Environmental factors in Carcinogenesis

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ABSTRACT

Ever since Sir Percival Pott linked cancer scrotum to chimney sweeps in 1775, there have a series of studies and observations which have in turn unmasked a number of chemicals, radiation and microbes as the underlying cause of, or at least association with numerous malignancies. Carcinogenesis is now known to be a complex multistage process, in which both genetic factors and environmental factors are implicated. At least about 170 different environmental factors have been found to cause malignancy. Studies have also found some of the mechanisms of carcinogenesis of such factors. This article reviews the current knowledge of environmental carcinogens and their mechanisms of carcinogenesis in commonly encountered malignancies.

Keywords: chemical carcinogens, radiation, microbial carcinogens.

Introduction and Historical Perspective

The history of environmental causes of carcinogenesis is punctuated by key epidemiologic observations and animal experiments. These have identified cancer-causing factors, which in turn has led to increasingly insightful experiments to establish molecular mechanisms, and also to reduction of human exposure[1].

Any agent that contributes to tumour formation is a carcinogen, and it can be any of several chemical, physical or biologic agents. Global epidemiologic studies have identified several environmental and occupational chemicals as carcinogens. The International Agency for Research on Cancer (IARC) maintains a registry of human carcinogens that is available on the Internet (www.iarc.fr). These are categorized into five groups based on epidemiologic studies, animal models, and short-term mutagenesis tests

Table 1. IARC categories of human carcinogens[4].

Group	Features	Examples
1	Proven human carcinogens. (n=108).	Arsenic, Benzene, Nickel, Tobacco smoke, HTLV-1 infection.
2A	Probable human carcinogens. Limited evidence in humans but sufficient evidence in experimental animals. (n=63).	Clonorchis sinensis infection, Ethylene Dibromide.
2B	Possibly human carcinogens. Limited evidence in humans and less than sufficient evidence in experimental animals. (n=248)	Antimony trioxide, Lead, HIV-2 infection, HPV-6 and 11 infection
3	Not Classifiable as to its carcinogenicity to humans. (n=515)	Acrolein, Coal Dust
4	Probably not carcinogenic. (n=1)	Caprolactam

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Our knowledge regarding environmental carcinogens has accumulated gradually over time, starting with Potts' observation regarding cancer scrotum in chimney sweeps 235 years ago[2], to the first experimental induction of cancer in rabbits exposed to coal tar performed in Japan by Yamagiwa and Ichikawa[3] in 1918, to the research on the mutagenicity of Aflatoxin B1 and its classification as a carcinogen[4], etc. In the present day, emerging hypothesis such as anticarcinogens[5], overlapping pathways to malignancy[6], coordinated changes in gene expression[7], epigenetic silencing by chemical carcinogens[8] and oncogene addiction[9] are just beginning to be explored.

The implications of research in this field are far-reaching, both from the points of view of prevention as well as treatment of cancers. Public opinion can be directed towards avoiding carcinogens, and indeed this was demonstrated with the very first study, i.e. with Sir Percival Potts' study, over 2 centuries ago, with the Danish Chimney Sweeps association ruling that its members must bathe daily in response to the same.

Molecular Basis of Carcinogenesis

Carcinogenesis has a molecular basis[10]. It is beyond the scope of this article to mention the complete details available regarding carcinogenesis; however, some fundamental principles of the molecular basis of carcinogenesis are enumerated as below.

1. Nonlethal genetic damage lies at the heart of carcinogenesis[11].
2. A tumour is formed by the clonal expansion of a single precursor cell that has incurred genetic damage (i.e., tumours are monoclonal)[12].
3. Four classes of normal regulatory genes—the growth-promoting proto-oncogenes, the growth-inhibiting tumour suppressor genes, genes that regulate apoptosis or programmed cell death, and genes involved in DNA repair—are the principal targets of genetic damage.
4. Carcinogenesis is a multistep process[13] at both the phenotypic and the genetic levels, resulting from the accumulation of multiple mutations. Recently completed genome-wide sequencing analysis of breast and colon cancers has revealed that individual tumours accumulate an average of 90 mutant genes[14].
5. The first step is initiation[15] which is exposure of the patient to the carcinogen, which will lead to permanent DNA mutations. This step is rapid and irreversible.
6. The next step is promotion[15] which involves exposure of initiated cells to promoters. Tumours do not result when the promoting agent is applied before the initiating agent. Thus, promoters by themselves are not carcinogenic. Their effect is reversible.
7. Emergence of malignant tumours requires mutational loss of many genes, including those that regulate apoptosis and senescence
8. Cancer cells have several distinct properties[16]:

a. Deregulated cell proliferation: Loss of negative regulators (suppressor oncogenes, i.e., Rb, p53), and increased positive regulators (oncogenes, i.e., Ras, Myc). Leads to aberrant cell cycle control and includes loss of normal checkpoint responses.

b. Failure to differentiate: Arrest at a stage prior to terminal differentiation. May retain stem cell properties. Frequently observed in leukemias.

c. Loss of normal apoptosis pathways: Inactivation of p53, increases in Bcl-2 family members. This defect enhances the survival of cells with oncogenic mutations and genetic instability and allows clonal expansion and diversification within the tumour without activation of physiologic cell death pathways.

d. Genetic instability: Defects in DNA repair pathways leading to either single or oligo-nucleotide mutations, (as in microsatellite instability, MIN) or more commonly chromosomal instability (CIN) leading to aneuploidy. Caused by loss of function of p53, BRCA1/2, mismatch repair genes, and others.

e. Loss of replicative senescence: Normal cells

stop dividing after 25–50 population doublings. Arrest is mediated by the Rb, $p16^{INK4a}$, and p53 pathways. Further replication leads to telomere loss, with crisis. Surviving cells often harbour gross chromosomal abnormalities.

f. Increased angiogenesis: Due to increased gene expression of proangiogenic factors (Vascular Endothelial Growth Factor or VEGF, Fibroblast Growth Factor or FGF, interleukin-8 or IL-8) by tumour or stromal cells, or loss of negative regulators (endostatin, tumstatin, thrombospondin).

g. Invasion: Loss of cell-cell contacts (gap junctions, cadherens) and increased production of matrix metalloproteinases (MMPs). Often takes the form of epithelial-to-mesenchymal transition (EMT) with anchored epithelial cells becoming more like motile fibroblasts.

h. Metastasis: Spread of tumour cells to lymph nodes or distant tissue sites. Limited by the ability of tumour cells to survive in a foreign environment.

i. Evasion of the immune system: Downregulation of MHC class I and II molecules; induction of T cell tolerance; inhibition of normal dendritic cell and/or T cell function; antigenic loss variants and clonal heterogeneity.

9. Oncoproteins encoded by oncogenes generally serve functions similar to their normal counterparts.

10. Mutations convert proto-oncogenes into constitutively active cellular oncogenes that are involved in tumour development because the oncoproteins they encode endow the cell with self-sufficiency in growth[17].

Environmental Carcinogens and Their Cellular Interactions

Environmental carcinogens can be grossly divided into 3 broad categories[10]:

1. Chemicals
2. Radiational
3. Microbial

1. Chemical Carcinogens

Hundreds of [redacted] carcinogenic ever since Sir Percival Pott's observations. Chemicals are most commonly encountered in the industrial belts all over the world. A majority of the Class 1 and 2A agents are chemicals[4]. Some of the major chemical carcinogens, their means of exposure and the predominant tumours caused by them are included in the following table.

Table 2 – Selected Chemical Carcinogens[4] on next page

Mechanism of chemical carcinogenesis:

All initiating chemical carcinogens are highly reactive electrophiles (have electron-deficient atoms) that can react with nucleophilic (electron-rich) sites in the cell. Their main target is the DNA, although they may also affect RNA and proteins[10]. In some cases these interactions cause cell death. Although any gene may be the target of chemical carcinogens, the commonly mutated oncogenes and tumour suppressors, such as RAS and p53, are particularly important targets. The initiated cell is thereby mutated and then passes on the DNA lesions to its daughter cells.

Categories of initiators[10]: Chemicals that can cause initiation of carcinogenesis can be classified into two categories: direct acting and indirect acting. Direct acting chemical carcinogens do not require any metabolism before affecting the cell whereas indirect acting chemical carcinogens require to be metabolized to an ultimate carcinogen. Examples of each are in the table below.

Table 3. Categories of Chemical Carcinogens[10]

Alkylating Agents

β-Propiolactone
Dimethyl sulfate
Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others

Acylating Agents

1-Acetyl-imidazole
Dimethylcarbamyl chloride

PROCARCINOGENS (REQUIRE METABOLIC ACTIVATION)

Polycyclic and Heterocyclic Aromatic Hydrocarbons
Benz[a]anthracene

Table 2 – Selected Chemical Carcinogens[4]

CHEMICAL CARCINOGEN	MEANS OF EXPOSURE	PREDOMINANT TUMOUR TYPE
Aflatoxins	Ingestion of contaminated maize and peanuts grown in hot, humid climates	Hepatocellular carcinoma
Arsenic	Ingestion; also inhalation by smelter workers	Skin cancer
Asbestos	Inhalation	Mesothelioma, lung cancer
Benzene	Inhalation, especially in gasoline-related industries or in the production of other chemicals from benzene	Leukemia
Benzidine	Inhalation by workers in the dye industry	Cancer of the urinary bladder
Beryllium	Inhalation by workers in metal refining and production of beryllium-containing products; also those in the aircraft, aerospace, electronics, and nuclear industries	Lung cancer
Cadmium	Inhalation by workers in cadmium production and refining, nickelcadmium battery manufacturing, other cadmium-related industries	Lung cancer
Chromium compounds	Inhalation during chromium plating, chromate production, welding	Lung cancer
Coal tars	Inhalation, transcutaneous absorption in a variety of industrial settings	Skin cancer, scrotal cancer
Ethylene oxide	Inhalation during the production of various industrial chemicals, e.g., ethylene glycol	Leukemia, lymphoma
Nickel	Inhalation, ingestion, or skin contact in nickel or nickel alloy production plants, welding, or electroplating operations	Lung cancer, nasal cancer
Radon	Inhalation in underground mines	Lung cancer
Tobacco smoke	Inhalation	Lung cancer, oral cancer, pharyngeal cancer, laryngeal cancer, esophageal cancer
Vinyl chloride	Inhalation during production of polyvinyl chloride	Hepatic angiosarcoma, hepatocellular carcinoma, brain tumors, lung cancer, hematopoietic malignancies

Benzo[a]pyrene
Dibenz[a,h]anthracene
3-Methylcholanthrene
7,12-Dimethylbenz[a]anthracene

Aromatic Amines, Amides, Azo Dyes

2-Naphthylamine (β-naphthylamine)
Benzidine
2-Acetylaminofluorene
Dimethylaminoazobenzene (butter yellow)

Natural Plant and Microbial Products

Aflatoxin B_1
Griseofulvin
Cycasin
Safrole
Betel nuts

Others

Nitrosamine and amides, Polychlorinated biphenyls

Vinyl chloride, nickel, chromium, Insecticides, fungicides

Role of cytochrome P-450 monoxygenases: Most of the known carcinogens are metabolized by cytochrome P-450–dependent mono-oxygenases. The genes that encode these enzymes are quite polymorphic, and the activity and inducibility of these enzymes have been shown to vary among different individuals. Therefore, the susceptibility to carcinogenesis is regulated in part by polymorphisms in the genes that encode these enzymes. It may be possible to assess cancer risk in a given individual by genetic analysis of such enzyme polymorphisms.

2. Radiation Carcinogenesis

Radiant energy is a well-established carcinogen. The two most important forms of radiation causing malignant change in humans are ultraviolet (UV) and ionizing radiation.

a. **Ultraviolet Radiation** - The UV portion of the solar spectrum can be divided into three wavelength ranges: UVA (320–400 nm), UVB (280–320 nm), and UVC (200–280 nm). Of these, UVB is believed to be responsible for the induction of cutaneous cancers. UVC, although a potent mutagen, is not considered significant because it is filtered out by the ozone shield around the earth; with the depletion of the ozone layer, it may well be a major carcinogen in the future. Melanomas are associated with intense intermittent exposure to UV radiation, whereas other skin cancers are associated with total cumulative exposure to the same[18].

The carcinogenicity of UVB light is attributed to its formation of pyrimidine dimers in DNA[10]. This type of DNA damage is repaired by the nucleotide excision repair pathway, which in turn involves 5 steps and at least 30 proteins. It is postulated that with excessive sun exposure, the capacity of the nucleotide excision repair pathway is overwhelmed, and error-prone nontemplated DNA-repair mechanisms become operative that in turn lead to cancer.

b. **Ionizing radiation** includes both electromagnetic (x-rays, gamma rays) and particulate (alpha particles, beta particles, protons, neutrons) forms. All forms are carcinogenic. Ionizing radiation leads to rapid, global, and persistent activation of the microenvironment. Inflammation results in the production of reactive oxygen species or reactive nitrogen species (or both) by tissue macrophages or neutrophils. Long-term sublethal exposure to these inflammatory products may cause genomic instability in parenchymal cells, eventually leading to chromosomal abnormalities, gene mutations, or both. In addition, it is becoming apparent that irradiated stroma has a persistent "activated" phenotype. Irradiated stroma has been shown to contribute to the selection and proliferation of malignant clones in animal models.

Most frequent malignancies induced by radiation are the acute and chronic myeloid leukemias. This is followed by papillary carcinoma of the thyroid in the young. In the intermediate category are cancers of the breast, lungs, and salivary glands. However, skin, bone, and the gastrointestinal tract are relatively resistant to radiation-induced neoplasia.

3. Microbial carcinogenesis

Infectious agents may cause or increase the risk

for malignancy by a number of mechanisms, including direct transformation, expression of oncogenes that interfere with cell cycle checkpoints or DNA repair, expression of cytokines or other growth factors, and alteration of the immune system. Some microbial carcinogens are enumerated below along with the predominant malignancies they cause.

Table 4. Selected Microbial Carcinogens[19]

Microbial Carcinogens	**Predominant Malignancies**
Epstein-Barr virus (EBV)	Burkitt's lymphoma, Hodgkin's disease, immunosuppression-related lymphoma, nasopharyngeal carcinoma
Hepatitis B	Hepatocellular carcinoma
Hepatitis C	Hepatocellular carcinoma
Human immunodeficiency virus (HIV) type 1	Kaposi's sarcoma Non – Hodgkin's Lymphoma
Human papillomavirus (HPV) types 16 and 18	Cervical cancer, anal cancer
Human T-cell lymphotropic virus type I (HTLV-1)	Adult T-cell leukemia
Helicobacter pylori	Gastric adenocarcinoma
Opisthorchis viverrini	Cholangiocarcinoma, hepatocellular carcinoma
Schistosoma haematobium	Cancer of the urinary bladder

Microbial carcinogens have multiple mechanisms of carcinogenesis. Some of the more important carcinogens are discussed below:

1. Epstein-Barr virus (EBV):

The molecular basis of B-cell proliferations induced by EBV is complex[20]. An EBV gene, latent membrane protein-1 (LMP-1), acts as an oncogene by behaving like a constitutively active CD40 receptor, which is a key recipient of helper T-cell signals that stimulate B-cell growth. LMP-1 activates the NF-κB and JAK/STAT signaling pathways and promotes B-cell survival and proliferation, all of which occur autonomously in EBV-infected B cells. Concurrently, LMP-1 prevents apoptosis by activating BCL2. Another EBV gene, EBNA-2, encodes a nuclear protein that mimics a constitutively active Notch receptor. EBNA-2 transactivates several host genes, including cyclin D and the src family of proto-oncogenes. The EBV genome contains a viral cytokine, vIL-10, that was hijacked from the host genome. This viral cytokine can prevent macrophages and monocytes from activating T cells and helps evade the immune system.

2. Hepatitis B:

Hepatitis B virus probably involves a combination of indirect and direct mechanisms. The HBV X protein (HBx) may also act as a potential viral oncoprotein[21]. As a transcription factor, it acts on a number of viral and cellular promoters. HBx also binds p53 and inhibits several critical p53-mediated processes, including DNA sequence–specific binding, transcriptional transactivation, and apoptosis. Chronic liver injury secondary to persistent viral infection leads to necrosis, inflammation, and hepatocyte regeneration. The constitutive induction of liver cell progression into the cell cycle overwhelms DNA repair mechanisms in the presence of mutational events. This may induce fixed DNA mutations and chromosomal rearrangements, which are major determinants of cell transformation; concurrently, fibrosis disrupts the normal lobular structure and modifies cell-cell and cell-ECM interactions, with further loss of control over cell growth.

3. Hepatitis C:

A number of HCV proteins have been implicated in its carcinogenic activity[21]. Both the HCV core protein and NS3 protein modulate expression of the cyclin-dependent inhibitor p21WAF1 and affect the activity of p53. NS5A protein acts as a transcription factor and interacts with cellular signaling pathways and various cell cycle regulatory kinases to block the apoptotic cellular

response to persistent HCV infection.

4. Human papillomavirus (HPV) types 16 and 18:

The HPV genome is integrated into the host genome. The site of viral integration in host chromosomes is random, but the pattern of integration is clonal. Cells in which the viral genome has integrated show significantly more genomic instability. Furthermore, there is no consistent association with a host proto-oncogene. Integration interrupts the viral DNA within the E1/E2 open reading frame, leading to loss of the E2 viral repressor and overexpression of the viral oncoproteins E6 and E7. Together, they interact with a variety of growth-regulating proteins encoded by proto-oncogenes and tumour suppressor genes[10].

5. Human T-cell Lymphotropic Virus type 1:

HTLV-1 does not contain an oncogene, and no consistent integration next to a proto-oncogene has been discovered. In leukemic cells, however, viral integration shows a clonal pattern, i.e. although the site of viral integration in host chromosomes is random, (the viral DNA is found at different locations in different cancers); the site of integration is identical within all cells of a given cancer. The secrets of its transforming activity are locked in the tax gene[22]. The product of this gene, the Tax protein, can activate the transcription of several host cell genes involved in proliferation and differentiation of T cells.

6. Helicobacter pylori:

Strains with the cytotoxin-associated antigen A (cagA) gene are associated with gastric carcinoma. Once intracellular, CagA is tyrosine phosphorylated by SRC family kinases and is then able to specifically bind and activate the cellular oncoprotein SHP2, causing a 'gain of function'[10].

7. Human Immunodeficiency Virus – 1:

HIV-1 is predominantly associated with B-cell Non Hodgkin's Lymphoma and Kaposi's sarcoma. The mechanisms underlying the development of lymphoma in the setting of HIV are not fully understood. Infection by HIV is associated with a myriad of immunologic aberrations. These abnormalities include functional and quantitative defects of CD4+ T cells and chronic antigenic stimulation of B lymphocytes by antigens, mitogens, or viruses, including Epstein-Barr virus (EBV)[23] and HIV itself[24]. Ongoing B cell expansion and activation result in the development of reactive B cell hyperplasia in lymphoid tissues (PGL)[25] and polyclonal hyper gamma globulinemia in the serum[26]. Lymphomas may develop after acquisition of genetic errors occurring during the course of polyclonal B cell proliferation in the setting of underlying immunodeficiency. Errors include specific chromosomal translocations in AIDs-related Burkitt's lymphoma, including t(8;14), t(8;22), and t(8;2)[27,28,29], c-myc dysregulation[30], bcl-6 dysregulation[31], p53 mutations or deletions, etc. Kaposi's Sarcoma, on the other hand is associated with Human Herpes virus – 8 (HHV-8), which possesses a number of genes including homologues of the IL-8 receptor, Bcl-2, and cyclin D, which can cause malignant transformation of the host cell[10].

Conclusion

Carcinogenesis is a complex multistage process which in addition to genetic factors also involve multiple environmental factors – at the least about 170 environmental agents are directly implicated in one or the other malignancy as per the IARC Groups 1 and 2A. These agents may be either of chemicals, radiation or microbes.

Such environmental agents may be encountered in day to day life, contribute to occupational hazards, and in general, may be overlooked as a cause of malignancy. We need to keep this in mind, especially when dealing with patients from areas which have a high concentration of such agents, most commonly the industrial belts.

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