43. Raghavachar A, Thiel E, Bartram CR. Analysis of phenotype and genotype in acute lymphoblastic leukaemias at first presentation and in relapse. *Blood* 1987, **70**, 1079–1983.
44. von Lindern M, Poustka A, Lerach H, Grosveld G. The t(6;9) chromosome translocation associated with a specific subtype of acute nonlymphocytic leukemia leads to aberrant transcription of a target gene on 9q 34. *Mol Cell Biol* 1990, **10**, 4016–4026.
45. Toksoz D, Farr CJ, Marshall CJ. *ras* genes and acute myeloid leukaemia. *Br J Haematol* 1989, **71**, 1–6.
46. Senn HP, Tran-Thrang C, Wodnar-Filipowicz A, *et al.* Mutation analysis of the N-*ras* proto-oncogene in active and remission phase of human acute leukemias. *Int J Cancer* 1988, **41**, 59–64.
47. Senn HP, Jiricny J, Fopp M, Schmid L, Moroni C. Relapse cell population differs from acute onset clone as shown by absence of the initially activated N-*ras* oncogene in a patient with acute myelomonocytic leukemia. *Blood* 1988, 72, 931–935.
48. Farr CJ, Saiki RK, Erlich HA, McCormick F, Marshall C. Analysis of *ras* gene mutations in acute myeloid leukemia by polymerase chain reaction and oligonucleotide probes. *Proc Natl Acad Sci USA* 1988, **85**, 1629–1633.
49. Kwok S, Higuchi R. Avoiding false positives with PCR. *Nature* 1989, **339**, 237–238.
50. Lo YMD, Patel P, Wainscoat JS, Sampietro M, Gillmer MDG, Fleming KA. Prenatal sex determination by DNA amplification from maternal peripheral blood. *Lancet* 1989, **ii**, 1363–1365.
51. Martens ACM, Schultz FW, Hagenbeek A. Nonhomogeneous distribution of leukemia in the bone marrow during minimal residual disease. *Blood* 1987, **70**, 1073–1078.
52. Fujimura FK, Northrup H, Beaudet AL, O'Brien WE. Genotyping errors with the polymerase chain reaction. *N Engl J Med* 1990, **322**, 61.
53. Kohler S, Galili N, Sklar JL, Donlon TA, Blume KG, Cleary ML. Expression of *bcr/abl* fusion transcripts following bone marrow transplantation for Philadelphia chromosome-positive leukemia. *Leukemia* 1990, **4**, 541–547.
54. Sawyers CL, Timson L, Kawasaki ES, Clark SS, Witte ON, Champlin R. Molecular relapse in chronic myelogenous leukemia patients after bone marrow transplantation detected by polymerase chain reaction. *Proc Natl Acad Sci USA* 1990, **87**, 563–567.

Acknowledgements—Research was supported by grants from the Swiss National Science Foundation (31.9392.88 (M.F.F.) and 31.9141.87 (A.T.)), the Deutsche Forschungsgemeinsschaft (A.E.K.) and the Deutsche Krebshilfe (T.E.H.H.). We thank Prof. C.R. Bartram (Ulm) for critical comments on the manuscript.

Eur J Cancer, Vol. 27, No. 1, pp. 94–104, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Smoking and Cancer with Emphasis on Europe

C. La Vecchia, P. Boyle, S. Franceschi, F. Levi, P. Maisonneuve, E. Negri, F. Lucchini and M. Smans

A summary of smoking and cancer in various European countries is presented. Important points are the tobacco/alcohol interaction in the elevated mortality rates from upper digestive and respiratory tract neoplasms in France and other southern European countries, the delay in the lung cancer epidemic in females compared with the situation in North America (with the major exception of the United Kingdom) and the different pattern of lung cancer rates in younger compared with older generations (which suggests that eastern and southern European countries will have the highest lung cancer rates at the beginning of the next century in the absence of urgent intervention). The efficacy of anti-smoking policies in Scandinavian countries which now have the lowest lung cancer rates in Europe and the persisting importance of high-tar dark-tobacco cigarettes in eastern and southern Europe in enhancing the risk not only of cancer of the lung but also of upper digestive and respiratory and bladder neoplasms are also discussed.
Eur J Cancer, Vol. 27, No. 1, pp. 94–104, 1991.

INTRODUCTION

CLEMMESEN [1] comprehensively reviewed the historical development of cancer epidemiology, including associations between tobacco smoking and cancer. Several observations were made in the last century about associations between pipe smoking and the occurrence of cancer of the lip in particular and other oral sites. The general conclusion was that local trauma, including thermal irritation, was an important risk factor. In 1936 Fleckseder [2] reported from Vienna that 51 of 54 patients with bronchial carcinoma were cigarette smokers. Similar findings were reported by Muller [3] from Cologne in 1940, with the advantage of observations in a comparison ("control") series of patients, age-matched to the cases. Thus, associations between smoking and cancer were being noted by European clinicians even before they were quantified in one of the first modern epidemiological studies by Doll and Hill [4] in 1950.

Today it is recognised that cigarette smoking is by far the most important cause of lung cancer, and an important determinant of cancer risk for at least six other anatomical sites—oral cavity and pharynx, oesophagus, larynx, pancreas, kidney and bladder. Estimates of relative risk of cancer from a vast amount of epidemiological data, for current smokers, are of the order of 10 to 20 for the lung, between 5 and 10 for the oral cavity and

Correspondence to P. Boyle.
C. La Vecchia and E. Negri are at the Istituto di Ricerche Farmacologiche "Mario Negri" Milan, Italy; C. La Vecchia is also at, and F. Luccini is at the Départmente de l'Intérieur et de la Santé Publique, Institut Universitaire de Médecine Sociale et Préventative Epidémiologie et Prévention, Lausanne, Switzerland; P. Boyle, P. Maisonneuve and M. Smans are at the SEARCH Programme, Unit of Analytical Epidemiology, International Agency for Research on Cancer, 150 cours Albert-Thomas, F-69372 Lyon Cedex 08, France; S. Franceschi is at the Servizio di Epidemiologia, Centro di Riferimento Oncologico, Aviano, Italy; and F. Levi is at the Institut Universitaire de Médecine Sociale et Préventive, Registre Vaudois des Tumeurs, Lausanne, Switzerland.
Received 25 Oct. 1990; accepted 30 Oct. 1990.

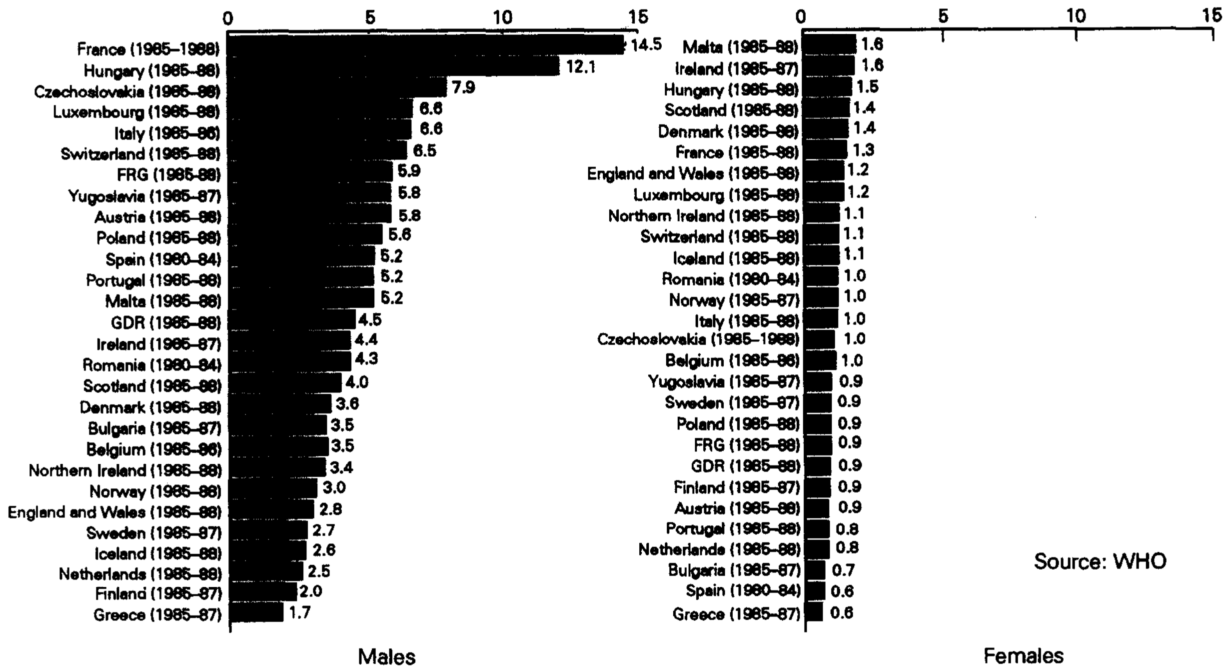

Fig. 1. Mortality rates from cancer of the mouth and pharynx (ICD 140–9) in males and females in Europe.

pharynx, larynx and oesophagus and between 2 and 4 for pancreas, bladder and kidney [5, 6]. A causal association with smoking has been suggested although not definitely established for other cancer sites, including stomach, liver and cervix uteri [5, 6]. The available evidence has led to the estimation that about one-third of all cancer deaths in the USA in the late 1970s was due to tobacco smoking [7]. Trends in smoking prevalence have, however, followed different patterns in various countries, and in various generations and between sexes within each country, more as a consequence of different social and economical influences than as a response to the accumulating evidence regarding the adverse health consequences of smoking [8]. It is thus important that estimates from the USA are not transposed uncritically to the European population, and that attention is paid to the specific situation in Europe. This is not an easy task, because of the substantial heterogeneity in patterns and trends in smoking (and other lifestyle habits) in various European countries and, sometimes, a lack of consistent sources of information.

We have assessed smoking and cancer in Europe using age-standardised national mortality rates from major tobacco-related sites [9]. Most attention has been paid to lung cancer rates, for which efficacy of anti-smoking strategies can be best assessed. Whenever useful and possible, information on age-specific trends, as well as from analytical epidemiological studies, has been integrated.

ORAL CAVITY AND PHARYNX

Figure 1 shows age-standardised mortality from neoplasms of the oral cavity and pharynx in 28 European countries, excluding the Soviet Union and a few small countries such as Liechtenstein, over the period 1985–1988, wherever possible. In males the overall variation is almost 10 fold, with very high rates in France and Hungary—nearly double that in Czechoslovakia, where the next highest rate is found. The lowest mortality rates are registered in Greece, the Scandinavian countries and the UK. In France, deaths from oral and pharyngeal cancer account for

Table 1. *Interaction between tobacco and alcohol on cancers of upper digestive and respiratory tract**

	Alcohol intake (total drinks per week)†			
Smoking status	<35	35–59	60⁺	Total
Oral cavity/pharynx				
Non-smokers	1‡	1.6	2.3	1‡
Light	3.1	5.4	10.9	3.7
Intermediate	10.9	26.6	36.4	14.1
Heavy	17.6	40.2	79.6	25.0
Total	1‡	2.3	3.4	
Larynx				
Non-smokers	1‡	1.6	–	1‡
Light	0.9	5.0	5.4	1.0
Intermediate	4.5	7.1	9.5	5.4
Heavy	6.1	10.4	11.7	6.7
Total	1‡	1.4	2.8	
Oesophagus				
Non-smokers	1‡	0.8	7.9	1‡
Light	1.1	7.9	9.4	2.5
Intermediate	2.7	8.8	16.7	4.0
Heavy	6.4	11.0	17.5	6.6
Total	1‡	3.1	5.7	

*From a case-control study of males with cancer of oral cavity and pharynx (n = 291), oesophagus (288) and larynx (162), and 1272 controls from Northern Italy [10].

†Estimates from multiple logistic regression: allowance was made for age in quinquennia, area of residence and years of education.

‡Reference category.

*Table 2. Role of tar yields in cigarettes on risk of upper digestive and respiratory track neoplasms**

Type of cigarette	Relative risk estimate (95% CI)†		
	Oral cavity and pharynx	Oesophagus	Larynx
Never-smokers	1‡	1‡	1‡
Current cigarette smokers (tar yield, mg)			
<22	10.9 (4.7–25.0)	3.7 (2.1–6.3)	5.5 (2.6–11.6)
≥22	30.0 (12.7–71.2)	13.6 (7.3–25.2)	12.3 (5.3–28.5)

*From a case-control study of males with cancer of oral cavity and pharynx (n = 291), oesophagus (288) and larynx (162), and 1272 controls from Northern Italy [13].
†Estimates from multiple logistic regression: allowance was made for age in quinquennia, area of residence, years of education and alcohol consumption (g per day).
‡Reference category.

over 10% of total cancer mortality in males, and in one registration area (Calvados) the oral cavity is the first-ranked site of cancer incidence in males, the rate being even higher than that for lung cancer [9]. Female rates are substantially lower than those of males, and their distribution largely different, with high rates in Scotland, Ireland, Denmark and England and Wales, and low rates in Bulgaria, Eastern Germany, Austria, Greece and Spain.

While rates of oral cancer for females correlate well with those of the lung, with higher rates in areas (UK and Ireland) where smoking became common earliest in women, the pattern in males reflects the combined effect and the interaction of tobacco and alcohol on the risk of these neoplasms (Table 1), with extremely high rates in France and other areas where both habits are common.

Still, case-control studies [10–12] have shown that the relative risks for tobacco are similar to, if not higher than, those of alcohol. Further, since in terms of population attributable risks most of the cases could be avoided by removal of one of the two major risk factors, most of the excess of incidence and mortality from oral cancer in these high-risk areas can also be attributed to tobacco, in whose absence the alcohol-related risk could be substantially reduced.

An additional important component of the high oral cancer rates in France, Switzerland, Italy and possibly some eastern European countries is the high tar yield of cigarettes together with the type (colour) of tobacco smoked [13] and an elevated prevalence of pipe and cigar smoking, at least in older generations [14, 15]. Case-control studies have shown that the risk of these neoplasms is strongly related to the use of pipes and cigars [10–14], and that there is a 2 to 3 fold difference in the relative risk for smokers of high-tar/dark cigarettes compared with low-tar/blond cigarettes, even after allowance is made for age at which smoking started, duration, quantity and other relevant covariates. In areas with a high prevalence of use of high-tar/dark-tobacco cigarettes (at least in the past), the relative risk of oral cancer is increased over 10 fold in ever-smokers, and over 15 fold in heavy smokers (Table 2).

Examination of incidence and mortality trends shows that oral cancer is increasing in frequency [16].

OESOPHAGUS

The pattern of oesophageal cancer mortality rates (Fig. 2) is largely similar to that of the oral cavity. The highest rates are registered in France, and elevated rates are also observed in Luxembourg, Switzerland and Italy.

The UK, however, and particularly Scotland, are among the countries with high oesophageal cancer rates, not only in females but also in males. The overall range of rates is around a factor of ten in both sexes. Part of this substantial variation may be due

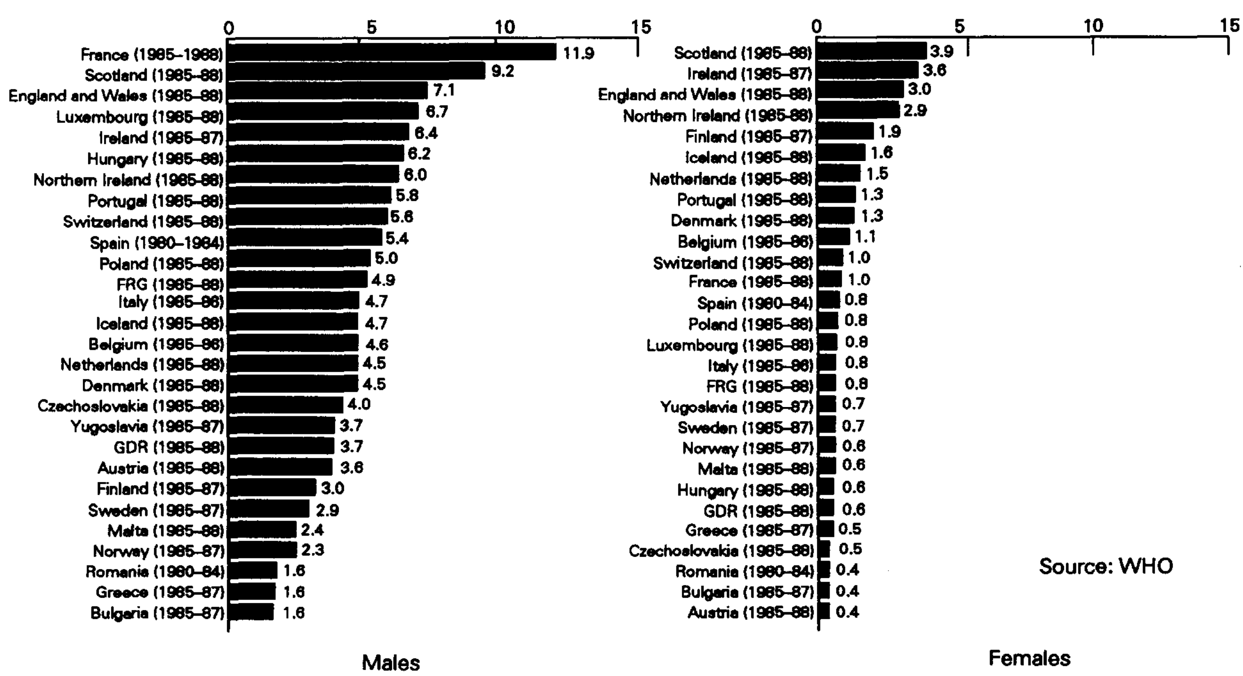

Fig. 2. Mortality rates from cancer of the oesophagus (ICD9-150) in males and females in Europe.

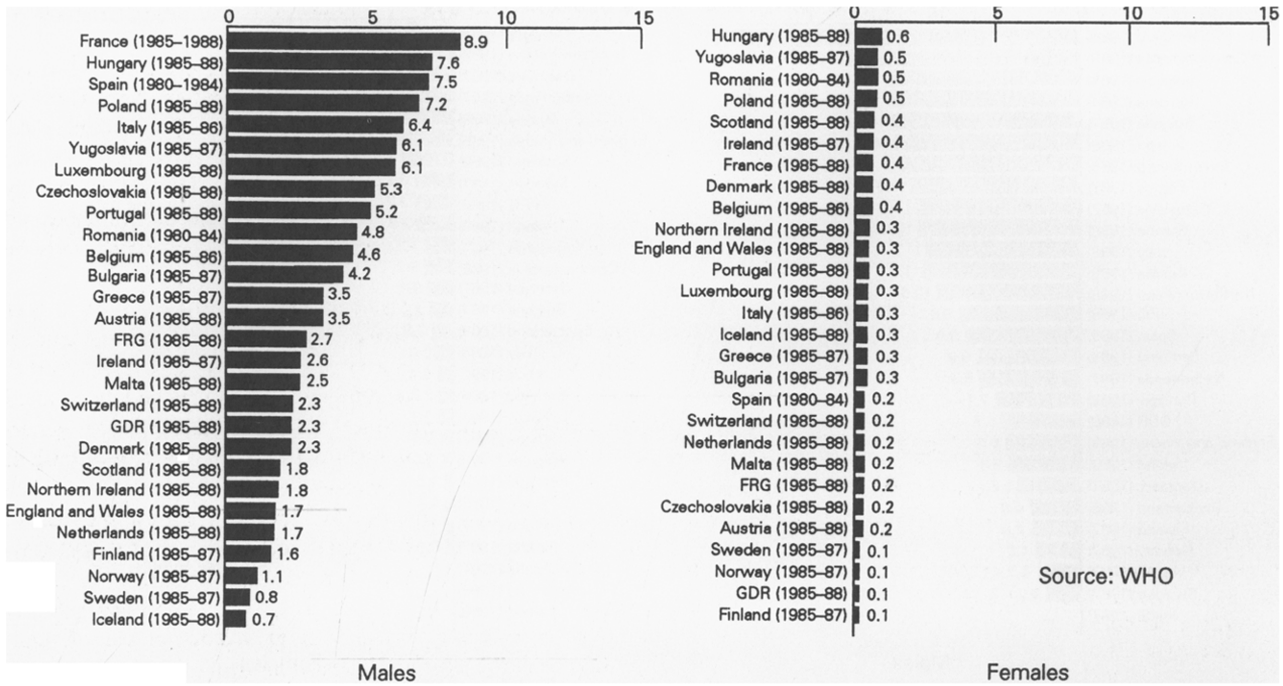

Fig. 3. Mortality rates from cancer of the larynx (ICD9-161) in males and females in Europe.

to classification problems for tumours arising in the cardial region, especially in eastern Europe where the stomach is a much commoner site of cancer [17] and misclassification of a small proportion of stomach tumours may lead to apparently high levels of oesophageal cancer. Other factors of major importance in the aetiology of oesophageal cancer are alcohol consumption and, probably, diet [18, 19]. However, smoking alone, or the interaction of smoking and alcohol (Table 1), can explain most of the variation.

A study in the early 1970s in the French department of Ille-et-Vilaine had already shown that the combination of high consumption of alcohol and tobacco (over 10 g per day) could explain more than 85% of the attributable risk [20]. Several other subsequent studies, mainly in France and Italy, found a strong association with tobacco, and relative risks of the order of 5 or more in heavy smokers [10, 13, 18, 19]. For the oral cavity, the association is particularly strong for the use of pipes and cigars, and among cigarette smokers, for high-tar dark tobacco cigarettes (Table 2) [9]. In these areas, oesophageal cancers related to tobacco (or to the interaction between tobacco and alcohol) represent an important public health problem and a large component of the smoking-related cancer burden, since

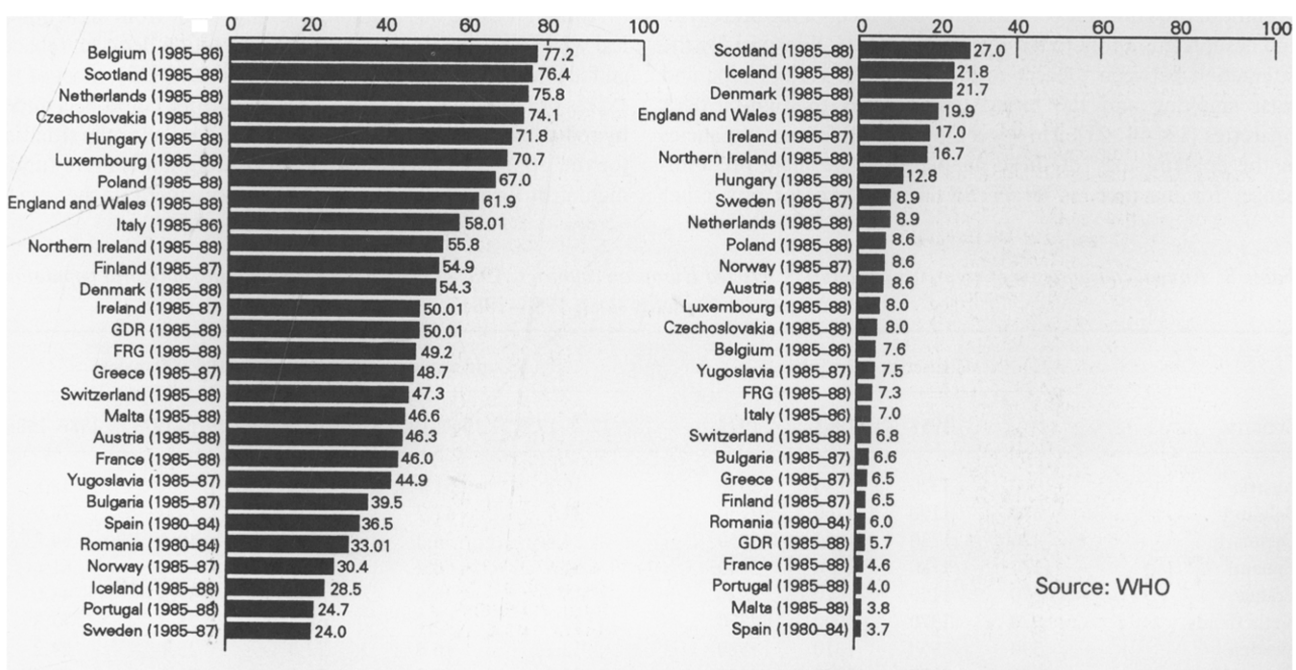

Fig. 4. Mortality rates from cancer of the lung (ICD9-162) in males and females in Europe.

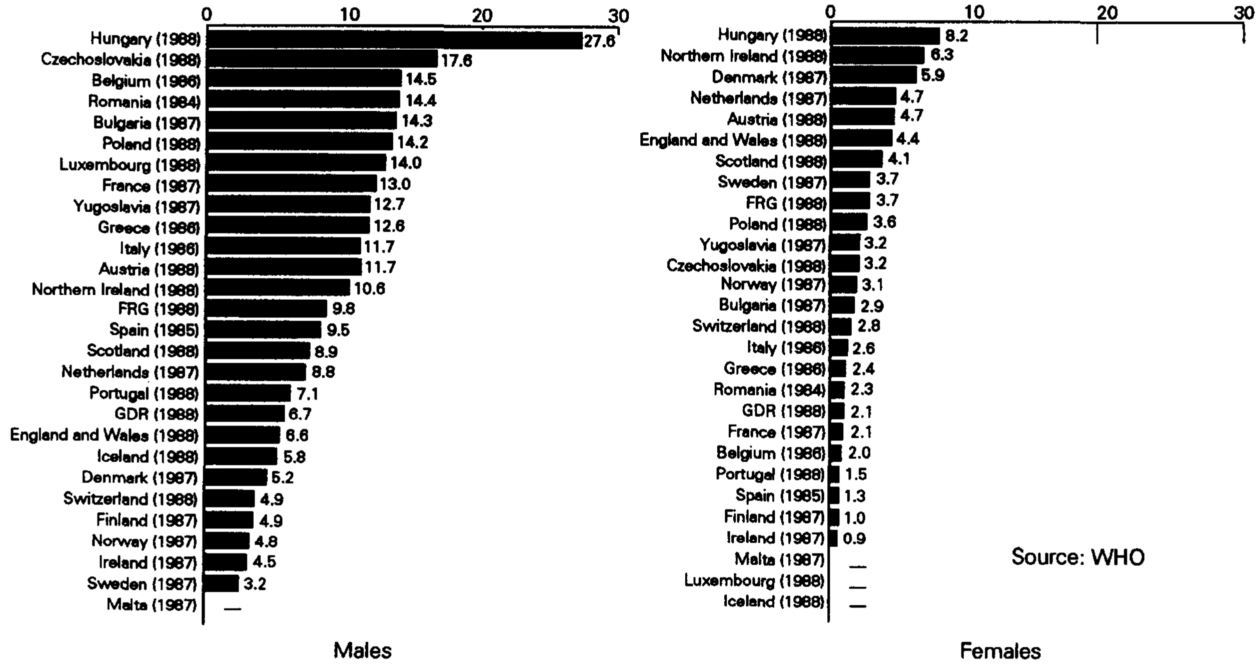

Fig. 5. Truncated (age 35–64) mortality rates from cancer of the lung in males and females in Europe.

each one of these sites accounts for over a quarter the rate observed for lung cancer [9].

LARYNX

National mortality rates from laryngeal cancer are, again, highest in France, followed by Hungary, Spain, Poland and Italy, and lowest in the UK and other northern European countries (Fig. 3). Rates for females are less stable, reflecting the substantially lower absolute numbers of cases and deaths, but the overall pattern is apparently different, since mortality rates were, as for cancers of the upper digestive tract, high in Ireland and the UK.

Some of the same lines of reasoning for cancer of the oral cavity and oesophagus apply to laryngeal cancer as well, especially the interaction between tobacco and alcohol, the role of pipe and cigar smoking and the higher risk related to high-tar/dark cigarettes [13, 14, 21]. However, there are a few discrepancies in the epidemiology of these neoplasms. The male predominance, for instance, is larger for larynx than for any other (tobacco-related) neoplasm [9], and the pattern in other southern European countries is more similar to that of lung cancer. In addition, appreciable differences in the cohort pattern were observed for the oesophagus and even more for the oral cavity (e.g. systematic upward trends for cancer of the upper digestive tract but not of the lung in most recent generations in most European countries) [22, 23].

Some of these differences may be due to the quantitatively different influence of tobacco (and alcohol) on the different subsites of the larynx, since the tobacco-related risk is higher for the hypolarynx than for the epilarynx/hypolarynx, which come in direct contact with alcohol [21].

Although these observations are important from an aetiological viewpoint, bearing in mind the interaction between tobacco and alcohol on laryngeal cancer risk (Table 1) [10], most of the excess of laryngeal cancer in southern Europe could be avoided by reducing or abolishing tobacco alone. Similar to the situation for the upper digestive tract, this consideration is more fundamental in formulating a quantitative assessment of the impact

Table 3. Annual consumption of cigarettes per adult in selected European countries, 1933–1973, *and male age-adjusted (world population) lung cancer mortality rates,* 1955–1984

	Cigarettes per adult				Lung cancer mortality rates per 100 000 males				
Country	1933	1953	1963	1973	1955–1959	1960–1969	1970–1974	1975–1979	1980–1984
Austria	1000	1320	1840	2550	46.2	51.1	51.3	50.5	48.8
Belgium	880	1190	1760	2730	31.1	47.7	64.8	74.0	78.9
Denmark	420	1230	1580	1850	24.6	36.2	45.4	49.4	54.3
Finland	1170	1780	2190	2040	51.9	62.4	66.6	65.8	61.6
France	570	1120	1420	1920	18.7	26.8	33.0	39.3	43.0
Netherlands	670	1370	1900	2370	35.6	53.2	68.2	75.3	77.3
Sweden	390	950	1310	1580	12.2	16.8	22.0	25.1	24.2
United Kingdom	1470	2370	2790	3230	57.1	69.2	74.6	73.3	68.5

of smoking on cancer in southern Europe than in northern Europe and North America.

LUNG

The lung is the major tobacco-related site of cancer. Indeed lung cancer rates in self-reported non-smokers from various studies are of the order of only 10 to 15 per 100 000 [6]. The *Monograph on Tobacco Smoking* [6] gave estimates of the proportions of lung cancer deaths attributable to tobacco smoking in five developed countries (Canada, England and Wales, Japan, Sweden and the USA): 83–92% for males and 57–80% for females.

In males of all European countries, except Portugal, lung cancer is the leading cause of cancer death and (in all except a few Scandinavian countries) it is the commonest tumour in terms of incidence as well.

The range of variation for mortality is over a factor of three in both sexes (Fig. 4), the highest rates being observed in the UK, Belgium, the Netherlands and Czechoslovakia, and the lowest rates being reported in southern Europe but also in Norway and Sweden in both sexes. Of course, this overall pattern of age-standardised lung cancer mortality rates conceals important and diverging cohort effects in various countries. For instance, some of the countries which are now in the lower part of the distribution (such as southern Europe) experienced a later uptake and spread of tobacco use, but now appear among the countries with the most elevated rates in the younger age groups (Fig. 5). This suggests that these countries, including Italy, Greece, France, Spain and several in eastern Europe, will have some of the highest lung cancer rates in males at the beginning of the next century, in the absence of rapid and adequate intervention [24].

As an example of the time-relation between different levels of cigarette consumption and lung cancer mortality in males, Table 3 shows annual consumption of cigarettes per adult in selected European countries and contrasting lung cancer mortality rates in the same countries between 1955 and 1984. Besides tobacco consumption, past or current yields of tar in cigarettes have probably also played some role, since rates in young males are more elevated in those countries of southern and eastern Europe which have maintained high tar levels over more recent periods [25].

When data on a provincial rather than on a national level are considered (Fig. 6), the highest rates in males are seen in central and north-eastern England, central and western Scotland, southern Belgium and western Holland. A group of rates above the average is observed in northern Italy. In FRG, France, central and southern Italy, and most of Ireland, rates are either average, below average or low. The map for females (Fig. 7) is different, with all rates in Great Britain being above average, and those in southern and central Scotland and around Newcastle, London and Liverpool being especially high. In Ireland rates are again above average with a concentration of high risks in those areas facing the Irish sea. The excess rates seen in males in Belgium and the Netherlands are not observed in women. In Denmark, female rates are above average, especially in Copenhagen. On a regional scale within the EC, the mortality from lung cancer ranges from 87.0 per 100 000 in northern England to 20.2 in Basilicata, South Italy, in males and between 20.1 in Scotland and 2.5 in Basilicata in females. A more important inference from Fig. 4 is related to the low lung cancer rates in Scandinavian countries which have adopted, since the early 1970s, integrated central and local policies and programmes against smoking [26], possibly as a consequence of the limited influence of the pro-tobacco lobby in these countries. This provides convincing evidence of the favourable impact, after a relatively short delay, of well-targeted large-scale interventions on the most common cause of cancer deaths.

One of the major determinants of tobacco consumption (at least in the short term) is the price of cigarettes, which is given in Table 4 for various countries of the EC. When the ratio price to per capita gross internal product is considered, there is a difference of more than a factor of seven between the highest (Ireland) and the lowest (France) value, and the countries in the upper part of the distribution are those now showing lower lung cancer rates in the young.

With specific reference to females, current rates in most European countries (except Britain and Ireland) are still substantially lower than in the USA where lung cancer is now the leading cause of cancer death in females [27]. In several countries, including France, Switzerland, Germany and Italy, where smoking is now becoming more common in younger and middle-age women, overall national mortality rates are still relatively low, although appreciable upward trends have been registered over the past two decades [15, 23, 28]. This is particularly worrisome, since smoking prevalence is still increasing in subsequent generations of younger women in these countries. Thus, the observation that lung cancer is still relatively rare in females, and that smoking accounts for only a proportion (about 40–60% [15]) of all lung cancer deaths cannot constitute a reason for delaying efficacious interventions against smoking specifically targeted to women. The currently more favourable situation in Europe compared with the USA [27], together with the observation that smoking cessation reduces lung cancer risk after a delay of several years, should hopefully help in avoiding a lung cancer epidemic in European women.

In conclusion, the overwhelming role of tobacco smoking in the causation of lung cancer has been repeatedly demonstrated over the past 50 years [5–7]. Current lung cancer rates reflect cigarette smoking habits of European males and females in the past decades, but not necessarily current smoking patterns, since there is an interval of several decades between the change

Table 4. Prices, fiscal charges and ratio between fiscal charges and per capita gross internal product in various EC countries, 1986

Rank	Country	Price (ecu)	Per capita gross external product (× 1000 ecu)	Fiscal charges	Ratio price/fiscal charges
1	Ireland	2.54	6.8	1.88	0.37
2	Portugal	0.73	2.8	0.50	0.28
3	United Kingdom	2.35	9.4	1.76	0.25
4	Denmark	3.16	15.1	2.76	0.24
5	Spain	0.73	5.7	0.38	0.13
6	FRG	1.77	14.2	1.30	0.12
6	Italy	1.02	8.5	0.73	0.12
6	Netherlands	1.38	11.4	0.97	0.12
9	Belgium	1.24	10.9	0.87	0.11
9	Greece	0.43	3.8	0.26	0.11
11	Luxembourg	0.97	13.6	0.65	0.07
12	France	0.68	12.4	0.51	0.05

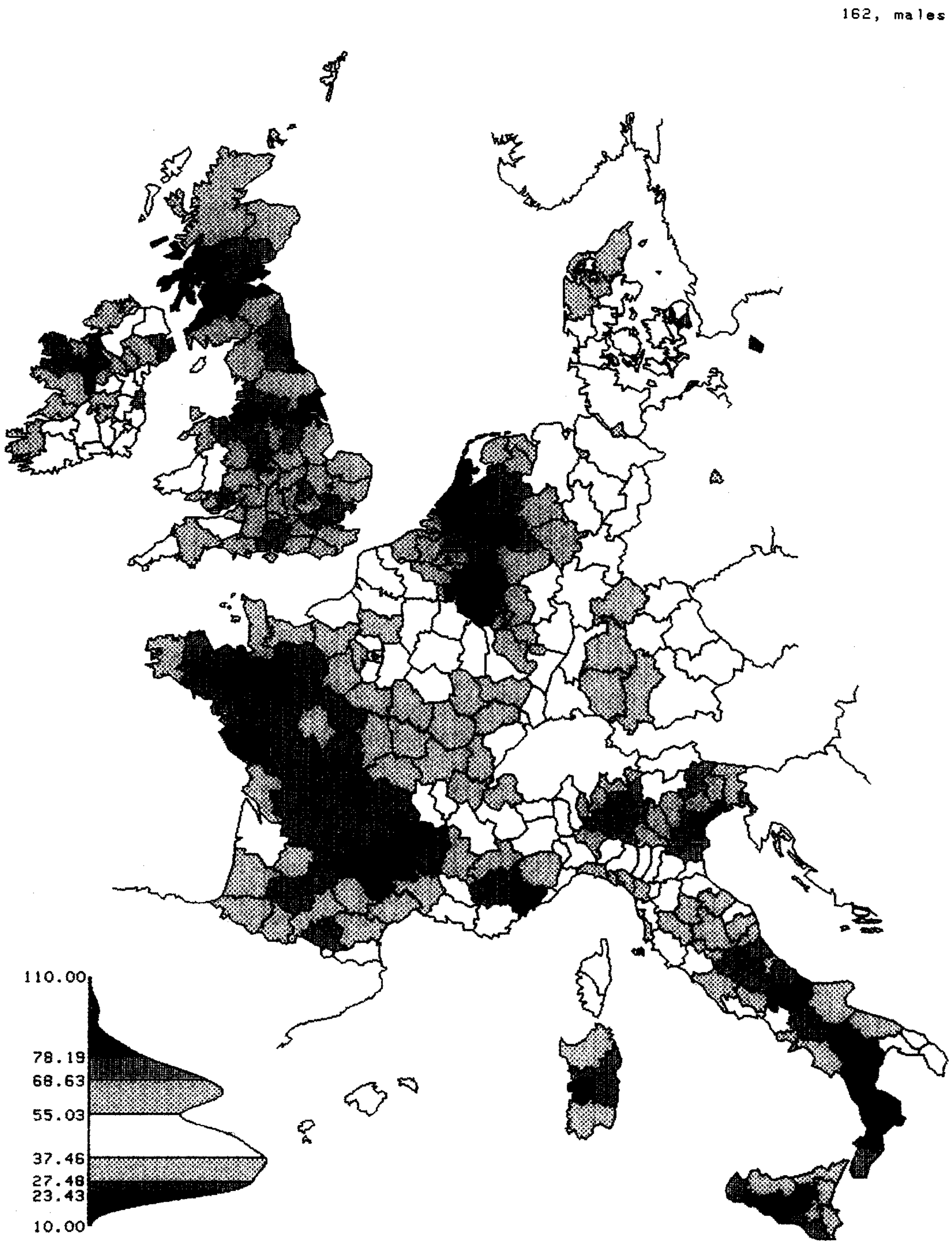

Fig. 6. Lung cancer mortality in regions of EC in males [38]. Insert shows the rate per 100 000 and distribution of rates.

in smoking habits in a population and its consequences on lung cancer rates. A proportion of lung cancers, varying in various countries and geographical areas, may be due to exposures at work, and a small proportion to atmospheric pollution. There are, however, good reasons to believe that the effect of atmospheric pollution in increasing lung cancer risk is chiefly confined to smokers [7].

PANCREAS

The pancreas is another tobacco-related site where most cohort and case-control studies show relative risks of the order of two to three in current as compared with never-smokers, and a direct dose–risk relation [5, 6]. With such an order of magnitude in the relative risk, the proportional attributable risk is approximately between 30 and 50% for males and between 15 and 25% for females in most developed countries.

Such a proportion is not easily identifiable from histograms of national mortality rates in various European countries (Fig. 8), especially since the pancreas is a site where diagnostic problems can be severe [7]. However, there is a satisfactory consistency between national mortality rates and those observed in areas covered by cancer registration systems [9], and some consistency between the European patterns of mortality from cancer of the pancreas and that of the lung, since the lowest

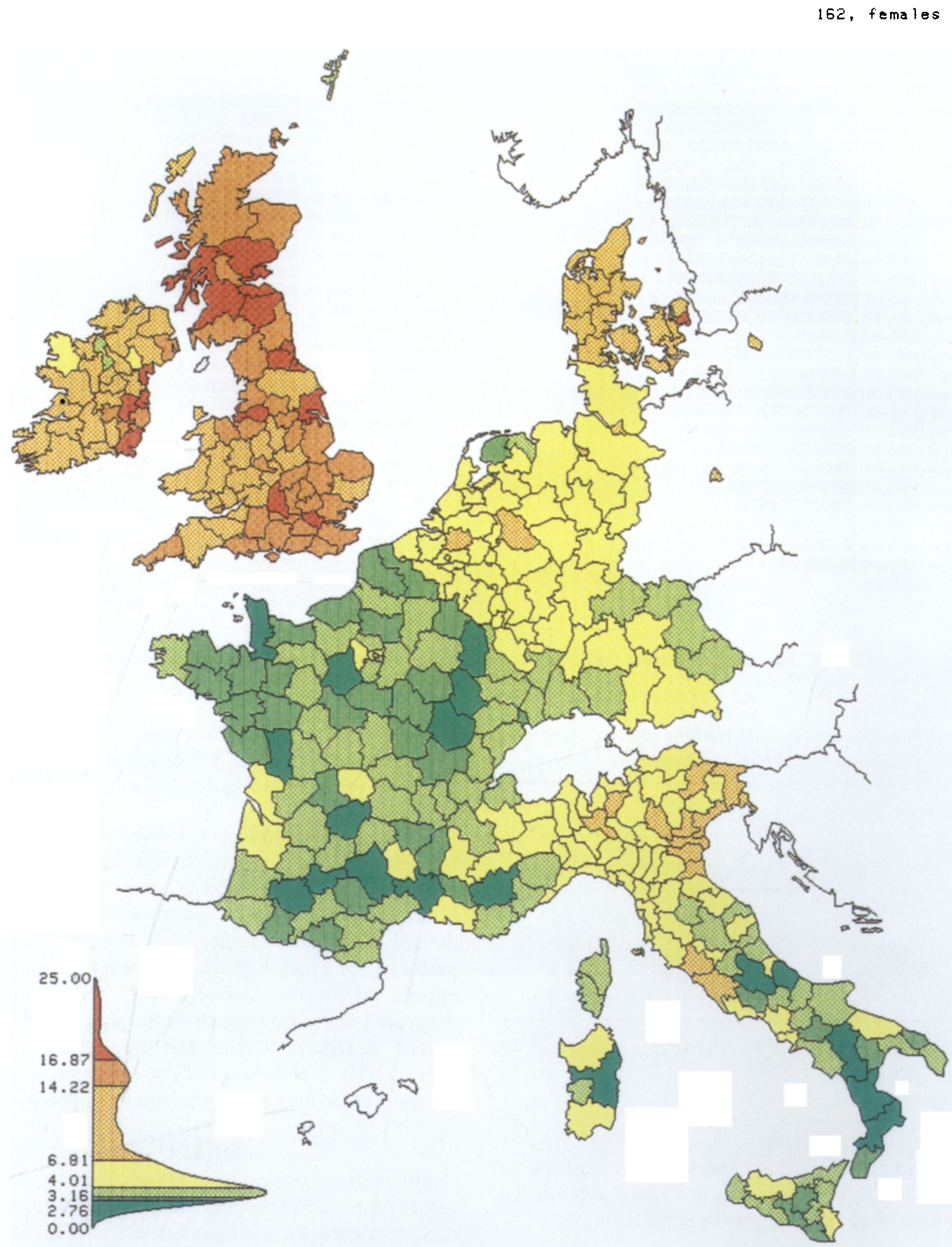

Fig. 7. Lung cancer mortality in regions of EC in females [38].

rates were observed in Spain, Portugal and Greece. The highest rates, however, are recorded in Scandinavian countries while the UK has intermediate values.

Since little is currently known about other risk factors for cancer of the pancreas [29], it is difficult to discuss any potential interaction or modifying factor.

BLADDER

Bladder cancer is a well recognised tobacco-related neoplasm, although there is still some uncertainty on the strength of the association: the relative risks for smokers compared with non-smokers ranged between 1.4 and 2.9 in eight cohort studies, and the range of variation was even larger (between 1.2 and 7.3) among twenty published case-control studies [5, 6, 30]. Some of the difference may be due to the type of tobacco smoked, since there is consistent evidence that black tobacco (which is richer in aromatic amines, a known bladder carcinogen) is associated with higher bladder cancer risk compared with blond tobacco [30–34]. Further, other correlates of bladder cancer risk, particularly occupation (Table 5) and urinary tract infections, may be important modifying factors [30–34].

Tobacco, at least in males and in northern Europe, is the single most important avoidable bladder cancer risk factor, with a population attributable risk of over 50% [30]. This could explain at least part of the 3 fold difference in bladder cancer mortality between those areas with the highest rates in Denmark,

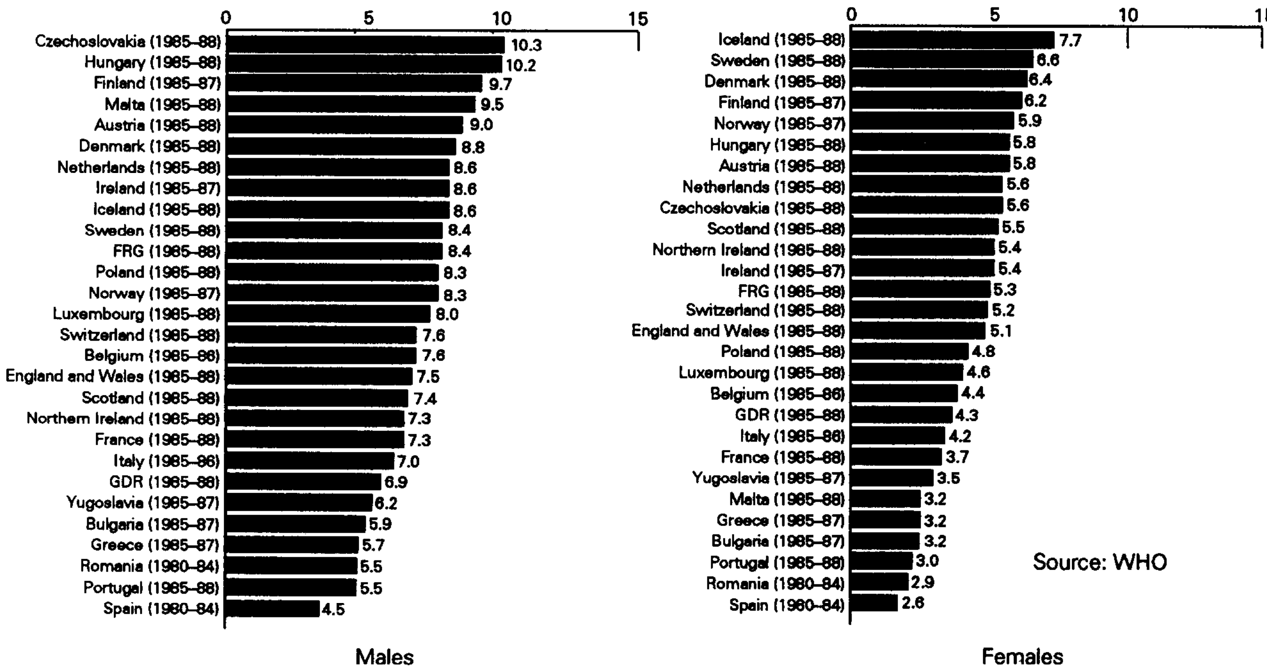

Fig. 8. Mortality rates from cancer of pancreas (ICD9-157) in males and females in Europe.

*Table 5. Interaction between cigarette smoking and high risk occupations on risk of bladder cancer**

	Relative risk (95% CI) for ever-employed in high risk occupations	
	No	Yes
Never-smoker	1†	2.5 (1.0–6.8)
Ever-smokers	2.8 (1.9–4.2)	3.7 (1.9–7.3)

*From a case-control study of 337 cases of bladder cancer and 392 controls in northern Italy [30].
†Reference category.

Italy, Belgium and the UK, and the lowest ones in southern and eastern Europe (although the low rates in Finland and Sweden, like those for lung cancer, should also be noted) (Fig. 9).

KIDNEY

There is considerable evidence that cancer of the kidney is also tobacco-related. Although the risk estimates of various case-control and cohort studies are heterogeneous, they are consistent with an approximately 2 fold increased risk of renal cell cancer in smokers [5, 6, 35]. In quantitative terms, tobacco thus has a substantial relevance in renal cell carcinoma on a population scale, although the relative risk is probably lower than that for transitional cell cancer of the kidney and other urinary tract tumours.

This comparatively lower relative risk can probably explain, at least in part, the heterogeneous pattern of mortality rates from kidney cancer compared with other major tobacco-related sites, with high rates in northern Europe, Czechoslovakia and German-speaking areas, intermediate rates in central Europe, and the lowest ones in eastern and southern Europe (Fig. 10). Furthermore, the less strong association certainly precludes reliable estimation of the proportion of tobacco-related kidney cancers in various European countries.

TOBACCO-RELATED CANCERS OF OTHER SITES

There are several indications that the relative risk of cancers of the stomach, liver and cervix uteri are increased by 50–100% in smokers compared with non-smokers [5, 6]. Uncertainties in the risk estimates, together with diagnostic and certification problems for cancers of the liver and cervix uteri, however, impede any precise assessment of the role of smoking in incidence and mortality from these neoplasms in Europe. A proportion of cancers at other and unspecified sites is probably tobacco-related, since some of these neoplasms are secondaries of cancer of the lung and other common tobacco-affected sites.

CONCLUSIONS

Although any comprehensive assessment of the smoking and cancer problem in Europe is hampered by the different patterns and prevalence of smoking and cancer rates in various countries and subsequent generations of males and females, as well as by the non-homogeneous availability of tobacco statistics and reliability of death certification data, there are at least six points that deserve careful consideration in the picture of tobacco-related neoplasms in Europe.

(1) Cigarette smoking is unquestionably the single most important cause of cancer in man. The evidence associating cigarette smoking with the risk of certain common forms of cancer is vast and consistent. All the usual criteria of causality are present in the association between smoking and a number of cancer sites. Confounding or biases of certain forms have been ruled out as alternative explanations of the association with lung cancer and certain other forms of cancer. Cigarette smoking is a known cause of certain cancers, some of which are very common. A substantial proportion of cancers could unquestionably be avoided by elimination of cigarette smoking.

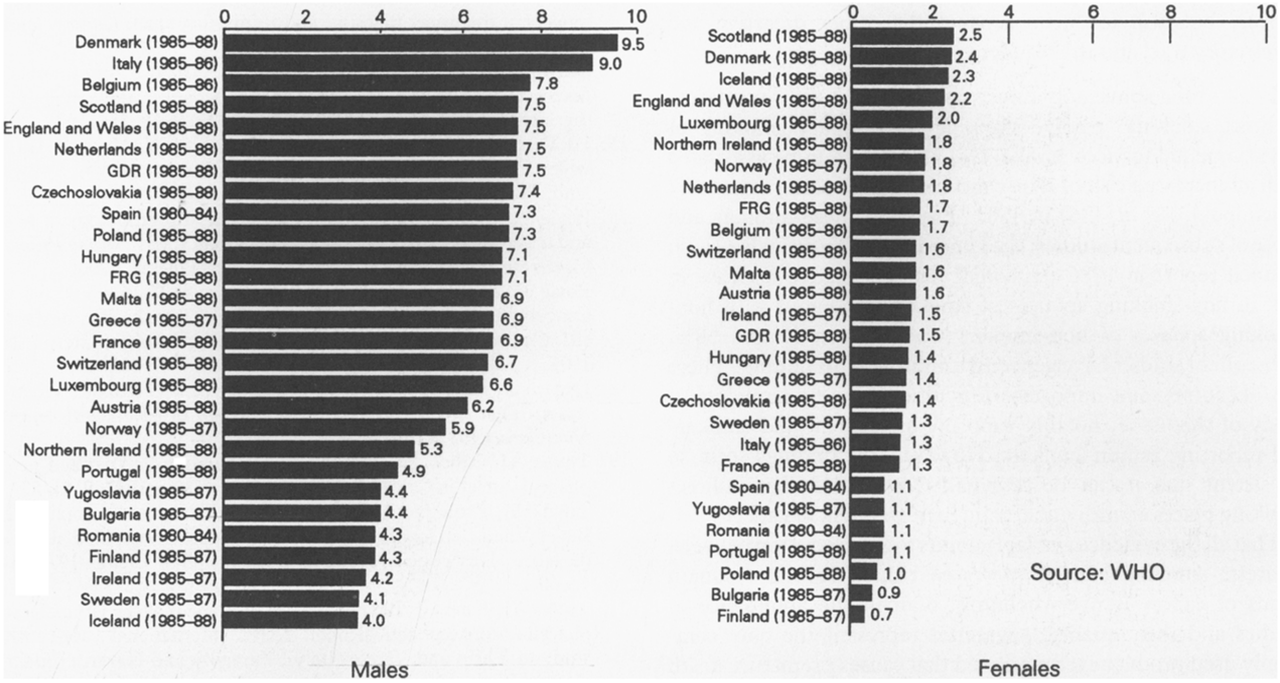

Fig. 9. Mortality rates from cancer of the urinary bladder (ICD9-188) in males and females in Europe.

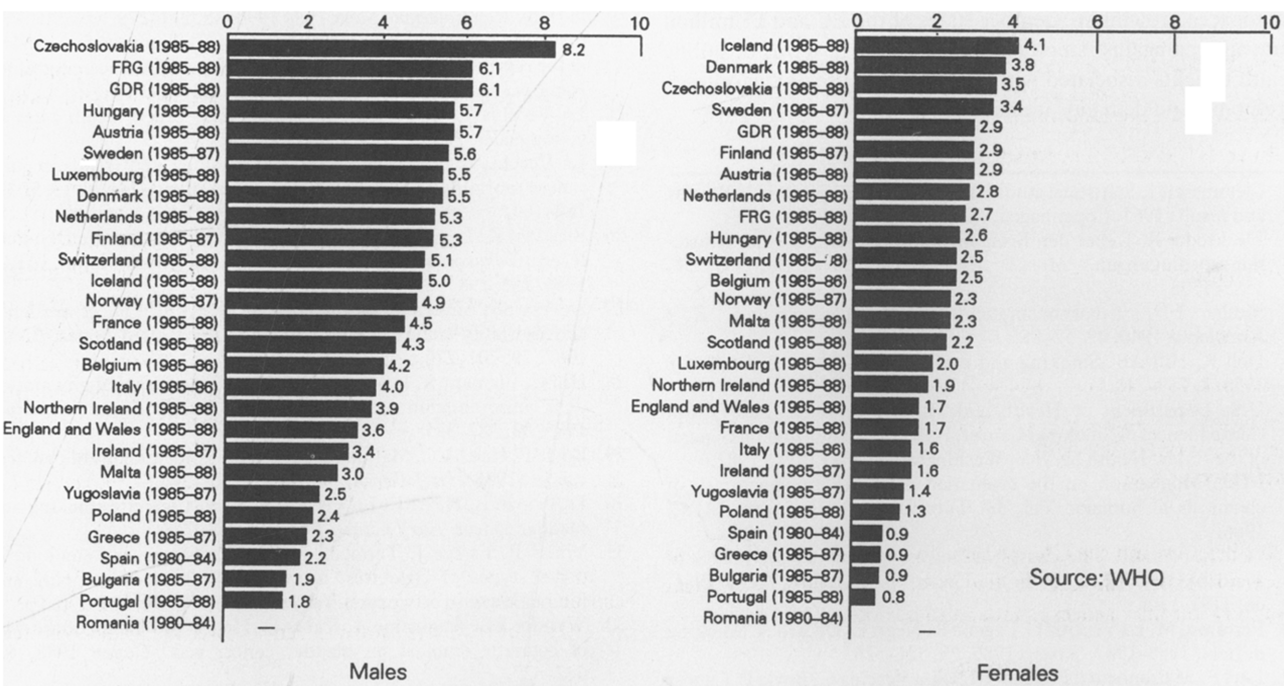

Fig. 10. Mortality rates from cancer of the kidney (ICD9-189) in males and females in Europe.

(2) In France and, to a lesser extent, in Switzerland, Italy and Spain, the interaction between tobacco and alcohol is the major factor responsible for the elevated rates of upper digestive and respiratory tract neoplasms, which therefore represent a public health issue of high priority.

(3) With the main exception of the UK, lung cancer rates in European females are still relatively low, although trends have recently been upwards. There is, therefore, ample scope for urgent intervention aimed at limiting a tobacco-related major lung cancer epidemic among women in the near future.

(4) In males, the lowest lung cancer rates are observed not only in countries with a later spread of tobacco smoking, but also in those areas (such as Scandinavia) where more comprehensive policies against tobacco have been adopted.

(5) The geographical distribution of lung cancer mortality in the younger age groups suggests that countries of southern and eastern Europe, where the prevalence of tobacco smoking in the young is higher and high-tar dark-tobacco cigarettes are still common, will probably have the highest lung cancer rates at the beginning of the next decade.

(6) High-tar dark-tobacco cigarettes in eastern and southern Europe are still a relevant aggravating factor not only for lung

cancer, but also for neoplasms of the upper digestive and respiratory tract and the bladder.

In all of the above only direct smoking has been considered. Indirect smoking (passive smoking, involuntary smoking or environmental tobacco smoke) was first shown to be associated with an increased risk of lung cancer in non-smoking women by Trichopoulos *et al.* [36] in 1981. Based on these findings and those of subsequent studies, the United States National Research Council report in 1986 estimated that the relative increase in risk in non-smoking spouses of smokers compared with non-smoking spouses of non-smokers was between 20 and 50%. Subsequent studies have generally confirmed this finding. There are, of course, some important difficulties in the epidemiological study of this issue, notably exposure assessment and smokers self-reporting as non-smokers. However, the findings seem so consistent that it can be reasonably concluded that indirect smoking places an individual at an increased risk of cancer.

That all the evidence available points to an association between cigarette smoking and an increased risk of several common forms of cancer is overwhelming, both in the abundance of studies and their quality. Cigarettes represent the only commonly used product ever marketed that causes premature death and significant morbidity among those who use the product as the manufacturer intended. At a time when the Commission of European Communities spends annually £740 million subsidising tobacco growing in member states of the EC and £5 million campaigning against smoking [37], the case in terms of public health benefits associated with restriction of use of cigarettes is irrefutable and demands immediate action.

1. Clemmesen J. Statistical studies in malignant neoplasms. 1. Review and results 1965, Copenhagen, Munksgaard.
2. Fleckseder R. Ueber den Bronchialkrebs und einge seiner Entstehungsbedingungen. *Munch Med Wochenschr* 1936, Nr 36, 1585–1593.
3. Muller FH. Tabaksmisbrauch und Lungenkarzinom. *Z f Krebsforsch* 1940, **49**, 57–85.
4. Doll R, Hill AB. Smoking and carcinoma of the lung. *Br Med J* 1950, 2, 739–748.
5. U.S. Department of Health and Human Services: The Health Consequences of Smoking: Cancer. A Report of the Surgeon General of the Public Health Service, Washington, U.S. G.P.O., 1982.
6. IARC Monograph on the evaluation of the carcinogenic risk of chemicals to humans: Vol. 38. Tobacco smoking. Lyon, IARC, 1986.
7. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *JNCI* 1981, **66**, 1191–1308.
8. Ferraroni M, La Vecchia C, Pagano R, Negri E, Decarli A. Smoking in Italy, 1986–1987. *Tumori* 1989, **75**, 521–526.
9. Levi F, Maisonneuve P, Filiberti R, La Vecchia C, Boyle P. Cancer incidence and mortality in Europe. *Soz Praeventivmed* 1989, **34** (Suppl. 2), S1–S84.
10. Franceschi S, Talamini R, Barra S, *et al.* Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx and oesophagus in Northern Italy. *Cancer Res* 1990, **50**, 6502–6507.
11. Blot WJ, McLaughlin JK, Winn DM, *et al.* Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 1988, **48**, 3282–3287.
12. Merletti F, Boffetta P, Ciccone G, Mashberg A, Terracini B. Role of tobacco and alcoholic beverages in the etiology of cancer of the oral cavity/oropharynx in Torino, Italy. *Cancer Res* 1989, **49**, 4919–4924.
13. La Vecchia C, Bidoli E, Barra S, *et al.* Type of cigarettes and cancers of the upper digestive and respiratory tract. *Cancer Causes Control* (in press).
14. Ferraroni M, Negri E, La Vecchia C, D'Avanzo B, Franceschi S. Socioeconomic indicators, tobacco and alcohol in the aetiology of digestive tract neoplasms. *Int J Epidemiol* 1989, **18**, 556–562.
15. La Vecchia C, Levi F, Decarli A, Wietlisbach V, Negri E, Gutzwiller F. Trends in smoking and lung cancer mortality in Switzerland. *Prev Med* 1988, **17**, 712–724.
16. Boyle P, Macfarlane GJ, McGinn R, *et al.* Epidemiology of head and neck cancers. In: De Vries N, Gluckman J, eds. *Second Primary Cancers in Head and Neck*, Stuttgart, Georg Thieme, 1990.
17. Boyle P, Maisonneuve P, Levi F, Zatonski W, La Vecchia C. Cancer patterns in central Europe. In: Zatonski W, Boyle P, eds. *Cancer: Epidemiology through Prevention*, Warsaw, Interpresse, 1991.
18. Decarli A, Liati P, Negri E, Franceschi S, La Vecchia C. Vitamin A and other dietary factors in the etiology of esophageal cancer. *Nutr Cancer* 1987, **10**, 29–37.
19. Tuyns AJ, Riboli E, Doornbos G, Péquignot G. Diet and oesophageal cancer in Calvados (France). *Nutr Cancer* 1987, **9**, 81–82.
20. Tuyns AJ, Péquignot G, Jensen OM. Le cancer de l'oesophage en Ille-et-Vilaine en fonction des niveaux de consommation d'alcool et de tabac. Des risques qui se multiplient. *Bull Cancer* 1977, **64**, 45–60.
21. Tuyns AJ, Estève J, Raymond L, *et al.* Cancer of the larynx/hypopharynx, tobacco and alcohol: IARC international case-control study in Turin and Varese (Italy), Zaragoza and Navarra (Spain), Geneva (Switzerland), and Calvados (France). *Int J Cancer* 1988, **41**, 483–491.
22. La Vecchia C, Boyle P, Cislaghi C, Decarli A, Negri E. Descriptive epidemiology of cancers of the upper digestive and respiratory tract in Italy. *Rev Epidémiol Santé Publ* 1990, **38**, 271–273.
23. Cislaghi C, Negri E, La Vecchia C, Levi F. Trend surface models in the representation and analysis of time factors in cancer mortality. *Rev Epidémiol Santé Publ* 1990, **38**, 237–243.
24. La Vecchia C, Franceschi S. Italian lung cancer death rates in young males. *Lancet* 1984, **i**, 406.
25. La Vecchia C. Patterns of cigarette smoking and trends in lung cancer mortality in Italy. *J Epidemiol Community Health* 1985, **39**, 157–164.
26. Bjartveit K. Legislation and political activity. In: Zaridze DG, Peto R, eds. *Tobacco: a Major International Health Hazard*. Lyon, IARC, 1986, 285–298.
27. Devesa SS, Silverman DT, Young JL Jr, *et al.* Cancer incidence and mortality trends among whites in the United States. *JNCI* 1987, **79**, 701–770.
28. Hill C, Flamant R. Une cause d'épidémie majeure: l'augmentation de la consommation de tabac en France. *Rev Epidémiol Santé Publ* 1985, **33**, 387–395.
29. Boyle P, Hsieh CC, Maisonneuve P, *et al.* Epidemiology of pancreas cancer (1988). *Int J Pancreatol* 1989, **5**, 327–346.
30. D'Avanzo B, Negri E, La Vecchia C, *et al.* Cigarette smoking and bladder cancer. *Eur J Cancer* 1990, **26**, 714–718.
31. Vineis P, Estève J, Terracini B. Bladder cancer and smoking in males: types of cigarettes, age at start, effect of stopping and interaction with occupation. *Int J Cancer* 1984, **34**, 165–170.
32. Wynder EL, Augustine A, Kabat G, Hebert JR. Effect of the type of cigarette smoked on bladder cancer risk. *Cancer* 1988, **61**, 622–627.
33. Clavel J, Cordier S, Boccon-Gibod L, Hémon D. Tobacco and bladder cancer in males: increased risk for inhalers and smokers of black tobacco. *Int J Cancer* 1989, **44**, 605–610.
34. Burch JD, Rohan TE, Howe GR, *et al.* Risk of bladder cancer by source and type of tobacco exposure: a case-control study. *Int J Cancer* 1989, **44**, 622–628.
35. La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Smoking and renal cell carcinoma. *Cancer Res* 1990, **50**, 5231–5233.
36. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B. Lung cancer and passive smoking. *Int J Cancer* 1981, **27**, 1–4.
37. Dean M. King tobacco under attack. *Lancet* 1990, **336**, 865–866.
38. Smans M, Boyle P, Muir CS. *Cancer Mortality Atlas of the European Community*. IARC Scientific Publication, IARC, Lyon (in press).