CHAPTER 6

CANCER MORTALITY PATTERNS BY SITE

Introduction

In this chapter, the patterns of the distribution of cancer mortality throughout the 25 European Union (EU) and three European Economic Area (EEA) Member States are examined for the common forms of cancer, broadly following the numerical order of the codes in the 9th revision of the International Classification of Diseases (WHO, 1977).

Not all sites of cancer have been mapped, for three main reasons. First, the level of detail supplied by national vital statistics offices varies, which means that some data have had to be presented for broad groupings of cancer sites. Thus, ICD-9 codes 140-149, which cover such diverse cancers as those of the lip, mouth, tongue, salivary gland, nasopharynx and the various parts of the pharynx, have had to be presented as a group although, in the commentary, information is given about most of these sites separately.

Second, the numbers of deaths from a variety of cancers such as those of the small intestine (ICD-9 152), the mediastinum (ICD-9 164), male breast (ICD-9 175) and the eye (ICD-9 190) were too small to merit mapping. Any apparent variability in their mortality rates could well have been due solely to chance.

Third, for some cancers, the recorded cause of death is imprecise. Accurate recording of the precise site of cancer of the large bowel is often difficult, and so deaths from cancers of the colon (ICD-9 153) and rectum (ICD-9 154) have been combined along with cancers of the intestinal tract, part unspecified (ICD-9 159.0). Although maps of the mortality data for cancers of the cervix and the body of the uterus (ICD-9 180 and 182, respectively) have been presented separately, they have been combined as "all uterus" for descriptive purposes, as deaths from cancer of the cervix frequently appear as cancer of the uterus on death certificates (Cuzick and Boyle, 1988; Primic Žakelj et al., 2001). This inability to distinguish the cervix from the remainder of the uterus in mortality data in several countries is to be regretted, as the risk factors for these cancers are quite different. Results have, however, also been given for deaths from all uterus cancers in females under the age of 50. The vast majority of these deaths will have been from cervical cancer, as cancer of the body of the uterus occurs predominately in older females (Parkin et al., 2002).

In addition, although Hodgkin's disease (ICD-9 201) is mapped separately, the various forms of non-Hodgkin's lymphoma (ICD-9 200 and 202) have been grouped together as there are national differences in the nomenclature and classification of these forms of malignant disease. All the forms of leukaemia have had to be grouped together (ICD-9 204-208) because death certificates frequently cite *leukaemia* without further specification, the cell type involved not being mentioned.

Secondary cancers (metastases) and those of unknown primary site (ICD-9 195-199) are, however, mapped as these reflect the level of imprecision in certification of cancer deaths.

Following each cancer site title there appear two numbers, the overall average age-standardised mortality rates per 100,000 population for males and for females across the 28 EU-EEA countries. For

example: Trachea, bronchus and lung (ICD-9 162) (M 50.3; F 10.3). The national mortality rates for all the cancer sites are given in the table in Annex 2.

Following a description of spatial patterns, attention is drawn to the broad regions with the highest and lowest rates for each sex. For this comparison, in general only rates based on 100 or more deaths are presented. When two or more regions had the same mortality rate, the region with the greatest number of deaths has been chosen. All rates are age-standardised to the world standard population and are expressed as average annual rates per 100,000 population (see Chapter 2, and Boyle & Parkin, 1991).

To place the European mortality rates in a wider context, they are sometimes compared with those seen around 1995 in the USA, Japan and Australia, nations with a similar socio-economic level. Japan has been chosen as representing an industrialised country with a standard of living comparable to that of the EU-EEA, but with major differences in life-style and risk. Australia has sizeable communities of migrants from several EU-EEA countries.

In the descriptions that follow, the emphasis is on broad regional differences and patterns rather than dissection of variation at the EU-EEA level II or III areas. The reader should bear in mind that a given colour on the main maps may, for common cancers, embrace quite a large variation in level of mortality in absolute terms. Thus, for male lung cancer, the yellow areas that represent 30% of all values cover age-adjusted rates that lie between 37.5 and 55.0. Conversely, for infrequent cancers, the absolute range covered by one colour may be quite small – the yellow areas for male malignant melanoma represent the much narrower range of 5.0 to 7.6. Further, the ranges of mortality represented by a given colour may differ quite considerably between the sexes for the same cancer. So to enable rapid visual comparisons to be made between rates for males and females for the same cancer, and between different cancers, the smaller maps presented in the lower right of each chart also illustrate the variability in mortality rates, but using the *same* (21 point) colour scale for every cancer site (see Chapter 2 for further details).

In formulating their comments, the editors have ignored isolated 'hot spots', preferring to draw attention to regions where there seem to be groups of areas with high or low mortality rates (some problems in interpretation of these patterns are presented in Alexander & Boyle (1996)). For example, oesophageal and laryngeal cancer mortality is high in western and north-eastern France. Gastric cancer mortality is high in virtually all of the north of Italy and low in most of the south of France. Similarly, the higher levels of breast cancer mortality in Denmark, Ireland, The Netherlands and the United Kingdom contrast with the much lower levels in southern Italy, a contrast all the more interesting in that there is a gradient of mortality in-between. While describing the broad picture, the editors recognise that there may be local pockets of truly elevated risk which may be due to the presence of a relevant regional exposure.

It may be argued that many marked differences in cancer mortality rates seem to occur at national boundaries, and that this reflects habits of death certification rather than a true difference in risk (see Chapter 3). For example, oesophageal cancer, so common in west and north-east France, is much rarer on the other side of the border with Belgium. There may also be artefactual variations within countries. However, some of the variability is in opposite directions – for example, the higher levels of mortality from cancer of the stomach in Poland and the three Baltic Countries contrast with the lower rates for cancer of the large bowel in those countries. It is highly unlikely that these two sites would be confused with each other. Within Italy, the validity of the lower mortality rates for many sites in the south than in the centre or north has been examined as part of the DG SANCO project described in Chapter 3.

Interpretation of any apparent cancer mortality patterns is further complicated by the fact that mortality is influenced to a certain degree both by the stage of the disease at diagnosis and by the effectiveness of treatment. Hence the death rate for a cancer of equal incidence (i.e. of diagnosed cases) may be different from one country to another. Conversely, two countries with similar death rates may have quite different incidence. There is considerable evidence that both treatment and survival rates vary widely across Europe (Berrino et al., 2003).

Following the description of the patterns for each site, comments are presented on the

known causes of the respective cancer, and, where possible, on how they may relate to the mortality pattern observed. As many cancers have several component causes, it may not be possible to explain more than a proportion of the deaths seen. The comments are not meant to be exhaustive, and review papers have frequently been cited rather than original articles. Where possible, recent research undertaken in the EU-EEA is described.

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Cancer sites with the highest mortality rates in the EU-EEA

The form of cancer with the highest mortality rate in males was lung cancer (50.3 per 100,000) with large bowel (19.2) having the second highest rate (Figure 6.1 (a)). Prostate cancer (15.4) had the third highest rate, followed by cancers of the stomach (12.0), pancreas (7.5), liver (6.9) and bladder (6.8). The next highest rates of cancer mortality were in sites in the upper digestive tract: oral cavity and pharynx (6.5) and oesophagus (5.9). The leukaemias (5.5) had the tenth highest cancer mortality rate in males.

In females, breast cancer (20.6 per 100,000) had the highest rate of cancer death followed by cancer of the large bowel (12.4) (Figure 6.1 (b)). Cancer of the lung had the third highest rate (10.3) although the rate was only one fifth of that in males. The gynaecological cancers, ovary (6.3) and uterus (6) had the next highest rates, followed by cancers at the digestive sites of the stomach (5.5) and pancreas (4.8). The next highest mortality rates were for leukaemia (3.4), brain and central nervous system (3.2) and non-Hodgkin's lymphoma (2.7).

Mortality from "other and ill-defined" cancers

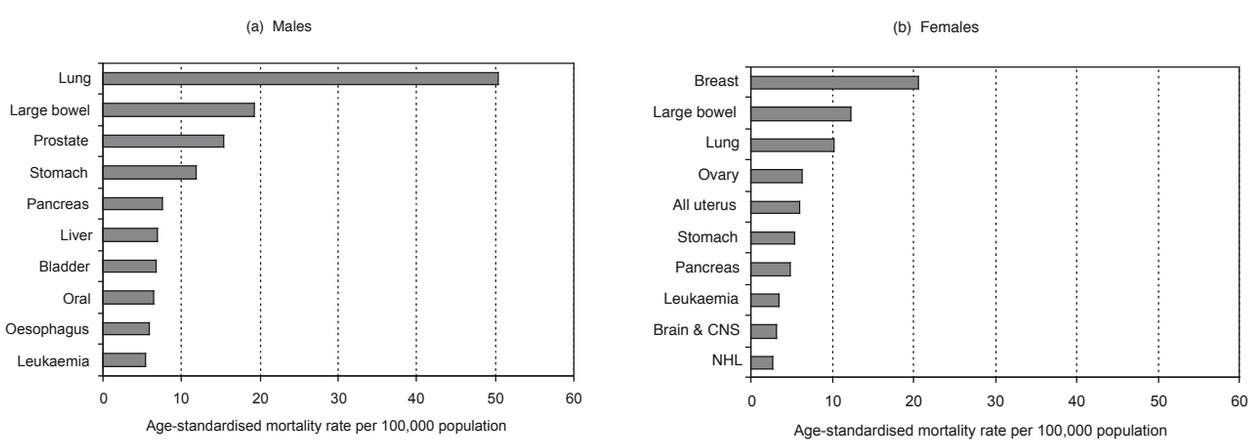
It is important have information on the pattern and rates of other and ill-defined cancer sites, because in areas where such cancers represent high proportions of the rates for all cancers combined, the rates for some (or many) individual cancers may appear to be lower than they really are.

Overall, the mortality rates for other and ill-defined cancers tended to be slightly higher at a national level in males than in females. The highest rates in males were found in the United Kingdom (15.0 per 100,000), Greece (11.8), Denmark (11.7), Ireland (11.1), Luxembourg (11.1), Spain (11.0) and The Netherlands (11.0); these rates represented 6% to 9% of the corresponding national mortality rates for all cancers. The lowest rates were in Latvia (3.0), Slovakia (3.1), Hungary (3.4) and Iceland (3.4); these represented 1 to 2% of the rates for all cancers.

In females, the highest national mortality rates for other and ill-defined cancers were found, as in males, in the United Kingdom (10.5), Denmark (9.9) and Greece (7.6), representing 9%, 7% and 10%, respectively, of the corresponding national rates for all cancers. The lowest rates were in Latvia (1.4), Lithuania (1.6), Slovakia (1.6) and Iceland (2.9), forming 1 to 2% of the rates for all cancers.

The maps [p.256-257] clearly illustrate the patterns of generally high rates of other and ill-defined cancer mortality in the United Kingdom, Ireland, Denmark and Greece, and the low rates in Austria, the Baltic Countries, the Czech Republic, Hungary, Iceland, Italy, Slovakia and Switzerland.

Figure 6.1: Cancer sites with the highest mortality rates



6.1: Oral cavity and pharynx (ICD-9 140-149)
(M 6.5; F 1.1)

This group encompasses cancers arising at all sites within the oral cavity and pharynx and will be referred to as *oral cancer*. Unfortunately, such a broad grouping of intra-oral sites may obscure important variations in both the mortality and the effect of aetiological factors for the different cancer sites.

Overall, the mortality rates for these cancers in the EU-EEA were about 4% of the rate for all cancers in males and about 1% of that in females.

International comparisons

Overall in the EU-EEA, the mortality rate for oral cancer was almost six times higher in males (6.5 per 100,000) than in females (1.1 per 100,000). In each of the 28 countries the mortality rate was considerably higher in males than in females, with large – almost 10-fold – variation in national rates in males but little in females (Annex 2).

In males, the highest rates were in Hungary (19.2) and neighbouring Slovakia (17.2) – both considerably higher than the countries with the next highest rates: France (11.3), Slovenia (11.1), and the three Baltic Countries – Estonia (9.3), Latvia (9.3) and Lithuania (8.6). The lowest rates were found in Greece (2.0), Sweden (2.2) and Finland (2.4).

In females, with the exception of the highest rate, in Hungary (2.4), there was relatively little variation, with the vast majority of countries closely grouped around a rate of 1 per 100,000. The ratio between the male and female rates in each country varied widely, from around 2:1 in several countries including Finland, The Netherlands, Sweden and the United Kingdom, up to more than 10:1 in Slovenia and Slovakia.

Regional variation (box and whisker plots)

In males, there was some variation both within and between countries, although there was little variation apparent in the countries with the lowest national rates [p. 210]. In females, while there was variation within most of the countries, there was little evidence of variation between the 28 countries (apart from the high rate in Hungary mentioned above) [p. 211].

Description of the maps

The outstanding features of the map depicting mortality from cancer of these sites in males is the higher levels of mortality in almost the whole of Hungary and Slovakia, in much of Slovenia, and France with concentrations of excess in the north-west and north-east of the country [p. 210]. There was also a belt of high rates extending across northern Germany and an aggregation of high rates in north-east Italy bordering Slovenia. Rates were generally low in the Nordic Countries, the United Kingdom and Ireland, much of Spain and Italy, and in Greece.

The geographical distribution of areas of high cancer risk for oral cancer demonstrate that while the higher mortality rates in France end abruptly at the border with Belgium – the risk being around one half in Belgium (5.9) of that in France (11.3) – this phenomenon is not seen in the south, with rates in south-east France and in the north of Italy, and in southwest France and northern Spain being at much the same levels. This suggests that there were likely to have been comparable exposures in the south, whereas exposures and/or protective agents may have been different in the north.

In looking at the map for females [p. 211], it must be remembered that the mortality rates were much lower than in males and that the range of mortality rates was very much narrower. Hence in contrast to the map for males, a false impression of important differences in level of mortality can easily be obtained. With the exception of the high rates across the whole of Hungary, there is no clear pattern apparent, although some of the

areas with higher rates in northern France in males also have higher rates in females.

Statistical aspects

The relative risk standard deviation (RRSD) for males was 0.55, the fifth highest of all sites considered, indicating substantial relative variation in the rates. The regional variance associated with country was high compared with most other sites at 0.38 (third highest) and 86% of the total regional variability was associated with differences between countries. This was associated with the higher rates throughout most of France and almost all of Slovakia, Slovenia and Hungary. The country with the most relative variation in the rates was Italy, with an RRSD of 0.41. This is seen in the map as a north-south gradient with high rates in northern Italy and low rates in the south. The Moran's I statistic was 0.79 (ranked 3) indicating substantial spatial autocorrelation; this is evident in the large tracts with low rates in the Nordic Countries, and central and southern Italy and Greece, in addition to the large areas with high rates mentioned above.

The results for females were quite different. There was much smaller regional variation, with the RRSD of 0.28 among the lower values for females. The regional variance associated with country was only slightly higher than that within countries, indicating that there was no strong pattern associated with countries and that there was as much variation within countries as between them. The highest RRSD values were in Belgium, Latvia and Lithuania. Spatial autocorrelation was estimated as 0.24, one of the smallest of all Moran's I values for females. It is common in the map to find areas of high rates bordered by areas of low rates and there is no clear spatial pattern in this map, except for the markedly high rates across most of Hungary. The correlation between the male and female rates was low at 0.41.

Comment

As noted above, the broad groupings of intra-oral sites may obscure important differences in both mortality and the effect of aetiological factors among the different cancers in this group. In addition, there may well be differences in the distribution of the different cancers across countries or regions which could also influence overall oral cancer mortality patterns. Tongue cancer, mouth cancer and pharyngeal cancer have been combined in the majority of analytical studies. These are important forms of cancer with incidence and mortality rates rising among younger persons in many parts of the world. However, several important risk factors have been clearly established.

It is estimated that between 25 and 30% of all cancers in developed countries are tobacco related. For both sexes combined, the proportion of cancers arising in the oesophagus, larynx and oral cavity attributable to the effect of tobacco, either acting singly or jointly with the consumption of alcohol is between 43 and 60%. Cigarette smoking and alcohol consumption have been found to be independent risk factors for oral cancer, and their combined effects seem to be multiplicative. After 5 or 10 years of smoking cessation, risk among ex-smokers reduces to a level similar to that in lifelong non-smokers.

Although the greatest hazard is caused by cigarette smoking, cigars are similar hazards if their smoke is inhaled, and cigar and pipe smoking are comparable hazards for cancers for the oral cavity, pharynx, extrinsic larynx, and oesophagus. Use of oral snuff and of a fine home-ground tobacco powder have been associated with an increased risk of oral cancer.

There is convincing epidemiological evidence that the consumption of alcoholic beverages increases the risk of cancers of the oral cavity, pharynx and larynx and of squamous cell carcinoma of the oesophagus. The risks tend to increase with the amount of ethanol drunk, in the absence of any clearly defined threshold below which no effect is evident. There is wide variability among EU-EEA countries in per capita average alcohol consumption and preferred type of alcoholic beverage.

Although alcohol drinking increases the risk of upper digestive and respiratory tract neoplasms, even in the absence of smoking,

alcohol drinking and tobacco smoking together greatly increase the risk of these cancers, each factor approximately multiplying the effect of the other. Compared with never-smokers and non-alcohol drinkers, the relative risk of these neoplasms is increased between 10- and 100-fold in people who drink and smoke heavily. Indeed, if there were total abstinence from drinking and smoking, the risk of oral, pharyngeal, laryngeal and squamous cell oesophageal cancers would be extremely low.

Poor dental hygiene may be an independent contributory factor. Oral cancer risk is reduced by frequent consumption of fruits and vegetables.

Nasopharyngeal cancer has a different epidemiological pattern from that for tumours of the mouth which have been discussed above. An association with Epstein-Barr Virus (EBV) infection has been suggested by a large number of ecological observations. Clinical progression of the disease is accompanied by increases in antibody levels and nucleic acid hybridisation has shown the presence of EBV DNA in squamous epithelial cells, this latter observation being a strong argument against the virus being only a passenger in the process of carcinogenesis. Despite the fact that nasopharyngeal cancer is smoking related, cigarette smoking seems not to be a major determinant of risk. Results from China and Hong Kong indicate increased risks of nasopharyngeal cancer linked to consumption of salted fish, notably in childhood, and preserved and fermented foods.

Taking account of known risk factors, the high levels in males appear to be generally in regions where there is a prevalent habit in the population of drinking strong alcoholic beverages. Reduction of this, together with avoidance of cigarette smoking, would lead to a large reduction in risk.

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6.2: **Oesophagus** (ICD-9 150)
(M 5.9; F 1.2)

The oesophagus is a 25 cm long tube which connects the pharynx with the stomach. Cancer of the upper third of the oesophagus is almost invariably *squamous cell carcinoma* while cancer of the lower third is usually *adenocarcinoma*.

Overall in the EU-EEA, the mortality rate for cancer of the oesophagus was around five times higher in males (5.9 per 100,000) than in females (1.2 per 100,000). In each of the 28 countries, the mortality rate was considerably higher in males than in females, but there was wider variation in national rates in males than in females (Annex 2). Mortality rates from cancer of the oesophagus represented about the same proportions of the rates for all cancer deaths as for oral cancer: 3% in males and 1% in females.

International comparisons

In males, the highest rate was in France (9.3), closely followed by Hungary (8.9), then the United Kingdom (8.5) and Ireland (8.0) (Annex 2). The lowest rates were in Greece (1.5), and Finland, Norway and Sweden (all 2.9 per 100,000).

In females, there was less variation in rates across the countries, except for three noticeably high rates in the United Kingdom and Ireland (both 3.4) and Iceland (2.9). The lowest rates were in Latvia and Greece (both 0.4) and in Estonia, Spain, Lithuania and Austria (all 0.5).

The pattern of the ratios between the rates in males and females in each country was closely similar to that for oral cancer (section 6.1 above): several of the same countries had ratios of around 2:1 and several others again had ratios of around 10:1.

Regional variation (box and whisker plots)

In males, as with oral cancer there was variation both within and between countries, although there was little variation apparent in the countries with the lowest national rates [p. 212]. In females, there was variation within each country and evidence of considerable variation between the 28 countries, with three countries having rates around 3.0 per 100,000, three in the range 1.5 to 2.0, and the remainder almost all at or below 1.0 [p. 213].

Description of the maps

In males, the feature of the map is the concentrations of very high risk in northern France, extending up to the border with Belgium; there were also contiguous areas of above-average risk in the northeast of Italy, Slovenia and Hungary. Rates were also generally above average in the United Kingdom, particularly in parts of Scotland, and in Ireland [p. 212]. Lower rates were concentrated in Norway, Sweden and Finland, Greece and central and southern Italy. The geographic distribution was thus similar, but not identical, to that for oral cancer (see section 6.1) the main difference being above average mortality from oesophageal cancer in the United Kingdom and Ireland.

High rates among females were also apparent in the United Kingdom and Ireland. There was a belt of slightly above average rates across northern France, Belgium, The Netherlands and Denmark, but no evidence of the excess risk in northeast Italy, Slovenia, Slovakia and Hungary that was seen in males [p. 213].

Statistical aspects

Cancer of the oesophagus in males had regional variation in the middle of the range (RRSD of 0.45). But it had the most regional variation for females, with a RRSD of 0.76. Among males there was a large amount of regional variation associated with country (71%) with higher rates in the United Kingdom, Ireland, France and Hungary and lower rates in Scandinavia and some of the Mediterranean countries. A high percentage of variation (84%) was associated with country for females. There were considerable differences

among the countries for females which is evident in the bimodal shape of the histogram and in the boxplots and maps [p. 213].

Italy had RRSDs of 0.57 for males and 0.48 for females, implying large regional variation; this is associated with low rates in most of the southern and central areas and high rates in the mountainous region in the north. Portugal also had large internal regional variation for females, associated with a small group of regions – mostly in the north of the country – with relatively high rates.

Moran's I for females was 0.82, the largest value, indicating the greatest amount of spatial correlation of all the cancer sites. For males, Moran's I was 0.70 (seventh largest). The correlation between the male and female rates was 0.56, which is not very high. However, there were moderately high rates for males and very high rates for females in Ireland and the United Kingdom and to a lesser extent in The Netherlands, and regions in France with very high rates in males but only average rates in females.

Comment

Much of the discussion of risk factors in the section on oral cancer (section 6.1) is applicable to oesophageal cancer. For both sexes combined, the proportion of cancers arising in the oesophagus, larynx and oral cavity attributable to the effect of tobacco, either acting singly or jointly with the consumption of alcohol is between 43 and 60%. Cigarette smoking and alcohol consumption have been found to be independent risk factors for oesophageal cancer; their combined effects seem to be multiplicative. Although the greatest hazard is caused by cigarette smoking, cigars can cause similar hazards if their smoke in inhaled, and both cigar and pipe smoking are comparable hazards for cancers of the oral cavity, pharynx, extrinsic larynx, and oesophagus.

A high prevalence of alcoholism among patients with oesophageal cancer and an apparent association between the disease and employment in the production and distribution of alcoholic beverages has long been noted. The role of alcohol consumption was most clearly demonstrated in the French département of Ille-et-Vilaine, where the risk rose steadily with dose of alcohol consumed. The highest oesophageal cancer mortality rates in Europe were to be found in males in France and it has been estimated that 85% of such deaths could be attributable to cigarette smoking and alcohol intake.

As noted in section 6.1 above, there is convincing epidemiological evidence that the consumption of alcoholic beverages increases the risk of cancers of the oral cavity, pharynx and larynx and of squamous cell carcinoma of the oesophagus. The risks tend to increase with the amount of ethanol drunk, in the absence of any clearly defined threshold below which no effect is evident. There is wide variability among EU-EEA countries in terms of per capita average alcohol consumption and preferred type of alcoholic beverage.

Although alcohol drinking increases the risk of upper digestive and respiratory tract neoplasms, even in the absence of smoking, alcohol drinking and tobacco smoking together greatly increase the risk of these cancers, each factor approximately multiplying the effect of the other. Compared with never-smokers and non-alcohol drinkers, the relative risk of these neoplasms is increased between 10- and 100-fold in people who drink and smoke heavily. The risk has been shown to be increased among non-cigarette smokers by consuming alcohol and among non-drinkers of alcohol by smoking cigarettes. In heavy smokers of cigarettes, relative risks of between 5 and 10 have been found. As for cancers of the oral cavity, the association is particularly strong for pipes and cigars and, among cigarette smokers, for high-tar/dark tobacco cigarettes. If there were total abstinence from drinking and smoking, the risk of oral, pharyngeal, laryngeal and squamous cell oesophageal cancers in European countries would be extremely low.

The increasing incidence of adenocarcinoma of the oesophagus, restricted largely to males, is one of the most interesting epidemiological changes in cancer recorded in recent decades. Indeed, as well as this increase there is also an increase in adenocarcinoma at the adjacent anatomical portion of the stomach (the gastric cardia). This rules out changes in diagnostic and recording practices being solely responsible. Tobacco smoking, but not alcohol consumption,

appear linked to this type of cancer and it appears that obesity and gastroesophageal reflux disease increase the risk of adenocarcinoma of the oesophagus. This trend could have been detected much more clearly, and unambiguously, if attention in recording had focussed on an entity composed of adenocarcinomas at or near the oesophagogastric junction.

The geographical pattern observed in males can be related directly to the patterns of smoking and alcohol intake (in terms of ethanol) throughout Europe. It is much more difficult to ascribe the pattern of oesophageal cancer observed in females to either these or other known risk factors. The similarity of the pattern in the ratios between the rates in males and females in each country with the corresponding pattern for oral cancer confirms that the risks arise from common aetiological and/or cultural factors. There has undoubtedly been a move in the distribution of cases of oesophageal cancer from the upper to the lower third of the oesophagus during recent decades. The reasons for this remain largely unknown and it seems important to try to elucidate the responsible factors and thereby help increase prospects for prevention of this highly fatal cancer.

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6.3: Stomach (ICD-9 151)
(M 12.0; F 5.5)

Mortality rates from stomach cancer have been falling in Europe for many years (for decades in some countries). What was the commonest fatal cancer in the early part of the 20th century now has only the fourth highest mortality rate in males and the sixth highest in females, representing about 7% and 6%, respectively, of the rates for all cancers. The mortality rate in males in any given area is generally double that in females.

Overall in the EU-EEA countries, the mortality rate for cancer of the stomach in males (12.0 per 100,000) was just over twice that in females (5.5 per 100,000).

International comparisons

In males, the three Baltic Countries all had rates over 25 per 100,000; rates were around 20 per 100,000 in Portugal, Hungary, Poland, Slovakia and Slovenia (Annex 2). Denmark (6.4), Sweden (6.6), France (7.1) and Switzerland (7.2) were the countries which had the lowest national rates.

In females, as in males, the highest rates were in the three Baltic Countries, Portugal, Hungary and Slovenia (around 10 per 100,000) with the Czech Republic, Poland and Slovakia having rates of around 7 per 100,000. The lowest rates were recorded in France (2.7), Denmark (3.1) and Switzerland (3.2).

The ratios between the national mortality rates in males and females were remarkably uniform, clustered very closely around the average of just over 2:1.

Regional variation (box and whisker plots)

In males, there was both variation between countries and between regions [p. 214]. In females, as in males, there was variation within each country and evidence of variation between the countries.

Description of the maps

There are very striking – and closely similar – geographic patterns for stomach cancer mortality in males [p. 214] and females [p. 215]. Moving broadly from southwest to northeast, there is a concentration of high rates in Portugal and much of the adjoining parts of central and northern Spain. Rates were below average in the United Kingdom and Ireland, and in most of the mainland of western Europe; rates were also low in Scandinavia. Rates were then above average in northern (but not southern) Greece, central and northern Italy, Austria, the east of Germany and the Czech Republic, and were highest across almost all of Slovenia, Slovakia, Hungary, Poland and the Baltic Countries.

Statistical aspects

There was moderate regional variation in both males and females with RRSDs of 0.40 and 0.38 respectively. Both Greece and Italy had large regional variation within country characterised by lower rates in the south and higher rates in the north. Other than these two countries there was generally low regional variation within each country. The percentage of variation associated with country was 83% for males and 79% for females. The spatial autocorrelation was high, with Moran's I of 0.82 and 0.72 for males and females, respectively (ranked 1 and 6, respectively).

The most striking feature was the very high correlation of 0.90 between male and female rates, confirming the visual impression that that the patterns in the two maps were very similar.

Comment

Some fifty years ago, stomach cancer was the leading cause of death from cancer in males. Since then, mortality and incidence have fallen virtually everywhere, even in high-risk Japan, but none the less this form of malignant disease remained the second commonest fatal cancer within the EU countries around 1990. By the mid-1990s, the period covered by this atlas, stomach cancer mortality was the sixth commonest fatal cancer in females and the fourth commonest in males.

The reasons for this worldwide decline are not known precisely, although it is strongly suspected that the wider availability of fresh fruit and vegetables and better food preservation (for example, refrigeration rather than salting and pickling) may be one of the major factors. Many studies have shown the risk of stomach cancer to be higher among members of the lower socio-economic classes. While this may be true within a country, the distribution of this disease within the EU-EEA strongly suggests that other factors operate. Tobacco is a risk factor for this form of cancer and this association may go some way to explaining the differences in disease risk between males and females. The distribution of blood group A, known to carry a 10% greater risk, is not likely to vary sufficiently for this alone to influence mortality substantially.

Attention for prevention should continue to focus on diet, notably encouraging higher consumption of fresh fruit and vegetables. It seems paradoxical that in northern Italy (where fresh fruit and vegetables are likely to be much more readily available than in, say, England and Scotland), the stomach cancer mortality should be so much higher. In a study of the role of diet and gastric cancer in this region of Italy, green vegetables were found to have a protective role, with the risk being three times greater in low consumers than in high consumers. Risk was increased in those consuming polenta (a maize porridge) and cured ham.

Intervention with beta-carotene, vitamin E and selenium has been shown to reduce the mortality and incidence of cancer of all forms and particularly stomach cancer in Linxian County in China, where the rates of oesophageal cancer and stomach cancer were extremely high. The results are in some sense proof of principle and confirm the importance of micro-nutrients in the determination of stomach cancer risk – although the direct significance to the European situation is tenuous given that this population suffered for decades from a marginally vitamin deficient diet.

Studies of occupational mortality in both Scotland and in England and Wales have shown excess risk of stomach cancer in workers exposed to chemicals and metals. The excess risk is not necessarily due to exposure at the workplace, as these individuals may eat less fresh fruit and vegetables than others. The risk of stomach cancer has been reported as being elevated among atomic bomb survivors, especially for those individuals exposed at ages of less than twenty years, and among persons treated for *ankylosing spondylitis.*

Some of the decline in gastric cancer mortality rates could be due to the decreased prevalence of *Helicobacter pylori* infection in the gastric mucosa, following reduced contamination of drinking water and control of other sources of infection. Serological markers of *Helicobacter pylori* have been consistently related to stomach cancer risk and there is now consistent epidemiological evidence that *Helicobacter pylori* is associated with an approximately 6-fold increased risk of non-cardia gastric cancer. In Europe, about two thirds of the new cases of gastric cancer every year may be attributable to *Helicobacter pylori* (assuming that the prevalence of *Helicobacter pylori* in the general population is about 35%). The current therapy for *Helicobacter pylori* infection, based on the use of proton-pump inhibitors and antibiotics, is efficacious but poor patient compliance, antibiotic resistance and recurrence of infection complicate the issue. Furthermore, although treatment of *Helicobacter pylori* infection can induce regression of gastric lymphoma, it has not yet been shown to reduce gastric cancer risk. Unfortunately, the natural history of *Helicobacter pylori* infection and the characteristics of an effective anti-*Helicobacter pylori* immune response are still poorly understood, limiting the development of an effective vaccine at present.

A clear message from this atlas is the close similarity of the geographic patterns observed in males and in females. This is present when considering the maps visually and is re-enforced when statistical analyses are conducted. There are traditional explanations put forward to explain some of the patterns apparent in the maps: the high rates in Portugal have been associated with the widespread practice of eating salted fish and the high rates in Italy, Germany and Austria have been associated with cured meats. These hypotheses need to be re-assessed

and tested as does the aetiology underlying the regional variation in Greece. The important aetiological role of *Helicobacter pylori* in the aetiology of stomach cancer provides an unusual opportunity for prevention via the development of an effective vaccine. Although the risk of stomach cancer is diminishing throughout Europe, pinpointing the risk factors responsible could help accelerate the decline of this form of cancer which has relatively poor survival (European average 22% in males and 26% in females at five years after diagnosis).

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6.4: **Large bowel** (ICD-9 153, 154 and 159.0) (M 19.2; F 12.4)

There have been several studies demonstrating the difficulties in accurate recording of the precise site of cancer of the large bowel on death certificates. Although resulting in some loss of information, the sites of colon and rectum have been combined as "large bowel" in this atlas as any misclassification is likely to be within this categorisation. Cancer of the large bowel (also known as colorectal cancer) is the second commonest form of cancer death in both sexes.

The overall EU-EEA mortality rate was considerably higher in males (19.2 per 100,000) than in females (12.4), a ratio of 1.6:1. In each of the EU-EEA countries the mortality rate was higher in males than in females, with a similar degree of variation present in the rates in males and females.

International comparisons

The highest national mortality rates in males were in the Czech Republic (34.2) and Hungary (33.1), followed by Slovakia (26.6), Ireland (25.4) and Slovenia (24.0). The lowest rates were in Greece (9.3), Finland (12.0), Iceland (13.8) and Sweden (13.8) (Annex 2).

In females, the highest national rates were recorded in Hungary (19.0) and the Czech Republic (17.5). The lowest national rates in females were in Greece (7.4), Finland (8.3), Switzerland (9.2) and France (9.6).

As with stomach cancer (section 6.3) there was remarkable consistency across the 28 EU-EEA countries in the ratios between large bowel cancer mortality rates in males and females: those for all but two of the countries fell in the narrow range 1.3 to 1.7:1

Regional variation (box and whisker plots)

In males, there was variation between countries and between regions, although there was little variation apparent in most of the countries with the lowest national rates [p. 216]. The patterns were broadly similar in females.

Description of the maps

It is apparent from the maps that the pattern of geographical distribution in both males [p. 216] and females [p. 217] is substantially the same, with a broad band of high rates running east-west across the middle of Europe. Higher than average rates were found in Ireland and the northern parts of the United Kingdom, Denmark, southern parts of Norway, Germany and eastern Austria. Rates were also above average in parts of northern Italy and southern Portugal – more markedly in males than in females. The highest rates were in the Czech Republic, Slovakia, Slovenia and Hungary. Low rates were found in Finland, Sweden and Poland, and in much of southern Europe: Greece and southern Italy, France, Switzerland and Spain.

Statistical Aspects

Cancer of the large bowel had quite low regional variation, with similar levels in males (RRSD = 0.25) and females (RRSD = 0.24). There was, however, evidence of regional variation associated with country (86% in males and 85% in females) associated with the high rates in the Czech Republic and Hungary and lower rates in Finland, Sweden and southern Europe.

Moran's Index was high at 0.74 for males and 0.70 for females, indicating strong spatial correlation. The correlation between the rates for males and females was very high at 0.83. Although there were strong geographic patterns, the range in the rates from the low areas to the high areas was quite narrow compared with liver cancer, for example, which also has a strong geographic pattern but has a bigger relative difference between the low and high rates.

Comment

Cancer of the large bowel is an important public health problem: there are nearly one

million new cases of colorectal cancer diagnosed world-wide each year and half a million deaths. Edwards et al recently reported that in the United States, colorectal cancer was the most frequent form of cancer among persons aged 75 and older. Given that the majority of cancers occur in older people, and with the ageing of the population in mind, this observation gives further impetus to investigating primary and secondary prevention and treatment strategies for this major cancer.

The disease is not uniformly fatal, although there are large differences in survival according to stage of disease. Five year survival in resected tumours at an early stage (Dukes' A) is around 80 per cent and survival following simple resection of an adenomatous pedunculated polyp containing carcinoma *in situ* (or severe dysplasia) or intramucosal carcinoma is generally close to 100 per cent. There is now firm evidence from randomised trials that faecal occult blood testing (FOBT) can lead to a reduction in mortality from cancer of the large bowel. Strong findings from observational studies indicate that endoscopic screening, either sigmoidoscopy or colonoscopy, also appears to have the potential to reduce mortality and incidence of the disease by diagnosing and removing polyps. Screening research, recommendations and implementation are obvious priorities.

A decade ago, the dietary aetiology of cancer of the large bowel seemed to be clearly understood: risk was increased by increasing consumption of dietary fat, particularly animal fat, and meat and was reduced by consumption of vegetables and fruits. Today this classical concept of risk is being increasingly challenged as more epidemiological data become available. It has been hypothesised that alterations to serum triglycerides and/or plasma glucose could be one possible vehicle for the effects of various aetiological factors.

The risk of cancer of the large bowel, and its precursor condition *adenomatous polyps*, is increasingly associated with physical activity and body mass index. For example, Giovannucci et al (1996) examined the influence of physical activity, body mass index and the pattern of adipose distribution on the risk of colorectal adenomas. After controlling for age, prior endoscopy, parental history of cancer of the large bowel, smoking, aspirin use and dietary intakes, physical activity was associated inversely with the risk of large adenomas (greater or equal to 1 cm) in the distal colon (RR=0.57, 95% C.I. (0.30, 1.08) – borderline significance), when those in the highest and lowest fifths of average weekly energy expenditure from leisure activities were compared. Much of this benefit came from activities of moderate intensity such as brisk walking. Additionally, body mass index was associated directly with risk of large adenomas in the distal colon (RR=2.21, 95% C.I. (1.18, 4.16)), for BMI 29 kg/m^2 or over compared with BMI values less than 21 kg/m^2. The relationships with BMI and physical activity were considerably weaker for rectal adenomas. This indicates that exercise appears to protect against adenomas and cancer of the large bowel, while increasing body mass index serves to increase the risk of both.

There is increasing evidence supporting an association between use of hormone replacement therapy (HRT) and a reduced risk of cancer of the large bowel. In an initial meta-analysis, the overall risk for cancer of the large bowel and oestrogen replacement therapy was 0.92 but this was not statistically significant (95% CI (0.74, 1.5)). There was also no apparent effect when colon and rectal cancer were considered as separate entities. Subsequent to this report there have been further studies published which have confirmed and extended the results. Despite these encouraging findings, it is important to emphasise that females using HRT tend to adopt life-styles choices that confer protection from colon cancer or other chronic conditions, and so confounding cannot be excluded with certainty from studies assessing HRT as a protective factor in colon cancer. For example, the practice of exercise involving increased physical activity, increased consumption of fruits and vegetables and reduced fat intake and/or past screening (colonoscopy, sigmoidoscopy or occult blood test) tend to be associated more with females who are HRT ever-users than with never-users. Beral and colleagues in their review of the use of HRT and the subsequent risk of cancer advocate caution in over-interpreting the suggested protective effect in colon cancer.

Thus there are prospects for primary prevention of cancer of the large bowel although it is difficult to know how to successfully

bring about such large-scale changes to large proportions of populations. The large bowel has not been traditionally considered as a site where the risk of cancer is linked to cigarette smoking although more recent evidence strongly points to the existence of such an association between cigarette smoking and an increased risk of both adenomatous polyps and colorectal cancer. There is also interesting evidence suggesting that specific chemopreventive strategies could prove useful in the prevention of colorectal cancer.

While there are many questions to be resolved, it is apparent that many facets of colorectal cancer are becoming increasingly understood and prospects for prevention are becoming apparent.

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6.5: Liver (classified as primary) (ICD-9 155)
(M 6.9; F 2.5)

The interpretation of data on primary cancer of the liver requires special attention, particularly regarding mortality, because the liver is an organ frequently attacked by metastases (secondary tumours). Observed mortality rates may be affected by the misclassification of primary and secondary neoplasms; the inclusion of the latter on death certificates will bias the mortality rates upwards and make any apparent geographic patterns difficult to interpret. In addition, in countries and regions covered by efficient cancer registries, the separation of metastases from primary liver cancers is likely to be better than elsewhere; this will be reflected on death certificates, resulting in lower mortality rates from liver cancer.

Overall in the EU-EEA countries, the mortality rate from primary liver cancer was almost three times higher in males (6.9 per 100,000) than in females (2.5). In all countries the national mortality rate was higher in males than in females (Annex 2) with a large degree of variation apparent between countries in both males and females. The mortality rates for liver cancer were about 4% of the rate for all cancers in males, and 3% of that in females.

International comparisons

In males, the national mortality rates were highest in Italy (13.1), Greece (13.0) and France (11.0), followed by Spain (8.4), Hungary (8.2) and the Czech Republic (8.0) (Annex 2). The lowest rates were recorded in Norway (1.4), Denmark (1.5), The Netherlands (2.1) and the United Kingdom (2.5).

In females, the highest national mortality rates were recorded in Greece (5.5) and Italy (4.7), followed by Poland (3.9), Hungary (3.8), Slovakia (3.6), the Czech Republic (3.5) and Spain (3.2). The lowest rates in females – as in males – were in Norway (0.8), Denmark (0.9), The Netherlands (1.0) and the United Kingdom (1.3).

The ratios between the mortality rates in males and females were generally close to the overall average, except for France where it was markedly above it (more than 5:1).

Regional variation (box and whisker plots)

In males, there was variation between countries and between regions, although there was less variation apparent in the countries with the lowest national rates [p. 218]. In females, while there was variation between the 28 countries, there was again less variation in countries with low rates.

Description of the maps

In males, higher than average rates were found in most of France, Italy and Greece and in southern Spain [p. 218]. In females, the higher rates were also found in most of Italy and Greece and in Spain – but not in France; there were also higher rates in the neighbouring countries of Hungary, Slovakia, the Czech Republic and Poland in central Europe, and in parts of Sweden but not elsewhere in Scandinavia [p. 219]. In both sexes, the lowest rates were to be found in the United Kingdom, Ireland, Belgium, The Netherlands, Denmark, Finland and Norway.

Statistical aspects

The RRSD was 0.60 (ranked third) for males, and 0.54 for females (seventh) indicating that there was substantial relative regional variation in the rates. There were also strong country patterns with 85% and 84% of the regional variation in the rates for males and females, respectively, associated with differences between countries. This is noticeable in the boxplots, which illustrate the low rates in northern Europe and higher rates in France (males only), Italy and Greece.

There was high spatial autocorrelation with Moran's I of 0.80 for males and 0.74 for females. The correlation between the rates for males and females was 0.73, which is high. In France, however, there were high rates for males but relatively low rates for females.

Comment

Patterns of hepatocellular cancer were generally related to the prevalence of chronic carriers of hepatitis B surface antigen (HBsAg) in the population. There is a strong and specific association between infection with hepatitis B virus (HBV) and hepatocellular carcinoma. The association is restricted to chronically active forms of HBV infection which are characterised by the presence in serum of HBsAg, commonly referred to as 'carrier status'. The association is strong: in a cohort study from Taiwan based on 22,707 subjects, of which 3,454 were HBsAg positive, the relative risk for hepatocellular carcinoma was found to be 104 (95% C.I. (51, 212)) and the calculated attributable risk was 94 per cent.

The relative risk is, however, about one order of magnitude smaller (i.e. by a factor of approximately 10) in studies conducted in Europe or the United States. This is probably related to some co-factors (particularly poorer diet in East Asia); but a different duration of exposure to the virus, which in the Far East is usually transmitted perinatally whereas in Europe and North America is contracted late in life, can by itself explain such a substantial difference. This hypothesis has found epidemiological support from a study conducted in Greece which demonstrated a tendency for cases of hepatocellular carcinoma to have a higher birth order. There does not appear to be an association with the presence of hepatitis B antibodies alone. With reference to implications for prevention, perinatal immunisation against hepatitis B could probably be the single most effective preventive action against cancer world-wide after the elimination of tobacco smoking.

Upward trends in incidence and mortality rates from liver cancer have been seen in the last two decades in males in France, Germany and Italy. Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) accounts for the majority of liver cancer cases in Europe. In a large case-series of liver cancer from six European Liver Centres only 29% of 503 liver cancer patients had no marker of either HBV or HCV infection.

HCV represents an increasing problem in several areas of the EU (especially in Italy, Greece and Spain) and in some population groups, notably intra-venous drug users. A vaccine is not yet available, and the effectiveness of treating all HCV-RNA-positive individuals with pegylated interferon-2α with or without ribavirin is still under evaluation. Hence the prevention of HCV infection relies for the moment on a strict control of blood and blood derivatives and avoidance of use of non-disposable needles in medical and non-medical procedures (e.g. acupuncture, tattooing, etc).

An increased frequency of primary liver cancer has been observed among individuals with a high alcohol intake in a number of studies although this is not a universal finding. Of four published cohort studies, two found an increased risk with increasing consumption of alcoholic beverages while in a further study, elevated risk was restricted to a subgroup. An overview of published studies of alcoholics shows a general tendency for alcoholics to have a 50 per cent excess of liver cancer over non-alcoholics. These risks, however, may well be underestimated, since alcohol-induced liver damage may induce reduction or cessation of alcohol consumption before the diagnosis of liver cancer.

Part of the excess liver can risk in alcoholics could be attributable to dietary deficiencies, since it has been shown that a diet poor in vitamin A and other (micro)nutrients is related to an increased risk of hepatocellular carcinoma. In tropical areas of Africa and Asia, aflatoxin, a product of metabolism of *Aspergillus flavus* which contaminates foods, particularly cereals, has been related to elevated risk of primary liver cancer with a positive interaction with hepatitis B virus and alcohol. The risk of primary liver cancer has been found to be greatly elevated among subjects exposed to more than one factor.

The use of combined oral contraceptives (OC) substantially increases the risk of liver cancer, and OCs are effective in the process of hepato-carcinogenesis in rodents. An association between long-term oral contraceptive use and hepatocellular carcinoma has been observed in five out five studies conducted in developed countries (though not in a sixth based mainly on developing countries). Primary liver cancer is still extremely rare in young females, and the public health impact of such as association is

small (unless such an association persists when the same generation of females become older).

The patterns apparent in the maps are compatible with an alcohol and hepatitis aetiology in males, with high rates in France (alcohol) and Greece, Italy and (southern) Spain (hepatitis). In females, where alcohol consumption levels are much lower, the geographic pattern is compatible with a hepatitis aetiology. Hepatitis B, and particularly hepatitis C, should be regarded as public health priorities in southern Europe. The difficulties in separating the diagnosis of metastases from primary liver cancer in many countries must, however, be borne in mind.

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6.6: Gallbladder and bile ducts (ICD-9 156)
(M 1.6; F 2.3)

ICD-9 code 156 includes not only the gallbladder cancers but also those arising in the bile ducts outside the liver. Unfortunately, these are not separated in the available mortality data. In general, the frequency of gallbladder cancer is about the same as that of bile duct cancers in males but double in females. The mortality rates from these cancers in the EU-EEA represented about 1% of the rates for all cancers in males and about 2% in females.

Overall in the EU-EEA countries, the mortality rate in females (2.3 per 100,000) was almost 50% higher than that recorded in males (1.6). In most countries, the national mortality rate was higher in females than in males, with considerable variation present in the national rates in both males and females (Annex 2).

International comparisons

In males, by far the highest national rates were in the Czech Republic (3.9) and Hungary (3.6), followed by a group of countries with rates around 2.0: Austria (2.3), Slovenia (2.3), Germany (2.2), Slovakia (2.0), Italy (2.0) and Sweden (1.9) (Annex 2). The lowest rates were recorded in the United Kingdom (0.5), Greece (0.7) and Ireland (0.7).

In females, the highest national rates were also in the Czech Republic (5.9) and Hungary (6.1), but rates were also high in the eastern parts of Germany and in Poland. The lowest national rates in females were in the United Kingdom (0.6), Greece (0.8), Ireland (1.0) and Latvia (1.0).

Regional variation (box and whisker plots)

In both males and females, there was noticeable variation between countries and between regions [p. 220-221].

Description of the maps

The distribution of gallbladder and bile duct cancer mortality in the EU-EEA was quite unlike that for any other form of malignant disease, with generally lower than average rates in the west of Europe, including Iceland, Norway, the United Kingdom and Ireland, Denmark, The Netherlands, Belgium, France, Spain and Portugal. Rates were above average in a band across most of the centre of Europe, extending from Italy in the south through Germany to Sweden in the north [p. 220]. The high rates also extended eastwards into eastern Austria, the Czech Republic, Hungary and parts of Slovakia in both males and females, and into Poland for females.

Statistical aspects

There was substantial regional variation for cancer of the gallbladder: the RRSDs of 0.51 was the seventh highest for males and that of 0.61 was the fourth highest for females. There was substantial variation associated with country, with percentages of 92% for males and 88% for females. Variability between countries was more important than within country variation; this is clearly seen in the maps and boxplots [p. 220].

The spatial correlation (Moran's I) of 0.58 was near the middle of the range for males, but that of 0.79 for females was one of the highest. The male-female correlation was high at 0.87, similar to the values for cancers of the stomach, large bowel and kidney.

Comment

Knowledge of risk factors for gallbladder cancer continues to be incomplete. Epidemiological studies have focused on the relation between this disease and gall stones. In all analytical studies, gall stones are the most important risk factor. It is, however, difficult to establish whether it is a causative relation or only an accompanying one (*e.g.* both cancer and gallstones may be related to an infection). Apart from the role of gall stones in the development of this disease, obesity and hormonal status in females have also been associated with it. Gallbladder cancer incidence has been shown to decrease with the growth in the number of cholecystectomies performed in a given country or population. According to estimates, 100 cholecystectomies prevent one gallbladder cancer.

Cancer of the gallbladder is a rare disease with low survival, resulting in relatively high mortality. It is one of the few cancer sites which are diagnosed more frequently in females than in males. The higher predominance of gallbladder cancer and the increasing fraction of extrahepatic malignancies of the bile ducts and the Ampulla of Vater, in females has been noted in many countries. This disease is also more frequently found in some ethnic groups. The literature offers hypotheses linking gallbladder cancer in some ethnic groups with the type of metabolism which developed during evolutionary adaptation. The Czech Republic, Slovakia, Hungary, Austria and Germany are the European countries where the highest gallbladder cancer frequency is found. These findings correlate with the high frequency of gallstones which has been observed for at least a century in this part of Europe. Interestingly, Jews emigrating from Central Europe to Israel face a higher risk of this cancer. Among the lowest frequencies of gallbladder cancer in Europe are found in Ireland and the United Kingdom, where the incidence has also showed a decline over recent decades. The United Kingdom has in the past been a country with a low frequency of gallstones compared with the rest of Europe.

The frequencies of gallbladder cancer and of gallstones tend to run in parallel. Thus the high risk of gallbladder cancer seen among American Indians is reflected in a spectrum of gallstone-related disease in this population. The distribution of gallstones shares many of the features of gallbladder cancer, including female predominance. Most epidemiological studies have examined the characteristics of patients with gallstones rather than the much rarer gallbladder cancer. There have been a few reports of an excess of gallbladder and bile duct tumours in workers in a rubber plant consistent with the ability of several chemicals, including those used in rubber processing, to produce such cancers in laboratory animals.

The striking geographical distribution of gallbladder and bile duct cancer within the EU-EEA again offers opportunities for collaborative epidemiological studies and the prospect of significant prevention of the disease.

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6.7: **Pancreas** (ICD-9 157)
(M 7.5; F 4.8)

Cancer of the pancreas can frequently be difficult to localise and report correctly in both incidence and mortality statistics. In general terms, it will tend to be under-reported rather than over-reported. The disease is highly fatal, and in the EU-EEA the mortality rates from pancreatic cancer were about 5% of those for all cancers in both males and females.

Overall in the EU-EEA countries, cancer of the pancreas had the fifth highest cancer mortality rate in males (7.5 per 100,000) and the seventh in females (4.8). In all countries, the national mortality rate was higher in males than in females with more variability in the national rates in females than in males (Annex 2).

International comparisons

In males, the highest national mortality rates were in Latvia (12.0), Hungary (11.4), the Czech Republic (11.1), Estonia (10.6) and Lithuania (10.4) (Annex 2). The lowest national rates were in Spain (5.9), Greece (6.1), Portugal (6.1) and the United Kingdom (6.5).

In females, the highest national mortality rates were in Iceland (7.1), the Czech Republic (6.8), Hungary (6.7), Sweden (6.6), Denmark (6.2) and Austria (6.2). The lowest national mortality rates were recorded in Portugal (3.3), Spain (3.5) and Greece (3.5).

Regional variation (box and whisker plots)

In males, there is clear evidence of both the variation in the national rates and also in the rates within each country [p. 222]. There is also evidence of between and within country variation in females.

Description of the maps

In males, there were several distinct aggregations of high rates. One extended over northern Sweden and Norway; a second covered all three Baltic Countries; and a third extended from northern Italy into eastern Austria, the Czech Republic, Slovakia and Hungary [p. 222]. There is marked contrast between the high rates in the north of Italy and the very low rates in the south of the country; and there were low rates in Portugal, Spain and most of Greece and the United Kingdom.

In females, the broad pattern was similar, but there were some noticeable differences, with high rates over most of the Nordic Countries, particularly Sweden, and in Austria, the Czech Republic and Hungary, but only average rates in the three Baltic Countries [p. 223]. As in males, there were low rates throughout Spain, Portugal, southern Italy and much of Greece.

Statistical aspects

Cancer of the pancreas had low RRSDs in both males and females: 0.20 and 0.21, respectively. Within country variation was high in Italy for both males and females and high among males in Greece. These were all characterised by north to south gradients with higher rates in the north of both countries. Regional variation associated with country was at the low end of the range in both males (72%) and females (73%). For both males and females the higher rates were grouped together in Scandinavia, Austria, the Baltic Countries, the Czech Republic, Slovakia and Hungary, and the lower rates in Spain, Portugal and Greece.

Spatial correlation was relatively low with Moran's I of 0.47 for males and 0.41 for females. These values are consistent with the between and within country variances for males and females. There was a moderate correlation of 0.43 between the regional rates for males and females.

Comment

Analytical studies based on patients with pancreatic cancer consistently demonstrate that

cigarette smoking increases the risk. This appears to be the major clearly demonstrated risk factor. A dose-response relationship is found with increasing pancreatic cancer risk and lifetime reported cigarette consumption and the risk is found to reduce among ex-smokers to a level compatible with lifelong smokers fifteen years after quitting.

Although it had been speculated that there was a positive association with coffee consumption, the overall evidence available does not support this relationship. There is no convincing evidence linking alcohol consumption to an increased risk of pancreatic cancer.

It appears likely that dietary factors could emerge as influential in determining pancreatic cancer risk. The SEARCH study found positive associations between intake of carbohydrates and cholesterol and inverse associations with dietary fibre and vitamin C. These associations were generally consistent among the five centres which undertook the study and the consistency, strength and specificity appear to suggest underlying causal relationships. In a large cohort of females in the United States participating in the Nurses' Health Study (n = 88,800), 180 case subjects with pancreatic cancer were diagnosed during 18 years of follow-up. Carbohydrate and sucrose intake were not associated with overall pancreatic cancer risk in this cohort. A statistically borderline significant 53% increase in risk of pancreatic cancer (RR = 1.53, 95% confidence interval [CI] = 0.96 to 2.45) was observed among females with a high glycaemic load intake, and a similar association was observed for fructose intake (RR = 1.57, 95% CI = 0.95 to 2.57). The associations of glycaemic load and fructose intakes with pancreatic cancer risk were most apparent among females with elevated body mass index of 25 kg/m^2 or higher or with low physical activity. Among females who were both overweight and sedentary, a high glycaemic load was associated with an RR of 2.67 (95% CI = 1.02 to 6.99; highest versus lowest quartile of intake; P for trend =0.03), and high fructose was associated with an RR of 3.17 (95% CI = 1.13 to 8.91; P for trend =0.04). It would seem warranted to investigate further these findings that impaired glucose metabolism may play a role in the aetiology of pancreatic cancer.

Some aspects of medical history have been associated with pancreatic cancer risk. It has recently been demonstrated that patients with chronic pancreatitis have an increased risk of developing pancreatic cancer: ten years after the initial diagnosis of chronic pancreatitis, the risk was 8.5. In particular, besides pancreatitis, there is some evidence that diabetes and gastrectomy may be associated with elevated pancreatic cancer risk, while allergies may represent an indication of reduced risk.

In terms of the pattern in the mortality maps for males and females, it is difficult to propose a simple explanation based on the current state of knowledge of risk factors. Cigarette smoking, a long-standing history of chronic pancreatitis and familial pancreatitis are all the risk factors which are known with certainty. There is still a need for a great deal of epidemiological work on this topic before prospects for prevention improve.

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6.8: Larynx (ICD-9 161)
(M 3.9; F 0.3)

Cancer of the larynx has a high survival rate when the disease is diagnosed at an early stage. Differences in the sub-site distribution within the larynx may contribute partially to the variation in mortality from this cancer throughout Europe. Overall, the mortality rate from cancer of the larynx in the EU-EEA was almost 15 times higher in males than in females. The rate was just over 2% of the rate for all cancers in males, but less than 0.5% in females.

Cancer of the larynx was much commoner overall in males (3.9 per 100,000) than in females (0.3 per 100,000). In all countries, the national mortality rate was higher in males than in females, there was considerable variability in the rates between countries in males, and national rates in females were consistently very low (Annex 2).

International comparisons

In males, the highest national mortality rates were in Hungary (9.1), Lithuania (7.5), Slovakia (7.5) and Poland (7.4); the lowest rates were in Sweden (0.6), Norway (1.0) and Finland (1.0) (Annex 2). In females, cancer of the larynx is very rare and all national mortality rates – except that in Hungary (0.7) – were 0.5 per 100,000 or lower.

Regional variation (box and whisker plots)

In males, there was clear evidence of both the variation in the national rates and also within each country [p. 224]. There was also evidence of between and within country variation in females, but the numbers of deaths were all very small.

Description of the maps

The pattern in males has several features in common with those of oral cancer and cancer of the oesophagus. The outstanding feature of the map for laryngeal cancer is the two areas of generally higher levels of mortality [p. 224]. One covers parts of Portugal, Spain, France and northern Italy; and the second covers Hungary, Slovakia, Poland and the three Baltic Countries. Rates were low throughout in the Nordic Countries, the United Kingdom, Ireland and most of Germany. The areas of high cancer mortality from laryngeal cancer in northern France did not end abruptly at the borders with Belgium, Germany and Italy as did those for oral cancer (section 6.1), strongly suggesting that there are likely to be comparable exposures in these areas.

In looking at the map for females [p. 225] it must be remembered that the mortality rates were much lower than in males and that the range of mortality rates is very much narrower. Most of the apparent differences in rates among the small areas is simply due to chance variation because of the small numbers of deaths, but there are generally slightly higher than average rates across Hungary and parts of Poland.

Statistical aspects

Among males, 92% of the regional variation was associated with between country differences, while for females the figure was lower at 75%. The RRSDs were 0.62 and 0.50, respectively, making larynx the second most variable site for males and the eighth most variable for females. Among males the very strong country pattern was associated with low rates in north Europe, and Germany, and much higher rates in two areas: southwest Europe, especially in Spain, Portugal, France and northern Italy; and central Europe, especially Hungary, Slovakia and Poland, and the Baltic Countries.

There was little association between the rates for males and for females: the correlation was the third lowest of all sites at 0.29. The Moran index was quite high for males at 0.76, though it was much lower for females at 0.21. This implies that there was a different spatial pattern for males than for females. The relatively high rates in Ireland, the United Kingdom and Norway among females compared with the relatively low rates there for males, and the reverse in Spain and Portugal, are

major factors in the weak association in the rates between males and females. It was difficult to estimate the RRSD for several of the countries for females because their rates were so low.

Comment

As noted above, there may well be differences in the sub-site distribution in different countries or regions which could influence mortality patterns. Several important risk factors for laryngeal cancer have been clearly established. Much of the discussion about oral cancer (section 6.1) and oesophageal cancer (section 6.2) is equally relevant in this section.

It is estimated that between 25 and 30% of all cancers in developed countries are tobacco-related. For both sexes combined the proportion of cancers arising in the oesophagus, larynx and oral cavity attributable to the effect of tobacco, either acting singly or jointly with the consumption of alcohol is between 43 and 60%.

Although the greatest hazard is caused by cigarette smoking, cigars can cause similar hazards if their smoke is inhaled and both cigar and pipe smoker cause comparable hazards of cancers of the oral cavity, pharynx, extrinsic larynx, and oesophagus.

There is convincing epidemiological evidence that the consumption of alcoholic beverages increases the risk of cancers of the oral cavity, pharynx and extrinsic larynx and of squamous cell carcinoma of the oesophagus. The risks tend to increase with the amount of ethanol drunk, in the absence of any clearly defined threshold below which no effect is evident. There is wide variability among EU-EEA countries in terms of per capita average alcohol consumption and preferred type of alcoholic beverage.

The separate effects of alcohol and tobacco on laryngeal cancer are quite strong. The risk of extrinsic laryngeal cancer is 2.5 fold increased in heavy drinkers-non-smokers and over 9-fold among current smokers-non-drinkers. Although alcohol drinking increases the risk of upper digestive and respiratory tract neoplasms, even in the absence of smoking, alcohol drinking and tobacco smoking together greatly increase the risk of these cancers, each factor approximately multiplying the effect of the other. Compared with never-smokers and non-alcohol drinkers, the relative risk of these neoplasms is increased between 10- and 100-fold in people who drink and smoke heavily. If there were total abstinence from drinking and smoking, the risk of oral, pharyngeal, laryngeal and squamous cell oesophageal cancers in European countries would be extremely low.

Taking account of knowledge of risk factors, the high levels in males appear to be generally in regions where there is a prevalent habit in the population of drinking strong alcoholic beverages. The big difference between cancer of the larynx and oral and oesophageal cancers in males is the concentration of high rates in Spain: this could be due to the prominent habit of black tobacco use. Reduction of alcohol consumption, or avoidance of cigarette smoking, could lead to large reductions in risk.

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6.9: Trachea, bronchus and lung (ICD-9 162)
(M 50.3; F 10.3)

Cancer of the trachea, bronchus and lung (lung cancer) has by far the highest rate of cancer death in males in the EU-EEA, and the third highest rate in females. Overall, the mortality rate for lung cancer was around five times higher in males (50.3 per 100,000) than in females (10.3 per 100,000) (Annex 2). In all countries, the national mortality rate was higher in males than in females but there was considerable variability in the rates between countries in males. The ratios of the national rates in males and females ranged from around 2:1 to over 10:1.

International comparisons

In males, by far the highest national lung cancer mortality rate was in Hungary (84.8), followed by Poland (71.4), Belgium (69.1), the Czech Republic (68.3) and Estonia (65.6) (Annex 2). The lowest rates were in Sweden (22.3), Portugal (29.3), Iceland (30.8) and Norway (31.5).

In females, the highest national mortality rates were in Denmark (27.7), Iceland (26.2), the United Kingdom (20.5), Hungary (19.0) and Ireland (17.3). The lowest rates were in Spain (3.9) and Portugal (4.6).

Regional variation (box and whisker plots)

In males, there was clear evidence of variation both in the national lung cancer rates and in the rates within each country [p. 226]. The between-country variation in females appeared to be less marked than that observed in males, but there was again wide variation in rates within countries [p. 227].

Description of the maps

The most prominent feature of the geographical distribution of lung cancer in males is the large area of high rates which extends from northern Italy through neighbouring Slovenia into Hungary, Slovakia, the Czech Republic, Poland, parts of northeast Germany and the Baltic Countries. There was a second, smaller, area with higher than average rates covering The Netherlands, Belgium and northern France [p. 226]. There were also small numbers of areas with high rates in central Scotland, southern Spain and the northern mainland of Greece. Rates were generally low in Portugal, central and northern Spain, southern France, Switzerland, southern Germany and Austria, as well as in all the Nordic Countries.

The pattern of lung cancer mortality in females [p. 227] was quite different from that observed in males. The highest rates were in the United Kingdom (particularly the north), Ireland, Denmark and Iceland, and parts of Norway and Sweden, all of which had generally lower than average lung cancer mortality rates in males. There were, however, similar areas of higher than average rates in females as in males in Belgium and The Netherlands, in north and west Poland, and in Hungary. Low rates aggregated particularly in Portugal and Spain, but also in France, Greece, southern Italy and Finland.

Statistical aspects

There was relatively low overall regional variation for males (RRSD = 0.29) but relatively high regional variation for females (RRSD = 0.55, the fifth highest). Among females there was large regional variation within Italy, with an RRSD of 0.36 as a result of a north-south gradient with lower rates in the south. There was also a north-south gradient in Italy for males, but the regional variation was similar in magnitude to that in other Mediterranean countries. Portugal was the country with the highest internal regional variation among males.

The percentages of variation associated with differences between countries were in the middle of the range for both males (77%) and females (79%). But, as with cancer of the larynx, there was a big difference between the geographical patterns of lung cancer mortality in males and females by country, as described above.

For both males and females there was strong spatial correlation, with Moran's I of 0.76 for males and 0.79 for females, confirming the strong geographical patterns observed.

As a result of the widely different geographical patterns in the rates for males and females, the correlation between the regional rates was the lowest of all the cancer sites at 0.19. There were two main groups of countries: those where the ratio between the rate in males and females was low, such as the United Kingdom, Ireland, Denmark, Norway and Sweden; and those in which the ratio was high – of these, there were very high rates in males in parts of both Hungary and Poland, but relatively low rates in Portugal.

Comment

The 20th century witnessed a remarkable epidemic of lung cancer. The words of Adler, published in 1912, today make salutatory reading. *"Is it worthwhile to write a monograph on the subject of primary malignant tumours of the lung? In the course of the last two centuries an ever-increasing literature has accumulated around this subject. But this literature is without correlation, much of it buried in dissertations and other out-of-the-way places, and, with but a few notable exceptions, no attempt has been made to study the subject as a whole, either the pathological or the clinical aspect having been emphasised at the expense of the other, according to the special predilection of the author. On one point, however, there is nearly complete consensus of opinion, and that is that primary malignant neoplasms of the lungs are among the rarest forms of the disease. This latter opinion of the extreme rarity of primary tumours has persisted for centuries."*

Now at the beginning of the 21st century, lung cancer is the most common form of cancer worldwide. It is the most common cause of cancer death in males in North America and in virtually all European countries, west and east, and it is increasingly common as a cause of death in developing countries in Asia, Latin America and Africa, although comparable high-quality data are not available from many of these populations. From being virtually an unknown and rare disease at the beginning of the 20th century, lung cancer developed into a true epidemic.

It is estimated that between 25 and 30% of all cancers in developed countries are tobacco-related. From the results of studies conducted in Europe, Japan and North America, around 90% of lung cancers in males, and between 57 and 86% of lung cancers in females, are attributable to cigarette smoking. Because of the length of the latency period, tobacco-related cancers observed today are related to the cigarette smoking patterns over several previous decades. On stopping smoking, the risk of cancer induced by smoking rapidly decreases. Benefit is evident within five years and is progressively more marked with the passage of time.

Tobacco smoke released to the environment by smokers, commonly referred to as environmental tobacco smoke (ETS) and which may be said to give rise to enforced "passive smoking", has several deleterious effects on people who inhale it. It causes a small increase in the risk of lung cancer and also some increase in the risk of heart disease and respiratory disease and is particularly harmful to small children. Smoking during pregnancy increases the risk of stillbirth, diminishes the infant's birth weight, and impairs the child's subsequent mental and physical development, while smoking by either parent after the child's birth increases the child's risk of respiratory tract infection, severe asthma, and sudden death.

The situation regarding smoking in Europe is particularly worrying. Of the six World Health Organization (WHO) regions, Europe has the highest *per capita* consumption of manufactured cigarettes and faces an immediate and major challenge in meeting the WHO target for a minimum of 80% of the population to be non-smoking. In 1990-1994, 34% of males and 24% of females in the European Union were regular smokers. In females the overall rate was influenced by the low rates in southern Europe, but the rates there are rising and seem set to continue to rise over the next decade. In the age range 25-39 years, the smoking rates are higher than the average (55% in males and 40% in females) and this can be expected to have a profound influence on the future mortality from lung cancer, as well as other smoking-related cancers.

The importance of adequate intervention is shown by the decline to low lung cancer rates in those Nordic Countries which, since the early 1970s, have adopted integrated central and local policies and programmes against smoking. In the United Kingdom, tobacco consumption has also declined, by 46% since 1970 and lung cancer mortality among males has been decreasing since 1980, although the rate still remains high. In France, there was an 11% reduction in tobacco consumption due to the implementation of anti-tobacco measures introduced by the *Loi Evin* between 1993 and 1998.

In terms of our understanding of lung cancer aetiology, the current geographical patterns better represent the smoking habits in the various countries 20-30 years ago than those of today. In particular, the high mortality from lung cancer in females in Denmark and the United Kingdom reflects the early uptake of the smoking habit by large portions of females in those countries. An epidemic of tobacco-related lung cancer in females throughout Europe has yet to materialise (as it has previously in males) and effective intervention is now needed urgently to avoid this catastrophe.

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6.10: **Pleura** (ICD-9 163)
(M 1.0; F 0.3)

The pleura is the lining of the lung and hosts two distinct types of cancer: *adenocarcinoma of the pleura* and *pleural mesothelioma,* the latter being the dominant form. Pleural mesothelioma is one of the forms of cancer which has very strong links to occupational exposure (to asbestos). The majority of cancers recorded to this site will be mesothelioma. Although not a common form of cancer, it is likely to be correctly recorded on death certificates in view of its strong occupational determinant.

Overall the mortality rate in the EU-EEA was much higher in males (1.0 per 100,000 per annum) than in females (0.3) and the national mortality rates were higher in every country in males than in females. In males, there was a fair degree of variability in the rates between countries (Annex 2).

International comparisons

In males, the highest national mortality rates were in The Netherlands (2.7), France (1.5), Norway (1.3) and Italy (1.3) (Annex 2). The lowest rates were in Portugal (0.1).

In females, cancer of the pleura was quite rare and all the national mortality rates were 0.5 per 100,000 or lower.

Regional variation (box and whisker plots)

For males, in addition to the wide variation in national rates, there was considerable variability within many countries, particularly those with the higher average rates [p. 228].

Description of the maps

This is the only form of cancer presented in this atlas in which the local rates are more important than the general geographic picture. In males, high rates occur around the European coastline in regions where shipbuilding (and heavy engineering) have been traditional industries [p. 228]. Thus there were high rates in Trieste, Venice, La Spezia and Genoa in Italy; Marseilles, Saint Nazaire and Le Havre in France: Belfast, Glasgow, Newcastle, Sunderland, Barrow-in-Furness and Liverpool in the United Kingdom; Rotterdam and the Hague in The Netherlands; Hamburg in Germany; and Vestfold in Norway. Rates were also high in western Slovenia where asbestos was used in the production of fibre cement boards.

In females, there was little variation in the national rates which were all very low. The map for females appears to be broadly similar to that for males, as their rates are also below average in most of Portugal, Spain, Greece, Hungary, eastern Poland and the three Baltic Countries, and above average in much of France and northern Italy. The rates for females in most of the shipbuilding areas mentioned above were, however, not elevated as were the rates in males [p. 229].

Statistical aspects

This cancer had by far the highest RRSD for males at 0.76, and the third highest for females at 0.66. Within many countries, but excluding Ireland, Estonia, Hungary, Spain, Portugal and Greece, there were both extremely high rates and extremely low rates. The Moran Index was at the low end of the range for both males (0.47) and for females (0.34) and the male-female correlation in the rates was 0.55.

Comment

Asbestos exposure causes a number of benign conditions of the pleura including pleural effusions, diffuse pleural thickening and calcified pleural plaques; it has also been convincingly demonstrated that occupational exposure to asbestos causes mesothelioma of the pleura. Mesotheliomas of the pleura are so rare other than after occupational or other unusual asbestos exposure that any case that occurs after well attested and substantial exposure to asbestos is commonly accepted as being due to that exposure – the only qualification being that the time elapsed since the exposure and the disease being diagnosed is sufficiently long to permit the disease to

have been produced. This delay is important as the delay between the first exposure and the realisation of the effect is longer for mesothelioma than for many other cancers, being seldom less than 15 years and possibly never less than 10 years.

As with many other cancers, increasing exposure increases the risk of developing the disease but, in the case of asbestos exposure and mesothelioma, does not affect the length of the induction period. Periods of 30 or even up to 50 years are common and the risk apparently continues to increase indefinitely with the time since the exposure first occurred. Results of modelling of data obtained from occupational cohorts indicate that the risk of mesothelioma increases in proportion to the cube of the time elapsed since first exposure and that each brief period of exposure causes an addition to subsequent incidence which increases approximately as the cube of the time since the exposure occurred. The available data indicate also that exposure durations of between 10 and 20 years and longer intervals produce little difference in risk. However, risk caused by shorter durations of exposure may be lower than predicted.

Projections suggest that the number of males dying from mesothelioma in western Europe each year will almost double from (approximately) 5,000 in 1998 to about 9,000 in 2018. Thereafter there will be a decline with a total of around a quarter of a million deaths over the next 35 years. The highest risk will be suffered by males born around 1945-1950, with approximately 1 in 150 dying from mesothelioma. Asbestos use in western Europe remained high until 1980 and substantial quantities are still in use in several European countries.

Asbestos exposure has been highest historically in traditional shipbuilding and heavy engineering industries, but significant exposures occurred in the building industry during the post-WWII building boom. In the United Kingdom, an analysis of occupations recorded on death certificates with mesothelioma between 1968 and 1992 indicated that building workers, especially plumbers, gas fitters, carpenters and electricians were the highest risk group. These occupations account for a large proportion of deaths from mesothelioma.

In view of the striking association between mesothelioma risk and exposure to asbestos, the finding of the highest mortality rates around coastal areas of the EU-EEA with traditional port and shipbuilding facilities is not unexpected.

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6.11: Melanoma of the skin (ICD-9 172)
(M 1.7; F 1.2)

The incidence of cutaneous malignant melanoma is increasing in Caucasian populations around the world and these trends may be exacerbated by further increases in acute exposures to sunshine (sunbathing), together with, perhaps, the depletion of the stratospheric ozone layer. Thus melanoma has been identified as one form of cancer which will become very important in public health terms in coming decades in the absence of effective intervention today.

Overall, the mortality rate in the EU-EEA was around 40% higher in males (1.7 per 100,000) than in females (1.2). Rates in most countries were higher in males than in females (Annex 2) with considerable variation in the mortality rates between countries.

International comparisons

In males, the highest national mortality rates were in Norway (3.7), Slovenia (3.1), Denmark (2.8), the Czech Republic (2.8), Sweden (2.6) and Switzerland (2.6) (Annex 2). The lowest rates were in Greece (0.5) and Portugal (0.8).

In females, the highest national mortality rates were recorded in Slovenia (2.7), Norway (2.3) and Denmark (1.9). The lowest rates were in Greece (0.4), Portugal (0.7) and Spain (0.8).

Regional variation (box and whisker plots)

For both males and females there was considerable variation in the rates between countries; and the within country variability appeared wider in some of the countries with high average rates [p. 230-231].

Description of the maps

The prominent features of the geographical distribution of melanoma in males are the high levels across (southern) Finland, Norway, Sweden and Denmark and into northern Germany and The Netherlands, in Austria, Switzerland, the Czech Republic, Slovakia, Hungary and Slovenia, and in southern England. Rates were low in most of Spain, Portugal, southern Italy and Greece [p. 230].

In females, the pattern was quite similar in broad terms with higher than average levels across (southern) Finland, Norway, Sweden and Denmark and into northern Germany and The Netherlands, in parts of Austria, Switzerland, the Czech Republic, Hungary and Slovenia, and in southern England. As in males, there were lower than average rates in Spain, Portugal, southern Italy and Greece [p. 231].

Statistical aspects

For males, the RRSD was 0.35, towards the lower end of the range, but 86% of the regional variation was associated with differences between countries. For females, the RRSD was 0.30, again one of the lower values, and 84% of the between region variability was associated with differences between countries. This is noticeable in the maps with higher rates in Scandinavia, the United Kingdom, Switzerland, Austria, the Czech Republic, Slovakia, Hungary and Slovenia, and lower rates in southern European countries.

Spatial correlation was quite low with Moran's I at 0.42 males and 0.32 for females. The correlation between the rates for males and females was quite high at 0.74.

Comment

There remains no doubt that the major environmental cause of skin cancer is sun exposure. Skin cancer is predominantly, but not exclusively, a disease of white skinned peoples. Its incidence, furthermore, is greatest where fair skinned peoples live at increased exposure to ultraviolet light, such as in Australia. The type of sun exposure which causes skin cancer however appears to differ for the three main types.

Melanoma is more common in people of high socio-economic status who work inside but who have the opportunity to spend leisure time in the sun. A history of sunburn, which is associated with intermittent sun exposure, has repeatedly been described as a risk factor for melanoma. The latitudinal gradient within Europe is to some extent the reverse of what one sees in Australia: within Europe, the highest melanoma rates were in the Nordic Countries where intermittency of sun exposure is exemplified. There the people tend to have fair skin; and while the winters are long and dark, the summer lifestyle is characterised by outdoor lifestyles and holidays in the sun, frequently taken in southern latitudes where the sun is even stronger.

The incidence of melanoma doubled in Europe between the 1960s and the 1990s; this is attributed to increased intense sun exposure. There is some suggestion that this increased incidence is levelling off in some countries which might suggest that health education efforts to reduce sunburn may have had an effect. There are concerns however that exposure to the sun may still increase within Europe as a whole in years to come both as a result of increased affluence and possibly because of climatic change. It is conceivable, but as yet unproven, that depletion of the ozone layer may result in increased ultraviolet B (UVB) exposures at the earth's surface. There are also concerns that global warming may result in warmer summers in northern Europe leading to greater time periods spent outdoors and therefore greater sun exposure.

All Europeans, however, are not equally susceptible to melanoma. The fairest skinned are more susceptible, particularly (but not exclusively) those with red hair, freckles and a tendency to burn in the sun. Such fair skinned people are at increased risk of all types of skin cancer and because they burn quickly in youth, they usually do reduce their sunbathing activities through life. It is often their perspective therefore that their sun exposure has been reduced, and they are surprised when skin cancer ultimately occurs. The fair skinned should take continuous sun avoidance measures throughout life, rather than merely avoiding sun bathing.

The strongest phenotypic risk factor for melanoma however, is the presence of large numbers of moles or melanocytic naevi; there is strong evidence from studies of twins that the major determinant of the number of moles is genetic, with an added contribution from sun exposure. These naevi may be normal in appearance but are also usually accompanied by so-called atypical moles: moles which are larger than 5 mm in diameter with variable colour within them and an irregular shape. The phenotype is described as the atypical mole syndrome phenotype (AMS). AMS is present in something like 2% of the north European population and is associated with approximately a ten times increased risk of melanoma. Advice about sun protection is therefore particularly of importance to this sector of the population. Some patients with AMS report a family history of melanoma and overall a strong family history (three or more cases) is the strongest predictor of risk. These families should avoid the sun and should be referred to dermatologists for counselling.

The best protection from the summer sun is to stay out of it, but the following advice is given in order to allow safer enjoyment of the outdoors. Keeping out of the sun between 11 am and 3 pm (12 noon and 4 pm, Central Europe Time) is effective, as nearly three quarters of the total daily ultraviolet (UV) dose is delivered to the Earth's surface during this time. Scheduling outdoor activities for other times is therefore important, particularly for children. Using shade is allied to this and clothing remains the second most important protective measure. Close weave heavy cotton affords good protection although the clothing industry increasingly is developing UV protective cloths with sun protective factors (SPFs) of around 30 which are very valuable particularly where it is difficult to keep out of the sun.

Sunscreens are helpful for skin on parts of the body which cannot be protected with clothing, such as the face, the ears and the hands. Concerns have mounted in recent times, however, about the way in which sunscreens are used and which type of sunscreen is used. Sunscreen may protect against squamous cell carcinoma but there is currently inadequate evidence for their preventive effect against basal cell carcinoma and melanoma; prolongation of sun exposure may be responsible for an increase risk of melanoma.

In terms of our understanding of the risk factors for melanoma, the pattern is consistent with high

risk in those European populations with light skins and who rarely have their body exposed to the sun for most of the year but who experience intense intermittent sun exposure. There is very large scope for significant behavioural change to greatly reduce the incidence, and hence the mortality, rate of melanoma in European populations. In some countries, for example Slovenia, the mortality rate could be reduced by earlier diagnosis (and hence better survival).

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6.12: Non-melanoma skin cancer (ICD-9 173)
(M 0.6; F 0.3)

The incidence of malignant tumours of the skin other than melanomas, which include mainly basal and squamous cell carcinomas, shows wide geographical variation. Given their high frequency of occurrence, and the fact that an individual may have several basal cell carcinomas over a lifetime, many cancer registries choose not to record them. Even when registered, the true incidence is frequently difficult to assess, however, as these tumours are often subject to under-reporting. The generally high survival rates for these cancers makes it difficult to assess the effects of risk factors by examination of mortality data.

Overall, the mortality rate in the EU-EEA was around twice as high in males (0.6 per 100,000) as in females (0.3). In all countries except Latvia, the national mortality rate was higher in males than in females (Annex 2).

International comparisons

In males, the highest national mortality rates were in Hungary (1.2), Poland (1.1), Slovakia (1.1), Greece (1.0) and Estonia (1.0) (Annex 2). The lowest rates were in Iceland (0.2) and Germany (0.3); six countries had rates of 0.4.

In females, the highest rates were in Slovakia (0.8), Greece (0.8), Hungary (0.7), Poland (0.7) and Estonia (0.7); three countries had rates of around 0.4, and most of the remaining countries had rates of 0.2 or lower.

Regional variation (box and whisker plots)

In both males and females there was considerable variability both between and within countries. To some extent, the apparent within country variation is due to random fluctuations arising from rates being based on very small numbers of deaths [p. 232-233].

Description of the maps

In males, there were many regions with high mortality rates in Portugal, Spain, Greece, Ireland, Poland, the Czech Republic, Slovakia and Hungary [p. 232]. Low rates tended to aggregate in the Nordic Countries, France, Belgium, The Netherlands and large parts of Germany and western Austria.

The map for females is substantially similar to that for males, with areas of high rates aggregating in Portugal, Spain, southern Italy and Greece, Poland, the Czech Republic, Slovakia and Hungary [p. 233]. Low rates were noticeable in Sweden, Finland and a large part of northern Germany.

Statistical aspects

Although the mortality rates for non-melanoma skin cancer were low, particularly for females, they do exhibit strong regional variation. For males the RRSD was 0.56, which was the fourth highest; and 77% of the regional variation was associated with differences between countries. Similar results were obtained for females, where the RRSD was 0.67 (second highest) and 82% of the regional variance was associated with countries. The main country differences for males were due to the high rates in two groups of countries: Spain, Portugal and Greece; and Poland, the Czech Republic, Slovakia and Hungary, and generally lower rates elsewhere.

Spatial correlation was moderate to low with Moran's I of 0.40 for males and 0.39 for females. The spatial correlation between male and female rates was 0.74 which is reasonably high.

Comment

The major environmental cause of skin cancer is exposure to the sun. Skin cancer is predominantly, but not exclusively, a disease of white skinned people. Its incidence, furthermore, is greater where fair skinned peoples live at increased exposure to ultraviolet light. The type of sun exposure which causes skin cancer however appears to differ in the three main types. Squamous cell carcinoma shows the clearest relationship between cumulative sun exposure and risk. This form of skin cancer is therefore most common in outdoor workers and there is a linear increase with age. The recipients of transplanted organs are particularly at risk of these tumours as

a result of the combined effects of the unchecked growth of human papilloma virus in their skin due to immuno-suppression, and exposure to the sun.

Basal cell carcinoma (BCC) is the commonest type of skin cancer but it is the least serious as it is only a locally invasive disease. Extremely small numbers of people die from this cancer; as in addition there are very large numbers of cases, in some countries BCCs are not even recorded by the cancer registries. This form of skin cancer appears to share with melanoma an aetiological relationship to sun exposure. The case-control study evidence for both appears to suggest a non-linear relationship between cumulative sun exposure and risk. For both, intermittency of exposure seems to be important. Further discussion on exposure to the sun and protective measures is given in section 6.11 above

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6.13: Breast (female) (ICD-9 174) (F 20.6)

There was no country with a truly low mortality rate for breast cancer, for which the overall rate in the EU-EEA was 20.6 per 100,000. Breast cancer accounted for one fifth of all cancer deaths and was the most common form of cancer death in females.

International comparisons

The highest national mortality rates were in Denmark (27.4), The Netherlands (25.9), Belgium (25.3), Iceland (24.9), the United Kingdom (24.8) and Ireland (24.4) (Annex 2). The lowest national rates were in Greece (14.8), Poland (16.0), Finland (16.6), Sweden (16.7), Slovakia (16.9) and Spain (16.9).

Regional variation (box and whisker plots)

There was some variability in rates between countries, but only relatively small variations within countries [p. 234].

Description of the maps

There are several notable features of the geographic distribution of breast cancer mortality in females in the EU-EEA. There was an aggregation of high rates which covers Denmark and westwards through northern Germany, The Netherlands and Belgium and then across to the United Kingdom and Ireland; mortality was also slightly above average in parts of Slovenia and Hungary. Rates were low in the Nordic Countries (apart from Denmark), Portugal, Spain, France, southern Italy and Greece [p. 234].

Statistical aspects

Overall, the RRSD was very low at 0.20 (second lowest); within each country there was low regional variation in many countries, though it was a little higher in some of the Mediterranean countries. Of the regional variation, 75% was associated with differences among the countries of Europe. This is lower than for many other cancers, although the Moran Index of spatial correlation was quite high at 0.70. The geographic pattern was of relatively and uniformly low rates in the Mediterranean countries and Scandinavia (except Denmark), and high rates in the United Kingdom, Denmark, Belgium, The Netherlands and Ireland.

Comment

The risk of breast cancer is increased by around 50% in nulliparous compared with parous females. Risk increases with increasing age of the mother at first birth until a first birth occurring after the age of (approximately) 35 years carries a higher risk than nulliparity, indicating that first childbirth after this age no longer confers protection against breast cancer. It has been estimated that a 3.5% increase in relative risk is associated with every year of increase in the mother's age at first birth. Risk appears to be reduced by a late age at menarche and increasing parity, although the role of breast-feeding remain controversial. Risk is increased by a late age at menopause, and an early menopause, whether natural or artificial, contributes to reducing risk.

Breast cancer risk is increased among current users of oral contraceptives, although this risk returns to that of never users within five to seven years of stopping use. An anti-estrogenic effect of cigarettes could theoretically lead to some protection against breast cancer, but the majority of published studies have given null results. Radiation to the breast in high doses has been shown to increase the risk of breast cancer; exposure around the menarche is associated with a particularly high risk. Risk seems to be increased by obesity (in postmenopausal females) and decreased by regular exercise.

Over 100 studies have consistently shown a modest increased risk of breast cancer in postmenopausal females with a high body weight. Epidemiological studies have shown an increase in breast cancer risk above a body mass index (BMI) of, on average, 24 kg/m^2. A pooled analysis of eight cohort studies of about 340,000 females

showed an increase in risk of 30% in females with a BMI of 28 kg/m^2 or above compared with those with a BMI of under 21 kg/m^2. Factors that have been shown to attenuate the association between obesity and breast cancer include family history (heavier females with a family history have a higher risk than similar females without a family history) and the use of hormone replacement therapy (the risk of breast cancer associated with obesity is greater in females who have never used HRT). In contrast, among premenopausal females obesity is not associated with an increase in risk.

The association of breast cancer with diet remains the subject of much research and debate. There is at present little support for an association with fat intake in any form. However, the evidence is increasing that alcohol consumption increases the risk of breast cancer. Of the other factors for breast cancer studied, a positive family history has the effect of increasing the risk of breast cancer, with the maximum effect apparent in premenopausal females who have a first-degree relative with breast cancer at premenopausal ages.

An increased risk of breast cancer with alcohol consumption has been consistently reported in epidemiological studies conducted in different populations. Although not strong (increase risk in the order of 10% for each 10 g/day increase in alcohol intake, possibly reaching a plateau at the highest levels of intake), the association is of great importance because of the apparent lack of a threshold, the large number of females drinking a small amount of alcohol and the high incidence of the disease. Indeed, more cases of breast cancer than of any other cancer are attributable to alcohol drinking among European females. It has been suggested that alcohol acts on hormonal factors involved in breast carcinogenesis, but the evidence is currently inadequate to identify a specific mechanism.

Forty years of clinical trials, the contribution of hundreds of scientists and health workers and the dedication of hundreds of thousands of females to participate in studies lasting for decades has resulted in adequate evidence to support the efficacy of mammographic screening for breast cancer, which has allowed its transfer to the arena of public health policy. Doctors and females can be assured that participation in organised screening programmes, with rigorous quality assurance standards implemented, is of benefit, provided appropriate diagnostic investigation and treatment are available. Special efforts should be made to encourage screening among the more socio-economically deprived members of society. It is important not to over-emphasise the benefit of screening, and to appreciate that this is but one step in the total care of females with the disease. Females should, however, be informed clearly of the level of benefit and of potential risks and costs.

There is nothing known about the aetiology of breast cancer that can explain the geographic pattern demonstrated on the map. The pattern will change in the future as national breast screening programmes make their effects in reducing breast cancer mortality.

The similarities and differences between the geographical patterns in mortality from breast and ovarian cancers are discussed in the section on ovarian cancer (6.15, below).

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6.14: Uterus (ICD-9 179-182)
at all ages (F 6.0) and under 50 years (F 1.7)

Cancer of the cervix, endometrium and other parts of the uterus are very difficult to separate reliably on death certificates. The geographic patterns are therefore presented for all parts of the uterus combined, both for all ages and for females under 50 years. Such deaths in the latter group will overwhelmingly be cancer of the cervix, and will give a good picture of the mortality from this form of cancer in younger females in Europe.

International comparisons

Cancer of the uterus had the fifth highest mortality rate (all ages) in the EU-EEA of 6.0 per 100,000 (Annex 2). There was considerable variation in the national mortality rates with the highest rates in Lithuania (12.3), Hungary (11.2), Poland (11.1), Slovakia (10.9), Estonia (10.6), the Czech Republic (10.3) and Latvia (10.1); rates were also higher than in most of the other countries in Slovenia (8.7) and Denmark (8.4). The lowest national rates were recorded in Greece (3.3), Finland (3.7), The Netherlands (4.0) and Iceland (4.3).

The pattern in the national mortality rates for cancer of the uterus under the age of 50 was closely similar to that at all ages with the highest rates in Lithuania (4.5), Hungary (4.2), Poland (3.8), Slovakia (3.7) and Estonia (3.3). The lowest rates were in Finland (0.5), Iceland (0.7), Luxembourg (0.8), The Netherlands (0.8), Sweden (0.8) and Switzerland (0.9). The pattern was also closely similar to that for mortality from cervical cancer at all ages which showed high rates in most of the former communist countries in central Europe, including the eastern part of Germany, and the Baltic Countries; rates were generally low in the Nordic Countries and western and southern Europe.

Regional variation (box and whisker plots)

There was considerable variation in mortality from cancer of the uterus within countries as well as between countries [p. 235]. There appears to be less variation between countries for uterus cancer mortality rates in females under age 50, although there was still variation within each country [p. 236].

Description of the maps

For mortality from all cancer of the uterus at all ages, the most notable features of the geographic pattern were the aggregations of higher rates in Denmark, southwards through the eastern part of Germany and into Austria and Slovenia [p. 235], while to the east, rates were generally very high in the three Baltic Countries, some western (but not eastern) parts of Poland, and the Czech Republic, Slovakia and Hungary. Rates were also higher in some of the regions of Portugal, but Spain, Italy and Greece had generally low rates. Rates were also low in Sweden and Finland.

When consideration is restricted to mortality in females under the age of 50, the band of higher rates from Denmark southwards to Austria and Slovenia was still present but less prominent, as were the higher rates in Portugal. Rates were again highest in central Europe and low in Italy and Greece as well as Finland and Sweden [p. 236].

Statistical aspects

For cancer of the uterus at all ages, the RRSD was 0.35, in the middle of the range. The spatial correlation (Moran's I) was among the highest at 0.77; and 86% of the total variation over regions was attributed to differences among the countries. This is driven by higher rates in many of the former communist countries: the Baltic Countries, Poland, Hungary, the Czech Republic, Slovakia, Slovenia and eastern Germany. Within each country there was similar, low, regional variation.

For deaths in females under age 50, compared with the all ages results, the rates exhibited more regional variation, with an RRSD of 0.54. There was, however, a similarly high percentage of variation (89%) associated with country – the result of higher rates in the Baltic Countries, Poland, Slovakia and Hungary. Spatial correlation was lower than for cancer of the uterus all ages, at 0.57. Latvia and Germany had the highest RRSDs of 0.35 and 0.34, respectively, followed by Greece at 0.32.

Comment

About 90% of cancers of the body of the uterus occur in the inner lining of the womb (endometrium). The main risk factors are similar to those for cancers of the breast and ovary: early age at menarche, low parity and late age at menopause. These are all related to hormone levels, and result in the uterus being exposed to either prolonged or increased amounts of oestrogen. Another source of oestrogen is hormone treatments that contain only oestrogen. Oestrogen-only hormone replacement therapy (HRT) and unopposed oestrogen therapy used for alleviating the symptoms and harmful effects of the menopause increase the risk of endometrial cancer (among females who have not had a hysterectomy). HRT formulations that include progestin appear to reduce the risk. Sequential oral contraceptives (oestrogen followed by progesterone) increase the risk, but combined oral contraceptives that contain both the hormones have a long-lasting protective effect. There is a slight increased risk of endometrial cancer in females treated with tamoxifen for breast cancer.

Excess body weight and physical inactivity account for over a quarter of cases of endometrial cancer. Hormones in the body are affected by obesity. Fatty tissue contains important enzymes used in the production of oestrogen-like compounds. The more fat in a woman's body, the more oestrogen it can make and the greater the risk of endometrial cancer. Excess body weight is also associated with high blood pressure and diabetes; this association increases the likelihood that those with such conditions may develop endometrial cancer.

Changes in the prevalence of the above aetiological factors over time may be responsible for much of the observed increases in the incidence of uterus cancer which have been observed in many countries in Europe. Differences in the prevalence of the risk factors may in part explain the variations in mortality from cancer of the uterus seen in the EU-EEA. In addition, there is evidence that the higher mortality rates in central Europe may in part have resulted from lower survival rates there than in western Europe.

In 1996, the NIH Consensus Statement concluded that carcinoma of the cervix is causally related to infection with the human papillomavirus (HPV). Reducing the rate of HPV infection by changes in sexual behaviour in young people and/or through the development of an effective HPV vaccine would reduce the incidence of this disease.

A dozen types of human papillomavirus (HPV) have been identified in 99% of biopsy specimens from cervical cancer worldwide and, in Europe, HPV 16 has been reported in 56% of over 3,000 cervical cancer specimens. Five HPV types (HPV 16, 18, 31, 33, 45) account for more than 85% of European cervical cancer cases. In females without cervical cancer, the prevalence of the indicated HPV types is several dozen-fold lower. There is no effective medical treatment against HPV, but very sensitive and specific tests for the detection of HPV DNA in cervical cells have become available. There is sufficient evidence for recommending HPV testing among females who show borderline or low-grade cytological abnormalities. Additionally, HPV testing improves the follow-up of females who have been treated for cervical intraepithelial neoplasia (CIN) lesions and, pending results of ongoing trials, may offer a more sensitive alternative to cytology in primary cervical cancer screening.

A prophylactic vaccine, based on late (L) 1 HPV 16 proteins, has been shown to be safe, highly immunogenic, and efficacious in preventing persistent HPV infections in a trial of 1,523 HPV 16-negative young females in the United States. A multivalent vaccine against the most common oncogenic HPV types may thus ultimately represent the most effective way to prevent cervical cancer worldwide, either alone or in combination with screening. Vaccination would benefit females who do not attend screening programs in the EU-EEA and, if combined with current screening programs, it would allow substantial savings (i.e. less frequent screening tests, fewer treatments, etc.).

Screening for cervix cancer by examination of a cervical smear is now widely recognised as leading to a reduction in the mortality from cervical cancer. It has also been demonstrated to be cost-effective in older females, particularly among those who have not been screened regularly. The impact is greatest where organised screening programmes exist with personal letters

of invitation: this leads to improved attendance, particularly among those females who are at high risk of cervical cancer.

It has been shown, particularly from the Nordic Countries, that a population-based and well-organised screening programme with a valid target age range, the right frequency of screening, and built-in quality assurance programmes at each stage of the screening process, is more successful than opportunistic screening, and that such a programme can be effective in reducing both the incidence and mortality from invasive cervical cancer. It would appear that the most successful programme in terms of reduction in risk of cervix cancer is in Finland, with an official recommendation that a screening programme be started at age 30 and that the smear be repeated every five years. Finland has markedly lower rates of cervix cancer mortality than most of the countries in the EU-EEA.

If cytological screening programmes seem to be effective in preventing invasive cervical cancer and reducing cervical cancer mortality, numerous reports have underscored that that method may fail to detect a certain number of cervix cancers, mainly of the glandular type. It has been estimated that the number of cases of invasive cervical cancer in the UK would have been 57% greater if there had been no previous screening; and in females under 70 years it would have been approximately 75% greater. The study further estimated that full adherence to current screening guidelines could have prevented 1,250 cases of invasive cervical cancer in the UK in the same year but that further steps would have to be sought to prevent some of the remaining 2,300 cases in females under the age of 70. The most frequent reasons evoked to explain the lack of sensitivity of cytological screening are inadequate cell sampling with the spatula and errors in the reading of smear slides. However, even in the best hands, a certain number of false negative cytological tests cannot be explained by sampling or reading problems. Hence, there is a strong feeling in the medical community that besides searching to improve screening coverage, there is also a need for additional ways to improve screening methods for cervical cancer. The first could be the improvement of the spatula used for cell sampling (with current preference for instruments such as the extended tip spatula) and in the automation of cytological reading. It remains, however, to be assessed whether these improvements in cytological methods will prevent all types of false negative results.

Given the implication of HPV infection in cervical cancer, detecting HPV could represent an appealing screening method. A study of 2,009 females having routine screening in England and Wales revealed that 44% of CIN lesions of grade 2/3 detected had a negative cytology and were found only by HPV testing (for types 16, 18, 31 and 33): a further 22% were positive for HPV but demonstrated only borderline or mild cytological changes. However, 25% of CIN 2/3 lesions were not detected by the four HPV tests. Hence, there is convergence between the results obtained when comparing HPV testing with cytology, and cervicography with cytology. However, although appealing, routine HPV testing for cervical cancer screening is still controversial as HPV infection is very common in females under 30 years old, and the females at highest risk are those over the age of 30 with a HPV infection that persists over a long period of time. As it is impossible currently to identify those females with a HPV infection who will develop cervix cancer, HPV testing is proposed to be used in various ways, for example, as an adjunct to cytology for sorting out the cytological results classified as atypical squamous cells of undetermined significance (ASCUS), with referring to colposcopy-biopsy of those ASCUS lesions which are positive for HPV infection. Another proposal consists in testing all females over 30 years of age for HPV, and referring to cytology only those positive for HPV. HPV testing is still to be thoroughly evaluated in order to find the best role it could play in cervical cancer screening.

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6.15: Ovary (ICD-9 183)
(F 6.3)

Ovarian cancer was the fourth commonest form of cancer death in females in the EU-EEA with an annual mortality rate of 6.3 per 100,000.

International comparisons

The highest national mortality rates for ovarian cancer were in Lithuania (9.0), Denmark (8.6), the Czech Republic (8.5), Ireland (8.4), Latvia (8.3), Estonia (8.1), the United Kingdom (8.1) and Norway (8.0) (Annex 2). The lowest rates were in Portugal (3.5), Greece (3.6), Spain (4.2) and Italy (4.8). There was considerable variation in national mortality rates.

Regional variation (box and whisker plots)

There was more variation between countries for mortality from ovarian cancer than for breast cancer, but again relatively small variation within countries [p. 237].

Description of the maps

While there are certain similarities with breast cancer in the geographic distribution of mortality from cancer of the ovary, there are also some potentially interesting differences. As with breast cancer, there were lower than average rates for ovarian cancer in Portugal, Spain, Italy, Greece and much of France. Rates were similarly above average in the United Kingdom and Ireland, Belgium, The Netherlands and Denmark. But rates for ovarian cancer mortality were above average in the Czech Republic, western Poland, the three Baltic Countries, and parts of Norway and Sweden where breast cancer mortality rates were generally below average [p. 237].

Statistical aspects

The RRSD was 0.26, towards the lower end of the range. At 88%, this cancer had the third highest percentage of variation associated with country among cancers in females. This results from the strong geographic pattern, with rates generally low in southern Europe and consistently high over much of northern Europe. Moran's Index was 0.57, roughly in the middle of the range. The within country regional variation was similar to that for breast cancer, with low internal regional variation in most countries but slightly higher such variation among Mediterranean countries.

The correlation between the (smoothed) regional mortality rates for breast and ovarian cancers was 0.48. This confirms the visual impression from the maps [p. 237] that many areas that had relatively high mortality rates for breast cancer also had relatively high rates for ovarian cancer, for example in the UK, Ireland, Belgium, The Netherlands and Denmark, while many areas had relatively low rates for both cancers, for example in France, Spain, Portugal, Italy and Greece. Areas with relatively high ovarian cancer mortality but low breast cancer mortality included the Czech Republic, Estonia, Latvia, Lithuania, Norway and Sweden.

Comment

Epithelial ovarian cancer is the commonest type of ovarian neoplasm and the leading cause of death from gynaecological neoplasms in most western countries. As for other female hormone-related neoplasms, its age-incidence curve tends to flatten off around the age of the menopause. These cancers are more frequent in nulliparous than in parous females, with the former having an approximately two-fold elevated risk compared with multiparous females. Increased risks related to late age at first birth, early menarche and late menopause have not been found consistently.

Oral contraceptive use is protective, the incidence of invasive epithelial cancer being reduced by approximately 40% in females who have ever used oral contraceptives, and to a greater extent in long-term users. Combined oral contraceptives have probably been the major determinant of the decrease in ovarian cancer incidence rates observed in several western countries.

As with breast and endometrial cancer, nutrition and diet remain major open questions in ovarian cancer epidemiology, although nothing is certain at present and further research is required in this area because diet may be more amenable to intervention than reproductive or menstrual history.

There is nothing known about the aetiology of ovarian cancer (or breast cancer – section 6.13 above) which can explain the geographic pattern demonstrated on the maps. There is a large randomised trial of ovarian cancer screening underway in the United Kingdom (UKTOCS) that should quantify the advantages and risks of screening for this form of cancer.

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6.16: Prostate (ICD-9 185)
(M 15.4)

The overall prostate cancer mortality rate in the EU-EEA was 15.4 per 100,000, the third highest rate in males behind cancers of the lung and large bowel. There was, however, considerable variation in the national rates.

International comparisons

The highest national mortality rates were in Norway (23.8), Switzerland (20.1), Denmark (19.8) and Iceland (19.8), followed closely by Belgium (19.4), The Netherlands (19.2) and Ireland (19.0). The lowest national rates were in Greece (9.2), Poland (10.9), Italy (11.2) and Slovakia (12.3) (Annex 2).

Regional variation (box and whisker plots)

Although there was about a two-fold variation in the national mortality rates for prostate cancer, there was relatively little variability within countries.

Description of the maps

High mortality rates from prostate cancer are apparent in Iceland, Norway, much of Sweden, southern Finland and Denmark; there were also higher than average rates in The Netherlands, Belgium and northern France, and Ireland [p. 238]. There was also a band of high rates from Switzerland eastwards into Austria and western Hungary. Low rates are notable throughout Poland, Greece and Italy, and much of Spain.

Statistical aspects

The RRSD for prostate cancer was 0.20, one of the lowest values for cancers in males. The variation associated with differences between countries was, however, quite high at 85%. Rates were higher in north Europe, especially Norway, and lower in southern Europe. Moran's I was quite high at 0.66. Prostate cancer is an example of a site with low regional variation and high spatial correlation.

Comment

Prostate cancer has become the most commonly diagnosed cancer in males in several developed countries. With increasing age, most males will develop microscopic foci of prostate cancer whether or not they live in a population at a high or low risk for the invasive form of the disease. Although a majority of males will develop microscopic disease, only a small percentage of these slow-growing tumours will develop into invasive prostate cancer and an even smaller proportion will cause premature death. The principal focus of epidemiological investigations of prostate cancer, therefore, has to be the identification of factors – amenable to intervention – that cause the common microscopic form to progress to invasive disease.

Prostate cancer incidence is highest in western populations and particularly so among the black population of the United States. The disease is uncommon in populations of many Asian and other developing countries. Consideration of the public health importance of prostate cancer should be tempered with the observation that in many countries the average age at death from prostate cancer is approaching 80 years. Indeed, as data from England and Wales demonstrate, the average age at diagnosis of prostate cancer is greater by a considerable margin than that for other common cancers, such as breast and colorectal.

The epidemiology of prostate cancer has been notoriously difficult to study and the disease continues to present formidable challenges to epidemiologists. Much of the difficulty is linked with our lack of knowledge of disease specificity. Both the phenotype(s) and genotype(s) of prostate cancers are heterogeneous and studies that combine all forms of prostate cancer together are, therefore, likely to attenuate any associations that might only arise with particular sub-types. This problem has gained more widespread recognition in recent years and epidemiologists have attempted to increase disease specificity in their studies largely by stratifying on

severity e.g. histological grade, Gleason scores, stage of disease, progression and death. So far, although this approach has occasionally produced strengthened associations with various factors, it has not greatly advanced our understanding.

The causes of prostate cancer have been investigated in numerous case-control studies and a few prospective cohort studies. Apart from disease specificity, there have been other problems with epidemiological studies of prostate cancer, particularly small sample sizes and, therefore, poor statistical power, poor exposure measurement, and inappropriate study designs. The best available epidemiological evidence about prostate cancer is to be obtained from only a handful of large well-conducted case-control studies and cohort studies. Although historically case-control studies have identified numerous putative risk factors, only age and a family history of prostate cancer can be considered to have been well-established. During the 1990s, prospective studies suggested that specific fatty acids, antioxidant vitamins, and carotenoids may alter prostate cancer risk. There were also reports that changes in plasma levels of key hormones and associated molecules and naturally occurring variants in genes (polymorphisms) of the androgen, vitamin D and insulin like growth factor 1 (IGF-1) prostate cell growth regulatory pathways also alter risk, and conjectures that dietary factors may modulate risk by interacting with these pathways.

Although there are a number of new leads in regard to risk factors for prostate cancer, more research is required to confirm them. There is little purpose in conducting further case-control studies of prostate cancer, particularly since the widespread use of PSA testing, and much more attention will have to be paid in future epidemiological studies to prostate tumour sub-classification in terms of method of detection, markers of biological "aggressiveness" and genetic changes. Many of these new leads involve the possible influence of polymorphisms in key genes involved in important physiological processes in the prostate. To fully explore the complexity of interrelationships between the several elements in these pathways will require very large cohort studies in which blood is sampled prior to diagnosis. Such studies will be important for identifying which modifiable aspects of lifestyle (diet, alcohol, tobacco, physical activity etc.) might be targeted for intervention to reduce risk.

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6.17: **Testis** (ICD-9 186)
(M 0.4)

Testicular cancer mortality was very low – although the incidence was much higher and has been increasing. The successful outcome of treatment for testicular cancer was one of the major events in medical oncology during the last three decades of the 20th century.

International comparisons

Overall, the mortality rate for testicular cancer in the EU-EEA was 0.4 per 100,000. In all the countries of western Europe the national mortality rates were very low, less than 0.5 per 100,000, except in Denmark (0.7). Rates were, however, well above average in several of the countries in central Europe: the Czech Republic, Latvia and Hungary (all 0.9), and Poland, Slovakia, Lithuania and Estonia (all 0.7) (Annex 2).

Regional variation (box and whisker plots)

There were considerable differences between countries, with the rates clustering in two groups at 0.7 to 0.9 per 100,000 and around 0.3; as would be expected with generally very small numbers of deaths and low rates, there was wide variability in the values within countries [p. 239].

Description of the maps

The main feature of the geographic distribution of testicular cancer mortality is the grouping of areas with high rates in the former communist countries – the eastern part of Germany, Poland, the Czech Republic, Slovakia, Hungary, and the three Baltic Countries. The patchwork appearance of the remainder of the map simply reflects the wide random variation inherent in rates based on very small numbers of deaths [p.239].

Statistical aspects

There was moderate to high regional variation for cancer of the testis with an RRSD of 0.54 which gives it a rank of 6 out of 22. Moran's I statistic was 0.29 which is quite low and 77% of the total regional variation was associated with differences between countries. These statistics all confirm the visual impression of the map (described above).

Comment

The incidence rates of testicular cancer are increasing almost everywhere for reasons that are not entirely clear. Hypotheses to be studied are complicated and exposure assessment is difficult. For a form of cancer which is increasing so much, there is some degree of complacency in undertaking aetiological studies because of the very low, and generally declining, mortality rates.

A decline in mortality from testicular cancer has been widely demonstrated in many countries following the demonstration of effective therapy of platinum based drugs (in 1977) even against a background of increasing incidence. The decline in mortality rates from testicular cancer was evident in nearly all countries which adopted the new therapy between 1975 and 1985, with large decreases in the relative risk of death apparent almost everywhere. It is widely appreciated that the application of chemotherapy in the treatment of germ cell tumours exemplifies the best results to be expected from this approach to solid tumours, since the majority of patients treated are now cured. 80-90% of patients with testicular cancer could expect to be cured of their disease and in most countries this seemed to be so, but not in central Europe where about 1 in 2 cases were still dying in the mid-1980s. Any fundamental difference in biological behaviour in central Europe is unlikely and a more likely explanation is that the differences in mortality were related to lack of curative chemotherapy, including cisplatin, or to deficiencies in patterns of referral.

The poor outcome from testicular cancer in central Europe could be related to the lack of financial resources to purchase the expensive drugs necessary to treat disseminated testicular cancer.

The economic situation in many of these countries has been changing rapidly, including in Slovakia where there has been an effective population-based cancer registry for many years, making comparison of trends in incidence and mortality from testicular cancer possible. Another interesting aspect of testicular cancer treatment in Slovakia has been the establishment in 1982 of a specialist treatment centre for non-seminoma testicular cancer in the Department of Urology in the School of Medicine of Bratislava. This centre initially treated approximately 50 new patients per annum with this disease, employing a multidisciplinary approach. Following this, there has been the establishment of similar specialist units in the largest hospitals in central and eastern Slovakia and whereas the incidence rate of testis cancer has gradually increased between 1968 and 1990, the mortality rate has declined slightly since the early 1980s following an initial increase between 1968 and 1980. The gap between incidence and mortality is widening, indicating increasingly efficacious therapy of patients with testicular cancer in Slovakia.

In no country of central Europe was the economic change as rapid as in the former German Democratic Republic (DDR, known as East Germany). Mortality data from East Germany have become available since 1980. In the former Federal Republic of Germany (FRG, known as West Germany), the mortality rate from testicular cancer peaked around the mid-1970s and by 1995 had reached 0.4 per 100,000, less than one-third the mortality rate in 1977 (1.4 per 100,000) when details of treatment advances were first published. In East Germany, however, the mortality rate remained essentially unchanged until the opening of the border in 1989 (1.5 per 100,000) and has subsequently declined to almost the same level as in the former West Germany.

Thirty years ago, testicular cancer was almost invariably fatal, whereas today, in most developed countries, testicular cancer is almost always curable. This has been a major achievement for cancer control. Testicular cancer could become a very rare cause of death around the world if the knowledge currently available could be implemented world-wide. It is clear that when the economic situation is such that the necessary drugs become available, large reductions in mortality can occur quite rapidly. It is clear also than when treatment can be centralised, outcome also improves.

This emphasises the fundamental difference between the control of testicular and prostate cancers. Testicular cancer could be very nearly eliminated as a cause of death by implementing what is currently known.

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6.18: **Bladder** (ICD-9 188)
(M 6.8; F 1.4)

Bladder cancer had the seventh highest cancer mortality rate in males the EU-EEA, but was of far less importance in females. Overall, the mortality rate for cancer of the urinary bladder (bladder cancer) in the EU-EEA was about five times higher in males than in females. There was considerable variation in the national mortality rates in males, but little variation in females, in whom the rates were consistently much lower.

International comparisons

In males, the highest national mortality rates were in Denmark (9.1), Malta (8.5), Spain (8.5), Latvia (8.4), Poland (8.1), Hungary (8.1), Italy (7.7) and Lithuania (7.7) (Annex 2). The lowest rates were in Finland (4.0), Sweden (4.2) and Ireland (4.4).

In females, the highest national mortality rates were also in Denmark (2.7) and Malta (2.3), followed by the United Kingdom (2.0). A large number of countries had low rates of around 1.0: Finland, France, Greece, Italy, Poland, Portugal, Spain, Sweden, Estonia, Latvia and Lithuania.

Regional variation (box and whisker plots)

Although there was around a two-fold range in the national mortality rates for males, there appeared to be relatively low variability within countries [p. 240]. For females, there was much less between country variation, but there was wide variability within countries (partly due to the rates being based on much smaller numbers of deaths) [p. 241].

Description of the maps

An intriguing feature of the geographic map of bladder cancer in males is the high rates in coastal areas of Spain and parts of the Mediterranean coastlines of France (including Corsica) and Italy (including Sardinia and Sicily) [p. 240]. There were high rates in other regions of Spain, northern Italy and northern Greece. Rates were high in Denmark and in the northern part of the former East Germany and Poland, and in Lithuania and Latvia. There were low rates throughout the Nordic Countries (other than Denmark), Ireland, the south of Germany, Austria and Switzerland.

In females, rates were high in Denmark and northern Germany (as in males) but were also high in parts of the United Kingdom (especially Scotland) and The Netherlands [p. 241]. There were areas of low rates in the north of Europe except Norway: Sweden, Finland, the Baltic Countries and much of Poland; and in most of southern Europe: Portugal, Spain, France, Italy and Greece.

Statistical aspects

The three main spatial statistics all had similar values in males and females. The RRSD was 0.24 in males and 0.32 in females, both towards the lower end of the range. The variation explained by differences between countries was 67% in males and 60% for females, the lowest for males and second lowest for females. Spatial correlation was 0.51 in males and 0.46 in females, both in the middle of the range. Given these similarities, the correlation between the male and female rates was low at 0.23. This is because there were only relatively weak spatial patterns that were not the same in males as in females. There was relatively large within country variation in Germany in both males and females, and in Austria, the Czech Republic, Lithuania and Poland but only for females. In Germany this variation was associated with low rates in the south of the country and areas of high rates in the north and east.

Comment

The evidence for an association of bladder cancer with cigarette smoking is overwhelming: the only remaining question surrounds the strength of the association. In different regions of the world, smoking accounts for one third to a half of bladder cancers diagnosed among males and about one quarter of that among females. For all cigarette smokers, estimated relative risks for smokers (relative to non-smokers) have been generally

around 2.0, although some higher estimates have been reported. The large majority of studies find relationships between bladder cancer risk and 'dose' of cigarettes smoked. Furthermore, smokers of black tobacco appear to have around a 40% higher risk than smokers of blond cigarettes.

Cohort studies on mortality according to level of alcohol consumption find no excess of bladder cancer. A large number of case-control studies have also investigated the association between alcohol intake and bladder cancer risk and have found no association. Only a few studies conducted in Germany, France and Turkey reported some increased risk and an element of dose-response. Generally, the risk estimates in these studies were significant only for the heaviest drinkers. Taken together, the available data show no association between risk of bladder cancer and alcohol consumption.

Overall, the data from studies of coffee consumption are consistent with a weak positive relationship with the occurrence of bladder cancer, but the possibility that this is due to bias or confounding cannot be excluded. However, there is a certain amount of lack of internal consistency within most of the positive studies which should keep the question of a causal association open: in some studies the association is present in females but not in males and in others *vice versa* and there is a lack of a consistent dose-response relationship.

Several other factors are related to cancer of the bladder, including occupational exposure to aromatic amines, coal tar and, possibly, other chemicals; exposure to *Schistosoma haematobium* and other infectious agents; and exposure to some drugs such as phenacitin, chlornaphazine and cyclophosphamide. Occupational exposures have generally been considered to be the second most important risk for bladder cancer after smoking. The proportion of bladder cancers attributable to occupation ranges between 16 and 24 per cent in several investigations conducted in different countries. Among occupations most frequently reported to be associated with an increased risk of bladder cancer are printing, plastics and synthetics, rubber, mining, metal, and dyestuff industries, and those professions which involve exposure to dyes, spray paints, zinc, oils, petroleum stone dust, metal dust/fumes and herbicides. Relative risks for bladder cancer in males and females who are engaged in these occupations are generally around a factor of 2 with higher risk for chemical and metal workers, press operators, and those who exposed to dyes, paints and herbicides. The most common occupational carcinogens related to bladder cancer are benzidine 4-aminobiphenyl, 2-naphthylamine, aminobiphenyl, dichlorobenzidine, orthodianisidine and orthotolidine. Most of these exposures are regulated and occupational bladder cancer may be shrinking in importance in many western countries through a combination of legislation against carcinogens and a cleaner workplace: some of the practices responsible for bladder cancer in the west may, however, be in the process of being exported to the developing world where occupational hygiene standards may not be so rigorously enforced.

In terms of explaining the geographic pattern, the high rates in males in Spain could well be associated with the prevalent habit of smoking black tobacco, which carries an excess risk of bladder cancer over Virginia cured tobacco. The high rates in Denmark are a reflection of the high incidence rates which have persisted there for decades. The pattern of high risk areas in males – but not females – in areas around the Mediterranean coast is interesting and may be related to differences in smoking habits between the sexes.

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6.19: Kidney and other urinary organs (ICD-9 189)
(M 4.8; F 2.1)

Renal cell carcinoma in adults represents around 80% of the cancers of the kidney, renal pelvis and ureter that are grouped together under this ICD code. In general, rates for renal pelvis and parenchymal cancers correlate well. In children, most of the cancers are nephroblastomas.

Overall, the mortality rate in the EU-EEA for cancer of the kidney and other urinary organs (kidney cancer) in males (4.8 per 100,000) was over twice that in females (2.1). There appears to be considerable variation in the national rates between countries.

International comparisons

In males, by far the highest national mortality rate was in the Czech Republic (10.8); several countries had rates between 6 and 8 per 100,000: Estonia (7.9), Lithuania (7.6), Latvia (6.9), Iceland (6.8), Hungary (6.6), Slovakia (6.4) and Poland (6.3) (Annex 2). The lowest rates were in Portugal (2.3), Greece (2.6), Spain (3.3) and Ireland (3.5).

In females, the highest national mortality rate was also in the Czech Republic (4.9), followed by Iceland (3.7), Estonia (3.3) and Lithuania (3.1). The lowest mortality rates were recorded in Portugal (1.0), Greece (1.1) and Spain (1.2).

Regional variation (box and whisker plots)

There was considerable variation in national mortality rates in both males and females [p. 242-243]. The within country variability was generally small in countries with low rates, but was wider in some countries with higher rates, particularly in females.

Description of the maps

The strongest feature of the geographic distribution of kidney cancer mortality in males is the strong gradient from the low rates in Portugal, Spain, southern Italy and Greece through rates generally close to the average in France, northern Italy, Switzerland, Slovenia, Belgium, The Netherlands and the United Kingdom and Ireland, to high rates in eastern Germany and Austria, the Czech Republic, and western parts of Poland, Slovakia and Hungary. Rates were also generally high in all three Baltic Countries. Mortality rates in all the Nordic Countries were generally close to the average [p. 242].

The map for females shows that both the between- and the within-country variability in mortality rates were closely similar to the patterns in males. There were generally low rates in Portugal, Spain, Italy and Greece and around average rates in Ireland, the southern parts of the UK, France, Belgium and Switzerland. High rates, as in males, occurred in northeast Germany, the Czech Republic, eastern Austria, and western Poland, Slovakia and Hungary, and in the Baltic Countries. Many areas in the Nordic Countries had above average rates in females but not in males [p. 243].

Statistical aspects

Overall regional variation was not very high, with RRSDs of 0.33 for males and 0.36 for females. For both males and females, Italy had the highest internal regional variation (RRSDs of 0.29 and 0.31, respectively). There was almost as much relative variation in Italy as there was in the whole of Europe. From the maps [p. 242-243] it can be seen that this manifests itself as an increase in rates from south to north. The spatial correlation of the rates was 0.63 for males and 0.54 for females, both around the middle of the range, but there was a high male-female correlation of 0.84 in line with the similar spatial patterns visible in the maps.

Comment

The incidence of kidney cancer increased at the end of the 20th century, rising by 38% over the period 1974-1990. An increased detection rate, with the use of newer radiological imaging techniques, appears responsible for much of the increased incidence. The

five-year survival observed in kidney cancer patients has improved from 52%, in patients diagnosed in 1974-1976, to 57% among patients diagnosed from 1990 to 1994. The gain in survival is in great part due to an earlier detection of localised resectable tumours; mortality from this malignancy has not declined over the same period. A rise in the detection of advanced kidney cancer has also been reported, pointing to a genuine increase in kidney cancer incidence.

Cancers of the upper and lower urinary tracts are important, although somewhat neglected, public health problems. Currently there are over 100 population-based cancer registries providing cancer incidence data of recognisably high-quality; the most recent data available cover the period 1998-2002 (Curado et al., 2007). Out of a total of over 7,000,000 cancer cases (excluding non-melanoma skin cancers) registered in males there were around 450,000 bladder tumours (6.4% of all cancer in males), 200,000 kidney cancers (2.9%), 80,000 testicular cancers (1.1%) and 15,000 cancers of the penis (0.2%). In total, just over 10% of all incident cancers in males world-wide occur at urological sites (other than prostate). In females, there were a total of 6,500,000 incident cases of cancer in the same populations. Of these, around 150,000 were bladder cancers (2.3% of all cancers in females) and 125,000 were kidney cancers (1.9%). A total of just over 4% of all cancers in females were of urological origin.

Cigarette smoking is the best identified aetiological agent and a major cause of bladder cancer, cancer of the renal pelvis and adenocarcinoma of the kidney, although the latter association remains less well quantified. There is no consistent evidence on the role of alcohol or methylxanthine-containing beverages on the risk of renal cell cancer. Historically, occupational exposures have been investigated as causes of bladder cancer, although the proportion of bladder tumours related to such exposures is probably in decline. Hormonal influences are frequently cited as being aetiologically important in cancers of the prostate and testis although the precise hormonal determinant(s) remains unclear and further research is needed. Dietary and nutritional factors appear to have essential roles in the aetiology of most forms of urological tumours although the risks and the mechanisms have yet to be established and quantified. Recent studies have investigated the roles of obesity, physical activity, hypertension, diuretics, and phenacetin and paracetamol abuse. Within the constraints of our knowledge, up to one half of urological cancers could be avoided, about one-third by cessation of cigarette smoking alone. The increases in the incidence of urological cancers should serve to focus activity on the development of programmes focused on primary prevention.

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6.20: Brain and central nervous system (ICD-9 191 and 192) (M 4.6; F 3.2)

Primary tumours of the brain and nervous system are not uncommon, but their reported incidence depends to some extent on the standard of medical care which is available and the ability to exclude metastatic tumours. Most of these neoplasms are intracranial, with intraspinal tumours representing about ten percent of the total. This disease group includes a disparate range of tumour types (including gliomas and meningiomas which are derived from different tissues) and the various histological types have different prognosis and biological behaviour.

Overall, the mortality rate in EU-EEA from cancer of the brain and central nervous system (brain cancer) was about 50% higher in males (4.6 per 100,000) than in females (3.2).

International comparisons

In males, the highest national mortality rates were in Greece (7.3), Hungary (6.5), Ireland (6.1), Iceland (6.0) and Poland (6.0) (Annex 2). The lowest mortality rates were in France (3.9), Italy (4.0), Latvia (4.2), Spain (4.2), The Netherlands (4.2), Portugal (4.3), Austria (4.3) and Norway (4.4).

In females, the highest national mortality rates were in Iceland (5.1), Greece (4.6), Hungary (4.5), Ireland (4.4), Luxembourg (4.3), Belgium (4.1), Finland (4.1) and Estonia (4.1). The lowest national rates were in France (2.6), Italy (2.7), Portugal (2.7), Spain (2.7) and The Netherlands (2.9).

Regional variation (box and whisker plots)

For both males and females, there were only low levels of variability in the mortality rates, both between and within countries [p. 244-245].

Description of the maps

In males, rates were generally low in the south and west of Europe, including Portugal, Spain, France, Italy, Switzerland, Austria and southern Germany. Rates were noticeably higher than average in most of Greece, Hungary, the Czech Republic, Slovakia and Poland, and in parts of northern Germany and Belgium [p. 244]. The map for females shows both that the between- and within-country variability in the rates were very closely similar to those in males [p. 245].

Statistical aspects

The RRSD for males was 0.18 (rank 21 of 22) and 76% of the total variation was associated with differences between countries. For females, the RRSD was 0.20 (rank 22 of 24) and 79% of the variance was associated with differences between the countries. The high regional component associated with country is mainly due to the generally higher rates in Greece, Ireland, Poland and Hungary and lower rates in France, Portugal, Spain and Italy.

Moran's I was 0.29 for males and 0.25 for females, both values towards the lower end of the range, and there was a correlation of 0.68 between the rates for males and females.

Comment

Epidemiological study of cancers of the brain and nervous system is greatly impaired for two reasons. First, there is a wide variety of distinct clinicopathological entities which appear in this disease group, some of which may be associated to varying degrees with different aetiological factors. Second, there are problems associated with the diagnosis of intracerebral and intraspinal tumours including differentiation between primary and secondary neoplasms; there is a related issue that many apparently benign neoplasms can be fatal depending on the exact anatomical site of the tumour and in consequence the degree to which benign tumours are recorded as malignant may vary. Analytical studies can be further hampered by difficulties in interviewing patients who may

have difficulty remembering or communicating responses regarding recent exposures or exposures in the distant past. Gliomas, meningiomas and other intracranial neoplasms have generally been grouped together in epidemiological studies despite the fact that gliomas and meningiomas are derived from different tissues and the various histological types have different prognosis and biological behaviour.

Adult brain tumours have been noted to occur more frequently in a number of different occupational groups including a number of professional and managerial occupations; some occupations with potential carcinogenic exposures in the workplace such as rubber industry workers; and in farming and the electrical industries. When cancer incidence rates are examined subdivided by histology, it has been found that the risk of astrocytoma was elevated among automobile repair workers, workers in justice, public order and safety, police and fire protection officers, and machinists; farmers had an increased risk for non-astrocytoma cell types. The risk of brain tumours has been shown to be increased by cigarette smoking but this has not been a consistent finding.

Primary tumours of the brain and nervous system are the second commonest cancer in children. Exposure to ionising radiation appears to be a risk factor for this form of cancer. Increased risk was found among children exposed in utero when mothers had pelvimetry late in pregnancy and among cohorts of children who received X-ray treatment for ringworm of the scalp. Tobacco smoke contains several known carcinogens and can induce DNA adducts in human placenta and haemoglobin adducts in foetuses. In a large, multicentre study, there was no association between the risk of brain tumours in the child and parental smoking prior to pregnancy, maternal smoking or regular exposure to others' cigarette smoke during pregnancy at home or at work, or passive smoking by the child during the first year of life. These results did not vary with the child's age at diagnosis, the histological type of tumour, or study centre.

The use of cellular phones and possible adverse health effects related to their use, attract much attention. Reports on brain tumour excesses occurring among phone users, case stories in the press and reports on thermal as well as magnetic effects on exposed tissue hypothesised to stimulate tumour growth, combined with the explosion in subscribers to cellular phones, raise public concern. The radiation from cellular phones is characterised as non-ionising alongside that from radar, microwave ovens and electrical wiring configurations. The radio frequency signals emitted from the devices range between 450 and 2200 MHz, i.e. in the microwave region of the electromagnetic spectrum. A recent comprehensive review on the epidemiological literature has been carried out and published by the Swedish Radiation Protection Authority. They conclude after review of nine major studies that no significant association was present between brain tumours and use of cellular phones, irrespective of duration of use, type of phone (digital or analogue), tumour morphology or laterality. The conclusions are supported by observing that there is no biological mechanism which supports a causal relation and there is no evidence of adverse effects from laboratory animals.

At present only a small proportion of brain tumours can be attributed to a defined cause; and there is more suspicion than proof surrounding the nature and weight of several other risk factors for tumours of the nervous system. There is nothing known about risk factors and their distribution in the European population which can explain the strong geographic patterns – so closely similar in males and females – observed in the maps.

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Chapter 6.21: Thyroid (ICD-9 193)
(M 0.4; F 0.5)

Thyroid cancer is relatively infrequent on a world-wide basis, representing 1-2% of all cancers, although in adolescents and young adults it is one of the most frequent neoplasms. Incidence rates are approximately three times higher in females than in males; the excess in females varies with age, being greater in the young. The majority of thyroid cancers are not fatal and there is a wide gap between incidence and mortality which must be borne in mind when examining geographical patterns in mortality.

Overall, mortality rates for thyroid cancer were low, with similar rates in males (0.4 per 100,000) and females (0.5) in the EU-EEA.

International comparisons

In males, the highest national mortality rates were in Austria (0.7) and Hungary (0.6); all other national rates were 0.6 or lower (Annex 2).

In females, the highest national mortality rates were in Hungary (0.8), Latvia (0.7), Slovakia (0.7), the Czech Republic (0.7), Lithuania (0.7) and Poland (0.7). All other national rates were 0.6 or lower.

Regional variation (box and whisker plots)

For both males and females, there was some variability between countries. As would be expected for rates based on small numbers of deaths, there was considerable variability in rates within countries [p. 246-247].

Description of the maps

In males, there appears to be an aggregation of high rates in the centre of Europe – the neighbouring countries of Austria, central and southern Germany, Switzerland and the west of the Czech Republic [p. 246]. There were generally low rates in the United Kingdom, Spain, Portugal, France and Greece.

In females, there was the same pattern of generally higher rates in Austria and adjacent countries, and mostly lower than average rates in much of western Europe [p. 247]. However, it must be kept in mind that all these mortality rates were very low in absolute terms.

Statistical aspects

There was average regional variability with RRSDs of 0.37 for males and 0.32 for females. There was some evidence of a country based pattern, with 76% of the regional variation in the rates for males associated with country and 70% for females. There was a tendency for higher rates in both sexes in Austria and in the former communist countries of central Europe.

Spatial autocorrelation was very low for both males and females with Moran's I values of 0.18 and 0.20, respectively; these were the lowest value for males and the second lowest for females. It can clearly be seen in the maps that for both sexes there are very scattered patterns of red and green areas and no aggregations of higher or lower rates except possibly in Austria. In part, this is because the numbers of deaths in most regions were very low, resulting in apparent random variation in the mortality rates. There was a spatial correlation of 0.53 between the rates for males and females.

Comment

Thyroid cancer is a rare form of cancer in general, but it is characterised by the wide variation in the degree of malignancy exhibited by the various histological types ranging over a whole spectrum from relatively benign to rapidly fatal. There is evidence that in many developed countries mortality has been decreasing while incidence has been increasing. Many factors complicate the interpretation of thyroid cancer trends, in large part because of the widening of the concept of thyroid malignancy since the early 1960s with the increasing emphasis on cytological rather than on architectural features and the subsequent inflation of thyroid cancer incidence rates. This change in attitude has been paralleled

by the spread of scintigraphy and fine needle biopsy and the increasingly aggressive approach to the management of thyroid nodules.

Ionising radiation is the only definitely established cause of thyroid cancer in humans, although only a small proportion of thyroid cancers can be accounted for by radiation. The thyroid tissue is particularly susceptible to radiation at young ages, and considerable excess rates have been observed in Hiroshima and Nagasaki, as well as in subjects irradiated for thyroid hypertrophy during childhood. The risk was elevated 20-fold for the papillary type and 50-fold for the follicular type in subjects irradiated below the age of 20 years. The thyroid gland is highly susceptible to ionising radiation presumably because of its superficial location, high level of oxygenation, and high cell turnover rate.

A pooled analysis of seven studies revealed that thyroid cancer was induced even by low doses of brief external gamma radiation in childhood, but rarely developed after exposure in adulthood. Data from the atomic bomb survivors underline the strong modifying effect of age at exposure, with no excess risk seen in individuals older than 20 years. The Chernobyl nuclear accident in April 1986 led to a massive release of radionuclides into the environment. Although vast areas of Europe were affected by Chernobyl-related ionising radiation, the accident had the greatest impact in Belarus, Ukraine, and the Russian Federation. Epidemiological studies that have investigated the link between the Chernobyl accident and cancer have largely focused on malignant diseases in children, specifically thyroid cancer and leukaemia. During the first fourteen years after the Chernobyl accident, approximately 1,800 thyroid cancers were diagnosed in the three most contaminated countries among children younger than 15 years, whereas only 3-4 childhood thyroid cancers were registered in the same area annually before the accident. No increased thyroid cancer as a consequence of the Chernobyl accident has been identified in adults.

The major concern regarding medical use of ionising radiation has been the possibility that thyroid examinations or treatments using radioiodine causes thyroid cancer. The annual number of thyroid examinations using radioiodine is currently 5 per 1000 individuals in the western world. Patients treated with ^{131}I for hyperthyroidism are almost all adults and no increased risk of thyroid cancer is seen among these patients. A study which estimated thyroid cancer risk in a cohort of 35,074 Swedish subjects who had been subjected to diagnostic ^{131}I with an average dose of 1.92 megabecquerel (0.5 Gy to the thyroid itself) and followed up for 20 years found 50 incident cases of thyroid cancer compared with 39.4 expected (Standardised Incidence Ratio 127, 95% Confidence Interval (94, 167)). These results were fairly reassuring, although thyroid cancer risk was found to be highest among those receiving the highest dose of ^{131}I. However, such observations could be confounded by those individuals receiving the highest doses being suspected of having thyroid disease. Prior thyroid diseases, benign nodules and goitre are also associated with substantially elevated risk.

Differences in iodine intake may be one factor explaining the geographic variation in incidence, high iodine intake being associated with a slightly increased risk of developing thyroid cancer. In general, lifestyle factors have only a small effect on the risk of thyroid cancer. The thyroid gland is highly sensitive to radiation-induced oncogenesis. This is verified by numerous reports from survivors after Hiroshima and Nagasaki, and from the Nevada, Novaja Semlja and Marshal Island atmospheric nuclear tests, as well as by investigations of earlier medical use of radiation for benign diseases in childhood. The thyroid gland of children is especially vulnerable to the carcinogenic action of ionising radiation and there appears to be a dose-response relation for the risk of developing cancer after exposure to radioactive iodine.

Apart from these factors, there is little conclusively known about the aetiology of thyroid cancer. The long suspected influence of iodine deficiency is not totally understood. Two current areas of epidemiological interest are diet and female hormones, thyroid cancer being one of the few cancers where the incidence rate is higher in females. With reference to diet, the scanty available data tend to suggest that a poorer diet, particularly if containing natural goitrogens, is related with elevated risk. Positive associations have also been reported with nulliparity, late age at first birth and the use of oral contraceptives or menopausal replacement treatment, but the evidence on these is still open to debate.

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6.22: **Hodgkin's disease** (ICD-9 201)
(M 0.7; F 0.4)

Hodgkin's disease is nowadays a highly curable neoplasm. Development of successful therapy for this malignancy is a great success for medical oncology. Hodgkin's disease is unusual among human malignancies in that the epidemiology suggests an infectious aetiology.

Overall in the EU-EEA, mortality in males (0.7 per 100,000) was about 65% greater than in females (0.4). These overall rates were very low, representing less than 0.5% of those for all cancers in both males and females.

International comparisons

In males, the highest national mortality rates were in Lithuania (1.4), Poland (1.4), Estonia (1.3), Latvia (1.2), Austria (1.2), the Czech Republic (1.2) and Greece (1.1) (Annex 2). The lowest national rates were recorded in Sweden (0.3), Norway (0.4), France (0.4) and Switzerland (0.4). No deaths were recorded from this cause among males in Iceland during this period.

In females, the highest mortality rates were in the Czech Republic (0.8), Austria (0.8), Lithuania (0.8), Latvia (0.8), Estonia (0.7) and Poland (0.7). Rates in most of the other countries were 0.2 to 0.4 per 100,000.

Regional variation (box and whisker plots)

There was considerable variation, four- to five-fold, in rates between countries for both males and females [p. 248-249]. As would be expected because the rates for small areas were generally based on very low numbers of deaths, there was very wide variability in the rates between countries.

Description of the maps

High mortality rates for Hodgkin's disease in males were found in much of central Europe: the eastern parts of Austria, and across the former communist countries – the eastern part of Germany, Slovenia, Hungary, the Czech Republic, Slovakia, Poland and the Baltic Countries; rates were also high in many regions of Greece. Rates were generally low in the western parts of Austria and Germany, as well as in the rest of western mainland of Europe and all the Nordic Countries [p. 248].

In females, the pattern was closely similar to that in males, with high rates across the former communist countries in central Europe and in Greece, and generally low rates in western Europe and the Nordic Countries [p. 249].

Statistical aspects

For both males and females the regional variation in the mortality rates for Hodgkin's disease was in the middle of the range, with RRSDs of 0.48 in males and 0.42 in females. There was extremely high internal regional variation within Austria, with RRSDs of 0.86 for males and 0.81 for females, associated with high rates in two regions in the east compared with the low rates in the other regions in Austria. There was some evidence of mortality differences between the countries, with 68% of the total regional variation associated with between country differences for males and 65% for females.

Spatial correlation was low, with Moran's I of 0.35 for males (rank 17 of 22), and 0.21 for females (rank 21 of 24). The correlation between the male and female rates was moderate at 0.56.

Comment

Hodgkin's disease is characterised by the presence of the Reed-Sternberg giant cell. Hodgkin's disease has been one of the few neoplasms for which considerable advances in survival have been achieved over the past twenty years through the impact of effective treatment. The disease has a bimodal age curve: incidence rates rise early in life, peak in the late 20s and then decline to around age 45. Thereafter the incidence subsequently increases with age. One

suggested explanation this bimodal distribution is that Hodgkin's disease may be the result of two distinct aetiological processes. This notion is supported by the observation that among younger adults, 15 to 39 years of age, Hodgkin's disease of the nodular sclerosing type predominates but at older ages the predominant type changes to the mixed cellularity form.

MacMahon (1957) first made the observation that Hodgkin's disease in young adults could have an infectious aetiology; the similarity of its age distribution with that of paralytic poliomyelitis and Epstein-Barr Virus (EBV) infections led to the formulation of the 'late-host-response' model. This excludes the effect of direct contagion but proposes that early exposure to some relatively common agent is benign and confers subsequent immunity but later exposure can (although not commonly) lead to Hodgkin's disease. Evidence supporting this hypothesis is found in a variety of studies linking limitation of childhood social contacts and higher childhood social class with subsequent increased risk of Hodgkin's disease.

Studies of space-time clustering have generally been inconsistent but more recent investigations of purely spatial clustering have consistently shown evidence of weak clustering. The overall results available suggest that shared social experience during childhood and adolescence may be a feature of subsequent Hodgkin's disease. Elevated risks of disease have been recorded among agricultural workers, who presumably are more likely to live in isolated areas, although other possible aetiological factors such as exposure to pesticides have to be considered. Some studies have reported increased risk of Hodgkin's disease associated with employment in wood-related industries, the chemical industry and among schoolteachers, although the evidence is not conclusive. It is not possible to provide quantitative estimates of the attributable risk for various occupational exposures. Other factors investigated including reproductive patterns, motivated by the observation of a lower incidence in females during reproductive life, and tonsillectomy, offer little consistent support for association.

Infectious agents are known or suspected to play a major role in haemo-lymphopoietic tumours (non-Hodgkin's lymphoma, Hodgkin's disease and leukaemia). Certain viruses (Epstein Barr virus (EBV); human immunodeficiency virus (HIV); human-T-cell leukaemia/lymphoma virus 1; Herpes Simplex type 8; and HCV and HPV) account for an ill-defined proportion of non-Hodgkin's lymphoma and Hodgkin's disease. Highly active anti-retroviral therapy (HAART) has had a favourable impact on the occurrence of Kaposi's sarcoma, but not, for the moment, of non-Hodgkin's lymphoma in HIV-infected patients (International Collaboration on HIV and Cancer, 2000). Recognising and treating infections linked to haemo-lymphopoietic tumours is a priority in the EU, on account of the steady increase in the number of cases and high-risk individuals (e.g. iatrogenically immuno-suppressed and HIV-positive subjects).

To determine the incidence of non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) in the United Kingdom haemophilia population during the 22 year period 1978-1999, an analysis of patient data included on the UK Haemophilia Centre Doctors' Organisation Lymphoma Register was conducted. The incidence of NHL in the HIV-positive cohort was significantly increased, with a ratio of observed to expected cases of 84 ($P < 0.001$) in the period 1985-1996. The ratio reduced to 42 during the period 1997-1999, presumably as a consequence of the introduction of HAART. There was a significant excess of HD in HIV-positive patients, with an observed to expected ratio of 10.5 between 1985 and 1999 (based on five cases, $P < 0.001$). During the whole observation period, there was a significant excess of HD in HIV-negative patients, with an observed to expected ratio of 2.66 (based on eight cases, $P < 0.05$). The incidence of lymphoma is significantly higher in HIV-positive UK haemophilia patients compared with HIV-negative individuals. Since the introduction of HAART, the incidence of lymphoma has tended to fall in the HIV-positive group.

The Epstein-Barr virus (EBV) is associated with a proportion of cases and this association is believed to be causal. In these cases the Hodgkin and Reed-Sternberg (HRS) cells express the EBV-encoded proteins LMP1 and LMP2, which can mimic CD40 and the B cell receptor, respectively, and therefore may play a critical role in facilitating the survival of HRS cells. EBV-associated and

non-EBV-associated Hodgkin's disease cases have different epidemiological features and recent data suggest that delayed exposure to EBV is a risk factor for the development of EBV-associated Hodgkin's disease in young adults. It has been suggested that Hodgkin's disease can be divided into four entities on the basis of EBV status and age at presentation, with three groups of EBV-associated cases and a single group of EBV-negative cases. The aetiology of the latter cases is obscure although involvement of an infectious agent(s) is suspected.

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6.23: Non-Hodgkin's lymphoma (ICD-9 200 and 202) (M 4.3; F 2.7)

Historically, reticulum cell sarcomas were generally more common, by 30%, than lymphosarcomas in most populations, irrespective of the overall incidence. However, due to temporal and geographical variations in coding practice of non-Hodgkin's lymphoma it is difficult to make such comparisons at the present time with any degree of certainty. Burkitt's lymphoma remains a distinct pathological entity, arising from B-lymphocytes, occurring among children in both sexes and often involving the jaw or ovary. However, it is a rare cause of death in Europe.

Overall in the EU-EEA, the mortality rate from non-Hodgkin's lymphoma was about 60% higher in males (4.3 per 100,000) than in females (2.7), but in both sexes the rate was around 2.5% of that for all cancer deaths. In all countries, mortality was higher in males than in females and, apart from the very low rates in Greece, there was about a two-fold range in rates across the countries (Annex 2).

International comparisons

In males, the highest national mortality rates were recorded in Finland (5.6), The Netherlands (5.2), Sweden (5.1) the United Kingdom (5.1) and Norway (5.0) (Annex 2). The lowest rates were recorded in Greece (1.4), Slovakia (2.2), Lithuania (2.4) and Latvia (2.8).

In females, the highest national mortality rates were in Finland (3.9), Norway (3.4), The Netherlands (3.3), the United Kingdom (3.3) and Ireland (3.2). The lowest rates were recorded in Greece (0.9), Lithuania (1.3), Latvia (1.4), Slovakia (1.5) and Poland (1.6).

Regional variation (box and whisker plots)

There was moderate variation in national mortality rates for both males and females, but relatively little variation between countries for either sex [p. 250-251].

Description of the maps

In males, there were high regional mortality rates in the south of Norway, Sweden and Finland, in the United Kingdom and in northern Italy [p. 250]. There were aggregations of low rates in the Baltic Countries, much of central Europe including Austria, and southern Italy, Spain, Portugal and Greece.

The broad geographical pattern of the variability in mortality rates in females was very closely similar to that for males, with high regional rates in parts of Norway, Sweden and Finland, in the United Kingdom, and northern, but not southern, Italy [p. 251]. There were aggregations of low rates in central and southern Europe.

Statistical aspects

There was smaller regional variability in the mortality rates for non-Hodgkin's lymphoma than for Hodgkin's disease, but, as with Hodgkin's disease, the regional variability in males was similar to that in females, with RRSDs of 0.27 and 0.31, respectively. There was evidence of a regional pattern associated with countries as 88% and 90% of the regional variation was associated with differences between countries for both males and females, respectively.

There was moderate spatial correlation with Moran's I of 0.51 for both males and females. There was, however, a high correlation of 0.81 between the rates for males and females – this can be seen immediately in the maps.

Comment

This disease group includes a wide spectrum of cyto- (and almost certainly aetio-) pathological entities whose incidence and mortality have generally been rising in most developed countries during the past decades, possibly in association with generalised improvements in diagnosis and certification.

For some histological types there is a recognised viral aetiology, as, for example, in Burkitt's lymphoma. This disease is a well-defined patho-clinical entity comprising an undifferentiated, monoclonal lymphoma composed of malignant B-cells. It is common in children in many parts of sub-Saharal Africa where the incidence rate is up to 8 per 100,000 compared with the usual 0.1 to 0.3 per 100,000 in European populations of children. Burkitt's lymphoma has been associated with endemic malaria and there is evidence that successful chemotherapy for malaria is associated with a reduced incidence of the disease. Markers of Epstein-Barr Virus (EBV) (DNA or antigens) are found in 96% of tumours from subjects living in endemic areas of Africa but in only 15% of the so-called sporadic tumours: the corollary is that EBV is unlikely to be involved in the aetiology of Burkitt's lymphoma in 85% of the cases outside Africa.

B-cell lymphomas occur more frequently than expected in subjects with depressed immunological systems and most of these lymphoproliferations are (at least at the beginning of the disease) polyclonal B-cell malignancies – in contrast to the monoclonal Burkitt's lymphoma. The rate of these malignancies is observed to be considerably elevated in organ transplant recipients, who are treated with immunodepressants to reduce the risk of organ rejection, and among patients with virus-induced immunodeficiencies such as acquired immunodeficiency syndrome (AIDS) or genetic immunodeficiencies. Interestingly, the increased risk among transplanted organ recipients has a short latency of between several months and a few years after starting treatment. Aetiological links with aspects of disturbed or aberrant immunity were first suggested by a British case-control study which showed significant associations with past history of several diseases including skin conditions, malignancies, pneumonia, scarlet fever and diabetes.

Higher risk of non-Hodgkin's lymphoma has been associated with agricultural activity; this may be reconciled with a possible viral aetiology, although exposure to phenoxy-acid herbicides, chlorophenols, organic solvents and insecticides have also been postulated as being involved in the aetiology of this group of diseases. Increased risks have also been suspected among workers exposed to wood, meat and other food processing and certain chemical agents.

Cancer remains a significant burden for human immunodeficiency virus (HIV)-infected individuals. Most cancers that are associated with HIV infection are driven by oncogenic viruses, such as EBV, Kaposi's sarcoma-associated herpesvirus (KSHV) and human papillomavirus. Gaining insight into the epidemiology and mechanisms that underlie AIDS-related cancers has provided us with a better understanding of cancer immunity and viral oncogenesis. While Kaposi's sarcoma is the most common neoplasm that occurs in patients with AIDS (AIDS-KS), AIDS-lymphoma is a significant cause of morbidity and mortality in human immunodeficiency virus (HIV)-infected individuals. Over 50% of AIDS lymphomas are associated with EBV and/or KSHV infection. EBV activates B-cell precursors, leading to a transformed phenotype.

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6.24: **Multiple myeloma** (ICD-9 203)
(M 2.1; F 1.5)

Multiple myeloma, originally classified as a bone tumour, was recognised as a separate entity in the early 1950s. Diagnosis of multiple myeloma has greatly improved following the introduction of newer diagnostic techniques such as serum electrophoresis, in whose absence several deaths from multiple myeloma were missed and attributed to renal insufficiency or infections. There is a strong age dependence in incidence, with a rather late age of onset.

Overall in the EU-EEA, mortality from multiple myeloma was around 40% higher in males (2.1 per 100,000) than in females (1.5). Rates in each country were higher in males than in females; and across the EU-EEA the ratios of the rates in males and females were very close to the overall average of 1.4:1.

International comparisons

In males, the highest national rates were in Ireland (3.2), Norway (3.1) and Iceland (3.0) (Annex 2). The lowest rates were in Poland (1.4), Latvia (1.4), Greece (1.5), Lithuania (1.5) and Estonia (1.5).

In females, the highest national rates were in Norway (2.1), Ireland (2.1), and Iceland (2.0). The lowest rates were in Greece (0.7), Estonia (0.9), Latvia (1.0), Poland (1.1), Portugal (1.2), Lithuania (1.2) and Slovakia (1.2).

Regional variation (box and whisker plots)

There was about a two-fold range in the national rates in both males and females, and generally low levels of variability in regional rates within countries [p. 252-253].

Visual Description of the Maps

In males, regions with high rates were apparent in the Nordic Countries, Ireland and the United Kingdom, and in Belgium, The Netherlands and in northern Germany. In central and southern Europe, regional rates were generally low [p. 252].

The map for females shows substantially the same pattern of variability as that for males. There were high rates in Iceland, southern parts of Norway, Sweden and Finland, in northern Denmark and Germany, and in Ireland and the United Kingdom. Rates were low in most regions of central and southern Europe [p. 253].

Statistical aspects

Multiple myeloma exhibited a low level of regional variation: for males the RRSD was 0.20 (with rank 19 of 22) while for females it was 0.23 (rank 20 of 24). As with NHL and leukaemia, a large percentage of variation was associated with differences between countries: 86% for males and 83% for females. This is due to slightly, but consistently, higher rates in Scandinavia, the United Kingdom and Ireland, and lower rates throughout the Baltic Countries, Poland, Hungary and Greece. There was large internal variation within Germany, where the RRSDs were 0.27 for males and 0.31 for females. This was not associated with an obvious geographic pattern.

There was a low spatial autocorrelation of 0.33 for both males and females. The correlation between the rates for males and females was quite high at 0.71

Comment

Increases in the incidence of multiple myeloma during the 20th century implicate environmental factors as important causal agents. The molecular and cytogenetic alterations which occur in multiple myeloma are under investigation, but the precise causes of these abnormalities are largely unknown. Exposure to chemical substances and ionising radiation are associated with an increased risk of multiple myeloma. A single exposure is probably not sufficient to induce the disease, which results from the clonal expansion of an idiotypic plasma cell after cumulative mutational damage has altered its genetic makeup. Multiple myeloma does not have the same biology in all patients; it is best viewed as a heterogeneous disease with a different prognosis, clinical course, and response to therapeutic interventions in different subjects.

Ionising radiation is the single established risk factor for multiple myeloma. An overview of several cohorts of irradiated subjects has shown an approximately threefold elevated incidence of myeloma. As with many kinds of leukaemia, multiple myeloma can be produced by irradiation to the bone marrow. A small increased risk of multiple myeloma was observed in atomic bomb survivors and among patients treated by radiotherapy for cervical cancer. The increase became evident after a longer latent period than for leukaemia. Other studies carried out among personnel employed in the nuclear industry have not reported any consistent increase in multiple myeloma.

This association is interesting since, although radiation is linked to myeloid leukaemia, there is little evidence of association with chronic lymphatic leukaemia which, like myeloma, is a tumour of B lymphocytes. The elevated risk of myeloma becomes evident ten years after exposure, and persists up to 30 years.

Other risk factors are largely undefined. Occupational exposures to asbestos and lead have been sporadically reported, and an excess of myeloma in farmers, agricultural workers and wood workers has been found. This may be related to infectious agents, as are sporadic clusters of myeloma in families. Along the same lines, associations have been suggested with history of autoimmune diseases or other chronic antigenic stimulations, but the evidence on these is largely inconsistent.

Our current knowledge of aetiological factors for multiple myeloma cannot explain the geographic mortality patterns in the EU-EEA.

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6.25: Leukaemia (ICD-9 204-208)
(M 5.5; F 3.4)

The leukaemias are a group of cancers having their origin in cells that arise from bone marrow and circulate in peripheral blood. Leukaemias are classified by cell type in the International Classification of Diseases, distinction between the acute and chronic forms being made at the fourth digit level. However, the precise type of leukaemia is poorly recorded on death certificates and the enforced aggregation of data into a single group results in a considerable loss of information.

Overall, leukaemia had mortality rates in the EU-EEA of 5.5 per 100,000 in males and 3.4 in females. These rates were each just over 3% of the corresponding rates for all cancer deaths. Rates in each country were higher in males than in females and across the EU-EEA the ratios of the national rates in males and females were very close to the overall average of 1.6:1.

International comparisons

In males, the highest national mortality rates recorded were in Luxembourg (7.6), Hungary (7.2), the Czech Republic (6.8) and Lithuania (6.7) (Annex 2). The lowest rates were in Finland (4.4), Norway (4.4), Sweden (4.6) and the United Kingdom (4.6).

In females, the highest national mortality rates were in Hungary (4.6), Estonia (4.6), the Czech Republic (4.2), Lithuania (4.1) and Latvia (4.0). The lowest rates were in Iceland (2.3), Norway (2.8), Finland (2.8) and Switzerland (2.9).

Regional variation (box and whisker plots)

There was very little variation in the mortality rates between countries in either males or females, with the vast majority of rates clustered closely around the respective EU-EEA average. There was moderate variability in rates within countries [p. 254-255].

Description of the maps

In males, the features of the geographic distribution are the generally low rates in the Nordic Countries and most of the United Kingdom and Ireland, and the areas of above average rates in parts of the Baltic Countries (particularly Lithuania), the Czech Republic and Hungary, southern Belgium and Luxembourg, and central and northern Italy [p. 254].

The patterns in the variability in the rates in females were closely similar to those in males: generally low rates in the Nordic Countries (except Denmark) and the United Kingdom, and areas of high rates in the Baltic Countries, the Czech Republic and Hungary [p. 255].

Statistical aspects

Leukaemia exhibited the smallest RRSD of all the cancers, for both males and females, with values of 0.14 for both sexes, i.e. there was very low relative regional variation in the mortality rates. There was some evidence of differences among the countries with just over 80% of the variance associated with country differences for both males and females. This was associated with slightly higher rates in Hungary, the Czech Republic and Lithuania and slightly lower rates in the United Kingdom and the Nordic Countries (except Denmark).

Overall there was little spatial correlation, with Moran's I of 0.20 for males and 0.16 for females. These were the lowest value for females and the second lowest for males. The correlation between the mortality rates for males and females was 0.52. Overall, this cancer site had virtually no regional variation and no spatial aggregation.

Comment

Ionising radiation is an undoubted cause of leukaemia and the observations originally made from the survivors of the atomic bombs in Hiroshima and Nagasaki have never seriously been challenged. Age at exposure influences both the type of the resulting leukaemia and the latent interval: the younger the age at exposure the more likely it is that acute lymphoblastic leukaemia (ALL) will occur after a short latent period. With first exposure at older

ages, it is more likely that acute myeloid leukaemia (AML) will be produced after a much longer latency. Chronic myeloid leukaemia (CML) appears at any age and apparently the same rate. Approximately one in 450 of individuals exposed to radiation from the explosion of atomic devices in Japan developed leukaemia, as did subjects in the two major studies of iatrogenic radiation and its sequelae.

The situation regarding leukaemia risk and exposure to low doses of ionising radiation remains controversial. There is a degree of consensus regarding the increased risk of childhood leukaemia associated with in utero X-ray exposure. These X-ray exposures appear to confer a modest risk increase which has now largely disappeared as a result of a combination of changes in clinical practice and changes in the X-ray equipment which have resulted in lower doses. No excess leukaemia risk has been shown to result as a consequence of the similarly small doses received in diagnostic procedures by children postnatally or by adults. Similarly, the radiologists themselves have little or no apparent increase in risk nowadays.

Various studies have been carried out of cancer rates in the vicinity of nuclear installations in recent years, mostly in Western Europe and North America; there does not appear to have been a general increase in rates of adult cancers around nuclear installations. Some – but not all – studies have indicated increased rates of childhood cancers and particularly childhood leukaemia. The evidence for such increases has tended to be strongest in the vicinity of the nuclear reprocessing plants; in particular, Sellafield and Dounreay in the UK and, to a lesser extent, La Hague in France. Assessments of radiation doses to those living near these installations do not suggest that the raised childhood leukaemia risks can be explained on the basis of radioactive discharges. Non-radiation factors such as population mixing have been mentioned as possible explanations for the raised risks, but it is unclear whether these factors could explain all of the results.

Many studies have been carried out of cancer among nuclear industry workers. Some of the worker studies have been limited by relatively small population sizes and/or short follow-up periods. The larger studies include a combined analysis of about 95,000 workers in Canada, the US and the UK, and cohorts of over 100,000 nuclear workers in Japan (although with a short follow-up) and the UK. Most of the analyses have looked only at mortality. There has been some variation in the findings, which may be due in part to low statistical precision. However, mortality has often been lower than in the general population, due probably to factors associated with selection into and continuation of employment. The larger studies have tended to indicate an increasing trend in leukaemia risk with increasing dose, whereas the evidence for a dose-related increase in solid tumour risks has generally been less. However, the confidence limits for these trend estimates have been relatively wide, and encompass risks extrapolated from the Japanese atomic bomb survivors as well as a range of values, both higher and lower.

Power lines produce extremely low frequency (ELF) electromagnetic fields in range of 50 Hz to 60 Hz. Electric fields do not reach people inside houses but magnetic fields go through most materials and cause an additional exposure higher than the typical background field (about 0.1 μT) up to a distance roughly 50 meters from the power line, depending on the voltage and wire configuration. Health effects on humans related to this non-ionising type of radiation have been investigated in epidemiological studies for over two decades.

The first report of an association between childhood cancer and power line exposure was published in 1979, and after that at least 24 studies on the same topic have been published. There are two meta-analyses published lately which both show a significant 1.7 to 2.0-fold excess of childhood leukaemia in the extremely rarely existing fields above 0.3 or 0.4 μT. Part of the excess may be attributable to patient selection and publication bias, and a plausible biological mechanism is not known.

It appears on the basis of studies with large numbers of cancer cases that there is no excess risk of cancer among adults living close to power lines, but the results of occupational studies are suggestive of an association with some cancers including adult leukaemia. The results of epidemiological studies suggest that appreciable magnetic field effects, if any, are concentrated among relatively high and uncommon exposures.

A number of studies have examined possible links between various chemical exposures and several

types of leukaemias, producing an unconvincing array of positive, negative and null findings. The best known risks are those resulting from exposures to chemotherapeutic agents used in the treatment of prior malignant diseases, producing mainly adult acute myeloid leukaemia in adults, and the increased risks of a variety of adult leukaemias and myelodysplasias associated with chronic benzene exposures. A number of studies have suggested a link between employment in agriculture and increased risk of leukaemia.

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6.26: All forms of cancer (ICD-9 140-208)
(M 177; F 100)

Overall, in the EU-EEA, the mortality rate from all forms of cancer was almost 80% higher in males (177 per 100,000) than in females (100 per 100,000). Rates were higher in males than in females in every one of the EU-EEA countries. Rates in males were only 10-30% higher than in females in three of the Nordic Countries: Denmark, Iceland and Sweden; but were around twice as high as in females in France and Spain, and in most of the former communist countries in central Europe: the Baltic Countries, the Czech Republic, Hungary, Poland, Slovakia and Slovenia.

International comparisons

In males, the highest mortality rate for all cancers combined was in Hungary (268 per 100,000), around 20% higher than the rates in the Czech Republic (228) and Slovakia (218) (Annex 2). All the other former communist countries had rates around 200 per 100,000: Estonia (206), Poland (205), Slovenia (202), Lithuania (201) and Latvia (198). The highest rates in western Europe were in Belgium (194) and France (188). The lowest cancer mortality rates in males were in Sweden (121), Iceland (138) and Finland (139).

In females, the highest national cancer mortality rates were in Denmark (139) and Hungary (138). Rates were around 20% above the average in the Czech Republic (125), Iceland (122), Ireland (118) and the United Kingdom (117). The lowest rates were in Greece (76), Spain (78), Portugal (84), France (84) and Finland (85).

Regional variation (box and whisker plots)

There was variation in the mortality rates between countries for both males and females. There was much wider variability in rates within some countries than in others, particularly in males. The pattern of the variability in males, with high rates in all central Europe and generally low rates in western Europe was, however, not the same as that in females, where the rates in most of central Europe were around the average [p. 258-259].

Description of the maps

In males, the high total cancer mortality rates across the whole of Hungary extend both northwards into Slovakia, the Czech Republic (particularly its western part), western and northern Poland, northeast Germany and the Baltic Countries – and southeastwards into Slovenia and northern Italy. Rates were generally low in Greece, southern Italy, Portugal, large parts of Spain, and Switzerland, Austria and southern Germany as well as in the United Kingdom, Ireland and the Nordic Countries [p. 258].

The geographical pattern of the variability in the mortality rates for all cancers combined in females was similar to that in males in some respects, but very different in others. As in males, rates were high across all of Hungary, the Czech Republic (particularly its western part) and western and northern Poland; and low rates were found throughout Spain and Portugal, central and southern Italy, and Greece [p. 259]. Unlike in males, however, there were high rates in Denmark and in the United Kingdom and Ireland, the rates in the Baltic Countries were only around the average, and rates in almost the whole of France were low.

Statistical aspects

The regional variation in the mortality rates for all cancers was low (RRSDs of 0.17 in both males and females); and for both sexes just over 80% of variability was associated with differences between countries. This confirms the visual impression of the maps where the rates tend to be consistently higher or lower than average in any particular country, but there is general uniformity in the colours of the regions within countries. Exceptions to this were Italy, with lower rates in the south than in the north (especially for males), and Poland, with lower rates in the east than in the northwest.

There was evidence of spatial autocorrelation in males (Moran's I of 0.77) and in females (0.78).

The correlation between the rates for males and females was quite low at 0.44; this reflects the differences in the rates between the sexes described above.

Comment

The pattern of high cancer mortality rates in males appears to be dominated by those regions where mortality from smoking- and alcohol-related cancers was particularly high – such as in some, but not all, of the former communist countries in central Europe and in northern France. The pattern of high rates in females appears to be dominated by areas where lung cancer or breast cancer mortality (or both) was high – such as Hungary, parts of the Czech Republic and Poland, Denmark, the United Kingdom and Ireland.