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Mechanisms in Carcinogenesis and Cancer Prevention

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CHAPTER 1

Causes of Cancer and Opportunities for Prevention

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A. Cancer Burden and Health Challenge by Cancer

The global incidence of cancer is soaring due to the rapidly aging populations in most countries. In 2000, there were ten million new cancer cases, six million cancer deaths, and 22 million people living with cancer (Parkin 2001). By the year 2020, there will be an estimated 20 million new cancer patients each year. Almost three quarters of them will be living in countries that between them have less than 5% of the resources of cancer control (Sikora 1999).

Lung cancer was the most common cancer worldwide in 2000, both in terms of incidence, with 1.2 million new cases, or 12% of the world total, and mortality (1.1 million deaths or 18% of the total) (Fig. 1). This is by far the most frequent cancer of men, with the highest rates in North America and Europe (especially eastern Europe). Moderately high rates are also seen in temperate South America, Oceania, and in parts of Asia (Singapore, Hong Kong, the Philippines). In women, the incidence rates were lower (overall, the rate of 11 per 10^5 women, compared with 35 per 10^5 in men). The major cause of lung cancer is tobacco smoking, and in general, incidence rates in a country closely reflect the past history of tobacco smoking (Doll and Peto 1981). Heavy smoking increases the risk by around 30-fold, and smoking causes over 80% of lung cancers in Western countries.

Breast cancer is by far the most common cancer of women (22% of all new cancers) and ranks overall second (with 1.05 million cases) when both sexes are considered together. Breast cancer is the most prevalent cancer in the world today; there are an estimated 3.9 million women alive who have had breast cancer diagnosed within past 5 years (Pisani et al. 2001). Incidence rates are about five times higher in Western countries than in the developing countries and in Japan. Incidence rates of breast cancer are increasing in most countries, but especially in those countries where the rates have previously been low.

The major influences on breast cancer are environmental and lifestyle related (reproductive factors, diet, physical activity, energy balance). Much of the international variation is due to differences in established reproductive risk factors such as age at menarche, parity and age at births, and breastfeeding, but differences in dietary habits and physical activity may also contribute.

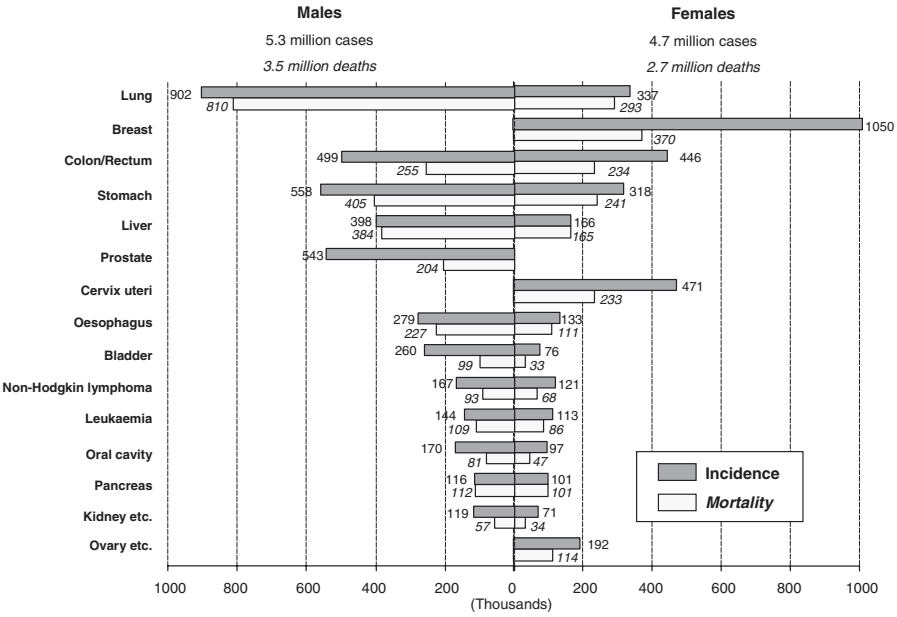

Fig. 1. Estimated number of new cases (*incidence*) and deaths (*mortality*) by sex and site. (Data from Globocan 2000)

Colorectal cancer accounted for about 9.4% of new cases in 2000, and ranked third in frequency of incidence (Parkin 2000). Numbers were similar in males and females. The highest incidence rates are in "developed" parts of the world; they are about tenfold higher in developed than in developing countries. Rates in Africa are very low (except in South Africa). Incidence rates have been increasing in countries where they were previously low. The relatively good prognosis means that colorectal cancer is the second most prevalent cancer in the world, with estimated 2.4 million people alive with the disease diagnosed in the previous 5 years.

Dietary exposures are the main risk factors. The best established dietary-related factor is overweight/obesity. Physical activity has been consistently associated with decreased risk (IARC 2002). Consumption of diet rich in fruits and vegetables has shown protective effects in numerous observational epidemiological studies; however, results from recent large prospective studies have been inconsistent.

Stomach cancer is the fourth in rank overall incidence (about 9% of the total). Almost two-thirds occurred in developing countries. Until about 20 years ago, stomach cancer was the most common cancer in the world; mortality rates have been falling in all Western countries and stomach cancer is now much more common in Asia than in Europe and North America. Stomach

cancer incidence was highest in Japan in 2000. High incidence was also found in eastern Asia and Central and South America. Migrant studies have demonstrated that there is a strong environmental component in stomach cancer etiology. Infection with *Helicobacter pylori* is an established risk factor. Stomach cancer has been shown to develop in patients with *H. pylori* infection but not in uninfected patients (Uemura et al. 2001). According to Japanese data, stomach cancer develops in 5% of *H. pylori*-positive persons over 10 years. The introduction of refrigeration has been associated with decreased risk, probably through reducing intakes of salted foods and facilitating year-round fruit and vegetable availability.

Liver cancer was the fifth most common cancer in the world in 2000. It is primarily a problem of developing countries, where over 75% of cases occur. Most liver cancers are hepatocellular carcinomas. The major risk factors for this type of cancer are chronic infection with hepatitis viruses (HBV and HCV) and, in tropical parts of Asia and Africa, where contamination of food grains with the fungus *Aspergillus flavus* is common, exposure to mycotoxins (aflatoxin B1). Chronic infections with hepatitis viruses carry a substantial increase in risk (more than 20-fold); furthermore, there is a clear (multiplicative) interaction with concomitant exposure to aflatoxins and hepatitis B virus. Excessive alcohol consumption is the main diet-related risk factor for liver cancer in Western countries, probably via cirrhosis and alcoholic hepatitis.

Cholangiocarcinoma, a tumor of the epithelium of the intrahepatic bile ducts, is particularly high in some locations where infection with liver flukes is common, such as northeast Thailand.

Prostate cancer is the third in importance in men overall (10.2% of all new cancer cases). Incidence rates are influenced by screening asymptomatic individuals, so that where this practice is common, the "incidence" may be very high (104 per 10^5 in the USA, for example). Incidence is also high in Europe and Australia/New Zealand. The estimated prevalence in 2000 was 1.6 million. There has been a rapid increase in incidence of prostate cancer over the past 20 years, also in low-incidence countries such as in Japan and China.

Little is known about the etiology of prostate cancer, although ecological studies suggest that it is positively associated with a Western-style diet. Hormones control the growth of the prostate, and interventions that lower androgen levels are moderately effective in treating prostate cancer. Prospective epidemiological studies suggest that the risk may be increased by high levels of bioavailable androgens and of insulin-like growth factor-1 (Chan et al. 1998; Stattin et al. 2000).

Cervical cancer is second in frequency in women worldwide; almost 80% of cases occur in less developed parts of the world. The geographical pattern is a complete contrast to breast cancer; the highest incidence is observed in parts of Africa, Asia and Latin America. In developed countries, the incidence rates are generally low.

The major etiological agents are the oncogenic subtypes of human papilloma viruses (HPV); indeed, it may be that the disease does not occur in the

absence or infection. Other cofactors, such as parity and oral contraceptives, may modify the risk in women infected with HPV.

Esophageal cancer is the eighth most common cancer worldwide (4% of the total number of new cases). It is mainly a cancer of developing countries. Tobacco and alcohol are the main cause of the squamous cell cancer of the esophagus; in Europe and North America, over 90% of cases can be attributed to these causes. Chewing of tobacco and betel quid is an important risk factor in India. Hot beverages have been shown to increase the risk. Nutritional deficiencies are thought to underline the high risk in central Asia, China and southern Africa. Overweight and obesity are associated with increased risk specifically for adenocarcinoma (but not squamous cell carcinoma) of the esophagus.

Bladder cancer, the seventh most frequent cancer in men, is considerably less common in women (15th rank). Tobacco smoking is the main cause of bladder cancer. In regions in Africa, high endemic urinary schistosomiasis is known to be associated with risk of squamous cell cancer of the bladder.

Kidney cancer was estimated to account over 336,000 cases in 2000.The geographic variation in incidence is moderate, with the highest incidence in Scandinavia and among the Inuit. Overweight/obesity is an established risk factor for cancer of the kidney, and may account for up to one third of kidney cancers in both men and women (IARC 2002).

B. Main External Causes and Cancer Control

The identification of chemical, physical, and biological agents and factors with potential for cancer causation, the potential of gene–environment interaction, increasing knowledge of the pathways of carcinogenesis on the path to cancer, increased knowledge from the human genome projects – all of these present difficult challenges for prevention (see Fig. 2).

I. Tobacco Smoking

Tobacco smoking is the largest preventable risk factor for morbidity and mortality worldwide. It has central importance in the etiology of cancers of the lung, head and neck, urinary tract, pancreas, and esophagus. More recent evidence indicates that several other types of cancers, of which the most important worldwide are stomach, liver and probably cervix, are also increased by smoking. The relative importance of different smoking-related diseases varies between populations, as smoking usually multiplies the background rate due to other factors (Peto 2001). The prevalence of smoking among adults in Europe is currently around 30% or more. China, with 20% of the world's population, produces and consumes about 30% of the world's cigarettes. The overall proportion of male cancer deaths caused by smoking in China in 1990

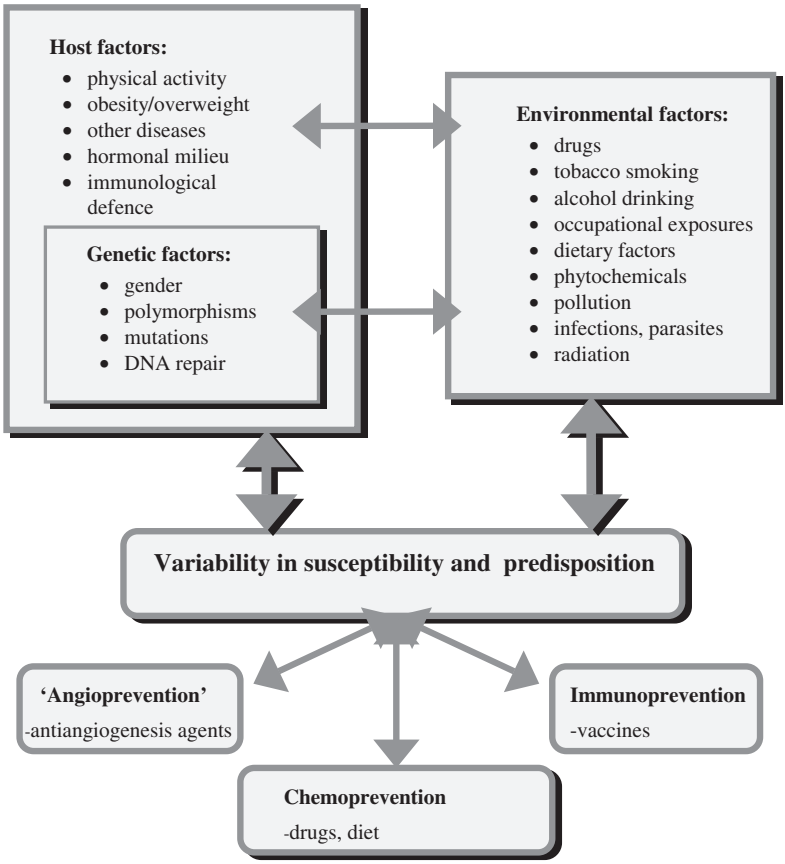

Fig. 2. Host–environmental interactions in carcinogenesis

was 22% and rising (Liu et al. 1998). Chronic obstructive pulmonary disease causes more deaths due to tobacco than lung cancer in China. Smoking also causes more premature deaths from liver cancer than from heart disease in China.

II. The Effect of Diet and Overweight

Diet and nutrition is an important life-style factor modulating carcinogenesis. Dietary factors include both genotoxic compounds and those having promotional effects. Genotoxic dietary compounds include heterocyclic amines produced upon heating processes and producing cancers in breast, colon, and prostate although epidemiological evidence is not always evident (Sugimura 2000). Although many micronutrients and flavonoids may be protective, even