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Environmental and Infectious Causes of Malignancy

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Et al.

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Summary and Key Points

1. Exposure to many environmental agents is associated with an increased incidence of certain malignancies, although causation is usually difficult to prove.
2. Certain chemicals, infections (parasitic, viral, and bacterial) and ionizing radiation are known carcinogens.
3. Variable genetic susceptibility to carcinogenesis is apparent.
4. Up to two-thirds of human cancers are believed to have an environmental component.

Introduction

Carcinogenesis may be triggered by a variety of causes, including genetics, diet, poor oral hygiene, environmental, and infectious sources. (Watch this YouTube video: What Causes Cancer? Start at minute 7 of 14.) The scientific information in this chapter is changing rapidly. It is not intended as a comprehensive catalogue, but instead to present a summary of the most relevant causative agents. Genetic susceptibility to an environmental insult plays a role for some if not all of these agents, but that role is not yet well defined. For example, some families have a high incidence of lung cancer despite little or no smoking history, while some 100-pack-year smokers remain cancer free.

An environmental factor for cancer was first recognized in London chimney sweeps exposed to soot. These men experienced an increased incidence of an uncommon skin cancer on the scrotum.[1] This phenomenon and the connection to occupation were initially noted in the nineteenth century. Since that time, many other carcinogens have been identified (e.g., tobacco, asbestos, radon). However, even these well-known carcinogens cause more types of cancer than commonly understood. In addition, there are hundreds of other known carcinogens with exposure rates ranging from rare to common. The most accessible compendium of carcinogens is the Report on Carcinogens from the United States Public Health Service National Toxicology Program. The thirteenth edition was issued in 2014, and lists 243 carcinogens, 56 "Known human carcinogens" (including 1 new substance) and 187 "Reasonably anticipated to be human carcinogens" (3 new). This report is cumulative.[2]

Chemical Carcinogens

Tobacco use is a well-known causative agent in lung cancer, and in the last twenty years, the dangers of second-hand and even third-hand smoke have been better understood. However, the link to other types of cancers – including head and neck, esophageal, bladder, and cervical cancer – remains underappreciated. The exposure to toxins in the smoke can explain tumors in the region of direct contact with smoke, but the link to bladder and cervical cancer is less well understood[3].

Recent research has also considered the proposed phenomenon of third-hand smoke. For example, a non-smoker who works with smokers is exposed to second-hand smoke in the workplace, and in turn exposes his family to third-hand smoke on arriving home, despite never touching tobacco products himself[4].

Mesothelioma, a rare form of thoracic cancer, is linked to asbestos exposure. Unfortunately, this is not the only industrial dust that has been linked to cancer. Silica and talc inhalation have both been linked to an increased risk of lung cancer. Additionally, there is a possibility that peritoneal tumors are more common in women who use feminine hygiene powders due to small amounts of talc entering the peritoneum via the female reproductive tract.

Other work-related exposures include a number of metals that have been shown to be associated with increased risk of malignancy. Often these

metals must be aerosolized or molten to cause harm, and associated lung cancers have largely been found in clusters of machinists, welders, and others who work with these materials. Arsenic, a common contaminant in water supplies, is known to be linked to lung, skin, and bladder cancer. A number of solvents, including benzene, carbon tetrachloride, and chloroform have been linked to various hematologic cancers. Dyes have been linked to an increased risk of bladder cancer. Finally, agricultural work can be associated with heavy pesticide exposure, leading to the risk of anti-cholinergic crisis as well as increased cancer risk (Table 1).

Table 1. Carcinogens and Related Cancer(s)

Carcinogens		Cancer(s)
Tobacco		Lung, Esophagus, Larynx, Mouth, Throat, Kidney, Bladder, Pancreas, Stomach, Cervix, Acute myeloid leukemia
Asbestos		Lung, Mesothelioma, Larynx, Ovaries
Metals and metalloids	Arsenic	Lung, Skin, Bladder
	Antimony	Lung
	Beryllium	Lung
	Cadmium	Lung
	Chromium	Lung
	Cobalt	Lung
	Lead	Kidney, Brain
	Nickel	Lung
	Vanadium	Lung
Solvents	Benzene	Leukemia
	Carbon Tetracholoride	
	Chloroform	
Pesticides		
Dyes		Bladder
Polycyclic aromatic hydrocarbons		Lung, Skin, Urinary
Nitrites & Nitrates		Stomach
Aflatoxin		Hepatoma
Ethanol		Head & Neck, Esophagus, Liver

Occasionally, there are claims made linking certain foods to an increased risk of cancer. While many of these claims have not been proven by the gold standard of rigorous clinical trials, there have been a few foods clearly linked to cancer. For example, nitrites, present in processed meats, have been shown to cause an increased risk of malignancy. Charcoal grilled foods contain cancer-causing polycyclic aromatic hydrocarbons linked to lung, skin, gut, and urinary cancers.

Dietary habits are linked to colon cancer risk, possibly via decreased fiber and vegetable consumption. One of the most common malignancy in the world, hepatoma, can be associated with food items (though chronic viral hepatitis may be the most common etiologic factor associated with hepatoma – see below). Aflatoxin is a byproduct of a mold that commonly contaminates peanuts, particularly in Africa. It can be spread to humans by ingesting nuts, grains, or meat and dairy products produced by animals fed with infected grain. Most countries screen peanuts for this toxin.

Alcohol (ethanol) consumption is known to be associated with liver disease and often presents an increased risk of trauma. Less well recognized is the fact that alcohol consumption contributes to the development of head and neck, esophageal and liver cancers. This increased risk appears to be associated with direct organ exposure to alcohol itself and it does not seem to be dependent upon the type of alcohol (liquor, beer or wine) consumed. The risk of head and neck cancers is significantly increased in heavy drinkers who also smoke.

Many therapeutic drugs have the potential to cause harm, warranting careful weighing of risks versus benefits when considering their use. Cancer risk is one aspect of this tradeoff for several chemotherapy medications and hormone treatments. Post-menopausal hormone replacement therapy with combined estrogen and progesterone hormones increases the risk of breast cancer, but decreases the risk of colorectal cancer. Tamoxifen, a selective estrogen receptor modulator used in breast cancer treatment, increases the risk of endometrial cancer.

Infectious Carcinogens

A number of infectious agents have been linked to cancers. Currently, there is evidence that 15-20% of human cancers have a link to a chronic infection[5]. The most notable are shown in Table 2. The exact mechanisms by which these infectious agents cause cancer are not known for all of them.

Oncogenic human papilloma virus (HPV) serotypes elaborate the viral proteins E6 and E7 which bind to p53 and Rb, respectively. Infection of squamous epithelium by HPV can lead to inactivation of these tumor suppressor proteins, resulting in dysregulated cellular proliferation.

By contrast, rather than causing cancer by a direct effect on infected cells, Helicobacter pylori appears to stimulate an immune response which, in uncommon instances, results in growth of a monoclonal clone of B-lymphocytes and a subsequent B cell lymphoma. It also is associated with gastric adenocarcinoma.

HIV's role in the etiology of malignancies is mostly immunosuppression. For example, human herpesvirus-8 (HHV-8- also referred to as Kaposi's sarcoma-associated herpesvirus (KSHV)) infection is required for Kaposi's sarcoma and HPV infection for cervical cancer to occur in HIV patients.

Identification of infectious causes of cancer can lead to a reduction in cancer incidence if effective techniques exist to interfere with infection. For example, it appears that vaccine programs against Hepatitis B, begun in China in the 1990's, have already resulted in a reduction in deaths due to hepatoma in that country. It is hoped that vaccines for HPV will result in reduced rates of cervical, anal, and oropharyngeal cancers.[5] HPV infections appear to be the cause of about 5% of human malignancies, and are associated with a new epidemic of head and neck cancer, particularly or-pharyngeal cancer, in non-smokers.[6]

Hepatitis C (Hep C) was only identified in 1989; before that physicians were well aware that this disease existed but did not know the causative agent. The exact mechanism of carcinogenesis is not yet known, but it is clear that the induction period is very long – decades. Hep C is a ribonucleic acid (RNA) virus, which reproduces in the cytoplasm of liver cells. Chronic Hep C infection appears to change the genetic stability of hepatocytes, increasing the risk of malignant transformation, and this is a field effect, involving the entire organ. Many patients were infected before 1989, and more are becoming infected due to the intravenous drug issue. In the United States, the incidence of hepatocellular carcinoma has been steadily rising for the last decade.[7]

Table 2. Infectious Agents and Related Cancer(s)

Infectious Agent(s)		Cancer
Parasites	Schistosoma haematobium	Bladder cancer
	Liver flukes (Chlonorchis, Opisthorchis)	Cholangiocarcinoma
Bacteria	H pylori	Gastric cancer, gastric lymphoma
Virus	Hepatitis B&C	Hepatoma
	EBV (Epstein Barr)	Burkitt's lymphoma, nasopharyngeal carcinoma
	HTLV-I (Human T-cell Leukemia Virus)	Leukemia
	HHV8 /KSHV (Herpes virus)	Kaposi's sarcoma, primary effusion lymphoma
	HPV (Human Papilloma Virus), particularly types 16, 18, 31, 45	Cervical, anal, vulvar, penile, oropharyngeal
	HIV	Kaposi sarcoma, lymphoma, cervical cancer

Radiation Carcinogens

One of the most feared carcinogens is radiation. Most of the radiation experienced by humans is from natural sources such as cosmic rays, naturally occurring radioisotopes, and solar radiation. It is estimated that up to 10% of human malignancy is attributable to radiation exposure. Natural radiation in space places astronauts at risk for cancers and may preclude long distance space travel.[8]

Radiation causes cancer by the same mechanism it causes genetic mutations– by damaging deoxyribonucleic acid (DNA). Different types of radiation vary in their likelihood of causing DNA damage– usually double

strand DNA breakage. Ultraviolet (UV) radiation cannot penetrate into the body very deeply, so it is primarily associated with skin cancers. Skin cancer is strongly linked to solar radiation or other ultraviolet exposure such as that from a tanning salon.

X-rays and gamma rays – photons- are weak mutagens; neutrons are very potent, because they transfer a lot of energy into cells as they transit the body.

Radon, a naturally occurring isotope, is associated with as many as 20,000 lung cancer deaths in the United States annually. For this reason, many states now mandate radon testing as part of a comprehensive home inspection. Fallout from nuclear testing and accidents such as Chernobyl has clearly caused increased cancer risk. In addition, the technology used for medical imaging can lead to an increased individual radiation burden.

The use of "backscatter" imaging as a security measure is an issue that has raised much controversy, given the concern that it may be a source of increased individual radiation burden, although scanners currently in service use radio waves, which pose no known risk. The risk to frequent fliers is actually from cosmic radiation at common flight elevations; especially at high latitudes.[9] (Table 3).

Table 3. Radiation Carcinogenesis

Type of Radiation		Source	Cancer
Ionizing	Natural	Cosmic rays	Skin
		Radon gas	Lung
		Naturally occurring radioisotopes (uranium)	Lung
	Man-made	Fallout (I-131)	Thyroid
	Medical	Diagnostic (X-ray, CT)	Lung
		Therapeutic (Radiation therapy)	Sarcoma, Lung
Ultraviolet	Natural	Sunlight	Skin
	Man-made	Tanning beds	Skin

Conclusion

The number of known carcinogens is rising steadily. Chemicals, dusts, and particularly infectious agents unsuspected a decade ago have emerged as significant carcinogens. Cancer-causing substances have been identified through human studies, often case controlled.[2] Animal and cell studies are even more important, as the exposure studies can be randomized and even blinded. Some viruses have been implicated with the discovery of their genomes buried in the genomes of cancerous cells.

The risk associated with environmental carcinogens is not well understood, aside from a few specific exposures. However, it is likely that many cancer deaths are linked to avoidable environmental risk factors such as tobacco, alcohol, and diet.

Carcinogens vary in their potential to cause disease, and the type of exposure, whether direct or indirect, ingested or via skin, may affect the risk of carcinogenesis. For many agents such as tobacco, ionizing radiation, and ultraviolet light, there is a clear dose-dependent risk. Additionally, the age of the individual at the time of exposure and the individual's genetic susceptibility affect the risk of developing cancer following exposure to these agents.

If people choose to modify their lives to avoid these carcinogens, the incidence of malignancies is likely to decline, as demonstrated by the decline in lung cancer in males after smoking waned in that group.[10]

Thought Questions

1. As noted in this chapter, tobacco smoking is associated with a number of malignancies, including bladder and cervical cancers. Suggest plausible hypotheses that would explain how smoking can cause bladder and cervical cancer.

   Your answer

   Expert Answer

2. A sixteen year old girl is treated with thoracic radiation for a lymphoma. Fourteen years later she is advised to begin screening breast MRI exams because therapeutic chest irradiation of female adolescents is associated with a marked increase in the risk of breast cancer. Explain why radiation would convey a higher risk of breast cancer when given to an adolescent, compared to a child (before onset of puberty) or a mature woman.

   Your answer

   Expert Answer

Glossary

Anti-cholinergic crisis- A very uncomfortable state, characterized by fever, mydriasis (pupil dilation) often with blurred vision, facial flushing, dry mouth, eyes and skin, and delirium, sometimes with hallucinations

Backscatter imaging- Millimeter wave imaging, which enables the body to be seen without clothes, used in security checkpoints at airports

Blinded- Investigators are unaware of which subject receives agent and which subject receives placebo

Carcinogenesis- The process by which normal cells are transformed into cancer cells

Hepatoma- Hepatocellular carcinoma

Induction period- Interval between exposure to a disease causing agent and onset or diagnosis of disease

Oncogenic- An agent causing or associated with the cause of a malignancy

Second-hand smoke- Exposure to smoke through another individual's actions, such as smoking a cigarette or other burning material

Third-hand smoke- Constituents of smoke that are transmitted via smokers' and non-smokers' hair and clothing contaminated with tobacco smoke

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