

# Global Cancer Statistics, 2002

D. Max Parkin, MD; Freddie Bray; J. Ferlay; Paola Pisani, PhD

**Dr. Parkin** is Chief, Unit of Descriptive Epidemiology, International Agency for Research on Cancer, Lyon, France.

**Mr. Bray** is Epidemiologist, Unit of Descriptive Epidemiology, International Agency for Research on Cancer, Lyon, France.

**Mr. Ferlay** is Informatics Officer, Unit of Descriptive Epidemiology, International Agency for Research on Cancer, Lyon, France.

**Dr. Pisani** is Scientist, Unit of Descriptive Epidemiology, International Agency for Research on Cancer, Lyon, France.

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**ABSTRACT** Estimates of the worldwide incidence, mortality and prevalence of 26 cancers in the year 2002 are now available in the GLOBOCAN series of the International Agency for Research on Cancer. The results are presented here in summary form, including the geographic variation between 20 large “areas” of the world. Overall, there were 10.9 million new cases, 6.7 million deaths, and 24.6 million persons alive with cancer (within three years of diagnosis). The most commonly diagnosed cancers are lung (1.35 million), breast (1.15 million), and colorectal (1 million); the most common causes of cancer death are lung cancer (1.18 million deaths), stomach cancer (700,000 deaths), and liver cancer (598,000 deaths). The most prevalent cancer in the world is breast cancer (4.4 million survivors up to 5 years following diagnosis). There are striking variations in the risk of different cancers by geographic area. Most of the international variation is due to exposure to known or suspected risk factors related to lifestyle or environment, and provides a clear challenge to prevention. (CA Cancer J Clin 2005;55:74–108.) © American Cancer Society, Inc., 2005.

## INTRODUCTION

For the last 30 years, the International Agency for Research on Cancer has prepared estimates of the global cancer burden. Beginning in 1975 with broad estimates of numbers of new cases for 12 common types of cancer in different areas of the world,<sup>1</sup> we were able to provide detailed country-specific estimates of incidence, mortality, and prevalence, by sex and age group for 26 types of cancer in the year 2000.<sup>2</sup> The latter set of estimates<sup>3</sup> has recently been updated using newer sources of data and improved methods of estimation to prepare global estimates for the year 2002.<sup>4</sup> As before, the emphasis is on three measures of the burden of cancer worldwide: incidence, mortality, and prevalence.

*Incidence* is the number of new cases occurring, expressed as an absolute number of cases per year or as a rate per 100,000 persons per year. The latter approximates the average risk of developing a cancer in one year and is used for comparisons between countries or world areas, or within populations over time. Primary prevention strategies aim to reduce incidence, although increasing incidence does not necessarily reflect failure in primary prevention. The introduction of programs for early detection results in a temporary increase in incidence as subclinical cancer cases are discovered. This increase will be maintained if some of the cases being detected represent “overdiagnosis” (ie, cancers that would otherwise never have been diagnosed in the individual’s life).

*Mortality* is the number of deaths occurring, and the mortality rate is the number of deaths per 100,000 persons per year. Mortality is the product of the incidence and the fatality for a given cancer. Fatality, the inverse of survival, is the proportion of cancer cases who die; mortality rates therefore measure the average risk to the population of dying from a specific cancer within a specified period (usually one year), while fatality (1-survival) represents the probability that an individual with cancer will die from it. Mortality rates are often used (instead of incidence) as a convenient proxy measure of the risk of acquiring the disease, but this assumes that fatality (or survival, which is 1-fatality) is constant between the populations being compared. This may be so for cancers with a poor prognosis, but it is much less likely for those for which early diagnosis and/or therapy can markedly influence outcome.

*Prevalence* describes the number of persons alive at a particular point in time with the disease of interest. For cancer, there is no clear agreement on what is meant by “having” the disease. Some authors take it to mean ever having been diagnosed with cancer, even if this was many years ago, and the subject is cured. This makes little sense. It would be more useful to

consider as “alive with cancer” those persons still receiving some form of treatment (or at least being followed up medically for the disease). Such a statistic is not only hard to obtain, but its magnitude and interpretation would certainly vary between populations, depending on medical practice. For comparison purposes, therefore, prevalence is generally presented as the number of persons still alive after a given number of years following diagnosis. Survival up to five years postdiagnosis is frequently used since “cure” is often taken to equate with survival beyond five years, at least for statistical purposes,<sup>5</sup> and this is the definition of prevalence used in GLOBOCAN. The number of survivors to five years in the United States is about 4 million. The frequently cited figure of 9 million cancer survivors represents persons diagnosed in the past 26 years.

The GLOBOCAN estimates give information on the relative importance of different cancers worldwide in terms of the absolute numbers and rates of persons developing, living with (five-year prevalence), or dying from cancer in the year 2002.

#### ESTIMATION

The global estimates are built up from estimates of incidence, mortality, and prevalence in each of the national populations of the world. The methods used have been described with respect to earlier estimates for 1990.<sup>5–7</sup> The basic data are the best available information on incidence, mortality, and survival in a country. Incidence rates are obtained from cancer registries. They may cover entire national populations or selected regions. Because registries also record mortality from cancer, the ratio of cases to deaths allows incidence to be estimated from mortality in similar populations. Mortality data, derived from the registration of deaths, are available for many countries, via WHO (<http://www.who.int/whosis/>), although the degree of detail and quality of the data (both the accuracy of the recorded cause of death and the completeness of registration) vary considerably. To reduce this problem, two types of correction have been applied: an adjustment for quantified underrecording of deaths and a redistribution of deaths

recorded as “uterus cancer” to the specific sites of cervix or corpus uteri. Estimation methods are used when recorded data are not available. For example, national incidence rates would be derived, in order of priority, from:

- National incidence data from good quality cancer registries
- National mortality data, with estimation of incidence using sets of regression models, specific for site, sex, and age, derived from local cancer registry data (incidence plus mortality). The models may be specific to country, region, or developing countries as a whole.
- Local (regional) incidence data from one or more regional cancer registries within a country
- Frequency data, when only data on the relative frequency of different cancers (by age and sex) are available. The frequencies are applied to an estimated “all sites” incidence rate derived from existing cancer registry results in the same region. The eight regions were the five areas of Africa, the Middle East, the Caribbean, and “Other Oceania” (island states of the Pacific).
- No data: The country-specific rates are those of the appropriate world area (calculated from the other countries for which estimates could be made).

Analogous procedures were followed for mortality, so that for countries where mortality data were unavailable or known to be of poor quality, they were estimated from incidence, using country/region-specific survival.

The country-specific incidence and mortality rates were estimated for 26 different types of cancer by sex, for five broad age groups (0–14, 15–44, 45–54, 55–64, and 65 years and over). Age-standardized rates (ASRs) were also calculated; these take into account differences in the age structure of the populations being compared. This is necessary because the incidence and mortality rates for most cancers increase rapidly with age, so that populations containing a high proportion of old people will tend to have a higher overall (crude) rate than one with mainly young people. Because we wish to know the risk *irrespective* of this incidental (confounding) effect, we compare populations *as if*

they had exactly the same age structure—that of the so called world standard population. The weights of the world standard population for the five age group are: 0.31, 0.43, 0.11, 0.08, and 0.07. The cumulative risk of developing a cancer before the age of 64 was also calculated using the age-specific rates and expressed as a percentage.<sup>8</sup>

Estimates for 20 world areas, as defined by the United Nations Population Division (Figure 1), were obtained by combining age- and sex-specific rates for component countries as a weighted average (using the corresponding country populations).

Prevalence was estimated from incidence and survival.<sup>5</sup> Survival data were more extensive than had been previously available. As well as data for European countries,<sup>9</sup> the United States (Surveillance, Epidemiology, and End Results Program

[SEER]),<sup>10</sup> Australia, Japan, China and India, and estimates of survival specific to Africa,<sup>11,12</sup> and for other developing countries<sup>13</sup> were used.

A full description of the data used for each country and the detailed set of estimates are available in GLOBOCAN 2002.<sup>4</sup> The database itself may be downloaded from the Internet (<http://dep-iarc.fr>). The most recent incidence and mortality data on which the estimates have been based are from periods between 1993 and 2001. These rates are used together with population estimates for the year 2002<sup>14</sup> as the best possible estimate of global cancer burden in the year 2002. Incidence and mortality rates were not projected to the year 2002. For one thing, time trend data are necessarily based on historic patterns, which are not always a sound basis for future projections. In addition, for most of the world, there simply are insufficient historical data



FIGURE 1 Map Showing the 20 World Areas Studied.

to permit such modeling. It is not easy to predict what effect the use of old rates (mainly from 1997–2000) will have on the accuracy of the burden estimate for 2002. For cancer sites where rates are generally increasing worldwide (eg, prostate cancer and breast cancer incidence), there will be an underestimate of new cases, and where there is a global decrease (eg, stomach cancer), an overestimate. However, unless the rate of change is very large, the effect will be rather small (for example, a rate of change of  $\pm 1.5\%$  a year would change the estimated rates by about 10% in 7 years). In any case, for several sites, trends are in different directions in different world regions and are moreover likely to have changed direction in the last decade (eg, lung cancer, colorectal cancers, and cervix cancer), so that the net effect is difficult to guess but likely to be rather modest.

It should be clear that the estimates are more or less accurate for different countries, depending on the extent and validity of the data available. For example, for the Nordic countries, there are high quality incidence and mortality statistics available nationally, while for several developing countries (eg, Afghanistan, Madagascar, Ghana), there are no available data at all, and the estimate is made from data obtained from neighboring populations. Nevertheless, the method does rely on what is best available at the country level and permits continuous updating of the GLOBOCAN database as newer data become available.

#### THE 2002 ESTIMATES

The results are presented in terms of global totals and by world area (Figure 1). *Developed countries* comprise areas 9, 10b, and 14 to 18 of Figure 1, and *developing countries* comprise the remainder. The terms “Westernized” and “industrialized” are used as synonyms of “developed.” Incidence of Kaposi sarcoma has been estimated only for Africa; even with the epidemic of acquired immunodeficiency syndrome (AIDS), it is a rare cancer elsewhere, and so it only appears within the overall totals for these areas. No attempt has been made to estimate

incidence or mortality of nonmelanoma skin cancer because of the difficulties of measurement and consequent lack of data. The total “All Cancer” therefore excludes such tumors.

We estimate that there were 10.9 million new cases, 6.7 million deaths, and 24.6 million persons living with cancer (within 5 years of diagnosis) in the year 2002. Table 1 shows the estimated numbers of cases and deaths for 26 cancers in men and women, together with the age standardized incidence and mortality rates and the cumulative risk (%) between ages 0 and 64. There are some differences in the profile of cancers worldwide depending on whether incidence or mortality is the focus of interest. Lung cancer is the main cancer in the world today, whether considered in terms of numbers of cases (1.35 million) or deaths (1.18 million), because of the high case fatality (ratio of mortality to incidence, 0.87). Breast cancer, the second most common cancer overall (1.15 million new cases), ranks less highly (fifth) as a cause of death because of the relatively favorable prognosis (mortality to incidence ratio, 0.35), and cancers of the stomach (934,000 cases, 700,000 deaths), liver (626,000 cases, 598,000 deaths), and colon and rectum (1.02 million cases, 529,000 deaths) rank more highly.

Figure 2 summarizes these results, showing the ranking of cancers for men and women as number of new cases, together with the corresponding numbers of deaths in the developing and developed regions of the world. In men, although lung cancer is the most common cancer worldwide, it is in second place behind cancers of the prostate in developed countries. In women, cervix cancer, second in importance in developing countries, is but seventh in the developed world, with fewer cases (83,000) than for cancer of the corpus uteri (136,000) and ovary (97,000).

#### Survival

Statistics on survival from cancer are available from cancer registries and are sometimes published in a format permitting comparisons between different centers within a country (eg, the US SEER registries<sup>10</sup>) or between cancer registries in different countries (eg, EUROCARE 3<sup>9</sup>)

TABLE 1 Incidence and Mortality by Sex and Cancer Site Worldwide, 2002

	INCIDENCE						MORTALITY					
	MALES			FEMALES			MALES			FEMALES		
	Cases	ASR (World)	Cumulative risk (age 0–64)	Cases	ASR (World)	Cumulative risk (age 0–64)	Deaths	ASR (World)	Cumulative risk (age 0–64)	Deaths	ASR (World)	Cumulative risk (age 0–64)
Oral cavity	175,916	6.3	0.4	98,373	3.2	0.2	80,736	2.9	0.2	46,723	1.5	0.1
Nasopharynx	55,796	1.9	0.1	24,247	0.8	0.1	34,913	1.2	0.1	15,419	0.5	0.0
Other pharynx	106,219	3.8	0.3	24,077	0.8	0.1	67,964	2.5	0.2	16,029	0.5	0.0
Esophagus	315,394	11.5	0.6	146,723	4.7	0.3	261,162	9.6	0.5	124,730	3.9	0.2
Stomach	603,419	22	1.2	330,518	10.3	0.5	446,052	16.3	0.8	254,297	7.9	0.4
Colon/rectum	550,465	20.1	0.9	472,687	14.6	0.7	278,446	10.2	0.4	250,532	7.6	0.3
Liver	442,119	15.7	1.0	184,043	5.8	0.3	416,882	14.9	0.9	181,439	5.7	0.3
Pancreas	124,841	4.6	0.2	107,465	3.3	0.1	119,544	4.4	0.2	107,479	3.3	0.1
Larynx	139,230	5.1	0.3	20,011	0.6	0	78,629	2.9	0.2	11,327	0.4	0.0
Lung	965,241	35.5	1.7	386,891	12.1	0.6	848,132	31.2	1.4	330,786	10.3	0.5
Melanoma of skin	79,043	2.8	0.2	81,134	2.6	0.2	21,952	0.8	0.0	18,829	0.6	0.0
Kaposi sarcoma*				1,151,298	37.4	2.6				410,712	13.2	0.9
Breast				493,243	16.2	1.3				273,505	9.0	0.7
Cervix uteri				198,783	6.5	0.4				50,327	1.6	0.1
Corpus uteri				204,499	6.6	0.5				124,860	4.0	0.2
Prostate	679,023	25.3	0.8				221,002	8.2	0.1			
Testis	48,613	1.5	0.1				8,878	0.3	0.0			
Kidney	129,223	4.7	0.3	79,257	2.5	0.1	62,696	2.3	0.1	39,199	1.2	0.1
Bladder	273,858	10.1	0.4	82,699	2.5	0.1	108,310	4.0	0.1	36,699	1.1	0.0
Brain, nervous system	108,221	3.7	0.2	81,264	2.6	0.2	80,034	2.8	0.2	61,616	2.0	0.1
Thyroid	37,424	1.3	0.1	103,589	3.3	0.2	11,297	0.4	0.0	24,078	0.8	0.0
Non-Hodgkin lymphoma	175,123	6.1	0.3	125,448	3.9	0.2	98,865	3.5	0.2	72,955	2.3	0.1
Hodgkin disease	38,218	1.2	0.1	24,111	0.8	0.1	14,460	0.5	0.0	8,352	0.3	0.0
Multiple myeloma	46,512	1.7	0.1	39,192	1.2	0.1	32,696	1.2	0.1	29,839	0.9	0.0
Leukemia	171,037	5.9	0.3	129,485	4.1	0.2	125,142	4.3	0.2	97,364	3.1	0.2
All sites but skin	5,801,839	209.6	10.3	5,060,657	161.5	9.5	3,795,991	137.7	6.4	2,927,896	92.1	4.9

\*Africa only.

or several developing countries.<sup>13</sup> Survival statistics are usually presented as relative survivals, or the probability of dying from a specific cancer relative to the probability in the general population. Comparison of results from different centers requires some form of age standardization; otherwise, the age distribution of the patient population, which may markedly influence the survival probability, may be quite different.

The ratio of mortality to incidence represents the approximate case fatality ratio for a given cancer; a figure of 0.7, for example, means that 70% of new cases will die (or conversely, that 30% will survive). Because the great majority of deaths due to cancer occur within five years of diagnosis, survival, as obtained from (mortality/incidence) is rather close to the five-year survival rate obtained by the actual follow-up of groups of new cancer cases.<sup>15,16</sup>

In Table 2, we show estimates of survival based on the ratio of age-adjusted mortality and incidence of 11 major cancers in 8 populations to give an idea of the differences between regions. The average value for all developed and developing areas is also shown. In general, survival is better in the developed countries/areas than in developing, although Eastern Europe is an exception, with an estimated survival that is inferior to that in South America for most cancer sites.

#### Prevalence of Cancer

Figure 3 shows the most prevalent cancers worldwide in men and women, together with the number of annual new cases at the same site. In terms of prevalence, breast (17.9%), colorectal (11.5%), and prostate (9.6%) cancers

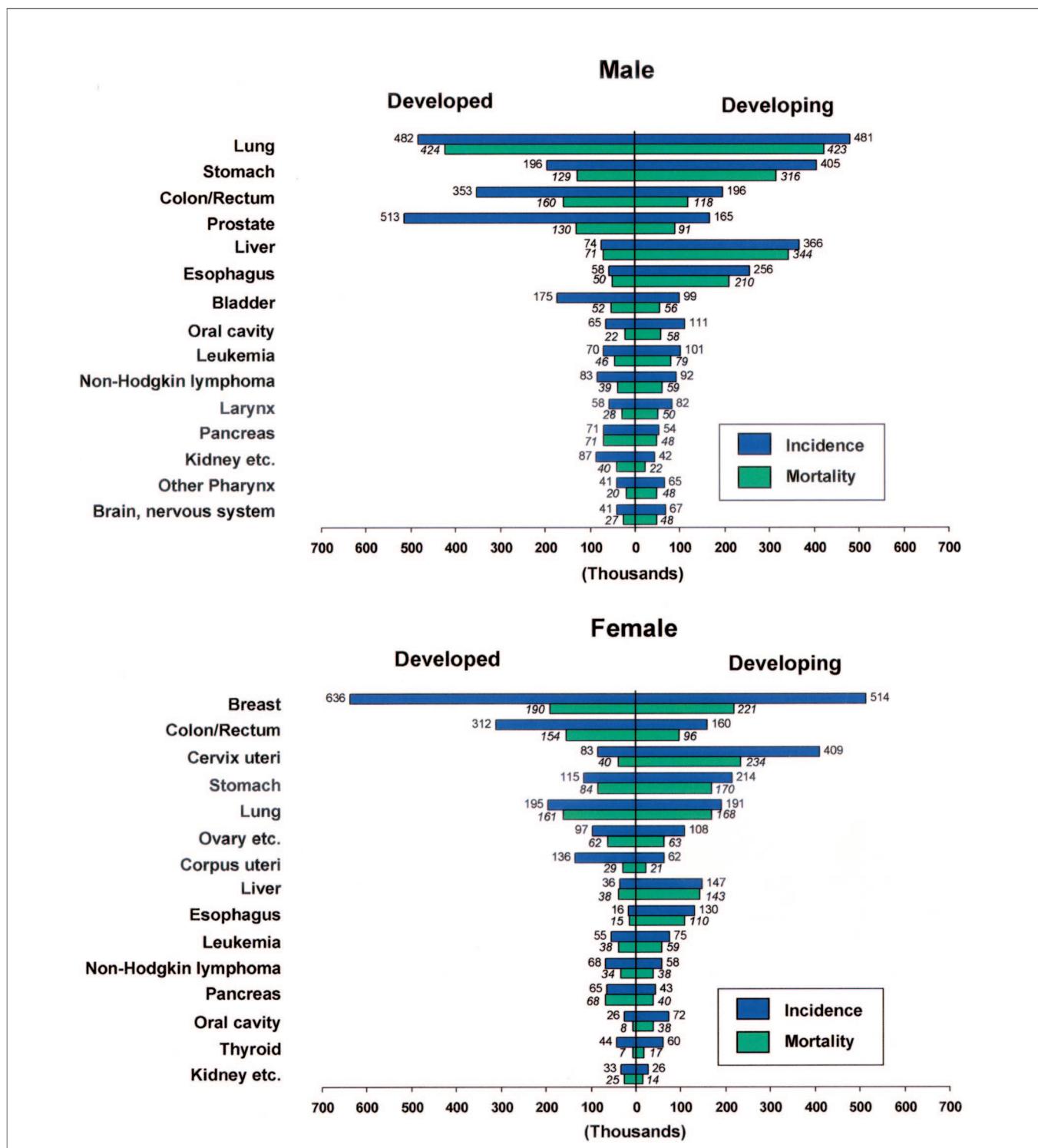


FIGURE 2 Estimated Numbers of New Cancer Cases (Incidence) and Deaths (Mortality) in 2002. Data shown in thousands for developing and developed countries by cancer site and sex.

are the most common. The ratio between prevalence and incidence is an indicator of prognosis; thus, breast cancer is the most prevalent

cancer in the world, despite there being fewer new cases than for lung cancer, for which the outlook is considerably poorer.

TABLE 2 Estimated Age-adjusted Survival (%) from 11 Cancer Types, by Country/Area

	DEVELOPED AREAS					DEVELOPING AREAS					All developing areas
	United States	Eastern Europe	Western Europe	Japan	All developed areas	South America	India	Thailand	Sub-Saharan Africa		
Esophagus (male)	14	6	18	25	15	7	13	13	4	17	
Esophagus (female)	8	2	14	15	8	5	14	10	5	16	
Stomach (male)	44	15	30	54	35	25	14	12	7	21	
Stomach (female)	33	16	24	51	31	24	14	14	5	20	
Colon/rectum (male)	66	35	56	65	56	50	28	37	13	39	
Colon/rectum (female)	65	36	53	58	54	50	31	37	14	39	
Liver (male)	20	≈0	≈0	9	6	≈0	4	3	2	5	
Liver (female)	0	≈0	≈0	12	0	≈0	9	3	1	3	
Lung (male)	21	9	9	15	13	8	12	5	4	12	
Lung (female)	26	10	14	22	20	1	11	5	5	12	
Kaposi sarcoma (male)										11	
Kaposi sarcoma (female)										12	
Breast	81	58	74	75	73	67	46	62	32	57	
Cervix uteri	70	51	66	65	61	55	42	58	21	41	
Corpus uteri	89	69	83	79	82	70	59	67	61	67	
Prostate	87	44	72	55	76	62	35	36	21	45	
Leukemia (male)	43	29	43	25	40	24	19	15	14	19	
Leukemia (female)	45	29	45	29	39	24	19	15	17	19	

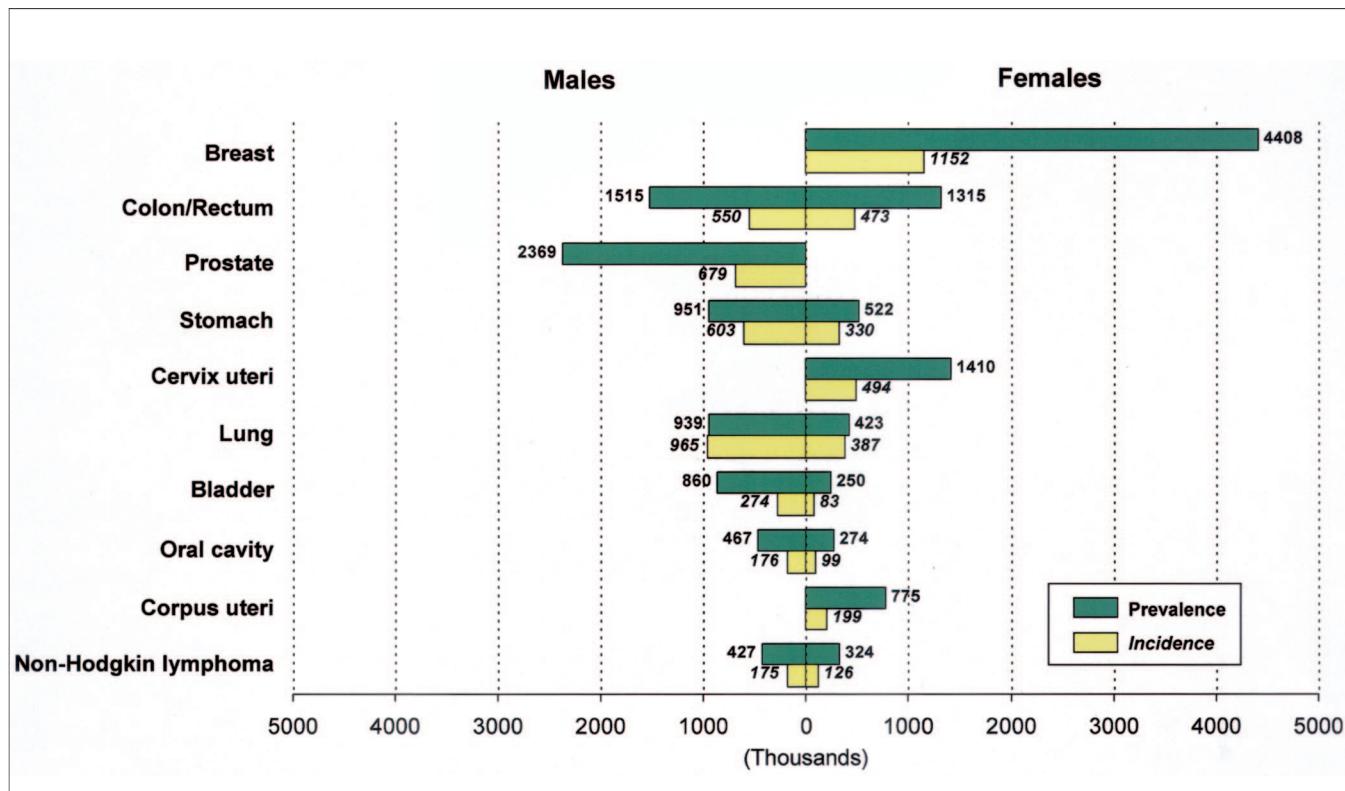


FIGURE 3 Estimated Numbers of New Cancer Cases (Incidence) and Prevalent Cases (Five-year Survival) in 2002. Data shown in thousands by cancer site and sex.

## Overall Cancer Rates

Figure 4 shows the numbers of new cases, deaths, and persons living with cancer by continent and for several larger countries. The numbers of new cancer cases range from 2.2 million cases in China (20.3% of the world total) and 1.6 million in North America (14.4%) to about 1,400 in Micronesia/Polyneisia. For the world as a whole, the sex ratio for cancer deaths is 1.3 (M:F), greater than the sex ratio of incidence (1:15) because, overall, the cancers with high fatality (lung, stomach, liver, esophagus) are more common among men than women.

Table 3 shows ASRs and the cumulative risk (as a percentage) of developing or dying from a cancer before the age of 65 by world area and sex. For men, the incidence of cancer is highest in North America (ASR, 398.4 per 100,000, or a cumulative risk to age 64 of 18.2%), a consequence, as described below, of the high contemporary rates of prostate cancer. The risk of dying from cancer, in contrast, is highest in Eastern Europe, with an ASR for all sites of 197.2 deaths per 100,000 population and a cumulative risk of dying from cancer before age 65 of 10.4%. Mortality rates for males in all other developed regions are around 160, although incidence is somewhat more variable (260–350). As in males, the region with the highest incidence of cancer in women is North America (ASR, 305.1 per 100,000; cumulative incidence, 16.7%) while mortality is highest in East Africa (ASR, 122.7 per 100,000; cumulative Mortality, 8.2%) followed by Northern Europe (ASR, 118.1 per 100,000), North America, Southern Africa, and Western Europe.

A striking feature of these results is to demonstrate that cancer is not a rare disease in most developing countries of the world. Indeed, if viewed in terms of mortality, there is little difference—in men, cumulative mortality before age 65 is just 18% higher in developed than developing countries, while in women, cumulative mortality in developing countries is actually *higher* than in the developed world.

There are several reasons for this. As described below, the majority of cancers in developed countries are those associated with affluence—the

so-called Western lifestyle—such as cancers of the colon and rectum, breast, and prostate, with a rather good prognosis. In developing countries, cancers of the liver, stomach, and esophagus are relatively more common; these all have a poor prognosis. Furthermore, as cancer survival data become increasingly available, it is clear that prognosis is much poorer in developing countries, so that the ratio of deaths to cases is much less favorable. The estimated survival rates in Table 2 show that, for cancers with a poor prognosis (liver, lung), there is little difference in outcome between world regions; however, for those cancers where early diagnosis and treatment can materially influence prognosis (colon-rectum, breast, leukemia), survival is generally considerably better in developed countries. Finally, in sub-Saharan Africa, the AIDS epidemic has created a new cancer problem in the form of Kaposi sarcoma. Formerly a rather rare, relatively indolent cancer found in East and Central Africa, we estimate that with the epidemic of AIDS, some 57,000 new cases occur in Africa each year and, due to the poor prognosis of cases associated with AIDS, some 52,000 deaths.

## Patterns by Cancer Type

### Lung Cancer

Lung cancer has been the most common cancer in the world since 1985,<sup>17</sup> and by 2002, there were 1.35 million new cases, representing 12.4% of all new cancers. It was also the most common cause of death from cancer, with 1.18 million deaths, or 17.6% of the world total. Almost half (49.9%) of the cases occur in the developing countries of the world—a big change since 1980, when it was estimated that 69% were in developed countries. Worldwide, it is by far the most common cancer of men, with the highest rates observed in North America and Europe (especially Eastern Europe). Moderately high rates are also seen in Australia/New Zealand and eastern Asia (China and Japan) (Figure 5). In women, incidence rates are lower (globally, the rate is 12.1 per 100,000 women compared with 35.5 per 100,000 in men). The highest rates are in

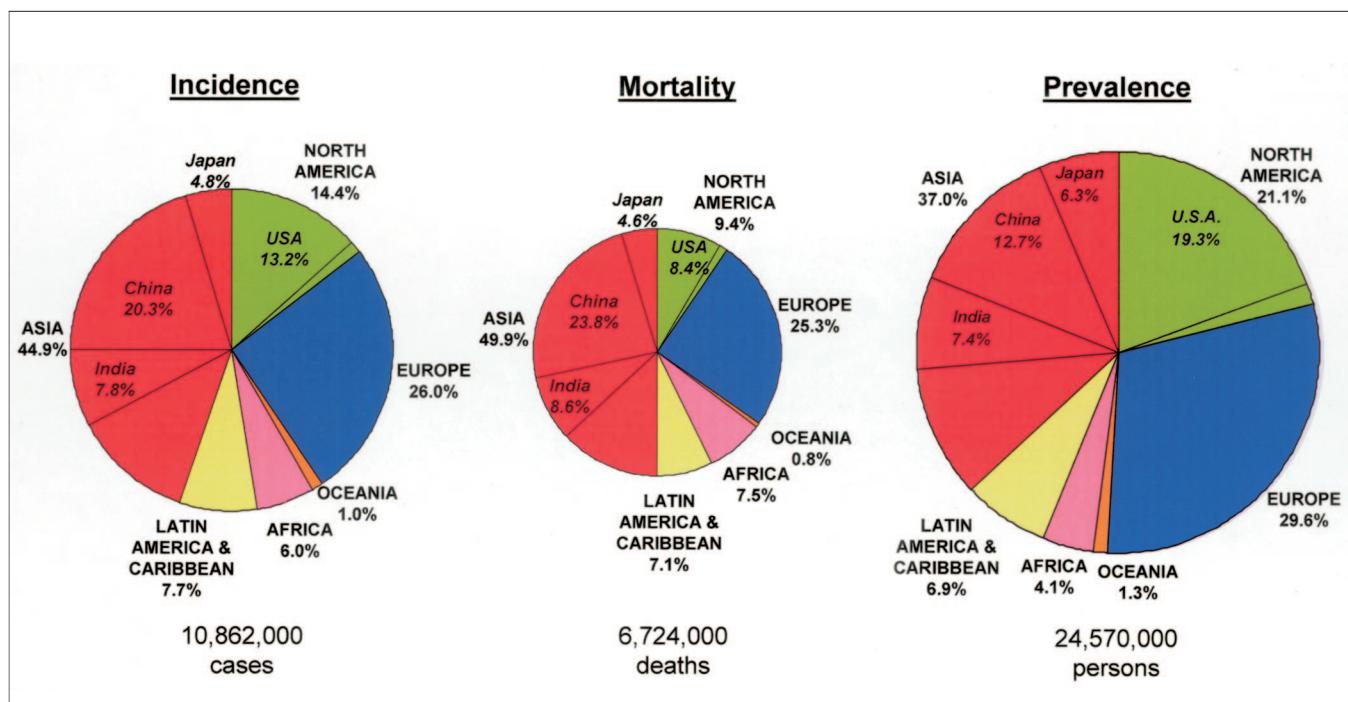
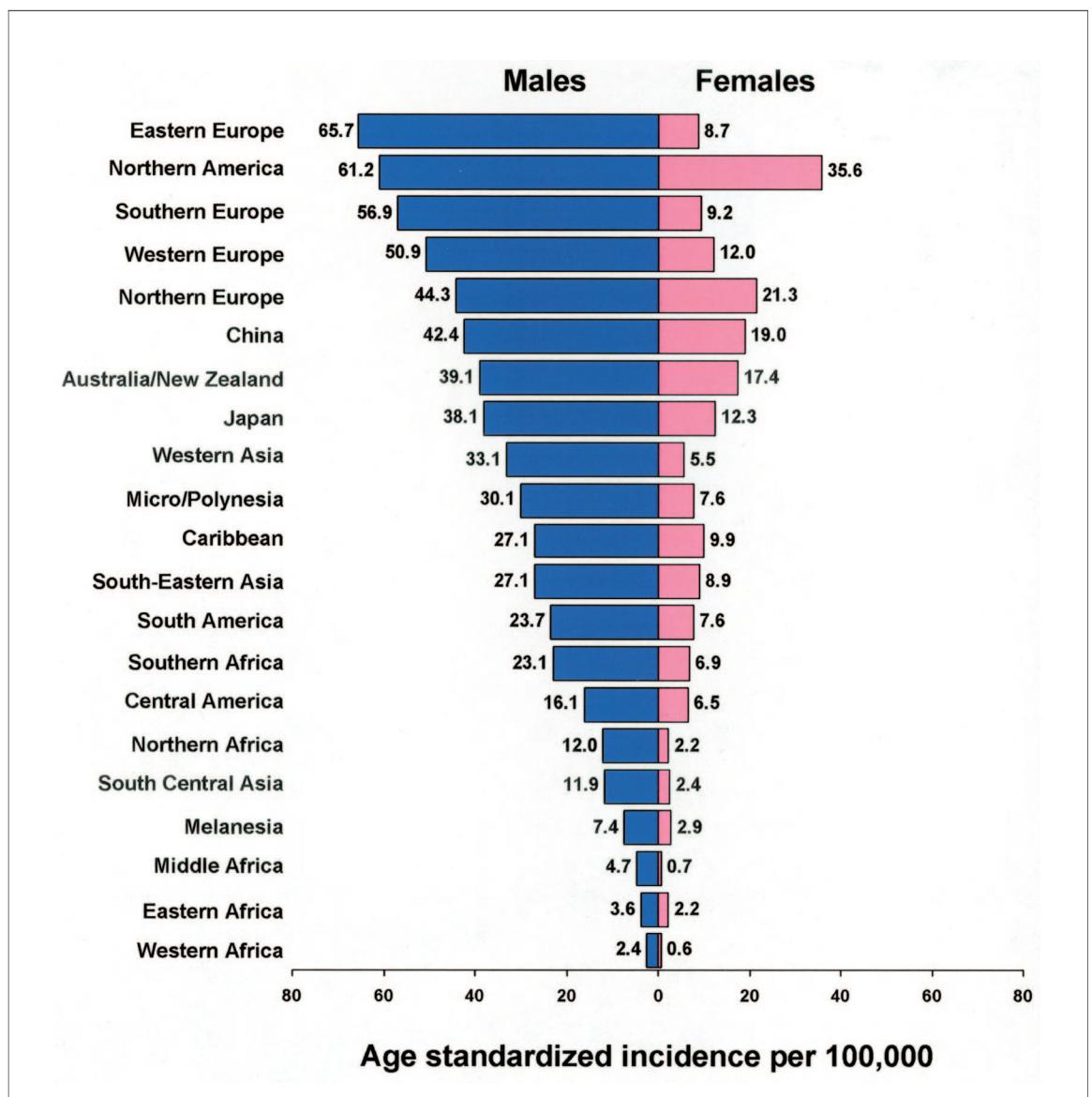


FIGURE 4 Incidence, Mortality, and Prevalence by Location.

TABLE 3 Incidence and Mortality by World Area

	INCIDENCE				MORTALITY			
	MALE		FEMALE		MALE		FEMALE	
	ASR (World)	Cumulative risk (age 0–64)						
Eastern Africa	158.7	9.1	156.7	10.6	133.2	7.5	122.7	8.2
Middle Africa	141.9	8.4	121.5	8.4	120.8	7.1	99.0	6.7
Northern Africa	99.0	5.7	85.2	5.8	83.1	4.6	65.1	4.3
Southern Africa	213.7	11.8	163.2	10.5	158.5	9.1	106.3	6.9
Western Africa	90.0	5.9	104.4	7.6	73.5	4.8	79.7	5.8
Caribbean	194.4	8.0	164.9	9.2	135.8	5.1	98.4	4.9
Central America	146.1	6.3	153.3	8.8	95.1	3.5	89.6	4.5
South America	216.4	9.9	191.6	10.8	131.8	5.5	102.2	5.0
Northern America	398.4	18.2	305.1	16.7	153.0	5.8	112.1	4.9
Eastern Asia	219.4	11.2	136.8	8.0	161.8	7.7	86.3	4.4
China	204.9	11.0	129.5	7.8	159.8	7.9	86.7	4.6
Japan	261.4	11.1	167.4	9.1	154.3	5.7	82.2	3.5
Southeastern Asia	130.4	7.0	120.9	7.9	102.5	5.4	76.2	4.7
Southcentral Asia	105.5	6.2	110.1	7.7	78.0	4.4	69.9	4.8
Western Asia	149.5	7.9	125.7	7.8	108.7	5.5	74.0	4.3
Eastern Europe	257.7	14.1	175.1	10.8	197.2	10.4	101.9	5.6
Northern Europe	283.1	11.7	252.3	14.0	161.0	5.8	118.1	5.2
Southern Europe	299.4	14.2	208.1	12.0	170.1	7.1	92.2	4.2
Western Europe	326.4	15.5	244.6	14.1	173.9	7.0	106.1	4.6
Australia/New Zealand	349.7	15.0	280.3	15.6	149.1	5.3	103.4	4.5
Melanesia	145.1	7.9	165.0	11.2	104.6	5.8	104.6	7.2
Micro/Poly	161.1	8.5	152.1	9.5	121.0	6.5	93.3	5.9
More developed countries	314.1	14.8	228.0	13.1	169.6	7.2	102.5	4.8
Less developed countries	158.7	8.5	128.8	8.1	119.2	6.1	83.1	4.9
World	209.6	10.3	161.5	9.5	137.7	6.4	92.1	4.9



**FIGURE 5** Age-standardized Incidence Rates for Lung Cancer.  
Data shown per 100,000 by sex.

North America and Northern Europe (Figure 5). It is of note that the incidence in China is rather high (ASR, 19.0 per 100,000), similar to that in, for example, Australia/New Zealand (17.4 per 100,000).

Lung cancer remains a highly lethal disease. Survival at 5 years measured by the SEER program in the United States is 15%, the best recorded at the population level. The average survival in Europe is 10%, not much better than the 8.9% observed in developing countries.

Geographic patterns of lung cancer incidence and mortality are very much influenced by past exposure to tobacco smoking,<sup>18</sup> and the geographic pattern in women reflects the rather different historical patterns of smoking from those in men. The proportion of lung cancer cases due to tobacco smoking can be estimated by comparing observed incidence (or mortality) in different areas with that expected based on rates in nonsmokers from several large cohort studies.<sup>19,20</sup> For the year 2000, an estimated 85% of lung cancer in men and 47% of lung cancer in women

is the consequence of tobacco smoking. The percentage is 90% to 95% of cases in men in Europe and North America, and only in the lowest incidence areas of East and West Africa are there no attributable cases. The fractions are lower for women, and several areas (where incidence rates are lower than in nonsmoking women in the United States and Japan), including south-central Asia, have no attributable cases. The highest fractions are in North America (85%), northern Europe (74%), and Australia/New Zealand (72%), where women have been smoking the longest.

The estimated numbers of lung cancer cases worldwide has increased by 51% since 1985 (+44% in men and +76% in women). In men, this increase is due solely to population growth and aging; there has actually been a small (−3.3%) decrease in the actual age-standardized incidence (risk). However, the ASRs have increased by 22% in women. This overall upward trend disguises considerable difference between countries. In men, several populations have now passed the peak of the lung cancer epidemic, and incidence rates are now declining (eg, United States<sup>21</sup> and the countries of Northern and Western Europe<sup>22</sup>). In contrast, incidence and mortality are increasing rapidly in Southern and Eastern European countries.<sup>23</sup> In women, the epidemic is less advanced; most Western countries are still showing a rising trend in incidence and mortality, although in some this is recent and affecting only recent generations (Spain), while for others (United Kingdom), it seems that the peak of risk may now have been reached.<sup>22,24</sup>

### Breast Cancer

Breast cancer is by far the most frequent cancer of women (23% of all cancers), with an estimated 1.15 million new cases in 2002, ranking second overall when both sexes are considered together. More than half of the cases are in industrialized countries—about 361,000 in Europe (27.3% of cancers in women) and 230,000 in North America (31.3%). Incidence rates are high in most of the developed areas (except for Japan, where it is third after colorectal and stomach cancers), with the highest age-standardized incidence in North America (99.4 per 100,000)<sup>24</sup> (Figure 6). In part,

the high incidence in the more affluent world areas is likely because of the presence of screening programs that detect early invasive cancers, some of which would otherwise have been diagnosed later or not at all.<sup>25</sup> The incidence is more modest in Eastern Europe, South America, Southern Africa, and Western Asia, but it is still the most common cancer of women in these geographic regions. The rates are low (<30 per 100,000) in most of Africa (with the exception of South Africa) and in most of Asia. The lowest incidence is in Central Africa (ASR, 16.5 per 100,000).

The prognosis from breast cancer is generally rather good, as illustrated by the estimated survival rates in Table 2—the average in developed countries is 73% and in developing countries 57%. As a result, breast cancer ranks as the fifth cause of death from cancer overall, although still the leading cause of cancer mortality in women (the 411,000 annual deaths represent 14% of female cancer deaths). The very favorable survival of breast cancer cases in Western countries (89% at five years, in cases registered by the US SEER Program in 1995–2000)<sup>10</sup> is also a consequence of the presence of screening programs.

The very favorable survival in the more affluent developed countries and poor survival in some of the least affluent developing countries results in the differences in mortality rates worldwide being much less marked than for incidence (Figure 6). The estimated mortality rates in Africa and the Pacific (Micronesia and Polynesia), for example, are not greatly inferior to those in Europe.

Because of its high incidence and relatively good prognosis, breast cancer is the most prevalent cancer in the world today; there are an estimated 4.4 million women alive who have had breast cancer diagnosed within the last 5 years (compared with just 1.4 million survivors—male or female—from lung cancer). It has been estimated that 1.5% of the US female population are survivors of breast cancer.<sup>26</sup>

Genetic factors, including the major susceptibility genes (BRCA1, BRCA2), may account for up to 10% of breast cancer cases in developed countries,<sup>27</sup> but their prevalence in the population is too low to explain much of the interna-

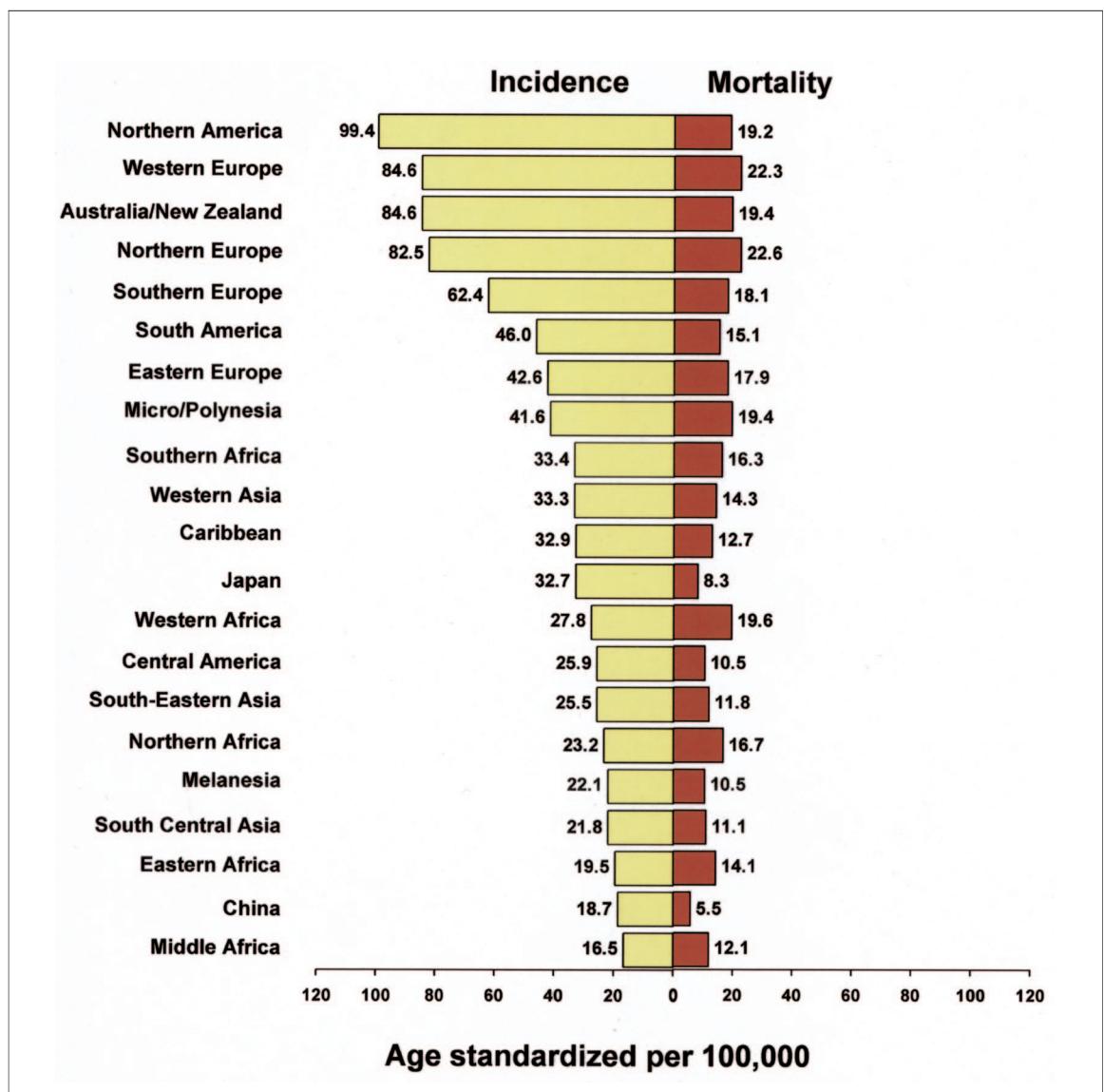


FIGURE 6 Age-standardized Incidence and Mortality Rates for Breast Cancer.  
Data shown per 100,000.

tional variation in risk. The majority must therefore be a consequence of different environmental exposures. This is evident from studies of migrants, which show quite clearly that incidence rises following migration from low to high incidence countries, particularly if this takes place at young ages. The major influences on breast cancer risk appear to be certain reproductive factors, body size/obesity, alcohol, physical activity, exogenous hormones (oral contraceptives, hormone replacement therapy), and, possibly, diet. There have, however, been few attempts to quantify the magnitude of risk differentials be-

tween populations that might be explained by such factors.

Incidence rates of breast cancer are increasing in most countries, and the changes are usually greatest where rates were previously low.<sup>2</sup> Since the estimates for 1990, there has been an overall increase in incidence rates of about 0.5% annually. At this rate of growth, there would be around 1.4 million new cases in 2010. However, cancer registries in China are recording annual increases in incidence of 3% to 4%, and in those elsewhere in eastern Asia, increases are not much less. Assuming a 3%

growth in East Asia, the world total in 2010 would be 1.5 million.

### *Colon and Rectum Cancers*

Colon and rectum cancers accounted for about 1 million new cases in 2002 (9.4% of the world total), and unlike most sites, numbers were not so different in men and women (ratio, 1.2:1). In terms of incidence, colorectal cancers rank fourth in frequency in men and third in women. Survival estimates (in men) at 5 years are 65% in North America, 54% in Western Europe, 34% in Eastern Europe, and 30% in India (Table 2). The overall relatively good prognosis means that mortality is about one half that of incidence (about 529,000 deaths in 2002), while prevalence is second only to that of breast cancer worldwide, with an estimated 2.8 million persons alive with colorectal cancer diagnosed within 5 years of diagnosis (Figure 3).

There is at least a 25-fold variation in occurrence of colorectal cancer worldwide. The highest incidence rates are in North America, Australia/New Zealand, Western Europe, and, in men especially, Japan (Figure 7). Incidence tends to be low in Africa and Asia and intermediate in southern parts of South America. The geographical distribution of colon and rectal cancer is similar, although the variation between countries is more striking for colon cancer. In high-risk populations, the ratio of colon to rectal cancer incidence is 2:1 or more (rather more in females). In low-risk countries, colon and rectal cancer rates are generally of the same magnitude.

These large geographic differences for colon and rectal cancers are probably explained by different environmental exposures. There are strong international correlations between risk of large bowel cancers and per capita consumption patterns of meat,<sup>28</sup> fat (specifically animal fat),<sup>29</sup> and fiber.<sup>30</sup> Epidemiologic studies find consistent evidence that physical inactivity, excess body weight, and a central deposition of adiposity have a major influence on risk of colon cancer.<sup>31</sup> That the risk of colon cancer is quite labile to environmental change is evident from the study

of migrants; when populations moved from low-risk to high-risk areas, the incidence of colorectal cancer increases rapidly within the first generation,<sup>32,33</sup> implying that dietary and other environmental factors constitute a major component of risk. Japanese individuals born in the United States now have higher rates than those of US Whites (38.4 per 100,000 in men, 27.6 per 100,000 in women), and the rates in Japanese individuals living in Hawaii (51.2 per 100,000 in men, 30.8 per 100,000 in women) and Los Angeles (48.0 per 100,000 in men, 32.8 per 10<sup>5</sup> in women) are among the highest in the world.<sup>34</sup>

In general, rates of incidence of colorectal cancer are increasing rather rapidly in countries where overall risk was formerly low (especially in Japan, but also elsewhere in Asia), while in high-risk countries, trends are either gradually increasing, stabilizing (North and West Europe), or declining with time (North America).<sup>2</sup> Such moderations with time have been noted particularly in younger age groups.

### *Stomach Cancer*

Until recently, stomach cancer was the second most common cancer worldwide, but now, with an estimated 934,000 new cases per year in 2002 (8.6% of new cancer cases), it is in fourth place behind cancers of the lung, breast, and colon and rectum. It is the second most common cause of death from cancer (700,000 deaths annually). Almost two-thirds of the cases occur in developing countries and 42% in China alone. The geographical distribution of stomach cancer is characterized by wide international variations; high-risk areas (ASR in men, >20 per 100,000) include East Asia (China, Japan), Eastern Europe, and parts of Central and South America. Incidence rates are low (<10 per 100,000 in men in Southern Asia, North and East Africa, North America, and Australia and New Zealand) (Figure 8). Patterns in women are broadly similar to those in men. Although it has been suggested that gastric cancer is rare in Africa,<sup>35</sup> the incidence in Central (Middle) Africa is not very low,<sup>36</sup> with an estimated age standardized rate in

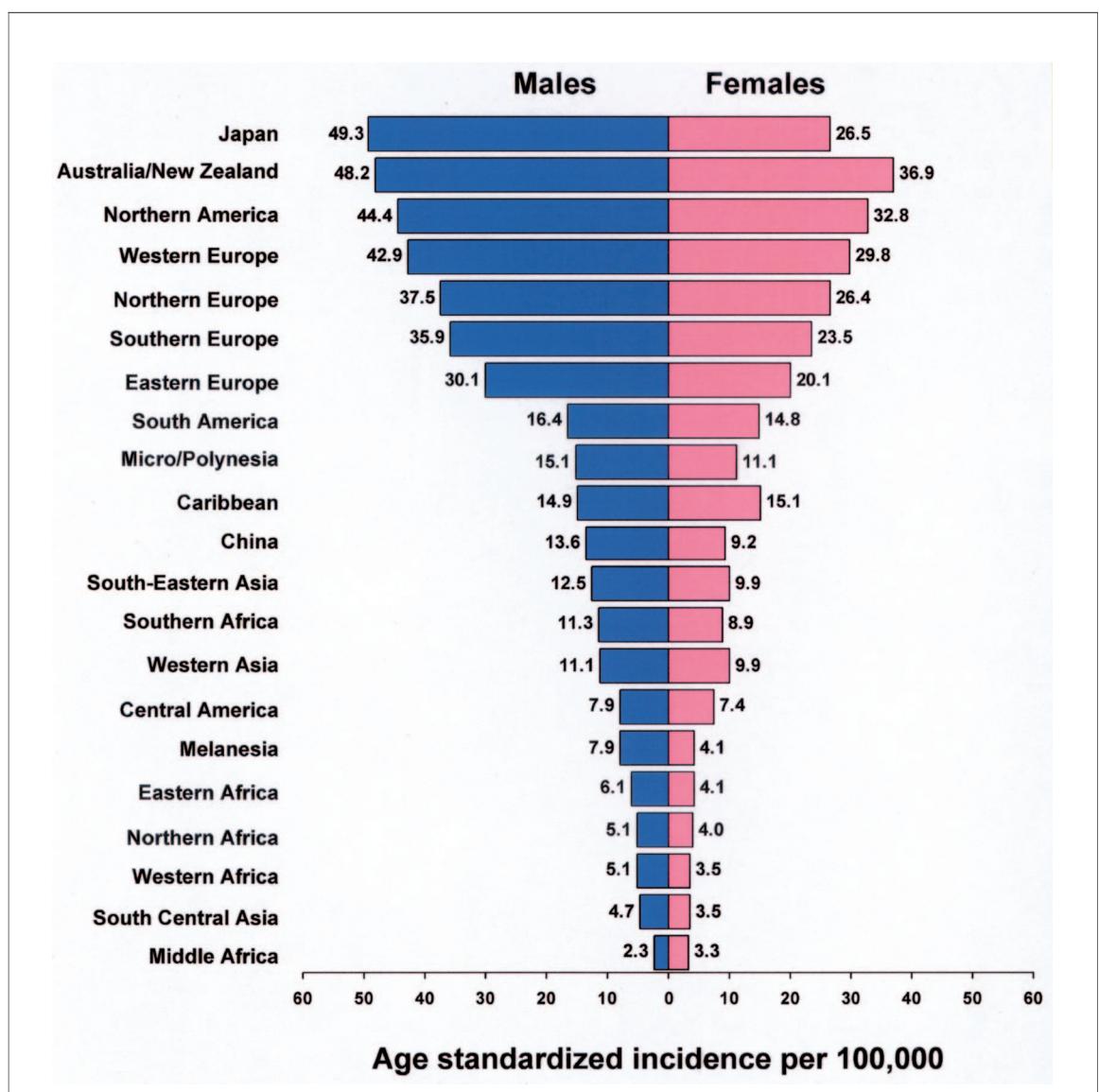


FIGURE 7 Age-standardized Incidence Rates for Colorectal Cancer.  
Data shown per 100,000 by sex.

women (12.6 per 100,000) similar to that in Eastern Europe (Figure 8).

Survival for stomach cancer is moderately good only in Japan (52%), where mass screening by photofluoroscopy has been practiced since the 1960s. Survival is also relatively high in North America (21% based on the SEER data, 40% age-adjusted estimate (Table 2)), possibly due to early diagnosis following a greater number of endoscopic examinations performed for gastric disorders. Survival is 27% (estimated) in Western Europe while it is as low as 6% in sub-Saharan Africa.

There is clearly a strong environmental component to the risk differences. Migrant populations from high risk parts of the world show a marked diminution in risk when they move to a lower risk area, although this is quite gradual and seems to depend on the age at migration.<sup>32</sup> The data fit with observations concerning the importance of childhood environment in determining risk.<sup>37</sup> The evidence linking *H. pylori* infection to cancer of the stomach was considered sufficient by IARC<sup>38</sup> to classify this bacterium as carcinogenic in humans. Its action is probably indirect by pro-

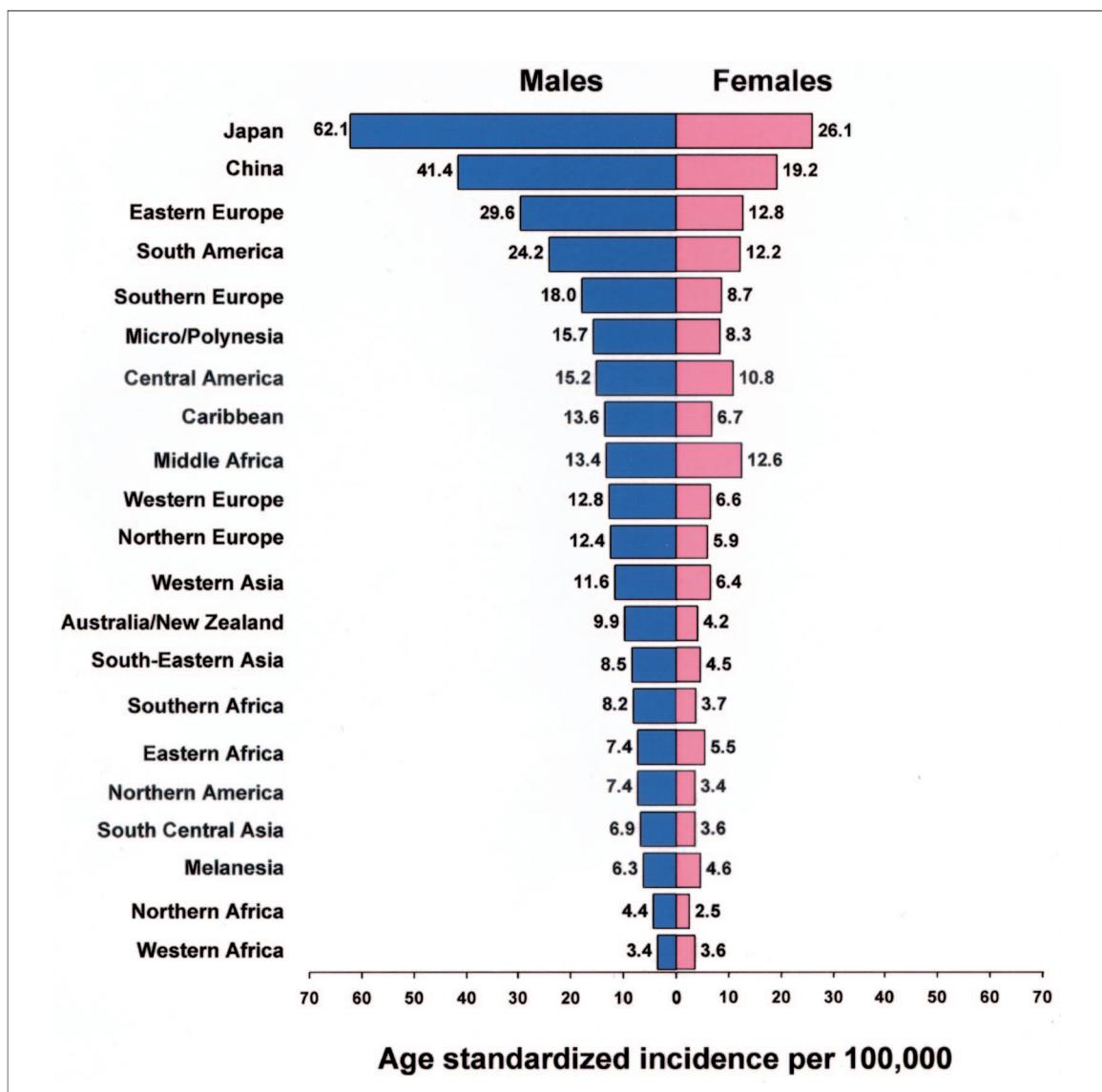


FIGURE 8 Age-standardized Incidence Rates for Stomach Cancer.  
Data shown per 100,000 by sex.

voking gastritis, a precursor of gastric atrophy, metaplasia, and dysplasia. Infection is acquired in childhood, and prevalence within populations is certainly related to socioeconomic status.<sup>39</sup> The international variation in prevalence bears a certain similarity to that of stomach cancer; the overall estimate of *H. pylori* prevalence in adults is 76% in developing countries and 58% in developed countries. However, it is clear that with such high prevalence and relatively small international variation, that factors other than *H. pylori* are of major importance. Diet certainly plays an important role. Risk is

increased by high intakes of some traditionally preserved salted foods, especially meats and pickles, and with salt per se. Risk is decreased<sup>40,41</sup> by high intakes of fruits and vegetables,<sup>40,41</sup> which may be in part related to their vitamin C content. Tobacco smoking has also been clearly accepted as increasing the risk of stomach cancer.<sup>42</sup>

There has been a steady decline in the risk of gastric cancer incidence and mortality over several decades in most countries.<sup>43</sup> The worldwide estimates of age adjusted incidence (22.0 per 100,000 in men and 10.3 per

100,000 in women) are about 15% lower than the values estimated in 1985.<sup>17</sup> This decline may be related to improvements in preservation and storage of foods; it may also represent changes in the prevalence of *H. pylori* by birth cohort, perhaps as a result of reduced transmission in childhood, following a trend to improved hygiene and reduction of crowding.<sup>44,45</sup> If the observed secular decline continues, the expected number of new cases in 2010 will be around 1.1 million (an increase of 19%), rather than the 21% additional cases due simply to a population growth and aging.

### *Prostate Cancer*

There were 679,000 new cases of prostate cancer worldwide in 2002, making this the fifth most common cancer in the world and the second most common in men (11.7% of new cancer cases overall; 19% in developed countries and 5.3% in developing countries). The prognosis is relatively good; it is a less prominent cause of mortality with 221,000 deaths (5.8% of cancer deaths in men and 3.3% of all cancer deaths). Three-quarters of all cases are in men aged 65 or more. Incidence rates are now influenced by the diagnosis of latent cancers by screening asymptomatic individuals, so that where this practice is common, the “incidence” may be very high (124.8 per 100,000 in the United States, for example, where it is now by far the most commonly diagnosed cancer in men). Incidence is high also in Northern and Western Europe (Figure 9) and Australia/New Zealand. Mortality is affected by survival, and survival is significantly better in high-risk countries (ratio of age-standardized rates is 87% in the United States versus 45% in developing countries (Table 2)), but much of this a consequence of more latent cancer being detected by screening procedures. In fact, the relative survival in the United States in 1995–2000 is reported to be 99%.<sup>10</sup> As a result, mortality rates are probably a better guide to the risk of invasive prostate cancer in different populations. Mortality rates are high in the Caribbean, Southern and Central Africa, North and West Europe, Australia/New Zealand, and North and South America,

and low in Asian populations and North Africa (Figure 9). Variations in mortality rates between China and the United States are 16-fold (almost 80-fold for incidence).

Migrants from low-risk countries to areas of higher risk show quite marked increases in incidence (for example, Japanese living in the United States). Some of this change reflects an elimination of the “diagnostic bias” influencing the international incidence rates (see below), but part is almost certainly due to changes in environment (possibly related to diet). Nevertheless, the interethnic variations in incidence observed in international data are mirrored by ethnic variation in risk within certain countries; for example, the Black population has the highest incidence (and mortality) rates in the United States,<sup>46</sup> some 70% higher than in Whites, who in turn have rates considerably higher than populations of Asian origin (eg, Chinese, Japanese, and Korean males). Similarly, in São Paulo, Brazil, the risk of prostate cancer in black males was 1.8 times that of white men (95% CI, 1.4–2.3).<sup>47</sup> The differences in ethnic-specific risk may be mediated via population differences in alleles of genes coding for enzymes involved in testosterone metabolism.<sup>48</sup>

Until the middle of the 1980s, prostate cancer incidence (and mortality) rates in the United States were gradually increasing, partly due to a genuine increase in risk and partly due to increasing diagnosis of latent, asymptomatic cancers in prostatectomy specimens resulting from the increasing use of transurethral resection of the prostate.<sup>49</sup> With the introduction of PSA testing in 1986, there was a huge surge in incidence, especially in localized and regional stage disease, so that recorded rates doubled between 1986 and the peak in 1992 (1993 in Blacks). Since then, incidence rates have declined, although they remain substantially higher than before.<sup>10,50</sup> Prostate cancer mortality rates in the United States began to fall in 1992 for White men and in 1994 for Black men, and are now substantially lower than the rates in 1986. The recent declines in mortality are a consequence of declines in the incidence of distant stage disease, rather than change in

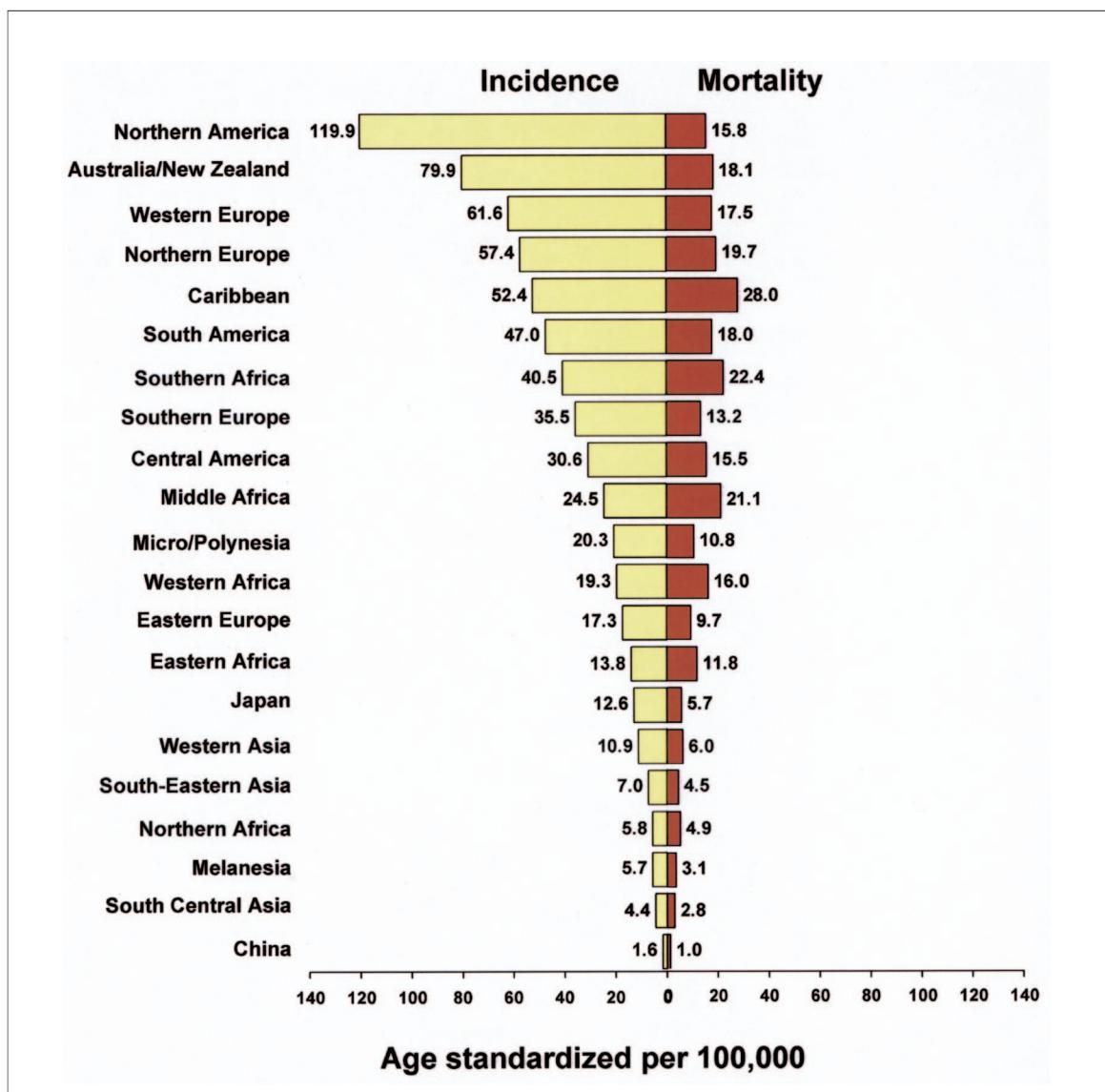


FIGURE 9 Age-standardized Incidence and Mortality Rates for Prostate Cancer.  
Data shown per 100,000.

survival,<sup>51</sup> suggesting they are largely the consequence of screening.

Hsing et al.<sup>52</sup> reviewed data on international trends in prostate cancer incidence and mortality. As in the United States, they observed the largest increases in incidence in high-risk countries, especially in younger men. This is probably partly the effect of increasing detection following transurethral resection of the prostate and, more recently, due to use of PSA. But there were also large increases in low-risk countries between 1975 and 1990: 104% in Singapore, China; 84% in Miyagi, Japan; 55%

in Hong Kong; and 44% in Shanghai, China. 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. Increases in mortality have also been substantial, although they are generally less marked than for incidence, especially in countries where the incidence rates are relatively high. However, since the 1990s, there have been declines in mortality rates of several developed countries, which may be the result of earlier detection and improved treatment.<sup>53,54</sup>

The average increase in the estimated age-adjusted incidence of prostate cancer worldwide between 1985<sup>17</sup> and 2002 was around 1.1% annually. As noted above, a fair bit of this was due to the huge surge in the United States (9.5% annual increase between 1985 and 1990). But even if there were no further increase in the United States, a continued increase of this magnitude would mean that there would be almost 900,000 new cases per year by the year 2010.

### *Liver Cancer*

Liver cancer is the sixth most common cancer worldwide in terms of numbers of cases (626,000 or 5.7% of new cancer cases) but because of the very poor prognosis, the number of deaths is almost the same (598,000). It is therefore the third most common cause of death from cancer. Survival rates are 3% to 5% in cancer registries for the United States and developing countries.

82% of cases (and deaths) are in developing countries (55% in China alone). The areas of high incidence (Figure 10) are sub-Saharan Africa, eastern and southeastern Asia, and Melanesia. The incidence is low in developed areas (only in southern Europe is there any substantial risk), Latin America, and southcentral Asia. The overall sex ratio (male:female) is around 2.4, much greater in the high-risk areas and less in low-risk areas.

Worldwide, the major risk factors for liver cancer are infection with the hepatitis B and C viruses, both of which increase the risk of liver cancer some 20-fold.<sup>55</sup> Because hepatitis B virus (HBV) is more prevalent, the distribution of infection worldwide largely explains the patterns of liver cancer. The exception is Japan, where chronic infection with HBV is low, but where the generations most at risk of liver cancer have a relatively high rate of infection with hepatitis C virus.<sup>56</sup> More than 75% of cases worldwide, and 85% of cases in developing countries, are caused by these two viruses.<sup>57</sup>

Exposure to aflatoxins is probably also an important contributor to the high incidence of liver cancer in those tropical areas of the world where contamination of food grains with the fungus *Aspergillus fumigatus* is common. There

is a multiplicative interaction between aflatoxin exposure and chronic HBV infection, suggesting different carcinogenic mechanisms.

Cholangiocarcinoma, a tumor of the epithelium of the intrahepatic bile ducts, comprises 10% to 25% of liver cancers in men in Europe and North America, and a much larger proportion in women. The incidence shows little international variation, with rates in males between 0.5 and 2.0, and lower in females.<sup>58</sup> However, the incidence is very much higher in some localized areas, where infection with liver flukes is common (eg, Northeast Thailand).

Primary prevention of the majority of liver cancer cases worldwide is now feasible, thanks to the development of a vaccine against HBV. This has been shown to be effective in preventing infection in childhood. A dramatic demonstration of the results of community vaccination is already available from Taiwan, where HBV immunization of newborns was introduced in 1984; for children aged 6 to 9 years in birth cohorts receiving vaccination, there was a dramatic decrease in incidence of liver cancer.<sup>59</sup>

### *Cervical Cancer*

Cervix cancer is the seventh in frequency overall, but the second most common cancer among women worldwide, with an estimated 493,000 new cases and 274,000 deaths in the year 2002. In general terms, it is much more common in developing countries, where 83% of cases occur and where cervical cancer accounts for 15% of female cancers, with a risk before age 65 of 1.5%. In developed countries, cervical cancer accounts for only 3.6% of new cancers, with a cumulative risk (0 to 64) of 0.8%.

The highest incidence rates are observed in sub-Saharan Africa, Melanesia, Latin America and the Caribbean, southcentral Asia, and southeast Asia (Figure 11). Incidence rates are now generally low in developed countries, with age-standardized rates less than 14.5 per 100,000. This pattern is relatively recent, however; before the introduction of screening programs in the 1960s and 1970s, the incidence in most of Europe, North America, and Australia/New Zealand was similar to developing countries today.<sup>60</sup> For example, incidence was 38.0 per 100,000 in the

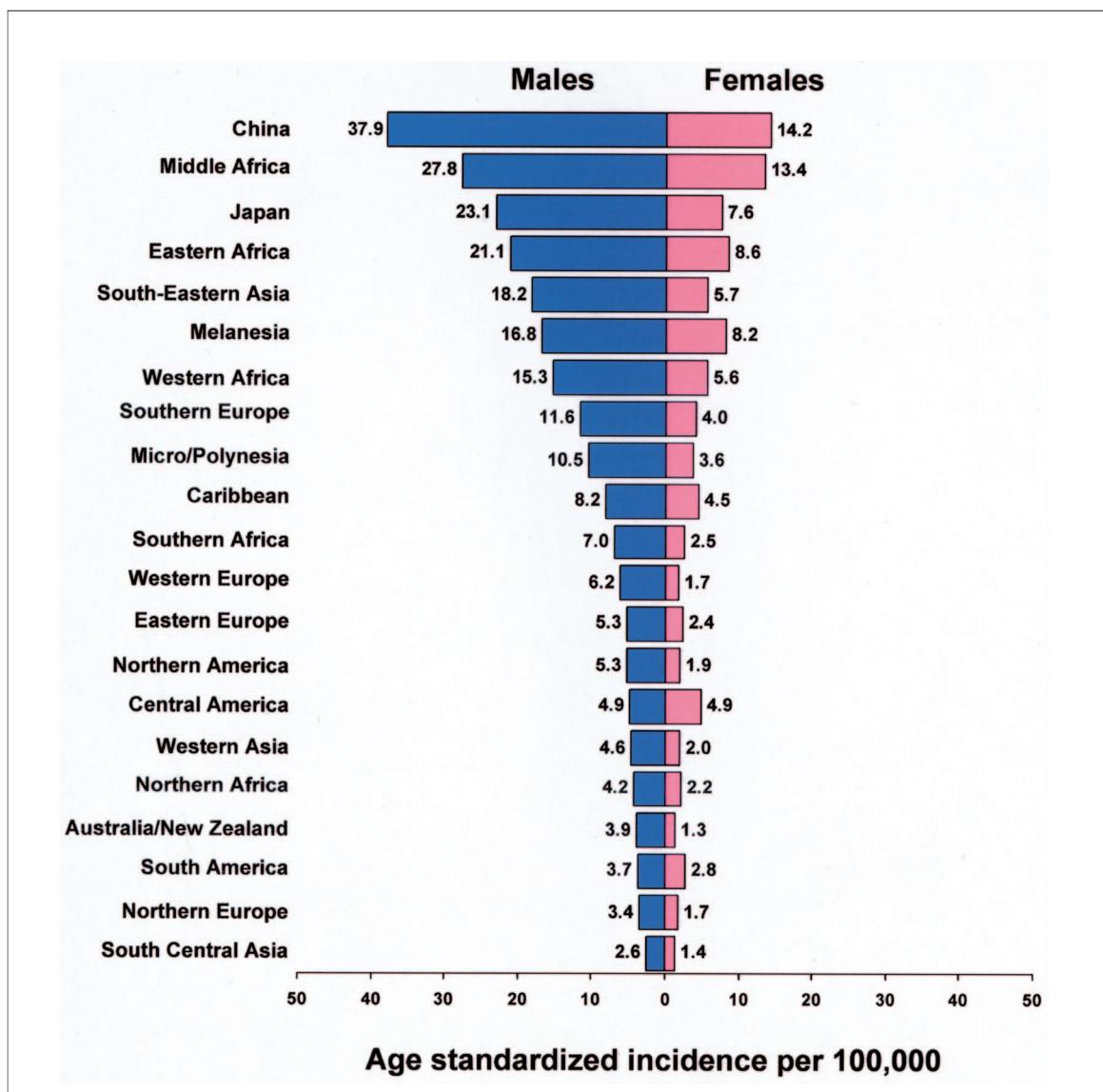


FIGURE 10 Age-standardized Incidence Rates for Liver Cancer.  
Data shown per 100,000 by sex.

Second National Cancer Survey of the United States.<sup>61</sup> Very low rates are also observed in China (6.8 per 100,000) and Western Asia (5.8 per 100,000); the lowest recorded rate is 0.4 per 100,000 in Ardabil, northwest Iran.<sup>62</sup>

Mortality rates are substantially lower than incidence. Worldwide, the ratio of mortality to incidence is 55%. Survival rates vary between regions with quite good prognosis in low-risk regions (74% in SEER and 63% in the European registries). Even in developing countries, where many cases present at relatively advanced stage, survival rates are fair (Table 2).

It is quite clear that the major etiological agents are oncogenic subtypes of the human papilloma virus (HPV).<sup>63</sup> Recent geographic studies using sensitive polymerase chain reaction DNA testing methods to detect a wide spectrum of HPV types have generally observed HPV prevalences to correlate with the population risks of cervical cancer, although it has not always been possible to take into account the relative efficacy of regional screening programs.<sup>64,65</sup> Other cofactors (eg, high parity, tobacco smoking, and use of oral contraceptives) probably modify the risk in women infected with HPV.

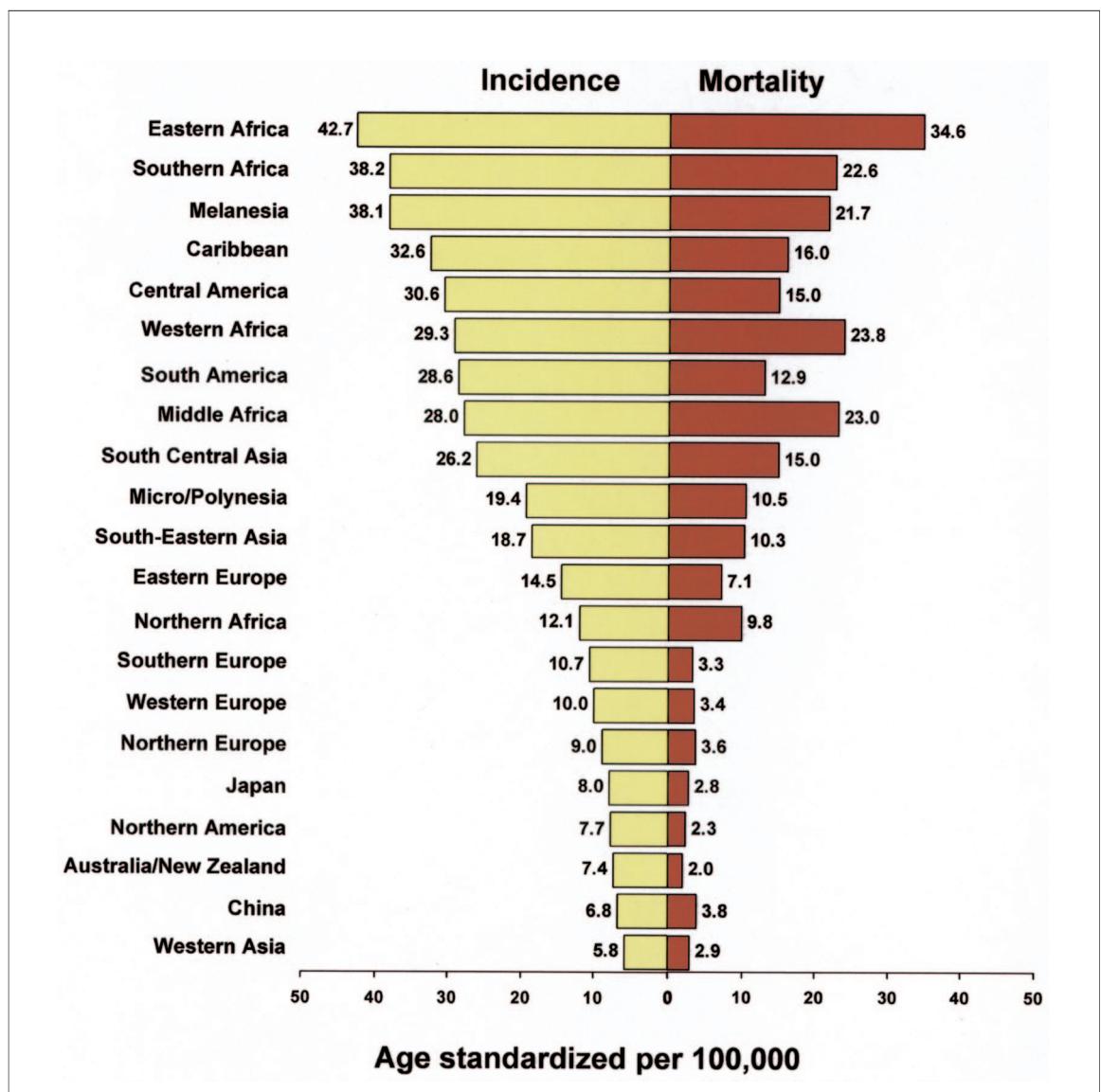


FIGURE 11 Age-standardized Incidence and Mortality Rates for Cervix Uteri Cancer.  
Data shown per 100,000.

There have been quite substantial declines in cervical cancer incidence and mortality, most clearly observed in Western countries where there are well-developed screening programs. Declines are also evident in some developing countries; this is particularly striking in China, where the estimated age-standardized incidence rate in 2002 was 6.8, compared with 17.8 in 1985. Although some of the difference reflects changing data sources, cancer registry results also indicate a fairly dramatic decline in rates in recent years. As a result of these trends, cervical cancer has ceded its place as the leading

cancer in developing countries to breast cancer; only in sub-Saharan Africa, Central America, southcentral Asia, and Melanesia is it now the main cancer affecting women.

#### Esophageal Cancer

Esophageal cancer is the eighth most common cancer worldwide, responsible for 462,000 new cases in 2002 (4.2% of the total), and sixth most common cause of death from cancer with 386,000 deaths (5.7% of the total). Cancer of the esophagus has a very poor survival: 16% of the

cases in the United States<sup>10</sup> and 10% in Europe<sup>9</sup> survive at least five years. Geographic variation in incidence is very striking. Even at the level of world area, a 20-fold variation is observed between high-risk China and low-risk western Africa. Other areas of relatively high risk are southern and eastern Africa, southcentral Asia, and (in men only) Japan (Figure 12). Esophageal cancer is more common in males in most areas—the sex ratio is 7:1 in Eastern Europe, for example—although in the high-risk areas of Asia and Africa, the sex ratio is much closer to unity.

This geographic variability is even more marked when smaller units are studied—for example, between countries or even within countries (eg, in China, South Africa, or France). It seems that the environmental carcinogens responsible also show important geographic differences.<sup>66</sup> Tobacco and alcohol are the main agents involved in Europe and North America, where over 90% of cases can be attributed to these causes. Chewing of tobacco (and betel) is important in the Indian subcontinent. Hot beverages have been shown to increase risk, and drinking hot maté is probably responsible for high rates in Uruguay, southern Brazil, and northern Argentina. Nutritional deficiencies (specifically of micronutrients) are thought to underlie the high risk in central Asia, China, and southern Africa. Here other factors such as pickled vegetables, nitrosamine-rich foods, and mycotoxins may also be involved, as well as consumption of opium residues (in Iran) or pipe stem residues (in the Transkei of southern Africa).<sup>66</sup> On the other hand, genetic predisposition may explain the rather high rates of esophageal cancer in Japan and US Japanese.<sup>46</sup> Polymorphisms of two genes controlling the alcohol-metabolising enzymes, alcohol dehydrogenase 2 (ADH2) and aldehyde dehydrogenase 2,<sup>67</sup> are notably frequent in populations in east and southeast Asia.<sup>68</sup>

Worldwide, most esophageal cancers are squamous cell carcinomas, arising in the middle and low third of the esophagus. Recently, there appears to be an increase in western countries in relative and absolute numbers of adenocarcinomas of the lower third of the esophagus.<sup>69</sup> Since both histological types are related to al-

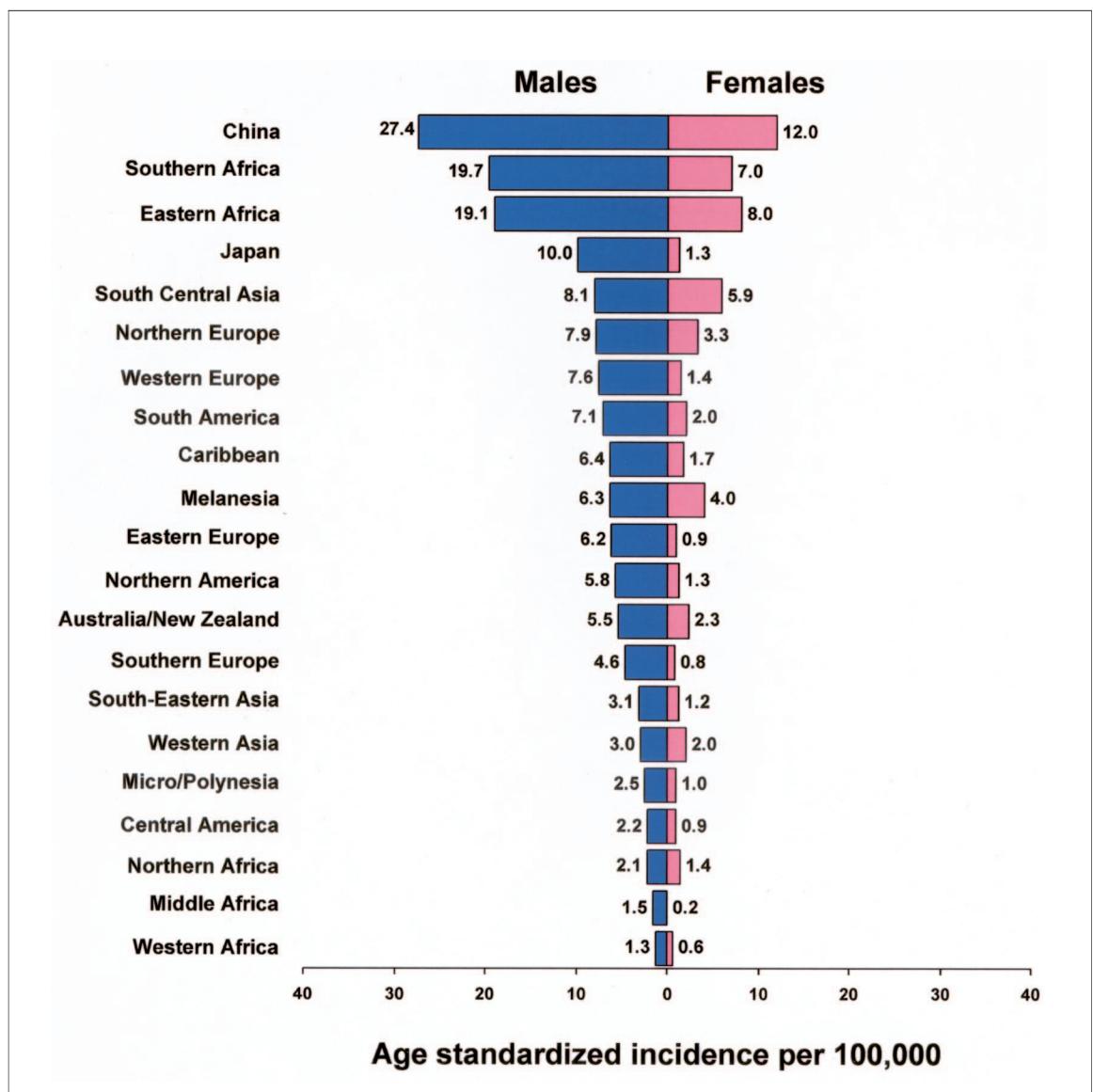
cohol and tobacco smoking, changes in these two exposures cannot explain the differential trends. The most likely explanation for the increases in incidence of adenocarcinoma seems to be the increasing prevalence of Barrett's esophagus as a consequence of gastroesophageal reflux, which is becoming more common with increasing levels of obesity.<sup>70,71</sup>

### *Bladder Cancer*

An estimated 357,000 bladder cancer cases occurred in 2002, making this the ninth most common cause of cancer for both sexes combined. There were 145,000 deaths, with population-based five-year survival rates ranging from 40% to 80% depending on whether noninvasive lesions are included in the computation. It is relatively common in developed countries, where 63% of all incident cases occur. The majority (77%) of bladder tumors occur in men. The variation in international incidence is not particularly striking relative to other cancers, however (Figure 13). Rates are high in many southern and eastern European countries where smoking (in men) has been prevalent, and in parts of Africa and the Middle East where bladder cancer, particularly of the squamous cell type, is linked to chronic infection with *Schistosoma hematobium*.<sup>38</sup> Some occupational exposures contribute to the high risk of developed countries. The highest recorded incidence rate is that found in Egypt, where the estimated world-standardized rate in men is 37 per 100,000. In the United States, the incidence in Whites is higher than in Blacks—about double among men and 50% greater among women. It is unlikely that this is due to differences in exposure to environmental carcinogens, and explanations based on differential susceptibility have been proposed, including, for example, genetic polymorphisms of metabolic enzymes such as *N-Acetyltransferase* (NAT) and *Glutathione S-transferase 1* (GSTM1).<sup>72,73</sup>

### *Non-Hodgkin Lymphoma*

The 301,000 cases of non-Hodgkin Lymphoma (NHL) that occurred in 2002 (2.8% of all cancers) comprise an extremely heteroge-



**FIGURE 12** Age-standardized Incidence Rates for Esophageal Cancer.  
Data shown per 100,000 by sex.

neous group of malignancies displaying distinct behavioral, prognostic, and epidemiological characteristics. Advances in molecular biology, genetics, and immunology have resulted in extensive changes in the classification of lymphoid tumors in the last few decades. The WHO classification<sup>74</sup> distinguishes tumors primarily by cell lineage defined by immunophenotype and groups together lymphomas and leukemias, acknowledging that some solid tumors also pass through circulating leukemic phases. Three broad categories are now recognized: B-cell neoplasms, T/NK-cell neoplasms,

and Hodgkin disease. Lymphocytic leukemias fall within the B-cell neoplasm group.

NHLs are slightly more common in developed countries (50.5% of cases worldwide), with rates highest in Australia and North America, intermediate in Europe (except eastern Europe) and the Pacific islands, and relatively low throughout Asia and eastern Europe (Figure 14). In most African populations, incidence of NHL is not high overall, but the relative frequency is above the world average in sub-Saharan Africa because of the high incidence of Burkitt lymphoma in children in the tropical zone of Africa. The relatively high esti-

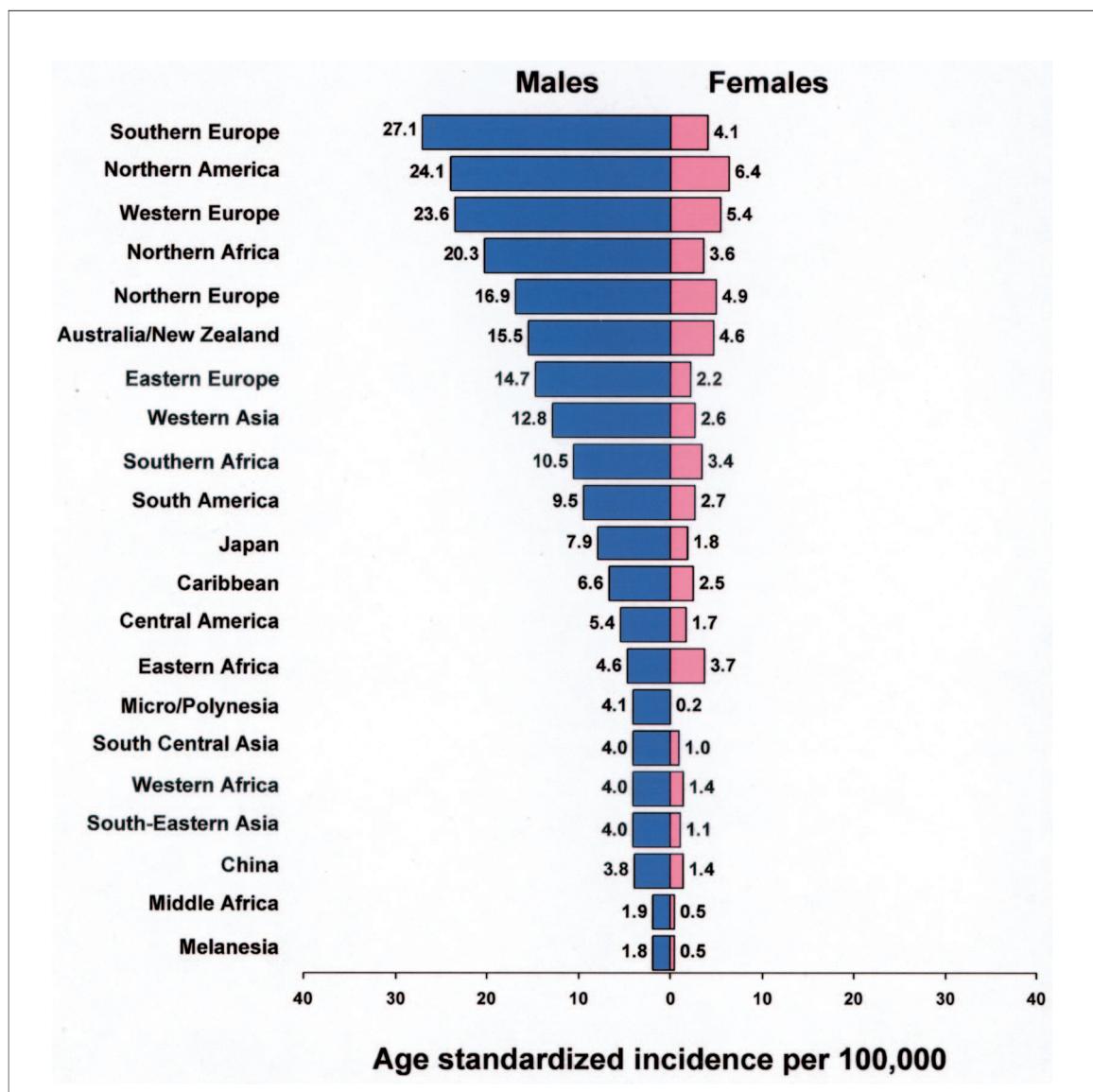


FIGURE 13 Age-standardized Incidence Rates for Bladder Cancer.  
Data shown per 100,000 by sex.

mated incidence in females in central Africa (Figure 16) is a consequence of high relative frequency of such cancers in the few available datasets from this area.

Approximately 5% to 10% of HIV-infected persons will develop a lymphoma, and NHL is the AIDS-defining illness in about 3% of HIV-infected patients.<sup>75</sup> In most parts of the world, B-cell lymphomas tend to dominate, although peripheral T-cell tumors comprise the majority of NHLs in eastern Asia and the Caribbean.<sup>76</sup> Adult T-cell leukemia/lymphoma (ATL) ac-

counts for a high proportion of NHL cases in southern Japan.<sup>77</sup>

There have been marked increases in the incidence of NHL in many parts of the world. While this may in part be due to improved diagnostic procedures and changes in classification, there can be little doubt that much of the change is real<sup>78</sup> and the reasons for it have been the subject of much debate. The increase is seen in both sexes across Europe since the 1960s. Increases of about 1% to 2% per year in incidence rates in both sexes by period of diagnosis are seen

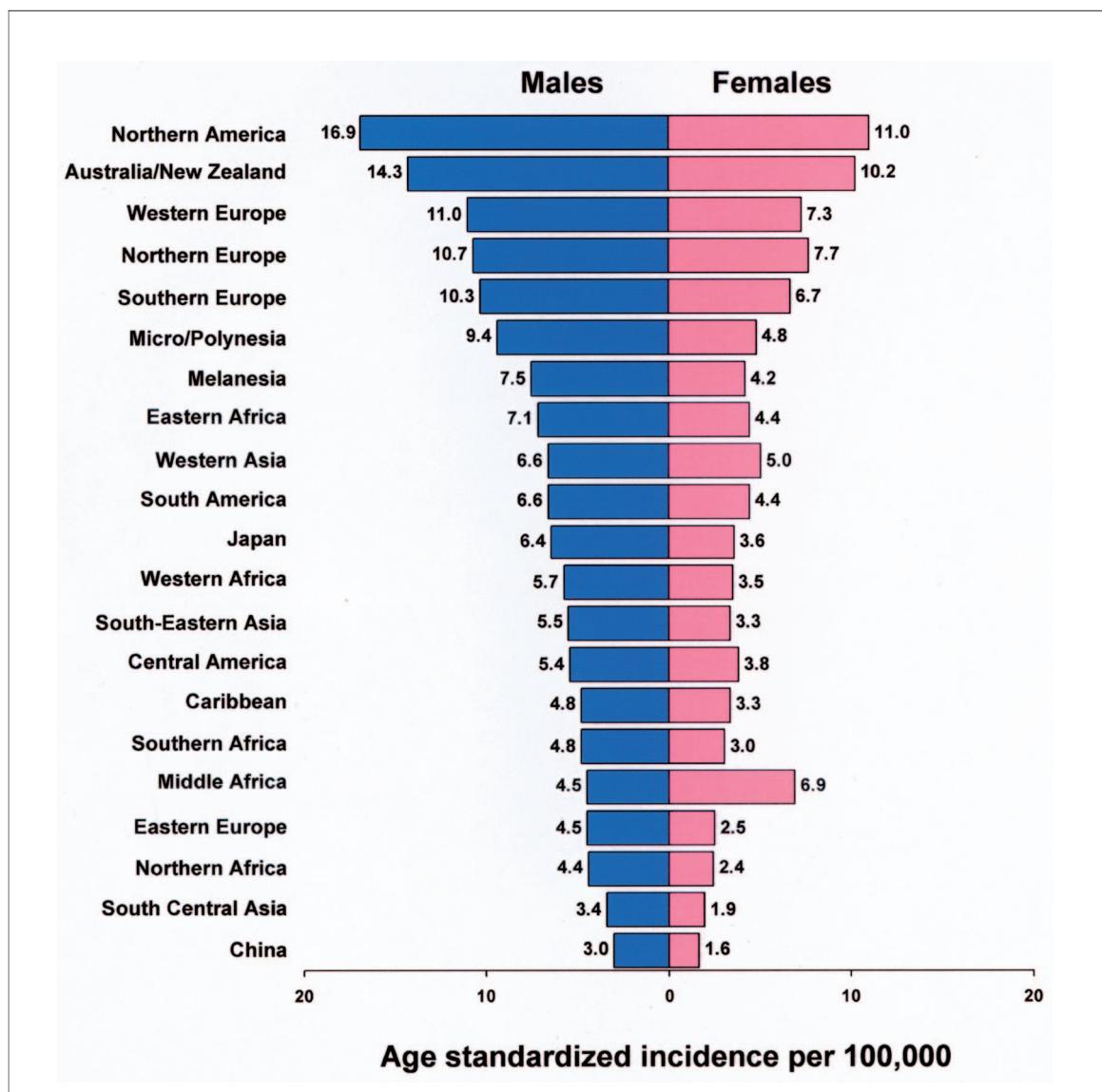


FIGURE 14 Age-standardized Incidence Rates for Non-Hodgkin Lymphoma. Data shown per 100,000 by sex.

in Australia and, at a lower level, in South America and Asia. In the United States, the rapid rises (particularly in younger men) may be partially attributable to the onset of the AIDS epidemic in 1981, while the declines during the 1990s may be due in part to a decrease in the incidence of HIV infection and successful antiretroviral therapies.<sup>79</sup>

AIDS cannot, however, account for all of the observed increases, as subtypes not associated with AIDS are continuing to increase. Other established risk factors, such as those related to disorders of the immune system (eg, transplant patients, autoimmunity, congenital immunodeficiency), are not likely to explain more than a fraction of the observed incidence. The biological evidence that ultraviolet exposure from sunlight can result in immune modulation and increased NHL risk is credible, but results from the epidemiological studies have been so far conflicting.<sup>76</sup>

**Leukemia**

Leukemia accounts for some 300,000 new cases each year (2.8% of all new cancer cases) and 222,000 deaths. This rather high ratio of deaths/cases (74%) reflects the poor prognosis of leuke-

mia in many parts of the world, where the somewhat complex treatment regimes required are not available. There is relatively little geographic variation; the range of incidence rates is about five- to sevenfold, with the lowest rates in sub-Saharan Africa (probably representing failure of diagnosis to some extent) and the highest in North America and Australia/New Zealand. The geographic patterns will not be the same for different leukemia subtypes. For example, chronic lymphocytic leukemia (equivalent to small lymphocytic (B-cell) lymphoma in current classifications) is numerically the most important diagnosis in western Europe, but is extremely rare in east and southeast Asia. Variations in mortality are significantly less than for incidence, due to better survival (and hence lower mortality) in developed countries where survival is twice that in developing countries (Table 2).

#### *Oral Cancer*

Cancers of the oral cavity accounted for 274,000 cases in 2002, with almost two-thirds of them in men. The world area with the highest incidence is Melanesia (31.5 per 100,000 in men and 20.2 per 100,000 in women). Rates in men are high in western Europe (11.3 per 100,000), southern Europe (9.2 per 100,000), south Asia (12.7 per 100,000), southern Africa (11.1 per 100,000), and Australia/New Zealand (10.2 per 100,000). In females, incidence is relatively high in southern Asia (8.3 per 100,000). These patterns reflect prevalence of specific risk factors, such as tobacco/alcohol use in western Europe, southern Europe, and southern Africa, and the chewing of betel quid in southcentral Asia and Melanesia. The high rate of oral cancer in Australia is due to lip cancer (related to solar irradiation). Mortality is on average less than half the incidence, because of the moderately good survival.

#### *Pancreatic Cancer*

Pancreatic cancer is responsible for 227,000 deaths per year, and is the eighth most common cause of death from cancer in both sexes combined, a relative position higher than for incidence (thirteenth) because of the very poor prognosis (the M/I ratio is 98%). The sex ratio is

close to one. Most cases and deaths (61%) occur in developed countries, where incidence and mortality rates are between 7 and 9 per 100,000 in men and 4.5 and 6 per 100,000 in women, with lower rates in developing countries. This probably reflects diagnostic capacity rather than etiology. Among the developing countries, the highest rates are observed in Central and South America. Little is known of the etiology of this cancer, although tobacco smoking increases the risk.<sup>42</sup>

#### *Kidney Cancer*

Kidney cancer (208,000 new cases, 1.9% of the world total; 102,000 deaths) has the highest rates in North America, Australia/New Zealand and western, eastern, and northern Europe. Incidence rates are low in Africa, Asia (except Japanese males) and the Pacific. Little is known of the etiology of kidney cancer, although tobacco smoking is an important cause,<sup>42</sup> as well as some environmental chemicals, especially arsenic. The risk is increased by obesity.<sup>80</sup>

#### *Ovarian Cancer*

Ovarian cancer (204,000 cases and 125,000 deaths) is the sixth most common cancer and the seventh cause of death from cancer in women (4.0% of cases and 4.2% deaths). Incidence rates are highest in developed countries (Figure 15), with rates in these areas exceeding 9 per 100,000, except for Japan (6.4 per 100,000). Incidence in South America (7.7 per 100,000) is relatively high. Incidence rates have been slowly increasing in many Western countries and Japan. The risk of ovarian cancer is reduced by high parity and use of oral contraceptives.<sup>81</sup>

#### *Corpus Uteri Cancer*

Cancer of the Corpus uteri has a rather similar geographic distribution to ovarian cancer. However, it appears more important as a cause of new cases (199,000 or 3.9% of

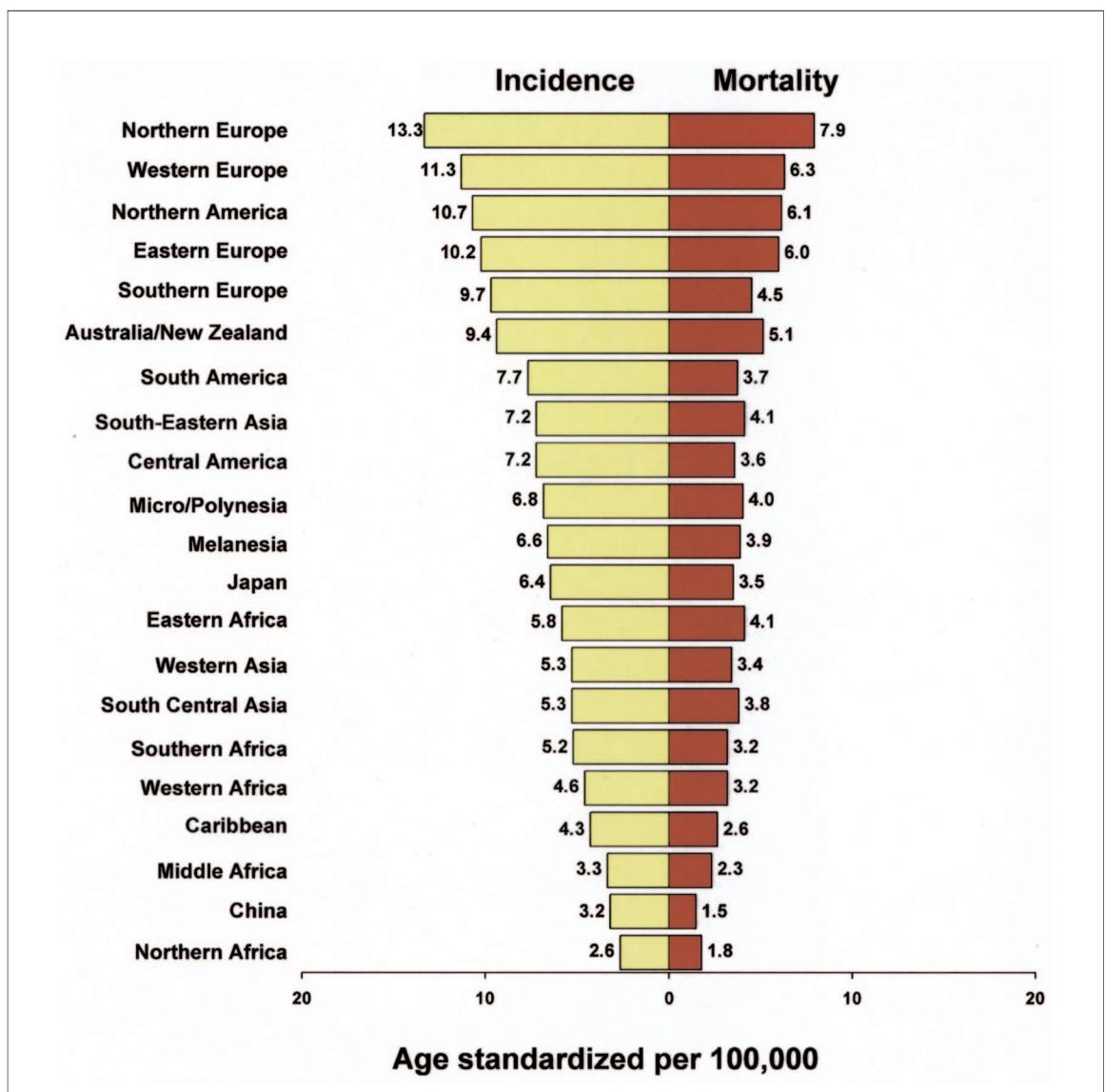


FIGURE 15 Age-standardized Incidence and Mortality Rates for Ovarian Cancer.  
Data shown per 100,000.

cancers in women) than in terms of mortality (50,000 deaths or 1.7% of cancer deaths in women) because of the much more favorable prognosis. It is a cancer of postmenopausal women; worldwide, 91% of cases occur in women aged 50 and older. Survival is rather good and similar to that of breast cancer—86% in the US SEER registries and 78% in European registries. The proportion of these cases surviving up to five years in developing countries is greater than the corresponding proportion of breast cancers (Table 2). The highest incidences are in North America (22.0) and

Europe (11.8 to 12.5). Rates are low in southern and eastern Asia (including Japan) and most of Africa (less than 3.5 per 100,000).

#### *Brain and Nervous System Cancer*

Cancers of the brain and nervous system account for some 189,000 new cases and 142,000 deaths annually (1.7% of new cancers; 2.1% of cancer deaths). The highest rates are observed in developed areas (Australia/New Zealand, Europe, and North America) and are lowest in Africa and the Pacific islands. This

suggests that the availability of diagnostic facilities may well be important in determining geographic patterns, at least in part. The incidence is probably underestimated in many developing countries. Mortality statistics tend to be unreliable also, in part because of confusion between primary and metastatic cancers.

### *Melanoma*

Malignant melanoma of skin accounts for 160,000 new cases annually, with slightly more occurring in women than in men (M:F sex ratio, 0.97). It is a tumor particularly common in White populations living in sunny climates. High rates of incidence are found in Australia/New Zealand, North America, and northern Europe (Figure 16). Survival from melanoma is very favorable in developed areas (91% in the US SEER registries and 81% in Europe). Females have better survival than males, probably because the site distribution permits earlier diagnosis (thinner lesions). Survival in developing countries is poorer (around 40%), in part due to late diagnosis and limited access to therapy, but also because the tumors are generally acral melanomas located on the soles of the feet, which have a generally poorer prognosis than other melanomas. Thus, the range of mortality rates between world areas is much less than for incidence. In all, there were an estimated 41,000 deaths in 2002, with more in men than in women (M:F sex ratio, 1.2). Rapid increases in incidence and mortality are observed in both sexes in many countries, even where rates were formerly low, such as Japan. In the Nordic countries, for example, this has averaged some 30% every five years.

### *Larynx Cancer*

Larynx cancer (159,000 new cases and 90,000 deaths) is predominantly a cancer of men, in whom it comprises 2.4% of cases and 2.1% of deaths. The sex ratio (almost 7:1) is greater than for any other site; it is a rare cancer in women, particularly in developed countries. There is a large geographic variability in the disease frequency. High-risk countries are found in southern Europe (France, Italy, Spain), eastern Europe (Russia, Ukraine), South America (Uruguay, Argentina), and western Asia (Turkey, Iraq) (Figure

17). In western Asia, larynx cancer accounts for 4.7% of cancers in men.

The risk of larynx cancer is greatly increased by tobacco smoking and alcohol consumption, an effect which is multiplicative. Populations at high risk are therefore those where both habits are common.

Relative survival of larynx cancer patients varies between 60% and 70% in Europe and North America, but is lower in developing countries. It is highly dependent on the subsite of the disease, which itself is dependent on the etiological factors involved. In countries with elevated alcohol consumption, the prognosis is poorer because there are more tumors of the upper part of the larynx, which have a lower survival.

### *Thyroid Cancer*

Thyroid cancer (141,000 new cases) is one of the few malignancies that are more common in females than in males (M:F sex ratio, 0.36); it comprises 2.1% of cancers in women. It is known that diagnostic practices (ie, histological examination of resected goiters or at autopsy) can influence apparent rates of incidence. This may account for the particularly high rates observed in the United States. Rates are also high in Australia/New Zealand, Japan, and Central America (in women only). The prognosis for thyroid cancer is good (M:I ratio worldwide, 0.25), so it accounts for rather few deaths (35,000 or 0.5% of all cancer deaths).

### *Myeloma*

Myeloma, a malignant tumor of the plasma cells in the bone marrow, constitutes 0.8% of all cancers worldwide (86,000 new cases). Incidence rates vary from 0.4 to 5 per 100,000, and is very rare in persons under 40 years of age. The incidence is high in North America, Australia/ New Zealand, northern Europe, and western Europe compared with Asian countries. Within the United States, the incidence in Blacks is about double that in Whites, whereas persons of Japanese and Chinese origin have lower rates.<sup>46</sup> The moderately high incidence rates observed in the Caribbean and southern and central Africa would accord with increased risk in persons

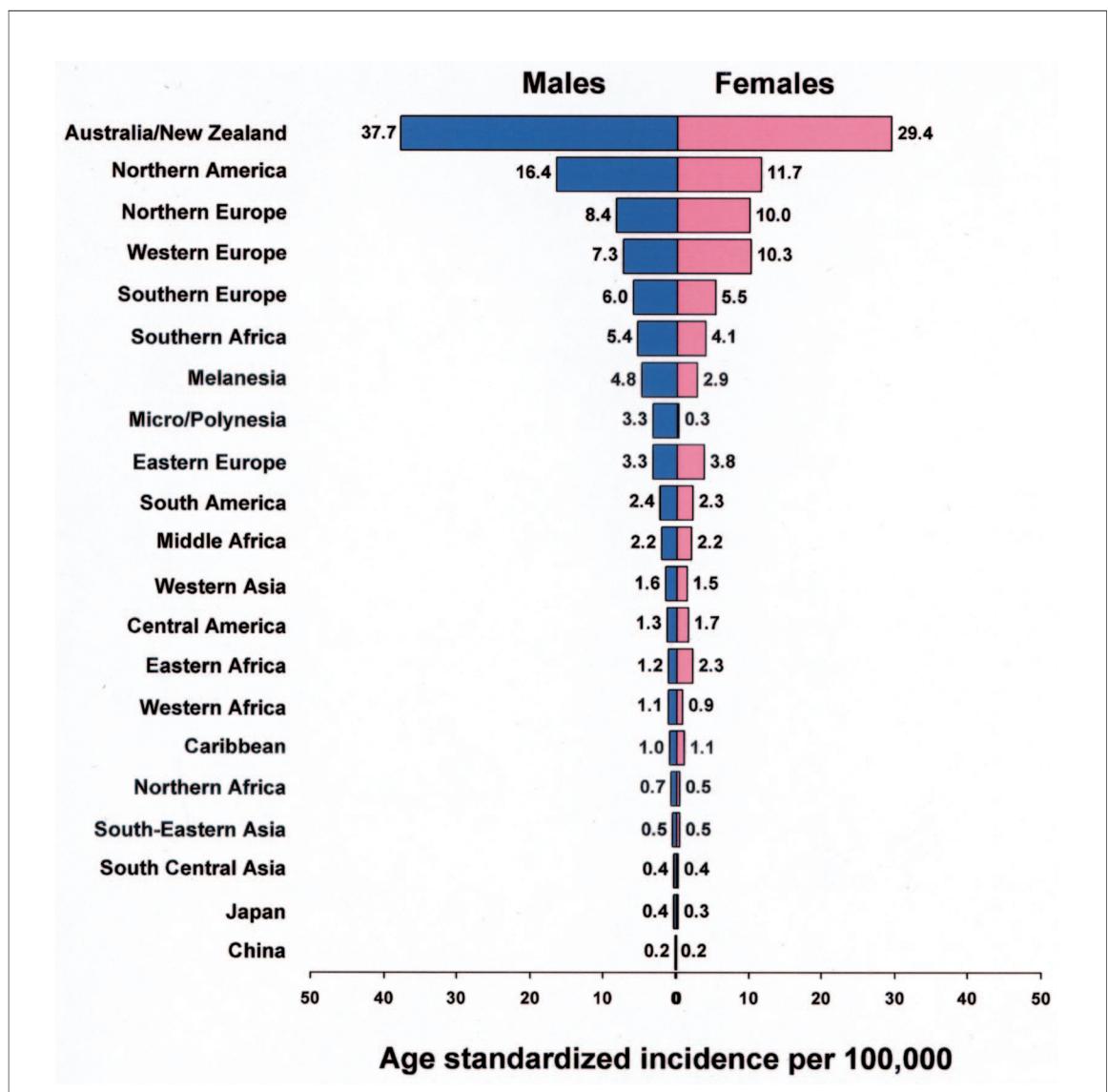


FIGURE 16 Age-standardized Incidence Rates for Melanoma.  
Data shown per 100,000 by sex.

of African descent, although incidence is low in West Africa (possibly due to diagnostic difficulty). A slow increase in incidence and mortality from myeloma is observed in most regions of the world, the reason for which is unknown. Exposure to ionizing radiation is the only well-established risk factor for multiple myeloma, although some chemicals and occupational exposures have been reported to be associated with an increased risk. The five-year survival rate for patients with myeloma is 15% to 20%.

#### Nasopharyngeal Cancer

Nasopharyngeal cancer (NPC) is relatively rare on a world scale (80,000 new cases per year, 0.7% of all cancers), but it has a very distinctive geographic distribution. Thus, the age-standardized incidence rate is generally less than 1 per 100,000, with the exception of populations living in or originating from southern China (in whom the rates are very high), and in populations elsewhere in China, southeast Asia, northeast India, North

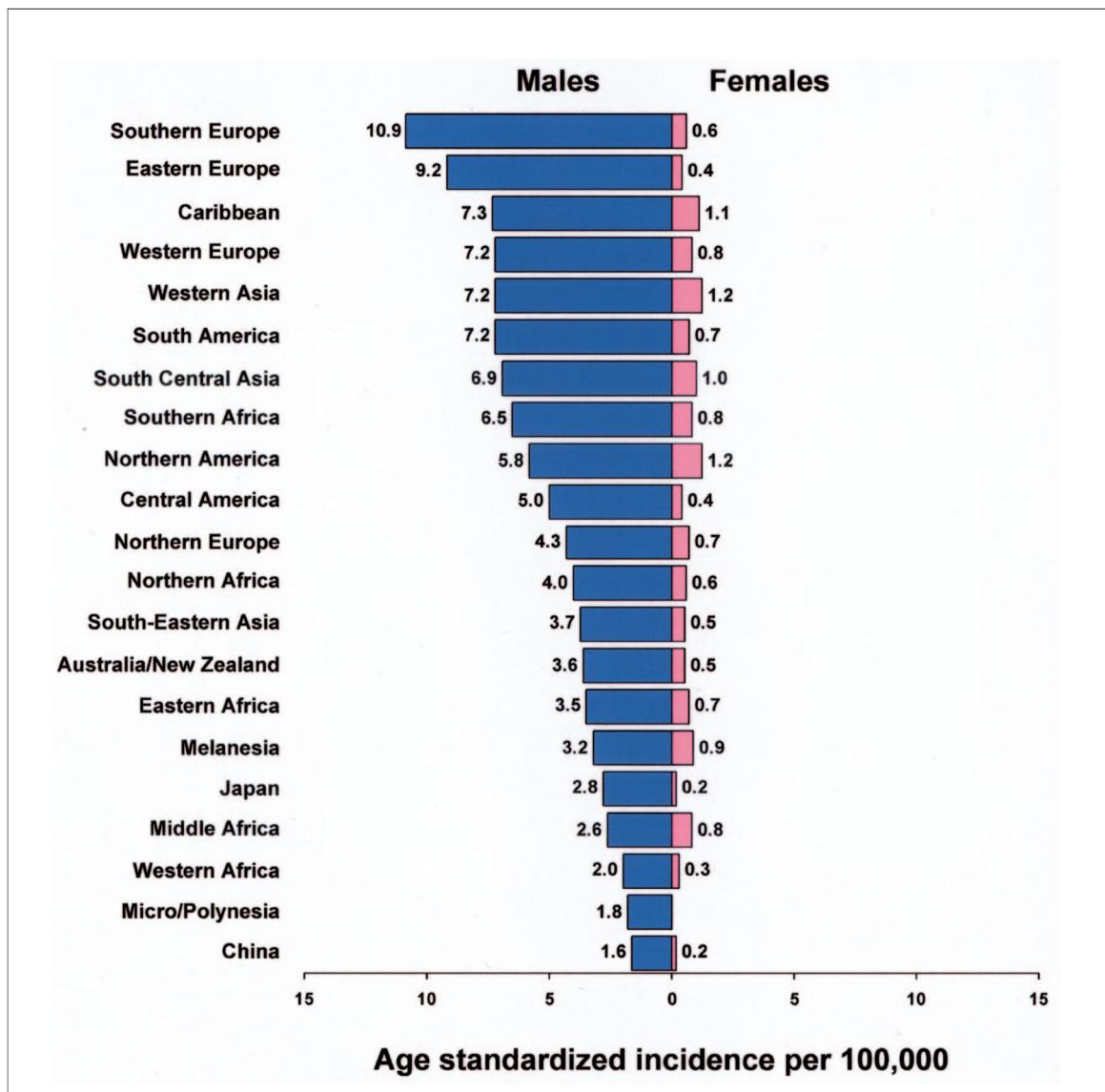


FIGURE 17 Age-standardized Incidence Rates for Larynx Cancer.  
Data shown per 100,000 by sex.

Africa and Inuits (Eskimos) of Canada and Alaska, all of whom have moderately elevated rates. Males are more often affected than females (M:F sex ratio, 2.3:1), and in most populations, there is a progressive increase in risk with age. However, in moderate risk populations (most notably in North Africa), there is a peak in incidence in adolescence.

There is clearly a strong genetic component to risk, as shown by the elevated risk in migrant populations of Chinese or North African origin,

and also in their children born in a new host country. An association between human leukocyte antigen profile and risk of NPC has been reported; a study of affected siblings in Singapore identified a gene locus close to human leukocyte antigen with a 20-fold risk for NPC. Infection with Epstein-Barr Virus is also clearly important in etiology.<sup>82</sup> This virus is not found in normal epithelial cells of the nasopharynx, but is present in all NPC tumor cells and even in dysplastic precursor lesions. In addition, various environmental factors have been found to play a role.

The most important are dietary, and in particular, the consumption of certain salted, preserved, or fermented dietary items; this may be a consequence of the raised nitrosamine content of such items. Fresh vegetables and fruits are protective.

Tobacco smoking has been found to be important in low-risk populations. There has been a decrease in incidence over time in some high-risk populations (eg, Hong Kong).

#### *Hodgkin Disease*

Hodgkin disease is distinguished from other lymphoid neoplasms in that the malignant cell is the Reed-Sternberg cells of lymph nodes. It comprises about 17% of malignant lymphomas worldwide (62,000 annual cases). There is a strong male predominance (M:F sex ratio, 1.6:1). Two disease entities are recognized: nodular lymphocyte-predominant Hodgkin lymphoma and classical Hodgkin lymphoma. Within the latter, four subtypes have been distinguished: nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-depleted.<sup>74</sup> In developing countries, Hodgkin disease occurs mainly in children (most cases are the mixed cellularity subtype) and in the elderly, whereas in developed countries there is a peak in young adults of the nodular sclerosing subtype. Overall, therefore, incidence is highest in developed countries (North America and Europe) and very rare in Asian populations; in childhood, however, some developing regions feature more prominently (Figure 18).

In Europe and North America, there is an association between risk of Hodgkin disease and socioeconomic status, but this is confined to cases in young adults and to the nodular sclerosis subtype.<sup>83</sup> This is consistent with Mueller's<sup>84</sup> observations that cases of Hodgkin disease in developing countries are predominantly of mixed cellularity and lymphocytic depletion subtypes, while the young adult peak of developed countries involves mainly the nodular sclerosing type.

Much evidence points to an association between Hodgkin disease and Epstein-Barr virus (EBV),<sup>82</sup> and markers of EBV infection or EBV DNA can be detected in tumor tissue from a proportion of subjects. The virus

appears to be located within the Reed-Sternberg cells in up to 50% of patients and is more common in populations of lower socioeconomic status, cases of mixed cellularity type, and cases occurring in children or the elderly.<sup>85</sup>

#### *Testicular Cancer*

Testicular cancer is relatively rare, with 49,000 new cases annually of 0.8% of cancers in men. The highest rates are observed in western Europe (7.9 per 100,000), northern Europe, Australia/New Zealand, and North America (5.4 per 100,000). The incidence is low in Asia: 0.4 per 100,000 in China, for example. The highest incidence rates occur in men aged 15 to 44, and testicular cancer is the most common cause of cancer among men in this age range in developed countries (13.4% of new cases). Testicular cancer is a rare cause of cancer mortality (9,000 deaths per year), although the good prognosis depends on availability of expensive chemotherapy. Therefore survival, though very favorable in developed countries (M:I ratio, 0.09), is much less optimistic in the developing world (M:I ratio, 0.3). A rapid increase of the incidence has been observed in most countries. The reasons for such trends are not well understood. Improved diagnostic procedures account for a small part of the increase. Conversely, mortality has markedly declined since the introduction of effective chemotherapy in the mid 1970s.

#### *Kaposi Sarcoma*

Before the epidemic of HIV/AIDS, Kaposi Sarcoma (KS) was a rare cancer in Western countries (cumulative incidence in the United States and Europe was less than 0.5 per 100,000, comprising about 0.3% of male and 0.1% of female cancers). It was seen mainly among immigrants from the Mediterranean littoral and African regions, and immunosuppressed transplant recipients. In Africa, endemic KS had a quite distinct geographic distribution; while rare in northern and southern Africa, it comprised up to 10%

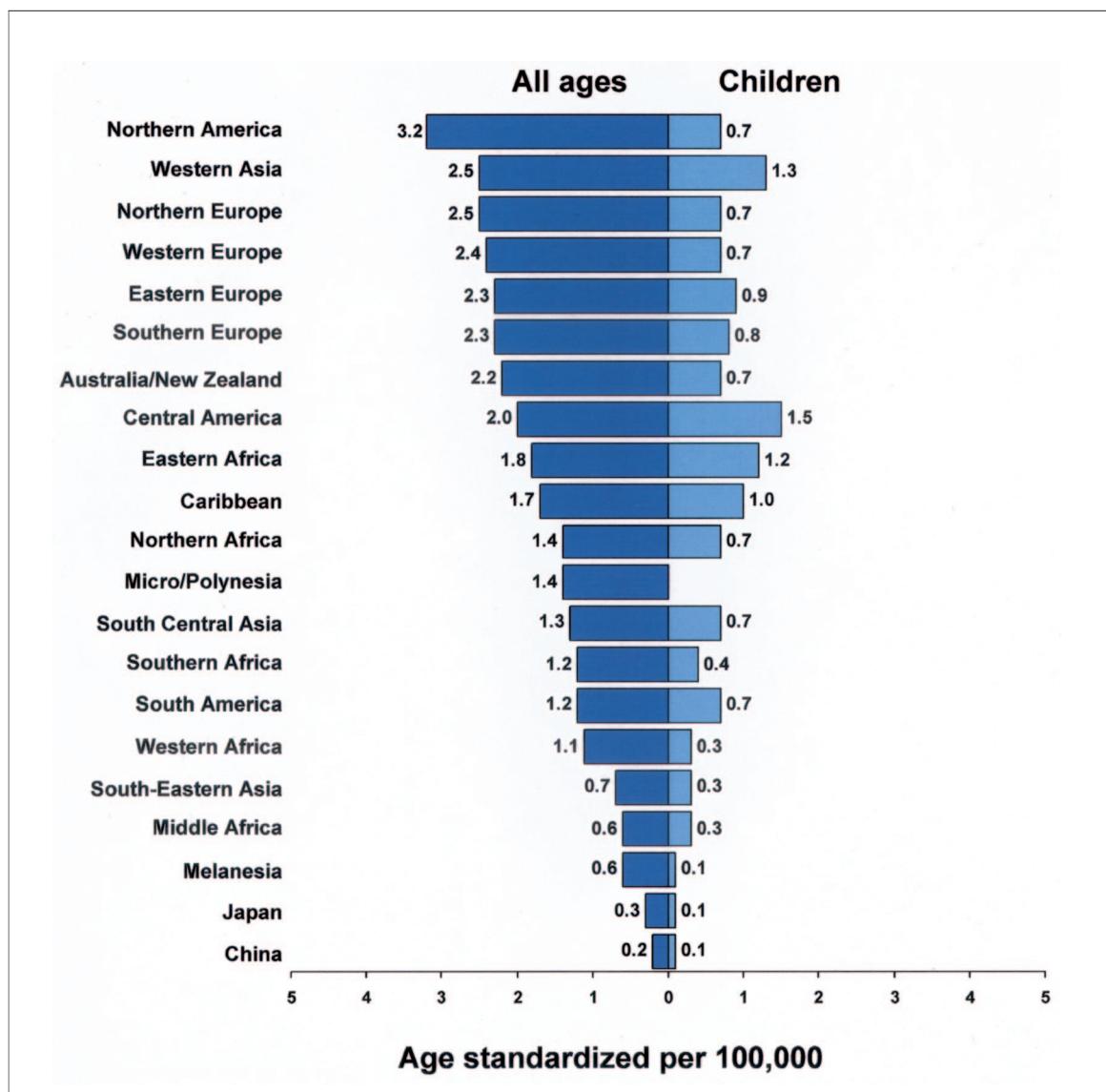


FIGURE 18 Age-standardized Incidence Rates for Hodgkin Disease.  
Data shown per 100,000 for males.

of cancers in men in some case series from certain parts of central and eastern Africa.<sup>86,87</sup> Since the 1980s, in those areas where endemic KS had been relatively common before the epidemic of HIV/AIDS such as Uganda, Malawi, Zimbabwe, and Swaziland, the incidence of KS has increased about 20-fold, such that it is now the leading cancer in men and the second leading cancer in women.<sup>36</sup> In Western countries, the incidence of KS has increased over a thousand-fold in populations at high risk of HIV,<sup>88,89</sup> al-

though in numerical terms it remains a rare cancer. For example, based on the incidence rates recorded in the US SEER program in 2000 to 2001, there were probably fewer than 2000 cases annually. KS is extremely rare in Asian populations, even those with quite high prevalence of HIV infection.<sup>90</sup> The explanation for these disparities probably lies in the role of human herpes virus-8 (HHV-8) in the etiology of KS, as subjects infected by both HHV-8 and HIV are at particularly high risk of KS.<sup>91,92</sup> The effect of

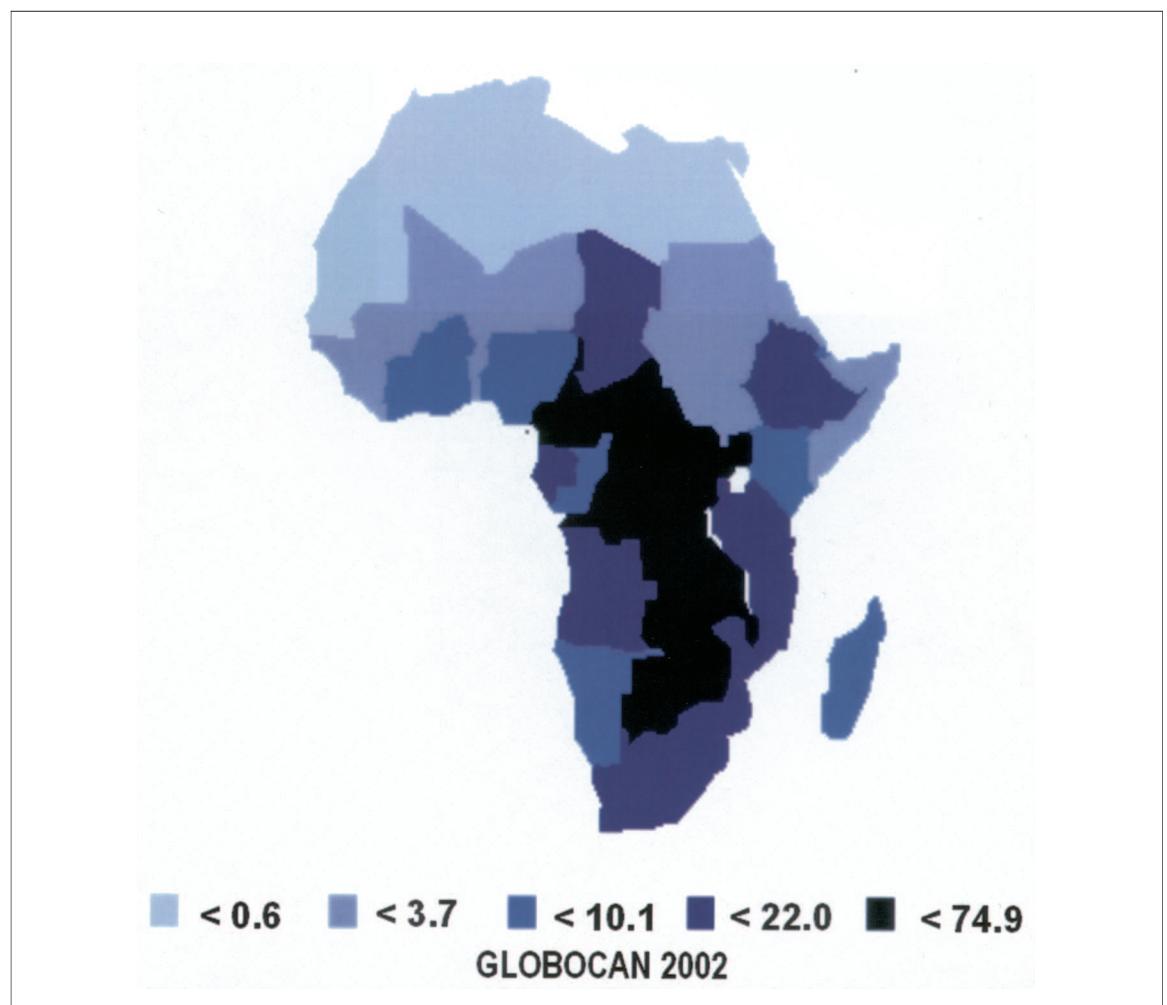
HIV is probably through immunosuppression, by allowing HHV-8 to escape control and increase viral load, for example. The epidemiology of this virus probably explains the geography of KS pre-AIDS, and the relative rarity of the cancer in western and southern Africa, despite the increasing prevalence of HIV.

Using the most recent estimates, 40,000 cases of KS in males and 17,200 cases in females are estimated for 2002 for the sub-Saharan African region; only 260 cases were estimated to occur in northern Africa. The region most affected is central Africa (30 per 100,000), followed by eastern, southern, and western Africa, in line with the background prevalence of HIV in each of these regions (Figure 19).

Antiretroviral therapy for treating HIV in adults has caused a decline in the incidence of KS in Western countries.<sup>93</sup>

#### CONCLUSIONS

The facts and figures presented in this paper are a mixture of real data, extrapolations from limited samples, and informed guesses. They are, nevertheless, the best contemporary information on global patterns of cancer incidence and mortality. They show, even at the rather crude level of 20 large so-called world areas, a tremendous range of diversity in the risk of different cancers and of death from cancer. The figures show which are the priority areas for research and indicate where implementation of



**FIGURE 19** Incidence of Kaposi Sarcoma. Data shown for males of all ages, from GLOBOCAN 2002.

current technology (in treatment and prevention) would be most fruitful.

The global disparities in incidence of certain preventable cancers (eg, cervical), as well as in survival from several that are treatable (eg, lymphoma, leukemia, testicular), are a demonstration of a lack of equity in health apparently determined solely by the hazard of where one is born.

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