1 Lessons from epidemiology

We begin by looking at cancer patterns worldwide. These are of interest because they show marked variations in the forms of the disease that afflict different populations. These differences indicate the importance of environmental factors that include lifestyle – for example, what we eat and tobacco use – in determining both the type of cancer and the frequency of occurrence. Although there is variation in cancer types, there is a broad trend of rising incidence across the world, for which a major driving force is increasing longevity. In the developed world lung, breast, bowel and prostate cancers head the mortality table. Taking all cancers together, the last 30 years has seen a gradual increase in the five-year survival rate, although there remain significant variations between nations and even within some countries. For the developing world the outlook is more depressing: not only is the annual number of new cases rising but inadequate screening programmes often mean that diagnosis is delayed until tumours have spread to secondary sites in the body and therefore become very difficult to treat. Analysis of cancer mortality in different age groups revealed many years ago that the additive effects of about half a dozen discrete events drives cancer development – the first direct evidence that the accumulation of mutations is the underlying cause.

Incidence

Every year over 12 million people worldwide are diagnosed with cancer. Europe and North America together contribute about 40% of this figure with just over half of all new cases (54%) arising in developing countries. Of the various types of cancer that contribute to these figures, lung cancer heads the list with 1.4 million new cases annually (12.5%) followed by breast (1.2 million, 10.6%) and colorectal (1 million, 9.4%) cancers (Fig. 1.1). The names of these three cancers will be familiar to American and British readers because they are also in the top four of their national figures for both incidence and deaths due to cancers. The other member of the Big Four in those countries, and in most of the developed world, is prostate cancer (679,000, 6.3%). However, in the world rankings prostate is pushed down to sixth on the list by stomach and cervical cancer (934,000 and 692,000 cases annually, respectively).

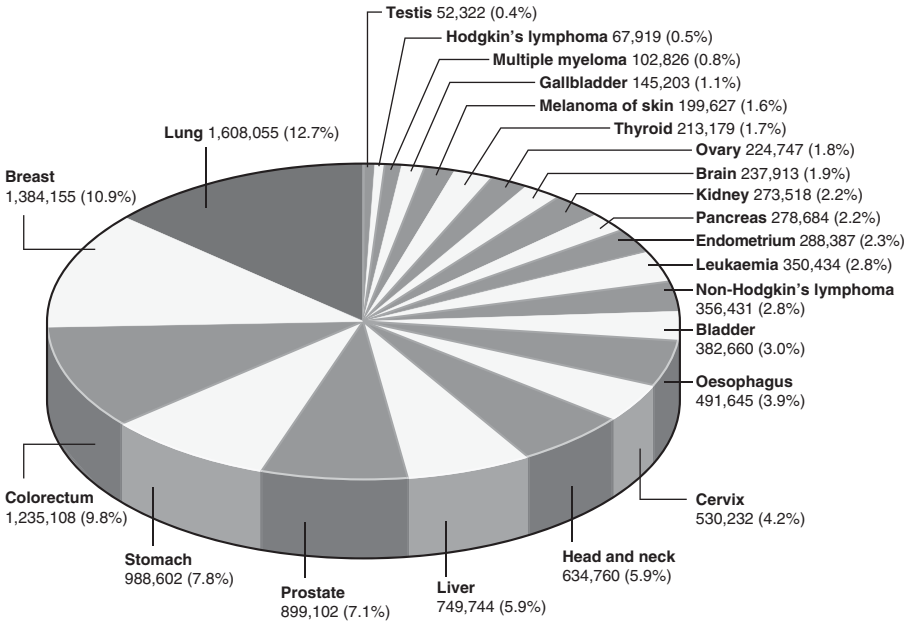

Figure 1.1 **Incidence of major cancers worldwide, 2008.** Shown in rank order with number of cases and percentage of the total number (12,662,554).

Incidence varies widely around the world being highest in the USA for both men and women. For all forms of cancer the lowest rates are about five times less than the USA figure (e.g. in Gambia), although some specific cancers show much greater variation (e.g. there are about 300 new skin cancer cases in some parts of Australia for every one in Kuwait).

In the UK in 2008 there were 309,527 new cancer cases: for the USA in 2012 the estimate is that there will be 1,638,910 new cases. For women breast cancer is the most common: 48,788 British women were diagnosed in 2009, and one in six Americans will get it, which means over 226,800 cases in 2012, about the same percentage in the two populations.

Deaths

Collecting numbers about the distribution of disease is called epidemiology and it has a fascination of its own but, as we shall see, when you get to the scale of the major cancers it can be very informative. Every year over 7 million people die from the disease – that's 13% of the total of 56 million deaths in the world from all causes each year (Fig. 1.2). Unsurprisingly, the ten most common cancers worldwide are also among the leading causes of mortality. Bladder and **non-Hodgkin's lymphoma**, however, are displaced in the mortality table by pancreatic cancers and **leukaemias**. In part this reflects the fact that there are no effective treatments for tumours of the pancreas and it may be noted that this cancer joins the Big Four in the leading causes of USA and UK cancer deaths.

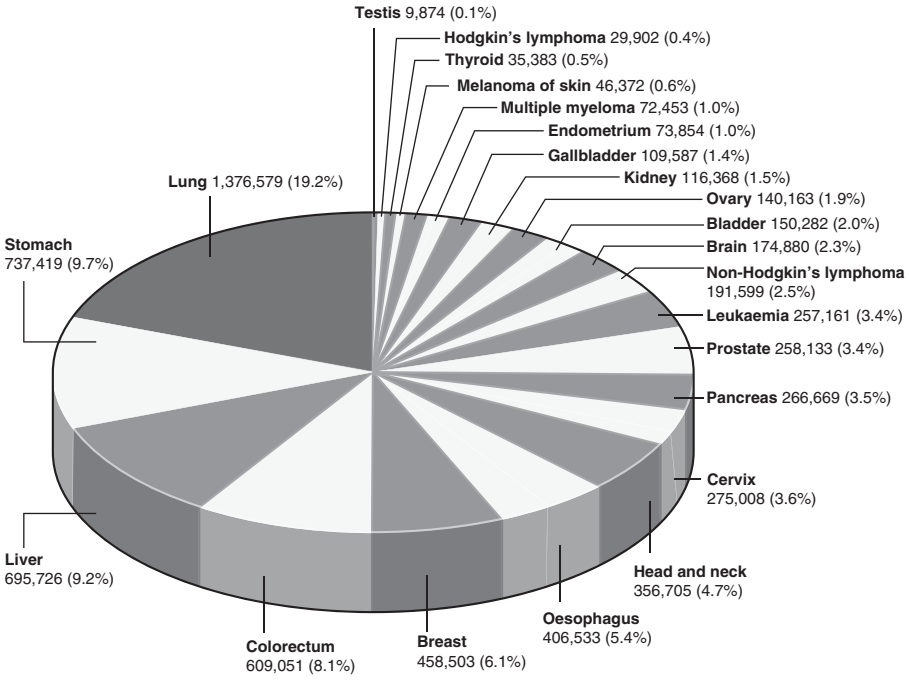

Figure 1.2 **Deaths from major cancers worldwide, 2008.** Shown in rank order with percentage of the total number (7,564,802)

To put cancer in its place we might note that mankind's biggest scourge is heart disease, which claims over 13.5 million deaths per year (24%) – this total comprises deaths caused by ischaemic heart disease, cerebrovascular disease and hypertension. After heart disease, the next biggest killers all fall some way behind cancer, namely, HIV/AIDS (4.9%), tuberculosis (2.7%) and malaria (2.2%). Much less well known is the figure of 2.2 million children (3.9%) who will die from diarrhoea this year – largely caused by ingesting germs through living in insanitary conditions.

Gradual shifts have occurred in the worldwide cancer pattern over the last century due to changes in lifestyle. The most dominant factor is that we are living longer, which gives us more time to develop the disease, and this together with other factors, has led the International Union Against Cancer to conclude that the number of new cases each year will rise to more than 16 million by 2020.

Patterns around the world: how many cancers and what sort?

UK and USA

Unsurprisingly, the death toll that results from the avalanche of new cases also has lung cancer at the top of the list with 1.2 million (17.5% of all cancer deaths). However, the next biggest worldwide cancer killers are stomach (0.7 million), liver (598,000) and

colon (529,000), accounting for 10.4%, 8.9% and 7.9% of all cancer deaths, respectively. In 2009, the UK weighed in with a contribution of 156,090 to the 7 million. In 2010, the USA provided 299,200 male and 270,290 female cancer deaths. We've already noted that on the UK and USA incidence lists prostate displaces stomach and so it's unsurprising that it does the same on the killer lists, with stomach cancer being sixth in the UK and thirteenth in the USA (Fig. 1.3). All the same, 'twas not ever thus: go back 80 years in the USA and stomach cancer was the biggest cancer killer, albeit that in 1930 the total death toll was only ~120,000. Nowadays nearly two-thirds of stomach cancers occur in the developing world, to which we will return in a moment, but there too the incidence is declining, as it has done in the USA, for reasons that are not entirely evident but may include the increasing availability of fresh fruit and vegetables and of meat preserved by refrigeration rather than by salting. Nevertheless 10,540 will die of stomach cancer in the USA in 2012.

Despite having the second highest incidence, breast cancer is only fifth on the mortality list with 458,503 deaths in 2008 (11,633 in the UK in 2010; 39,840 in the USA in 2010). This figure of about half a million represents 1.6% of all female deaths but again there is an imbalance – this time in the other direction. In rich countries 2% of all female deaths are due to breast cancer but in poor countries the figure is only 0.5%. Here the difference roughly reflects incidence – about five times lower in developing countries where the average age of populations is younger. The distribution pattern of cancer mortality between men and women in the USA is closely mirrored in the UK (Figs. 1.4 and 1.5). The two notable exceptions are liver cancer, comparatively common in the USA, and stomach cancer, which is more significant in the UK. The latter may reflect dietary differences in at least some regions of Britain and high protein and cholesterol diets may be a factor in the USA liver rates.

Europe

The pattern across European nations (Fig. 1.6) shows the overall cancer death rates to be generally higher in eastern Europe (Hungary is the highest with 234 per 100,000) with the lowest being in Finland (138 per 100,000). Even so, for women over the period 2000–2004, Denmark, Scotland and Hungary were the top three (141, 123 and 132/100,000, respectively). One might expect that the variations between countries in total cancer mortality would be strongly dependent on differences in the toll of the major cancers. Indeed the pattern of breast cancer, for example, broadly follows that of total cancer deaths, although there is one notable exception: Poland has the third highest rate of total cancer deaths but one of the lowest breast cancer rates. Despite these generalities it should be borne in mind that breast cancer and other major cancers, such as **melanoma** and prostate cancer, vary markedly in national impact.

Russia has by far the highest population of any European nation (148 million) but in terms of cancer it remains something of an enigma. In the period after 1960 there was a gradual decline in Russian cancer death rates but this reversed in the early 1980s. The major contributors to the reversal were male lung and female breast cancer. In the 1990s, however, the trend reversed again, mainly due to a drop in cancer deaths among the elderly. Broadly similar trends have also occurred in the Ukraine (52 million),

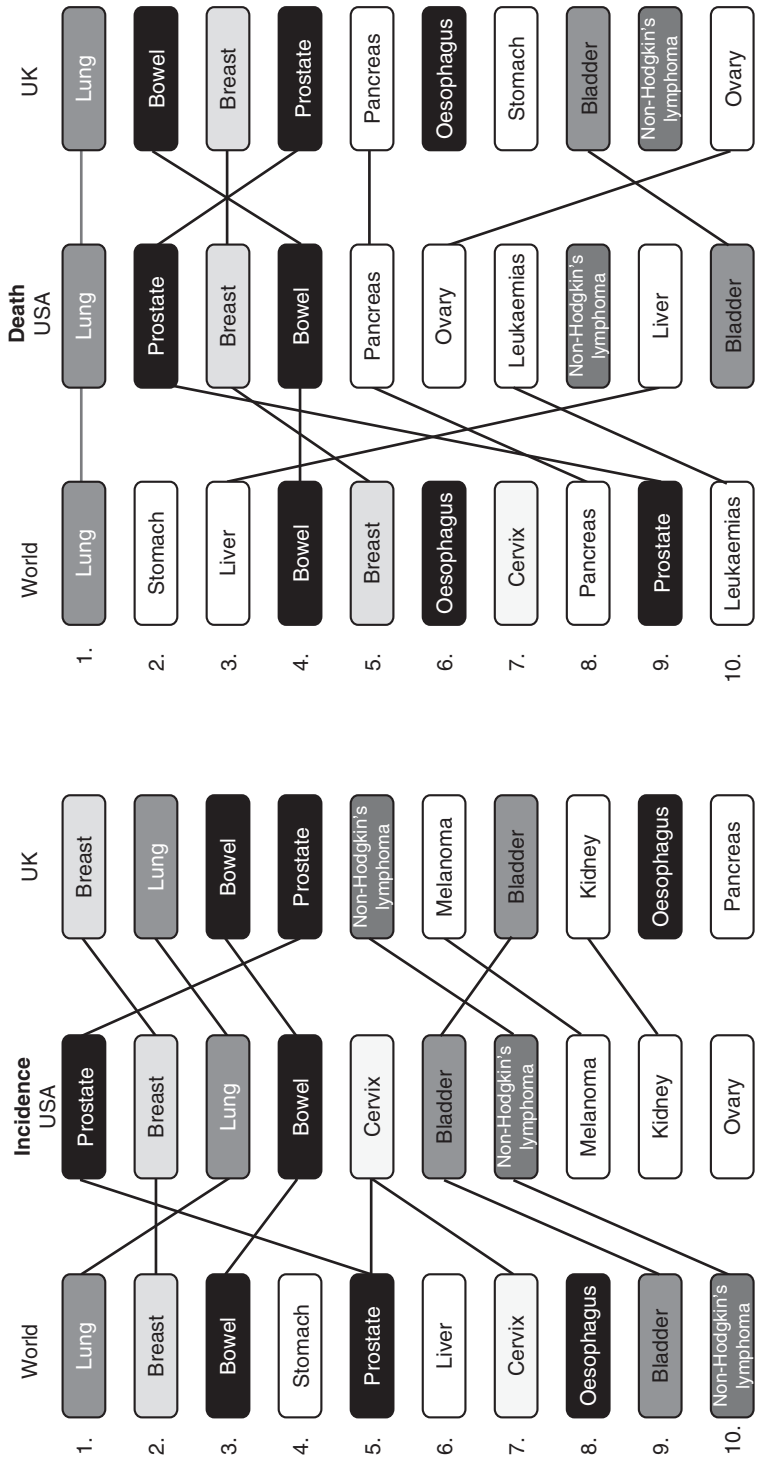

Figure 1.3 Top ten world rankings for incidence and death compared with UK and USA positions.

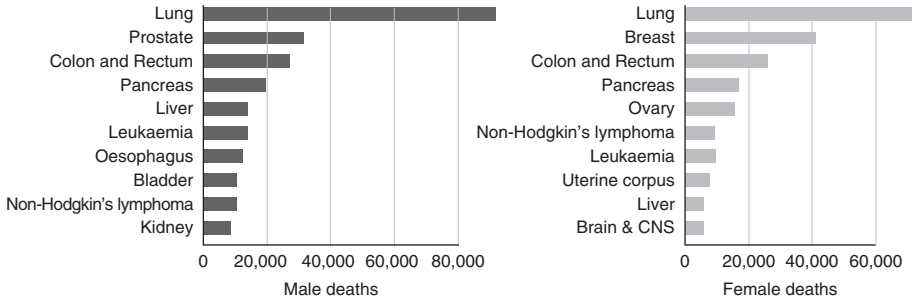

Figure 1.4 The ten most common causes of cancer death estimated for the USA for 2008.

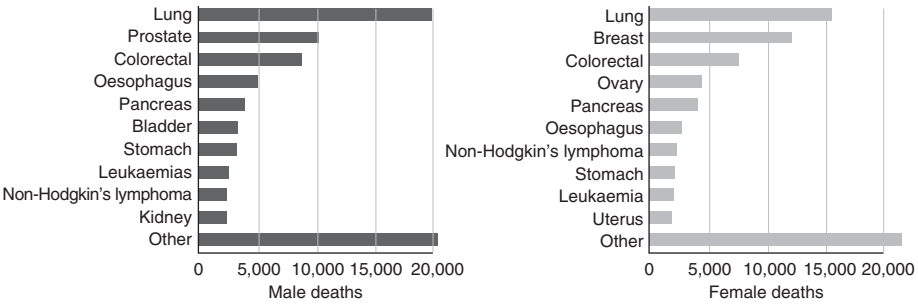

Figure 1.5 The ten most common causes of cancer death in the UK in 2008.

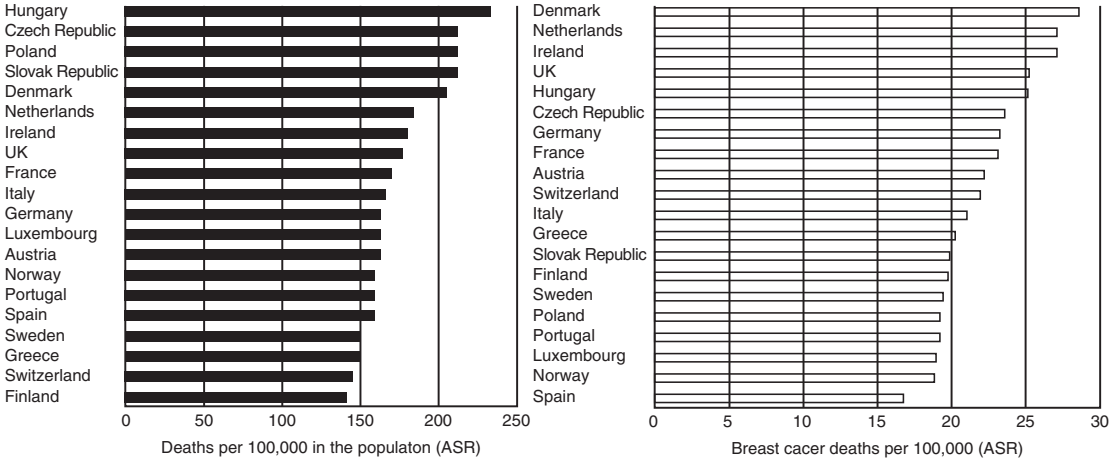

Figure 1.6 Total cancer deaths and breast cancer deaths in 20 European countries in 2006, shown as the **Age Standardised Rate (ASR)** per 100,000 of the population.

which was, of course, part of the Soviet Union until 1991. Analysing Russian data is particularly problematic partly because the quality of the information has varied over time and with the area from which it has been collected. There has also been a competitive effect from large rises in other causes of death, notably heart diseases and accidents. As in other countries, improvements in health care have also begun to make an impact. In addition, the turbulence of the twentieth century has produced marked birth cohort effects, a major example being those who reached their early teens during the Second World War when the living conditions for Russians were even more severe than usual. One can only guess whether history has been a driving factor but smoking in Russia is strikingly prevalent with about 40 million lighting up – that's 63% of men and 12% of women. There's no national anti-smoking campaign and Russia has not signed the World Health Organization (WHO) Framework Convention on Tobacco Control. To make the outlook even worse, a recent survey of doctors and nurses revealed that they smoke even more than the general population. Historically Russia has had a relatively low rate of breast cancer, the early age of first childbirth being a contributory factor but, in a contrary shift, the trend in the last decade has seen the mortality rate rise to 17.3/100,000. Russia is also slightly at odds with general worldly wisdom in producing one survey showing that a bottle of vodka a day keeps breast cancer at bay – that is, heavy drinkers have a lower breast cancer death rate. Unsurprisingly, this level of drinking greatly increases overall mortality, so that whether the effect is real or not, it is of little relevance to strategies for cancer therapy.

In the UK about 100 people die each day from lung cancer and another 33 from breast cancer. Within the European Union there is a diagnosis of breast cancer every 2.5 minutes and a woman dies from the disease every 7.5 minutes. Altogether in Britain there are over 400 cancer deaths every day. That's roughly the number of people in a typical commuter train with all seats taken and the standing space full – dying. Every day. For students of twentieth century European history the train analogy may have chilling resonances but perhaps that's appropriate given, as we shall see, that cancer is a bit of a mixture, in part due to things beyond our control but with a hefty leavening of what human beings do to themselves and each other.

The rest of the world

We've already seen that there are big contrasts in the prevalent types of cancer across the world, and stomach and liver cancer are not alone in this respect. In fact most forms of cancers show marked variation between countries that differ significantly in what might broadly be called lifestyle. Thus, for example, as recently as 2002 the chances of a woman developing or dying from breast cancer were about three times lower in Japan than in Britain or the USA (Fig. 1.7). Lung cancer, highest incidence, biggest killer in the developed world, is rare in East Africa.

We know that these differences reflect lifestyle because of what has happened when significant numbers of people have emigrated. Thus, for example, after the Second World War a considerable number of Japanese people moved to the USA: within a generation the women had acquired the statistical profile for breast cancer of American women. Similar shifts have been observed in the incidence and mortality of colon

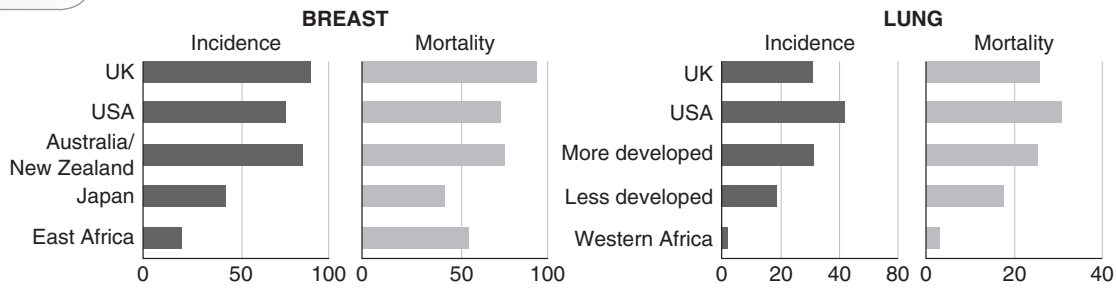

Figure 1.7 Worldwide variation in breast and lung cancer. The numbers are rates per 100,000 of the population. The total figures (2008) for incidence were 1,384,155 (breast) and 1,608,055 (lung) and for mortality 458,503 (breast) and 1,376,579 (lung).

cancer following group migrations. Even so, the gap in breast cancer incidence between the USA and Japan is closing, presumably as Western habits swamp traditional Japanese lifestyles.

The picture is, however, complicated by the fact that such differences occur not only between countries but also within national populations. Thus, for example, we noted that in the USA stomach cancer is thirteenth on the list of killers but in 2009, for every white person that this disease claims, 2.3 African Americans will die despite 66% of the population being white and only 14% African Americans. A further 15% of the USA population is Hispanic or Latino, originating mainly from Mexico, Puerto Rico, Central and South America, Cuba and Dominica, 60% of these having been born in the USA. For this group, overall cancer death rates are lower than for non-Hispanic whites (419 versus 574/100,000 in the period 2000–2003). This is because the rates for the major cancers (prostate, breast, colorectal and lung) are lower although Hispanic rates are higher for stomach, liver, cervix, acute lymphocytic leukaemia and gallbladder cancers. This difference appears to be more sustained than occurred in the cohorts of migrants mentioned earlier, but the cancer rates in descendants of Hispanics are nevertheless approaching those of non-Hispanic whites.

Latin America

For the Caribbean (Fig. 1.8) the overall cancer mortality rate is similar to that of South America (around 120 per 100,000) but both are significantly greater than in Central America (92). Taken together the average cancer mortality for Latin America is somewhat below that of North America (Canada and the USA being very similar). As might be anticipated, the rates vary markedly between countries. For men, Uruguay, Argentina and Chile have the highest mortality and for women it is Colombia and Chile. A significant factor is tobacco use, which varies widely across the region but is high in Uruguay where the male lung cancer rate is the highest in Latin America. In Argentina male lung, prostate and colorectal cancers are high but in Chile, Colombia, Ecuador and

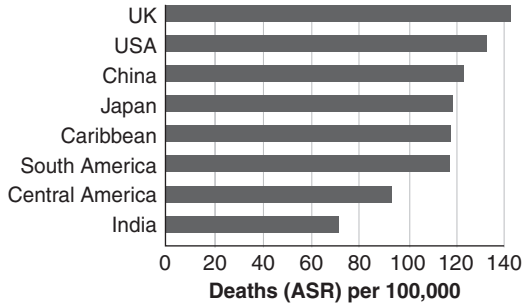

Figure 1.8 Cancer mortality rates in the Americas, China, Japan and India compared with the UK.

Peru stomach cancer is the major male cancer and, for females in those countries, it is also one of the most common, together with cervical cancer. The latter, together with breast cancer, are major causes of female death throughout South America. There is some evidence that stomach cancer deaths may be declining across Latin America as food quality improves. However, the effect of smoking together with the trend towards excess weight and obesity in the entire region is a significant factor in the increasing cancer mortality evident in most countries, Chile being an exception where there has been a slight fall since 1996.

China

In the most populous country in the world, with over 1,300 million people spread over a vast area, the difficulty in obtaining cancer figures is even greater than for elsewhere. Notwithstanding data collection problems, it is clear that by the 1990s cancer had become the second most common cause of death in China, as in so many other countries (Fig. 1.8). In 2008 the major cancers were of the lung, stomach, liver and bowel for both sexes, together with oesophageal cancer for men and breast cancer for women. The rates are rising, there being, for example, 130,000 more deaths from breast cancer in 2005 than there were in 2000 and this is the trend for leukaemia and cancers of lung, liver, bowel and prostate in men, and for breast, lung, liver, bowel and cervical cancer in women. At the same time the incidence of some cancers is declining – notably stomach, oesophagus and nasopharynx – as is mortality from cervical cancer. These improvements are due to the dramatic changes occurring in China as sanitary conditions and diets improve and screening programmes are introduced. The latter are extensive for employees of the government and major companies who provide annual health checks that may be beginning to have an impact on mortality rates for some cancers. On the other hand, as in the Western world, these changes are increasing lifespan and, together with the continuing widespread use of tobacco, the overall result is that cancer rates in China are rising by about 3% each year. Currently lung cancer kills over 1,200 Chinese every day and the WHO estimates that by 2025 there will be a million new cases a year. By then annual tobacco deaths in China will exceed three million.

India

With a population (1,140 million) only slightly smaller than that of China, India is also undergoing a transition to being a 'developed' nation (Fig. 1.8). This means that there is migration from country to city, a general change in lifestyle and a rising life expectancy. Overall cancer rates are lower than in more developed countries (by about three times compared with the USA, for example) despite the rates for oral and oesophageal cancers being among the highest in the world (chewing betel is generally held to be responsible). The most common Indian cancers in men are lung, oesophageal, stomach and larynx; for women they are cervical, breast, ovarian and oesophageal and the total cancer death figure is currently about 600,000 per year. Unfortunately the socio-economic changes taking place mean that, like many other developing nations, the numbers of people dying from non-communicable diseases such as cancer and heart disease are growing.

Africa

We have noted the prediction of 16 million new cancer cases in 2020, 70% being in the developing world. Sub-Saharan Africa will contribute over 1 million of these but, as might be predicted, the patterns across the different regions of Africa show wide variation (Fig. 1.9). The major forms are liver and prostate in men and breast and cervical cancer in women, although AIDS has propelled the otherwise rare **Kaposi sarcoma** to the top of the table in some countries (Uganda, Swaziland, Malawi and Zimbabwe). Seventy per cent of cervical cancers arise from infection by human papillomavirus (HPV). Liver cancer, the major cancer in males, is caused by hepatitis viruses, mainly hepatitis B virus (HBV), which is carried by about 12% of the population. More than 2 billion people, mostly in Africa and Asia, are infected with HBV, accounting for a good deal of the 600,000 deaths a year from liver cancer.

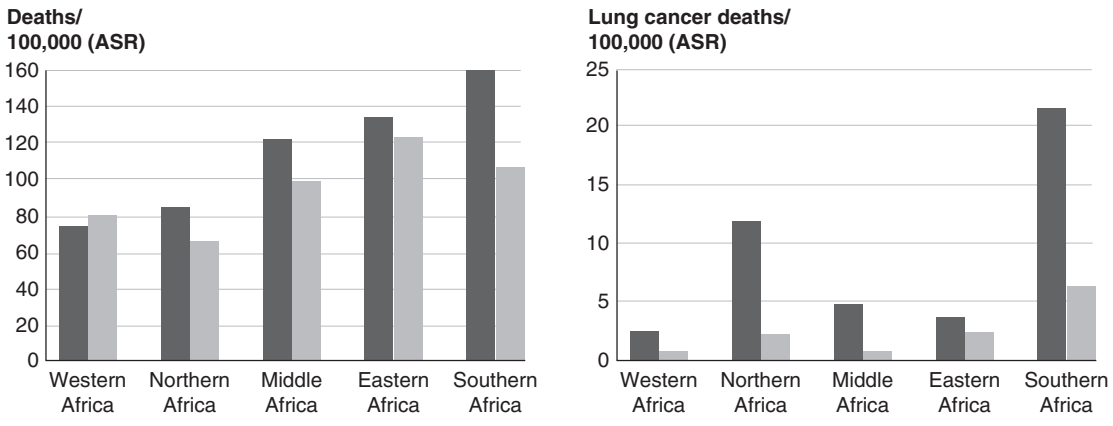

Figure 1.9 Total cancer deaths in regions of Africa and lung cancer deaths in the same regions (men and women).