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International variation

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There were an estimated 10 million new cases, 6 million deaths and 22 million persons living with cancer in the year 2000. The most common cancers are, in terms of new cases, lung (1.2 million), breast (1.05 million), colon–rectum (945 000), stomach (876 000) and liver (564 000). The geographic distributions of some 20 types of cancer for which national estimates have been made are summmarized. These patterns are examined with respect to the likely reasons in terms of variation in exposure to carcinogens (in the external environment or through lifestyle choices) or in genetic susceptibility to them. Related data from studies of migrant populations (that allow comparisons of genetically similar populations living in different environments) and from comparisons between different ethnic groups living in the same country are used to help in the interpretation of the geographic patterns. Information on the burden of disease also has a very important role in the planning and monitoring of programmes of cancer control.
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Introduction

The first comprehensive study of 'geographical pathology', as a means of understanding environmental determinants of disease that vary by place, is generally attributed to Hirsch (1883). Observing international variations in disease risk remains valuable to the epidemiologist in broadly differentiating between the relative contributions of 'environment' and 'genetics' in the aetiology of specific cancers. Although both are concerned in the causation of all cancers, it is useful, at least from the perspective of 'preventability', to consider the contribution to risk in the inhabitants of different places that may be due to variation in exposure to carcinogens (in the external environment, or through lifestyle choices), or in genetic susceptibility to them. Usually, in addition, marked geographic variations in incidence are suggestive of possible causative factors in the environment or in lifestyle (the so-called 'hypothesis forming' role). Information on disease burden is also used to permit rational priority setting of health-care activities (prevention, screening and therapy) and monitoring the results of interventions through the health-care system (WHO, 2002).

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Indices, sources of data

Incidence, the number of new cases occurring, can be expressed as the annual *number* of cases (the volume of new patients presenting for treatment) or as a rate per 10^5 persons per year. The latter approximates the average risk of developing a cancer, and is used for comparisons between populations (countries, ethnic groups or different time periods). Primary prevention strategies aim to reduce incidence. Incidence data are produced by population-based cancer registries. Registries may cover national populations or, more often, certain regions. In developing countries, in particular, coverage is often confined to the capital city and its environs. It was estimated that, in 1995, about 16.3% of the world population was covered by registries, 52.4% of developed countries and 7.5% of developing countries. The latest volume of 'Cancer Incidence in Five Continents' (8th) contains comparable incidence information from 186 registries in 57 countries, mainly over the period 1993–1997 (Parkin *et al*., 2002).

Mortality is the number of deaths occurring and the mortality rate is the number of deaths per 10^5 persons per year. It is the product of incidence and fatality (the inverse of survival) of a given cancer. Mortality rates measure the average risk to the population of dying from a specific cancer, while fatality (1-survival) represents the probability that an individual with cancer will die from it. Mortality data derive from vital registration systems, where the fact and 'underlying' cause of death are certified, usually by a medical practitioner. Their great advantage is comprehensive coverage and availability. By 1990, about 29% of the world population was covered by vital registration systems producing mortality statistics on cancer. This includes all of the developed countries and many of the developing countries. National level statistics are collated and made available by the WHO (http://www-depdb.iarc.fr/who/menu.htm). Mortality rates are usually used as a convenient proxy for incidence, in comparisons of risk between populations and over time. The validity of such comparisons depends on assumptions of equal survival/fatality in the populations being compared. This may be reasonable for some cancers with a poor prognosis, but may be quite unrealistic for

cancers for which early diagnosis and/or therapy can markedly influence survival between countries, population subgroups or over time.

Prevalence is the proportion of a population that has the disease at a given point in time (Rothman and Greenland, 1998). For many diseases for which the time of onset is imprecise (e.g. hypertension, diabetes), prevalence may be used as a substitute for incidence in comparative studies between populations. This is not necessary for cancer, and prevalence is not a useful indicator if the focus of interest is disease risk, and its possible causes. Even as an indicator of burden (and need for services) total prevalence ('ever had a cancer') is not useful; the figure will include many persons diagnosed in the past, some of whom have been 'cured' and no longer have an excess risk of death. A pragmatic alternative is '*partial prevalence*'(Pisani *et al*., 1999), which refers to cases alive within a defined period following diagnosis (1, 3 and 5 years, say).

Estimation

As national cancer incidence and mortality data are available for only a minority of countries of the world, estimation procedures are required to obtain a comprehensive global picture of the cancer profile and its evolution over time.

Estimation may be approached in different ways. In preparing estimates of the global pattern of mortality by group of causes, the WHO/World Bank project 'global burden of disease' (Murray and Lopez, 1996) made use of regression models, based on 'all cause' mortality for a country or region. Cancer mortality is estimated based on the observation that the proportion of deaths due to certain groups of diseases (such as infectious and parasitic diseases, maternal mortality and chronic diseases) correlates closely with the overall (all cause) mortality rate. The precise profile of different cancers, within the total, is derived using any available data on the relative frequencies of different types of cancer. IARC, in its 'GLOBOCAN' estimates, prepares national estimates of incidence, mortality and prevalence of cancer that are based on actual data from all available sources in different countries. The level of accuracy depends on the extent and quality of locally available data. The sources of data and the methods used are summarized in several recent reports (Parkin *et al*., 1999a; Pisani *et al*., 1999, 2002). The most recent country-level estimates have been provided for 24 different cancers and five broad age groups. These estimates are available on CD-ROM (Ferlay *et al*., 2000), and, in a format allowing rather less flexibility in analysis and presentation, on the Internet (http://www-dep.iarc.fr/globocan/globocan.html).

Variation by place

National populations are often chosen as the unit of study in geographic comparisons of incidence or mortality from cancer. The reason is that statistics – especially mortality – are collected and published at the national level. Although differences between countries may be very large, national boundaries have not always been based on levels of exposure to environmental risk factors of cancer, or of the genetic homogeneity of the populations within them. Thus, study of smaller geographic units within, and sometimes across, national boundaries has been particularly informative. Cancer atlases are a popular way of presenting such data. Perhaps the most celebrated example is the Chinese Atlas of Cancer Mortality (Editorial committee, 1979), which was prepared using cancer mortality data collected during a 3-year (1973–75) national survey of deaths; it shows an amazing level of variation in mortality rates for 15 cancers in 2392 geographic units (counties) nationwide (Figure 1). Atlases have been prepared for regions of the world that include several countries, when the disease data are considered to be

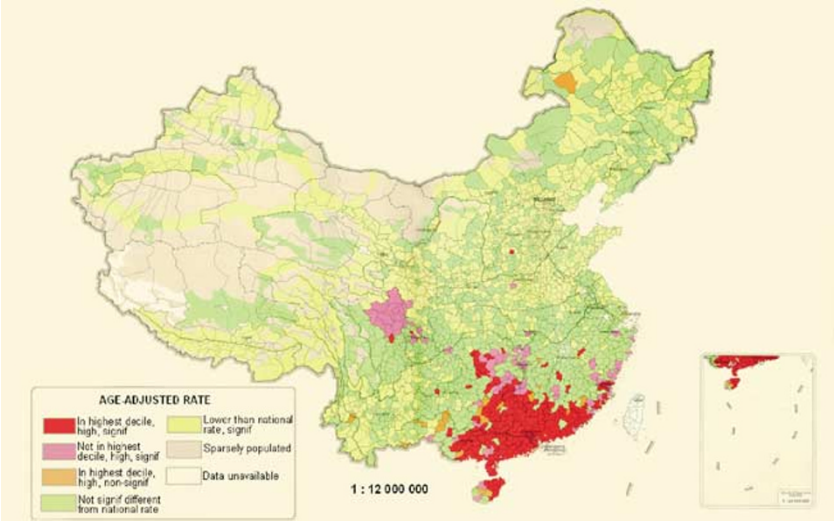

Figure 1 Mortality from cancer of nasopharynx (males) in China, 1973–1975 (Atlas of Cancer Mortality in the People's Republic of china. China Map Press, 1976)

comparable across national boundaries; examples are the atlases of cancer mortality in Europe (Smans *et al*., 1992) and of cancer incidence in the Nordic countries/ Northern Europe (Pukkala *et al*., 2001).

Interpretation of geographic variation in disease risk

The first consideration, in interpreting differences in cancer rates internationally, is to exclude bias in the statistical data being used. This is a potential pitfall when they have been taken from a source for which accuracy is not a criterion for inclusion. Mortality data published by WHO, for example, are not of the same quality for all countries; for some, coverage of the population is manifestly incomplete (so that the so-called mortality rates produced are implausibly low), and in others, validity of cause of death information is low (Silvi, 2003). There are other specific problems, such as the certification of varying proportions of deaths due to cancer of the cervix and corpus uteri, to 'Uterus NOS' (ICD-10 C55), so that some sort of correction must be applied, before valid comparisons can be made (Arbyn and Geys, 2002).

Person or place? If bias can be excluded, the main interest of measuring geographic differences in risk is to quantify how much may be due to variation in exposures to carcinogens (or 'risk factors') and how much is the result of inherent differences in susceptibility to such exposures of the population resident in a particular place (and hence genetically determined). Of course, the major exposure to carcinogens is not through variations in the external environment (air pollution, water contaminants, radiation, etc.) so much as in differences in lifestyle (reproduction, diet, tobacco use, etc.). These are culturally determined exposures, and so are linked closely to sociocultural groups of the world population. In identifying the component of disease risk associated with specific places, we should ideally study genetically homogenous populations living in different environments, within a country (or region) or in different parts of the world.

Migrant studies Studies of migrant populations have been particularly fruitful in this respect (Parkin and Khlat, 1996). The risk of different cancers in a given migrant population is compared with the risk in the host population (similar environment, different genetics) and with the population living in the place from which the migrants originally came (similar genetics, different environment). Ideally, such comparisons can take into account the age at migration, or the duration of residence in the two environments (original (origin), new (host)), as a crude means of quantifying 'exposure' to the new environment. They may also be able to compare the risk in the migrants with that in their offspring, who have lived in the new 'environment' throughout life. In the context of classical migrant studies, relying upon routinely collected information (descriptive studies), all environmental exposures are subsumed by a single variable (place of residence). Many specific exposures are associated with this, not only via the external environment (air, soil, water) but also through sociocultural factors (diet, fertility, smoking, etc.).

Ethnicity In studying the component of risk associated with genetic characteristics of a population ('ethnicity'), the differences observed within the same geographic locality are more pertinent than international comparisons, since at least some of the environmental differences present in the latter are reduced or eliminated. There are plenty of examples of such studies from multiethnic populations in all parts of the world – for example, the white and black populations of Harare, Zimbabwe (Bassett *et al*., 1995), the Chinese, Indian and Malay populations of Singapore (Lee *et al*., 1988) and, above all, from the United States (Miller *et al*., 1996). From an epidemiological point of view, the variable 'ethnicity' or 'race' defines a constellation of genetic factors, which may be associated with susceptibility to a given cancer. Of course, there is considerable genetic variation *within* a given ethnic or racial group (however this is defined), but there are often sufficiently large differences between the population means to yield distinctive patterns of risk. Genetically determined risk may be mediated through germline mutations of major susceptibility genes that are normally concerned with the regulation of cell growth (oncogenes, tumour suppresser genes), or via variation in the genes (polymorphisms) that modulate the impact of environmental carcinogens (Easton, 1994; Ishibe and Kelsey, 1997; Norppa, 1997; Vineis, this issue). The fact that genetic factors can markedly influence population rates of disease is evident from the study of childhood cancer. Some malignancies of children show large differences in risk by ethnic group – for example, Wilms' tumour and Ewing's sarcoma – for which no plausible environmental 'exposure' can be imagined. Any such exposure would have to be very carcinogenic (to act so early in life), very tissue specific and be very unevenly distributed by ethnic group. In any case, some genetically determinant traits (e.g. skin pigmentation) are manifestly connected with susceptibility to carcinogens (UV light) so that it is easy to imagine that others, not producing such clearly visible phenotypes, are too.

Global burden

There were an estimated 10.1 million new cases, 6.2 million deaths and 22 million persons living with cancer (within 5 years of diagnosis) in the year 2000. The total 'All Cancer' excludes nonmelanoma skin cancers, because of the difficulties of measurement and consequent lack of data. The 2000 estimate represents an increase of around 22% in incidence and mortality since 1990 (Parkin *et al*., 1999a; Pisani *et al*., 1999). The cancer profile is rather different, depending on whether incidence or mortality is the focus of interest, as shown in Figure 2. In terms of incidence, the most common cancers are lung (12.3%), breast (10.4%) and colon–

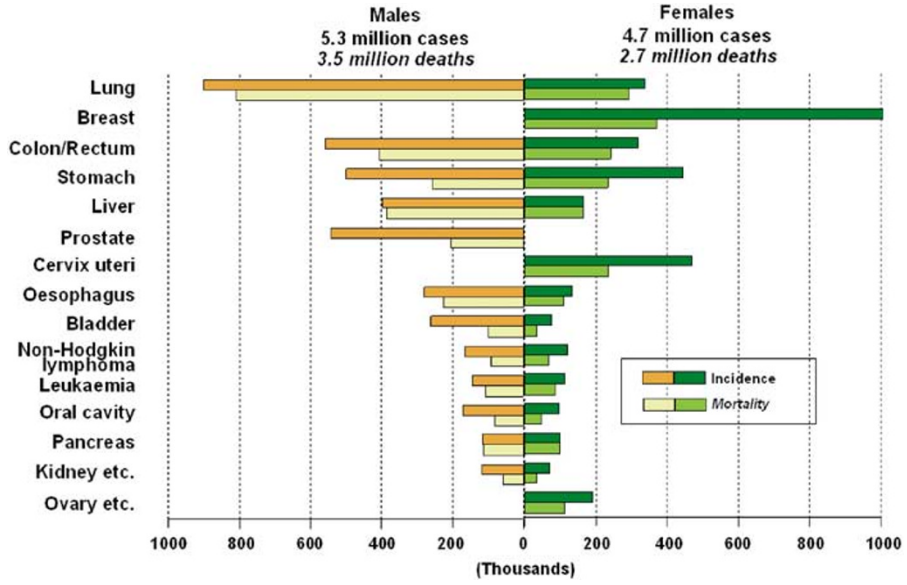

Figure 2 Estimated new cases and deaths worldwide, by sex, in 2000 (Parkin, 2002)

Table 1 Incidence rates for all cancers (excluding nonmelanoma skin cancer) by world region (Parkin, 2001)

	ASR (World) per 100 000		*Cumulative risk (%) (age 0–64 years)*	
	Male	*Female*	*Male*	*Female*
Eastern Africa	177.7	176.4	9.4	11.3
Middle Africa	141.8	121.6	7.7	7.9
Northern Africa	124.5	106.8	6.8	7.2
Southern Africa	217.5	153.7	9.4	8.7
Western Africa	81.2	94.1	4.8	6.6
Caribbean	187.9	177.2	7.6	9.7
Central America	178.5	213.8	7.5	11.9
South America	201.4	201.8	9.3	11.2
Northern America	357.4	281.5	16.2	15.3
Eastern Asia	205.3	126.6	10.5	7.3
South-Eastern Asia	131.1	120.1	7.0	7.8
South Central Asia	106.6	112.0	6.2	7.8
Western Asia	151.1	111.3	8.0	6.9
Eastern Europe	290.0	197.2	16.2	12.4
Northern Europe	263.4	235.1	10.9	13
Southern Europe	275.4	194.3	13.3	11.1
Western Europe	318.7	230.6	14.9	13.2
Australia/New Zealand	358.6	283.2	15.6	15.8
Melanesia	149.8	178.3	7.4	10.9
Micronesia	175.5	149.6	9.4	9.1
Polynesia	200.7	216.3	9.9	13.1
More-developed countries	301.0	218.3	14.4	12.5
Less-developed countries	153.8	127.9	8.2	8.0
World	201.9	157.8	10.0	9.2

rectum (9.4%). The most common causes of death due to cancer are cancers of the lung (17.8%), stomach (10.4%) and liver (8.8%).

Table 1 shows the incidence for all cancers (excluding skin), by world area, and sex, as age-standardized rates per 10^5 (standardized to the World standard population), and the cumulative rate (percent), from birth to age 65 years. Both indicators allow comparisons between populations that are not influenced by differences in their age structures. Age-standardized rates in developed countries are about twice those in developing countries; the differential is less for the cumulative rate, which ignores disease rates in the 65 and over age groups. On average, worldwide, there is about a 10% chance of getting a cancer before the age of 65 years. Incidence (and mortality) rates are highest in North America, Australia/New Zealand and Western Europe and lowest in parts of Africa. This overall risk is, of course, dependent on the contributions of different types of cancer. For example, in West Africa, incidence of almost all cancers is low (except for cervix cancer in women and liver cancer in men). This contrasts with Southern Africa, which has, in addition, high rates of lung and oesophagus cancer, and with East Africa, with high rates of AIDS-related tumours, notably Kaposi sarcoma.

Lung cancer This was the most common cancer in the world in 2000; there were an estimated 1.2 million new cases (12.6% of all new cancers) and 1.1 million deaths in 2000 (17.8% of cancer deaths). The sex ratio (M : F) is 2.7, and it is relatively more important in the developed (22% cancer deaths) than developing (14.6% of deaths) countries. In men, the areas with the highest incidence and mortality are Europe – especially, Eastern Europe, North America, Australia/New Zealand and South America. The rates in China, Japan and South-East Asia are moderately high, while the lowest rates are found in Southern Asia (India, Pakistan) and sub-Saharan Africa (excluding Zimbabwe and South Africa) (Figure 3). In certain population subgroups (e.g. US blacks, New Zealand Maoris), incidence is even higher, and with current incidence rates, men in these two

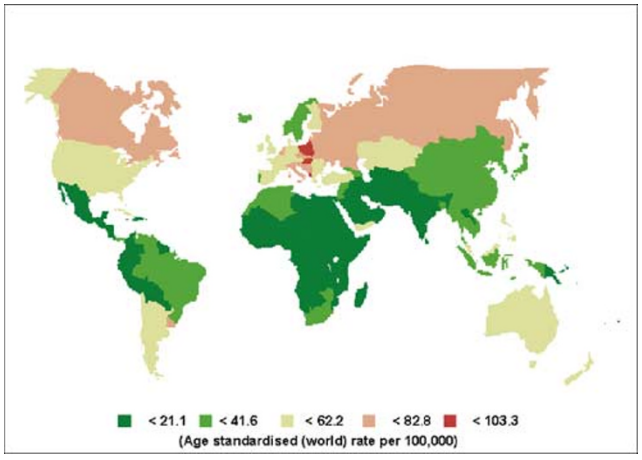

Figure 3 Incidence of lung cancer in males

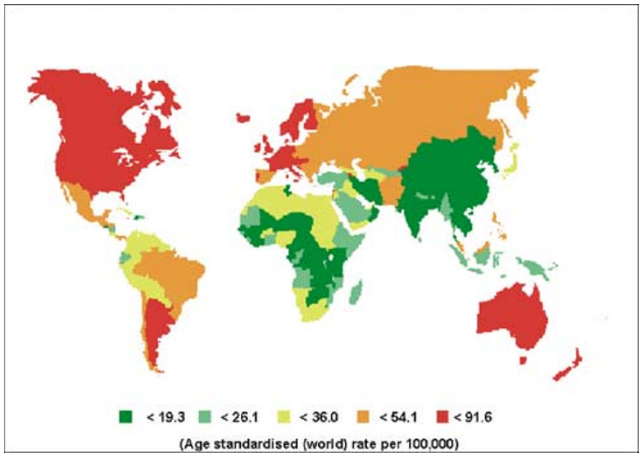

Figure 4 Incidence of female breast cancer

groups have about a 13% chance of developing a lung cancer before the age of 75 years. In females, incidence rates are lower (worldwide, the rate is 11.1 per 10^5 women, compared with 34.9 per 10^5 in men). The highest rates are in the USA and Canada, UK and Denmark. It is of note that the incidence in China is rather high (age-standardized rate 15.7 per 10^5), similar to that in, for example, Australia and the Netherlands (17.5 per 10^5). Geographic patterns are very much influenced by past exposure to tobacco smoking (Doll and Peto, 1981), and the geographic pattern in women reflects the rather different historical patterns of smoking from those in men. The proportion of lung cancer cases due to tobacco smoking can be estimated by comparing observed incidence (or mortality) in different areas with that expected based on rates in nonsmokers from several large cohort studies (Parkin *et al*., 1994; Peto *et al*., 1994). For the year 2000, an estimated 85% of lung cancer in men and 47% of lung cancer in women is the consequence of tobacco smoking. The percentage is 90–95% of cases in men in Europe and North America, and only in the lowest incidence areas of East and West Africa are there no attributable cases. The fractions are lower for women, and several areas (where incidence rates are lower than in nonsmoking women in the US and Japan), including South Central Asia, have no attributable cases. The highest fractions are in North America (85%), Northern Europe (74%) and Australia/New Zealand (72%), where women have been smoking the longest.

Breast cancer Breast cancer is by far the most frequent cancer in women (22% of all cancers) with an estimated 1.05 million new cases in 2000, and it ranks second overall when both sexes are considered together. More than half of the cases are in industrialized countries – about 346 000 in Europe (27% of cancers in women) and 202 000 in North America (31%). Breast cancer is relatively less common among women in developing countries, although it still accounts for 18% of female cancers, and the incidence is increasing. The country with the highest incidence is the Netherlands (ASR of 91.6 per 10^5). The incidence in the USA is 91.4; within the US, there are populations with age-adjusted rates of 100 or more – for example, white women in California and Hawaiian women (Parkin *et al*., 2002). High rates are also observed in Europe, Australia and New Zealand, and in Uruguay and Argentina. In contrast, low rates are found in most African and Asian populations, although they are increasing; in some Asian populations they are already the same as in Southern Europe, and in some cases (e.g. the Philippines) even higher (Figure 4). The incidence in the Jewish population of Israel is especially high (87.1 per 10^5).

Genetic factors, including the major susceptibility genes (BRCA1, BRCA2), may account for up to 10% of breast cancer cases in developed countries (McPherson *et al*., 2000), but their prevalence in the population is too low to explain much of the international or interethnic variation in risk. Most must therefore be a consequence of different environmental exposures. This is clear from studies of migrants, which show quite clearly that incidence changes following migration – for example, a rise in the risk of breast cancer in populations from European countries at a relatively low risk (Italy, Poland) occurs after migration to Australia, particularly if they migrate as children (Geddes *et al*., 1993; Tyczynski *et al*., 1994). Furthermore, studies comparing the risks in migrants and their offspring (particularly among Asians migrating to the USA) demonstrate that there are major increases in risk between first, second and third generations (Ziegler *et al*., 1993).

The major influences on breast cancer risk appear to be certain reproductive factors, body size/obesity and, less certainly, diet. There have, however, been few attempts to quantify the magnitude of risk differentials between populations that might be explained by such factors. Internationally, there is some association between national incidence (or mortality) rates of breast cancer and population averages for various variables related to fertility (Parkin, 1989) or body weight (Bergström *et al*., 2001). However, such models can explain only a minor component of the variation in

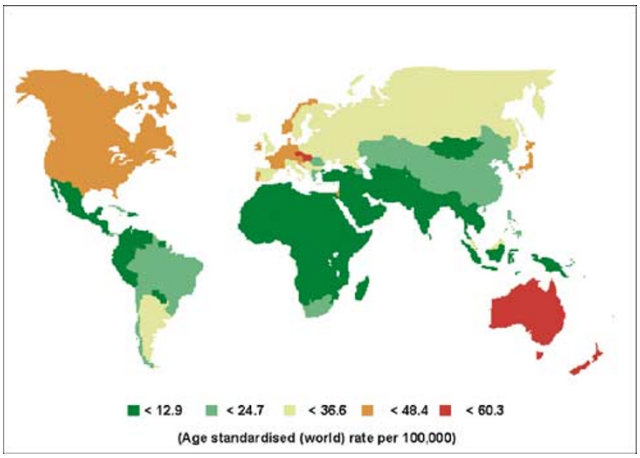

Figure 5 Incidence of colorectal cancer in males

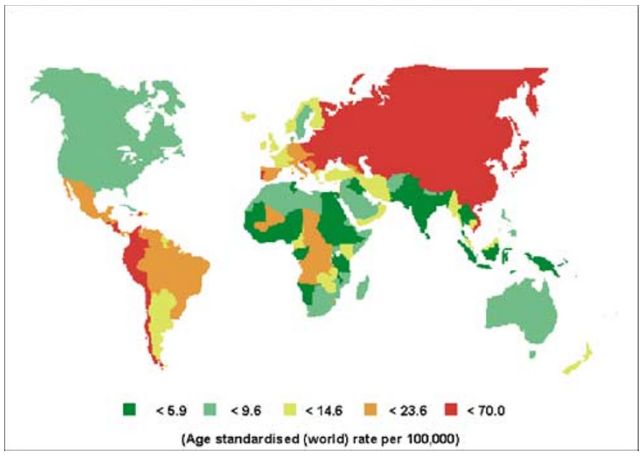

Figure 6 Incidence of stomach cancer in males

incidence. In the USA, Brinton *et al.* (1997) calculated that the difference in incidence between whites and blacks, at least in women aged 40–54 years (20%), was entirely explicable in terms of the different prevalence of certain reproductive and 'lifestyle' variables.

Colorectal cancer Cancers of the colon–rectum accounted for 945 000 new cases in 2000 (9.4% of the world total). Numbers were similar in males and females (ratio 1.05 : 1). There is at least a 25-fold variation in occurrence worldwide. The highest incident rates are in North America, Australia/New Zealand, Western and Eastern Europe (rates in the Czech Republic (60.3 per 10^5) and Hungary (59.8 per 10^5) are among the highest worldwide) and Japan (Figure 5). Rates from several Japanese registries are particularly elevated, notably in Hiroshima (86.7 per 10^5) (Parkin *et al.*, 2002). The incidence tends to be low in Africa and Asia and intermediate in southern parts of South America (Figure 5). The geographical distribution of colon and rectal cancer is similar, although the variation between countries is more striking for colon than rectal cancer. In most populations, the rates of cancer of the rectum are some 20–50% higher in men than women; thus, in high-risk populations, the ratio of colon to rectum cases is 2 : 1 or more (rather more in females). In low-risk countries, rates are generally of the same magnitude.

These large geographic differences probably largely represent the effects of different environmental exposures, presumably mainly dietary. There are strong international correlations between risk of large bowel cancers and *per capita* consumption patterns of meat (Armstrong and Doll, 1975), fat (specifically animal fat) (Prentice and Sheppard, 1990) and fibre (McKeown-Eyssen, 1994). That the risk of colon cancer is quite labile to environmental change is evident from the study of migrants, when populations moved from low- to high-risk areas; the incidence of colorectal cancer increases rapidly within the first generation (Kolonel *et al.*, 1980; McMichael *et al.*, 1980), implying that dietary and other environmental factors constitute a major component of risk. Japanese born in the USA now have higher rates than those of US whites (38.4 per 10^5 in men, 27.7 per 10^5 in women), and the rates in Japanese living in Hawaii (51.0 per 10^5 in men, 30.8 per 10^5 in women) and Los Angeles (48.0 per 10^5 in men, 32.8 per 10^5 in women) are among the highest in the world (Parkin *et al.*, 2002).

Stomach cancer Stomach cancer is the fourth most frequent cancer with 876 000 new cases (8.7% of the total) and 647 000 deaths (10.4% of cancer deaths). Almost 2/3 cases occur in developing countries. Age-standardized incidence rates are highest in Japan (69.2 per 10^5 in men, 28.6 in women). High rates are also present in both sexes in East Asia (Korea, China), Eastern Europe and Central and South America (especially the Andean countries). Moderately high rates are observed in some countries of Central and West Africa. Incidence rates are low (<10 per 10^5 in males in Southern Asia, in North and East Africa, North America, and Australia and New Zealand (Figure 6).

Incidence in men is twice that in women, although age-specific rates in women often exceed those in men in the youngest age groups (Griffith, 1968). This may be related to differences in the frequency of different subtypes of adenocarcinomas–intestinal and diffuse (Lauren, 1965). Diffuse carcinoma tends to affect younger individuals and is relatively more common in females (Correa *et al.*, 1973). Intestinal adenocarcinoma predominates in the high-incidence areas (particularly in males and in older age groups), and this subtype is responsible for much of the international variation (Muñoz, 1988).

There is clearly a strong environmental component to the risk differences. Migrant populations from high-risk parts of the world show a marked diminution in risk when they move to a lower risk area, although this is quite gradual and seems to depend on the age at migration (McMichael *et al.*, 1980). The data fit with observations concerning the importance of childhood environment in determining risk (Coggon *et al.*, 1990). The evidence linking *Helicobacter pylori* infection to cancer of the stomach was considered sufficient by

Figure 7 Prevalence of *H. pylori* in asymptomatic adults, by worldwide area. Data from population-based surveys of healthy adults, noncancer cases from prospective (cohort) studies or control series from case–control studies (subjects without gastrointestinal diseases). The prevalence estimates from different studies within individual countries were averaged to provide a single figure and the value by area obtained as the weighted (by population size) average

IARC (1994) to classify this bacterium as carcinogenic in humans. Based on a meta-analysis of prospective (cohort) studies (*Helicobacter* and Cancer collaborative Group (HCCG) 2001), the OR for the association between HP infection and the subsequent development of gastric cancer was found to be 2.36 (95% CI 1.98–2.81); there was no increase in risk for cardia cancers (OR 0.99), while the overall risk for noncardiac cancers was 2.97 (95% CI 2.34–3.77). Its action is probably indirect, by provoking gastritis, a precursor of gastric atrophy, metaplasia and dysplasia. Infection is acquired in childhood, and prevalence within populations is certainly related to socio-economic status (Sitas *et al*., 1992). The international variation in prevalence (Figure 7) bears a certain similarity to that of stomach cancer; the overall estimate of *H. pylori* prevalence in adults is 76% in developing countries and 58% in developed countries. However, it is clear that with such high prevalence, and relatively small international variation, that factors other than *H. pylori* are of major importance. Dietary and other exogenous factors (e.g. tobacco smoking and alcohol) surely play a synergistic or antagonistic role, and are important in determining differences in the risk between countries and over time, as they have been shown to relate to individual risk in epidemiological studies (Muñoz and Franceschi, 1997; WCRF, 1997; McCullough & Giovanucci, this issue).

Liver cancer This is the fifth most common cancer in the world (564 000 or 5.6% of new cancer cases) but, because of the very poor prognosis, the number of deaths is almost the same (549 000), and it is the third most common cause of death from cancer. In all, 81% of cases occur in the developing countries (with 54% in China). The highest incidence rates are in West and Central Africa (where it accounts for almost one-quarter of cancer in men), Eastern and South-Eastern Asia and in Melanesia. Incidence is low in developed countries

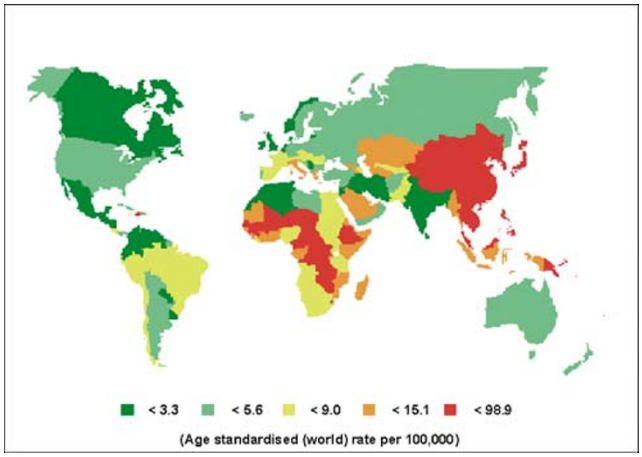

Figure 8 Incidence of liver cancer in males

(<9 per 10^5 in males), except for Japan (29.2 per 10^5 in males), and the moderately elevated incidence in some Southern European countries (especially Italy (13.5 per 10^5 in males) and Greece (12.1 per 10^5)) (Figure 8). The overall sex ratio is around 2.6, rather greater in the high-risk areas and less in low-risk areas.

Most liver cancers are hepatocellular carcinomas, the major risk factors for which are chronic infection with the hepatitis viruses, hepatitis B and C. Both increase the risk of liver cancer some 20-fold (Donato *et al*., 1998). As hepatitis B virus is the more prevalent, the prevalence of chronic infection worldwide largely explains the patterns of liver cancer. The exception is Japan, where the prevalence of infection is low, but where the generations most at risk of liver cancer have a relatively high rate of infection with hepatitis C virus (Tanaka *et al*., 1994). More than 3/4 of cases worldwide, and 85% of cases in developing countries, are caused by these two viruses (Parkin *et al*., 1999b).

Exposure to aflatoxins is probably also an important contributor to the high incidence of liver cancer in those tropical areas of the world where contamination of food grains with the fungus *Aspergillus fumigatus* is common. There is a multiplicative interaction between aflatoxin exposure and chronic HBV infection, suggesting different carcinogenic mechanisms.

Cholangiocarcinoma, a tumour of the epithelium of the intrahepatic bile ducts, comprises 10–25% of liver cancers in men in Europe and North America and a rather larger proportion in women. The incidence shows little international variation, with rates in males between 0.5 and 2.0, rather lower in females (Parkin *et al*., 1993). However, the incidence is very much higher in some localized areas, where infection with liver flukes is common (e.g. Northeast Thailand).

Prostate cancer There were 543 000 new cases worldwide in 2000, making this the sixth most common cancer in the world, and third in importance in men (10.2% of new cancer cases – 16.6% in developed countries and 4.5% in developing countries). The prognosis is relatively good, so that it is a less prominent cause of

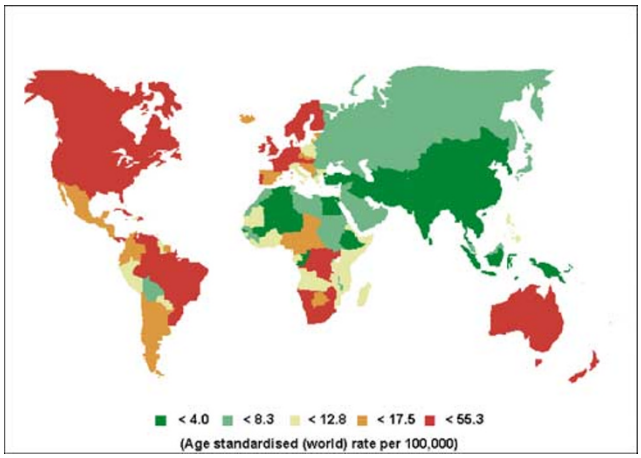

Figure 9 Mortality from prostate cancer

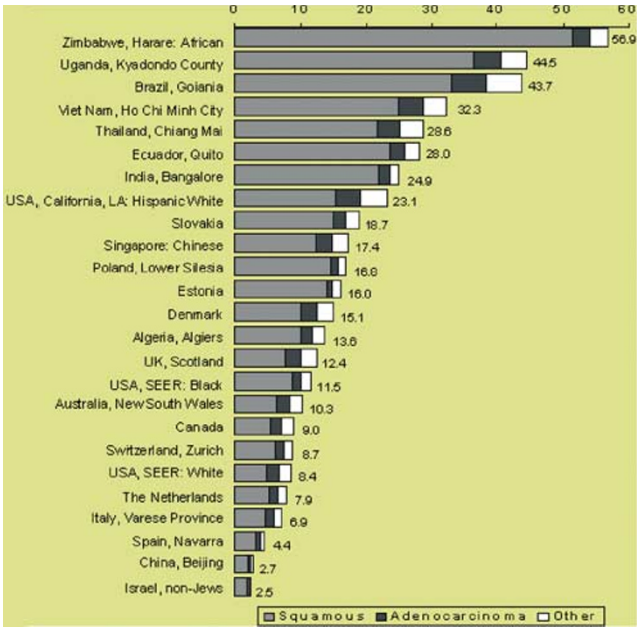

Figure 10 Incidence of cervix cancer (ASR per 10^5) by histological type

mortality, with 204 000 deaths (5.8% of cancer deaths in men, 3.3% of all cancer deaths). In all, 78% cases are in men aged 65 years or more. Incidence rates are now influenced by the diagnosis of latent cancers by screening asymptomatic individuals, so that where this practice is common, the 'incidence' may be very high (95.1 per 100 000 in the United States, for example, where it is now by far the most commonly diagnosed cancer in men). Incidence is also high in Northern and Western Europe, and Australia/New Zealand. Mortality is affected by survival, and survival is significantly better in high-risk countries (80% in the USA *vs* 40% in developing countries), but much of this is a consequence of more latent cancer being detected by screening procedures. As a result, mortality rates are probably a better guide to the risk of invasive prostate cancer in different populations. Mortality rates are high in North and West Europe, Australia/New Zealand, in the Caribbean and North and South America and also in much of sub-Saharan Africa. Mortality rates are low in Asian populations and in North Africa (Figure 9). The difference in mortality between China and the USA is 26-fold (while it is almost 90-fold for incidence).

These international differences are mirrored by ethnic variation in risk within the United States (Miller *et al*., 1996), where the black population has the highest incidence (and mortality) rates, some 70% higher than in whites, who in turn have rates considerably higher than populations of Asian origin (e.g. Chinese, Japanese and Korean males). Similarly, in São Paulo, Brazil, the risk of prostate cancer in black males was 1.8 (95% CI 1.4–2.3) times that of white men (Bouchardy *et al*., 1991). The differences in ethnic-specific risk are probably mediated via population differences in alleles of genes coding for enzymes involved in testosterone metabolism (Shibata and Whittemore, 1997).

Even before PSA screening, international differences reflected diagnostic bias to some extent. Many elderly men are found to harbour latent cancers in their prostate, the prevalence of which greatly exceeds the cumulative incidence in the same population. Two international studies have compared the prevalence of latent prostate cancer at autopsy and incidence of clinical disease in different populations (Breslow *et al*., 1977; Yatani *et al*., 1982). The prevalence of latent cancer increases steeply with age, but shows much less geographic variation than clinical cancer, although the country/ethnic-specific ranking was much the same; the differences between populations were largely due to variations in the prevalence of the infiltrative type of latent cancer. The frequency of latent carcinoma of prostate in Japan is increasing (as with clinical prostate cancer) and approaching the prevalence for US whites. This suggests that promotion of latent carcinoma may be important in explaining international differences.

Cervix cancer Cancer of the cervix uteri is the second most common cancer among women worldwide, with an estimated 471 000 new cases and 233 000 deaths in the year 2000. Almost 80% of the cases occur in developing countries, where, in many regions, it is the most common cancer among women. The highest incidence rates are observed in Latin America and the Caribbean (average 33.5 per 10^5), sub-Saharan Africa (31.0 per 10^5), South Asia (26.5 per 10^5) and South-East Asia (18.3 per 10^5). Incidence rates are now generally low in developed countries, with age-standardized rates less than 14 per 10^5. This pattern is relatively recent; however, before the introduction of screening programmes in the 1960s and 1970s, the incidence in most of Europe, North America and Australia/new Zealand was much as we see in developing countries today (Gustafsson *et al*., 1997): it was 38.0 per 10^5 in the Second National Cancer Survey of the United States, for example (Dorn and Cutler, 1959). Very low rates are also observed in China (5.2 per 10^5) and in Western Asia (4.8 per 10^5); the lowest recorded rate is 0.4 per 10^5 in Ardabil, North West Iran (Sadjadi *et al*., 2003).

The majority of cases of cervix cancer are squamous cell carcinomas (SCCs). Adenocarcinomas are rarer, but the proportion of cases with this histology is higher in the low-incidence areas (25–30%) than high risk (10–15%) (Figure 10). This is probably the result of screening programmes, which are more effective in preventing squamous cell cancers than adenocarcinomas (Fu *et al*., 1987; Sigurdsson, 1995).

It is quite clear that the major aetiological agents are oncogenic subtypes of the human papilloma virus (HPV) (Bosch *et al*., 2002). Recent geographic studies using sensitive PCR DNA testing methods to detect a wide spectrum of HPV types have generally observed HPV prevalences to correlate with the population risks of cervical cancer, although it has not always been possible to take into account the relative efficacy of regional screening programmes (Muñoz *et al*., 1992; Pham *et al*., 2002). Other cofactors (e.g. parity, contraceptives) probably modify the risk in women infected with HPV.

Oesophageal cancer About 391 000 cases of cancer of the oesophagus occurred in 2000, of which over 80% were in developing countries; there were 355 000 deaths. Geographic variation in incidence is very striking. The highest risk areas of the world are in the Asian 'oesophageal cancer belt' (stretching from Northern Iran through the Central Asian republics to North-Central China); the incidence in Cixian, China, in 1993–1997 was 184 per 10^5 in men and 123 per 10^5 in women, while the rates recorded in Gonbad, North East Iran in the 1960s were 109 per 10^5 in men and 175 per 10^5 in women (Mahboubi *et al*., 1973). High rates are also present in parts of East and South East Africa (for example, in Eastern Kenya, Zimbabwe and the Transkei region of South Africa (Parkin *et al*., 2003)), in South-Eastern South America (Southern Brazil, Uruguay, Paraguay, Northern Argentina) and in certain parts of Western Europe (especially France and Switzerland). For women, the pattern is much the same, with the Indian subcontinent added to the high-ranking areas. Oesophageal cancer is more common in males in most areas – the sex ratio is 6.5 : 1 in France for example – although in the high-risk areas of Asia and Africa the sex ratio is much closer to unity.

There are also very marked variations in incidence *within* countries in the high-risk areas. For example, within the oesophageal cancer belt, the Chinese counties with the highest rates are located in the central/north provinces of Shanxi and Henan, while in central Asia, the high-risk areas are in parts of Turkmenistan (in particular) and Kazakhstan. In Northern Iran, there is quite a dramatic difference as one passes east to west of the Caspian littoral (Muñoz and Day, 1996). Other workers have shown the large geographic variations within the high-risk areas of South Africa (Rose and McGlashan, 1975) and Northern France (Tuyns and Masse, 1973, 1975).

These must represent exposures to important carcinogens, but it seems that these are quite different in the various high-risk areas. Tobacco and alcohol are the main agents involved in Europe and North America, where over 90% of cases can be attributed to these causes. Chewing of tobacco (and betel) is important in the Indian subcontinent. Hot beverages have been shown to increase risk, and drinking hot maté is probably responsible for raised rates in Uruguay, Southern Brazil and Northern Argentina. Nutritional deficiencies (specifically of micronutrients) are thought to underlie the high risk in central Asia, China and Southern Africa. Here, other factors such as pickled vegetables, nitrosamine-rich foods and mycotoxins may also be involved, as well as consumption of opium residues (in Iran) or pipe stem residues (in the Transkei of Southern Africa) (Muñoz and Day, 1996). On the other hand, genetic predisposition may explain the rather high rates of oesophageal cancer in Japan and US Japanese (Miller *et al*., 1996). Polymorphisms of two genes controlling the alcohol-metabolizing enzymes, alcohol dehydrogenase 2 and aldehyde dehydrogenase 2, (Yokoyama *et al*., 2002) are notably frequent in populations in East and South-East Asia (Goedde *et al*., 1992).

Bladder cancer An estimated 340 000 bladder cancer cases occurred in 2000, when it was the ninth most common cause of cancer for both sexes combined. There were about 130 000 deaths. It is relatively common in developed countries, where 40% of all incident cases occur. The majority (70%) of bladder tumours occur in men. The 10-fold variation in international incidence is not particularly striking, however, relative to other cancers.

Bladder cancer rates are high in many Southern and Eastern European countries where smoking (in men) has been prevalent, and in parts of Africa and the Middle East, where bladder cancer, particularly of the squamous cell type, is linked to chronic infection with *Schistosoma haematobium* (IARC, 1994). The highest recorded incidence rate is that found in Egypt, where the estimated world-standardized rate of 45 per 10^5 is 60% higher than its nearest counterpart (Israel). In the United States, the incidence in whites is higher than in blacks – about double among men and 50% greater among women; it is unlikely that this is due to differences in exposure to environmental carcinogens, and explanations based on differential susceptibility have been proposed. Certainly, migrants to France from Algeria and from West Africa (both relatively high-risk populations) appear to retain rates higher than the local-born population of France (Bouchardy *et al*., 1995, 1996). Genetic polymorphisms of metabolic enzymes such as *N*-acetyltransferase and glutathione *S*-transferase 1 may play a role (Yu *et al*., 1994, 1995).

The most common histological type of bladder cancer in industrialized countries is transitional cell carcinoma (TCC), which comprises, for example, 90% of cancers in England and Wales, and 95% in the Netherlands and France (Parkin *et al*., 2002). In the United States, the differences in histology by race are not particularly striking, with whites having about 95% TCC and just

over 1% SCC, while the proportions are about 89 and 3%, respectively, in blacks.

Non-Hodgkin lymphomas (NHL) This rather diverse group of cancers account for 287 000 annual cases. The highest incidence is observed in the developed areas of North America (16.0 per 10^5 in males), Australia/New Zealand (14.4 per 10^5) and Europe (although rates in Eastern Europe are moderate). Currently, the highest rates are observed in populations that are most affected by the epidemic of IDS (white males in San Francisco, ASR 24.6 per 10^5). High-incidence rates are also observed in the central part of Africa, in part the consequence of very high rates in the childhood age range, due to Burkitt's lymphoma. The lowest risk is in Eastern Asia (3.7 per 10^5 in males) and Southern Asia (3.4 per 10^5). Incidence rates of NHL have increased in practically all populations since the 1970s and probably before this too; the environmental exposures (or modified host responses to them) that underlie this is a mystery – the HIV epidemic can account for only part of it, in certain geographic areas (Hartge and Devesa, 1992).

Cancers of the oral cavity accounted for 267 000 cases in 2000, almost two-thirds of them in men. The world area with the highest incidence is Melanesia (36.3 per 10^5 in men and 23.6 per 10^5 in women). Rates in men are high in Western (12.5 per 10^5) and Southern Europe (9.2 per 10^5), South Asia (13.0 per 10^5), Southern Africa (12.4 per 10^5) and Australia/New Zealand (12.1 per 10^5). In females, the incidence is relatively high in Southern Asia (8.6 per 10^5). These patterns reflect the prevalence of specific risk factors – tobacco/alcohol in Western and Southern Europe, and Southern Africa, and the chewing of betel quid in South Central Asia and Melanesia. The high rate of oral cancer in Australia is due to lip cancer (related to solar irradiation).

Leukaemias were the 12th most frequent type of cancer in 2000, with an estimated 257 000 new cases. There is relatively little geographic variation, although rates are low in sub-Saharan Africa (possibly related in part to under-recording). The incidence is highest in North America and Australia/New Zealand. The geographic patterns will not be the same for different leukaemia subtypes. For example, chronic lymphocytic leukaemia (equivalent to small lymphocytic (B-cell) lymphoma in current classifications) is numerically the most important diagnosis in Western Europe, but is extremely rare in East and South-East Asia.

Pancreas cancer (21 600 cases a year, 2.1% of the total) is slightly more common in men than in women (ratio 1.2 : 1). Geographic variation is not large; the higher rates in most developed areas probably reflect diagnostic capacity rather than aetiology.

Ovarian cancer (192 000 cases, 1.9% of all cancers, 4.1% of cancers in women) is, in general, a tumour of women in developed countries. It occurs in almost all with age-standardized rates in excess of nine per 10^5 – the exceptions are in Southern Europe (Portugal (6.7 per 10^5), Greece (7.2), Spain (8.3) Italy (8.7)), and in Japan (6.6 per 10^5). incidence in Temperate South America is moderately high (average 11.3 per 10^5).

Kidney cancer (189 000 new cases, 1.9% of the world total) has the highest rates in North America and Western, Northern and Eastern Europe, while incidence rates are low in Africa, Asia (except Japanese males) and the Pacific.

Cancer of the Corpus uteri (189 000 cases, 1.9% of all cancer, 4.4% of cancer in women) is, in general, a tumour of women in developed countries. The high-risk areas are North America (ASR 15.5 per 10^5), Scandinavia (14.2), Southern (13.8) and Central Europe (12.6) and Temperate South America (23.4 per 10^5). Corpus cancer is rare in Asia – including Japan – and in sub-Saharan Africa, with age-standardized rates inferior to five per 100 000).

Cancers of the brain and nervous system account for some 176 000 new cases annually (1.8% of new cancers). The highest rates are observed in developed areas (Australia/New Zealand, North America, Northern Europe) and lowest in Africa and the Pacific islands. This suggests that the availability of diagnostic facilities may well be important in determining geographic patterns, at least in part. The incidence is probably underestimated in many developing countries.

Larynx cancer (161 000 new cases) is predominantly a cancer of men, in whom it comprises 2.7% of cases. The sex ratio (more than 7 : 1) is greater than for any other site. For men, the high-risk areas are Europe (East, South, West), Temperate South America and Western Asia. In Western Asia, larynx cancer accounts for more than 5% of cancers in men. Tobacco smoking is estimated to cause two-thirds of all cases in men.

Malignant melanoma of skin accounts for 133 000 new cases annually, with slightly more occurring in women than in men (sex ratio 0.95). The highest rates are observed in Australia/New Zealand (ASR 39.9 per 100 000 in men, 32.3 in women), North America and Northern Europe (especially Scandinavia). The lowest rates (ASR less than 0.6 per 10^5) are observed in East and South-East Asia, and in South Asia.

Conclusions

International cancer patterns, in terms of disease risk (incidence) or mortality, continue to have important practical applications, both to the cause-of-disease-orientated epidemiologist, and to those concerned with planning and evaluation of cancer control activities. This chapter provides some background on the tools available (measures, and availability of data), as well as a brief overview of the most obvious geographic patterns observed for the major cancers. It is very unlikely that future changes in fashion and focus in cancer research will diminish the value of comparisons of risk and outcome between populations, and indeed there is every reason to seek to extend the availability and accuracy of such data, and to encourage their intelligent analysis.

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