (IARC Press, 1977; IARC Press, 2002). Likewise, wood-dust-related cancers, although their occurrence is mostly limited to joiners or cabinet makers is limited, are also occupational cancers, insufficiently declared (ethmoid cancers) or even not yet declared (sinus cancers) (Hayes *et al.*, 1986; Blot *et al.*, 1997). Solvents, paints, dyes, gasoline and other petroleum products can also cause occupational cancers. After the leukemogenic effect of benzene was first recognized (Goguel *et al.*, 1967; Surralles *et al.*, 1997), the mutagenic effect of other solvents was established. Moreover mineral oils and lubricants have been associated with some types of cancers, including larynx, skin and bladder cancers (Kane *et al.*, 1984; Mackerer *et al.*, 2003). Phthalates are widely used since the last world war, due to their plasticizing and emulsifying properties. For this reason, they are added to polyvinyl chloride (PVC) in particular in common medical devices and cosmetics. Di(2-ethylhexyl)phthalate (DEHP) and butyl-benzyl-phthalate have been suspected to be carcinogenic (Shea, 2003). In addition, vinyl chloride monomer, but not PVC, is mutagenic and thus can cause liver angiosarcoma and hepatocellular carcinoma (HCC). A major concern is the risk of childhood cancers following either parental or child exposure to occupational pollutants. Several studies, evaluating the effect of parental exposure to solvents, paints, and gasoline exhaust, showed an increased risk of leukemia and brain tumors in children (Feingold *et al.*, 1992; Smulevich *et al.*, 1999).

Biocides and pesticides

Many of biocides especially those belonging the organochlorines, carbamates and carbinols groups are rated as probable or possible carcinogens, according to the US EPA and the IARC classification (IARC Press 1991) while several are recognized as

carcinogens in humans. In children, several epidemiological studies revealed an increased relative risk of cancers associated with parental exposure to pesticides, be it occupational or non-occupational (Zahm *et al.*, 1998). Paternal exposure to pesticides is associated with an excess relative risk of leukemia (Ma *et al.*, 2002), and of central nervous system tumors (Feychting *et al.*, 1998; Cordier *et al.*, 2001) as well as of Wilms tumors (Fear *et al.*, 1998). A positive link between pesticides and breast or prostate cancers has been put forward in some studies (Charlier *et al.*, 2003; Muir *et al.*, 2004; Ibarluzea *et al.*, 2004; Mills and Yang, 2006). However, a strong association between pesticides and the relative risk of sarcoma (Dich *et al.*, 1997), Hodgkin and NHL (Hardell *et al.*, 1999; Zheng *et al.*, 2001; Hardell *et al.*, 2003) has been found for 1,1,1-trichloro-2,2-bis(pchlorophenyl) ethane (DDT), chlorophenols and phenoxyherbicides. Pesticides can contaminate the body not only through ingestion, but also through air inhalation and skin contact, accumulate in adipose tissue (Lassiter and Hallam, 1990; Geyer *et al.*, 1997), more specifically in fatty breast tissue (Muscat *et al.*, 2003), pass through the placenta (Simonich and Hites, 1995) and accumulate in the milk of nursing mothers (Sharpe and Irvine, 2004).

Food contaminants and food additives

Nitrates, pesticides and dioxins can contaminate drinking water and food. Nitrates are used in intensive farming. They are not intrinsically carcinogenic, but can be endogenously transformed into nitrites by the digestive bacterial microflora, which in turn can be further transformed into N-nitroso compounds (NOC), i.e. into alkyl-nitrosamines and nitrosamides through nitrosation (Tannenbaum *et al.*, 1980; Ward *et al.*, 2005). These are highly mutagenic molecules. Secondary or tertiary amines and amides are found as common dietary contaminants (Ward *et al.*, 2005). Long-term exposure to food additives, including nitrite preservatives and artificial azodyes, may be also involved in chemically-induced carcinogenesis, due to their mutagenic properties (Palmer and Mathews, 1986; Weisburger, 1986; Sasaki *et al.*, 2002). In addition, bisphenol A, a xenoestrogen used in plastic food containers, because it can migrate in food and be repeatedly ingested, has been recently suspected to be carcinogenic in humans on the basis of results obtained from animal studies aiming at reproducing breast (Durando *et al.*, 2007) and prostate cancer genesis (Ho *et al.*, 2006; Prins *et al.*, 2007).

Metals and metalloids

Several metals and metalloids have been rated as certain or probable carcinogens by the IARC (IARC Press 1980). Inhalation of arsenic oxides can cause lung cancer, but if swallowed, cancer can develop in the bladder, kidney, liver and lung (Szymanska-Chabowska *et al.*, 2002). Thus exposure to arsenic oxides has been reported to be associated with a very large spectrum of common cancer types. Aside from arsenic oxides exposure, lung cancer has been also reported to be associated with exposure to many metals, including lead, hexavalent chromium and nickel (IARC Press 1990). Furthermore, exposure to hexavalent chromium or nickel has been found to be associated

with nasopharyngeal carcinoma, exposure to lead or mercury to brain tumors, exposure to lead or cadmium to kidney cancer and exposure to cadmium to prostate cancer (Hayes, 1997; Wesseling *et al.*, 2002; Waalkes, 2003).

Diet

There are few definite relationships between food and cancer, several studies have shown that heavy consumption of red and preserved meats, salt-preserved foods, and salt probably increase the risk of colorectal and stomach cancers. There is also evidence that a diet rich in fruits and vegetables may decrease the risks of esophageal, stomach, and colorectal cancers. Being overweight or obese appears to be one of the most important modifiable causes of cancer, after tobacco. Large population studies show a consistent association between obesity and certain kinds of cancer. The strongest links between diet and cancer are in case of breast cancer in older women, cancers of endometrium, kidney, colon and esophagus. There is strong evidence that physical inactivity increases the risk for colon and breast cancer. The beneficial effect of exercise is greatest among very active people. Together, it is estimated that inactivity and obesity account for 25 to 30 percent of the cases of several major cancers—colon, breast (postmenopausal), endometrial, kidney, and cancer of the esophagus. Fruits and vegetables rich in antioxidants and other micronutrients have a protective effect against diverse cancers, including lung, esophageal, oral, laryngeal, cervical and breast.

These micronutrients may act through a variety of mechanisms to block DNA damage, mutation and carcinogenesis by oxygen radicals, PAH, and other chemical carcinogens (Perera, 1997). Mycotoxins are toxic fungal metabolites, which are structurally diverse, common contaminants of the ingredients of animal feed and human food. Mycotoxins with carcinogenic potency in experimental animal models include aflatoxins, sterigmatocystin, ochratoxin, fumonisins, zearalenone, and some *Penicillium* toxins. Among them Aflatoxin B1 and fumonisins are worth paying particular attention to. Aflatoxin B1 (AFB1) is the most potent genotoxic agent. It is mutagenic in many model systems and produces chromosomal aberrations, micronuclei, sister chromatid exchange, unscheduled DNA synthesis, and chromosomal strand breaks and also forms adducts in rodent and human cells. Food contaminated with AFB1 is one of the major risk factors for HCC (Wang, 1999). Most of these carcinogenic mycotoxins, just like AFB1, are genotoxic agents with the exception of fumonisins, which is currently believed to act by disrupting the signal transduction pathways of the target cells.

Fumonisin, fungal toxins produced by *Fusarium moniliforme*, contaminate maize-based food and feeds throughout the world. Many parts of the developing world rely on maize-based foods as a major staple of their diet, and these populations can be chronically exposed to highly contaminated food. Ecological studies have linked consumption of fumonisin contaminated maize with esophageal cancer in human populations in South Africa and China. The development of biomarkers and their applications in epidemiological studies should be a priority for research on this kind of toxin (Turner *et al.*, 1999).

Environment, pregnancy and cancer

Leukemia is reported to be the second most common congenital malignancy, exceeded only by neuroblastoma. Nevertheless, it has a mortality rate considerably higher than any other congenital cancer. Therefore, many studies focus on the mechanism of catching this kind of disease. A preponderance of evidence, including the presence of high leukemic cell burdens at birth, autopsies of stillborn infants with leukemia, and the diagnosis of leukemia with identical abnormalities in monozygotic twins, supports for in utero-leukemogenesis. Investigation of the association of in utero exposure to marijuana and other substances found an 11-fold increased risk of AML developing in children whose mother smoked marijuana during pregnancy (Sande, 1999). Pediatric acute leukemia can also be initiated prenatally by illegitimate recombination and fusion gene formation in fetal haematopoiesis, it shows distinct characteristics. Up to 75 % of all leukemia diagnosed under 12 months of age show the gene-recombination involving MLL (mixed lineage leukemia) on chromosome 11q23 (Djabali *et al.*, 1992), but it is far less frequent in leukemia diagnosed in older persons. Taking children acute lymphocyte leukemia (ALL) with TEL-AML1, fusion gene as example, twin studies suggest that although they share the identical TEL-AML1 genomic fusion sequence, the concordance rate for all in non-infant twins is low (about 20%), which means that they show protracted and variable latency of ALL after TEL-AML1, gene fusion in utero. The striking difference in the postnatal latency period in the present twin pair most probably reflects that necessary secondary postnatal events required for the development of leukemia within the clone of preleukemic cells spawned prenatally were independently acquired at very different times. This situation could arise if such events occur entirely by chance or if they acquire promotion by particular patterns of exposure, such as infection, that can occur intermittently (Greaves, 1999; Ford *et al.*, 1998; Wiemels *et al.*, 1999).

Climate

Climate is one of the elementary and important ecologic environment in which we live, so it is important to study the influence of climatic factors on human diseases. Climatic factors persistently interacted with other ecologic and social factors, and exaggerated the influence of human life on diseases (Acuna-Soto *et al.*, 2002). Recent studies with respect to the relation between climate and cancer mostly focused on global warming, ozone depletion, ultraviolet radiation exposure and their influences on prostate cancer, skin cancer and retinoblastoma etc (Jemal *et al.*, 2000; Bodiwala *et al.*, 2003, Diffey, 2004). Peng *et al.* reported that there were significant relations between average temperature, precipitation and Environmental cancer (EC) and climate (Peng *et al.*, 2003). Studies conducted by Li *et al.* showed that there were positive relations between ultraviolet radiation, temperature and lung cancer, while there were negative relations between temperature, air pressure and liver cancer (Li *et al.*, 2005). Kinoshita *et al.* suggested that low solar radiation and low temperature might relate to the increasing risk of malignant neoplasm of the pancreas (Kinoshita *et al.*, 2007). There are many ecological studies concerning elevation and cancer, and many of them focused on the increase of ultraviolet exposure and hypoxemia along with the increase of altitude and their relations to cancer. Moehrle *et al.* believed that in the high altitude areas the

increased exposures to ultraviolet were linked with the increased incidence of cutaneous melanoma (Moehrle and Garbe, 1999). Krain *et al.* also suggested that high altitude exposure and/or aviator status correlated significantly with cancerous conditions of the skin, testicles, bladder, and thyroid; other less significantly associated conditions included leukemia, lymphosarcoma and Hodgkin's disease (Krain, 1991). A study conducted in northeastern Italy indicated that male residents living above 200 m were more possibly suffered from cancer of the oral cavity and pharynx, stomach and larynx, while less possibly suffered from cancer of colorectum and brain; women in locations above 200 m seemed significantly at risk for stomach cancer, but protected from cancer of the colorectum and kidney (Bidoli *et al.*, 1993). Our study suggested a negative relationship between altitude and EC, which is accorded with the result of Akhtiamov's study (Akhtiamov and Kairakbaev, 1983). Altitude might also influence other geographic environment such as geology, climate and social environment, thereby affected the EC mortality.

Conclusion: Cancer is a preventable disease

Cancer is largely caused by geneóenvironment interactions, it is a preventable disease. Furthermore, prevention methods should be just applied to the people who are at high risk, which is economical and effective. There are a number of different genetic and acquired susceptibility factors that modulate individual responses to environmental carcinogens. Modifiable risk factors are given in Table 3, just by changing some habits one can help in prevention of cancer. The prevention measures include (1) purifying the environment, mainly air, water and food supply, which is the most essential to life. However, as the rapid development of industry, pollution is getting more and more serious. Putting the policy of "sustainable development" into practice is essential not only to maintain and restore the ecological balance, but also to improve the public health conditions including those related to cancers; (2) education to mass population to help individuals modify hazardous life styles, such as tobacco smoke, dietary constituents and so on. Smoking is not only the important carcinogen for lung cancer and bladder cancer, but also is linked strongly with the pediatric leukemia that is developed in utero or just postnatal. Tumors most often found associated with maternal smoking in pregnancy or with postnatal exposure to environmental tobacco smoke are childhood brain tumours and leukemia-lymphoma (Sasco and Vainio, 1999). (3) Molecular and genomic biomarkers that can be used for risk assessment and as surrogate end points in clinical studies; chemo-preventive and dietary agent drug discovery and development; animal carcinogenesis models that mimic human disease.

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Table 1: Different environmental agents responsible for different types of cancer

Agents (Environmental)	Associated Tumor Types
Radiations Ultraviolet (UV) rays	Leukemia, lymphoma, thyroid cancers, skin cancers, sarcomas, lung and breast carcinomas skin cancers, mostly basal cell and squamous cell carcinoma, melanoma
Benzene, carbon tetrachloride, chloroform, dichloromethane (methylene chloride), tetrachloroethylene, trichloroethylene and Benzidine	Leukemia, Skin and Lung cancers
Silica dusts, Tobacco carcinogen (Nicotine), Asbestos, Vinyl chloride	Lung cancer
Polycyclic aromatic hydrocarbons (PAHs)	Lung, Skin and Urinary cancers
Metals compounds Arsenic compounds Beryllium, Chromium and Cadmium compounds Lead compounds Nickel compounds	Skin, Lung, Bladder, Kidney and Liver cancers Lung cancer Kidney and Brain cancers Nasal cavity and Lung cancers
Lead acetate and Lead phosphate	Kidney and Brain cancer
Vinyl chloride	Lung cancers, angiosarcomas (blood vessel tumors), liver and brain cancers
Tamoxifen, Fenretinide	Breast Cancer
Long-term use of oral contraceptives	Breast and Liver cancers
Diethylstilbestrol (DES)	Cervical, Vaginal and Breast cancers
13-cis-retinoic acid	Head/Neck cancer
Vitamin E , Selenium	Prostate cancer
Calcium and Non-steroidal anti-inflammatory (NSAID)	Colon cancer
Cyclophosphamide, chlorambucil, melphalan	Increase the occurrence of second cancers, including leukemia
Cyclosporin and azathioprine	Lymphoma

Table 2: Biological agents associated with Human Cancers

Agent	Human tumors
Human papilloma virus	Cervical cancer, anogenital cancer, skin cancer, oral cancer, esophageal cancer, oropharynx cancer
Epstein-Barr virus (EBV)	NHL, HD, Nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's lymphoma
Kaposi's sarcoma-associated herpes virus	Kaposi's sarcoma(KS), primary effusion lymphoma
HTLV-1	Adult T-cell leukemia (ATL)/ lymphoma (ATL)
HIV/HHV-8	KS, NHL, cervical, testicular, Lung conjunctival SCC, multiple myeloma, leiomyosarcoma
Hepatitis B virus	Liver cancer
Hepatitis C virus	Liver cancer
<i>Helicobacter pylori</i>	Stomach cancer, Lymphoma
<i>Schistosoma haematobium</i>	Bladder carcinoma
<i>Opisthorchis viverrini</i>	Cholangiocarcinoma
<i>Schistosoma japonicum</i>	Liver, colorectal cancer
<i>Clonorchis sinensis</i>	Cholangiocarcinoma

Table 3: Modifiable Risk Factors

Primary Prevention	Secondary prevention
Healthy Diet	Breast self-examination
Exercise	Testicular self-examination
Tobacco, beetal use	Mammography
Alcohol	Skin examinations
Rest	Pap smears
Sunscreen use/safety	Digital rectal examinations, PSA
Safe sex practices	Colonoscopy
Genetic testing	Fine Needle Aspiration Cytology
Health maintenance: regular check-ups	Other screening tests, e.g., thyroid and liver function, cardiac function (EKG)

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