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Cancer burden in the year 2000. The global picture

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1. The burden of cancer: information and estimation

1.1. Indices of 'burden'

Although the general idea of 'burden' of a disease to a community seems fairly straightforward, there are multiple dimensions in which it may be expressed, either in terms of disease frequency (the 'need' for services) or the demand which it places upon them. In this review, we confine ourselves to three elementary measures of cancer frequency: incidence, mortality and prevalence.

Incidence is the number of new cases occurring. It can be expressed as an absolute number of cases per year (the volume of new patients presenting for treatment) or as a rate per 100 000 persons per year. The latter provides an approximation to the average risk of developing a cancer, and is necessary if we wish to compare the risk of disease between populations (countries, ethnic groups, or different time periods within a country, for example). When considering the impact of primary prevention strategies, a reduction in incidence (occurrence of new cases) is the appropriate statistic to use.

Mortality is the number of deaths occurring, and the mortality rate the number of deaths per 100 000 persons per year. The number of deaths provides one measure (and a rather unambiguous one) of the outcome or impact of cancer. It is the product of the incidence and the fatality of a given cancer. Fatality, the inverse of survival, is the proportion of cancer cases that die and this is generally assumed to be the most severe sequel of the disease. Mortality rates therefore 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 rates are sometimes used as a convenient proxy measure of the risk of acquiring the disease (incidence) when comparing different groups, since they may be more generally available (as described below). However, when used in this way, an assumption of equal survival/fatality in the populations being compared is introduced. Since this is rarely correct—there are, for example, quite large differences between countries—it is safer to use mortality as a measure of outcome rather than occurrence.

Prevalence: There is no agreed definition of 'prevalence' of cancer. Strictly speaking, it is the number of persons in a defined population alive at a given time who have had cancer diagnosed at some time in the past. However, the resource requirements for treating newly diagnosed patients are very different from those for supporting long-term survivors. Thus, overall prevalence is not particularly useful for healthcare planning purposes, especially as a large proportion of long-term survivors can be considered cured. *Partial prevalence*, which limits the number of patients to those diagnosed during a fixed time in the past, is therefore a more useful measure of cancer burden. Prevalence for cases diagnosed within 1, 3 and 5 years are likely to be of relevance to the different stages of cancer therapy, namely, initial treatment (1 year), clinical follow-up (3 years) and cure (5 years). Patients who are still alive 5 years after diagnosis are usually considered cured since the death rates of such patients are similar to those in the general population. There are some exceptions, primarily that of female breast cancer, for which the risk of death remains higher than the general population for many more years.

Several other more complex statistics have been used to measure the impact of disease, particularly in health economics. They include person-years of life lost (how many years of normal lifespan are lost due to deaths from cancer). This measurement may be refined by giving different values to life-years at different ages, so that a year saved at, for example, age 20 years, is valued

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more highly than one at age 60 years. A further refinement is to calculate disability or quality-adjusted life years lost. This requires giving a weight between 0 and 1 to the years of life lived between diagnosis and death, to reflect the quality of these life-years (where 0 = dead and 1 = perfect health). Such estimates require a lot of data (on incidence and duration), as well as a lot of guesswork about 'quality of life' in different circumstances and cultures.

Survival: The survival time of a cancer patient is defined as the time that elapsed between diagnosis and death. The most basic measure of patient survival is the observed survival, with the 5-year observed survival being the percentage of patients alive after 5 years of follow-up from the date of diagnosis. Not all deaths among cancer patients will, however, be due to the primary cancer in question. Deaths from other causes lower the observed survival rate and preclude comparison between groups for which probabilities of death in the general population vary. To avoid this problem of comparability, relative survival rates can be calculated. A relative survival rate is defined as the observed survival rate in a patient group divided by the expected survival of a comparable group in the general population with respect to age, sex and calendar period of investigation.

In this article, we shall present estimates of the incidence, mortality, and prevalence (5-year) of cancer. To illustrate global burden in terms of the relative importance of different cancers, absolute numbers of persons developing, living with, or dying from, cancer are given. Annual rates of incidence or mortality, per 100,000 population are used, in order to compare the risks of developing (or dying from) cancer in different populations. All of the rates quoted have been age-standardised (to the world standard population) in order to take into account differences in the age structure of the populations being compared.

1.2. Information sources

Mortality data derive from vital registration systems, where the fact and cause of death are certified, usually by a medical practitioner. The International Classification of Diseases (ICD) provides a uniform system of nomenclature and coding, and a recommended format for the death certificate. Mortality statistics are produced according to the underlying cause of death; this may not equate with the presence of a particular tumour. Comprehensive mortality statistics require that diagnostic data are available on decedents, which are transferred in a logical, standardised fashion to death certificates, which are then accurately and consistently coded, compiled and analysed. Many studies have investigated the accuracy of death certificate diagnosis [1–3], and have shown that the degree of accuracy of the stated cause of death declines as the degree of precision in the diagnosis increases. Thus, although the total number of deaths from cancer of all types may be only slightly underestimated, the distribution by site of cancer may be incorrect.

The great advantage of mortality statistics is their comprehensive coverage, and their availability. In 1990, approximately 42% of the world population was covered by vital registration systems producing mortality statistics on cancer. Not all of these are, however, of the same quality in all countries. In some, coverage of the population is manifestly incomplete, and the so-called mortality rates produced are implausibly low. In others, quality of cause of death information is poor. This can sometimes be predicted when non-medical practitioners complete substantial proportions of certificates. The World Health Organization (WHO) has in recent years provided useful tables in their 'World Health Statistics Annual' giving, for a few countries at least, estimates of completeness, and information on the percentage of non-medically certified deaths.

Incidence data are produced by population-based cancer registries [4], which collect information on all new cases of cancer in a defined population. Incidence rates derived from cancer registries are considerably more restricted in availability than mortality. The establishment of cancer registration worldwide has been a very haphazard process; in some countries there has been a (more or less) official policy to support and fund registries, elsewhere individual initiative of research-orientated clinicians and pathologists has often been a major factor. Cancer 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 1990, approximately 18% of the world population were covered by registries, 64% of developed countries and 5% of developing countries, although the situation is improving each year. The latest volume of 'Cancer Incidence in Five Continents' (CI5) contains comparable incidence information from 150 registries in 50 countries, primarily over the period 1988–1992 [5].

Survival statistics are also produced by cancer registries; they require follow-up of registered cancer cases, either actively or by matching death certificates against cancer notifications and assuming that unmatched cases are still alive. These population-based figures are available for many areas in the developed countries, but rather few centres in developing countries.

Frequency data: In the absence of a population-based registry and mortality statistics, some notion of the profile of cancer in a country or region may be obtained from other sources providing at least information on the relative frequency of different types of cancer.

Hospital-based cancer registries record information on cases seen at one (or several) institutions. They can

tabulate the cases receiving care in a given period, but as the cases cannot be related to a population-at-risk, it is impossible to calculate incidence. The data do provide an indication of the relative importance of different cancers, but there are problems in extrapolating the results to the general population, since such series are subject to various forms of selection bias. Hospital series include cases for which therapeutic facilities are available, and often exclude advanced or incurable cancers.

Pathology series are similar to hospital-based statistics, but comprise information only on histologically diagnosed cancers. As one individual with cancer may have several pathology examinations, there may be problems of distinguishing individuals from biopsies from labdocuments. Histopathology series include an excess of easily biopsied tumours, and a deficit of cancers usually diagnosed by other means [6]. It may be possible to include all histologically diagnosed cases in a population—several 'National Registers of Tumour Pathology' have been created.

1.3. Estimation

Using data on incidence, mortality, survival, and percentage frequency, it is possible to prepare estimates of the numbers of new and prevalent cancer cases and deaths by site, sex and age group, which are more or less accurate, for different countries, depending on the extent and accuracy of locally available data. The method we use is to estimate incidence, mortality, and prevalence rates for five broad age groups (0–14 years, 15–44 years, 45–54 years, 55–64 years and 65 years and over) and sex for all countries of the world, for 24 different types of cancer.

The sources of data and the methods used to produce estimates of incidence, mortality, and prevalence are summarised in several recent reports [7–9]. The estimates in this review are taken directly from GLOBOCAN 2000, which updates the previous estimates to the year 2000 [10].

Incidence rates for a country were obtained whenever possible from cancer registries serving the whole population, or a representative sample of it. The most recent national mortality data from the WHO mortality data bank were used to obtain information on cancer deaths. For some countries. a correction factor was applied to account for known and quantified under-reporting of mortality. Occasionally, mortality data from a sample of the country were used in the absence of national statistics. The most prominent example of this was the use of information from Disease Surveillance Points (DSP) representing a random sample of some 9.6 million (0.8%) of the Chinese population [11].

For some countries, data on mortality were available, but there were either no incidence data, or results from certain regions only. In this case, incidence was estimated using sets of regression models which, for a given area, cancer, sex and age group, predict incidence from mortality, based on cancer registry data from the same country, or area. Conversely, incidence rates were available for some countries where there were no data on mortality. For these countries, we used information on cancer survival for the same area to obtain estimates of mortality.

An alternative method of estimating national incidence is to apply the rates obtained by a regional cancer registry to the national population by direct standardisation. Although this may be the simplest approach, it does not allow for the non-representative nature of the population covered by the local registry. This can be taken into account by using local registry data and national mortality (as in the mortality/incidence method, described above). When there are several cancer registries in the country, their incidence rates must be combined into a common set of values by some weighted average, but any choice of weightings is sure to be rather arbitrary.

In the absence of either of these data sources, we built up an estimate of cancer incidence from available information on the relative frequency of different cancers (by age group and sex), applied to an overall 'all sites' incidence figure for the corresponding area. These 'all sites' figures were derived from such data as could be found for the corresponding geographical area. We no longer used an estimate of 'all sites incidence' derived from regression models of total cancer mortality [12–14], since these have been found to give quite misleading results for many developing countries, where the schedule of mortality (by major cause groups) is very different from the historical data from Europe, upon which the models are based.

Prevalence was estimated from incidence, and survival. Three sources of data on population-based survival were used: the Cancer Survival in Developing Countries project by the International Agency for Research on Cancer (IARC) [15] which provides cancer survival in populations of China, the Philippines, Thailand, India and Cuba for all of the sites considered; the Surveillance, Epidemiology and End Results (SEER) programme covering 10% of the US population [16] and the EUROCARE-2 project providing figures from several European cancer registries [17].

The objective of this review is to present data on the profile of cancer in the world in the year 2000. However, cancer data are always collected and compiled some time after the events to which they relate, so that the most recent statistics available are from earlier time periods. The degree of lateness varies but, for the most part, the disease rates we have used are for periods between 3 and 10 years earlier. The actual number of cancer cases, deaths and prevalent cases are calculated by applying

these rates to the estimated world population for 2000, obtained from the most recent projections prepared by the United Nations Population Division [18].

As will be evident from the review of time trends for the major cancer sites, it is not easy to predict what effect the use of the rates of disease from 1990 to 1997 will have on the accuracy of the 'burden' estimate for 2000. We have not attempted to project incidence rates to the year 2000. For one thing, time trend data are necessarily based on historical patterns, which are not always a sound basis for future projections. In addition, for most of the world, there simply are insufficient historical data to permit such modelling. For cancer sites where rates are generally increasing worldwide (for example, prostate cancer and breast cancer (incidence)), there will be an underestimate of new cases, and where there is a global decrease (e.g. stomach cancer), an overestimate. However, for several sites, trends are in different directions in different world regions, and are moreover likely to have changed direction in the last decade (e.g. lung cancer, colorectal cancers, cervical cancer), so that the net effect is difficult to guess.

1.4. Results

Based on the most recent incidence and mortality data available, we estimate that there will be over 10 million new cases (Table 1), 6.2 million deaths (Table 2), and 22.4 million persons living with cancer (Table 3) in the

Table 1
Estimated new cancer cases, World 2000

Cancer	Male	Female	Both sexes	%
Oral cavity	170 000	97 000	267 000	2.7
Nasopharynx	46 000	19 000	65 000	0.6
Other pharynx	101 000	22 000	123 000	1.2
Oesophagus	279 000	133 000	412 000	4.1
Stomach	558 000	318 000	876 000	8.7
Colon/rectum	499 000	446 000	945 000	9.4
Liver	398 000	166 000	564 000	5.6
Pancreas	116 000	101 000	216 000	2.1
Larynx	142 000	19 000	161 000	1.6
Lung	902 000	337 000	1 239 000	12.3
Melanoma of skin	650 00	67 000	133 000	1.3
Breast	0	1 050 000	1 050 000	10.4
Cervix uteri	0	471 000	471 000	4.7
Corpus uteri	0	189 000	189 000	1.9
Ovary, etc.	0	192 000	192 000	1.9
Prostate	543 000	0	543 000	5.4
Testis	49 000	0	49 000	0.5
Bladder	260 000	76 000	336 000	3.3
Kidney, etc.	118 000	71 000	189 000	1.9
Brain, nervous system	100 000	76 000	176 000	1.8
Thyroid	33 000	89 000	123 000	1.2
Non-Hodgkin's lymphoma	167 000	121 000	287 000	2.9
Hodgkin's disease	380 00	24 000	62 000	0.6
Multiple myeloma	390 00	34 000	74 000	0.7
Leukaemia	144 000	113 000	257 000	2.6
All sites but skin	5 318 000	4 738 000	10 056 000	100.0

Table 2
Estimated cancer deaths, World 2000

Cancer	Male	Female	Both sexes	%
Oral cavity	81 000	47 000	128 000	2.1
Nasopharynx	27 000	11 000	38 000	0.6
Other pharynx	64 000	15 000	79 000	1.3
Oesophagus	227 000	111 000	338 000	5.4
Stomach	405 000	241 000	647 000	10.4
Colon/rectum	255 000	238 000	492 000	7.9
Liver	384 000	165 000	549 000	8.8
Pancreas	112 000	101 000	213 000	3.4
Larynx	79 000	11 000	89 000	1.4
Lung	810 000	293 000	1 103 000	17.8
Melanoma of skin	20 000	17 000	37 000	0.6
Breast	0	373 000	373 000	6.0
Cervix uteri	0	233 000	233 000	3.8
Corpus uteri	0	45 000	45 000	0.7
Ovary, etc.	0	114 000	114 000	1.8
Prostate	204 000	0	204 000	3.3
Testis	9000	0	9000	0.1
Bladder	99 000	33 000	132 000	2.1
Kidney, etc.	57 000	34 000	91 000	1.5
Brain, nervous system	72 000	56 000	128 000	2.1
Thyroid	9000	17 000	26 000	0.4
Non-Hodgkin's lymphoma	93 000	68 000	161 000	2.6
Hodgkin's disease	16 000	9000	25 000	0.4
Multiple myeloma	30 000	27 000	57 000	0.9
Leukaemia	109 000	86 000	195 000	3.1
All sites but skin	3 522 000	2 686 000	6 209 000	100.0

Table 3
Estimated prevalence of cancer (% year), World 2000 (both sexes)

Cancer	5-year prevalence	%
Oral cavity	707 000	3.2
Nasopharynx	171 000	0.8
Other pharynx	249 000	1.1
Oesophagus	416 000	1.9
Stomach	1 398 000	6.2
Colon/rectum	2 379 000	10.6
Liver	268 000	1.2
Pancreas	112 000	0.5
Larynx	458 000	2.0
Lung	1 394 000	6.2
Melanoma of skin	533 000	2.4
Breast	3 860 000	17.2
Cervix uteri	1 401 000	6.3
Corpus uteri	716 000	3.2
Ovary, etc.	50 7000	2.3
Prostate	1 555 000	6.9
Testis	200 000	0.9
Bladder	1 000 000	4.5
Kidney, etc.	480 000	2.1
Brain, nervous system	295 000	1.3
Thyroid	475 000	2.1
Non-Hodgkin's lymphoma	673 000	3.0
Hodgkin's disease	197 000	0.9
Multiple myeloma	144 000	0.6
Leukaemia	421 000	1.9
All sites but skin	22 407 000	100.0

year 2000. No attempt has been made to estimate incidence or mortality of non-melanoma skin cancer because of the difficulties of measurement and consequent lack of data. The total 'All cancer' therefore excludes such tumours. The 2000 estimate represents an increase of around 23% in incidence and mortality since our most recent comprehensive estimates (for 1990).

Fig. 1 shows the distribution by type of cancer. In terms of incidence, the most common cancers are lung (12.3%), breast (10.4%) and stomach (8.7%). The most common causes of death due to cancer are cancers of the lung (17.8%), stomach (10.4%) and liver (8.8%). In terms of prevalence, the most common cancers are breast (17.2%), colorectal cancers (10.6%) and prostate (6.9%).

Fig. 2a and b shows the 15 most common cancers for males and females (as number of new cases), in the developing and developed regions of the world. 'Developed countries' comprise those of North America, Europe (including all of Russia), Australia/New Zealand, and Japan, 'Developing countries' the remainder. This convention is used throughout this paper. The terms 'westernised' and 'industrialised' are used as synonyms of 'developed'.

There are some differences in the profile of cancers worldwide depending on whether incidence or mortality is the focus of interest, as shown in Fig. 3. Fig. 4 shows the most prevalent cancers, in men and women, together with the number of annual new cases at the same site. The ratio between prevalence and incidence is an indicator of prognosis. This explains why breast cancer appears as the most prevalent cancer in the world, despite there being fewer new cases than lung cancer, for which the outlook is considerably poorer.

Lung cancer is the main cancer in the world today, whether considered in terms of numbers of cases (1.2 million) or deaths (1.1 million), because of the high case fatality (ratio of mortality:incidence = 0.9). However, breast cancer, although it is the second most common cancer overall (over one million new cases) ranks much less highly (5th) as a cause of death, because of the relatively favourable prognosis (ratio of mortality:incidence = 0.4). Colorectal cancer is third in importance in terms of number of cases (945 000 cases, 492 000 deaths), and stomach (876 000 cases, 647 000 deaths) fourth.

Fig. 5 shows the distribution of cancer cases and deaths (all types of cancer) by world region. Most cases (2.6 million) and deaths (1.8 million) occur in East Asia, with its huge population. North America comes second in terms of numbers of new cancer cases (1.4 million), but there are more deaths in South-Central Asia (800 000) than in North America (636 000). This reflects the different types of cancer occurring, rather than any large differences in prognosis.

2. The major cancers: burden, cause, trends and prevention

In this section, we consider the eight most common cancers today in terms of their overall frequency and geographical distribution, their recent trends in incidence and mortality and the more important causes (risk factors) which explain these observations. A brief

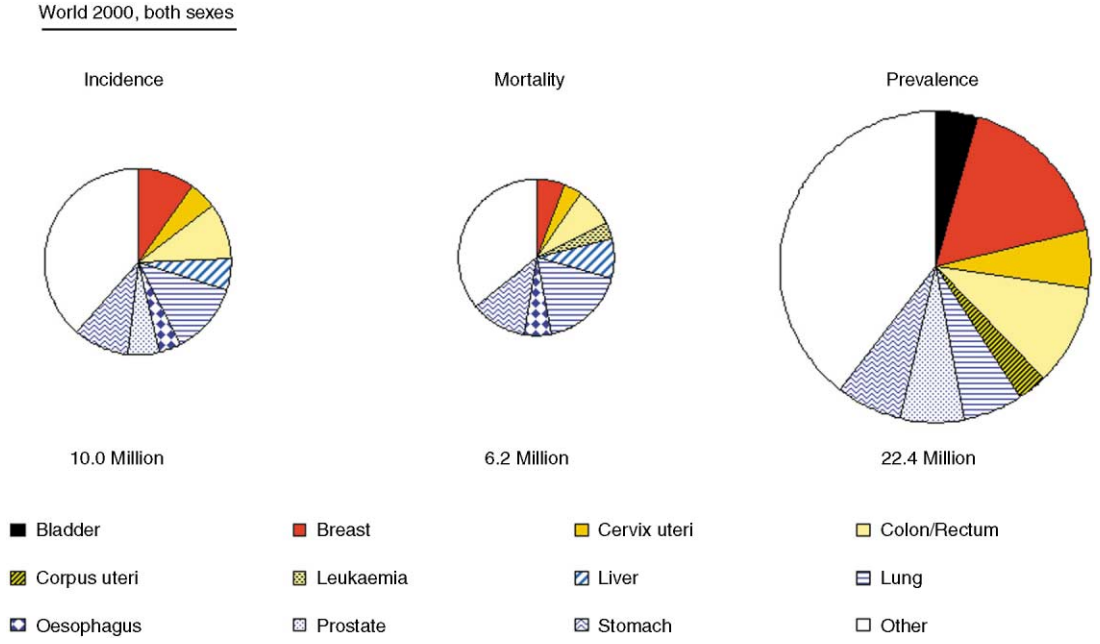


Fig. 1. Distribution by type of cancer incidence, mortality and prevalence, 2000.

summary of the most promising strategy for prevention, in the current state of knowledge, is also included.

With the exception of Africa, where presently there is a paucity of historical data, incidence and mortality trends over time are shown graphically for each cancer for several countries in each continent. The age-standardised incidence rates are taken directly from the CI5 volumes [5,19–24], while the 3-year rolling average mortality rates are based on data extracted from the WHO mortality databank. US incidence rates (as 3-year rolling averages as above) by race are calculated from data from the SEER registries [25] while the

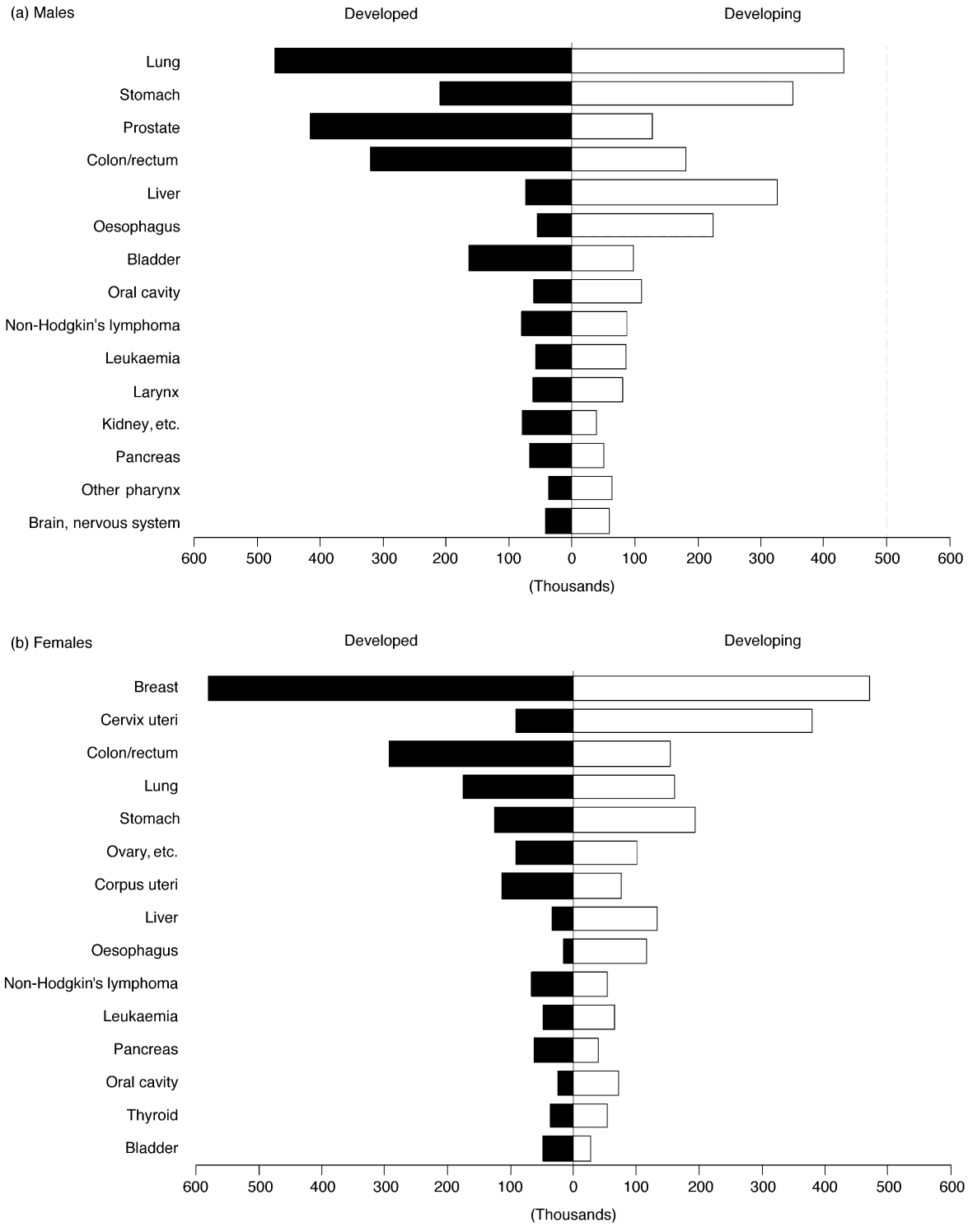


Fig. 2. Number of new cases of the 15 most common cancers in (a) males, 2000, (b) females, 2000.

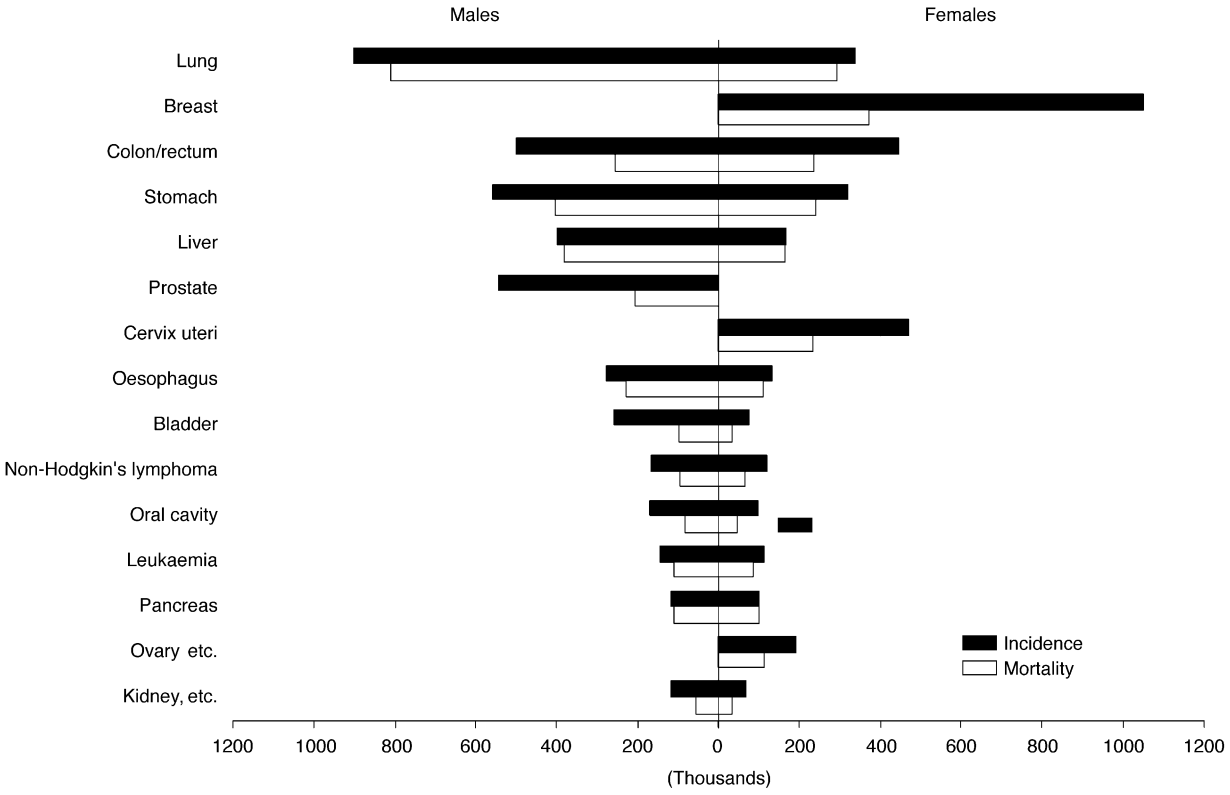


Fig. 3. Number of new cases and deaths worldwide for the 15 most common cancers, 2000.

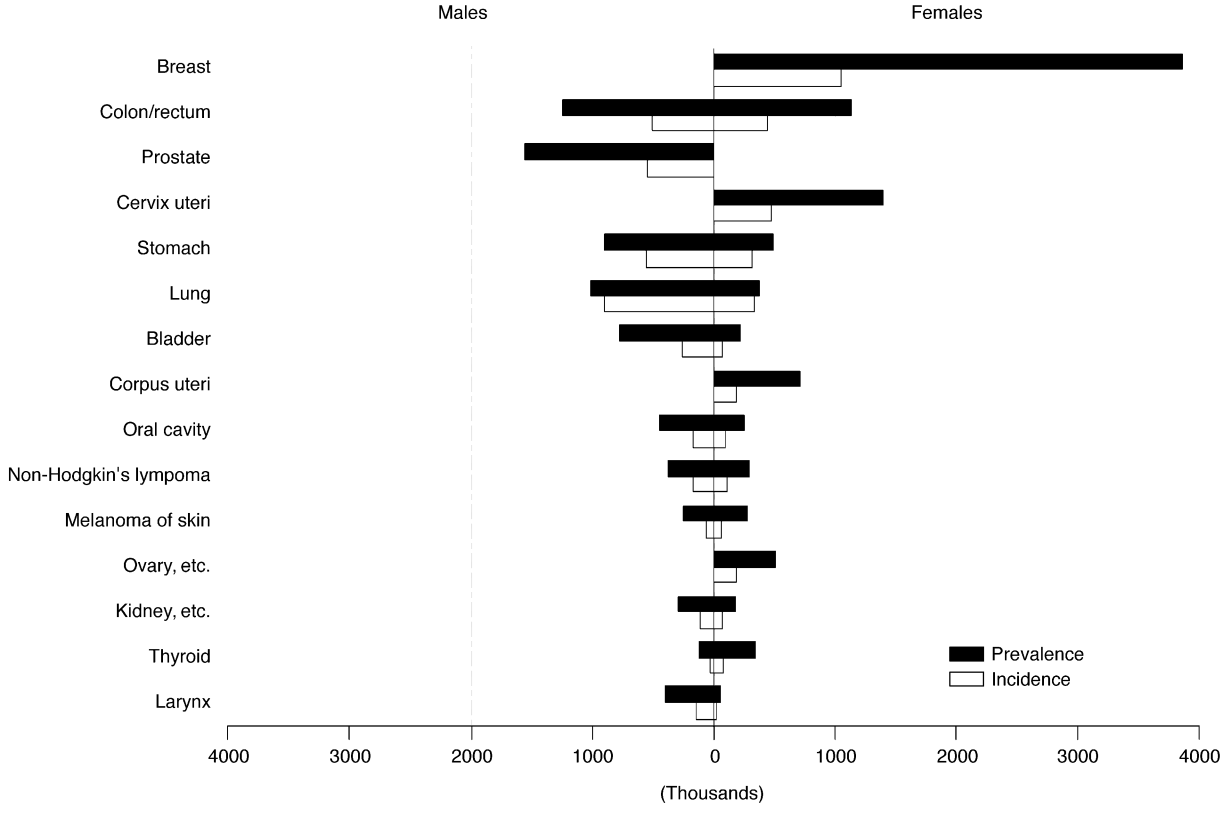


Fig. 4. Number of new cases and 5-year prevalence for the 15 most prevalent cancers, 2000.

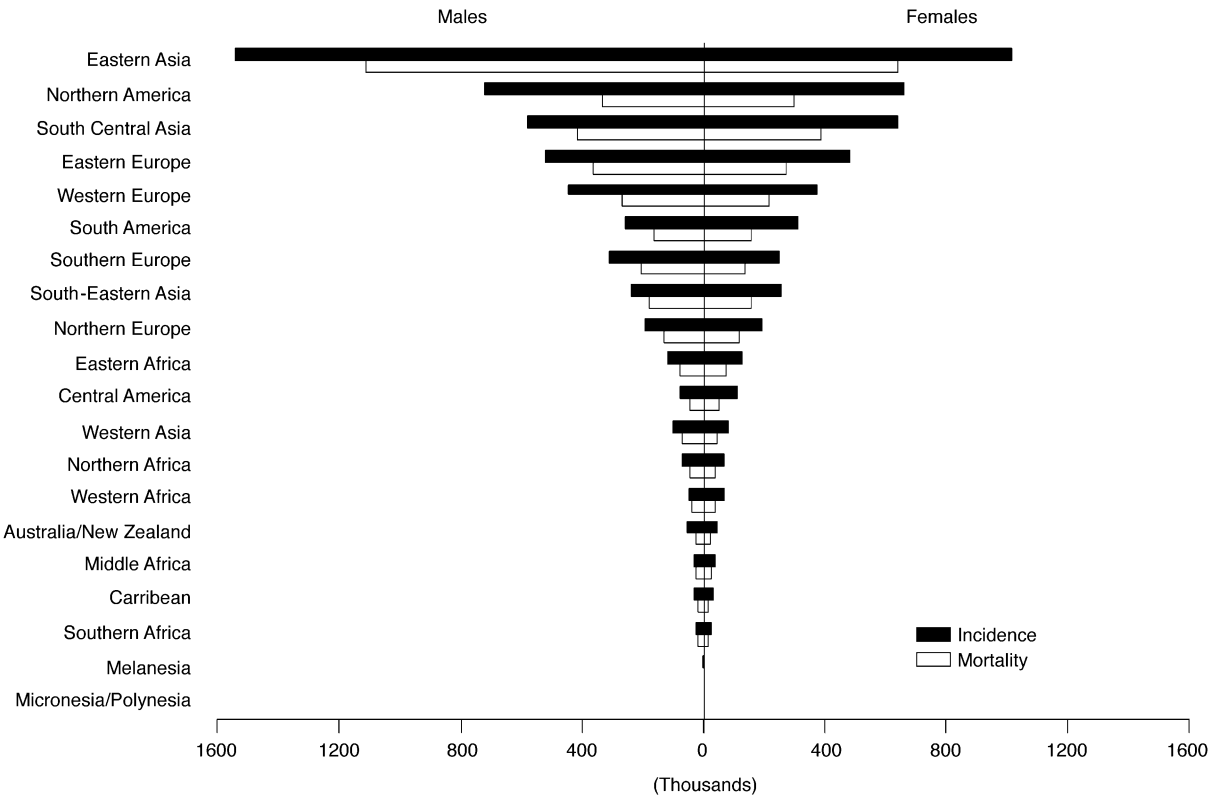


Fig. 5. Distribution of new cancer cases and deaths by world region, 2000.

corresponding US death rates are based on mortality data encompassing the whole country obtained from the National Center for Health Statistics (NCHS), again by race. The incidence and mortality rates were standardised using the weights from the world population. In tabulating the site-specific cancer data, the following ICD codes were used; oesophagus (ICD7-9 150), stomach (ICD7-9 151), colorectal (ICD7-9 153, 154), liver (ICD9 155.0, 155.1, 155.2), lung (ICD7 162, 163, ICD8-9 162), female breast (ICD7 170, ICD8-9 174), cervix uteri (ICD9 171, ICD8-9 180) and prostate (ICD7 177, ICD8-9 185).

2.1. Lung cancer

2.1.1. Burden 2000

Lung cancer is the commonest cancer in the world today (12.3% of all new cancers). There are estimated to be 1.2 million new cases in 2000, 52% of which occurred in the developed countries. The disease is more common in men (75% of the world total), and the areas with the highest incidence 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 (Fig. 6). In certain population subgroups (e.g. US blacks, New Zealand Maoris), incidence is even higher and, with current incidence rates, men in these two groups have about a 13% chance of developing a lung cancer before the age of 75 years. In developing countries the highest rates are seen where the tobacco smoking habit has been longest established—the Middle East, China, the Caribbean, South Africa, Zimbabwe and the Pacific. In women, the geographical pattern is a little different, reflecting different historical patterns of tobacco smoking. Thus, the highest incidence rates are observed in North America and North West Europe (UK, Iceland, Denmark) with moderate incidence rates in Australia and New Zealand and China (Fig. 7).

Patterns of lung cancer occurrence are determined very largely by past exposure to tobacco smoking. We have estimated the proportion of lung cancer cases due to tobacco smoking, by examining the observed incidence in different areas in comparison with that expected based upon incidence rates in non-smokers from several large cohort studies [26]. Updating the results to 1990, we find that some 86% of cases in men and 49% in women are due to smoking, although there is considerable regional variation in these figures. Thus, in countries/regions with a long history of smoking, some 90% or more cases in men are tobacco-related, while the fraction is much lower in Africa and Southern Asia. The proportions are more variable in women, even in Europe, where they range from 80% in the UK to virtually nil in Spain and Portugal, where incidence rates are the same as in non-smoking women in the US and Japan.

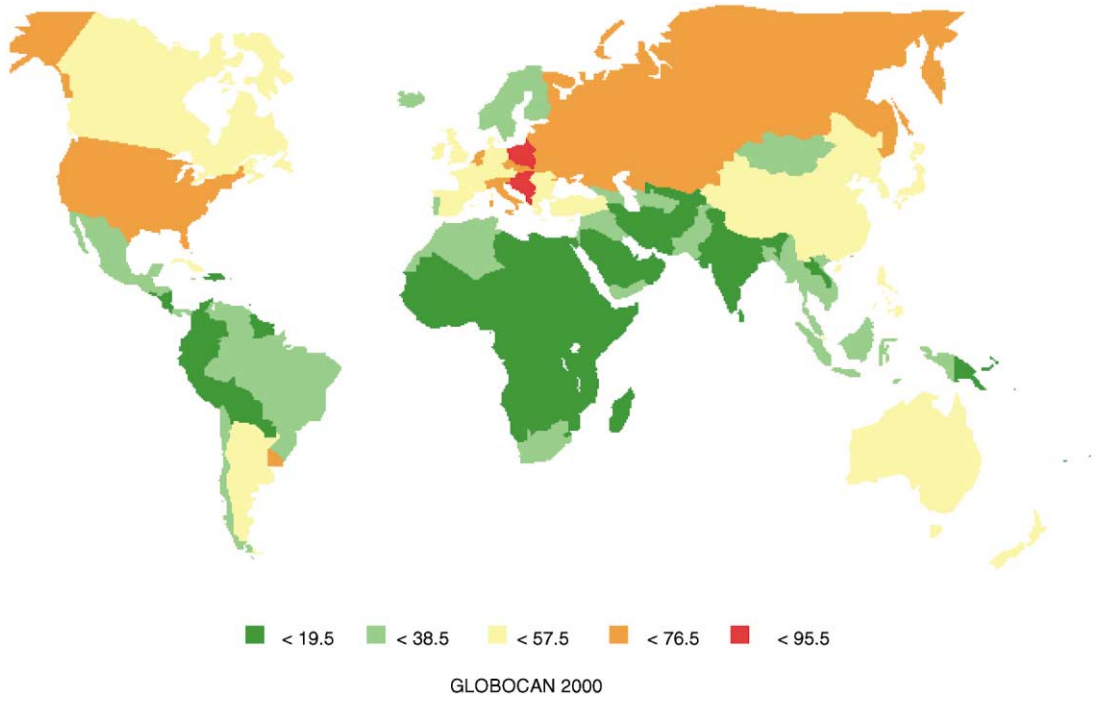


Fig. 6. Incidence of lung cancer: age-standardised rates (world, per 100 000)—males (all ages).

2.1.2. Risk factors

Tobacco smoking is by far the most important cause of lung cancer. The evidence has been reviewed many times [27,28]. There is a clear dose-response relationship between lung cancer risk and the number of cigarettes smoked per day, degree of inhalation and age at initiation. A lifetime smoker has a risk some 20–30 times that of a non-smoker. The risk is diminished in smokers of filter and low tar cigarettes, and increasing use of these has contributed to declines in risk in recent generations of smokers (as well as the declining prevalence of smoking). The early observation that pipe-smokers and

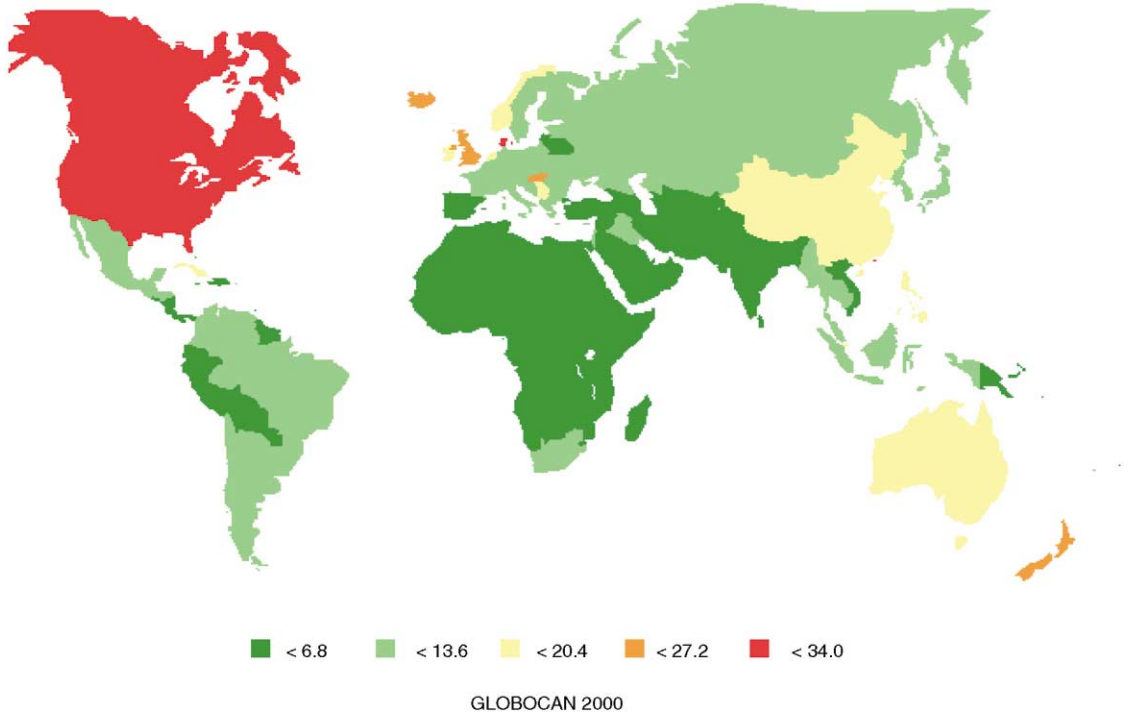


Fig. 7. Incidence of lung cancer: age-standardised rates (world, per 100 000)—females (all ages).

smokers of cigars had a lower risk of lung cancer than cigarette smokers is due simply to the lesser amount of tobacco smoked and to the lower degree of inhalation. Smokers of other types of tobacco (e.g. bidis in India) are at similar risk to smokers of cigarettes. Smoking increases the risk of all histological types of lung cancer, although the relative risk is greater for squamous cell and small-cell carcinomas than for adenocarcinomas. Adenocarcinoma has always been more common in women than in men in both smokers and non-smokers. Evidence that the risk of lung cancer may be greater in women than in men at equivalent levels of exposure to tobacco smoke [29,30] has been weakened by more recent studies from Europe which have concluded that risk is similar in the two sexes [31,32].

Passive exposure to tobacco smoke (ETS) is generally accepted as increasing risk by 30–50%. It has been known for some time that a family history of lung cancer increases the risk in individuals, irrespective of their smoking history. The explanation is probably the genetic mechanisms which define susceptibility to tobacco smoke (via the control of metabolism of carcinogens). Most of the genetic polymorphisms in carcinogen-metabolising enzymes investigated to date confer only modest relative risks (less than 2), but some are quite prevalent in the general population. For example, approximately 50% of the population are glutathione S-transferase-1 (GSTM1) deletion homozygotes [33]; several studies have found that this genotype is associated with an increased risk of lung cancer, or of bladder cancer, although the relative risks are not high—around 1.34 on meta analysis [34]. The fraction of disease attributable to these polymorphisms could, therefore, be around 15%. It is possible that some of the apparent differences in risk of lung cancer by ethnic group [29,35,36] are due to differential prevalence of such polymorphisms.

Chinese women, although few of them smoke, have a modestly raised incidence of lung cancer. The majority of lung cancers are adenocarcinomas, and the relative risk in relation to smoking is small, so that it can be calculated that the incidence of lung cancer in non-smoking Chinese women is some 3 times that in US non-smokers [26] a result confirmed by data from a large cohort study in Shanghai (data not shown). An increased risk of lung cancer due to exposure to environmental smoke, particularly cooking fumes [37,38] and indoor smoky coal emissions [39], have been found in studies in China, but it is not clear if these exposures can account for the large differences observed. It is possible that there are differences in susceptibility to lung cancer too; in Hawaii, Le Marchand and colleagues [35] reported that, having taken into account smoking, there remained a strong excess risk for lung cancer in Chinese females (i.e. not related to smoking), when compared with other ethnic groups.

Other factors known to increase risk of lung cancer are occupational exposures to asbestos, some metals (e.g. nickel, arsenic and cadmium), radon (particularly amongst miners) and ionising radiation. However, their contribution to total population rates is small.

There is considerable evidence that diets high in vegetables and fruits (especially green vegetables and carrots) can protect against lung cancer. Many epidemiological studies suggest that higher dietary intake of carotenoids is associated with a decrease in the risk of lung cancer, which is present in smokers and non-smokers, for all histological types. However, it seems unlikely that B-carotene itself is responsible for these observations rather than some other component of carotenoid-containing foods. Three large clinical trials indicate that supplementation with substantial doses of B-carotene does not prevent lung cancer; indeed, the risk was actually increased in individuals at high risk—heavy smokers or asbestos-exposed men [40].

2.1.3. Time trends

Trends in lung cancer incidence and mortality reflect the maturity of the smoking epidemic in different countries [41,42]. Study of time trends in lung cancer incidence or mortality by age group shows that the level of risk is closely related to the birth cohort; in the UK and US cohort-specific incidence is related to the smoking habits of the same generation [43,44]. Thus, in men, the countries where smoking was first established were first to see a diminution in smoking prevalence followed, in the same generations of men, by a decline in risk. As these generations of men reach the older age groups, where lung cancer is most common, a decline in rates is seen. The UK was the first to show this (incidence/mortality falling since 1970–1974), followed by Finland, Australia, The Netherlands, New Zealand, the USA, Singapore and, more recently, Denmark, Germany, Italy and Sweden (Fig. 8a and b). In most other countries, there is a continuing rise in rates, and this is most dramatic in the countries of Eastern Europe. In women, the tobacco habit has usually been acquired recently, or not at all. Thus, the most common picture in western populations is of rising rates (Fig. 8a and b), while in many developing countries (where female smoking generally remains rare), there is little change in risk. A few countries, where prevalence of smoking in women is declining, already show decreasing rates in younger women and in the UK, where this trend is longest established, there is already a decline in overall incidence and mortality since about 1990.

Time trends in mortality from lung cancer in the 15 countries of the European Union up to 1995 and, based upon these trends specific to birth cohort, projections to the year 2010, are shown in Figs. 9 and 10 for males and females, respectively.

There are, however, intriguing differences in trends of the histological subtypes (squamous cell carcinomas, adenocarcinoma, small-cell carcinoma) by race and sex. In the US [45,46] squamous cell carcinoma reached a maximum incidence in men in 1981, but the incidence of adenocarcinoma continued to rise (until approximately 1987 in black males and approximately 1991 in whites). As a result, these two cell types were equally common in white men in 1988–1992, whereas adenocarcinoma had only constituted a small minority of cases (around 5%)

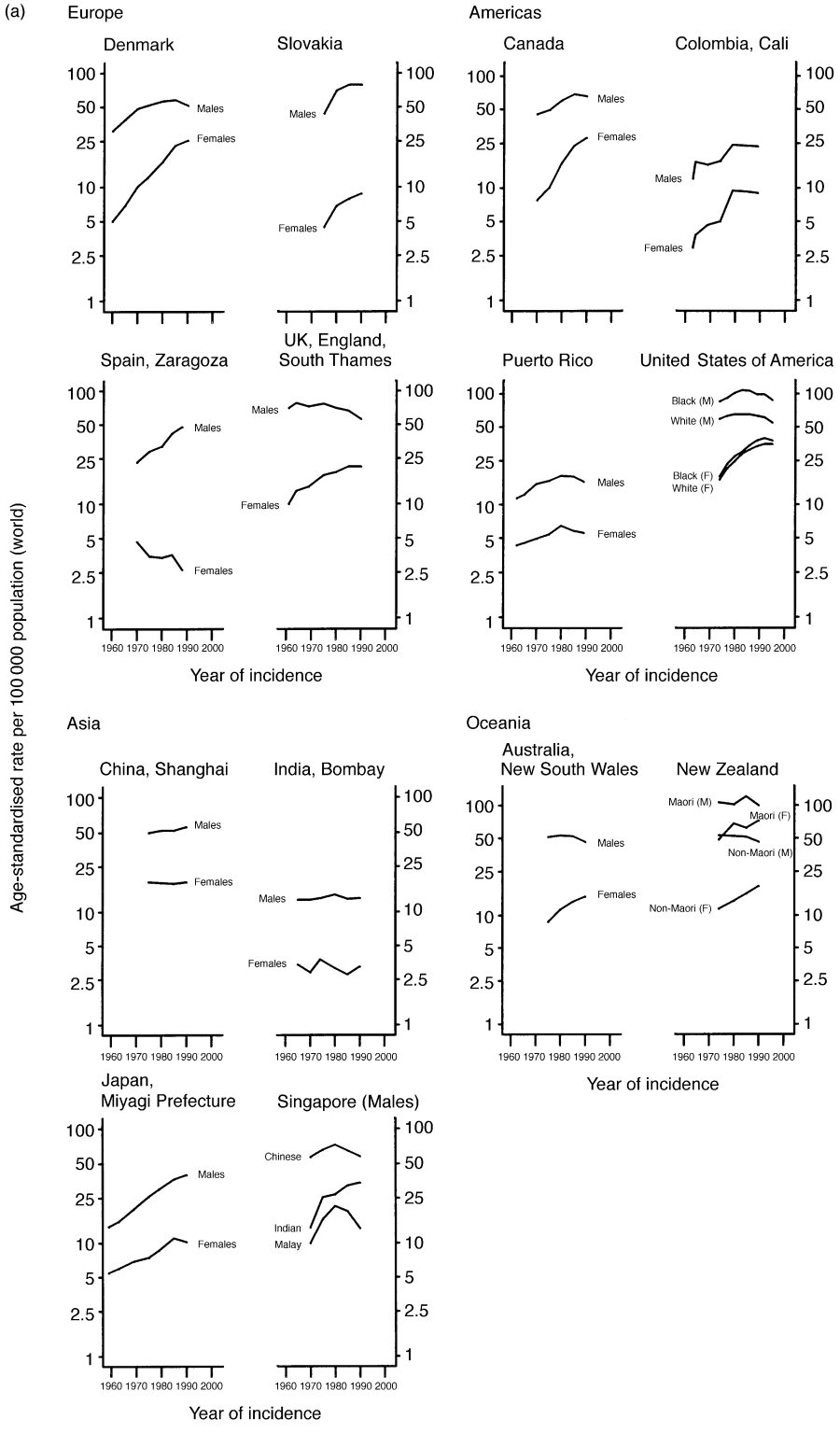


Fig. 8. Lung cancer: (a) incidence trends (source: CI5/SEER); (b) mortality trends (source: WHO/NCHS).

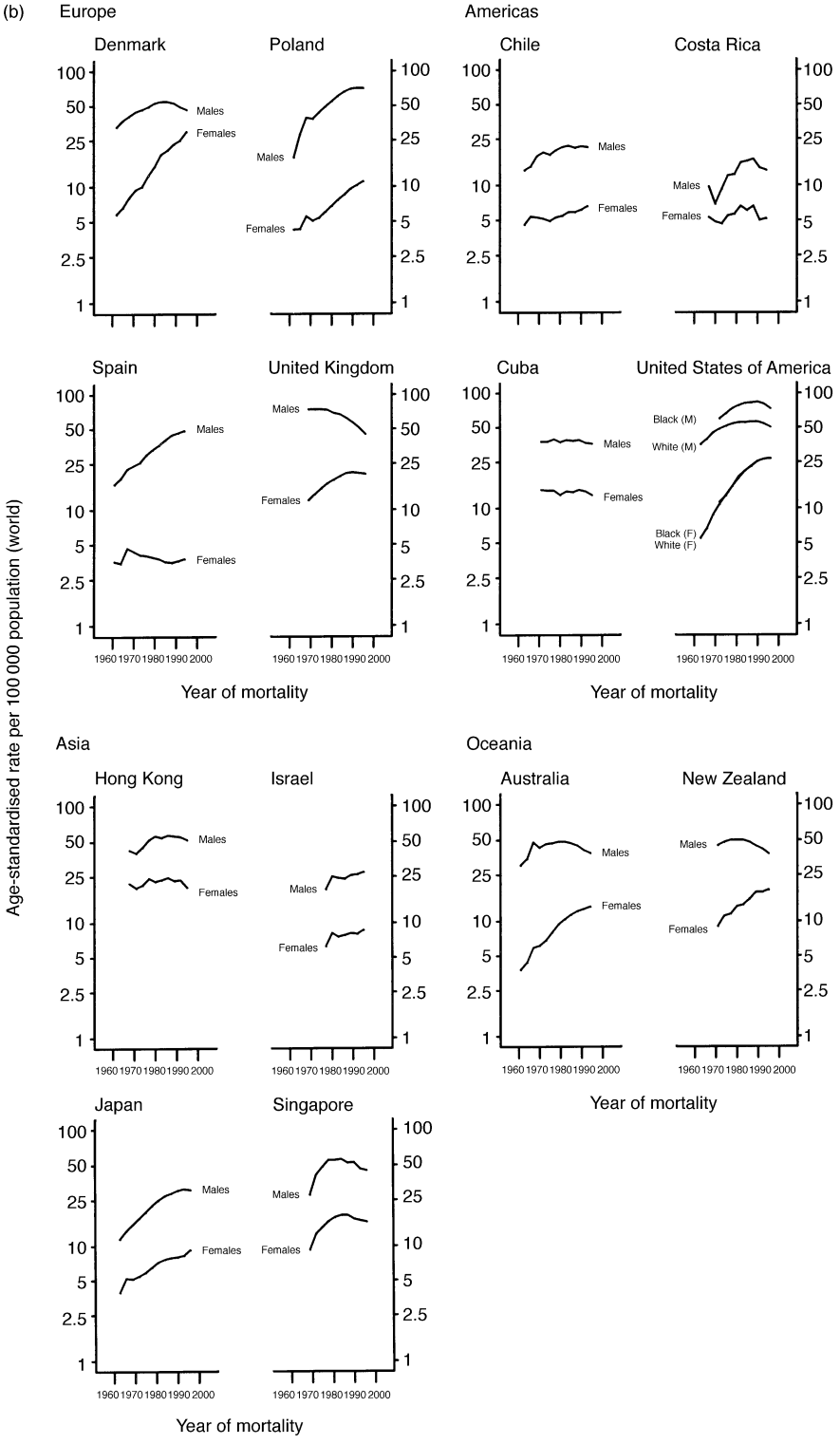


Fig. 8. (*continued*).

in the 1950s [47]. In contrast, the incidence of both histological types has continued to increase in females, although there is a suggestion that the incidence of squamous cell carcinomas had reached its maximum by 1990. These changes were related to specific birth cohorts, with maximum incidence in men in the 1925–1929 cohort for squamous cell carcinomas and 1935–1939 for adenocarcinomas, and in women some 10–20 years later [45,48]. Somewhat similar observations (increasing adenocarcinoma and decreasing squamous

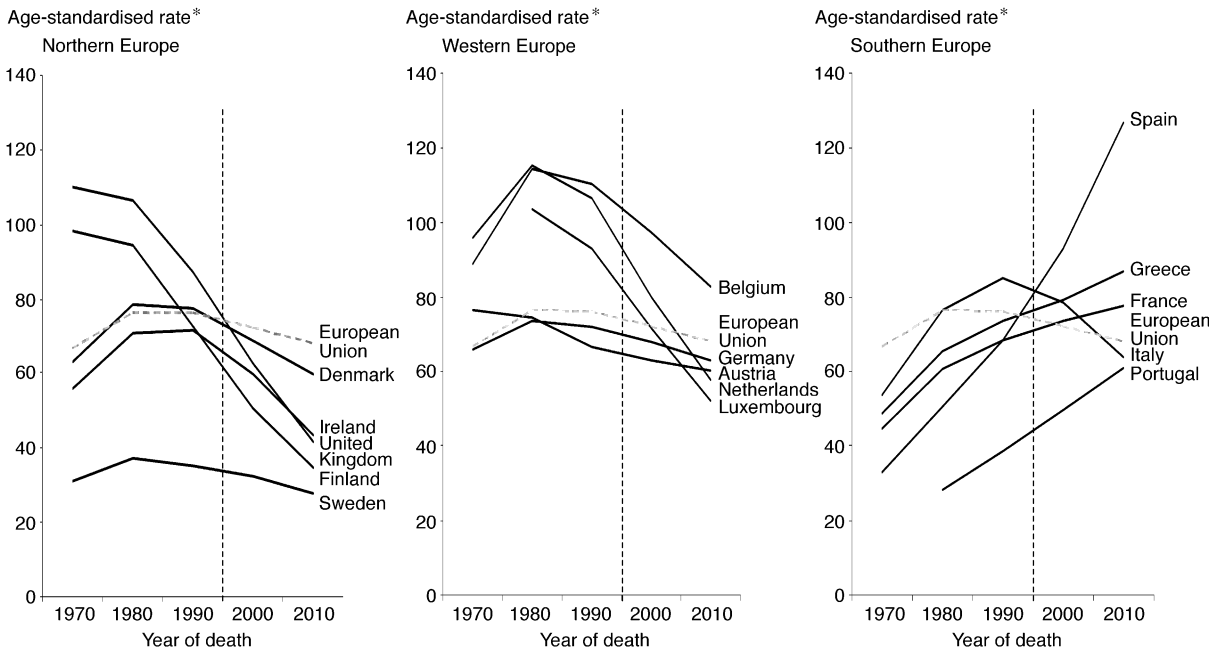


Fig. 9. Lung cancer mortality trends, males. *European Standard population.

cell carcinoma) have been reported from The Netherlands [49] and in Japan [50]. Possibly part of this differential trend may be due to artefact (changes in classification and coding, improved diagnostic methods for peripheral tumours). In part, it may be due to an ever increasing proportion of ex-smokers in the population, since the decline in risk of lung cancer on smoking cessation is faster for squamous cell tumours than for small-cell carcinomas and adenocarcinomas [51,52]. It also seems likely that changes in cigarette composition to low tar, low nicotine, filtered cigarettes are also responsible [53,54]. The manufacturers have changed the composition of these cigarettes so that they contain more nitrate, producing higher yields of carcinogenic tobacco-specific nitrosamine (TSNA) and, in particular, NNK, a systemic carcinogen producing adenocarcinomas in laboratory animals. Low tar/nicotine cigarettes result (in addicted smokers) to more intense smoking (more puffs, deeper inhalation) and hence greater exposure to these carcinogens. In addition, the greater puff

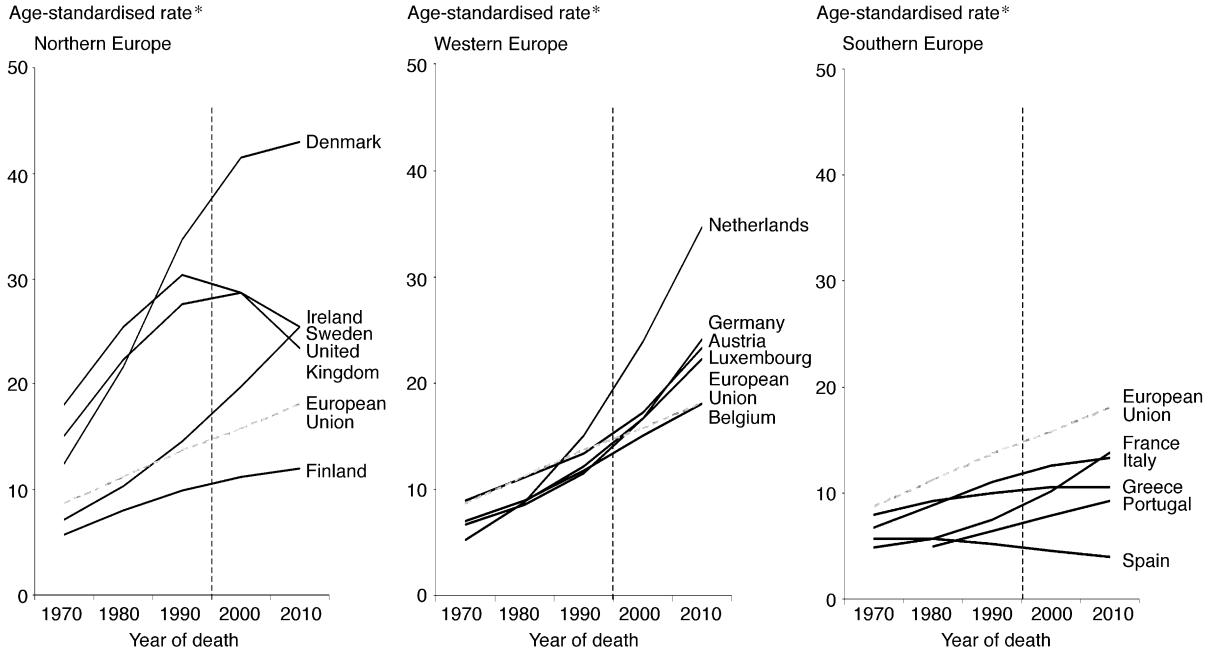


Fig. 10. Lung cancer mortality trends, females. *European Standard population.

volume allows smoke particles to be inhaled with greater velocity so that they reach peripheral parts of the lung where, in the tertiary bronchi and alveoli, they induce adenocarcinomas. Such effects would be greater in men who, until more recent generations (born post-1945), began by smoking high tar, unfiltered cigarettes, and have switched to 'safer' brands. Most women smokers have used filtered or lower-tar brands throughout their smoking careers.

2.1.4. Prospects for prevention

There is plenty of information about the effect of stopping smoking, both from the major cohort studies and from various case–control studies. On cessation, the annual excess risk of lung cancer appears to remain roughly constant for many years [55]. This appears as a progressively decreasing (with duration of cessation) risk, relative to continuing smokers, but it is not clear that the excess risk declines to zero. Nevertheless, it is easy to demonstrate that, from a public health point of view, a more immediate impact on deaths from lung cancer is achieved by persuading adult smokers to quit than in attempting to convince adolescents not to start smoking [56,57]. Although individuals can be convinced to give up smoking (and adolescents persuaded not to start), this is very difficult in the absence of reinforcing social pressures to make smoking unattractive and legislative framework to make smoking expensive and difficult. The opposing pressures (agricultural and finance ministries, tobacco companies) are enormous.

Because of the huge load of lung cancer, the continuing elevated risk in ex-smokers, and the poor results of treatment, early detection by screening seems an important potential approach. Screening for lung cancer by regular chest X-ray examination has been shown to be capable of detecting smaller cancers than those appearing in symptomatic individuals, with a resulting improvement in survival. Although this seems an encouraging finding, the results of five trials of screening are quite unequivocal in demonstrating that there is no benefit in terms of mortality in the screened populations [58]. The beneficial effects seem to be a combination of lead-time bias and 'overdiagnosis' of lung tumours in smokers who have a high risk of death from competing causes. The ability of spiral computed topography to detect small, asymptomatic lung cancers in heavy smokers aged over 60 years [59] has, however, rekindled interest in the potential of mass screening.

2.2. Breast cancer

2.2.1. Burden 2000

The second most common cancer in the world today, and by far the most common cancer in women, there are 999 000 new cases of breast cancer each year (about 22% of cancers in women) and 375 000 deaths. More than half of the cases are in industrialised countries—about 335 000 in Europe and 195 000 in North America, for example—and the disease is not yet as common among women in developing countries, although incidence is increasing. The country with the highest incidence is The Netherlands (ASR of 90.2), but there are populations within the US—e.g. white women in California—with age-adjusted incidence rates of 100 or more [5]. Overall, the US incidence rate is estimated at 86.9. High rates are also observed in Europe, Australia and New Zealand, and in the south of South America, especially Uruguay and Argentina. In contrast, low rates are found in most African and Asian populations, although they are increasing, and in some Asian populations they are already the same as in Southern Europe and, in some cases (e.g. the Philippines), even higher (Fig. 11).

Survival from breast cancer in Europe is 91% at 1 year and 65% at 5 years [17]. Stage of disease at diagnosis is the most important prognostic variable. For the SEER registries in the USA, 5-year survival for localised cases is 96.8%, while for cases with metastases it is only 20.6% [16]. Even in developing countries, the differences by stage at diagnosis are very marked [15]. Because of this relatively good prognosis, breast cancer is the most prevalent cancer in the world today; there are an estimated 3.7 million women alive who have had breast cancer diagnosed within the last 5 years (compared with just 1.3 million survivors—male or female—from lung cancer). Trends in survival show clear improvement over time.

The risk of breast cancer increases with age, but the rate of this increase slows down at approximately 50 years. The reason for this is the onset of the menopause with the very different hormonal environment afterwards, characterised by a lower level of oestrogens. The curves for different populations may, however, vary considerably, particularly after the menopause, when the slopes for low risk countries can be quite flat or even negative (Fig. 12). This phenomenon is observed when there is a progressive increase in risk from one generation (or birth cohort) to the next, which gives the impression of falling incidence on a simple curve of incidence versus age.

2.2.2. Risk factors

Most of the international and inter-ethnic differences in incidence of breast cancer are the consequence of differing environmental exposures/lifestyle. Studies of migrants show changes in risk following migration—for example, a rise in risk of breast cancer in populations from European countries at relatively low risk (Italy, Poland) occurs after migration to Australia, particularly if they migrate as children [60,61]. Studies comparing the risks in migrants and their offspring (particularly among Asians migrating to the USA) demonstrate that

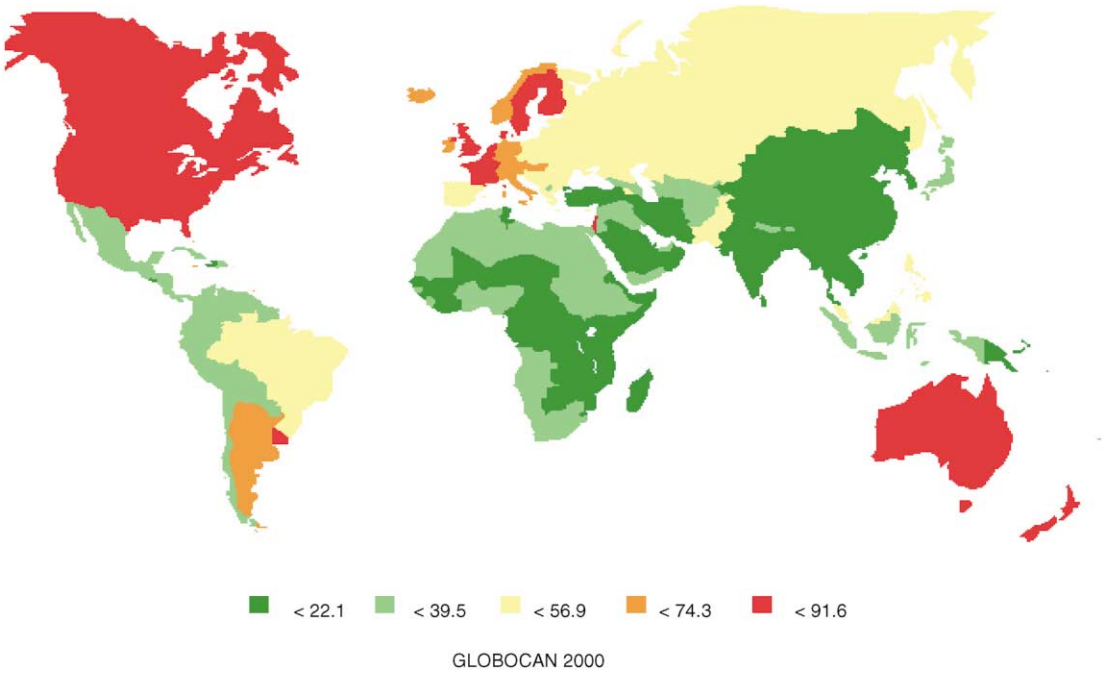


Fig. 11. Incidence of breast cancer: age-standardised rate (world) (all ages).

there are major increases in risk between first, second and third generations [62].

Risk of breast cancer incidence is associated with higher socio-economic status (as estimated by such factors as income, education, housing, etc.). Differences in mortality are partly due to poorer survival in lower social classes [63,64], and, for incidence, most of the gradient can be explained by the differing prevalence of known risk factors between social classes. In the USA, for example, the variation in risk by educational level or annual income is almost entirely explained by the differential distribution of factors such as parity, age at menstruation and menopause, obesity, height and alcohol consumption [65].

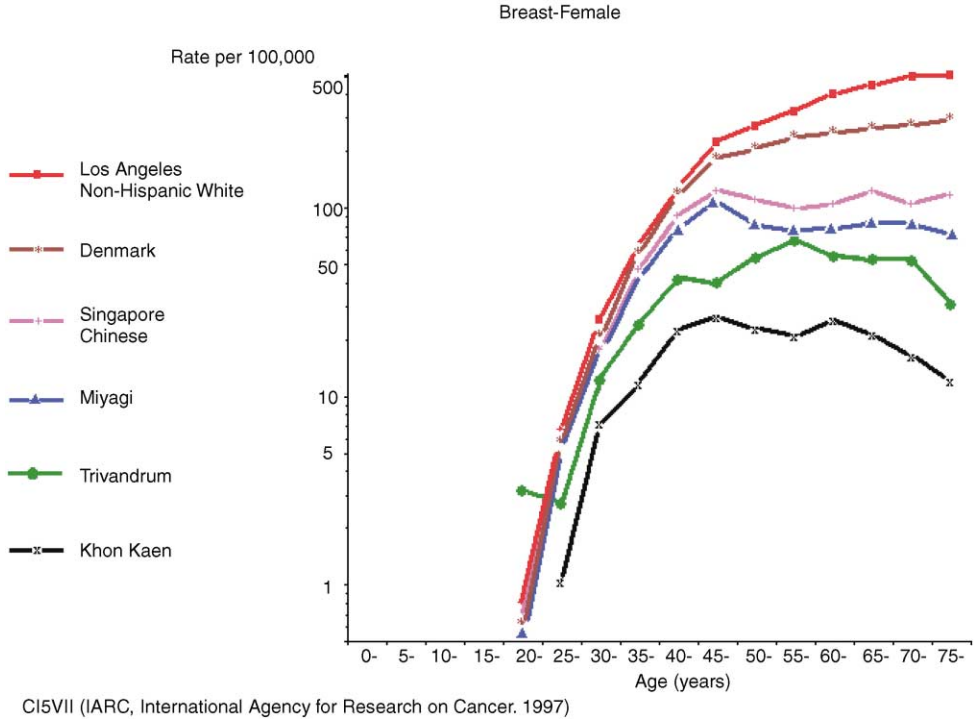


Fig. 12. Trends in breast cancer incidence by age in different populations.

The most important factors influencing risk of breast cancer are reproductive and hormonal factors; risk is increased by early menarche, late age at first birth, low parity and late menopause. All of these reflect a hormonal pattern with exposure to high levels of endogenous oestrogens, in particular free oestradiol. The possible effects of oral contraceptives have provoked a lot of concern. In fact, there is a small but detectable increase in risk in women taking combined oral contraceptives, but this diminishes when contraception ceases and, after 10 years, none of the excess risk remains [66]. Similarly, post-menopausal oestrogen, as hormone replacement therapy (HRT), increases risk slightly (1.5- to 2-fold) in long-term users [67], while a combined regimen of oestrogen and progestin has been shown to be associated with greater increases in risk than oestrogen alone [68].

The possible role of diet, in particular dietary fat, was suggested by observations of a strong correlation, at international level, between mortality from cancer of the breast and *per capita* intake of dietary fat [69,70]. The association remains when cancer incidence is studied and when other variables are introduced into the regressions [71]. However, in case–control and cohort studies of individuals, the association has never been conclusively demonstrated [72]. Obesity after menopause increases risk of breast cancer by 2% per unit BMI [73]. The effect of large weight gains after the age of 18 years has been shown to be a strong independent risk factor for breast cancer compared with preservation of constant body weight [74].

It remains possible that diet early in life (e.g. before or around menarche) is important, perhaps by influencing age at menarche. This would be consistent with migrant data which suggest that environmental change at a young age is important in modifying risk, although there is no direct evidence for an important role of diet during adolescence [75]. Alcohol intake has been shown to increase the risk [76–79].

The relatives of breast cancer cases are at increased risk of the disease. The risk is highest among relatives of young breast cancer cases. Three genes conferring dominant susceptibility to breast cancer have been mapped. *BRCA1*, on chromosome 17q, increases susceptibility to both breast and ovarian cancer. *BRCA2* has been localised to chromosome 13q. Germline mutations in the *TP53* gene also confer a high risk as part of the Li–Fraumeni syndrome. The frequency of carriers of *BRCA1* in Western populations can be estimated as about 1:800. This implies that around 2% of breast cancers would be due to *BRCA1*, though the percentage would be 10% below the age of 40 years [80]. In addition to these major susceptibility genes, it is quite probable that genes involved in the metabolism of oestrogens exist in different forms (polymorphisms) and confer a differential risk of disease. Candidates are the cytochrome P450c17α gene (*CYP17*), the 17β hydroxysteroid dehydrogenase 1 gene (*HSD 17B1*) and the oestrogen receptor gene (*ER*) [81].

2.2.3. Time trends

In developed countries, incidence of breast cancer is, in general, still increasing at all ages, although there are some exceptions (Fig. 13a). However, trends in mortality from breast cancer are less straightforward and in many countries there is evidence for a decline in death rates in recent years (Fig. 13b). This was first remarked upon in the USA [82,83], but it is also evident in Canada and in some European countries, e.g. the UK, The Netherlands, Denmark and Norway [84].

2.2.3.1. Trends in the USA. Age-standardised mortality has declined abruptly since 1989. Although pre-existing trends in age-specific mortality had suggested quite a clear cohort-specific trend in mortality [85] with, it seems, a maximum in those born around 1920, there appears to have been a period-specific decline in mortality for all age groups after 1989 [86]. Although the cohort-specific changes are quite well related to changes in fertility (nulliparity, or age at first birth) until 1946, the decline in mortality since then is the opposite of what would have been anticipated [82,83,87]. Incidence rates showed a dramatic increase between 1980 and 1986, and have then stabilised. This increase was almost entirely due to localised and, to a lesser extent, *in situ* disease. Survival, for both localised and regional disease, has improved since 1980 for women under 70 years of age.

The early changes in incidence (1980–1986) were almost certainly the result of the widespread screening for breast cancer which was introduced about that time. The mortality fall—beginning some 5 or more years later—is compatible with the effect of screening in detecting early stage cancer, but treatment has become more effective too, as shown by improved survival within stage. Improved treatment for node-positive disease (chemotherapy for menopausal women, tamoxifen for post-menopausal) became established practice in the mid-1980s, and for node-negative patients by the end of the decade.

2.2.3.2. Trends in the UK. For incidence, the most notable change has been an acceleration in the slow increases noted since the 1970s following the introduction of screening in approximately 1988. The age groups most affected are those in which screening has been most intense (50–64 years), as a result of detection of prevalent cancers during the first screening round [88]. This should reverse once this first screening is over. For mortality, there has been a recent decline in age-standardised rates. Examined by age, it seems that declines started first in younger women (born since around 1930). Hermon and Beral [84] suggest that this is related

to changes in birth-cohort-specific fertility patterns, although the decreases in mean age at first birth and proportion of childless women at age 40 years are rather small. In any case, the cohort-specific incidence changes do not correspond at all well to cohort-specific trends in fertility [89]. Recently—since approximately 1985 or so—there has been a decline in mortality in all age groups, a change which is too recent to ascribe to screening. A more likely explanation is that it is the result of improvements in therapy, as in the USA. Sur-

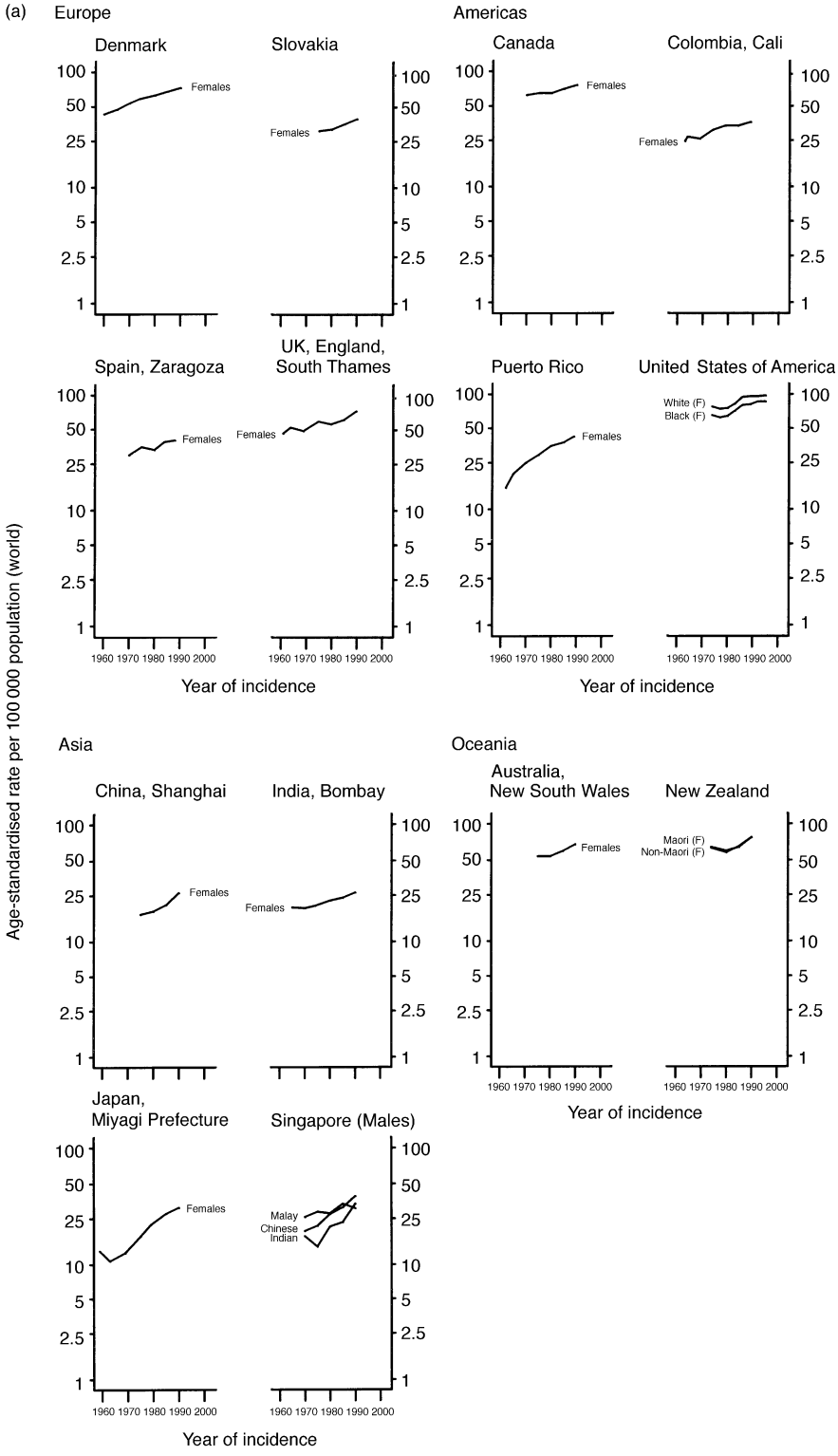


Fig. 13. Female breast cancer: (a) incidence trends (source: CI5/SEER); (b) mortality trends (source: WHO/NCHS).

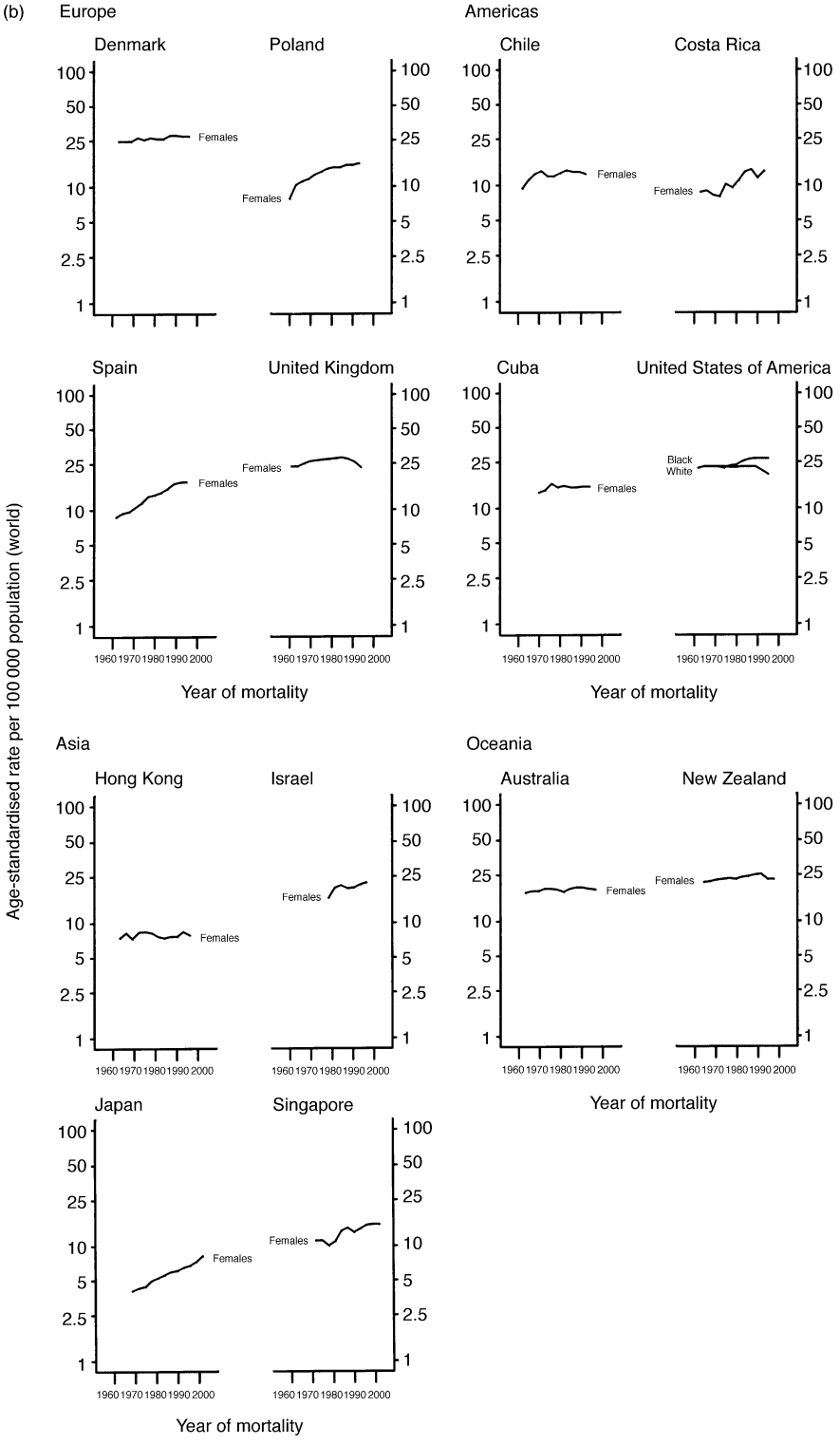


Fig. 13. (*continued*).

vival in the UK from breast cancer improved at almost 3% a year between 1978 and 1985 [90].

2.2.3.3. Other European countries. In Italy, as in France, there has been a rise in incidence overall and a possible reduction in mortality in younger generations (since 1945 or so), but little evidence that screening has had an effect on mortality. In Sweden, age-adjusted incidence rates increased progressively until 1990, but have declined since then [91]. In women aged 50–69 years,

there was a large increase in incidence between 1985 and 1990, followed by a fall; this is quite compatible with the introduction of mammographic screening at this time. However, although nationally the changes in mortality rates (to 1992) were rather modest [92], there are some differences by county which could be explained by the effect of mammographic screening [93]. In Finland, mortality has been traditionally much lower than in the other Nordic countries, but it has gradually caught up and is now only slightly below that in Norway and Sweden. However, it does appear that rates have declined in the screening age groups in the 1990s.

2.2.3.4. Japan. Breast cancer remains relatively rare in Japan, but the rates of incidence and mortality are increasing quite rapidly between successive generations. There are many possible explanations—decreasing age at menarche, increasing age at menopause, decreasing fertility and increasing age at first birth, and increases in height and weight [94]. Since 1975, the increase in incidence has been larger than the increase in mortality, indicating an improvement in survival.

2.2.3.5. Developing countries. For almost all countries where adequate time series can be assembled, increases in breast cancer incidence and mortality are present, often more marked in younger generations of women [95]. Reported increases were 1% per year between 1964 and 1985 in Bombay [96], 2.7% per year in Shanghai between 1972–1974 and 1992–1993 [97] and 3.6% per year in Singapore between 1968 and 1992 [98]. An exception may be the relatively high-risk populations in southern South American countries like Uruguay and Chile, where the observed mortality rates in younger women have been more or less constant [95]. The mortality data from Hong Kong do not suggest any increases in this population (Fig. 13b), and there are declines in the mortality rates of younger women.

2.2.4. Prospects for prevention

For the time being, the only proven strategy which is effective is early detection by mammographic screening. Large-scale randomised trials have shown that, in women aged 50–64 years, regular mammography can reduce mortality by approximately 30%. There is no consensus at present on the benefit to younger women. It seems quite probable that the results obtained as a community service will be inferior to those obtained in the circumstances of a formal trial (even though mammographic technology is improving), so that the results in practice may be inferior. The large investments needed to ensure regular population screening will mean that it is not a realistic option for many countries. In the developing world, detection by clinical breast examination may lead to a worthwhile downstaging of the disease. A reduction in mortality using this technique has not been demonstrated, but this procedure is used for mass screening in Japan where a case–control study has suggested a positive effect [99]. Breast self-examination (BSE) has intuitive appeal since it should result in earlier diagnosis and more effective treatment, if practised regularly. However, it has proved to be difficult to demonstrate a beneficial effect on mortality rates.

2.3. Stomach cancer

2.3.1. Burden 2000

Until recently, stomach cancer was the second most common cancer worldwide, but now, with an estimated 974 000 new cases per year in 2000 (almost 10% of new cancer cases) it is in third place behind cancer of the breast. It is the second most common cause of death from cancer (734 000 deaths annually). Almost two-thirds of the cases occur in developing countries. The geographical distribution of stomach cancer is characterised by wide international variations. High-risk areas include Japan, Central and South America and Eastern Asia; however, significant differences are observed even within these areas. Incidence rates are low in Southern Asia, in North and East Africa, and in North America (Fig. 14). It is worth noting that, contrary to popular belief, the incidence in Central Africa is not particularly low. Incidence in men is twice that in women in both high- and low-risk countries, although close inspection of age-specific incidence data shows that rates in women often exceed those in men in the youngest age groups (under age 40 years). The majority of gastric cancers are adenocarcinomas, which may be further distinguished as intestinal and diffuse subtypes [100]. Intestinal adenocarcinoma predominates in the high-incidence areas (particularly in males and in older age groups) [101], and this subtype is responsible for most of the international variation.

2.3.2. Risk factors

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. The change is quite gradual and seems to depend on the age at migration. In Japanese migrants to the USA, there is quite a substantial fall in the risk between the migrant generation and US-born Japanese [102]. These data fit with observations concerning the importance of childhood environment in determining risk [103].

There is convincing evidence that diets high in vegetables and fruit protect against stomach cancer [79]. Diets high in salt probably increase risk. There is good evidence that refrigeration of food also protects against this cancer by facilitating year-round consumption of fruit and vegetables and probably by reducing the need for salt as a preservative. Vitamin C, contained in

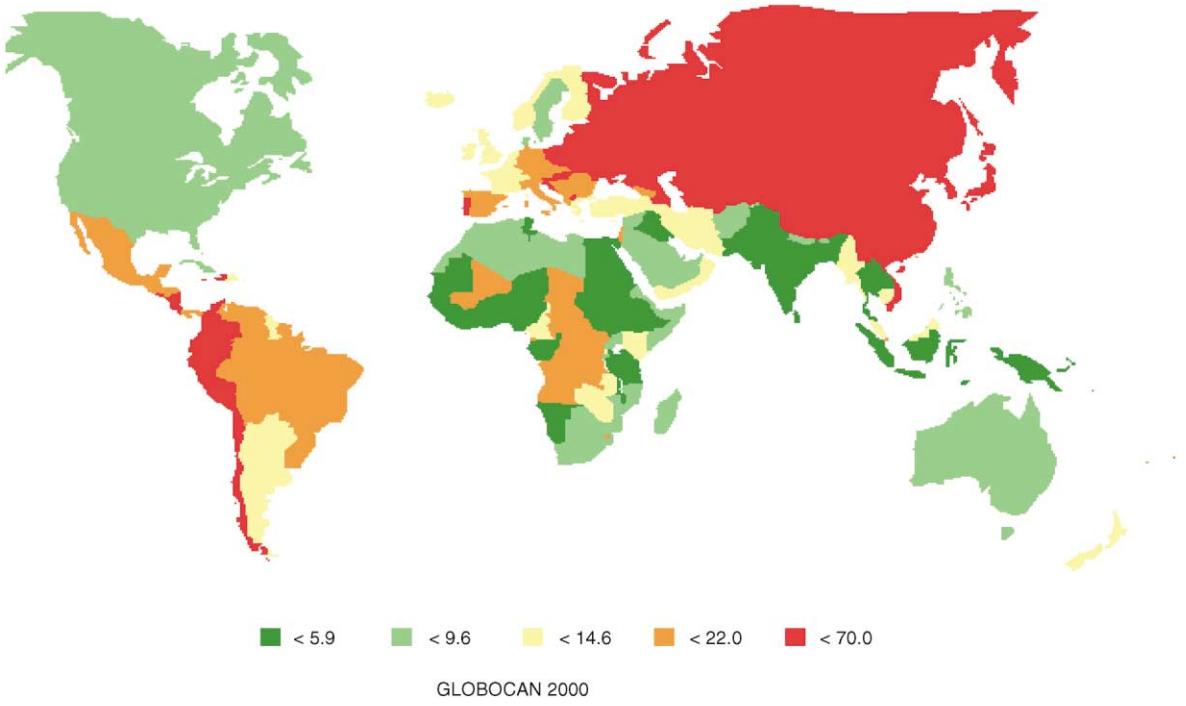


Fig. 14. Incidence of stomach cancer: age-standardised rate (world)— male (all ages).

vegetables and fruits and other foods of plant origin, is probably protective, and so too are diets high in whole-grain cereals, carotenoids and also green tea. Case–control studies of Chinese and Italian populations have indicated garlic and other allium vegetables may reduce risk [104,105]. Conversely, monotonous diets high in starchy food pose an increased risk, probably because they are deficient in the protective dietary constituents. Many studies suggest a small increase in risk (about 2-fold) in smokers, but alcohol does not affect risk, other than at the gastric cardia.

Helicobacter pylori infection has been accepted as being carcinogenic for humans [106,107]. The evidence is largely based on sero-epidemiological studies and the strength of the observed association is rather weak, particularly in developing countries. The prevalence of *H. pylori* infection in the general population is very high and it is clear, therefore, that other cofactors need to be considered such as the possibility that only some strains are involved in the carcinogenic process and/or the interaction with other factors [108–110]. The size of the risk conferred by *H. pylori* has been evaluated in prospective studies where *H. pylori* infection is measured prior to the onset of cancer (and, ideally, of any conditions which are intermediaries in the pathway leading to cancer, such as atrophic gastritis). A pooled analysis of nine such studies, in which *H. pylori* infection was evaluated by serology (anti-HP antibody), suggested an odds ratio (Mantel–Haenszel estimate) of 2.1 (95% CI: 1.6–2.7) [111]. In general, odds ratios increase with the interval between testing for anti-HP and diagnosis of gastric cancer.

International surveys [112,113] and the control series of retrospective studies (reviewed in Ref. [114]) indicate that the proportion of the population infected is large in developing countries, 80–90%; infection is contracted at a young age and persists throughout life. Acquisition is favoured by crowding/interpersonal contact, and hence is linked to low socio-economic status. As noted earlier, migration studies imply that the risk of gastric cancer is determined in childhood and changes relatively little following migration in adult life.

In developed countries, prevalence is lower and is maximum in older birth cohorts, suggesting that improved living conditions of young birth cohorts prevent the infection.

The mechanism of action of *H. pylori* is probably through causing superficial, and later atrophic, gastritis, and probably some strains of the bacterium are more active in this respect than others. Several genotypic markers are associated with elevated risk. Infection with a cagA-positive strain, for instance, greatly increases the risk of peptic ulcer disease and gastric cancer [115]. Genetic susceptibility may modify the response to *H. pylori*—a recent study has shown that *interleukin-1* gene cluster polymorphisms are associated with an increased risk of gastric cancer [116]. Because of the high prevalence of infection, *H. pylori* may be responsible for causing around 40% of all gastric cancer cases worldwide [111].

2.3.3. Time trends

The main epidemiological feature of gastric cancer is the steady decline observed in most affluent countries in the last 50 or more years [117,118]. Time trends in developing countries are less well documented, although in most areas where surveillance through cancer registries or mortality statistics is possible, stomach cancer risk is declining (Fig. 15a and b). As usual, there have been determined attempts to partition the declining rates into birth cohort-specific and period-specific com-

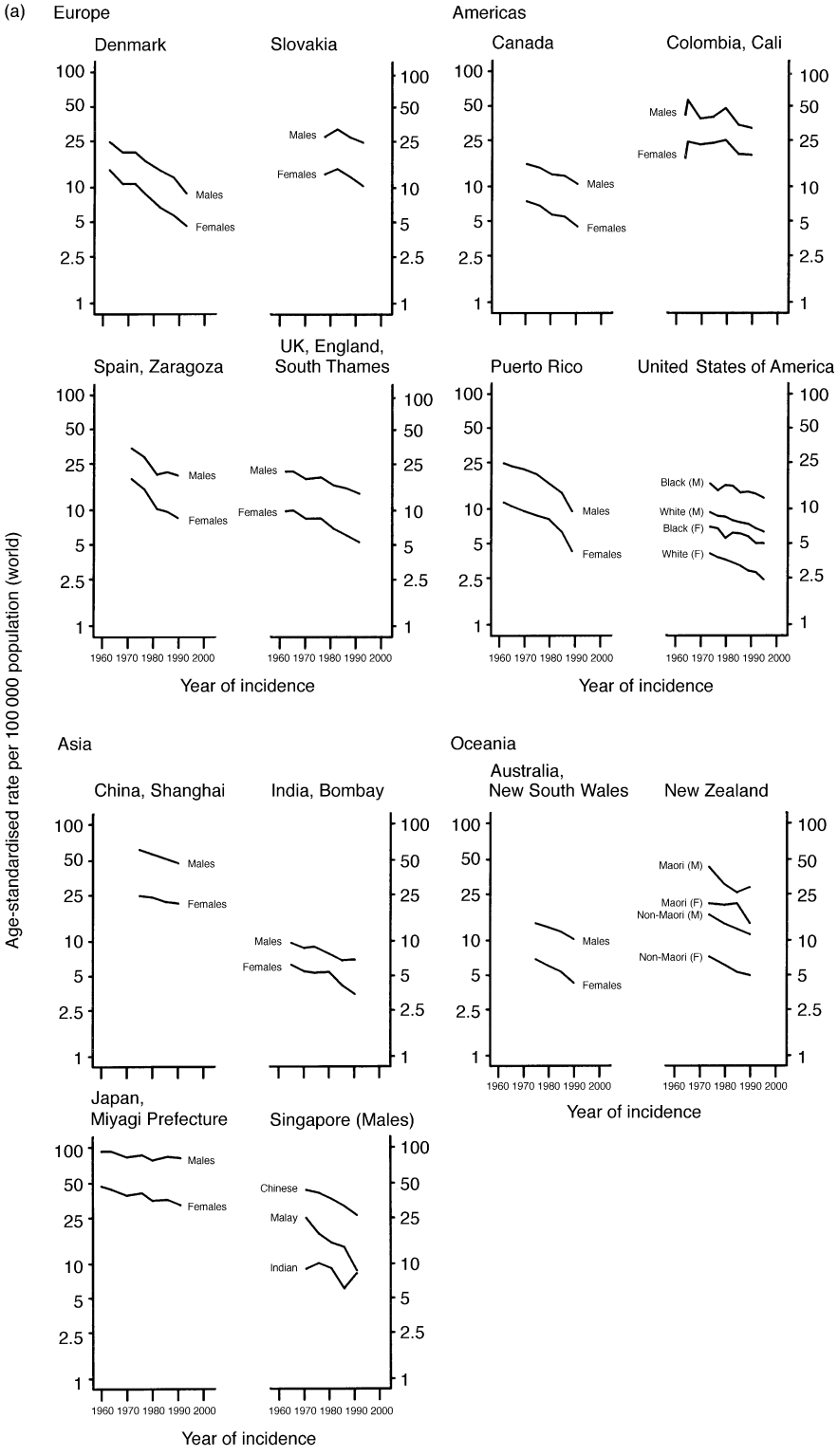


Fig. 15. Stomach cancer: (a) incidence trends (source: CI5/SEER); (b) mortality trends (source: WHO/NCHS).

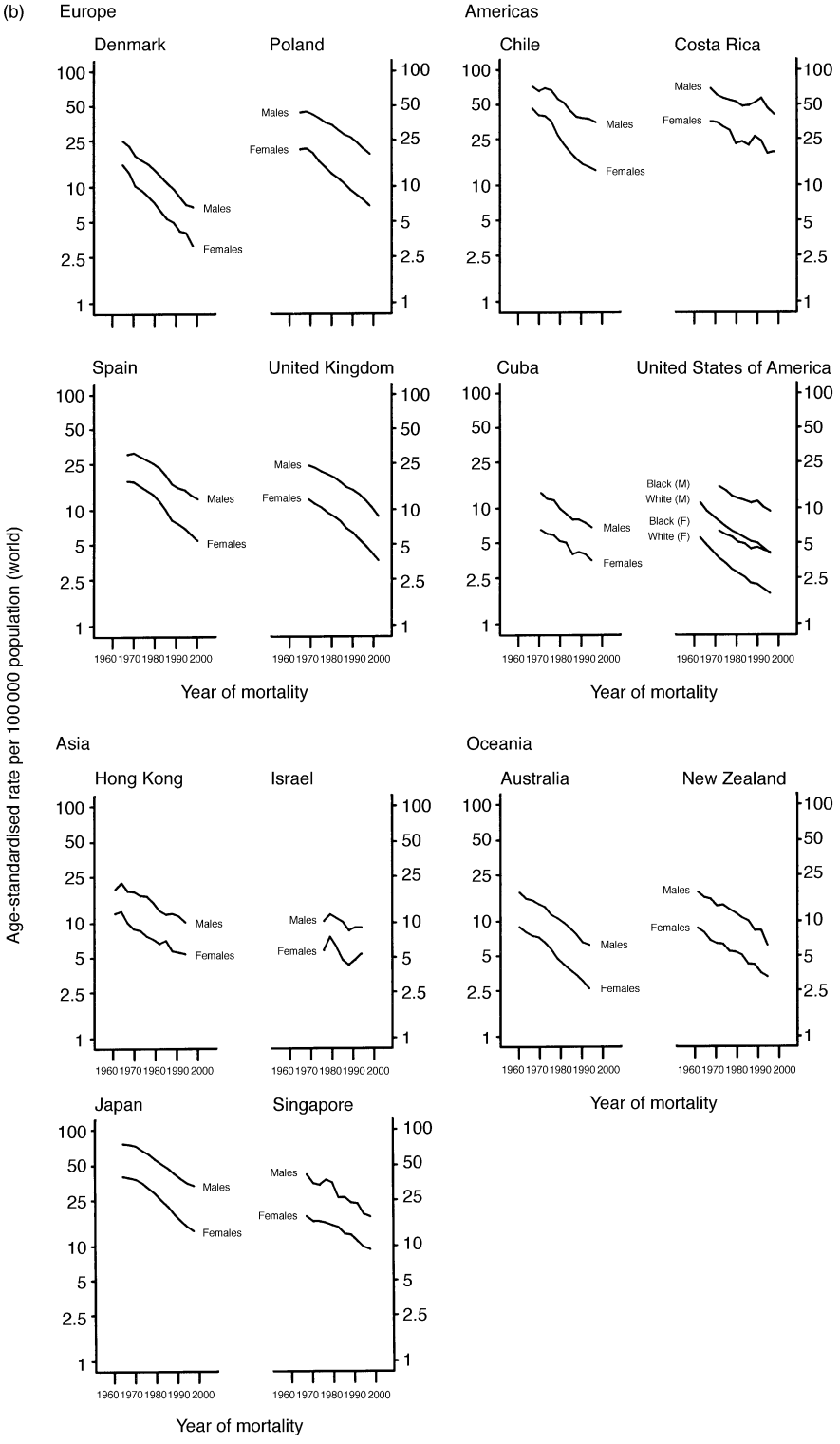


Fig. 15. (*continued*).

ponents. In general, this exercise is unrewarding as, in the face of a rather uniform decline in all age groups, such statistical manoeuvres are not helpful. Some studies have shown that declines in intestinal-type adenocarcinoma are responsible for the decrease of rates with rather little change in the incidence of diffuse-type carcinomas [119–121]. In contrast to the overall decreasing trend, there has been an increase of cancers localised to the cardia which is evident in several populations [122–124]. The reasons for this increase are not known; they

parallel the increased prevalence of Barrett's oesophagus and adenocarcinoma of the lower third of the oesophagus.

The constant decline of stomach cancer in the more affluent countries has been attributed to improved food preservation practices and better nutrition (more vitamins from fresh vegetables and fruits). The most important change may well be the invention of refrigeration for the transport and storage of food, making obsolete salting, smoking and pickling and leading to a lowered consumption of salt. Campaigns to reduce salt intake (as a means of controlling hypertension) have probably also had a beneficial effect, for example in Japan.

The availability of serum specimens from samples of the population over a lengthy time period allows comparison of infection rates with *H. pylori* in successive birth cohorts. There is evidence that, at least in Western countries, there is a progressive decline between successive generations, presumably related to steady changes in the childhood environment [125–127].

2.3.4. Prospects for prevention

The spontaneous disappearance of gastric cancer indicates its preventability. Can this be hastened by preventive interventions? Migrant studies provide powerful evidence that a change in environment can result in a decline in risk. Japanese migrants to Hawaii and the USA show a progressive decline in the high rates of gastric cancer between generations. Studies of Italian migrants to Australia show that the risk of gastric cancer is much lower in those who migrated as children rather than as adults. In his well-known cohort study in Japan, Hirayama [128] not only observed that there was a lower risk of stomach cancer in persons consuming green or yellow vegetables, but also that high-risk subjects who changed their diet could benefit from the protective effects. These observations provide a basis for dietary guidelines for preventing stomach cancer, comprising increasing consumption of fresh vegetables and fruit and reducing the intake of salty and cured foods.

The possible role of *H. pylori* in gastric carcinogenesis has prompted suggestions for large-scale eradication programmes to prevent the disease in individuals found to be infected [129]. However, since infected individuals comprise a large proportion of the population, their individual risk is low and the effectiveness of eradication schedules is questionable, this seems not a very sensible approach. Vaccination against *H. pylori* is more promising, either using therapeutic vaccines to eliminate infection or prophylactic vaccines to prevent it.

Screening for early disease has been mainly by X-ray (photofluoroscopy) followed by gastroscopy and biopsy of suspicious findings and this approach has been widely used in Japan since the 1960s. It is quite resource intensive and the results have been controversial. However, various studies suggest that the procedures do confer a benefit on those screened and mortality rates from gastric cancer have fallen rather more quickly than incidence rates in population groups subjected to screening [130]. A randomised trial of three interventions (amoxicillin/omeprazole, minerals/vitamins and garlic) aimed at reducing precancerous stomach lesions is currently underway in Shandong, China [131].

2.4. Cancer of the colon and rectum

2.4.1. Burden 2000

Colorectal cancer is the fourth most common cause of cancer in the world in both sexes and the second in developed countries. There are an estimated 943 000 new cases in 2000. Mortality is considerably lower (510 000 deaths annually), reflecting the moderately good prognosis. Overall, 5-year survival is of the order of 40–50% and the differences between developed and developing countries are not large. This relatively good prognosis means that colorectal cancer is the second most prevalent cancer in the world (after breast cancer) with an estimated 2.4 million persons alive with colorectal cancer diagnosed in the previous 5 years.

The incidence of large bowel cancer is most frequent in North America, Western Europe, Australia/New Zealand and the southern part of South America (Fig. 16). Incidence is low in Africa and Asia but it is increasing in several populations previously at low risk (see below). These geographical patterns are very similar in men and women. While cancer of the colon occurs with similar frequency in men and women, cancer of the rectum is 20–50% more frequent in men than women in most populations. The geographical distribution of colon cancer and rectal cancer is similar. However, the variation between countries is less for rectum than for colon cancer. Thus, in high-risk populations, the ratio of colon to rectum cases is 2:1 or more (rather more in females) while in low-risk countries rates are generally similar (there is even a slight excess of rectal cancer in India).

Migrant studies indicate that when populations move from a low-risk area (e.g. Japan) to a high-risk area (e.g. the USA), the incidence of colorectal cancer increases rapidly within the first generation of migrants, and Japanese born in the USA have a higher risk than the white population [132]. Almost all cancers are adenocarcinomas arising from the colorectal mucosa.

2.4.2. Risk factors

Epidemiological studies conducted both in developed and developing countries have consistently found a higher risk of colorectal cancer in subjects consuming a diet low in vegetables and in unrefined plant foods (i.e. whole cereals, legumes, etc.). Studies in developed countries have also found that frequent consumption of

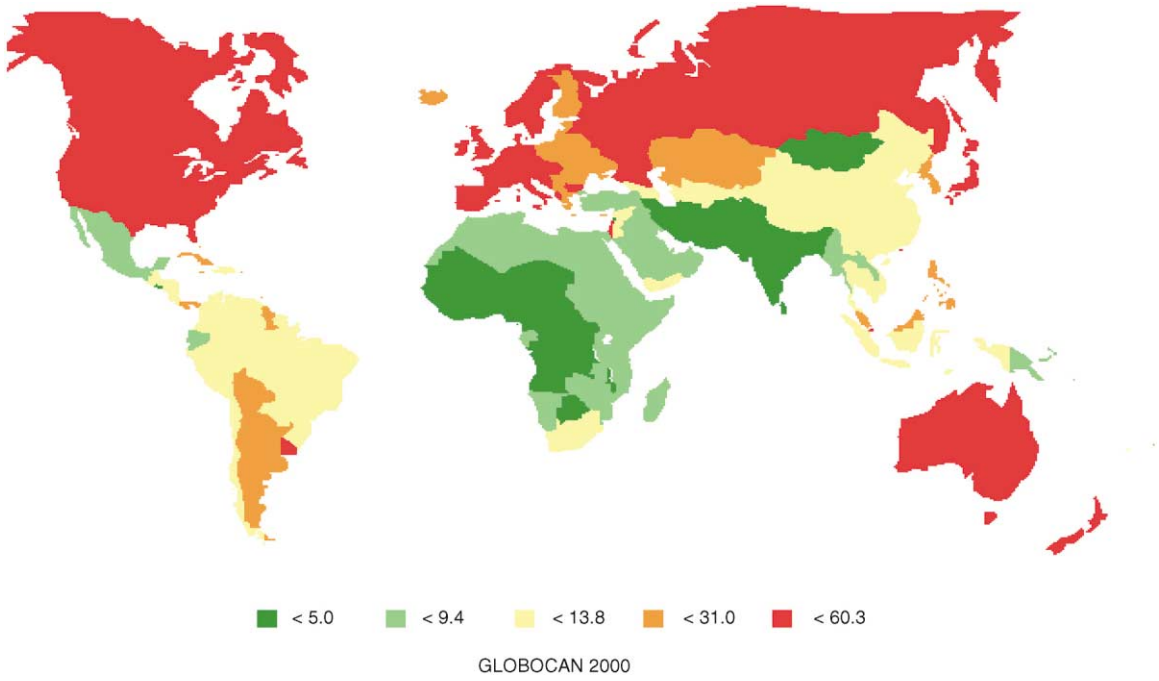


Fig. 16. Incidence of colon/rectum cancer: age-standardised rate (world)—male (all ages).

red meat (beef, lamb, etc.) and alcohol increases the risk, while consumption of fish and poultry has been found to be either unrelated to risk or even associated with a slight reduction in risk [79]. The mechanisms by which a diet rich in vegetables and whole plant foods and moderate in meat may protect against colorectal cancer have been investigated in experimental studies and, although no definite answer is available, they tend to support the epidemiological findings. Several studies suggest that regular physical exercise also protects against development of large bowel cancer, while obesity possibly increases risk.

Established non-dietary causes of colorectal cancer include genetic predisposition (both through the hereditary polyposis (and non-polyposis) colon cancer syndrome and polymorphisms in other enzyme systems), ulcerative colitis and infection with *Schistosoma japonicum*. It is possible that hyperinsulinaemia, as in non-insulin dependent diabetes mellitus, plays a role in the development of colon carcinoma [133]. Aspirin and other non-steroidal anti-inflammatory drugs decrease risk [134]. In post-menopausal women, there is some evidence that HRT may reduce the risk of colon cancer [135].

2.4.3. Time trends

In general, there have been increases in incidence in countries where the overall risk of large bowel cancer is low, while in high-risk countries there have been either stabilisations or decreases in incidence, particularly in the younger age groups (Fig. 17a) [136,137]. For colon cancer, the greatest increases in incidence are observed in Asia (Japan, Hong Kong, Singapore and Israel), as well as in countries of Eastern Europe and in Puerto Rico. In Western Europe and Oceania, the overall (age-adjusted) rates have remained fairly constant except for Spain, where quite large increases have occurred [138]. In the USA, incidence rates in white females have been showing a slight decline for some time, while rates in men were rising until the mid-1980s, since when there has been a decline in incidence in both sexes [139,141]. There has been no similar decline in the black population. Several studies have pointed out that the trends may differ for subsites within the colon. In high-risk countries, there has, in general, been an increase in the incidence of proximal tumours (ascending colon) relative to distal (descending and sigmoid colon) [140,142–145]. However, the reverse was observed in the low-risk populations of Singapore [146], and the increases in proximal and distal disease were similar in Shanghai [147]. For rectal cancers, the countries with the largest increase in incidence are in Eastern Europe and Japan. For mortality, the pattern is similar (Fig. 17b), with an increase for countries with a low initial rate (Eastern Europe, Japan and Singapore), small increases or stable rates in countries with moderate rates, and a decrease for high-rate populations (Western Europe and North America) [137,148]. In the USA, there has been a decline in females for many decades (paralleling the decline in mortality), but the rate of decline increased in the mid-1980s, when a decline was also observed in males [139].

The reasons for these changes are certainly multiple. The changes in mortality may be consequent to changes in incidence, to the general improvement in the results

of treatment or, as in the USA [139], they may include the effects of improved early detection, probably due to screening examinations, with consequent decreases in case fatality. It is possible too that the apparent declines in distal cancers (rectum and sigmoid) in some western populations result from detection and treatment of pre-malignant polyps [139,140]. However, the principal cause of the increased risk in the countries of Eastern Europe, Asia or Israel (Jews) is probably 'westernisation' of the way of life, particularly with respect to diet

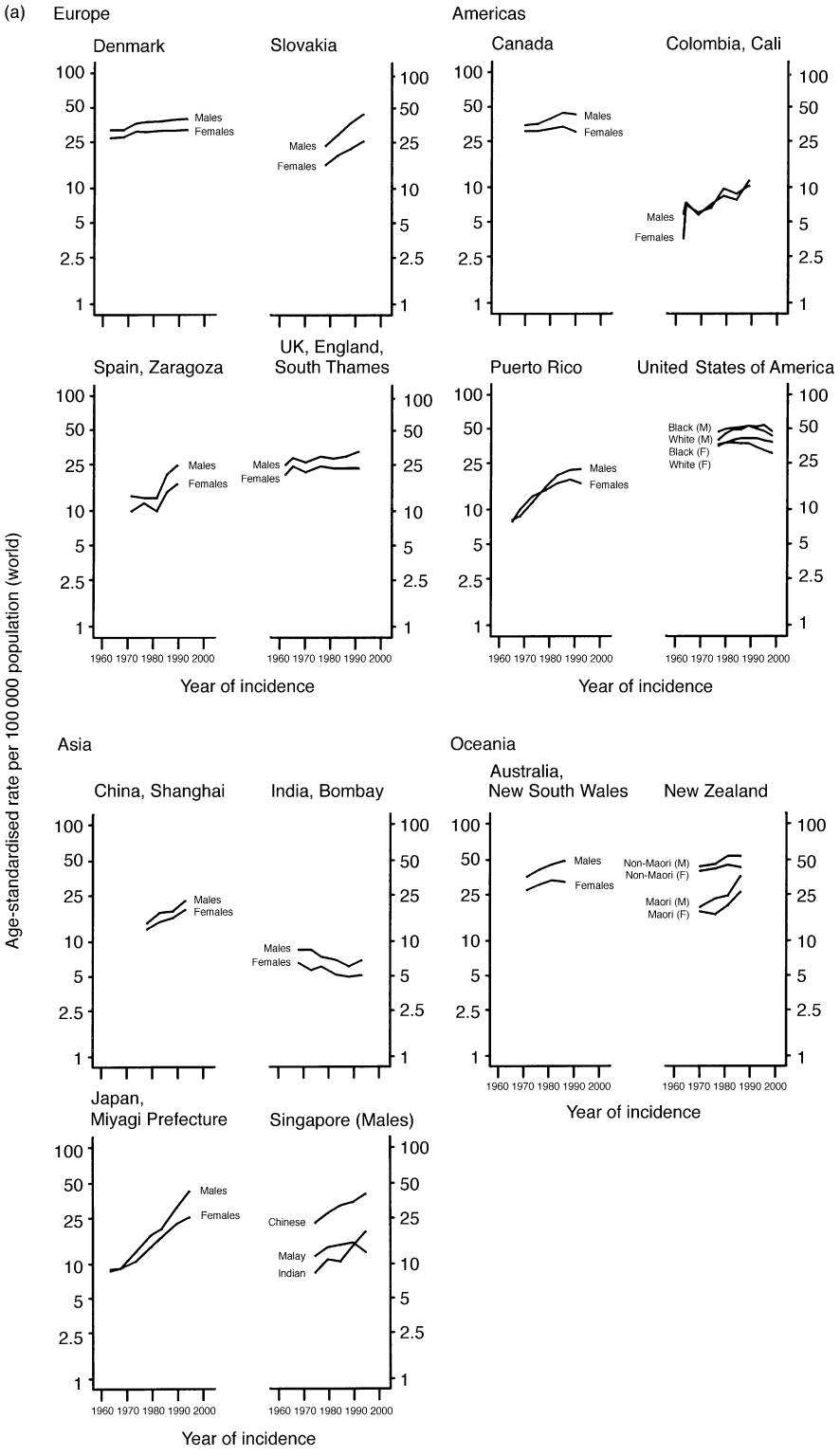


Fig. 17. Colorectal cancer: (a) incidence trends (source: CI5/SEER); (b) mortality trends (source: WHO/NCHS).

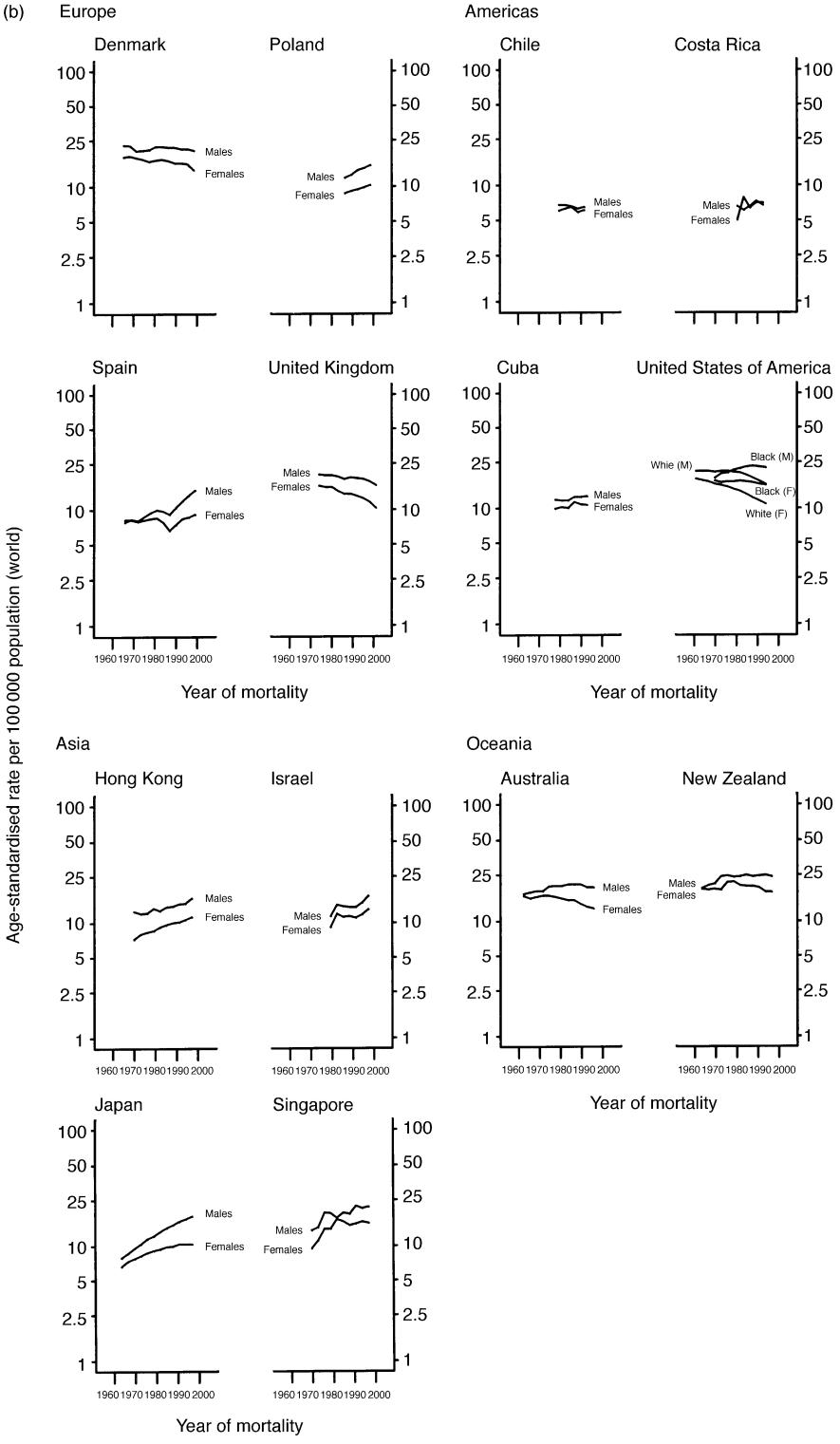


Fig. 17. (*continued*).

[79]. The converse effect, with some improvements in the quality of the diet in younger generations, may explain the observation, notably in the USA [136,149,150], of cohort effects with a decrease of incidence rates concerning younger age classes.

Looking at the evolution of dietary patterns, as reflected in the Food and Agriculture Organization (FAO) food balance sheets [151], it seems that, in the countries of Eastern Europe and Asia, there has been an increase (or stability) in the consumption of foodstuffs

categorised as risk factors for colorectal cancers (red meat and animal fat) and a decrease or stable consumption of protective ones (cereals, vegetables and fruits). For other countries (North America, Western Europe and Oceania), there is no generalised trend of a decreasing consumption of animal fat or red meat (in fact, most Western European countries have seen an increase in consumption except for Switzerland and the UK) but there is an important increase of vegetable and fruit consumption in most of these countries. Such comparisons of trends must be considered with considerable caution, in part because of the approximate relationship between 'food disappearance' which appears in the balance sheets and actual consumption, and the dangers of drawing causal inferences from population averages. However, the overall pattern does seem to fit the hypothesis of change in dietary habits as an explanation for the cancer trends.

For colon cancer, it is in Japan that some of the most dramatic increases in incidence (and to a lesser extent, mortality) are observed. Adoption of a 'western lifestyle' is probably a major factor in this evolution, but it may be that these effects are enhanced by genetic susceptibility [152].

2.4.4. Prospects for prevention

Epidemiological studies strongly suggest that consumption of a diet rich in vegetables and minimally refined plant food and moderate in red and processed meat can reduce colorectal cancer risk. Physical activity and avoidance of obesity are also probably preventive. Early detection of colorectal adenomatous polyps (precursors of colorectal cancer) and of localised cancers can be achieved by a laboratory test consisting of the detection of undigested blood in the faeces or by endoscopic examination of the large bowel. Results from two recent trials investigating whether high-fibre supplements may prevent colorectal cancer by reducing the rates of the recurrence of precursor lesions have however been disappointing, with little evidence to suggest that adenoma recurrence differs in high- and low-fibre groups [153,154].

2.5. Liver cancer

2.5.1. Burden 2000

By 2000, liver cancer was the fifth most common cancer worldwide, responsible for approximately 551 000 new cases (399 000 in men and 153 000 in women). Because of the very poor prognosis, the number of deaths (529 000) is not far short of the number of new cases, and it represents the third most common cause of death from cancer. The geographical distribution of liver cancer is very uneven; 83% of cases occur in the developing countries. 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 (Fig. 18). China alone accounts for 54% of the total cases in the world. The incidence rates are low in developed countries, except for Japan, with the highest incidence found in Southern Europe, especially in Greece.

Liver cancer comprises a variety of different cancers which show distinct epidemiological features. The most frequent subtype in most areas is hepatocellular carcinoma (HCC) and much of the geographical variation seen in Fig. 18 is due to this cancer. Cholangiocarcinoma (CCA), a tumour of the epithelium of the intra-

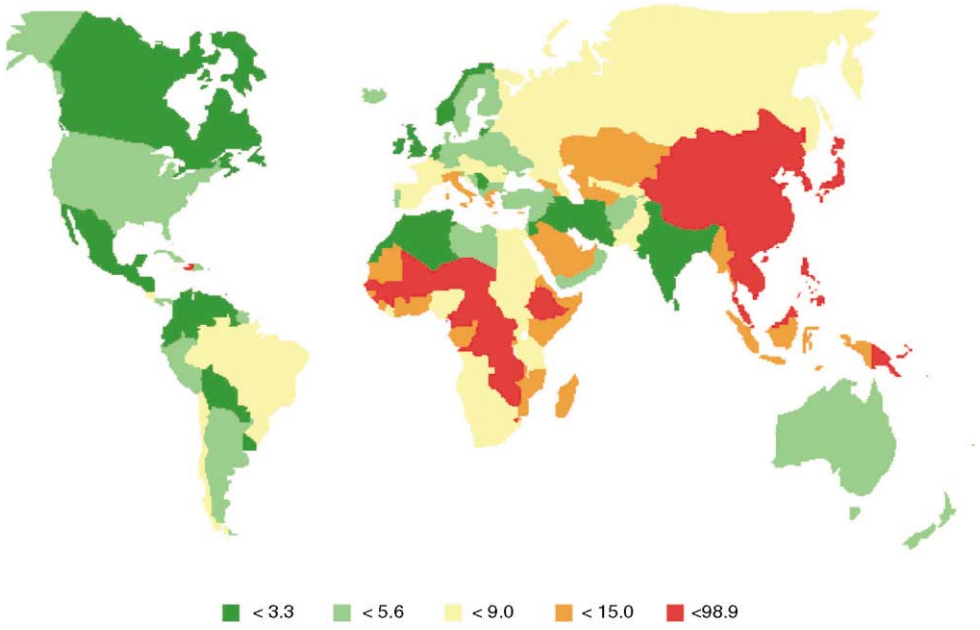


Fig. 18. Incidence of liver cancer: age-standardised rate (world)—male (all ages).

hepatic bile ducts, is generally less frequent, comprising approximately 10–25% of liver cancers in men in Europe and North America, but a rather larger proportion than this in women. This is because the incidence rates of CCA are rather similar in males and in females, while rates of HCC are some 2–3 times higher in males in low-risk areas, and more than this—up to 5-fold—in high-incidence populations (Eastern Asia and Africa). The incidence of CCA shows rather little variation worldwide, with rates in males between 0.5 and 2.0, rather lower in females [155,156], although incidence in some local areas is high (North East Thailand) or moderate (parts of China).

Other types of liver cancer are much less common. Hepatoblastoma is a tumour of young children, with 80% of cases occurring in the first 5 years of life. There is very little geographical variation in incidence. Malignant vascular tumours (haemangio-sarcomas) are even more rare and principally affect adults.

2.5.2. Risk factors

2.5.2.1. Hepatocellular carcinoma. Chronic carriage of the Hepatitis B virus (HBV), as shown by seropositivity for the HBV surface antigen (HBsAg), is associated with an incidence at least 20-fold that of non-carriers. The epidemiological evidence derives from a large number of case–control and cohort studies (at the time of the IARC review [106,107] which classified HBV as carcinogenic to humans, there were 17 cohort studies and 67 case–control studies). In general, cohort studies yield rather greater relative risks than case–control studies because the cases occurring during follow-up of apparently healthy individuals tend to be those detected at young ages, and hence more likely to be related to HBV carrier status.

Prevalence of chronic infection with HBV varies widely in different parts of the world, from 10–15% in sub-Saharan Africa, and East and South East Asia, to less than 1% in Western Europe (Fig. 19). Because of this, the proportion of liver cancer cases attributable to HBV infection varies from less than 10% (North America, Northern and Western Europe), to two-thirds or more in sub-Saharan Africa, China and South East Asia [111].

HBV infection in sub-Saharan Africa generally occurs during childhood; close personal contact (e.g. between siblings) favours infection. In East and South East Asia, maternal–child transmission at the time of birth is important. In adult life, parenteral and sexual transmission are the most important routes [106,107].

The mechanism of carcinogenesis of HBV is less clear. The virus is not integrated into any specific part of the genome of the host, and some HCCs in HBV carriers do not contain integrated HBV DNA [157]. One possibility is that cell proliferation associated with chronic hepatitis/cirrhosis is the important factor.

More recently, the importance of past infection with the Hepatitis C virus (HCV) has been recognised [106,107]. Case–control studies suggest that the presence of antibody to HCV is associated with a relative risk of approximately 25. However, the prevalence of antibody-positive subjects in the population is rather low in most countries (prevalence seems to be highest in Japan, Egypt and parts of sub-Saharan Africa). As a result, although the relative risk of HCV is high, the proportion of cases of liver cancer due to the virus is rather less than for HBV—perhaps 20–25% worldwide. Hepatitis-C is transmitted mainly by blood and blood products, and most infection worldwide seems to the consequence of blood transfusion or injections with unsterilised equipment. It seems that HCV causes liver cancer through causing chronic hepatitis and cirrhosis, both known as precursors of liver cancer through the intense hepatocyte regeneration occurring in these conditions.

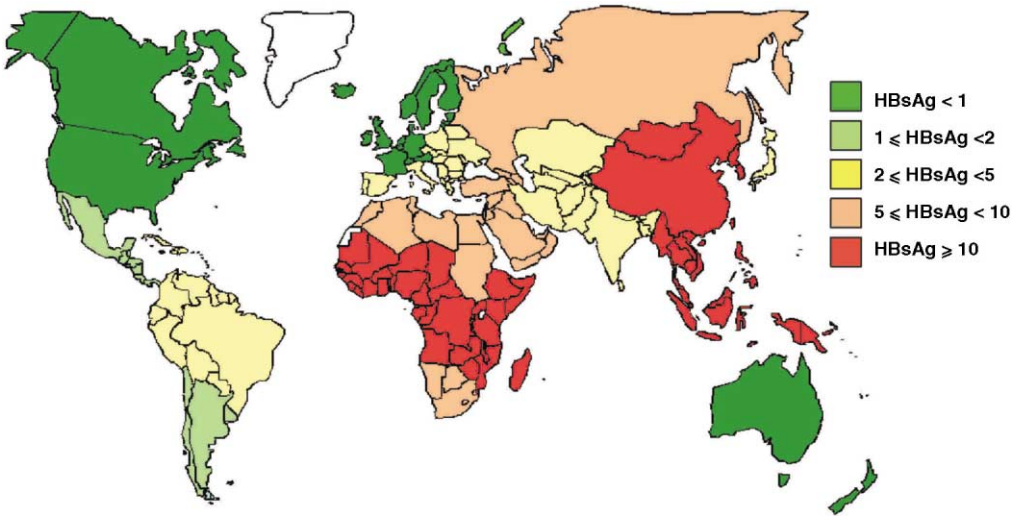


Fig. 19. % Prevalence of HBsAg carriers worldwide. HBsAg, Hepatitis B virus surface antigen.

The effects of combined infection with HBV and HCV are not clearly defined. A meta-analysis of case–control studies suggests that the combined effect lies somewhere between an additive and multiplicative effect [158], and one cohort study [159] is also compatible with this finding. Overall, 77% of the cases worldwide are attributable to infection with one of the hepatitis viruses; the attributable fraction is 85% in developing countries and 54% in the more affluent areas of the world.

Aflatoxin, a toxin produced by moulds of the Aspergillus species which infect stored grains and nuts, has long been known to cause liver tumours in animals [160]. The evidence for a possible role in humans came first from ecological studies, comparing environmental aflatoxin (measured in foodstuffs) with liver cancer incidence rates in different geographical locations. Measurement of aflatoxins in body fluids and tissues provided a more accurate measure of dietary exposure. The first and largest correlation study to utilise a biomarker of aflatoxin exposure (a composite measure of urinary aflatoxin metabolites) found no association between the biomarker and liver cancer in 48 counties of China [161]. However, the biomarker used was later shown not to reflect dietary aflatoxin intake on an individual level. The ability to measure aflatoxin bound to cellular macromolecules, including DNA and proteins in urine and serum, has sharpened the measure of exposure, providing a biomarker which does reflect individual intakes of aflatoxin [162]. Using urinary aflatoxin N7-guanine as a marker in a cohort study carried out in Shanghai, People's Republic of China, an increased risk of liver cancer was observed in individuals positive for the marker at enrolment compared with those that were negative [163]. Furthermore, there appeared to be a multiplicative interaction with chronic HBV infection (also a clear risk factor in this study), suggesting a different mechanism of action from the virus.

Recent work has focused on the role of genetic polymorphisms in modifying the risk of aflatoxin exposure. Chen and colleagues [164] observed that, among HBsAg carriers, the risk of liver cancer was related to serum AFB-albumin levels, but only in individuals with the null-genotype for the enzymes glutathione S-transferase (GST) M1 and GST T1, normally responsible for conjugation and detoxification of aflatoxin. In a case–control study in China [165], mutation in one or both alleles of the gene coding for epoxide hydrolase (EPHX)—another detoxifying enzyme—had a stronger association with HCC (OR 3.3) than did the null genotype of GSTM1 (OR 1.9).

Some liver tumours have a highly specific point mutation involving a G:C to T:A transversion in codon 249 of the *TP53* tumour-suppressor gene [166,167]. This mutation appears to be more frequently observed in populations where aflatoxin intake is thought to be high. In addition, the same base pair has been shown to be a hot spot for mutation by aflatoxin in hepatocytes *in vitro* [168] and to be more frequently mutated in non-tumorous liver tissue of patients originating from supposed high aflatoxin exposure regions than those from low exposure regions [169].

Excessive alcohol consumption is an important cause in western countries; in its evaluation in 1988, IARC [170] reviewed four cohort studies and six case–control studies and considered that the evidence was sufficient to indicate a causative association. Since that time, there have been further studies confirming the association, including cohort studies in Taiwan [164] and Japan [171]. Studies in Taiwan have suggested that the effects of alcohol and HBsAg positivity are independent and have a multiplicative effect [164], and that the same may be true for alcohol and infection with HCV [172]. Alcohol is believed to act through its action as a hepatotoxin, promoting liver cirrhosis and regeneration/rapid cell division, favouring oncogenic mutations.

Because of the close association of alcohol consumption and tobacco smoking, it has been difficult to establish whether tobacco smoking plays an independent role in the aetiology of liver cancer. In general, the evidence does suggest a weak association, independent of alcohol and HBV infection [173], although the effect is rather small (approximately a 3-fold increase in risk).

Use of oral contraceptives is well known to increase the risk of hepatic adenomas. The evidence is less convincing for HCC, although several studies suggest that there is an increased risk which is higher with more prolonged use [174], although no association has been observed in countries where HBV is endemic [316].

Haemochromatosis, a relatively common genetic disorder in which there is an increased intestinal iron absorption and tissue iron overload (including the liver parenchyma), is associated with liver cirrhosis and, in up to one-third of cases, liver cancer [175]. Iron overload occurs also in Southern Africa as a result of high intake and, possibly, genetic susceptibility [176]. It also has been associated with an increase in liver cancer risk [177].

A past history of thorotrast injection results in a very high risk of haemangiosarcoma of the liver and also of cholangiocarcinoma, but the risk of HCC is elevated also; Kato and Kido [178] estimated the relative risk as 21. Infection with *S. japanonicum* has been proposed as a risk factor for liver cancer in Japan, but the study quality was weak and the relation uncertain [106,107].

2.5.2.2. Cholangiocarcinoma (CCA). The aetiology of CCA is completely different. While hepatolithiasis, thorotrast and inflammatory bowel disease cause some cases, the most important cause is infection with the liver flukes, *Opisthorchis viverrini* (OV) and *Clonorchis*

sinensis [155,156]. IARC [106,107] concluded that OV was carcinogenic to humans, and *C. sinensis* probably so. *C. sinensis* was originally endemic in Korea, Japan, China and Vietnam. However, it is much less prevalent than it was and cholangiocarcinoma from this cause appears to be relatively infrequent in recent years. This is not the case for OV, the fluke found in North East Thailand. Recent population surveys suggest a continuing high prevalence of infection, and the incidence of liver cancer remains high—87.5 per 100 000 in men in 1992–1994, with 82% of cases being CCA [179]. Results from a recent prospective study of Japanese patients suggest HCV infection may also be a risk factor for CCA [180].

2.5.3. Time trends

Time trend studies are particularly difficult for liver cancer. Changes in the ICD classification meant that the three-digit rubric 155 included gallbladder cancers in the seventh revision (used until about 1965), and "Liver cancer, unspecified as whether primary or secondary" in the ninth revision (after 1980). In addition, mortality data are notoriously difficult to interpret because of the variable inclusion of metastatic liver cancers. Fig. 20a illustrates the incidence trends based on data from CI5 volumes III–VII corresponding to the eighth (volumes III and IV) and ninth revisions (volumes V–VII) of the ICD. Extra caution must be employed in interpreting these rates over time—"liver cancer, not specified as primary or secondary" was excluded from 155 in the eighth revision but included in the ninth revision. Fig. 20b and c shows trends in liver cancer mortality rates for males and females, respectively, based solely on the ninth revision of ICD. The code 155.0 corresponds to "primary cancer of the liver", 155.0–.1 to "primary cancer of the liver and intrahepatic bile ducts", and 155 to "malignant neoplasms of the liver and intrahepatic bile ducts", including "liver cancer not specified as primary or secondary".

Some of the changes shown in Fig. 20a–c have been noted in previous reviews [181,182]. They include the decreasing incidence in Singapore (the rising mortality is an artefact, due to decreasing certification of liver cancer deaths as 'unspecified'), and increases in incidence and mortality in Japan and several Western countries, especially the Nordic countries, the UK and the USA. Increasing mortality rates have also been noted in France [183].

The decline in incidence in Singapore Chinese is similar to that observed in Shanghai [97], and in mortality data from Hong Kong. It may reflect declines in prevalence of infection with HBV. In contrast, the rise in liver cancer incidence and mortality in Japan has been remarked for some time; it has been ascribed to increasing alcohol consumption (in men) [184] and to increasing prevalence of HCV infection [185]. Transmission of the virus, by non-sterile transfusions and injections, was maximum in the years after the Second World War, and the risk of liver cancer in Osaka (which has one of the highest rates in the world) has decreased in successive birth cohorts, born since approximately 1931–1935, along with prevalence of infection with HCV [186].

In Western countries, it is possible that some of the increase in mortality (and incidence) is due to improved detection of small cancers in patients with advanced cirrhosis. However, it is unlikely that increasing alcohol consumption is the explanation since there have been declines in mortality from cirrhosis of the liver in many of the countries experiencing increasing liver cancer mortality [187]. More interest has focused on the possible role of HCV infection, which is likely to become increasingly important as the generations infected (transfusion recipients and drug users) enter age groups at high risk for liver cancer [188,189].

2.5.4. Prospects for prevention

Prevention of chronic carriage of HBV became a reality with the development of vaccines in the early 1970s [190,191]. Early trials suggested that vaccination could prevent transmission of HBV infection from carrier mother by infant to approximately 70–75%. If Hepatitis B immune globin (HBIG) was given with the vaccine in the neonatal period, then 90–95% of the transmission was prevented [192,193].

Two randomised studies were set up to formally establish the effectiveness of vaccination against HBV in preventing liver cancer later in life. They are in the Qidong county, China [194] and in the Gambia, West Africa [195]. It will be many years before results are available. However, follow-up of the vaccinated children does demonstrate that there is a much lower rate of natural infection and a greatly reduced prevalence of chronic HBsAg carriers [196]. In Taiwan, mass vaccination against HBV was introduced in the 1980s, first to neonates born of HBsAg-positive mothers then, in 1984, for all new-borns. By 1994, it was possible to compare liver cancer incidence in children aged 6–9 years born before vaccination was introduced and after. There was a 4-fold difference in incidence [197]. These results are very encouraging, and suggest that vaccination will, indeed, be as successful as hoped.

Measures to control aflatoxin contamination of foodstuffs are important in those parts of the world where it may contribute to the risk of liver cancer. Maize and groundnuts are probably the major sources of aflatoxin in the world; where these form an important part of the diet, farmers may be assisted in constructing food storage facilities which minimise fungal contamination. Consumers can be educated to avoid obviously mouldy grains. A different approach to the prevention of aflatoxin–

glutathione conjugates, which are excreted from the body. Oltipraz is a drug which induces the enzyme GST and in animals (rats) this results in enhanced aflatoxin–glutathione conjugates excreted in the bile, a lowered formation of aflatoxin–DNA adducts in the liver, and inhibits aflatoxin B1-mediated hepatocarcinogenesis. In a small-scale trial in China [198], a relatively large dose of oltipraz has been shown to reduce the level of albumin–aflatoxin adducts in humans. It is doubtful whether this type of chemoprevention will have a practical application in the control of liver cancer, however.

Control of CCA has been based on preventing infection by liver flukes by educational campaigns aimed at

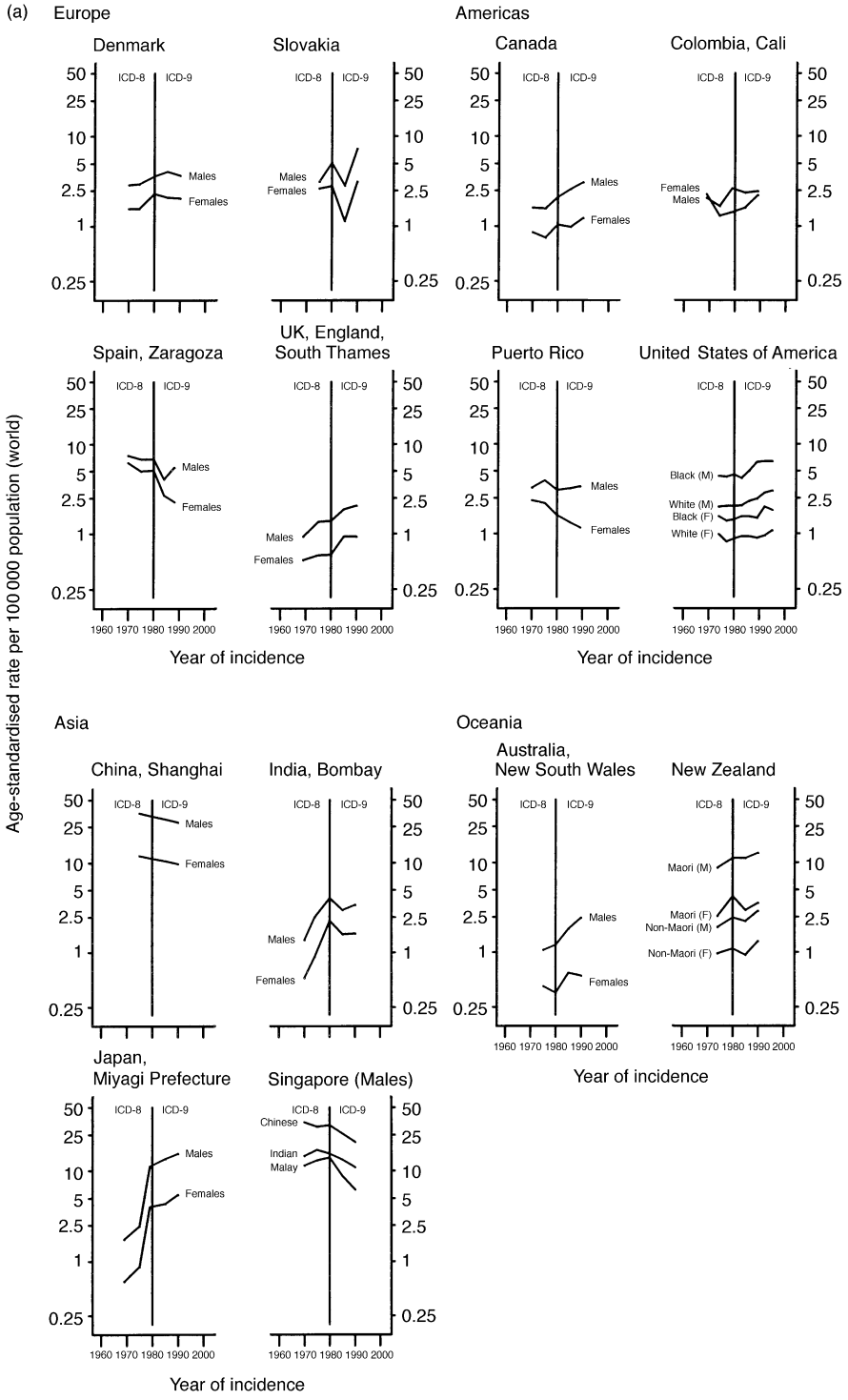
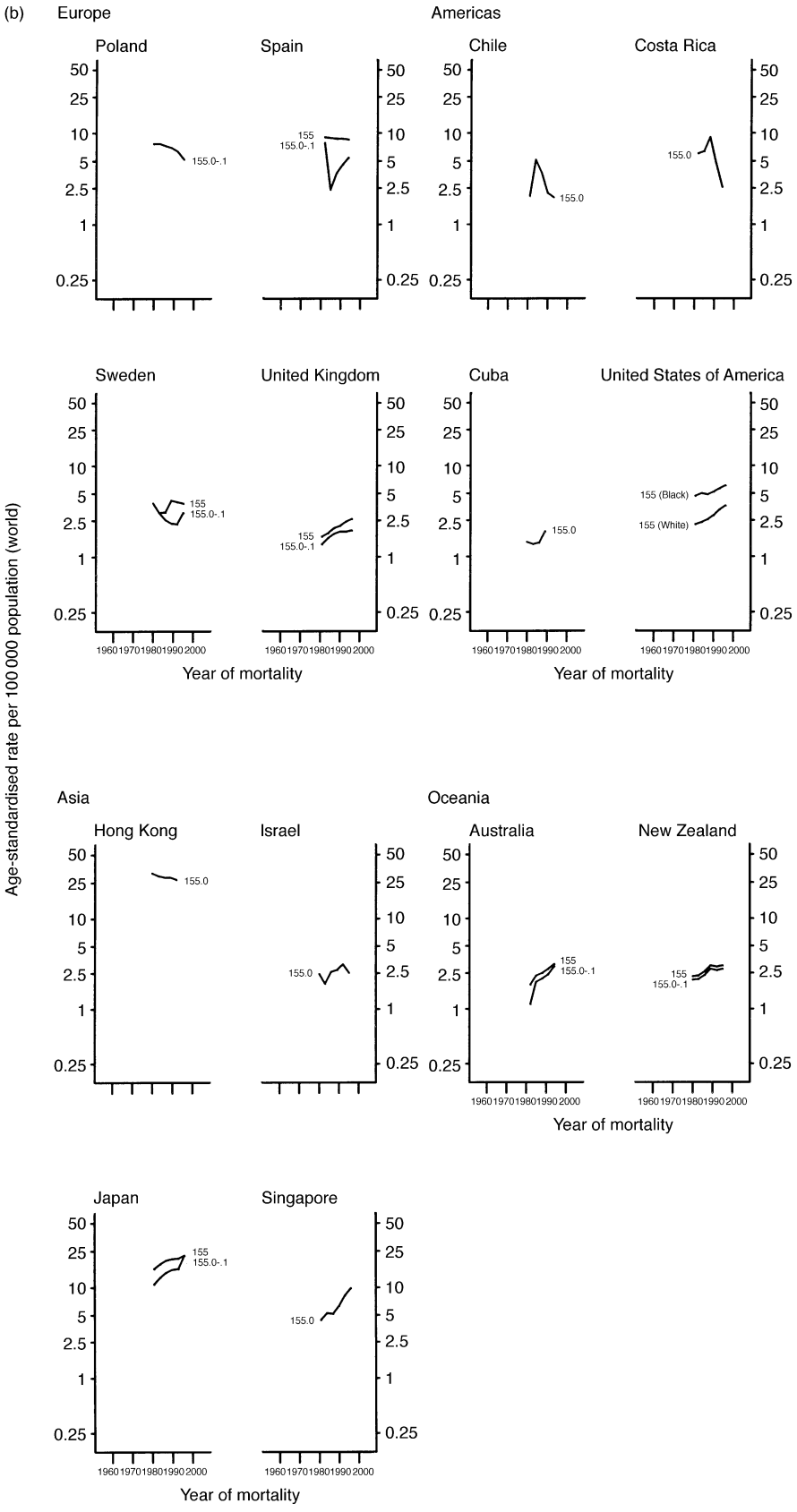


Fig. 20. Liver cancer: (a) incidence trends (source: CI5/SEER); (b) mortality trends, males (source: WHO, NCHS); (c) mortality trends, females (source: WHO, NCHS).



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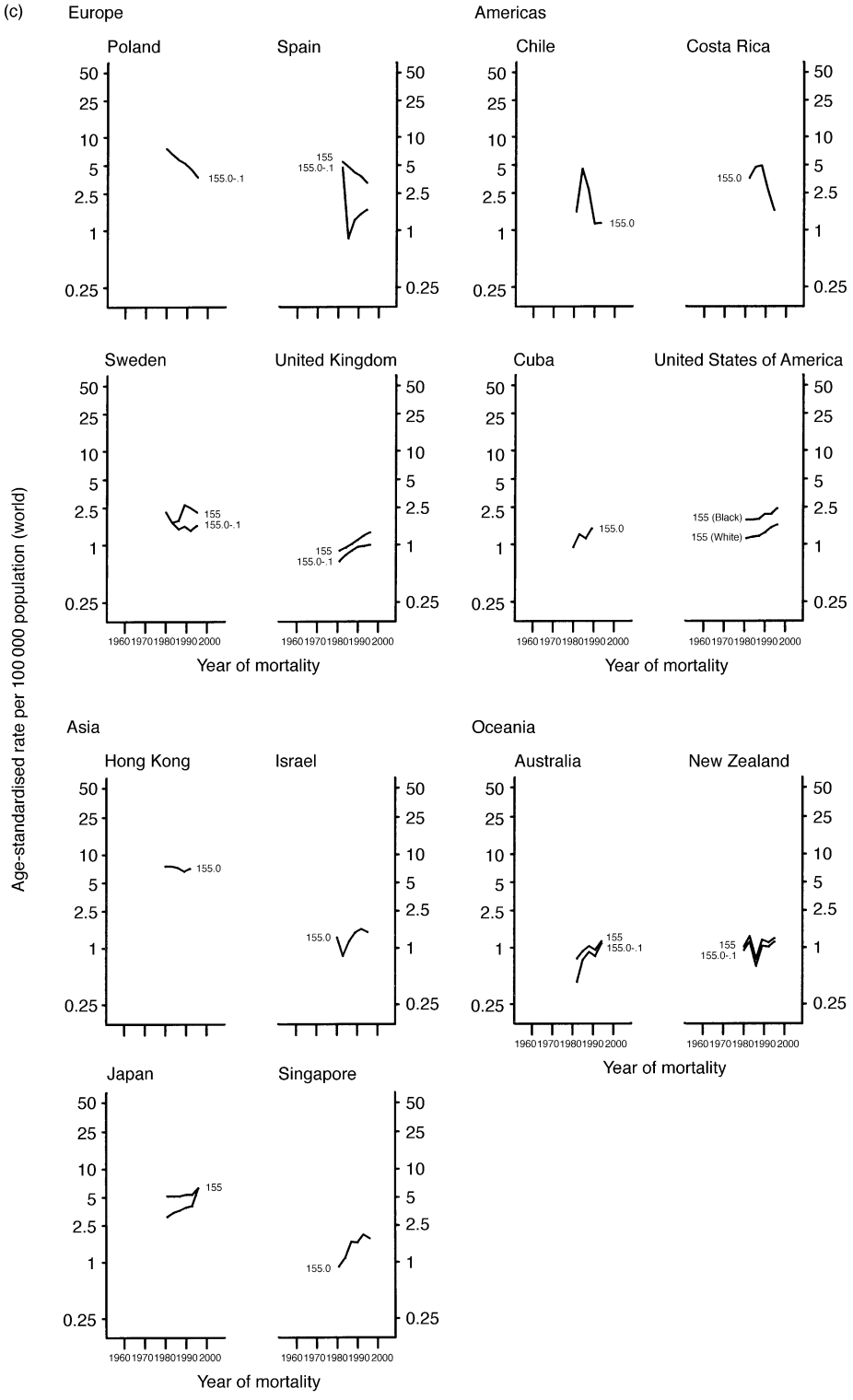


Fig. 20. (*continued*).

reducing or eliminating the habit of eating raw fish (the vector of the parasite). A single dose of praziquantel can eliminate the parasite [199], but re-infection after treatment is common [200], especially in highly endemic areas since ease of treatment has made the task of changing local eating habits even more difficult.

Because of its poor prognosis, there has been considerable interest in the possibility of detecting liver cancer at an early stage in order to improve results of treatment. For HCC, the main tactic has been to screen high-risk populations (chronic HBsAg carriers) through regular testing of serum levels of the tumour marker,

alpha foetoprotein (AFP). Surgical resection has been the principal approach to treatment of cases diagnosed early. A number of uncontrolled series have been reported (reviewed in Ref. [201]), but there have been only two large-scale randomised controlled trials, both reported in the Chinese literature. In Qidong county [164], there was very little benefit from the early detection programme, with mortality rates not significantly different in the screened and control populations. In contrast, a study in Shanghai [202] showed a greatly improved survival in the screened population.

2.6. Prostate cancer

2.6.1. Burden 2000

Prostate cancer is now the sixth most common cancer in the world (in terms of number of new cases), and the third in importance in men. The total annual number of cases is 513 000. This represents 9.7% of cancers in men (15.3% in developed countries and 4.3% in developing countries). It is a less prominent cause of death from cancer, with 201 000 deaths (5.6% of cancer deaths in men, 3.2% of all cancer deaths). The low fatality means that many men are alive following a diagnosis of prostate cancer—an estimated 1.5 million at 5 years, in 2000, making this the most prevalent form of cancer in men. More than any other, this is a cancer of the elderly. About three-quarters of cases worldwide occur in men aged 65 years or more.

Incidence rates are now influenced by the diagnosis of latent cancers, both by screening of asymptomatic individuals and by detection of latent cancer in tissue removed during prostatectomy operations or at autopsy. Thus, especially where screening examinations are prevalent, recorded 'incidence' may be very high (in the USA, for example, where it is now by far the most commonly diagnosed cancer in men). Incidence is very high also in Australia and the Scandinavian countries (probably also due to screening). The distribution of mortality rates is less affected by the effects of early diagnosis of asymptomatic cancers.

Mortality is affected by survival, and survival is significantly greater in high-risk countries (80% in the USA versus 40% in developing countries). However, this more favourable prognosis could well be due to more latent cancer being detected by screening procedures; this would also explain the absence of any change in mortality in the presence of the large increase in incidence [203]. Mortality rates are high in North America, North and West Europe, Australia/New Zealand, parts of South America (Brazil) and the Caribbean, and in much of sub-Saharan Africa (Fig. 21). Mortality rates are low in Asian populations and in North Africa. The difference in mortality between China and the USA is 26-fold (while it is almost 90-fold for incidence).

These international differences are clearly reflected within the USA, where the black population has the highest incidence (and mortality) rates, some 35% higher than in whites, who in turn have rates considerably higher than populations of Asian origin (e.g. Chinese, Japanese and Korean males). The prevalence of latent prostate cancer show much less variation than clinical prostate cancer, though the ethnic-specific ranks are much the same as for incidence [204]. The frequency of latent carcinoma of prostate in Japan is increasing (as with clinical prostate cancer) and approaching the prevalence for US whites.

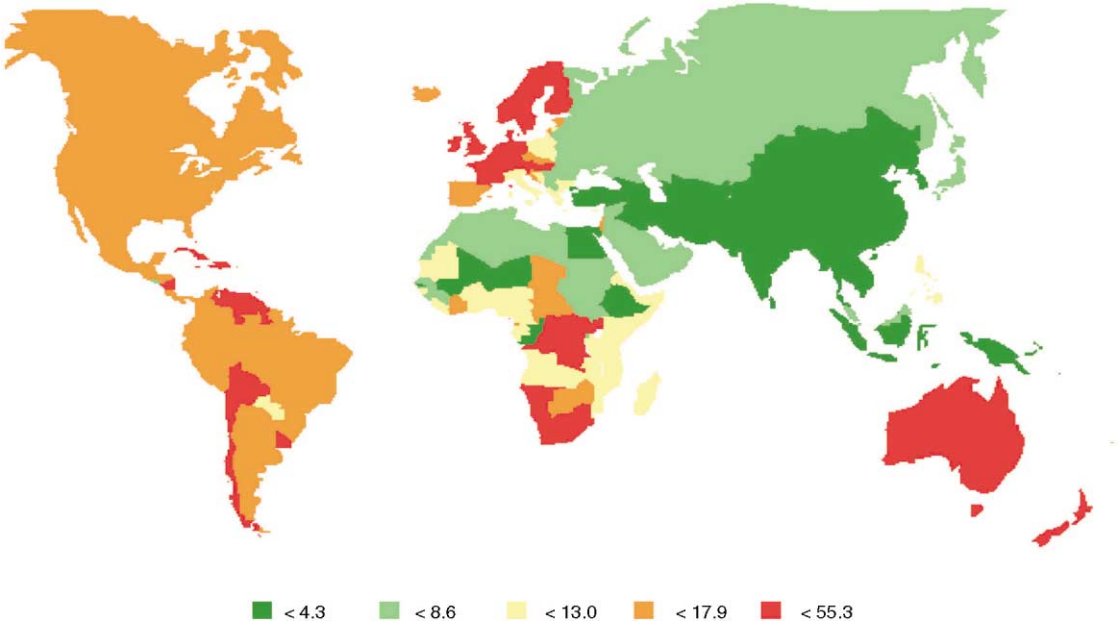


Fig. 21. Mortality from prostate cancer: age standardised rate (world) (all ages).

2.6.2. Risk factors

Migrants from low-risk countries to areas of higher risk show quite marked increases in incidence (for example, Japanese living in the USA). Some of this change reflects an elimination of the 'diagnostic bias' influencing the international incidence rates. Shimizu and colleagues [205] pointed out that localised prostate cancer forms a small proportion of cases in Japan (24%) compared with 66–70% in the USA, and that incidence in Japan could be 3–4 times that actually recorded if, for example, all transurethral prostatectomy (TURP) sections were carefully examined. However, rates in Japanese migrants remain well below those in the US white populations, even in Japanese born in the USA, which suggests that genetic factors are responsible for at least some of the differences between ethnic groups. Nevertheless, some of the changes in rates with time, and on migration, almost certainly are due to changes in environment or lifestyle. Despite extensive research, the environmental risk factors for prostate cancer are not well understood. Western-type diet seems to play a role, but there is no convincing evidence implicating any particular dietary components although some studies have suggested that consumption of fats, meat and dairy products increase risk [79]. The development of prostate cancer requires the presence of male hormones and there has been considerable interest in the possible role of endogenous androgen metabolism. The inter-ethnic variations in incidence and mortality imply that there are important genetic determinants of risk and that the prevalence of the relevant genes differs between populations. Currently, polymorphisms in the genes controlling androgen metabolism e.g. 5 alpha-reductase, seem to provide at least part of the explanation [206]. Other environmental factors (occupational exposures) or behavioural factors (sexual life) have been investigated but do not seem to play a clear role.

2.6.3. Time trends

Until the middle of the 1980s, prostate cancer incidence rates in the USA were gradually increasing, probably due to a genuine increase in risk coupled with increasing diagnosis of latent, asymptomatic cancers in prostatectomy specimens due to the increasing use of TURP [207]. Since 1988 there has been a huge surge in incidence (Figs. 22a and 23) coinciding with the introduction of testing with prostate-specific antigen (PSA), which permits the detection of preclinical (asymptomatic) disease [208]. The recorded incidence of prostate cancer doubled between 1984 and 1992, with the increase being mainly in younger men (under 65 years) and confined to localised and regional disease; there was even a decline in late-stage cancer. The incidence rates began to fall again in 1992 (1993 in black males). This probably reflects the fact that, by this time, most of the PSA tests being carried out were repeat examinations and that the supply of prevalent latent cancers in the subset of the population reached by opportunistic screening has been largely exhausted [16,203]. Prostate cancer mortality rates in the USA had been increasing slowly since the 1970s (Fig. 22b). With the introduction of PSA screening, and the dramatic surge of incidence induced by it, there was an increase in the rate of increase in mortality but this was very much less marked than the change in incidence. More recently, (since 1992 in white men, 1994 in black men), mortality rates have begun to fall (Fig. 23). It is the subject of considerable debate as to whether this is a consequence of screening [209–211]. In brief, this seems unlikely at this stage (although a genuine decline in deaths with time seems quite probable). The lead time (between screen detection and usual clinical presentation) would have to be very short if screening were to have such a rapid effect on mortality. Probably there has been some mis-certification of cause of death in a large group of men found to have a latent prostate cancer in the late 1980s and early 1990s, resulting in the small upturn in mortality which is now being reversed.

Similar trends have been reported in Canada [212], the UK [213], France [214], Australia [215], and The Netherlands [216], although, in general, they are less marked, or occur later, than in the USA.

Hsing and colleagues [217] have reviewed recent data on international trends in prostate cancer incidence and mortality. Some of these trends are shown in Fig. 22a and b. In keeping with the above observations in the USA, they observed the largest increases in incidence, especially in younger men, in high-risk countries, probably partly the effect of increasing detection following TURP and, more recently, due to use of PSA. However, there were large increases too in low-risk countries; 104% in Singapore Chinese, 84% in Miyagi, Japan, 55% in Hong Kong, and 44% in Shanghai, China, between 1975 and 1990. Only in India (Bombay) does there seem to have been little change in incidence (Fig. 22a).

Some of this increase may be due to greater awareness of the disease and diagnosis of small and latent cancers, but it is also probable that there is a genuine increase in risk occurring. This is confirmed by studying changes in mortality. These will not have been affected (not yet, anyway) by screening, and indeed, the increases in rates in the 'high-risk' countries were much less than for incidence, but quite substantial nevertheless (15–25%). In low-risk countries, the increase in mortality rates is large and not much inferior to the changes observed in incidence. Although some of this change in low-risk populations may relate to better detection and diagnosis, much of it probably relates to westernisation of lifestyles with increasing obesity, changes in diet (increased consumption of meat and fat) and decreased physical activity.

The overall average increase in the age-adjusted incidence of prostate cancer worldwide between 1985 and 1995 was around 2% annually. As noted above, a fair proportion of this was due to the huge surge in the USA (9.5% annual increase between 1985 and 1990 but, even supposing there is no further increase in the US, a continued increase of this magnitude would mean that there would be approximately one million new cases per year by the year 2015.

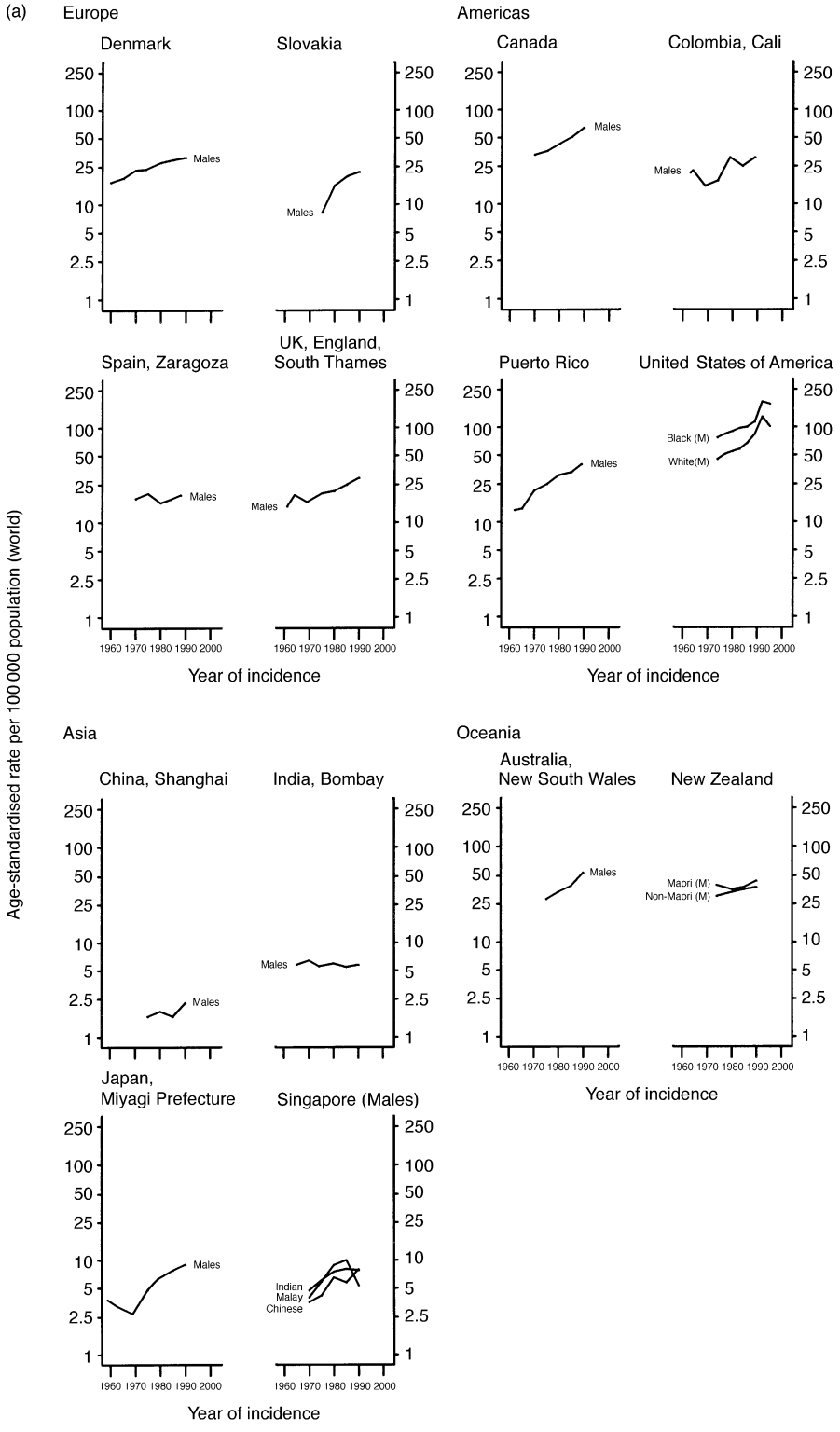


Fig. 22. Prostate cancer: (a) incidence trends (source: CI5/SEER); (b) mortality trends (source: WHO/NCHS).

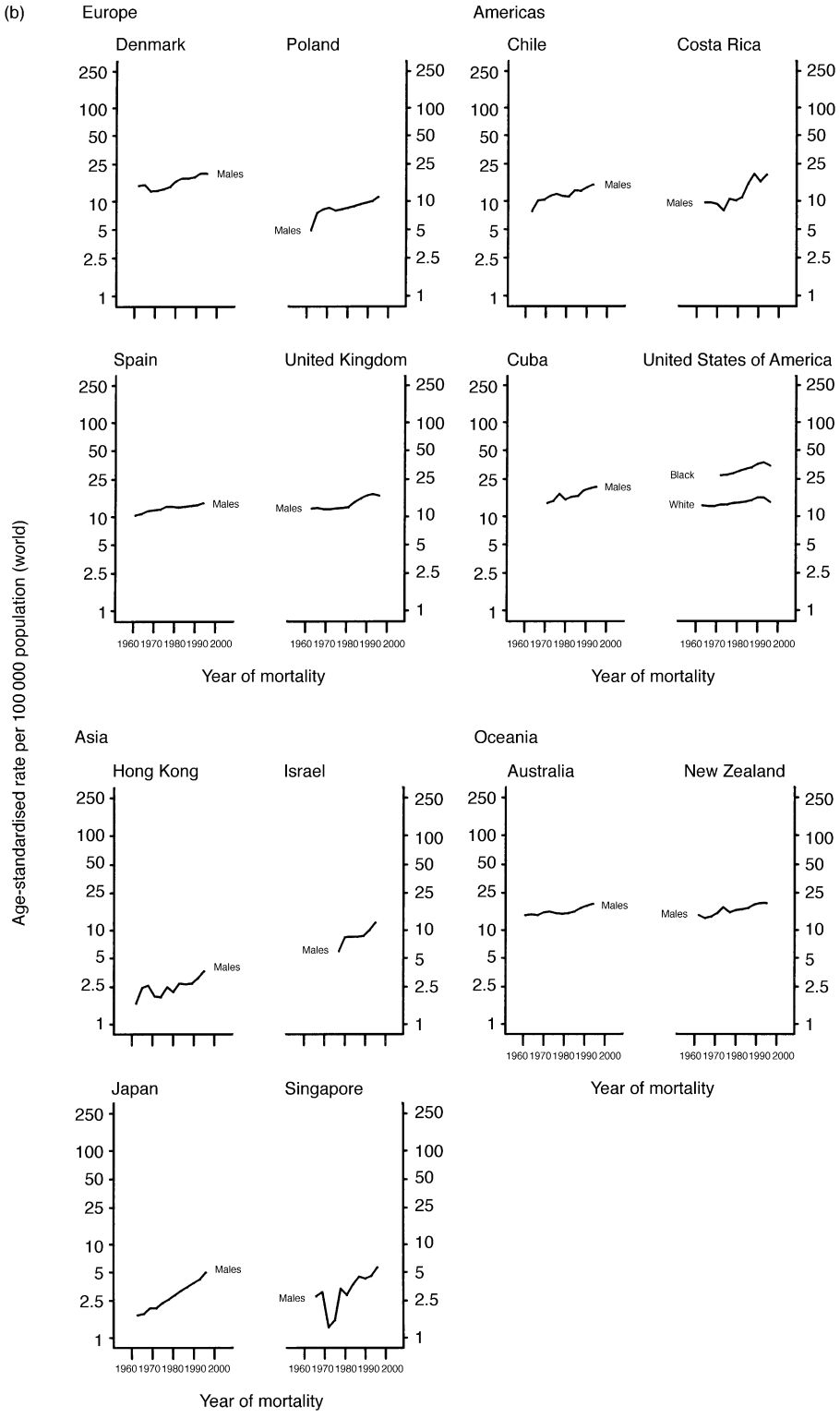


Fig. 22. (*continued*).

2.6.4. *Prospects for prevention*

As far as primary prevention is concerned, the only recommendations can be for individual action to avoid obesity, to take regular exercise and to consume a diet high in vegetables and low in fat, red meat and milk and dairy products. An increased intake of some micronutrients such as vitamin E and selenium may also have protective effects [218]. The Prostate Cancer Prevention Trial (PCPT) currently underway in the USA is evaluating the utility of 5 alpha-reductase inhibitor finasteride in primary chemoprevention of prostate cancer [219].

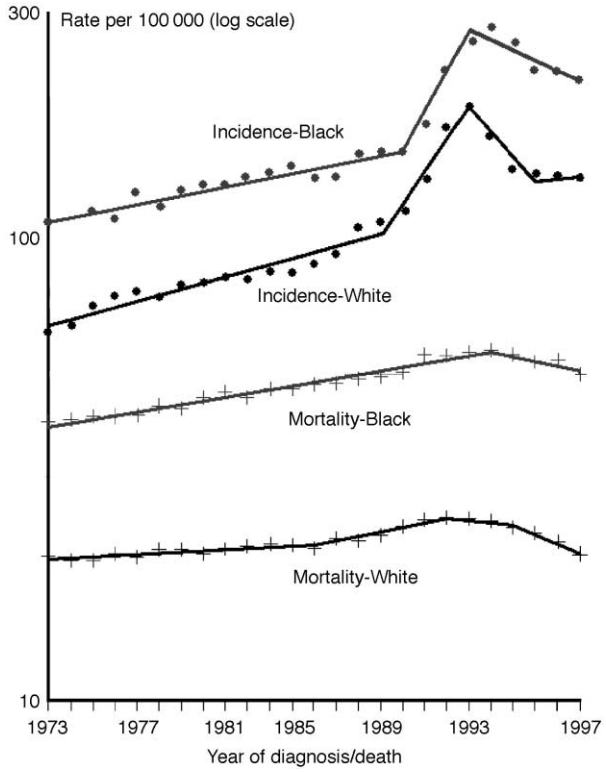


Fig. 23. Cancer of the prostate: US mortality and SEER incidence, 1973–1997. Rates are age-adjusted to the 1970 US standard million population. Regression lines are calculated using the Joinpoint Regression Program.

As noted earlier, the magnitude of the effect of prostate cancer screening on mortality from the disease is at present quite unclear [220]. There are two large-scale randomised controlled trials in progress, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) in the USA [221] and the European Randomized Study of Screening for Prostate Cancer (ERSSPC) trial in Europe [222]. It will be some time before results are available and, in the mean time, it is quite likely that mortality declines in the USA will lead to pressure to introduce widespread screening. However, particularly for this disease, it is imperative to be able to quantify the gains from screening (in terms of life years gained), so that they can be judged against the losses, both financial and in terms of reduced quality of life, for the many elderly men who will undergo unnecessary operations. This seems likely to be an area of increasingly lively debate for some years to come.

2.7. Cancer of the Cervix uteri

2.7.1. Burden 2000

Cancer of the cervix uteri is the second most common cancer among women worldwide, with an estimated 468 000 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, sub-Saharan Africa and South and South East Asia (Fig. 24). In developed countries, the incidence rates are generally low (probably because of screening), with age-standardised rates less than 14 per 100 000. Very low rates are also observed in China and in Western Asia (Fig. 24).

Incidence of cervix cancer begins to rise at age 20–29 years, and the risk increases rapidly to reach a peak usually around age 45–49 years in European populations, but often rather later in developing countries. Incidence rates then decline somewhat, although the slope is much less

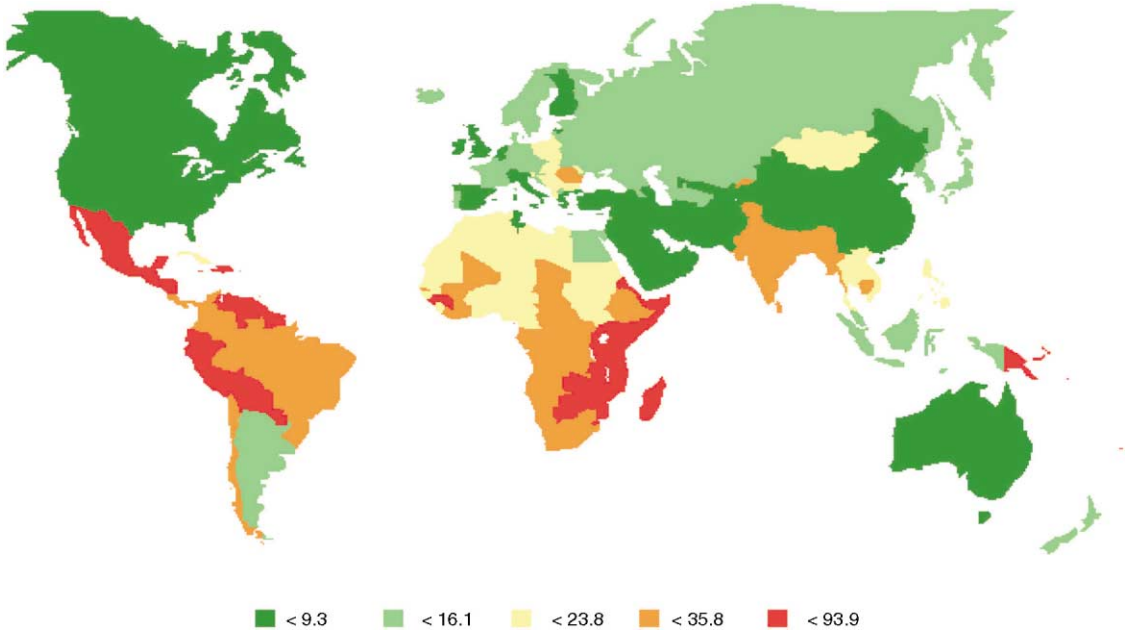


Fig. 24. Incidence of cervix uteri cancer: age-standardised rate (world) (all ages). Reprinted from *The Lancet Oncology* 2001, **2**(9), 533–543.

than for the increase in young women (Fig. 25). This pattern is profoundly changed by screening programmes [223].

Mortality rates are substantially lower than incidence. Worldwide, the ratio of mortality to incidence is 49%. Survival rates vary between regions with quite good prognosis in low-risk regions (69% in SEER and 59% in the European registries), but even in developing countries, where many cases present at a relatively advanced stage, survival rates are fair: 49% on average [15]. The poorest survival is estimated for Eastern Europe.

2.7.2. Risk factors

It was noted early that cervix cancer has quite marked differences in incidence according to classical demographical variables (social class, marital status, ethnicity and religion). Later, epidemiological studies (mainly case–control studies) showed a consistent association between risk and early age of initiation of sexual activity, increasing number of sexual partners of females or of their sexual partners, and other indicators of sexual behaviour. These findings were strongly suggestive of a causative role for a sexually transmitted agent. Additional factors included increasing number of pregnancies, smoking and possibly exposure to oral contraceptives and specific dietary patterns. Within the last 10 years, it has become established that certain sexually transmitted types of human papillomavirus (HPV)—notably 16, 18, 31 and 45—are responsible for the initiation of the disease in the vast majority of cases. The virus is found in almost all cancers and a much smaller proportion of controls, with relative risks reaching several hundreds for certain viral types in the most recent studies. Studies of the natural history suggest that HPV infection is very common in young women with the onset of sexual activity, but that prevalence of infection declines with time (or age), possibly reflecting elimination of the virus by immunological mechanisms. The women who remain infected into later age (30–50 years) are at risk of developing the epithelial abnormalities recognised as precursors of cancer.

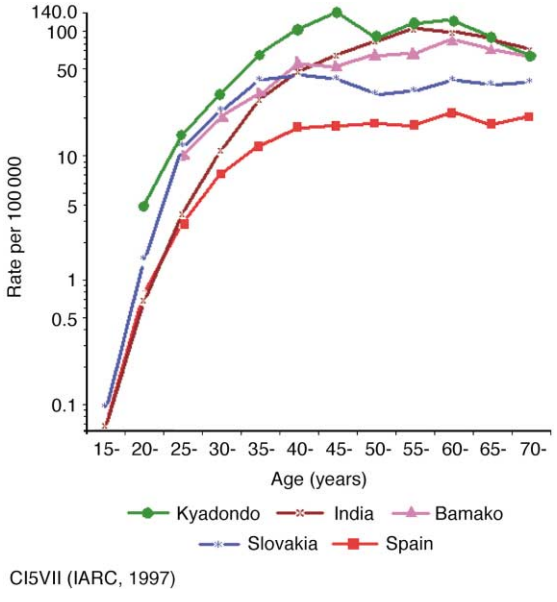


Fig. 25. Trends in cervical cancer incidence by age in different populations.

It does appear that prevalence of infection in women in different areas of the world varies but, although there are very few systematic studies, the range of variation (2–4-fold) seems too small to explain the large differences in risk of cancer between populations. Presumably geographical variation of other aetiological factors may explain some of the variation also, but there has been no attempt at quantitative assessment. In any case, HPV can be considered as a necessary (but not sufficient) cause of the disease and more work is needed to understand what co-factors are responsible for persistence and progression of the viral infection in a small subgroup of women infected.

Since 1993, cervical cancer has been considered to be an 'AIDS-defining' condition; that is, if it occurs in someone who is HIV-positive, that person is deemed to have AIDS. However, it is far from clear that the risk of invasive cervix cancer really is increased by HIV infection. With respect to cervical intraepithelial neoplasia (CIN), most studies failed to adjust for the fact that, for obvious reasons, women infected by HIV were very often also infected by HPV (with a consequently high risk of CIN). Careful adjustment for such confounding suggests that there is an independent effect of HIV on risk of CIN, but that it is small; there is an interaction between the effects of HIV and HPV, as might be expected if the role of HIV was indirect, through creation of immune dysfunction [224].

2.7.3. Time trends

Study of time trends of cervical cancer has been of considerable interest, in part through the light that may be shed on changes in exposure to aetiological factors (especially between women of different generations), and in part as a means of evaluating the success or otherwise of screening programmes. With respect to the latter, cytological screening, by enabling precursor lesions to be detected and treated, has the potential to effectively prevent the development of invasive cancer, thereby reducing incidence and mortality. Alas, no statistical legerdemain can decide the relative contributions of these two effects (and others, especially data artefacts) to observed trends, which must therefore be interpreted in the light of knowledge on likely screening patterns and exposure to risk factors. Time trend studies make use of both incidence and mortality data; the latter have the great advantage of longer time series and larger population coverage, advantages offset by the quality of the diagnostic information (especially failure to distinguish cancers of the cervix and corpus) and the

confounding effect of changes in survival. Though these are often (conveniently) dismissed as negligible, the work of Ponten and colleagues [225] and Sparen and colleagues [226] has shown what a dramatic effect trends in stage at diagnosis and treatment may have on cervical cancer mortality. Trend studies often fail to distinguish adenocarcinomas from squamous cell carcinomas, although their epidemiology is a little different and their susceptibility to detection by cytology screening very much so. Since most cervical cancers are squamous cell

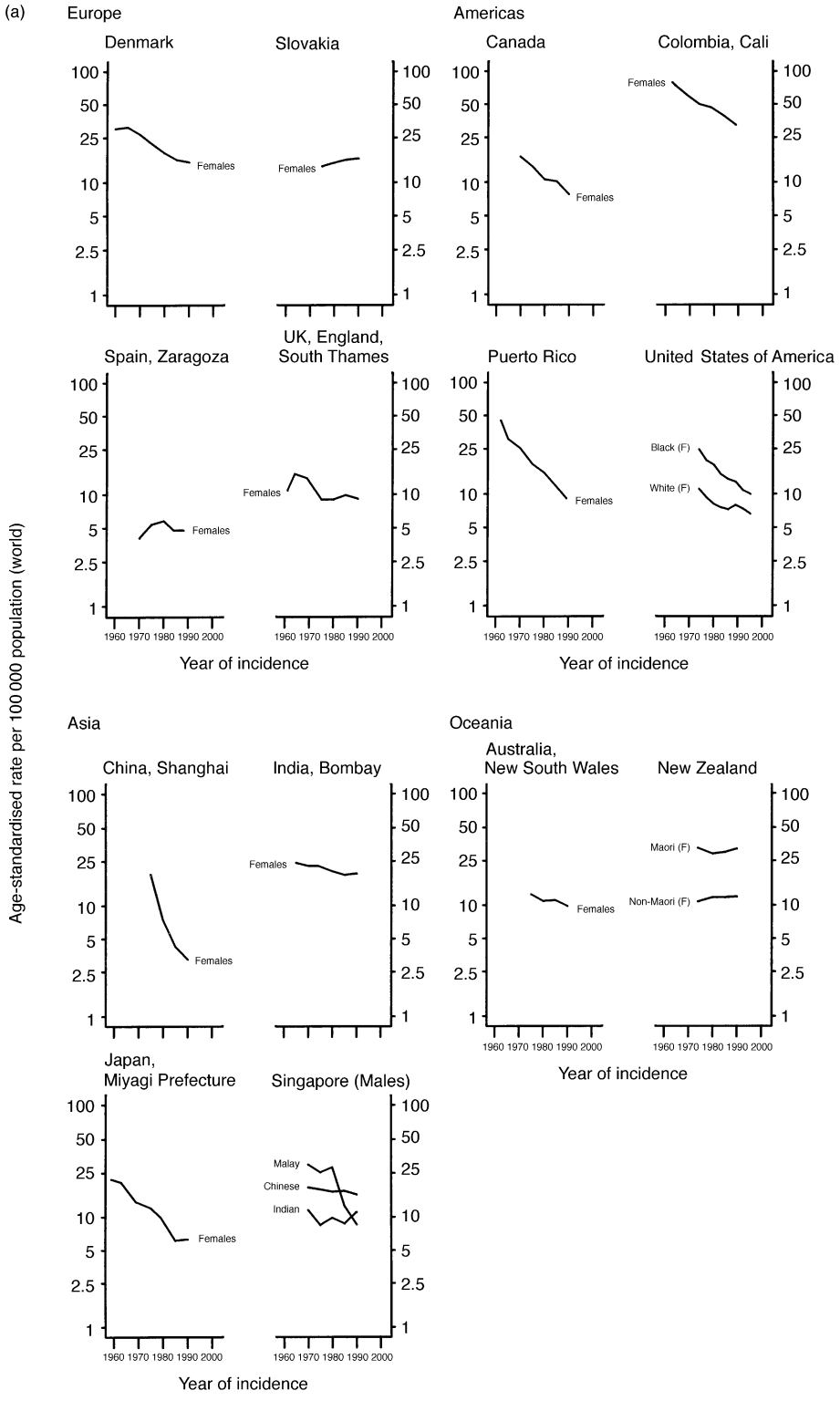


Fig. 26. Cervical cancer: (a) incidence trends (source: CI5/SEER); (b) mortality trends (source: WHO/NCHS).

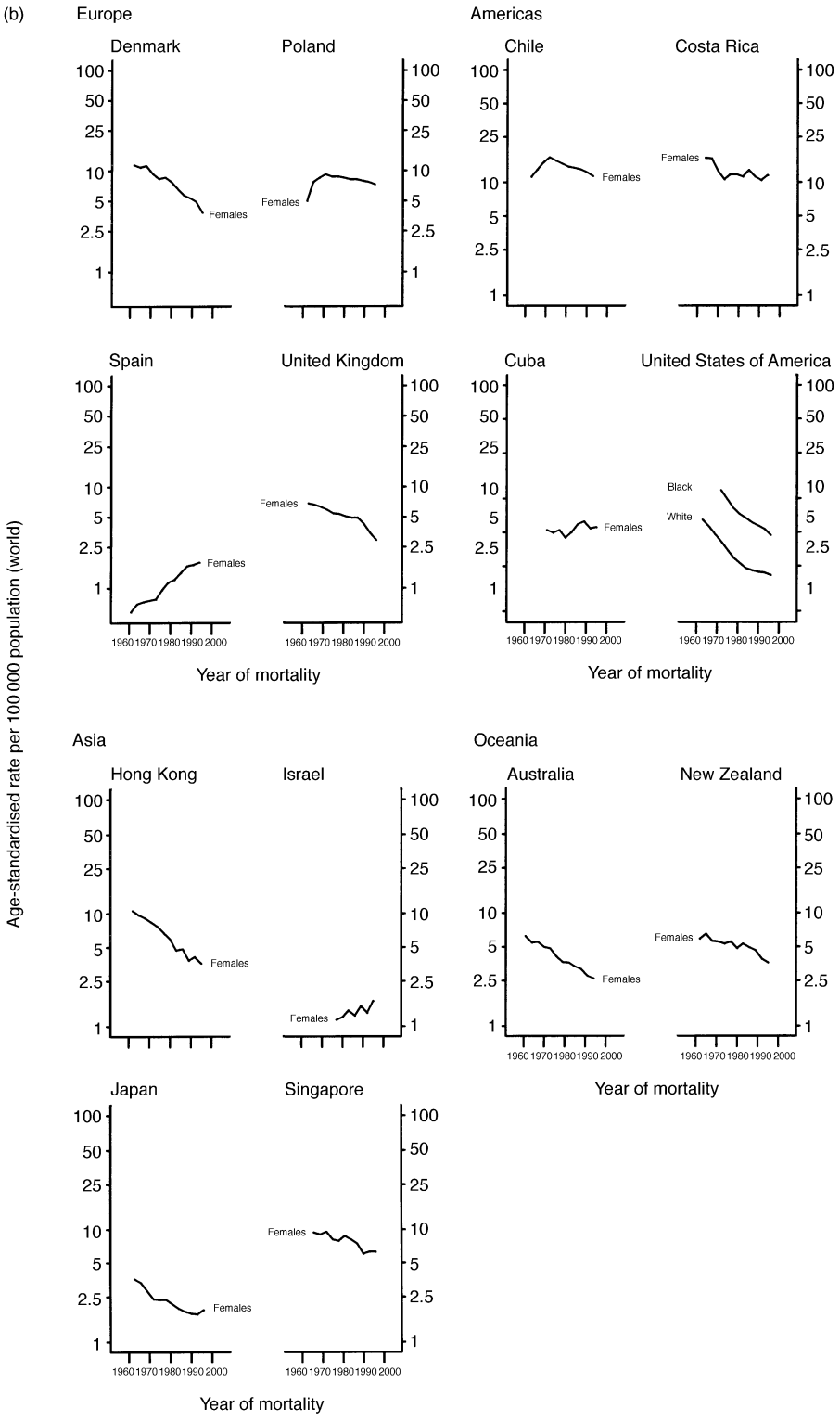


Fig. 26. (*continued*).

carcinomas, studies of all types will largely reflect trends in this histological type.

Overall, incidence and mortality have declined in the last 40 years in Western Europe, the USA, Canada, Australia, New Zealand and Japan (Fig. 26a and b). In general, this has been ascribed to a combination of a reduction in risk in older generations of women (genital hygiene, parity, etc.) with, more recently, the beneficial effects of population screening programmes based on exfoliative cervical cytology. Perhaps the best known studies of time trends in incidence are those undertaken for the Nordic countries, where it was possible to com-

pare the trends in incidence (and mortality) across countries with their different policies in relation to screening [12,13,227]. The extent of the decline in incidence and mortality was related to the coverage and extent of the organised programmes in the respective countries [228], and the declines in incidence were most marked in the age groups targeted by the organised programmes.

Several studies have pointed out, however, that within the overall decline in incidence/mortality, quite often there were increases occurring in young women. This seems to have been noted first in England and Wales where, although it occasioned much hand wringing about the effectiveness of the screening programme, it was clear that a cohort (generation-specific) effect was present, with generations of women born since about 1935 being at increasingly high risk [229–231]. A similar phenomenon has been observed in several countries, e.g. Australia [232], New Zealand [233], Belgium [234], Slovenia [235], Slovakia [236], Spain [237] and in several countries of Eastern Europe [238]. Even Finland, with its remarkably successful screening programme, which had reduced the incidence of cervical cancer in 1991 to 2.8 per 100 000, has observed quite marked increases in incidence in younger women (below 55 years of age) since 1990 [239]. The general consensus is that these trends are most likely due to changes in sexual habits and increased transmission of papillomaviruses in younger generations of women, but that the magnitude of the effect will depend upon the countervailing effects of screening. Thus, in some countries, e.g. Sweden, there has been no increase in risk in young women [240], and the upward trend in England and Wales has been successfully countered by a much improved screening programme, implemented in 1988 [241].

Analyses of time trends by histological subtype show that trends in squamous cell carcinoma are more or less those observed for cervical cancer as a whole. The large international study of Vizcaino and colleagues [242], of 25 countries, found declines in incidence for younger (25–49 years) and older (50–74 years) women in most countries. Exceptions were the increases in young women in the UK, Slovenia, Slovakia and Israel. With respect to adenocarcinomas, several studies have shown rising incidence rates in populations where—presumably as a result of screening—incidence rates from squamous cell carcinomas are declining [240,243]. The increasing risk of adenocarcinoma appears to affect relatively recent generations of women from many countries [244]. The cytological detection of adenocarcinoma or precursor lesions is undoubtedly less efficient than for squamous cell tumours [245,246] and a case–control study [247] has shown that the risk of adenocarcinoma is not reduced by screening. The increasing incidence may reflect increases in exposure to the HPV in recent generations (the effect of which in squamous cell tumours has been described as diminished by screening programmes). The use of oral contraceptives has also been linked to an increased risk of cervical adenocarcinoma [248].

There is less information on time trends in cervical cancer in developing countries; as might be expected, the situation is quite varied. In general terms, rates of incidence and mortality have been relatively stable or shown rather modest declines (Fig. 26a and b). This probably reflects the absence of any systematic screening programmes or, where they have been introduced, their low population coverage and poor quality cytology [249]. In Cuba [250] and Costa Rica [251], for example, the screening programmes seem to have had virtually no impact upon the incidence of cancer. In contrast, there appear to have been dramatic declines in the incidence of cervical cancer in China for reasons so far unexplained, though it does seem unlikely that they can be ascribed to screening. In Shanghai, for example, age-adjusted incidence of cervical cancer fell from 26.7 per 100 000 to 2.5 between 1972–1974 and 1993–1994 [97]. Finally, there is limited evidence that in Africa incidence may even have increased since the 1960s [252].

2.7.4. Prospects for prevention

Probably the greatest potential reduction in deaths from cervical cancer is achievable through health education and awareness programmes. Historically, the improving stage at presentation has meant that survival and death rates from cervical cancer have fallen markedly in developed countries [225], and every effort should be made to improve the dismal pattern of late presentation and poor survival observed in most developing countries [15].

The difficulties of implementing population-based organised cytological screening programmes in developing countries has prompted considerable research into the feasibility of using simpler approaches, especially so-called 'aided visual inspection'. These use techniques familiar to colposcopists—delineating epithelial abnormalities by application of protein denaturants such as dilute acetic acid or Lugol's iodine. Inspection of the cervix is performed either with the naked eye or with low-powered magnification. The technique seems to be about as sensitive as the PAP test (and very much simpler to implement), but there are many more false-positive tests (lower specificity). The applicability in practice depends on whether the resulting overtreatment will be acceptable or whether further diagnostic tests will need to be used. The development of simple tests to detect HPV DNA may allow the identification of women with persistent infection, who constitute a high-risk group that can be the focus for surveillance, by regular screening. Identification of the different antigens of the HPV has allowed the

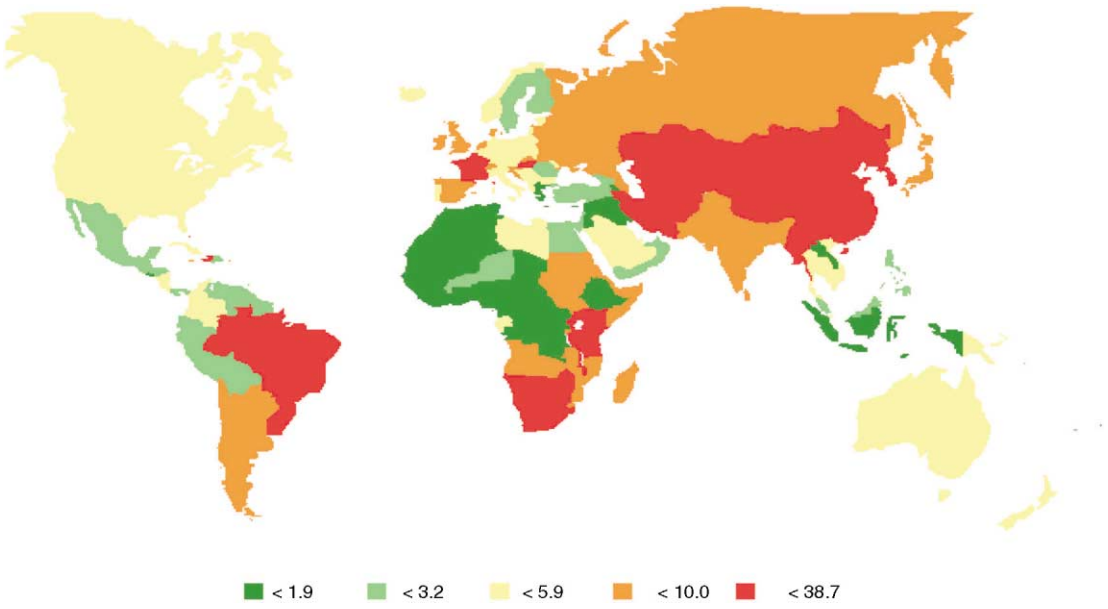


Fig. 27. Incidence of oesophagus cancer: age-standardised rate (world)—male (all ages).

development of therapeutic and prophylactic vaccines, and testing of these vaccines is already in progress.[1]

2.8. Oesophageal cancer

2.8.1. Burden 2000

Approximately 391 000 cases of cancer of the oesophagus occur worldwide each year, of which over 80% are in developing countries. Because of the poor prognosis, the number of deaths (355 000 per year) is not greatly inferior, and geographical patterns and trends in occurrence have frequently been studied in terms of mortality as well as incidence. The geographical variability in risk is very large—more than for almost any other cancer. 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), with incidence rates as high as 200 per 10^5 (and, in some areas, a female predominance). High rates are also present in parts of East and South East Africa (Uganda, Zimbabwe, Natal and Transkei) and eastern South America (Southern Brazil, Uruguay, Paraguay and Northern Argentina) and certain parts of Western Europe (especially France and Switzerland) (Fig. 27). 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 [253], although in the high-risk areas of Asia, the sex ratio is much closer to unity, e.g. 1.5 in Linxian County, Henan, China [254].

Even within the high-risk areas, there are striking local variations in risk. For example, within the oesophageal cancer belt in China, the 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 [255]. Other workers have shown the large geographical variations within the high-risk areas of South Africa [256] and in Northern France [257,258].

Worldwide, most oesophageal cancers are squamous cell carcinomas, arising in the middle and lower third of the oesophagus. Recently, there appears to be an increase in Western countries in relative and absolute numbers of adenocarcinomas of the lower third of the oesophagus, associated with Barrett's oesophagus (see below). The profile of genetic changes (mutations) is different in these two histological subtypes, implying different aetiologies.

2.8.2. Risk factors

It seems highly unlikely that the dramatic differences in risk observed within small geographical areas could be the result of inherited predisposition. Migrant studies confirm that persons from high-risk areas can quite rapidly lose their elevated risks after migration. For example, Chinese in Singapore, whose rates in the China-born tend to reflect their region of origin (highest in Teochew, Hokkien and lower in Cantonese from Southern China), have much lower incidence rates in the locally born [259]. Similar observations have been made with respect to migrants to Israel from Asian countries—their risk declined quite rapidly with duration of stay in Israel [260].

[1] Editor's note: On a related theme, please see the Special Issue on 'Cervical cancer screening in the European Union' (*EJC* 2000, issue 36, vol. 17).

Studies of squamous cell carcinoma in Western countries have consistently shown the aetiological importance of tobacco and alcohol, particularly in combination (their effect is multiplicative). Tobacco smoking accounts for 45% of cases in men worldwide but only 11% of cases in women. In the Indian subcontinent, chewing of tobacco has also been shown to increase risk. With respect to alcohol, it seems that the specific type of alcoholic drink (beer, wine or spirits) is less important than the quantity of ethanol consumed. The mechanism of action of alcohol is debated since it is not a carcinogen. However, its metabolite acetaldehyde is, and there is evidence that genetically determined differences in alcohol metabolism (polymorphisms of aldehyde dehydrogenase) may be important in influencing risk [261,262]. Trends in consumption of alcohol and tobacco have often been postulated as explaining the observed trends in incidence/mortality. Nevertheless, the association between these aetiological factors and oesophageal cancer has been shown to be parodoxically weak when one compares them with trends for cancer of the larynx, which are strongly associated with both alcohol and tobacco consumption, or the lung, for which trends are associated with tobacco [263]. It has been suggested that the effects of these risk factors may have been countered by the increase in consumption of fruit and vegetables [264].

With respect to the different histological types of oesophageal cancer, the strong association with tobacco smoking and alcohol consumption is primarily with squamous cell carcinoma [170], while recent studies in the USA have established an elevated risk of oesophageal adenocarcinoma in smokers relative to non-smokers [265–267]. A case–control study based in the population-based registry of Bangalore, India showed bidi smoking in males to be a risk factor for all three segments of the oesophagus, with the highest risk established in the upper third, less risk in the middle third and an even less (but still significant) risk in the lower third [268]. There is, however, little evidence that alcohol consumption is associated with the risk of adenocarcinoma of the oesophagus [265].

Poor diet has been implicated as an important causative factor of both squamous cell carcinoma and, to a lesser extent, adenocarcinoma of the oesophagus [269,270]. The frequent consumption of pickled vegetables has been shown to be associated with increased risk of oesophageal cancer in Hong Kong Chinese [271]. IARC [160] classed them as carcinogenic, perhaps due to their content of mycotoxin or nitrosamines. Fresh fruit and vegetables, especially citrus fruit and green leafy vegetables, in the adult diet in particular may provide a protective effect. More recent studies have established that obesity is associated with an excess risk of adenocarcinoma [270,272]. Evidence that low socio-economic status may be linked to the risk of adenocarcinoma has also been provided, although the differential is less than with squamous cell carcinoma [273]. The consumption of drinks and meals at very high temperature have been studied in relation to increased risk. Scalding food and drink, together with the overall volume and strength of tea drunk, were associated with an elevated risk of cancer of the oesophagus in the low-risk province of Heilongjiang in North East China [274], although other studies have shown green tea consumed at usual temperatures may have protective properties [275,276]. The drinking of hot spirits (particularly Calavados) has been shown to produce elevated risks of oesophageal cancers in males in North West France [277]. There is also some evidence to indicate that hot maté consumption may confer excess risk in populations studied in Southern Brazil [278]. Use of opium in the high-risk areas of Northern Iran was studied in the 1970s; the opium was taken from pipe residues, which were extracted (or eaten directly) and were shown to contain potent carcinogens [279,280]. Similar habits with respect to tobacco (pipe) smoking (eating pipe stem residues) were observed in Transkei [279]. In Africa, a role for fumonisins (mycotoxins) and contaminants of home-brewed alcohol has been suggested, mainly based upon observations of contaminated foodstuffs in the areas of highest oesophageal cancer risk [281].

The observations with respect to diet focused attention upon the possible role of deficiencies of specific micronutrients. The clearest associations are with deficits in certain vitamins (A, C, Beta-carotene, Riboflavin). Work, especially in South Africa, has suggested that certain mineral deficiencies might also be important. The importance (or otherwise) of such micronutrients should be evident from intervention trials. Three have been conducted in high-risk areas.

1. The Huixian trial used regression of precancerous lesions as the endpoint [282]. Riboflavin, retinol and zinc supplements were given. The result was unsatisfactory. Only when randomisation was broken and analysis carried out as for a cohort study (comparing subjects with sustained/increased levels before/after with those with decreasing levels) was a beneficial effect on histology seen.
2. In the Linxian trial, 30 000 adults were randomised to receive eight mineral/vitamin combinations. No significant reduction in incidence/mortality from oesophageal cancer was observed after 5 years treatment [283,315].
3. Oesophageal dysplasia cases (3300) received multivitamin supplementation versus placebo. There was a small and non-significant decline in deaths from oesophagus/gastric cardia cancer, although incidence was unchanged [284].

2.8.3. Time trends

Trends in oesophageal carcinoma by geographical location have been inconsistent, with disparate patterns emerging in different parts of the world (Fig. 28a and b). Owing to important differences in their descriptive epidemiology, more recent time trend studies have distinguished between two key histological subgroups, namely squamous cell carcinomas and adenocarcinomas of the oesophagus. There are, however, difficulties differentiating between adenocarcinomas located at the

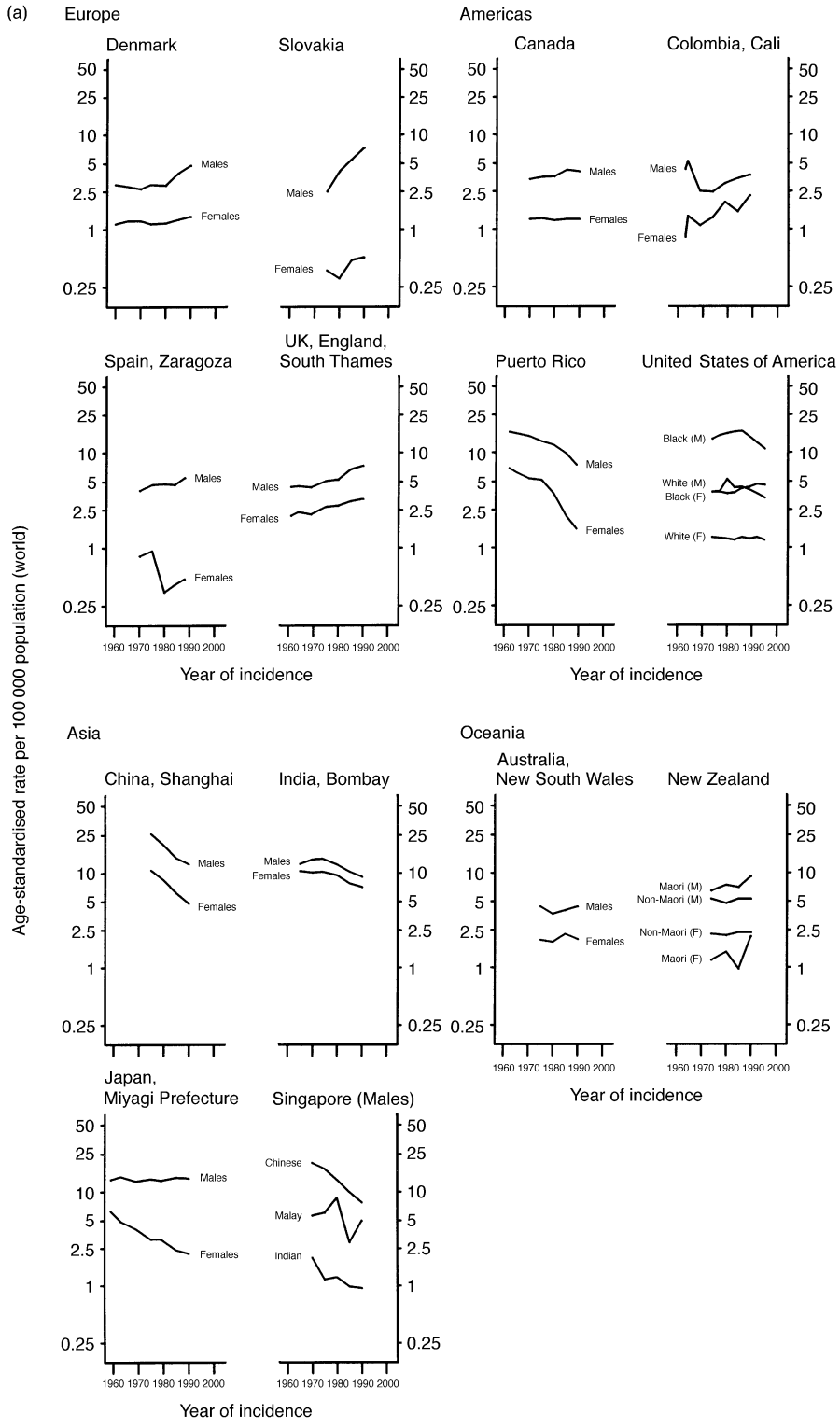


Fig. 28. Oesophageal cancer: (a) incidence trends (source: CI5/SEER); (b) mortality trends (source: WHO NCHS).

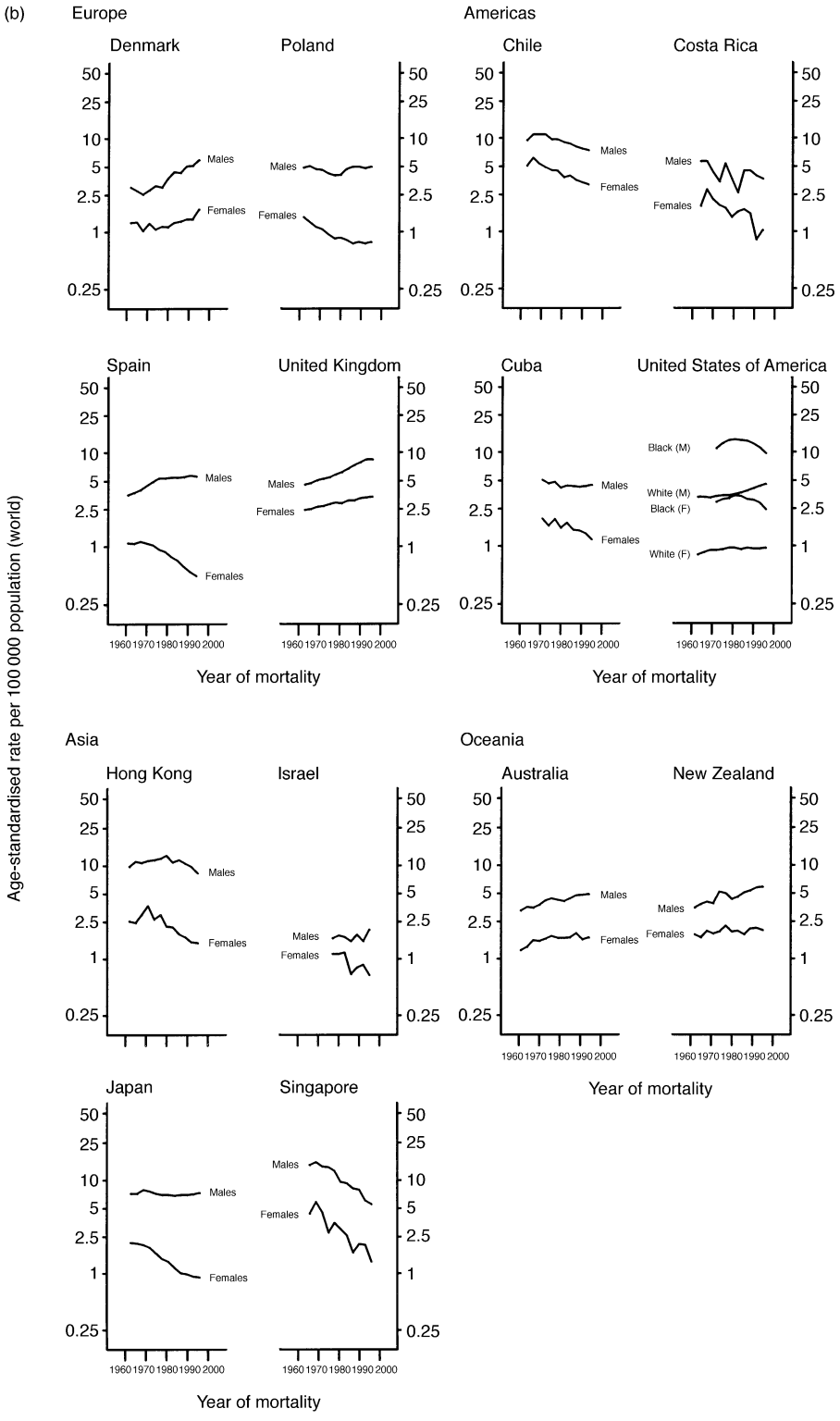


Fig. 28. (*continued*).

junction of the oesophagus and those of the gastric cardia and, to avoid classification biases, the trends in these two groups are often co-evaluated.

In areas of low risk such as Northern and Western Europe, there has been a slight increase in the incidence rates in males in the majority of populations in the period 1973–1987 [136]. In Finland, however, a clear decline in the incidence and mortality rates in males was observed over the period. In Eastern European males, increasing incidence rates were detected, particularly in

Hungary, Poland and the former Czechoslovakia. In Southern Europe, the rates in males remained relatively stable or even decreased. Compared with males, the risk in females was much lower in most European populations, with rates in most countries either stable or decreasing further. Studies investigating trends in European populations by cancer histology revealed more concordant trends within Europe. In both sexes there has been substantial increases in the incidence of oesophageal adenocarcinomas (in comparison with only moderate increases reported for squamous cell carcinomas) in Denmark [285], England [286], France [287,288], Norway [289], Scotland [290] and Sweden [291].

The overall rates in the USA have been increasing since the 1950s in both blacks and whites [82]. The incidence rates in women tend to be much lower but, nevertheless, an upward trend has been observed in recent years. The incidence of adenocarcinoma has been consistently rising in the USA, particularly in males [122,283,292,315]. By 1995, the rates in white men were some 350% higher than the baseline comparison two decades earlier [122]. Similar increases were observed in black males although the rates remained at lower levels. Rates in squamous cell carcinoma have consistently fallen in this period in both black and white males, and the incidence of adenocarcinoma had surpassed that of squamous cell carcinoma in white males by the mid-1990s. An age-period-cohort analysis has revealed that trends in the USA rates may have both period and cohort influences [293]. Similar patterns in adenocarcinoma in males were reported in a population-based registry study in Australia, rates increasing by 9.5% between 1982 and 1991 [294]. In New Zealand, increasing rates were observed in non-Maori men and women [295].

As noted above, adenocarcinomas are related to alcohol and tobacco smoking, but the increases in incidence seems to be the consequence of increased prevalence of Barrett's oesophagus. This is presumably due to gastro-oesophageal reflux becoming more common, perhaps as a consequence of increasing abdominal obesity.

In Shanghai, China, where risk is relatively high, substantial decreases in incidence have been reported [97], particularly in the younger age groups [296]. Among Chinese migrants in Singapore, the once very high risk of oesophageal cancer had dramatically fallen by the mid-1980s, with cohort trends suggesting that the cancer would become increasingly rare [297]. In the very high-risk area of Linxian, China, there appears to be a decline in mortality in those aged less than 60 years since about 1970 [254]. This pattern suggests a sudden dietary improvement.

In Japan, the patterns are quite different in males and females. Females show a decline in risk in most age groups so that overall mortality is declining, and seems likely to continue to do so. However, in men, there has been a rise in mortality in generations born since about 1920, and this parallels changes in deaths from cirrhosis [298], suggesting that rising alcohol consumption is important. Japanese (and possibly other Asian populations) may have increased susceptibility to alcohol because of a high prevalence of the null genotype of aldehyde dehydrogenase [261].

In Latin America and the Caribbean, where rates range from moderately high to high, declining trends in incidence in most countries have also been reported [136].

2.8.4. Prospects for prevention

Tobacco and alcohol control can clearly prevent many cases. Better nutrition will probably prevent many of the central Asian cases. As described, the attempts to prevent the disease by giving micronutrient supplements (chemoprevention) have not been very encouraging. Early detection by balloon cytology is purely experimental.

3. The future

Making provision for health services for cancer (prevention, early detection, treatment, rehabilitation and palliative care) requires not only a sound knowledge of the current pattern of occurrence, but also an estimate of the likely evolution of the cancer burden in the future. The future cancer burden can be projected on the basis of trends of incidence and mortality in the past. Recent methodological advances in forecasting allowed the researcher to use a Bayesian approach to specify smooth variation in cancer rates and to give more weight to recent, rather than distant, changes [299] to select appropriate models on the basis of recent trends (as well as through the usual goodness-of-fit tests) and provide sensible confidence intervals for the prediction [300,301]. However, in this publication we have not attempted to project cancer rates to the year 2000 and beyond from existing trends. For one thing, projections based on historical patterns are not always a sound basis for future predictions. There can be quite abrupt changes in trends in incidence and/or mortality with the development of successful early detection or new forms of treatment. We have already described how these have profoundly affected time trends for cancers of the prostate, breast and cervix. As a result, *post hoc* examination of real data versus projections can reveal gross inaccuracies in the estimates. It is not easy to foresee what further changes of this type will occur in the next decade, let alone in the next 50 years. Even preparing projections on a world scale is difficult; past trends are quite different in different regions of the world and in many cases the trends have been in differ-

ent directions in different age groups (or birth cohorts) within the last decade (e.g. lung cancer or colorectal cancers). For much of the world, we simply have too little detailed information on the evolution of age-specific incidence and mortality to make a comprehensive set of projections.

Therefore, in this section, we have chosen to examine the estimated population growth, ageing and urbanisation of the world population and assess the significant global impact such demographic changes will have on the emerging picture of cancer burden in the next few decades. Then we comment on how we believe these demographically driven changes may be modified by future changes in incidence or prognosis. Unless otherwise stated, the population projections cited are taken from the United Nations publication 'World Population Prospects' [18] using figures based on the 'medium-fertility variant'. 'Older' and 'elderly' persons are used as synonyms for those persons aged 65 years or over.

3.1. World population projections

3.1.1. Population growth and ageing

The major characteristics of the evolution of the world population in the next 50 years are the consequences of a projected gradual decline in fertility and increase in life expectancy. These imply, as well as an increase in the world population (at a progressively decreasing rate), a diminishing proportion of children and an increasing number of older persons worldwide. The global population has doubled from 2.8 billion in 1955 to over 6 billion in 2000. The projected increase of nearly 80 million people a year will mean by 2020 it will reach about 7.5 billion and, by 2050, 8.9 billion. The major changes in the world population will occur within the oldest age group; the number of elderly people will increase from 7% of the world population in 2000 to over 16% by 2050.

The rate of growth of the population after 2000 is expected to decrease in both developing and developed areas although, amongst the least developed areas, the demographic transition is some 20–25 years behind other developing regions. By 2050, 56 countries (including all European countries, Japan and China) are projected to have a negative growth rate. It is forecast that population size will peak in developed countries around 2020 and then decline—by 2050, the overall population should be some 2% less than the 2000 estimate. This contrasts with less developed countries—a 63% increase in the overall population is expected between 2000 and 2050. The expansion is particularly evident in Africa—the population is forecast to double by 2030 and its current 13% share of the world population is set to rise to one-fifth of the global population by 2050—although consideration of the catastrophic development of the AIDS epidemic, particularly in sub-Saharan Africa, may suggest this proportion will be less. The world population share of Europe and Northern America is projected to decline from 17 to 11.5% during this period.

As a result, almost all of the projected world population growth (about 97%) will be in the developing regions. About 57% of the global increase can be attributed to population expansion in just nine developing countries: India (20.6%), China (14.7%), Pakistan (5.2%), Indonesia (3.8%), Nigeria (3.2%), Brazil (2.8%), Bangladesh (2.7%), Mexico (2.0%) and the Philippines (2.0%).

Fig. 29 shows population estimates for 2000, 2010, 2020 and 2050 by sex and age group in developed and developing areas. It is clear that there is a shift in the underlying age structure of the two populations from younger to older age groups over time. As a result, the age pyramids in both populations will become increasingly 'top-heavy'. The effect is particularly striking in populations in more developed areas.

The rapid increase in the absolute and relative numbers of elderly people has been one of the principal characteristics of the world population in the 20th century. Cohorts born during the 'baby-boom' following the Second World War will soon be joining the over 65 years age group—improving life expectancy means that they will also live longer. Overall mortality rates in developing countries have been declining for over 50 years, raising life expectancy from 41 years (in the mid-1950s) to 64 years by 2000. By 2020, life expectancy in these regions is forecast to be around 71 years and by 2050 a further gain of 4 years of life is expected. Fig. 30 illustrates the increases in the number of elderly people projected in developed and developing countries. The proportion of older persons in developing regions is projected to increase from 5% in 2000 to 15% in 2050. In developed areas, the 14% proportion that are elderly in 2000 is forecast to rise to over 25% by 2050.

These changes will have a profound effect on the use and delivery of health services and on the allocation of resources for them. Fig. 31 shows the projected increase in population, by world region, and the percentage of elderly (aged 65 years and over) at three points of time. The number of people aged over 65 years is set to rise from approximately 420 million in 2000 to nearly 700 million by 2020 and to almost 1.5 billion by 2050 (approximately one in six of the total population). Large increases in the number of older persons are expected in many developing countries especially in Asia—and the numbers are very large in absolute terms—the continent has over half of the world's elderly population according to estimates for 2000, about 216 million people. It is projected to accommodate almost two-thirds of the global elderly population by 2050, representing approximately 914 million people.

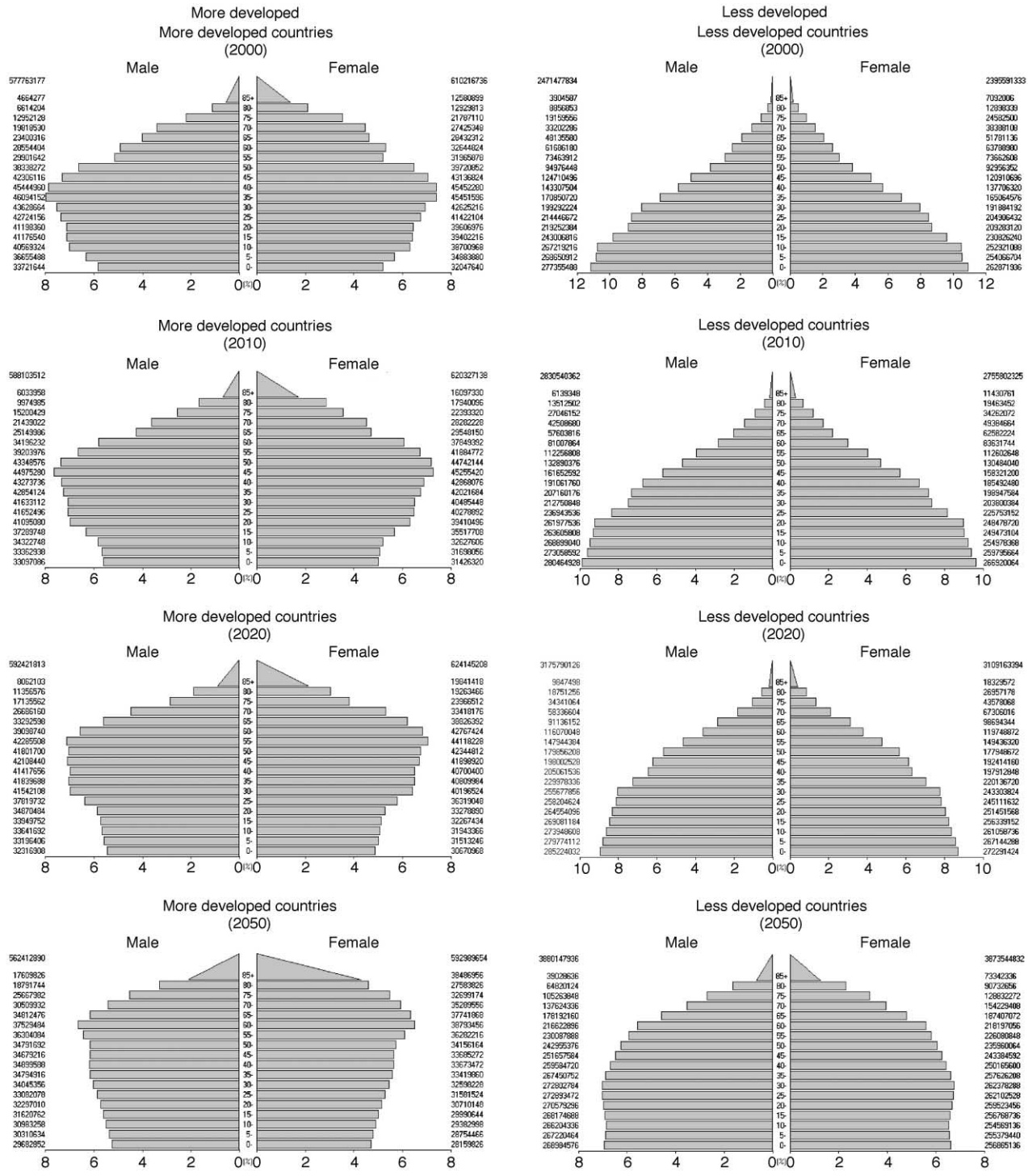


Fig. 29. Projected population pyramids in more and less developed regions in 2000, 2010, 2020 and 2050.

As well as the demographic changes taking place, major social and economic trends will also have an impact on the role and future support of elderly people, particularly so in less developed countries. Fundamental changes in society—such as that of family structure, modernisation and increasing education—will have consequences on the support and care of elderly persons [302].

3.1.2. Urbanisation

In the last few decades, a rapid increase in urbanisation has occurred in both developed and developing regions (Fig. 32). In 1950, 71% of the global population lived in rural areas compared with 29% in urban areas. By 1990, the proportions were 55% rural and 45% urban and by 2025 they are projected to be 35 and 65%, respectively. The shift from rural to urban settings

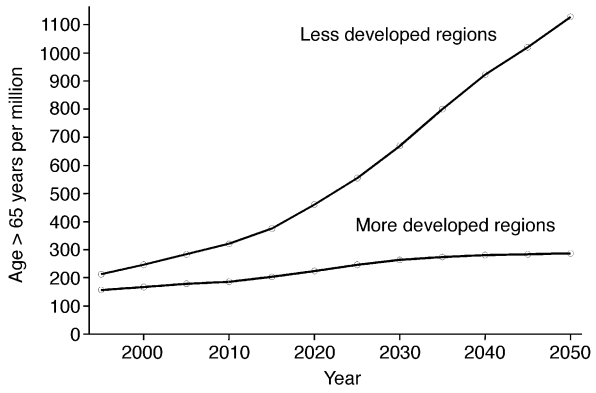


Fig. 30. Projected number of person aged 65 years or over in more and less developed regions, 2000–2050.

occurring within populations in developing areas is particularly dramatic—an anticipated 61% will live in urban areas by 2025 (compared with only 17% in 1950). This urban expansion has been accompanied by massive urban poverty [303]. The urban growth rate of 4.5% per annum around 1990 in less developed regions was twice that of the population growth rate, although such rapid change cannot be sustained for long into the future. In developed countries, urbanisation took place much earlier, current rates of urbanisation are less (0.8% around 1990) and will also decline in the future (to 0.5% by 2025). Currently, Latin America is the most urbanised of the less developing regions—by 2025 only 16% of the

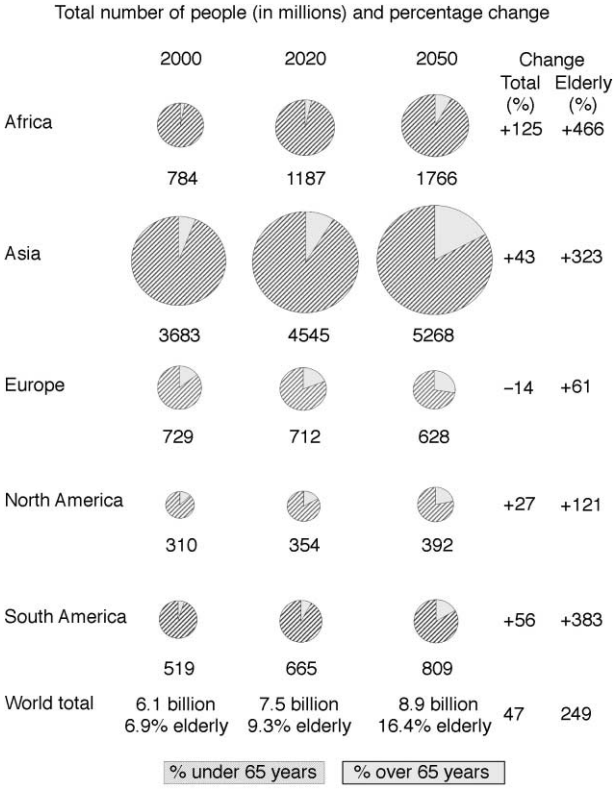


Fig. 31. Population growth and ageing: 2000–2050.

population will be living in rural areas according to UN projections.

The relationship between health status and rapid urbanisation is a complex one. The process equates with improved health status if urbanisation brings the beneficial effects of improved sanitation and refrigeration together with increased availability of and accessibility to healthcare facilities [304]. However, when one considers that about one-third of the current urban population of developing countries lives in slums and shanty towns, it is clear that this group are also at risk of adverse health effects [305]. Most studies investigating the urban poor have concentrated on environmental conditions and health rather than the effects of lifestyle modifications [305] such as changes in diet [306], smoking and alcohol consumption and sexual and reproductive behaviour [307,308], yet these are known to be the major determinants of risk for the most important cancers [309].

3.2. Projections using GLOBOCAN 2000

Age is a powerful determinant of cancer risk. In general terms, the risk of epithelial cancers (currently more than 90% of all cancers in the world) increase approximately as a fifth power of age [310]—approximately a 1000-fold difference in cancer rates between young (aged 20 years) and old persons (aged 80 years). Globally, an estimated 46% of the one million new cancers in 2000 occurred in persons aged 65 years or over.

This section examines the impact of the increases in the overall population and increasing proportions of elderly on the annual number of new cancer cases and deaths in the next half century. The most recent estimated rates of all cancers combined, and of six of the most common cancers in 2000 (stomach, colorectal, lung, female breast, cervix and prostate cancer), have been applied to the age and sex-specific population projections for 2000, 2010, 2020 and 2050.

3.2.1. Changes in total cancer cases and deaths

Fig. 33 shows the number of new cases and deaths from cancer in the major world regions, which are projected to occur at three future periods in the next half century, together with a histogram to illustrate the relative burden in each area by year of projection. Site-specific details of the projected numbers of cases and deaths at different future times are shown by world area in Tables 4 and 5.

It is clear that population growth and ageing, as it is projected to occur in the next 50 years, would have a massive impact on the number of new cancer cases and deaths. With current rates, the 10 million cases in 2000 would increase by a further 25% in each of the two decades that follow and, by 2050, the number of new cancers would be nearly 24 million. The number of

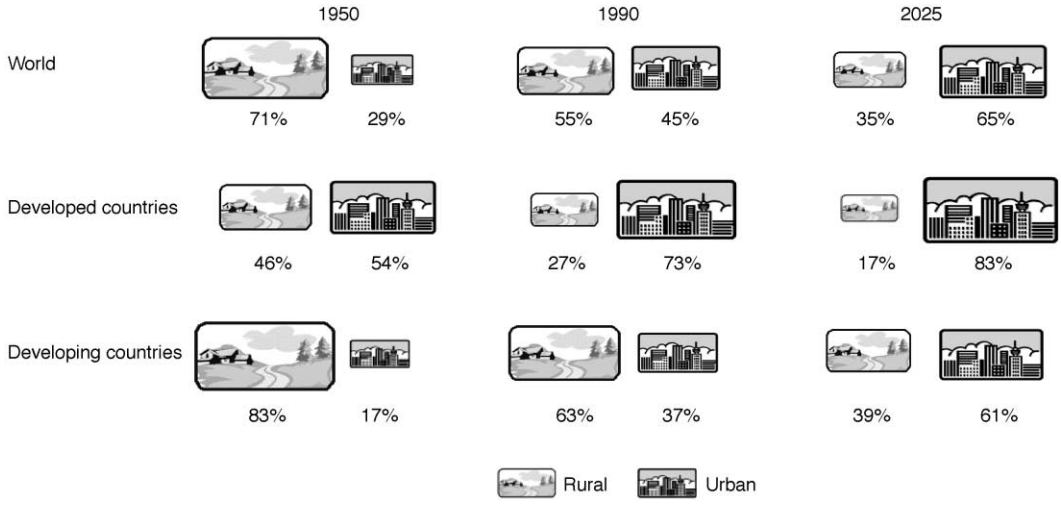


Fig. 32. Urban–rural division of the population.

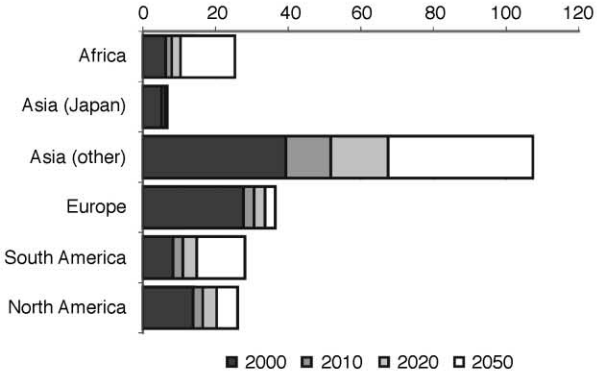
cancer deaths would rise from 6.2 million in 2000 to nearly 10 million by 2020 and, by 2050, 16 million deaths would occur globally.

In 2000, there were slightly more new cancer cases (53%) and deaths (57%) occurring in less developed than in developed countries. We have already noted that the biggest changes in the demography of the world in the next 50 years will take place in developing areas. Consequently, more and more of the relative future cancer burden will be in these regions—compare the estimated 50% increase in cancer incidence between 2000 and 2050 in more developed regions with that of developing regions where incidence is estimated to triple over the same period. Thus, by 2020, population projections suggest that some 9 million new cases will occur in developing countries compared with 6 million in more developed regions. By 2050, the burden will be over 17 million and 7 million new cases in developing and developed areas, respectively.

Population ageing means that the bulk of future burden of cancer will lie in the elderly populations of both the developed and less developed areas. In 2000, 46% of

(a)

The number of new cases (in 100 000s) of all cancers				
Region	2000	2010	2020	2050
World	100.6	123.4	153.5	238.3
More developed regions	46.8	53.1	60.3	67.9
Less developed regions	53.8	70.3	93.2	170.4
Africa	6.3	7.9	10.4	25.3
Asia (Japan)	5.2	6.1	6.7	6.5
Asia (other)	39.4	51.7	67.5	107.4
Europe	27.7	30.6	33.6	36.4
South America	8.3	11.0	14.8	28.1
North America	13.8	16.5	20.3	26.1
Oceania	1.1	1.3	1.6	2.4



(b)

The number of new deaths (in 100 000s) of all cancers				
Region	2000	2010	2020	2050
World	62.1	770	97.9	160.0
More developed regions	26.5	30.2	35.0	40.7
Less developed regions	35.6	46.8	62.9	119.3
Africa	4.0	5.1	6.7	16.7
Asia (Japan)	2.7	3.6	4.0	4.0
Asia (other)	27.1	35.8	47.9	86.0
Europe	17.1	18.9	21.3	24.0
South America	4.6	6.4	8.7	16.8
North America	6.4	7.7	9.7	12.8
Oceania	0.5	0.6	0.8	1.2

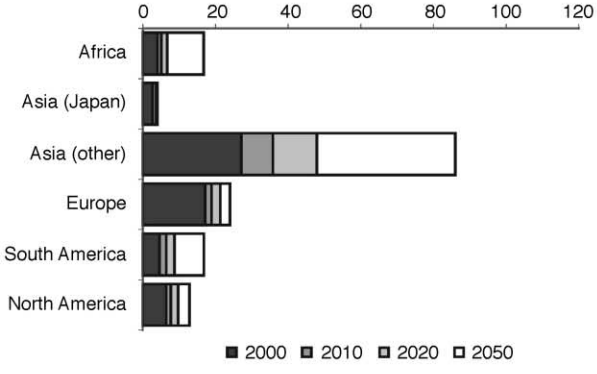


Fig. 33. Projected demographic effects on cancer burden: (a) incidence, (b) mortality. Part of this figure is reprinted from *The Lancet Oncology* 2001, **2**(9), 533–543.

Table 4
Projected demographic effects on cancer burden: incidence

	The number of deaths (thousands)			
	2000	2010	2020	2050
Stomach cancer				
World	880	1110	1440	2440
More developed regions	330	380	440	510
Less developed regions	540	730	990	1930
Africa	30	40	50	30
Asia (Japan)	120	140	150	150
Asia (other)	450	670	900	1510
Europe	190	240	260	300
South America	70	90	120	250
North America	30	30	40	50
Oceania	<10	<10	<10	10
Colorectal cancers				
World	940	1140	1390	2080
More developed regions	610	700	800	940
Less developed regions	330	440	590	1140
Africa	20	30	40	100
Asia (Japan)	80	100	110	100
Asia (other)	260	340	450	820
Europe	360	400	440	510
South America	60	80	100	210
North America	170	190	240	320
Oceania	10	20	20	30
Lung cancer				
World	1230	1540	2030	3160
More developed regions	650	750	840	990
Less developed regions	590	790	1190	2170
Africa	20	20	30	90
Asia (Japan)	70	80	90	90
Asia (other)	510	690	950	1780
Europe	380	420	480	520
South America	60	80	110	240
North America	210	260	330	420
Oceania	10	10	20	20
Female breast cancer				
World	1050	1250	1480	1970
More developed regions	580	640	690	710
Less developed regions	470	610	790	1260
Africa	60	80	100	230
Asia (Japan)	30	30	30	30
Asia (other)	320	420	520	750
Europe	350	370	390	380
South America	90	130	170	290
North America	200	230	270	330
Oceania	10	20	20	30
Cervical cancer				
World	470	600	740	1130
More developed regions	90	100	100	100
Less developed regions	380	500	640	1030
Africa	70	90	110	280
Asia (Japan)	10	10	10	10
Asia (other)	230	300	390	580
Europe	60	70	70	60
South America	80	100	130	210
North America	10	20	20	20
Oceania	<10	<10	<10	10

(continued)

Table 4 (*continued*)

	The number of deaths (thousands)			
	2000	2010	2020	2050
Prostate cancer				
World	540	660	820	1250
More developed regions	420	490	580	710
Less developed regions	130	170	240	540
Africa	30	30	40	140
Asia (Japan)	10	20	20	20
Asia (other)	50	60	90	200
Europe	190	210	250	310
South America	50	70	100	230
North America	210	250	330	430
Oceania	10	20	20	30

cancers occurred in people aged 65 years or more (57% cases in developed countries and 42% in developing countries). This can be projected to rise to 57% of all cancers occurring in the elderly in 2050 (71% in developed countries, and 53% in developing countries). Inevitably the increasing number of patients requiring care will put a strain on health resources in future decades yet, for many nations, adequate provision has not yet been planned [311]. Future practice and training of oncologists is also of considerable importance [312].

3.2.2. Changes for the major cancers

Projections based on demographic change alone result in rather little change in the relative importance of different cancers. Thus, lung cancer, the most common cancer globally in 2000, would remain so for the next 50 years. The current estimated number of new cases worldwide of 1.2 million is set to rise about a quarter in 2010 and in 2020, reaching over 3 million by 2050 (Table 4). The change in the number of deaths from lung cancer would be of the same magnitude, reaching nearly 2.9 million by 2050 (Table 5).

These figures are based on current incidence and mortality rates and we know for sure that these will not be maintained in future. As described, incidence of lung cancer is on the decline in men in many European countries, the USA, and Australia/New Zealand. In women, mortality is already declining in the UK (Fig. 8b) and will begin to decline in US women after 2000 [313]. Thus, the burden will be less than projected in these areas. However, in many Eastern European countries, lung cancer incidence is increasing rapidly due to the previous smoking habits of these populations.

In any case, any decrease in the global burden of this cancer observed in developed areas will be offset by both demographic and environmental changes occurring within less developed regions. It is estimated that population growth in developing nations alone will mean the lung cancer burden will be double that of developed areas by 2050 (Table 4). The anticipated upsurge of new cases as the penetration of manufactured cigarettes into these new markets takes effect will further increase the burden. For instance, in China (where two-thirds of men but few women smoke), an estimated one in three of the male population aged 0–29 years will be killed by smoking if the current cigarette uptake rates are not reversed [314].

We can be fairly sure that the projected numbers of stomach cancer cases and deaths are overestimated; rates of incidence and mortality have been declining in most countries in both developed and developing areas (Fig. 15a and b). This is ascribed to improved diet and especially to changes in food storage and preservation. It seems reasonable to expect these trends to continue. So, with an annual decrease in rates of 1%, an approximation based on global changes in recorded incidence in the last decade, the projected numbers would be 0.9 million in 2020 and less than 0.8 million in 2050. However, such assumptions, even in the apparently simple case of stomach cancer, may be hard to justify; in the next few years, the rates may begin to stabilise in developed countries as the margin for improvement in food conservation and diet, and of infections with *H. pylori*, become less.

There were over 0.94 million estimated new cases of colon and rectal cancer in 2000 and, based on current rates, by the mid-half of the century the figure is predicted to rise to over two million cases. The proportion of these cancers in developing and developing countries would change dramatically: the 35% share of world burden in developing countries in 2000 would, by 2050, reach 55% of all colorectal cancers occurring worldwide (Table 4). The proportions are similar for mortality (Table 5).

The annual number of new cases in Asia is projected to increase 3-fold due to demographic changes alone while, in South America and Africa, the projected changes are even more striking—an increase in burden of nearer 4- and 5-fold, respectively, is anticipated in these areas. It is quite likely that the incidence of colorectal cancer in these areas will exceed these projec-

Table 5
Projected demographic effects on cancer burden: mortality

	The number of deaths (thousands)			
	2000	2010	2020	2050
Stomach cancer				
World	650	810	1060	1900
More developed regions	230	260	300	360
Less developed regions	420	550	760	1540
Africa	20	30	40	110
Asia (Japan)	60	70	80	80
Asia (other)	340	460	640	1200
Europe	160	180	200	220
South America	50	70	100	200
North America	20	20	30	30
Oceania	<10	<10	<10	<10
Colorectal cancers				
World	490	590	740	1160
More developed regions	300	340	400	480
Less developed regions	190	250	340	680
Africa	20	20	30	70
Asia (Japan)	40	40	50	50
Asia (other)	150	190	260	500
Europe	200	220	250	290
South America	30	40	50	110
North America	70	80	100	140
Oceania	10	10	10	10
Lung cancer				
World	1110	1360	1740	2860
More developed regions	580	670	780	910
Less developed regions	520	690	960	1950
Africa	20	20	30	80
Asia (Japan)	50	70	70	80
Asia (other)	450	600	890	1590
Europe	350	390	440	500
South America	60	80	110	220
North America	180	220	280	370
Oceania	10	10	10	20
Female breast cancer				
World	370	450	540	770
More developed regions	190	210	230	250
Less developed regions	180	240	310	520
Africa	30	30	50	100
Asia (Japan)	10	10	10	10
Asia (other)	130	160	210	320
Europe	130	140	150	160
South America	30	40	60	100
North America	50	60	70	90
Oceania	<10	<10	10	10
Cervical cancer				
World	230	300	390	620
More developed regions	40	40	50	50
Less developed regions	190	260	340	570
Africa	40	50	60	150
Asia (Japan)	<10	<10	<10	<10
Asia (other)	120	170	220	340
Europe	30	30	30	30
South America	30	40	50	90
North America	10	10	10	10
Oceania	<10	<10	<10	<10

(continued)

Table 5 (*continued*)

	The number of deaths (thousands)			
	2000	2010	2020	2050
Prostate cancer				
World	200	250	320	580
More developed regions	130	150	180	240
Less developed regions	80	100	140	330
Africa	20	20	30	90
Asia (Japan)	10	10	10	10
Asia (other)	30	40	50	120
Europe	80	90	110	140
South America	30	40	60	140
North America	40	50	70	90
Oceania	<10	<10	10	10

tions—the rates in many parts of Asia are known to be increasing, as described earlier. In developed countries, where risk of these cancers is high, the converse may be true; rates in many countries have begun to decline in younger generations and this is already having an effect on overall (all ages) incidence in the USA and Canada (Fig. 17a). Therefore, the projected future incidence is probably overestimated. On top of this, it is clear that mortality rates are declining faster than incidence (Fig. 17b) due to earlier diagnosis and better treatment; perhaps this trend will continue in the developed world and perhaps it will become more generalised.

Breast cancer is projected to remain the most common cancer in women in the next half century. Changes in global population structure suggest that the one million cases estimated worldwide in 2000 will rise to nearly 1.5 million cases in 2020 (Table 4). By 2050, the number of new cases is projected to reach nearly two million. Mortality, though considerably lower than incidence, will reach 0.8 million by 2050 (Table 4). As population growth in the next 50 years will occur mainly in developing areas, the major increases in breast cancer burden reflect this—the burden will nearly triple between 2000 and 2050, reaching nearly 1.3 million. The number of deaths from breast cancer in these areas is set to rise to over half a million by 2050. As with many other cancers, Asia will continue to have the highest incidence and mortality in the developing world although very large increases are projected for Africa and South America relative to the 2000 estimates.

Rapidly increasing rates of breast cancer incidence in many developing countries suggest that the burden of this disease will be very much greater than projections based on demographic change alone imply. For the most part, incidence rates are still rising in developed countries, although the increases are much more modest. Some of these changes may related to declining fertility as well as to better nutrition and greater body size; quite possibly, both will continue into the future although the potential for further change is clearly greatest in the developing world. As far as mortality rates are concerned, it is likely that any increases will be less than for incidence as the improvements in survival (due to earlier diagnosis and better treatment) observed in the USA and UK become more widespread.

The worldwide burden from cervical cancer, the second most common cancer in women in 2000, is projected to double by 2050 to 1.1 million new cases annually (Table 4). Mortality, currently approximately 0.23 million, will rise to nearly two-thirds of a million by 2050 (Table 5). Today (in 2000), the great majority of cases (81%) and deaths (83%) occur in less developed areas. In developed areas, projected demographic change would mean that the annual incidence and mortality remained relatively constant—around 110 000 cases and 50 000 deaths per year. Almost all of the projected growth in cervical cancer burden will occur in less developed countries where, for many regions (e.g. Central America and Eastern Africa), the risk is already high. Nearly two-thirds of the burden will be in Asia—about 0.6 million cases are expected in 2050 based on demographics alone. In Africa, cervical cancer incidence would quadruple between 2000 and 2050.

It is possible that these projections will be modified by changes in incidence. There is probably not much scope for early detection to decrease incidence and mortality further in developed countries. However, this remains entirely feasible in developing countries and is one of the major challenges facing global cancer control. The advent of an effective vaccine against human papillomaviruses would have a profound effect although the delay before it influenced incidence rates would depend on whether this was a therapeutic vaccine (to eliminate established infection) or a prophylactic vaccine (to prevent it).

As might be expected, the biggest increase in incidence that would occur through population growth and ageing, is for prostate cancer—an annual growth of approximately 2%—to result in over 1.25 million new cases by 2050 (Table 4). Currently, around 78% of cases occur in the developed world but this will also change so that this proportion would be around 57% by 2050. In

fact, the projections probably considerably underestimate the future burden of prostate cancer. Although rates in some western countries—especially in the USA—have been raised by PSA screening, it seems as if the large 'wave' in incidence rates (due to detection of the pool of prevalent cases) has now largely subsided and it is not yet clear whether rates will decline beyond those observed in 1996 (Fig. 23). In contrast, incidence rates are rising rapidly in developing countries, especially in Asia and Africa, at rates of 2–5% annually. Increases of this order (3.5%) would imply over one million cases in developing countries by the year 2050 and a world total of over 1.8 million (assuming no change in rates in developed countries). This would rank prostate cancer above stomach cancer as the second most common cancer of men by the mid-half of the century.

4. Conclusions

Compared with most diseases, cancer is relatively easy to enumerate. As a result, disease registration is more successful as a means of surveillance than for almost any other condition. Our ability to supplement statistics on deaths with information on risk and survival greatly strengthens our ability to infer cause and to evaluate the effects of early diagnosis and therapy. For most countries of the world, some form of cancer data is available which permit us to estimate incidence, mortality and prevalence. As a result, we can build up a reasonably accurate picture of the current cancer profile worldwide and how this is evolving over time.

In this paper, we have summarised the global cancer pattern using the latest available data from different countries applied to the world population in the year 2000. We have also summarised current knowledge on the environmental and genetic determinants of eight major cancers, comprising almost two-thirds of the world total. Traditionally, geographical, ethnic and temporal differences in risk have been used to infer preventability of cancer (e.g. Ref. [317]) but when we have discussed qualification of the fraction of cancers attributable to a given agent, this has been based on information on the prevalence of exposure, and the magnitude of the risk which it poses.

Projections of past experience into the future are notoriously unreliable. There are quite formidable technical problems to overcome, including the requirement for fairly extensive historical data (in order to account for changes in risk or mortality between generations, or over time) and assumptions concerning the attenuation of logarithmic increases or decreases into the future. Even with perfect projections, we may be fairly sure that past experience of exposure to causative or preventive factors, or the availability of preventive and therapeutic procedures, is not a sure guide to the future. For this reason, future scenarios are confined to consideration of the effects of probable demographic changes, with a note on how this would be modified on the basis of existing patterns of change in risk and survival.

In any case, the only purpose of building up knowledge on the present and future cancer burden is as a guide to priorities for research and for implementation of existing knowledge on how to prevent, cure and alleviate suffering from cancer.

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