NEOPLASM

Lecture 3

Learing objectives

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The students must understanding the following:

- ✓ **epidemiology of cancer**
- ✓ GEOGRAPHIC AND ENVIRONMENTAL FACTORS
- ✓ GENETIC PREDISPOSITION TO CANCER
- ✓ Precancerous Conditions

Epidemiology

. Study of cancer patterns in populations can contribute substantially to knowledge about the origins of cancer. Epidemiologic studies have established the causative link between smoking and lung cancer, and comparison of diet and cancer rates in the Western world and Africa has implicated high dietary fat and low fiber in the development of colon cancer.

Major insights into the causes of cancer can be obtained by epidemiologic studies that relate particular environmental, racial (possibly hereditary), and cultural influences to the occurrence of specific neoplasms.

Certain diseases associated with an increased risk of developing cancer (preneoplastic disorders) also provide clues to the pathogenesis of cancer.

CANCER INCIDENCE

. The most common tumors in men arise in the **prostate, lung, and colorectum**.

In women, cancers of the **breast, lung, and colon and rectum** are the most frequent.

Cancers of the lung, female breast, prostate, and colon/rectum constitute more than 50% of cancer diagnoses and cancer deaths in the U.S. population.

.. Nearly 40% of the sex-specific decreases in cancer death rates is accounted for by a reduction in lung cancer deaths in men and breast cancer deaths in women.[1] Decreased use of tobacco products is responsible for the reduction in lung cancer deaths, while improved detection and treatment are responsible for the decrease in death rates for colorectal, female breast, and prostate cancer.[1] The last half century has seen a decline in the number of deaths caused by cervical cancer that relates to earlier diagnosis made possible by the Papanicolaou (Pap) smear.

Deaths from primary liver cancers have approximately doubled during the past 30 years. This number is expected to increase over the coming decades, as the large number of individuals infected with the hepatitis C virus (HCV) begin to develop hepatocellular carcinoma.

Although **race** is not a strict biologic category, it can define groups at risk for certain cancers.

GEOGRAPHIC AND ENVIRONMENTAL FACTORS

Although genetics and environmental triggers both play a role in the pathogenesis of cancer, environmental factors are thought to be the more significant contributors in most common sporadic cancers. In one large study the proportion of risk from environmental causes was found to be 65%, whereas heritable factors contributed 26% to 42% of cancer risk. Remarkable differences found in the incidence and death rates of specific forms of cancer around the world also suggest a role for environmental factors. For example, the death rate for stomach carcinoma in both men and women is seven to eight times higher in Japan than in the United States. In contrast, the death rate from carcinoma of the lung is slightly more than twice as great in the United States as in Japan. Although racial predispositions cannot be ruled out, it is generally believed that most of these geographic differences are the consequence of environmental influences.

There is no paucity of carcinogenic environmental factors: they lurk in the ambient environment, in the workplace, in food, and in personal practices. Individuals may be exposed to carcinogenic factors when they go outside (ultraviolet [UV] rays, smog), in their medication (methotrexate), at work (asbestos, vinyl chloride or at home (high-fat diet, alcohol).

.**Alcohol abuse** alone increases the risk of carcinomas of the oropharynx (excluding lip), larynx, and esophagus and, by the development of alcoholic cirrhosis, hepatocellular carcinoma

Smoking, particularly of cigarettes, has been implicated in cancer of the mouth, pharynx, larynx, esophagus, pancreas, bladder, and most significantly, about 90% of lung cancer deaths.

. Alcohol and tobacco together synergistically increase the danger of incurring cancers in the upper aerodigestive tract.

The risk of cervical cancer is linked to age at first intercourse and the number of sex partners, and it is now known that infection by venereally transmitted human papillomavirus (HPV) contributes to cervical dysplasia and cancer..

Arsenic and arsenic compounds ……..Lung, skin, hemangiosarcoma

Asbestos …….Lung, mesothelioma; gastrointestinal tract (esophagus, stomach, large intestine)

Benzene …….Leukemia, Hodgkin lymphoma

Beryllium and beryllium compounds…….. Lung

Cadmium and cadmium compounds……. Prostate

Chromium compounds …….Lung

Nickel compounds…….. Nose, lung

Radon and its decay products …….Lung

Vinyl chloride……. Angiosarcoma, liver

AGE

- Age has an important influence on the likelihood of being afflicted with cancer.
- Most carcinomas occur in the later years of life (>55 years).
- Cancer is the main cause of death among women aged 40 to 79 and among men aged 60 to 79;
- the decline in deaths after age 80 is due to the lower number of individuals who reach this age.
- The rising incidence with age may be explained by the accumulation of somatic mutations associated with the emergence of malignant neoplasms . The decline in immune competence that accompanies aging may also be a factor.

However, children are not spared; cancer accounts for slightly more than 10% of all deaths in children under age 15 in the United States, second only to accidents. However, the types of cancers that predominate in children are significantly different from those seen in adults.

Carcinomas, the most common general category of tumor in adults, are extraordinarily rare among children. Instead, acute leukemia and primitive neoplasms of the central nervous system are responsible for approximately 60% of childhood cancer deaths.

The common neoplasms of infancy and childhood include the so-called small round blue cell tumors such as neuroblastoma, Wilms tumor, retinoblastoma, acute leukemias, and rhabdomyosarcomas.

GENETIC PREDISPOSITION TO CANCER

One frequently asked question is: "My mother and father both died of cancer. Does that mean I am doomed to get it?" Based on current knowledge, the answer must be carefully qualified.

Evidence now indicates that for a large number of cancer types, including the most common forms, there exist not only environmental influences but also hereditary predispositions.

Less than 10% of cancer patients have inherited mutations that predispose to cancer, and the frequency is even lower (around 0.1%) for certain types of tumors.

Despite the low frequency, the recognition of inherited predisposition to cancer has had a major impact on the understanding of cancer pathogenesis.

Moreover, genes that are causally associated with cancers that have a strong hereditary component are generally also involved in the much more common sporadic forms of the same tumor.

Examples of Inherited Predisposition to Cancer (AUTOSOMAL DOMINANT) Gene Inherited Predisposition

RB---------- ----------Retinoblastoma

p53----------Li-Fraumeni syndrome (various tumors)

APC---------- ----------Familial adenomatous polyposis/colon cancer

BRCA1, BRCA2--------- -------Breast and ovarian tumors

Xeroderma pigmentosum----- Ataxia-telangiectasia

Bloom syndrome ----------Fanconi anemia

FAMILIAL CANCERS

Familial clustering of cases, but role of inherited predisposition not clear for each individual

Breast cancer

Ovarian cancer

Pancreatic cancer

Autosomal Dominant Inherited Cancer Syndromes.

Inherited cancer syndromes include several well-defined cancers in which inheritance of a single autosomal dominant mutant gene greatly increases the risk of developing a tumor. The inherited mutation is usually a point mutation occurring in a single allele of a tumor suppressor gene. The silencing of the second allele occurs in somatic cells, generally as a consequence of deletion or recombination.

There are several features that characterize inherited cancer syndromes:

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In each syndrome, tumors tend to arise in specific sites and tissues, although they may involve more than one site. There is no increase in predisposition to cancers in general.. Patients with familial adenomatous polyposis develop innumerable polypoid adenomas of the colon, and virtually 100% of those affected develop a colonic adenocarcinoma by age 50.

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Defective DNA-Repair Syndromes.

Besides the dominantly inherited precancerous conditions, a group of cancer-predisposing conditions is collectively characterized by defects in DNA repair and resultant DNA instability.

These conditions generally have an autosomal recessive pattern of inheritance. Included in this group are xeroderma pigmentosum, ataxia-telangiectasia, and Bloom syndrome, all rare diseases characterized by genetic instability resulting from defects in DNA-repair genes.

Familial Cancers.

Besides the inherited syndromes of cancer susceptibility, cancer may occur at higher frequency in certain families without a clearly defined pattern of transmission. Virtually all the common types of cancers that occur sporadically have also been reported to occur in familial forms. Examples include carcinomas of colon, breast, ovary, and brain, as well as melanomas and lymphomas.

Features that characterize familial cancers include:

- ✓ early age at onset
- ✓ tumors arising in two or more close relatives of the index case,

- ✓ sometimes, multiple or bilateral tumors.

Familial cancers are not associated with specific marker phenotypes.

It has been estimated that 10% to 20% of patients with breast or ovarian cancer have a first- or second-degree relative with one of these tumors. Although two breast cancer susceptibility genes, named BRCA1 and BRCA2, have been identified, mutation of these genes occurs in no more than 3% of breast cancers.

Interactions between Genetic and Nongenetic Factors.

What can be said about the influence of heredity on the majority of malignant neoplasms? It could be argued that they are largely of environmental origin, but lack of family history does not preclude an inherited component. It is generally difficult to sort out the hereditary and acquired basis of a tumor, because these factors often interact closely. The interaction between genetic and nongenetic factors is particularly complex when tumor development depends on the action of multiple contributory genes. Even in tumors with a well-defined inherited component, the risk of developing the tumor can be greatly influenced by nongenetic factors.

the genotype can significantly influence the likelihood of developing environmentally induced cancers. Inherited variations (polymorphisms) of enzymes that metabolize procarcinogens to their active carcinogenic forms can influence the susceptibility to cancer. Of interest in this regard are genes that encode the cytochrome P-450 enzymes .polymorphism at one of the P-450 loci confers inherited susceptibility to lung cancers in cigarette smokers. More such associations are likely to be found.

NONHEREDITARY PREDISPOSING CONDITIONS

Certain predisposing influences, such as environment, behaviors, and clinical conditions, can increase that risk. For example, regenerative, metaplastic, hyperplastic, and dysplastic proliferations are fertile soil for the origin of a malignant tumor, because cell replication is involved in neoplastic transformation. Indeed, proliferation may be required for neoplastic transformation in some settings, since it is proliferating cells that accumulate the genetic lesions required for carcinogenesis.

Chronic Inflammation and Cancer.

In 1863 Virchow proposed that cancer develops at sites of chronic inflammation, and the potential relationships between cancer and inflammation have been studied since then.This is exemplified by the increased risk of cancer in individuals affected by a variety of chronic inflammatory diseases of the gastrointestinal tract . These include ulcerative colitis, Helicobacter pylori gastritis, viral hepatitis, and chronic pancreatitis.

Although the precise mechanisms that link inflammation and cancer development have not been established, recent work has demonstrated that in the setting of unresolved chronic inflammation, as occurs in viral hepatitis or chronic gastritis, the immune response may become maladaptive, promoting tumorigenesis.

As with any cause of tissue injury, there is a compensatory proliferation of cells so as to repair the damage. Asbestosis, silicosis---------- Mesothelioma, lung carcinoma

Bronchitis---------- Lung carcinoma

Cystitis, bladder inflammation ----------Bladder carcinoma

Gingivitis, lichen planus ----------Oral squamous cell carcinoma

Inflammatory bowel disease ----------Colorectal carcinoma

Reflux esophagitis, Barrett esophagus -----Esophageal carcinoma

CANCERS ASSOCIATED WITH INFECTIOUS AGENTS

Gastric adenocarcinoma, MALT---------- Helicobacter pylori

Hepatocellular carcinoma ----------Hepatitis B and/or C virus

non-Hodgkin lymphoma and Hodgkin lymphoma ------Epstein-Barr virus

AIDS---------- Non-Hodgkin lymphoma, squamous cell carcinoma, Kaposi sarcoma

Human immunodeficiency virus------ human herpesvirus type 8

Precancerous Conditions.

Certain non-neoplastic disorders—the chronic atrophic gastritis of pernicious anemia, solar keratosis of the skin, chronic ulcerative colitis, and leukoplakia of the oral cavity, vulva, and penis—have such a well-defined association with cancer that they have been termed precancerous conditions.

This designation is somewhat unfortunate, because in the great majority of these lesions no malignant neoplasm emerges. Nonetheless, the term persists because it calls attention to the increased risk. Certain forms of benign neoplasia also constitute precancerous conditions. The villous adenoma of the colon, as it increases in size, becomes malignant in up to 50% of cases. It might be asked: Is there not a risk with all benign neoplasms? Although some risk may be inherent, a large cumulative experience indicates that most benign neoplasms do not become cancerous. Nonetheless, numerous examples could be offered of cancers arising, albeit rarely, in benign tumors—for example, a leiomyosarcoma beginning in a leiomyoma, and carcinoma appearing in long-standing pleomorphic adenomas.

Generalization is impossible, because each type of benign neoplasm is associated with a particular level of risk ranging from virtually never to frequently. Only follow-up studies of large series of each neoplasm can establish the level of risk, and always the question remains: Did the cancer arise from a nonmalignant cell in the benign tumor, or did the benign tumor contain, from the outset, a silent or indolent malignant focus?