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IMPACT OF ENVIRONMENTAL POLLUTION ON CARCINOGENESIS

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Abstract

The pathways of impact of the environment on the human body evidently are the systems that are exposed to hazardous materials, covering the external skin, and the internal respiratory and alimentary systems, each with an array of organs and functions, and with an ultimate bearing on the structures and organs of the body as a whole. While many ailments like asthma and allergies are known to be environment linked, cancer is the most significant in the environmental health profile. Tobacco is a known cause of cancer of the lungs, bladder, mouth, pharynx, pancreas, stomach, larynx, esophagus and possibly colon. In addition to tobacco use, certain chemicals can also cause cancer such as asbestos, benzene, vinyl chloride, arsenic, aflatoxin, DDT, formaldehyde and ionizing radiation (IR) such as x-rays, and radon have also been proven to cause cancer in humans. While tobacco and other environmental toxins are the causes of cancer, all smokers or those exposed to environmental hazards do not get cancer, indicating the importance of genetic alterations that occur in the DNA. Alterations in the sequences of certain genes, which are inherited, are equally responsible for carcinogenesis. A combination of tobacco exposure and genetic alterations will increase the risk for malignant transformation of normal cells. Our studies also revealed an increased correlation between tobacco use and cancer incidence. The fishermen in the coastal area of the Thiruvananthapuram city are regularly using tobacco (mostly chewing) when they are occupied with fishing and an increased incidence of oral cancer is also observed in this area. Another important observation is that in some families blood relations in two or more generations are affected by this deadly disease indicating the gene - environment interaction.

Environmental Cancer – An assay

The environment provides humans with essential life support systems, which is comprised of, air, water and land, but it also subjects man to a variety of hazards, which may jeapordize his health. If health is 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' (WHO) it represents a

balanced relationship of the body and mind and complete adjustment to the total environment. Disease, on the other hand, is maladjustment or maladaptation in an environment, a reaction for the worse between man and hazards or adverse influences in his *external* environment. The response of the individual to these influences is conditioned by his genetic make-up or *internal* environment. Environmental pollution may be described as the unfavorable alteration of our surroundings and occurs mainly from the action of man. Environmental pollution takes place through changes in energy patterns, radiation levels, chemical and physical constitutions and abundances of organisms. Pollution includes the release of materials into the atmosphere which make the air unsuitable for breathing, harm the quality of water or soil, and release substances which damage the health of human beings, plants and animals. Though the other environmental pollutants, odour and noise only initiate or disturb, they can also sometimes be a danger to health. The effects of pollution to our biosphere are numerous and are increasing alarmingly.

The pathways of impact of the environment in the human body evidently are the systems that are exposed to hazardous materials, covering the external skin, and the internal respiratory and alimentary systems, each with an array of organs and functions, and with an ultimate bearing on the structures and organs of the body as a whole.

Biological Aspects of Chemical Carcinogenesis

Carcinogenesis is a multiple step process. One of the characteristics of chemical or physical carcinogenesis is the usually extended period of time (latent period) between contact with the carcinogen and the appearance of a tumor. The latent periods of occupational cancers may extend from one to several years and commonly to several decades. Initiation and promotion are two stages in the development of tumors. Initiation is caused by chemical, physical, or biological agents, which irreversibly and heritably alter the cell genome. The mechanism of promotion is not well understood. There are many kinds of promoting agents with diverse molecular structures: phorbol esters, estrogen, prolactin, other endogenous hormones, drugs, and others. These changes trigger cell proliferation, an apparently necessary process in the "fixation" or expression of tumor initiation. Tumor promotion as studied in the animal model of skin carcinogenesis results mainly in the formation of papillomas and occasionally in the progression of papillomas to carcinomas. Progression, the third definable stage of neoplastic development, is separable from promotional stage. Furthermore, following the initiation-promotion stages of induction of skin carcinogenesis, a high incidence of carcinomas can be produced by subsequent applications of a different initiating agent, suggesting a second event ("second hit") in the induction of carcinomas. Molecular genetic mechanisms are implicated in tumor progression, leading to chromosomal rearrangements or mutations that activate proto-oncogenes. Thus, it appears that of the three stages of carcinogenesis - initiation, promotion, and progression - initiation, most certainly, and progression, most likely, involve molecular genetic changes.

The Effects of the Environment on Carcinogenesis

The environment in which we live can be considered as having three fundamental sets of components: Physical (energy of one form or another), Chemical (matter i.e. substances whether natural or man-made), Biological (living things).

Hazards can present themselves to us in various media e.g. air, water and soil. The influence they can exert on human health is very complex and may be modulated by our genetic make up, psychological factors and by the perceptions of the risks that they present. The cause and development of nearly every human disease is in some way related to environmental factors. Diet and nutrition, infectious agents, toxic chemicals, physical factors and physiological stress all play a role in the onset or progress of human diseases.

Physical Hazards

Electromagnetic radiation ranges from low frequency, relatively low energy, radiation such as radio and microwaves through to infrared, visible light, ultraviolet, X-rays and gamma rays. These last as well as other forms of radioactivity such as high-energy subatomic particles (e.g. electrons - Beta rays) and can cause intracellular ionization and are therefore called ionizing radiation. Exposure to ultraviolet (UV) radiation carries an increased risk of skin cancer such as melanoma. Some pollutants such as chlorofluorocarbons (CFCs) used as refrigerants or in aerosol propellants or in the manufacture of certain plastics can damage the "ozone layer" in the higher atmosphere (stratosphere) and thus allow more UV light to reach us, harming us directly. Radioactivity is associated with an exposure-dependent risk of some cancers notably leukemia. Contrary to popular belief however, most radiation to which the average person is exposed to is natural in origin, and of the man made sources, medical diagnosis and treatment is on an average the largest source to the individual. A very important issue is the extent to which radon gas arising from certain rock types beneath dwellings can contribute to cancer risk. According to some estimates it could result in a few thousand-cancer deaths per year in the U.K. (but still probably less than one twentieth of the cancer deaths alone caused by tobacco smoking). Ionising radiation from the nuclear industry and from fall out from detonations contributes less than 1% of the annual average dose to inhabitants of the U.K. The explanation for leukaemia clusters around nuclear power plants is not yet resolved. Similar clustering can occur in other parts of the country. The situation in Japan after World War II and the accident at the Chernobyl Atomic Reactor in Russia, revealed the role of ionizing radiation and the increased risk of cancer. An increased risk of breast cancer was also reported with the occupational exposure to ionizing radiations.

In a study conducted by the Regional cancer Centre, Thiruvananthapuram at Karunagappally, the Natural Background Radiation region in Kerala, cancer pattern among the population showed that lung cancer is the predominant cancer in men and cervix cancer and breast cancer among females. The above study is a unique attempt to

investigate the cancer occurrence in relation to the Natural Radiation because of availability of a large population and high radiation levels in the same place.

Chemical Hazards

Tobacco

Tobacco is the most widely disseminated carcinogen in the world. Several studies of lung, bladder and head and neck cancers addressing various aspects of the carcinogenic effects of tobacco smoke are reported (1). Numerous epidemiological studies have shown the linkage between oral, lung, bladder and breast cancer development and extensive use of tobacco, either in the form of smokeless tobacco or cigarette smoking (2-3). Though it is well known that overall mortality rates are higher among cigarette smokers than in non-smokers, very little is known about the effect of other forms of tobacco use widely prevalent in developing countries, such as bidi smoking and various forms of smokeless tobacco use. Two cohort studies in India addressed this issue, and one such study in Bombay, initiated in 1991, has recruited over 160000 subjects, in which 52568 individuals were traced, including 4358 deaths that were recorded.

Another cohort study in semi-urban areas of Thiruvananthapuram district in Kerala, southern India, initiated in December 1995 (conducted by the Regional Cancer Centre, Thiruvananthapuram) has recruited 125 000 subjects aged 35 years or more. A case-control study within this cohort addressed risk factors for oral pre-cancer.

Occupational Exposures

Although high occupational exposures to exhaust especially from diesel, and to benzene does increase the risk of some cancers, reliable direct evidence of an increased cancer risk to the population at large from the lower levels to which they are exposed is lacking. Toxic pollutants are in the air that cause or are suspected to cause cancer in those exposed to them. Cancer is the primary health effect studied due to the low exposure concentrations of the toxic substances such as benzene, and formaldehyde. Benzene has been shown to cause aplastic anemia and acute myelogenous leukemia in occupational studies of workers exposed to it. Known health concerns related to aldehydes include cancer, asthma, and respiratory tract irritation. Asbestos is one of the leading causes of all types of lung cancers among nonsmokers, and asbestos-exposed smokers have dramatically high rates of this disease. Malignant mesothelioma is a rare progressive cancer of the tissue lining the chest or abdomen, for which asbestos and similar fibers is the only known cause.

An increase in lung cancer risks has been suggested in a number of epidemiological studies of workers exposed to mercury in mining or milling of the metal, thermometer production and felt-hut manufacture (1). Women working in several high-risk occupations (identified from studies in men) were found also to have a higher risk for cancer. This was the case for bladder cancer in the rubber industry, lung caner in occupations with high prevalence of active smoking and high exposure to environmental tobacco smoke, pleural cancer in occupations such as craft and other production

processes with high potential for asbestos exposure, and non-Hodgkin's lymphoma in agricultural workers. Excess risks were also found for breast, skin and melanoma in clerical workers; cervical and ovarian cancer in shop workers; larynx, lung and cervix cancers in building caretakers and cleaners (1). In particular, for ovarian cancer, associations were seen with exposure to aromatic hydrocarbon solvents, bather dust, man-made vitreous fibres, asbestos and gasoline (4).

Pesticides

Agricultural use of the insecticide dichloro diphenyl trichloro ethane (DDT) was banned in 1973 in the United States and in most Western countries. However, some Eastern European countries and numerous developing countries still use DDT (5). Epidemiological data on cancer risk associated with exposure to DDT are suggestive, but limitations in the exposure assessment and the finding of small and inconsistent excesses complicate the interpretation. Elevated risks of non-Hodgkin lymphoma (NHL), in relation to potential exposure to DDT have been found in Washington State (6) and in Sweden (7). A slight increase of leukaemia occurred among Iowa farmers that used DDT and had other agricultural exposures (8).

DDT is considered to be the most emotive and controversial of pollutants. It is partially soluble in water and soluble in fat. The lypophytic property helps it to accumulate in the human body from air or water and is a risk factor for cancer and other gynecologic disorders because it acts like the hormone estrogen and is known as pseudo-estrogen. Breast cancer risk has been repeatedly associated with increased adipose and serum levels of DDE, the major and most persistent DDT derivative, in the general population (9). The p, p'-DDE concentration was elevated in the tumour tissue of patients suffering from uterine cancer as compared to surrounding normal tissue (10). A preliminary study of the mortality experience of DDT applicators in Sardinia and Italy found an increase in mortality from liver cancer and multiple myeloma (11). A case-control study on pancreatic cancer found a strong dose-related association with exposure to DDT (12) although its positive results have not been replicated thus far.

Endosulfan is one of a class of compounds called organochlorines. This class of chemicals is the most important of the persistent organic pollutants or POPs. There is now a move for a world-wide ban on POPs because of their link to cancer and long-term subtle effects on hormones, the immune system, and reproduction. Exposure to endosulfan happens mostly from eating contaminated food, but may also occur from skin contact, breathing contaminated air, or drinking contaminated water.

Exactly how cancers take root in children remains much of a mystery, despite broad investigations into the matter. A few studies support the idea that father's occupation just before conception may play a role (13). More specifically, the chemicals he is exposed to on the job may affect his children's health after birth, contributing to the development of nervous system tumours and more rarely leukaemia –the two common types of childhood cancer. The study, led by Maria Feychting of the Karolinksa Institute in Stokholin, Sweden, lends credence to the hypothesis that paternal occupational exposures may be important in the etiology of childhood cancer.

Dioxin

Dioxin came to public attention as the contaminant in Agent Orange, a controversial herbicide used by U.S. forces in Vietnam. Dioxin comes from both natural and industrial sources, such as medical and municipal waste incineration and paper-pulp production. The chemical enters the food chain when animals eat contaminated plants. Dioxin then accumulates in the fat of mammals and fish. It has been linked to several cancers in humans, including lymphomas and lung cancer. For a small segment of the populatio n who eat large amounts of fatty foods, such as meats and dairy products that are relatively high in dioxins, the odds of developing cancer could be as high as 1 in 100, the report says.

Biological Hazards

Natural and anthropogenic environmental factors account for most of the diseases, and this is particularly relevant for cancer, because of the cell mediated genome affected nature of the disease, which in fact defeats the earliest level of cancer detection. Microbial causes for carcinogenesis is one of the important areas. Human papilloma viruses, hepatitis virus, and helecobactor pyluri etc. are connected with various cancers. The table below shows different microbes and their role in carcinogenenis.

Microbe	Type of Cancer
Hepatitis B Virus	Liver Cancer
Human Papiloma Virus (HPV)	Cervical Cancer
Helicobacter Pylori	Stomach Cancer
HTLV-1	A type of Leukemia in Japan
Epstein- Barr virus (EBV)	Burketts Lymphoma, naso pharyngeal cancer
Kaposi's sarcoma Herpes Virus (KSHV)	Kaposi's sarcoma, and 100 % of Myeloma cases
Schistosomiasis	Bladder Cancer
Liver Flukes	Liver and biliary cancer
Helicobacter hepaticus	Liver cancer
Hepatitis C Virus	Liver cancer
Papillomaviruses (HPV-5,HPV-8,HPV-17)	Skin cancer
Polyomavirus (BK and JC)	Neural tumors? and insulinomas?
Retrovirus (HTLV-2)	Hairy-cell leukemia
Lyme Disease bacteria B. Burgdorferi	Skin and Breast cancer
Epstein-Barr Virus	Majority of Non-Hogkins lymphoma (sp)
Granuloma type Virus	Skin Cancer (Not confirmed)

Environment – Gene interaction

Tobacco use is a well-known risk factor for multiple cancers including those of the head and neck, esophagus, lung, bladder etc. Cofactors in several of these malignancies include alcohol, dietary factors and viral infection. Despite the risk of tobacco exposure, the majority of populations who smoke or chew do not get cancer. Factors that influence tobacco – exposed individuals developing a malignancy may thus include a combination of total tobacco exposure and genetic susceptibility. The environment – gene interaction in carcinogenesis is well reflected by phase 1 and phase 2 enzymes that are involved in the metabolism of carcinogens. The superfamily of Cytochrome p 450 (phase 1) enzymes catalyse the oxidative metabolism of most endogenous chemicals (e.g. hormones and fatty acids) and exogenous chemicals (e.g. polycyclic aromatic hydrocarbons, aromatic amines and mycotoxins). Many of the p 450 genes are known to exist in variant forms that have different activities. Since many carcinogens require metabolic activation before binding to DNA, individuals with an elevated metabolic capacity to activate specific carcinogens may be at an increased risk of cancer. Glutathione S transferase (GST) are a group of phase 2 enzymes that are primarily involved in detoxifying carcinogenic metabolites. The null null genotype (polymorphic form) of GST M1 has a decreased capability in detoxifying some carcinogens present in tobacco smoke. The balance between the CYP and GST enzymes therefore may substantially influence cancer risk (14).

Environment and Cancer Risk Assessment – A Study

In addition to the above factors, environmental health problems can be approached on four different levels: the molecular, the individual, the population and the ecosystem level (15,16). The main environmental health problems need to be defined at the population and ecosystem levels. In the simplest terms this means calculating population – attributable risks based on the prevalence of exposure and expected health effects derived from individual level studies. This activity is important especially in environmental health due to the very large number of low-level exposures, and is positively done in risk achievement. Identification and location specific geographical mapping of environmental pollution and cancer disease epidemiology will lead to the formulation of an environmental-genetical schedule for application in clinical practice, at the same time as laying a foundation for imparting environmental awareness and directions for disease prevention among the people in various ecosystems.

With these objectives we have undertaken a study in the Thiruvananthapuram city and surrounding areas, which is divided into three zones, viz. Residential zone, Commercial zone and Industrial zone and data collected by house hold visits using a questionnaire method. Residential zone covers 2/3 of the total area and only 1/3 covers both commercial and industrial zones. These three areas are having different ecosystem specificities. The industrial zone is the coastal ecosystem, where the Travancore Titanium Products Ltd. and other small-scale industrial units are located. The commercial zone is in the middle and the residential zone is more or less a highland ecosystem. As the

occupations, vehicular traffic, industrial pollution and other environmental factors are different in these three areas, the disease epidemiology is also different.

People in the industrial zone are suffering from marine stress and strain on one side and the industrial effluents on the other side. Vehicular pollution is very less due to wider open spaces, but indoor air pollution is high because of lapses of proper ventilation and use of wood fuels. Tobacco use is comparatively high mainly as chewing. The fisherman community predominating in this area is used to chewing when they are occupied with fishing. Oral cancer incidence is slightly higher in this area, though awareness campaigns and advice on the harmful effect of tobacco use are given time to time. Fish is the only regular non-vegetarian food they are consuming, the intake of vegetables is also not a regular feature. All cancer patients are not registered in the Regional Cancer Centre or any other hospital due to various reasons like lack of knowledge and/ or financial constraints. In this area few cases of oral cancer patients have their blood relations also suffering from cancer, mostly of oral cancer, which again elucidate the environment - gene interaction in carcinogenesis.

In the commercial area vehicular pollution is predominant in addition to solid waste and stagnant wastewater as health hazards. Tobacco use is also less in this area, but not negligible. Mostly vegetarians are in the commercial sector, because the Brahmin community is dominating this zone and a notable observation is that not one stomach cancer is reported from this area during the study period.

According to the RCC records and also from the field data, the residential area is having more incidence of cancer. But unlike industrial and commercial sectors, all the cancer patients in the residential zone are registered either in the RCC or elsewhere (according to the field data). The main reason for this is the awareness of the people about this deadly disease. Modern dietary practice and vehicular pollution are the main environmental problems in this area. Obesity has an important role in breast cancer and is well explained by the observations from the residential zone, breast cancer incidence is above 20% of all cancers reported from this area for the study period.

Oral cancer is comparatively less in the residential zone, only 10 % of the total cancer incidence, whereas in the commercial area it is 24 % and in the industrial zone 35%. A high incidence of prostate cancer is reported from the industrial zone. The distribution of various cancers are given in the table below:

Distribution of cancer incidence (%) in the Thiruvannathapuram city from January 2000-July 2003

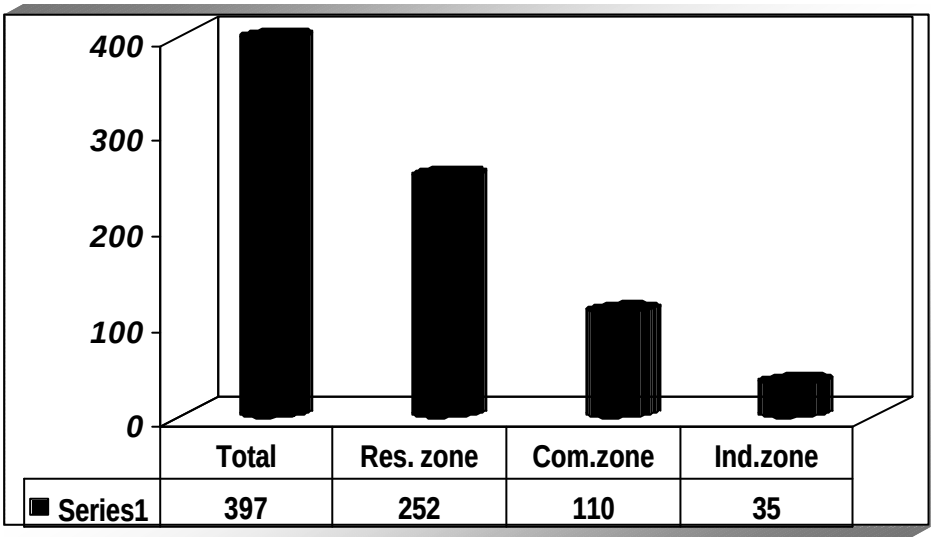
Type of Cancer	Residential zone	Commercial zone	Industrial zone
Oral	10.7	24.54	34.30
Breast	20.63	16.36	11.43
Cervix	8.30	6.36	14.30
Lung	7.50	2.72	-
Thyroid	7.14	5.45	-
Stomach	2.40	-	5.70

Lymphoma	3.57	7.27	5.70
Leukemia	1.98	5.45	-
Prostate	2.77	2.72	8.57
Liver	1.98	4.54	-
Ovary	5.55	6.36	2.80
Colorectal	5.55	4.54	2.80
Brain	3.96	4.54	2.80
Sarcoma	1.98	-	2.80

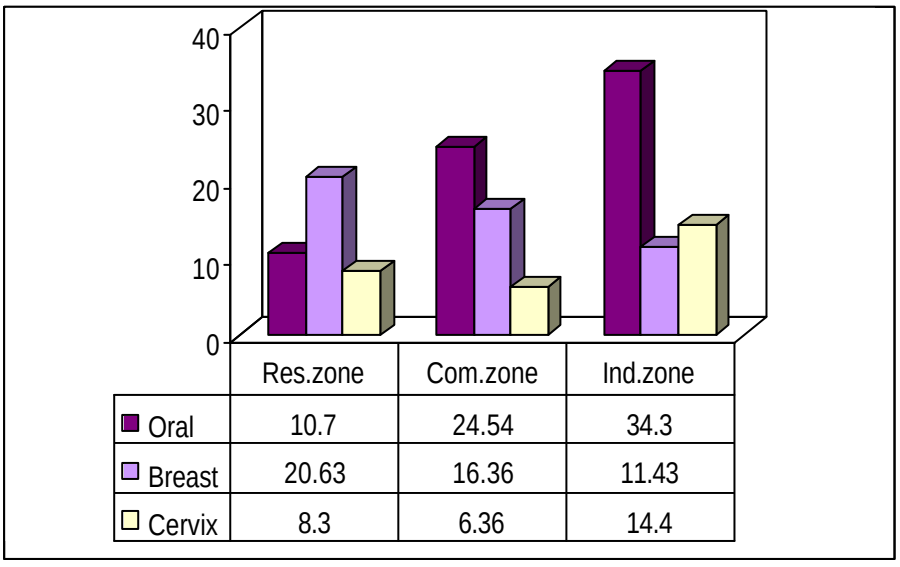
Incidence of familial cancers are also reported and proved for its inherited role in the carcinogenesis. Cancers of the breast, ovary, colorectum etc, showed an increased genetic relationship with the onset of the disease, whereas a limited number of oral cancers also reported as more than one number in a family.

Distribution pattern of total cancer incidence in the three zones of the Thiruvananthapuram city during the period January 2000 - July 2003

Distribution pattern of total cancer incidence in the three zones of the Thiruvananthapuram city during the period January 2000 - July 2003



Percentage of the three important cancers in the three zones of the Thiruvananthapuram city during the period January 2000 - July 2003



Concluding remarks

A wide range of perceptible effects provide substantial evidence to conclude that the environment may have and effect on human health. However, our knowledge is very far from exhaustive and for the sake of conciseness many hazards or their effects have not been mentioned. Moreover, the simplicity of the above has meant that very important concepts have not been discussed. These include the distinction between mere association, and causation, or the quantitative implications of understanding the difference between hazard and risk. In epidemiological studies, using reliable biomarkers of dose and of early effects yields better assessments of exposure and outcome. In addition, markers of genetic susceptibility to environmental agents allow the identification of individuals that are at particularly high risk. While tobacco and other environmental toxins are the causes of cancer, all smokers or those exposed to environmental hazards do not get cancer, indicating the importance of genetic alterations that occur in the DNA. Alterations in the sequences of certain genes, which are inherited, are equally responsible for carcinogenesis. A combination of tobacco exposure and genetic alterations will increase the risk for malignant transformation of normal cells.

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