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Review article

Environmental Factors Inducing Human Cancers

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Abstract

Background: An explosion of research has been done in discovering how human health is affected by environmental factors. I will discuss the impacts of environmental cancer causing factors and how they continue to cause multiple disruptions in cellular networking. Some risk factors may not cause cancer. Other factors initiate consecutive genetic mutations that would eventually alter the normal pathway of cellular proliferations and differentiation. Genetic mutations in four groups of genes; (Oncogenes, Tumor suppressor genes, Apoptosis genes and DNA repairing genes) play a vital role in altering the normal cell division. In recent years, molecular genetics have greatly increased our understanding of the basic mechanisms in cancer development and utilizing these molecular techniques for cancer screening, diagnosis, prognosis and therapies. Inhibition of carcinogenic exposures wherever possible should be the goal of cancer prevention programs to reduce exposures from all environmental carcinogens.

Keywords: Environmental factors, Cancer causing genes, Human cancers

Introduction

Current biological mechanisms of cancer suggest that all cancers are originated from both environment and genetics, meaning that there are multiple external factors combined with internal genetic changes will lead to human cancers. Prevention of the disruption of cellular signaling and protective pathways can be accomplished by preventing carcinogenic exposures from outside the body from any source. Prevention of carcinogenic exposures is still a major priority (1). Also, individuals with particular genetic predispositions may be more susceptible to the effects of environmental exposures than others. People with BRCA1, BRCA2 and p53 genetic alterations render those individuals less able to suppress the growth of cancer cells (2).

In fact, aromatic amines cause bladder cancer in chemical workers. DNA methylation is closely associated with histone deacetylases and histone methyltransferases that can modify histone amino-terminal lysine and develop specific histone codes, resulting in inactive chromatin formation which creates the unique features of cancer cells. It is well known that thousands of genes are deregulated in cancer cells. Cigarette smoking has been conclusively linked with the formation of several malignancies. Avoidance of cigarette smoking has been shown to reduce cancer incidence. Other potential modifiable cancer risk factors include alcohol consumption and obesity (3).

Prevention is defined as the reduction of cancer mortality by reduction in the cancer incidence. This can be accomplished by avoiding carcinogenic exposures, modifying lifestyle practices and early detection of cancerous lesions. The epidemiologic evidences indicate that people who are more physically active have a lower risk of certain malignancies than those who are inactive. Having one or more risk factors does not mean that you will get cancer. Some of the risk factors can be avoided. Others like family history and aging cannot be avoided. Several factors may act together

to change a normal cell to a cancer cell. The purpose of this paper is to review scientific evidences regarding the contribution of environmental exposures to all cancers in the world (4).

Discussion

In 1977, four scientists, Higginso, Muir, Doll, Peto explained the evidences that 80% of all cancers were caused by environmental factors. Their studies included the epidemiological data relating to migrants, geographical variation, changes in risk over time, correlation studies, clusters and case reports. In the past 30 years, there have been several efforts to estimate the proportion of cancer due to these involuntary exposures to environmental factors. Carcinogenesis refers to an underlying cancer causing elements that lead to cancer. Several models of carcinogenesis have been proposed. Two widely cited models of carcinogenesis are those of Vogelstein and Kinzler as well as Hanahan and Weinberg. The model of Vogelstein and Kinzler emphasizes that cancer is a disease of damaged DNA, comprised of a series of genetic mutations that can transform normal cells to cancerous cells (5).

The genetic mutations include inactivation of tumor suppressor genes and activation of oncogenes. Compared with cancers arising in the general population, individuals with a major inherited predisposition to cancer are born with inherited (germ-line) mutations in genes involved in cancer causation, giving them a head start on the pathway to cancer (6). Similar mutations would be expected to result in cancer progression among all individuals; however, in those without a major inherited cancer predisposition, the mutation would occur as a somatic mutation later during their lifetime. The model of Hanahan and Weinberg focuses on the hallmark events at the cellular level that lead to a malignant tumor. In this model, the hallmarks of cancer include sustained angiogenesis, unlimited replication, evading apoptosis, self-sufficiency in growth signals, and insensitivity to antigrowth signals, leading to the defining characteristics of malignant tumors by giving them the ability to invade and metastasize. This theory is based on the dual premise that carcinogenesis is driven by defects in tissue organization and that all cells are inherently in a proliferative state (7).

Cancer is a genetic disease of somatic cells which contain multiple abnormalities of both number and structure. The first direct evidence of cancer came from studies of tumor-specific translocations in leukemia and lymphomas. This revealed the importance of oncogenes and the transcriptional factor genes in cancer. A second major source of information about human cancer genes is hereditary cancer. Genetic predisposition of the autosomal dominant type imposes a high relative risk for one or more kinds of cancer. In the past decade or so, more than 30 mutant genes for such hereditary cancers have been cloned. Genes associated with human cancer formation include four classes of genes: 1. Tumor suppressor genes, 2. Proto-oncogenes, 3. DNA-mismatch repair genes, 4. Apoptotic genes. Up to 93% of all human cancers are non-hereditary which is caused by interaction with environmental factors. Only 7% of all human cancers are hereditary (8).

A few of the genes are oncogenes or DNA repair genes, but most are tumor suppressor genes. Some tumor suppressors regulate transcription, while others operate in signal transduction pathways that are involved in regulating processes of cell birth, differentiation, and death. The knowledge gained is stimulating new approaches to the treatment and prevention of cancer. Carcinogenesis requires a constellation of steps that often take place for decades. The complexity of carcinogenesis is magnified when one considers that the specific details of the carcinogenic pathway described by these models would be expected to have unique characteristics for each anatomic site (Table .1). Human cancer is really not a single disease but is a family of different diseases (9). The following factors were selected that appear to increase the risk of different types of human cancers:

1. Aging

The most important risk factor for cancer is growing older. Most cancers occur in people over the age of 55, but cancer can occur in younger ages as

well. Both cancer and ageing result from accumulating damage to the stem and progenitor cells. Certain genetic mutations cause the stem cells to divide out of control which lead to cancer. Normal somatic cells telomere losses are coupled with increasing age of the organism. Due to mutations in the *TERC* and *TERT* telomerase genes, telomeres will shorten in human premature ageing syndromes and dyskeratosis congenital (10). Environmental factors such as; stress, social status, smoking and obesity can also accelerate telomere shortening due to reduced telomerase activity. In contrast to normal somatic cells, most human tumors have activated telomerase to achieve immortal growth.

Table 1: Examples of biological, biophysical and biochemical association with human cancers

Carcinogens	Cancer Sites	Occupational Sources
Arsenic	Lungs, Skin	Electricians, Smelters, Medications.
Asbestos	Mesothelioma, Lungs	Roof and floor tiles
Benzene	Blood and lymph nodes	Petroleum, painting, detergent, rubber
Beryllium	Lungs	Missile fuel, Nuclear reactor
Cadmium	Prostate	Battery, painting and coating
Chromium	Lung	Preservatives, pigments, paints
Ethylene oxide	Blood	Ripening agent for fruits, gases
Nickel	Nose, Lungs	Battery, Ceramics, Ferrous alloys
Radon	Lung	Uranium decay, Mines, Cellars
Vinyl chloride	Liver	Refrigerator, glues
Smoke	Lungs, Colon	Cigar, air pollution, car smoke
Gasoline	Lung, Blood	Oil petroleum
Formaldehyde	Nose, Pharynx	Hospital/laboratory workers
Hair dyes	Bladder	Hairdresser and barber
Soot	Skin	Chimney cleaners
Ionizing radiation	Bone marrow	Radiology technician
Hepatic virus- B,C	Liver	Hospital workers, drug users
HPV/Herpes viruses	Cervix, skin, head/neck	Multiple sexual partners
Burkitt's virus	Lymph node	Black people in South Africa
Helico-bacteria pylori	Stomach	Chronic bacterium infection

2. Family history

Most cancers develop because of genetic mutations. Some genetic changes that increase the risk of cancer are passed from parent to child. Certain types of cancer do occur more often in some families than in the rest of the population, such as; colon cancer. Familial adenomatous polyposis (FAP) is a good example of hereditary colon cancer. People with FAP may have over hundred polyps in their colon. If it is untreated, one of these polyps will develop to cancer. The *APC* gene is associated with this syndrome should be examined for genetic mutation. Removing the polyps by early surgery will enhance the recovery. Another inherited syndrome that increases colon cancer is hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome. People with this syndrome have a higher risk of colorectal cancer. People with HNPCC have only a few polyps with a high risk of developing uterus, ovary, bladder, kidney and brain cancers. HNPCC is also caused by mutations in one of the DNA repair enzyme genes MLH1, MSH2, MSH6, PMS which can be tested for any possible genetic mutations. Also, inheriting a gene change does not mean that you will definitely develop cancer. It means that you have an increased chance of developing the disease. Following indications can increase the risk of developing cancers. Such as; tumor on the same side of the family, some of the

cancer linked inherited syndromes, two cases of rare cancers in the same family and family history of multiplicity of primary tumors (11).

3.Smoking

Tobacco use is the most preventable cause of death. Each year, more than 180,000 Americans die from cancer as a result of smoking. More than 85% of all lung cancers and 30% of all deaths are caused by smoking. Second hand smoke can also increase 5% the risk of cancer. Smokers are more likely than nonsmokers to develop different types of cancers, such as; lung, larynx, mouth, esophagus, bladder, kidney, throat, stomach, pancreas, cervix and acute myeloid leukemia. Smoking also contributes to cardiovascular, brain stroke, pulmonary, congenital deformities and sudden infant death syndrome. Among 4000 chemicals that have been identified in tobacco smoke, at least 400 are known to be harmful to human health, such as; hydrogen cyanide, carbon monoxide, and ammonia. Almost 40(10%) of these toxic chemicals are shown to be carcinogenic, such as; arsenic, benzene, chromium , ethylene oxide, nickel, polonium, vinyl chloride, formaldehyde, benzo[α]pyrene, toluene (12).

4. Alcohol

Alcohol consumption causes 3.6 % of all human cancers. Having more than two drinks each day for many years will increase the chance of developing cancers of the mouth, throat, esophagus, stomach, liver, colon, lymphomas, prostate, kidney, breast and ovaries. Alcohol has been classified by World Health Organization (WHO) as group-1- carcinogen. Liver can process 7 grams of ethyl alcohol each hour. When liver processes alcohol, it will produce acetaldehyde which is carcinogenic. Higher exposure to acetaldehyde will induce a defect in alcohol dehydrogenase gene and tumor suppressor gene (BRCA) inactivation that can lead to the upper gastrointestinal tract, breast and liver cancers. Iron accumulation, retinoic acid impairment, acetaldehyde genotoxicity, increased estrogen concentration, free radical production and folate metabolic alterations are induced by chronic alcohol abuse. Liver cirrhosis caused when liver cells are replaced with scars due to chronic alcohol use. Almost 5% of people with cirrhosis lead to liver cancer (13). The risk is 35% higher for drinkers with simultaneous smoking habits.

5.Sunlight and ionizing radiation

Ultraviolet (UV) radiation comes from the sun, sunlamps, and tanning booths. It causes early aging of the skin that can lead to skin cancer. You also should protect yourself from UV radiation which can penetrate light clothing, windshields, and windows. Wear long sleeves, long pants, a hat and sunglasses with lenses that absorb UV. Sunscreen (Sun Protection Factor) can prevent skin cancer. Stay away from sunlamps and tanning booths. They are not safer than sunlight. Three types of sun radiations include the visible (color), infrared (heat) and UV lights (UVA, UVB, UVC). The UV light from sun and tanning can cause skin damages, such as; benign, pigmentation, discoloration, freckles, sunburn, cancers (Basal cell carcinoma, Squamous carcinoma and Melanoma) and destruction of elastin and collagen proteins. Exposure to UV sunlight produces the same skin damages in winter as well as summer time. Skin damages could be reduced and /or prevented by: 1. Avoiding direct sunlight exposure between 10:00 a.m. and 3:00 p.m. 2. Use sun protection factor cream (SPF-50) 30 minutes before sun exposure. 3. Proper use of clothing protection and sunglasses with UV protection. 4. Regular self skin examination. Ionizing radiation can cause cell damage that leads to cancer (14).

This kind of radiation comes from outer space which includes; radioactive fallout, radon gas, x-rays which can cause cancers of the blood, thyroid, breast, lung, and stomach. Radon is a radioactive gas that you cannot see, smell, or taste. It forms in soil and rocks. People exposed to radon are at increased risk of lung cancer. Doctors use low-dose radiation to take pictures to diagnose broken bone and use the high-dose radiation to treat cancer. Radiation is energy in the form of high-speed particles or electromagnetic waves. Exposure to ultraviolet radiation and ionizing radiation can clearly cause cancer. Exposure to solar ultraviolet radia-

tion is the major cause of non-melanoma skin cancers, which are by far the most common malignancies in human populations. At low doses, the cells repair the damage rapidly. At moderate and high doses, the cells may be changed permanently or die from their inability to repair the damage. These altered cells may become cancerous or lead to other abnormalities (e.g. birth defects). The first line of evidence comes from studies of the development of cancer among Japanese atomic-bomb survivors. Even at low doses of radiation, atomic-bomb survivors were at a significantly increased risk of developing cancer. The second line of evidence comes from a population, following high-dose radiation therapy for malignant disease will increase the risk of secondary malignancy. The third line of evidence comes from an increased risk of cancer-specific mortality associated with exposure to medical ionizing radiation. The major sources of ionizing radiation are; x-rays, computed tomography [CT], fluoroscopy, nuclear medicine and naturally occurring radon gas in the basements of homes (15).

6. Organic and inorganic chemicals

A number of chemical substances revealed to be dangerous at high concentration chemicals to our health. These cancer causing agents are called carcinogens. We have more than 100,000 chemical elements in our environment in which 30,000 of them have been analyzed. Out of 30,000 analyzed ones, only 275 of them proved to be carcinogenic. People who have certain jobs such as; painting, construction, pesticide and petroleum workers have an increased risk of cancer. Many studies have shown that exposure to asbestos, benzene, benzidine, cadmium, nickel, arsenic, radon and vinyl chloride in the workplace can cause cancer. The study of physiological abnormalities during fetal development is called terotology which is caused by environmental substances called teratogens. Basically, a teratogen attacks the fetal genome and can result in various deformities. Four manifestational phenotypes can occur, such as; malformation (cleft palate), growth retardation (anencephaly), functional defect (ventricular septal defect) and death. About 10% of all birth defects are caused by prenatal exposure to teratogenic agents which include drug, maternal infections, environmental and occupational exposures. However, multifactorial interactions of teratogens and human genetic variability can contribute to the individual level of threshold susceptibility (16).

Arsenic is highly poisonous to human tissues, insects, bacteria and fungi. Contaminated groundwater with metallic arsenic has caused arsenic poisoning for millions of people worldwide. Arsenic has been associated with heritable changes in gene expression, such as; DNA hypermethylation of p16 and p53 tumor suppressor genes, histone modifications and RNA interference. Arsenic trioxide has been approved by FDA in year 2000 to be used for acute promyelocytic leukemia (APL) and psoriasis (17). Recently, the arsenic 74 has been used in pet scan (a positron emitter) for better imaging resolution.

Mutagen is a biological, physical or chemical carcinogenic agent that can alter the genetic composition of a cell. Several accumulated genetic mutations can change a normal cell to malignant one. Some mutations are caused spontaneously during cellular repair, replication and recombination without the mutagenic impact. The mutagens and produced free radicals can be removed from body tissues by effective antioxidants, such as; vitamins A, C, E , polyphenols, Flavonoids and selenium elements (18).

The presence and absence of these mutagens can be tested out by the Ames test, using salmonella bacterium lacking histidine biosynthesis. Many of the cosmetic products, such as; shampoos, hair conditioners, cleansers, lotions, soaps, detergents, deodorant, lipstick, moisturizers, perfumes, facial creams, eye make ups do not show any direct evidence to be associated with human cancers. Seven chemicals, such as; Dioxane, petrolatum, formaldehyde, synthetic fragrance, talc, parabans and phthalates are found in the cosmetic products are considered to be carcinogenic. Most chemicals in cosmetic products include the possibly carcinogenic elements which have potential for cancer but no strong link to human. Cosmetic products are not regulated by US-FDA before

marketing. Only hair dyes and colorful chemicals are regulated by FDA. Many of cosmetic products cause skin irritation, dermatitis and allergic reactions. Hair dyes contain a chemical carcinogen called arylamines which can be absorbed and accumulated in our body. If a person has inherited a mutated gene that normally controls the processing of arylamines. In the absence of the wild type processing gene, an increased risk of bladder cancer, lymphomas will be noted among those who use hair dyes for a long time. More scientific investigation will be needed to examine all the chemicals ingredients used in cosmetic production prior to FDA approval (19).

7. Viruses and Bacteria

Infectious micro-organisms have been estimated to cause 18% of all cancer cases. The burden of cancers caused by infections is much greater in developing nations (26%) than in developed nations (8%).

A. Human papilloma-viruses (HPVs): HPV infection is the main cause of cervical cancer. Infection with an oncogenic strain of human papillomavirus (HPV) is considered a necessary event for subsequent cervix cancer, and vaccine-conferred immunity results in a marked decrease in precancerous lesions.

B. Hepatitis B and hepatitis C viruses: Both viruses can cause liver cancer.

C. Human T-cell leukemia/lymphoma virus-1 (HTLV-1): Infection with HTLV-1 increases a person's risk of lymphoma and leukemia.

D. Human immunodeficiency virus (HIV): HIV is the virus that causes AIDS. People who have HIV infection are at great risk of lymphoma and Kaposi's sarcoma cancers (20).

E. Epstein-Barr virus (EBV): Infection with EBV has been linked to Burkitt's lymphoma (21).

F. Human herpesvirus-8 (HHV8): This virus is a main risk factor for Kaposi's sarcoma cancer.

G. Helicobacter pylori: This bacterium can cause stomach ulcers that can lead to MALT-lymphoma in the stomach and esophageal cancer (22).

H. Salmonella typhi: This bacterium can cause gallbladder cancer.

I. Streptococcus bovis: This bacterium can cause colon cancer (23).

8. Hormone therapy

Estrogen and progestin are hormones that may increase the risk of breast and uterus cancers, heart attack, stroke, or blood clots. Diethylstilbestrol (DES), is a form of estrogen, was given to some pregnant women in the United States between 1940 and 1971. Women who took DES during pregnancy showed a higher risk of developing breast and ovarian cancers. Best examples of hormonal therapy drugs in oncology are tamoxifen and aromatase inhibitors (letrozole and anastrozole) which more superior than tamoxifen for breast cancer treatment. When the function of aromatase is inhibited, estrogen production reduces tremendously in post-menopaused women which ceases cellular proliferation. Also, steroid hormones can induce gene expression in the nucleus of cancer cells which lead to reduced hormonal production and subsequent cellular growth arrest (24).

9. Diet and obesity

People who have a poor diet with reduced physical activity may be at increased risk of several diseases. Obese people will be at higher risk of coronary heart disease, stroke, high blood pressure, diabetes, and cancers (esophagus, breast, uterus, colon, rectum and prostate). Obesity can be calculated by Body Mass Index (BMI) by dividing a person's weight (in kilograms) by their height (in meters) squared. Fat tissue produces high quantity of estrogen which is linked to increased risk of cancers. Also, obese people may produce high amount of insulin-like growth factor-1 (IGF-1) in their blood which may lead to certain cancers. Leptin and adiponectin are produced by fat cells which can promote and inhibit cell proliferation, respectively (25,26). Aflatoxins are naturally made mycotoxins which are produced by Aspergillus (fungus). Two of the most common ones are Aspergillus flavus and Aspergillus parasiticus which are toxic and carcinogenic. Hepatic failure is manifested by hemorrhage, edema, changes in alteration in

digestion and absorption, followed by mental changes and coma. At least 14 different types of aflatoxins are produced in nature. Aflatoxin can intercalate with chromosome DNA base pairs through its epoxide moiety. These changes can cause genetic mutations in the p53 gene. Normally, this gene can prevent cell cycle progression when there are DNA mutations or apoptosis. The codon 249 of the p53 gene seems to be susceptible to aflatoxin causing mutation than other codon. Normal diet including vegetables reduces the carcinogenic effects of aflatoxins (27, 28).

Having a healthy diet, and being physically active may help to reduce cancer risks. Doctors suggest the following: A healthy diet includes plenty of foods that are high in fiber, low in fat, vitamins, minerals, whole-grain breads, cereals, fruits and vegetables every day (29). A good physical activity can help control your weight and reduce body fat. Scientific evidences show that physical activity is inversely associated with at least a few cancers. Some have advocated vitamin and mineral supplements for cancer prevention. A tested hypothesis is that antioxidant vitamins may protect against cancer based on the premise that oxidative damage to DNA leads to cancer progression. Hence, preventing oxidative DNA damage would prevent progression to cancer. Fast food side effects are obesity, worker exploitation and negative health outcome (30, 31). Most of the fast food prepared from processed ingredients which have its own benefits and risks. Toxin removal, preservation, marketing, distribution, seasonal availability and transportation are the benefits of food processing. Using food preservers and heating can destroy the food texture prior to canning.

The Federal Food, Drug and Cosmetic Act have banned the use of any food additives that might have carcinogenic effects, such as cyclamates and saccharin. Although, the risks and benefits of food additives have been controversial. Some artificial food additives have been associated with cancer and other human diseases. Sodium nitrite which has been used for meats to produce a fresh red color to the consumer. Sodium nitrite can be converted to nitrosamines which is highly carcinogenic. Since the food additives can absorb UV-radiation, this can aid to determine the additive concentration in a sample using external calibration. Any method of cooking can destroy some of the food nutrients based on water content, cooking time and temperature. However, it has been well documented that microwave cooking retains most of the food micronutrients due to short exposure time. Since microwave radiation is non-ionizing rays, it does not increase the cancer risks, as it has been shown by ionizing radiation like X-rays (32, 33).

10. Air and water pollution

Air and water pollution is the results of biological, biochemical and atmospheric particles which cause damages to our living environment. Air pollution is a significant risk factor for respiratory infections, cardiac disease and lung cancer. The main cause of air pollution includes particulate matter, damaged ozone, nitrogen dioxide, sulfur dioxide, carbon dioxide, carbon monoxide, ammonia, radioactive decay of radon gas, methane, hydrofluorocarbons and chlorofluorocarbons. Almost 3.5 million deaths are caused by both indoor and outdoor pollution worldwide (34). Water pollution is caused by several pathways; 1. Microorganism infection; bacteria, viruses, protozoa and parasitic worms. 2. Wastes that are decomposed by oxygen-requiring bacteria by oxygen reduction leading to fish death. 3. Acids, salts and toxic metals which cause the death of aquatic life. 4. Nutrients like water-soluble nitrates and phosphates which cause excessive growth of algae by using water's oxygen leading to fish death. 5. Water polluted by several organic compounds such as; oil, plastics, detergents, chloroform, petroleum, polychlorinated biophenyl, fertilizer, sulfur oxide, pesticides and trichloroethylene which cause various human diseases including cancer (35).

Conclusion

Cancer is a complex genetic disease as a consequence of environmental exposures which serve

as the driving force in initiating tumor development and progression. The scientific literatures provide substantial evidences of environmental and occupational causes of cancer. This will fully support an accelerated effort to prevent carcinogenic exposures. In addition to all of the evidences cited, there are many other indications that environmental exposures are linked to various human cancers. The single major risk factor for cancer is age, and the number of our geriatric people is rapidly increasing. If we look only at incident patterns among those aged 65 and 85 years old, there will be a significant increase number of cancer patients over the past 30 years. The same is correct for other ages as well. Cancer has become a widespread disease with epidemic proportions in certain cancer sites in a single generation. Currently, about one in four Americans could expect a cancer diagnosis at some point during his or her lifetime.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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