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# Cancer Prevention: Epidemiology and Perspectives*

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**Following increases up until the late 1980s, some decline in cancer mortality has been observed in North America and in Western Europe. Approximately half the decline can be attributed to the levelling off in lung and other tobacco-related cancer epidemics and the rest to several factors, including reduced exposure to occupational carcinogens, prevention and early diagnosis, and improved treatment. Between 25 and 30% of all cancer deaths in Europe are due to tobacco smoking. In this review the effect of tobacco smoking on cancer incidence and mortality is examined, together with other important aetiological factors including alcohol, diet and environmental and occupational carcinogens. The effect of new treatments and the potential for prevention of cancer are also discussed.** 

**Key words: cancer, epidemiology, tobacco, alcohol, diet, risk factors, review, prevention**
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## INTRODUCTION AND DESCRIPTIVE EPIDEMIOLOGY

CANCER INCIDENCE and mortality have been steadily rising throughout this century in most areas of the world. However, over the last few years, in North America and in Western Europe, some decline in cancer mortality has been observed. Thus, age-standardised cancer mortality rates for all neoplasms in the U.S.A. declined by 3.1% in both sexes combined between 1990 and 1995 [1]. Approximately half the decline was attributed to the levelling off in lung and other tobacco-related cancer epidemics, and the rest to several factors, including reduced exposure to occupational carcinogens, prevention and early diagnosis, and improved treatment.

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*Table* 1. *Age-standardised and sex-standardised mortality rates per* 100 000 *(world standard population) from selected causes in the European Union,* 1960–1994 [2]

| Year | All causes | All cancers | Lung cancer | Stomach cancer | Other cancers | CPM |
|---|---|---|---|---|---|---|
| 1960 | 824.2 | 140.5 | 19.5 | 24.9 | 96.1 | 17.7 |
| 1970 | 737.5 | 145.0 | 25.2 | 19.3 | 100.5 | 19.7 |
| 1980 | 635.2 | 146.1 | 29.7 | 13.7 | 102.7 | 21.9 |
| 1988 | 541.9 | 146.7 | 30.9 | 10.6 | 105.2 | 24.7 |
| 1990 | 526.2 | 143.9 | 30.2 | 9.9 | 103.8 | 24.7 |
| 1992 | 507.6 | 142.6 | 29.7 | 8.7 | 104.2 | 25.2 |
| 1994* | 468.0 | 133.1 | 26.9 | 8.2 | 98.0 | 25.8 |
| Change in rate 1988–1994 | −73.9 (−13.6%) | −13.6 (−9.3%) | −4.0 (−12.9%) | −2.4 (−22.6%) | −7.2 (−6.8%) | |

CPM, cancer proportional mortality. *Data were available up to 1992 for Belgium and 1993 for Denmark.

Within the European Union, mortality from all causes declined steadily by 43% between 1960 and 1994, but total cancer mortality rates in both sexes combined increased by 4.4%, to reach a peak in 1988 (Table 1). Thereafter, they declined by 9.3% in 1994. Likewise, lung cancer rates in both sexes combined increased by 59% between 1960 and 1988 and declined by 13% in 1994. Thus, over a third of the decline was accounted for by lung cancer alone, and approximately half by all tobacco-related neoplasms. Of the decline in total cancer mortality not attributable to tobacco, approximately half could be attributed to a steady fall in mortality from gastric cancer (Table 1).

Figure 1 illustrates the trends in mortality from major cancers in males and females in the European Union over the period 1955–1994. Since for several of these neoplasms there is little basis to expect substantial improvements in survival over the next few years, it is now clear that only through a better knowledge and more precise quantification of major causes and improved control, will it be possible to achieve a substantial reduction in cancer burden in the foreseeable future.

Across Europe, for total age-standardised (world standard population, period 1988–1992, excluding non-melanomatous skin cancers) incidence rates from all neoplasms, the overall variation was over a factor of two in males, with the highest (Trieste, 414/100 000) and the lowest incidence areas (Ragusa, 179/100 000) both in Italy (Figure 2). Other high incidence areas (>320/100 000) were in France, Northern Italy and Geneva, Switzerland. The lowest incidence rates (<230/100 000) were in Malta and Albacete, Spain. Several U.K. cancer registration areas had relatively low rates. For females, the range of variation was approximately a factor of two (Figure 2), between 262/100 000 in Denmark and 131/100 000 in Kielce, Poland. High incidence rates (>250/100 000) were also registered in Scotland, Trieste, Italy, Tyrol, Austria and the West Midlands, U.K. The lowest rates (<150/100 000) were in Belarus and some Spanish and Southern Italian registries.

These patterns in distribution of cancer incidence reflect the differing importance of lung and other tobacco-related sites in various European countries [5, 6], besides, the role of alcohol and diet on several common cancers, including stomach, colorectum, upper digestive and respiratory sites, but also breast, prostate and other genital sites.

Along these lines and with a specific focus on Europe, the major causes of cancer and, hence, the most important perspectives for prevention, will be reviewed.

## MAJOR AVOIDABLE CAUSES OF CANCER

*Tobacco*

In Europe, as well as in Japan and North America, between 80 and 90% of lung cancers in men, and between 55 and 80% of lung cancers in women, are attributable to cigarette smoking. Between 75 and 90% of cancers arising in the oesophagus, larynx and oral cavity are related to the effect of tobacco, both acting singly and jointly with alcohol consumption. Cancers of the bladder, pancreas, kidney and cervix are causally related to tobacco smoking, and there have been suggestions of an association with leukaemias, prostate and colorectal cancer, although the causal nature of these latter associations remains undefined. Thus, between 25 and 30% of all cancer deaths in Europe are due to tobacco smoking. Because of the length of the latency period, tobacco-related cancers observed today are mainly related to cigarette smoking patterns several decades ago [6].

There is now convincing evidence of the adverse health consequences of environmental tobacco smoking (ETS) or passive smoking. The United States Environmental Protection Agency declared in 1992 that ETS was a proven lung carcinogen in humans. The risk of lung cancer is increased by approximately 20% in non-smoking women who have husbands who smoke tobacco [7, 8].

There was a difference of a factor of four for male lung cancer incidence rates across Europe (Figure 3), between the highest rate in Lower Silesia, Poland (95/100 000) and the lowest in Sweden (24/100 000). The pattern was different in females since the highest lung cancer incidence rates (over 20/100 000) were in Scotland, U.K., Iceland and Denmark; the lowest were in Spain, Malta and Ragusa, in Southern Italy (Figure 3).

As in North America [9] in Europe [10] there have been important shifts in the incidence of different histological types of lung carcinoma, especially squamous cell carcinoma and adenocarcinoma. The latter seems to be at the origin of a new lung cancer epidemic, primarily attributable to changes in smoking patterns consisting chiefly of shifts to low-yield filtered cigarettes. The pattern of this epidemic is similar in the two genders, which suggests that similar exposures to (tobacco) carcinogens lead to similar histological type specific rates of lung carcinoma incidence among men and women [10].

Other specific and important points of the tobacco and cancer issue in Europe are the tobacco/alcohol interaction in the high mortality rates from upper digestive and respiratory

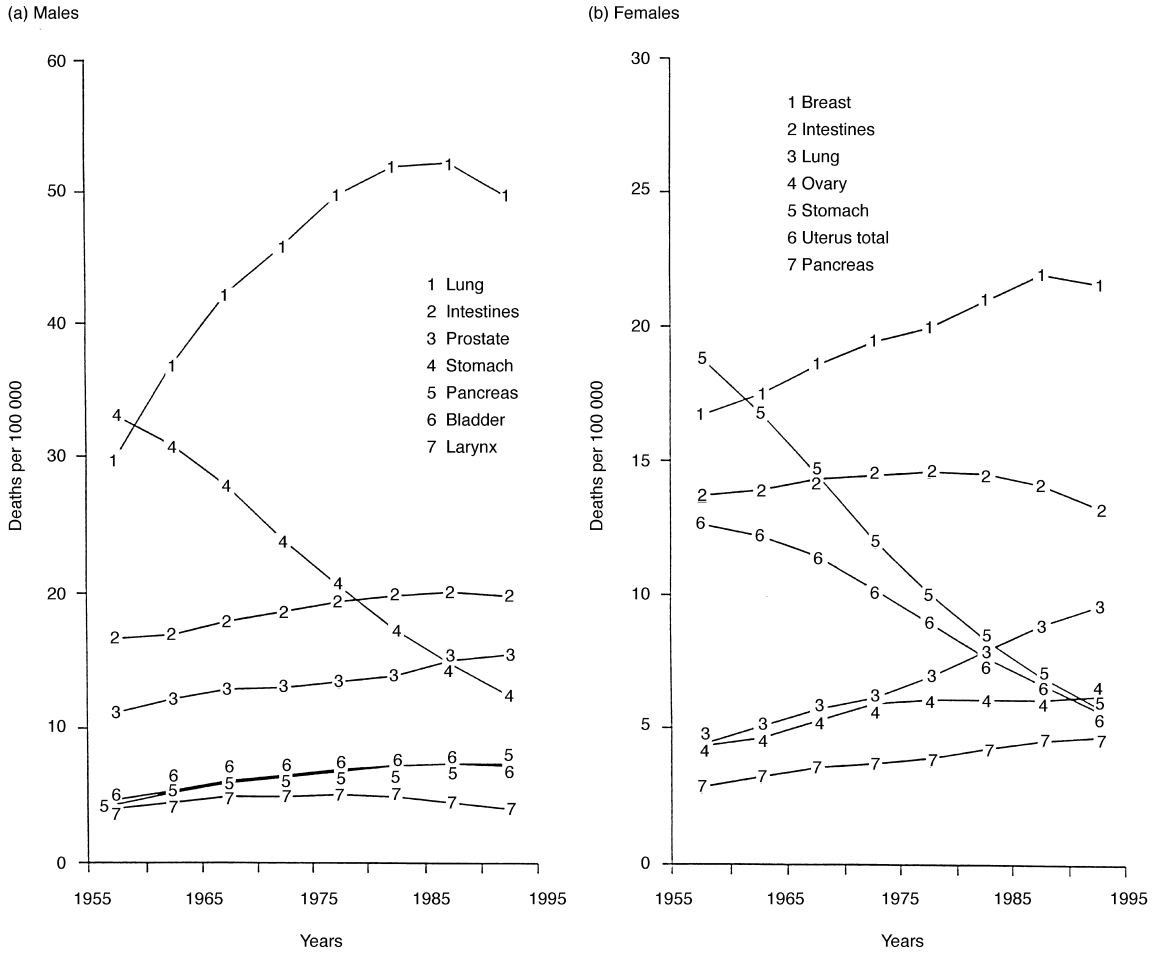



**Figure 1. Trends in age-standardised death certification rates (world standard) from seven selected cancers per 100 000 in the European Union, from 1955 to 1994 (source: WHO mortality database).**

tract neoplasms in France and other Southern European (and Eastern) countries, the delay in the lung cancer epidemic in females compared with the situation in North America (with the major exception of Denmark and the U.K.) and the different pattern of lung cancer rates in younger compared with older generations.

Trends in lung cancer mortality have reached, in the early 1990s, the highest rates ever registered within Europe in Hungarian and Polish males aged 35–64 years. Trends for males were also steadily upwards in other Eastern European countries, and in Southern Europe, including France, Spain and Greece, but not Italy (Figure 4). This indicates that Southern and, chiefly, Eastern European countries will have the highest lung cancer rates at the beginning of the next century, in the absence of urgent intervention on tobacco control [11–14].

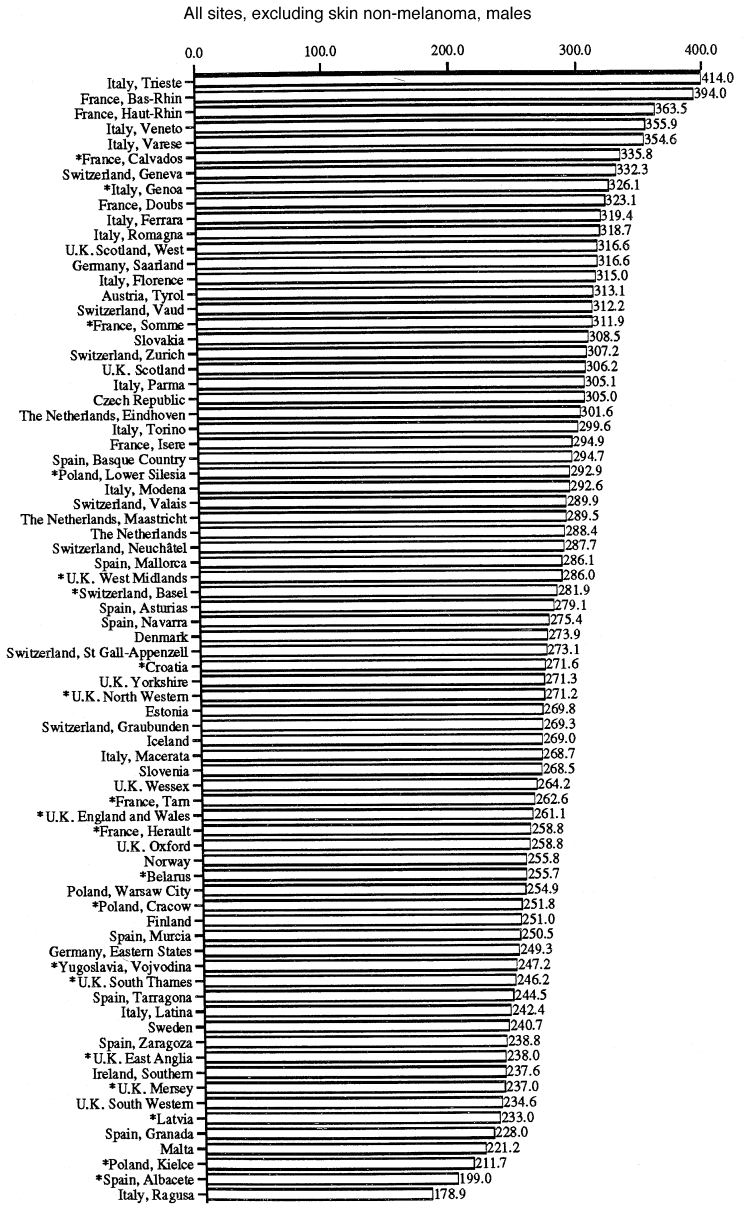
In Europe, approximately one in three adult males and one in four females are current cigarette smokers [15, 16]. In Central and Eastern Europe there is as yet no clear sign of a decrease in the smoking habit. The overall smoking prevalence of women, moreover, is lowered by the low rates in Southern Europe, but these rates are rising, and, in the absence of efficacious intervention, may continue to rise over the next decade. In addition, smoking prevalence in the age range 25–39 years is high (50% in men and 40% in women) and can be expected to have a substantial influence on the future cancer pattern.

A comprehensive European tobacco policy is necessary to reduce the health consequences of tobacco smoking, and this should be targeted via a variety of actions aimed at stopping young people starting smoking and to help smokers to quit. The importance of adequate interventions is demonstrated by the low lung cancer rates in Scandinavian countries which, since the early 1970s, have adopted integrated central and local policies and programmes against smoking. In the U.K., tobacco consumption has declined by 30% since 1970 and lung cancer mortality among men has decreased by over 30% since 1980, although the rate remains comparatively high. In France, between 1992 and September 1994 there was a 6% reduction in consumption of manufactured cigarettes due to the implementation of antitobacco measures introduced by Loi Evin [12].

Tobacco control remains more than ever an important public health priority. There are various elements to any tobacco control policy, but the importance of the medical and oncological community in setting an example is paramount. Health maintenance and disease prevention are increasingly important aspects of the work of the oncologist and the single most important of these is advice about the health hazards of tobacco smoking [9, 12].

*Alcohol*

Although alcohol is not known to be carcinogenic *per se* in animal experimentation, in humans there is strong epidemiological evidence that the consumption of alcoholic



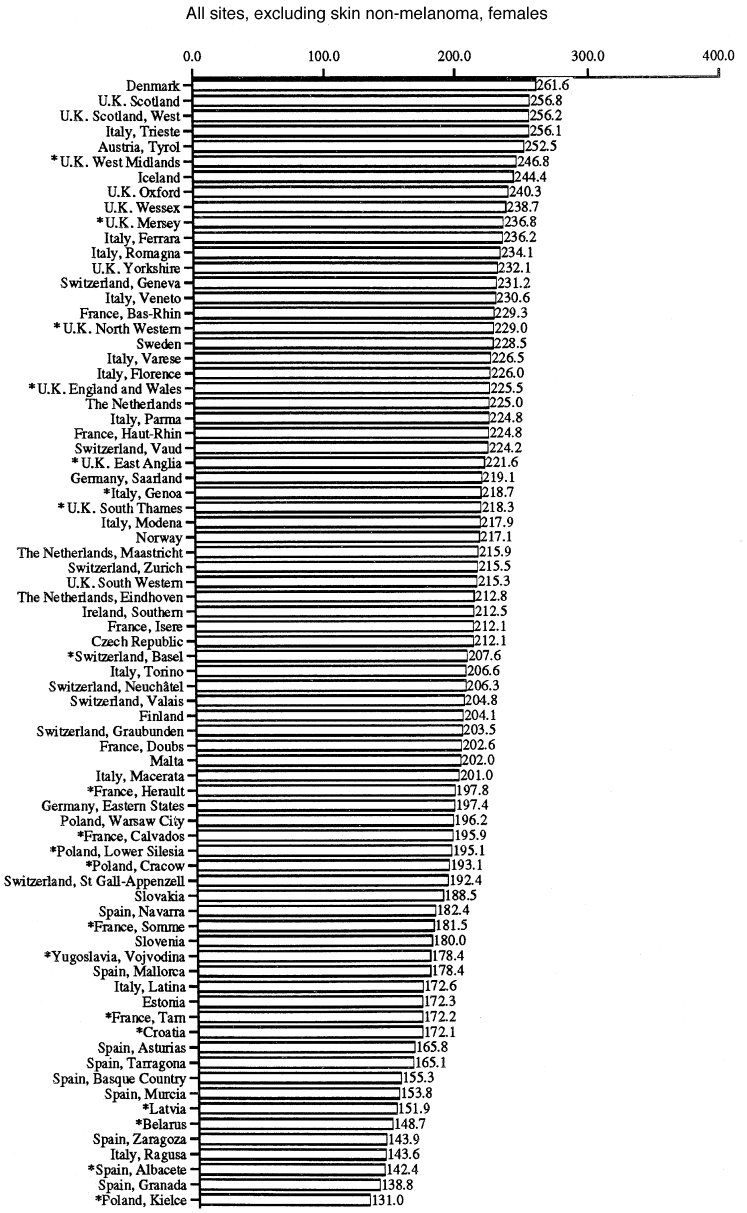




**Figure 2. Average age-standardised (world population) incidence rates of all cancer sites, excluding non-melanomatous skin cancers, per 100 000 in European cancer registry regions, 1988–1992 [4, 5].**

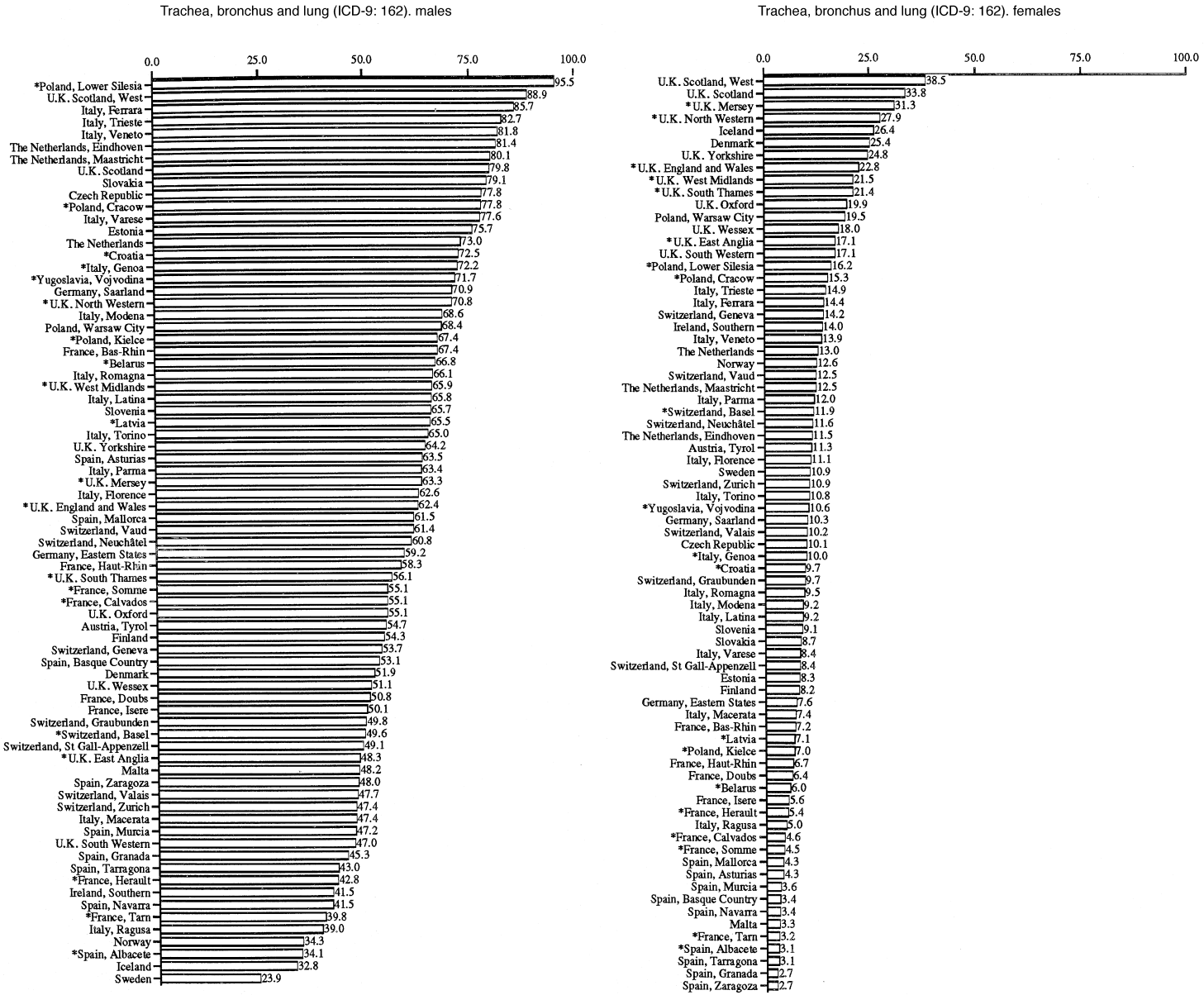



**Figure 3. Average age-standardised (world population) incidence rates of lung cancer per 100 000 in European cancer registry regions, 1988–1992 [4, 5].**

beverages increases the risk of cancers of the oral cavity and pharynx (other than the salivary glands and the nasopharynx), oesophagus and larynx. The risks are essentially due to ethanol content and appear to be linked to the most commonly used alcoholic beverage in each population. These risks tend to increase with the amount of ethanol drunk and it is unclear whether there is any defined threshold below which no effect is evident [17–19].

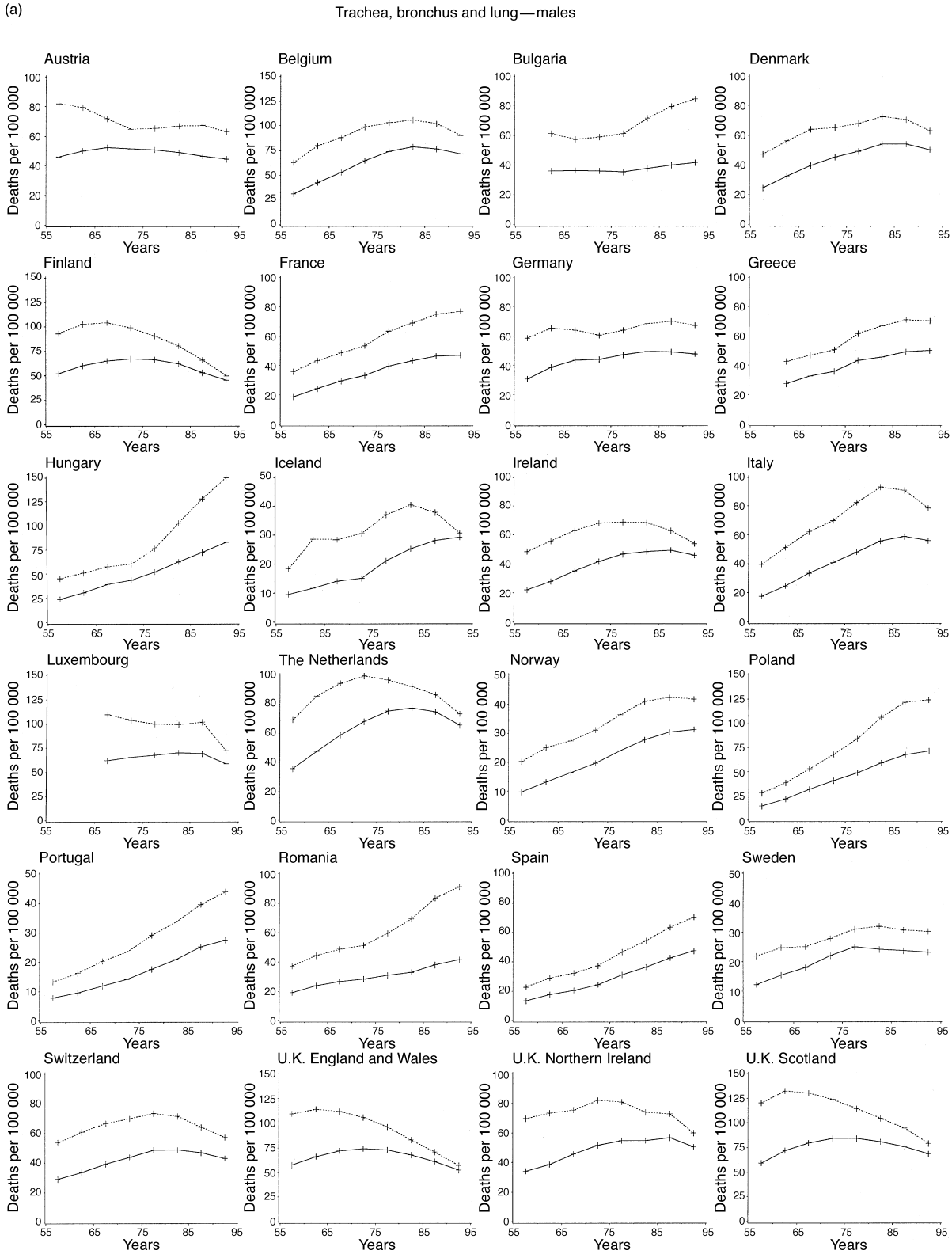



**Figure 4. Trends in age-standardised (world population) death certification rates from lung cancer at all ages and at age 35–64 years per 100 000 males (a) (+—+ all ages; +- - -+35–64 years) and females (b) (□—□ all ages; □- - -□ 35–64 years) in 24 European countries, 1955–1994 (source: WHO mortality database).**

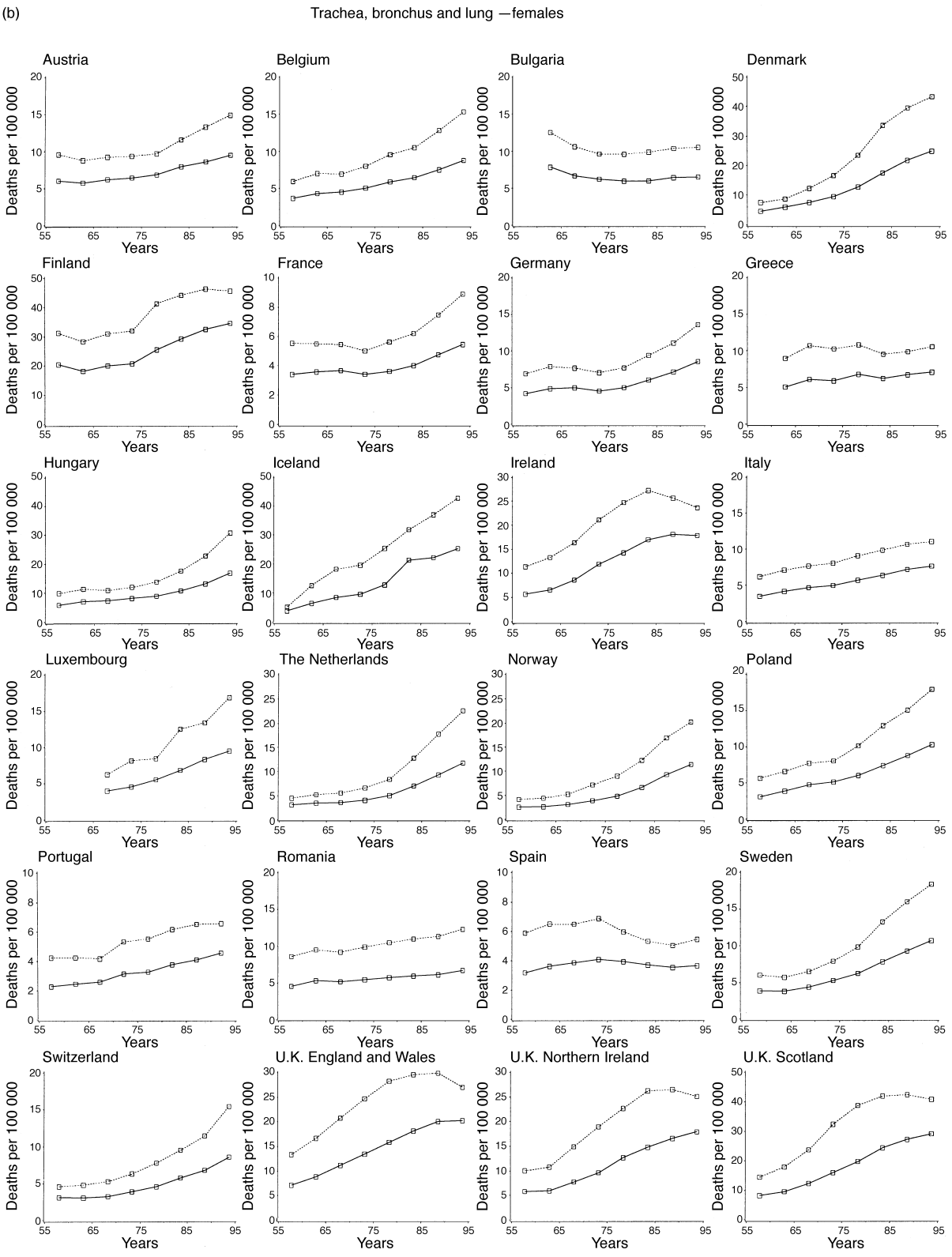



**Figure 4. (continued).**

The risk of alcohol on cancers of the upper digestive and respiratory tract is increased by smoking, each factor approximately multiplying the effect of the other: compared with people who have both never smoked and who were in the lowest drinking category, the relative risk of these neoplasms is increased several dozen times in heavy smokers and heavy drinkers [3, 18] (Table 2). Indeed, in the absence of drinking and smoking, the risk of oral, pharyngeal and laryngeal cancers in European populations is extremely low [18].

Alcohol increases the risk of upper digestive and respiratory tract neoplasms, even in the absence of smoking, although the risks are limited to populations from developed

*Table 2. Odds ratios (OR)* for oral cavity/pharynx, larynx and oesophageal cancers in males according to smoking and alcohol drinking habit: Northern Italy,* 1986–1989 [3]

| | Alcohol intake, drinks/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 | |

*Estimates from multiple logistic regression equation including age, area of residence, years of education, occupation, drinks per week and smoking habits, as appropriate. †Smoking status was defined in four categories: non-smokers; light, ex-smokers who quit ≥10 years ago, or smokers of 1–14 cigarettes/day for <30 years; intermediate, 15–24 cigarettes/day regardless of duration, 30–39 years' duration regardless of amount, 1–24 cigarettes/day for ≥40 years or ≥15 cigarettes/day for <30 years; heavy, smokers of ≥25 cigarettes/day for ≥40 years. ‡Reference category.

countries, unless the consumption is extremely high [20]. This suggests that alcohol may facilitate the carcinogenic effect not only of tobacco, but also of other carcinogenic agents to which the upper digestive and respiratory tract are exposed, including those of dietary origin [18]. With reference to the role of different types of alcoholic beverages, although it has been suggested that 'strong' drinks are more deleterious, at comparable levels of alcohol, the evidence is inconclusive. Indeed, the most frequently consumed beverage in each population (and, hence, probably the cheapest one) tends to be the one with the highest estimated relative risk in each population [21].

Besides these established associations, alcoholic beverages have also been linked to cancers of the large bowel in both sexes [18] and of the female breast [22]. Although these associations are moderate and, hence, remain open to discussion, these are the two most common neoplasms in Europe after lung cancer [5, 23, 24] and, therefore, even a small risk for alcohol drinking may have important public health implications.

For female breast cancer, there is some evidence showing that a daily alcohol intake as low as 15 g/day (i.e. approximately, one drink per day) may already be associated with some increase in risk. The lowest limit associated with a significant risk of other cancer sites (such as cancers of the upper digestive and respiratory tract, liver or colorectum) is probably somewhat higher (about 30 g/day) and this would be particularly true for males.

Within Europe, a major problem is due to the high alcohol consumption and alcohol-related mortality in most Central European countries. Hungary, the Czech Republic and Poland have now the highest mortality rates for cancers of the oral cavity and pharynx, oesophagus and larynx across Europe [5, 13, 25]. Urgent intervention on the alcohol-related cancer—and other major disease—epidemics in these countries is, therefore, required.

*Diet*

In 1981, Doll and Peto provided an estimate of the proportion of cancer deaths in the U.S.A. attributable to diet of 35%, with, however, a wide range of acceptable estimates, from 10 to 70% [26].

The substantial amount of epidemiological research published over the last 20 years has confirmed, at least in first approximation, that estimate, but restricted its range of acceptable variation. There is, however, still scope for discussion on how wide a range can now reasonably be accepted [27–29].

Thus, it is now established that a diet rich in fresh fruits and vegetables is protective to the risk of most common epithelial cancers. The relationship between frequency of consumption of vegetables and fruit and cancer risk was analysed using data from a series of case–control studies conducted in Northern Italy between 1983 and 1997 [30]. The relative risks for digestive tract neoplasms ranged from 0.2 to 0.5 for the highest compared with the lowest tertile of vegetable intake. Protective effects were also observed for several hormone-related neoplasms. Fruit was related to reduced relative risks for cancers of the upper digestive tract, stomach and of the urinary tract (Table 3). For digestive tract cancers, population attributable risks for a low intake of vegetables and fruit ranged between 15 and 40% [31].

Other aspects of diet are also likely to influence cancer risk, and among these, red meat is of specific relevance. In a coordinated series of studies from Italy, the multivariate relative risks for the highest tertile of meat intake (≥7 times per week) compared with the lowest (≤3 times per week) were 1.7 for stomach, 2.0 for colon, 1.9 for rectal, 1.6 for pancreatic, 1.5 for bladder, 1.5 for endometrial and 1.3 for ovarian cancer. This points to meat intake as the second most important factor (after vegetables and fruits) in the nutritional aetiology of human cancer [29].

Whole grain food intake has been consistently related to reduced risk of colorectal cancer, but also of several other sites. In an Italian network of case–control studies, the relative risks for the highest category of consumption of whole grain foods were 0.2–0.3 for upper digestive and respiratory tract neoplasms, 0.5 for stomach, colon and gallbladder, 0.7 for rectum, 0.6 for liver, 0.8 for pancreas and prostate, 0.9 for breast and endometrium, 0.6 for ovary, 0.4 for bladder and kidney, and approximately 0.5 for lymphomas and myeloma. Thus, even in the absence of an unequivocal and satisfactory biological interpretation, in that population, a higher frequency of whole grain food intake was an indicator of a reduced cancer risk [32].

With reference to a specific role of fibres, several case-control studies have reported a protective effect of fibre on colon and rectal cancer [33]. A combined analysis of 13 case–control studies reported relative risks of colorectal cancer of 0.79, 0.69, 0.63 and 0.53 for subsequent quintiles of intake compared with the lowest [34]. In an Italian case–control study [35] of 1225 cases of colon cancer, 725 of rectal cancer

*Table 3. Odds ratios* (and 95% confidence intervals) of selected cancers according to vegetable and fruit consumption (total number of cases=11 990; total number of controls=10 058). Italy, 1983–1997* [30]

| | Vegetables, level of consumption | | Fruit, level of consumption | | |
|---|---|---|---|---|---|
| Site of cancer | Intermediate | High | Intermediate | High | Total number of cases |
| Oral cavity and pharynx | 0.73 (0.6–0.9) | 0.74 (0.6–0.9) | 0.68 (0.5–0.9) | 0.45 (0.4–0.6) | 524 |
| Oesophagus | 0.49 (0.4–0.6) | 0.33 (0.3–0.4) | 0.62 (0.5–0.8) | 0.37 (0.3–0.5) | 410 |
| Stomach | 0.76 (0.6–0.9) | 0.49 (0.4–0.6) | 0.70 (0.6–0.9) | 0.44 (0.4–0.6) | 745 |
| Colon | 0.92 (0.8–1.1) | 0.56 (0.5–0.7) | 0.93 (0.5–1.1) | 0.63 (0.5–0.8) | 955 |
| Rectum | 0.99 (0.8–1.2) | 0.68 (0.6–0.9) | 1.10 (0.9–1.4) | 0.76 (0.6–0.9) | 625 |
| Liver | 0.74 (0.6–0.9) | 0.39 (0.3–0.5) | 1.33 (1.0–1.8) | 1.03 (0.8–1.4) | 435 |
| Gallbladder | 0.67 (0.4–1.2) | 0.30 (0.2–0.6) | 0.86 (0.4–1.6) | 0.42 (0.2–0.8) | 65 |
| Pancreas | 0.70 (0.6–0.9) | 0.39 (0.3–0.5) | 0.83 (0.6–1.1) | 0.65 (0.5–0.8) | 402 |
| Larynx | 0.66 (0.5–0.9) | 0.44 (0.3–0.6) | 0.54 (0.4–0.7) | 0.51 (0.4–0.7) | 388 |
| Soft tissue sarcomas | 1.05 (0.7–1.6) | 1.34 (0.9–1.9) | 1.08 (0.7–1.6) | 0.97 (0.7–1.6) | 217 |
| Breast | 0.91 (0.8–1.0) | 0.76 (0.7–0.9) | 0.93 (0.8–1.1) | 1.12 (0.7–1.3) | 3412 |
| Endometrium | 0.89 (0.7–1.1) | 0.52 (0.4–0.7) | 1.10 (0.8–1.4) | 0.90 (0.7–1.2) | 750 |
| Ovary | 0.97 (0.8–1.2) | 0.70 (0.6–0.8) | 1.17 (0.9–1.5) | 1.27 (1.0–1.6) | 971 |
| Prostate | 0.72 (0.5–1.1) | 0.16 (0.1–0.3) | 0.88 (0.6–1.4) | 0.48 (0.3–0.8) | 127 |
| Bladder | 0.78 (0.6–1.0) | 0.17 (0.1–0.2) | 1.07 (0.8–1.4) | 0.50 (0.4–0.7) | 431 |
| Kidney | 0.92 (0.7–1.3) | 0.24 (0.1–0.4) | 1.05 (0.7–1.6) | 0.63 (0.4–0.9) | 190 |
| Thyroid | 0.68 (0.5–0.9) | 0.83 (0.6–1.1) | 1.22 (0.9–1.7) | 1.26 (0.9–1.7) | 428 |
| Hodgkin's disease | 1.06 (0.7–1.6) | 0.90 (0.6–1.3) | 0.73 (0.5–1.1) | 0.82 (0.6–1.2) | 201 |
| Non-Hodgkin's lymphomas | 0.99 (0.8–1.3) | 1.10 (0.9–1.4) | 0.85 (0.6–1.1) | 0.95 (0.8–1.2) | 529 |
| Multiple myeloma | 0.92 (0.6–1.3) | 0.71 (0.5–1.0) | 1.03 (0.7–1.6) | 1.14 (0.8–1.7) | 185 |

*Estimates from multiple logistic regression equations including terms for age, area of residence, calendar period at interview, education, smoking, alcohol consumption and (when required) sex. Reference category=low level (i.e. lowest tertile) of consumption. Controls were patients admitted to hospital for acute, non-neoplastic conditions, unrelated to long-term dietary modifications. CI, confidence interval.

and 4154 controls, when the unit was set at the difference between the 80th and 20th percentiles, the odds ratios for colorectal cancer were 0.68 for total fibre, 0.67 for soluble non-cellulosic polysaccharides (NCP), 0.71 for total insoluble fibre, 0.67 for cellulose, 0.82 for insoluble NCP and 0.88 for lignin. Data from cohort studies are, however, less consistent [36].

In contrast, refined grain intake has been associated with increased risk of stomach, colorectal, breast, upper digestive sites and thyroid cancers in studies conducted in Mediterranean populations [37]. Whole grain foods should, therefore, replace refined cereal ones, whenever possible.

The issue of fats, and of specific types of fats, on the risk of colorectal and breast cancers, as well as of several other neoplasms, remains, in contrast, a major debatable issue on a prevention and public health level. In large studies from Italy, isocaloric substitution of 5% of total calories as saturated fats by unsaturated ones was associated with reductions in breast and colorectal cancer risk [37]. Part of the benefit of mono- and poly-unsaturated fats in the Italian diet, as well as in other populations, may be due to the positive correlation between (olive) oil and vegetable intake. It seems, in fact, that substituting (olive) oil for other seasoning fats has favourable effects on the risk of breast cancer [38–42].

In any case, a low risk diet for cancer would not only imply increasing fruit and vegetables, avoiding increasing red meat, but also refined carbohydrate consumption, and preferring olive oil and other unsaturated fats to saturated ones [37].

*Overweight*

Overweight and obesity are related to at least three cancer sites: gallbladder, endometrium and breast in postmenopausal women [43]. The relative risks are of the order of five for obese individuals as compared with leaner ones, for gallbladder and endometrium, but only approximately 30–50% higher for breast cancer. Since mortality rates from breast cancer are substantially higher than from gallbladder and endometrial neoplasms, the public health implications of elevated breast cancer rates in overweight individuals are probably greater than for other neoplasms [44].

Further, the American Cancer Society One Million Cohort Study [43], the cohort of 50 000 American Alumni [45] and several case–control studies found a direct association between measures of body weight and renal cell adenocarcinoma [46]. Overweight and obesity have been related to colorectal and prostatic cancer, too, although the extent of the association is still unclear.

The uncertainties and the limitations of published work, however, still cannot eclipse the importance, on a public health scale, of overweight and obesity as a cause of human cancer. In the U.S.A., in fact, approximately 2% of all cancer deaths are due to overweight [26]. Although in Europe this proportion may be somewhat lower, due to the lower prevalence of overweight in Europe [47], this is not only relevant from a public health viewpoint, but also has important and immediate implications for prevention.

Overweight is a major aspect of nutrition and diet to be so well defined in epidemiological terms as to open immediate perspectives for intervention and prevention. However, the prevalence of overweight and obesity has been rising over the last few decades in the U.S.A. [48] and in Europe (Table 4) [47], indicating the importance for re-defining the strategy for controlling this important risk factor on a population level.

*Table 4. Age-adjusted distributions of a representative sample of Italians according to body mass index, 1983–1994; Italian National Health Surveys* [47]

| | Men (%) | | | Women (%) | | | Total (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| Body mass index (kg/m$^2$) | 1983 ($n$=34 787) | 1990/1991 ($n$=24 602) | 1994 ($n$=6307) | 1983 ($n$=37 497) | 1990/1991 ($n$=26 090) | 1994 ($n$=6741) | 1983 ($n$=72 284) | 1990/1991 ($n$=50 692) | 1994 ($n$=13 048) |
| <20 | 7.5 | 4.4 | 5.4 | 19.8 | 17.2 | 18.1 | 13.9 | 11.0 | 12.0 |
| 20–24.9 | 51.4 | 49.4 | 48.6 | 51.3 | 52.2 | 50.5 | 51.3 | 50.8 | 49.6 |
| 25–29.9 | 34.1 | 39.2 | 39.6 | 21.3 | 24.5 | 25.0 | 27.4 | 31.6 | 32.0 |
| ≥30 | 7.1 | 7.0 | 6.5 | 7.6 | 6.1 | 6.3 | 7.4 | 6.5 | 6.4 |

*Occupational and environmental factors*

Estimates of the proportion of cancer deaths attributable to occupational and environmental carcinogens are complex and difficult, for any specific population, apart perhaps from the effect of past occupational exposure to asbestos, which may account by itself for 50% of all occupational cancer deaths [26].

Projections for the period 1995–2029 suggest that the number of men dying from mesothelioma in Western Europe each year will almost double over the next 20 years from more than 5000 in 1989 to at least 10 000 around 2018 and then decline, with a total of approximately 250 000 deaths over the next 35 years (Figure 5) [49]. The highest risk will be suffered by men born around 1945–1950, of whom approximately 1 in 150 will die of mesothelioma. Asbestos use in Western Europe remained high until about 1980 and substantial quantities are still used in several European countries.

Occupational causes of cancer represent a priority for research, occupational medicine and public health, since when a carcinogen is identified, it is possible to regulate, substantially modify or eliminate the exposure, as shown, for instance, by the measures adopted after identifying the association between vinylchloride monomer and angiosarcoma of the liver [50, 51].

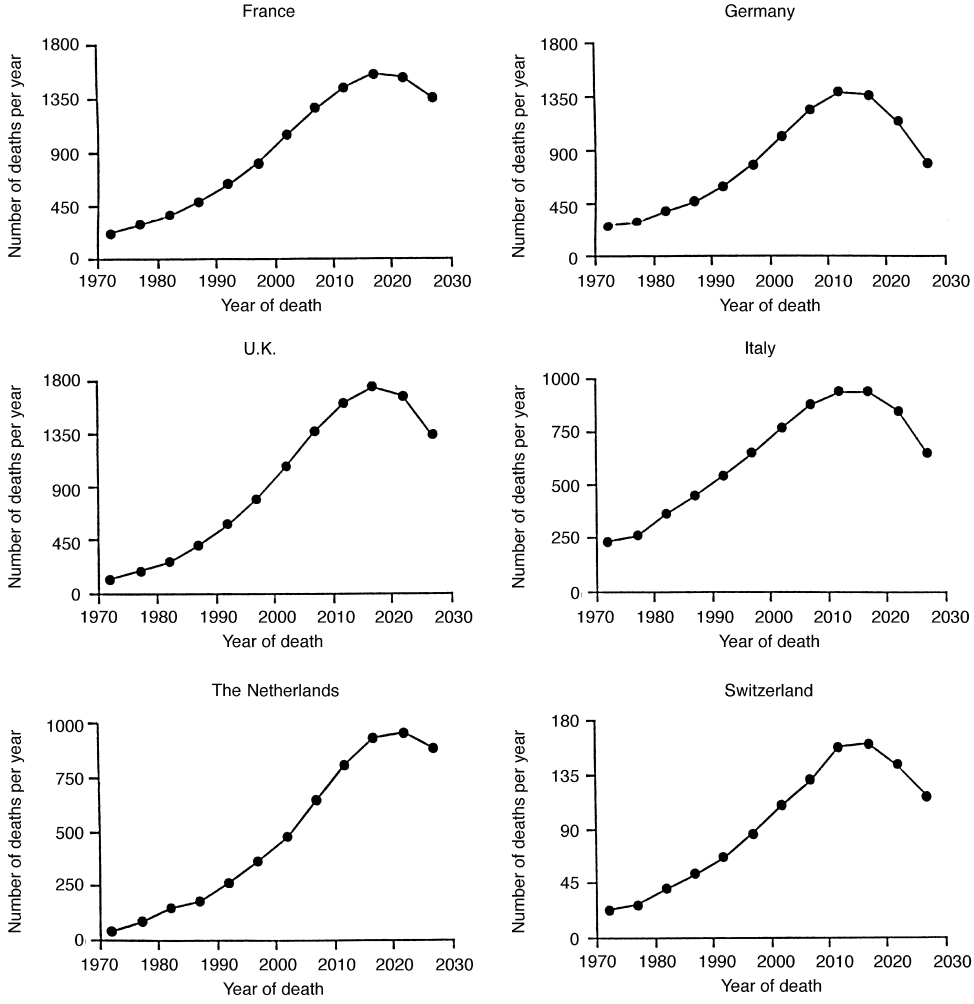



**Figure 5. Observed (to 1989) and predicted (1990–2029) annual numbers of pleural cancer deaths in men in six Western European countries [49].**

It is even more complex to quantify the role of environmental pollution, in consideration of the lowest levels and of the widespread nature of the exposure for the general population. Apart from ETS, the major environmental carcinogens have probably been related to air pollution in large urban conurbations in the past, which may have accounted for up to 5% of lung cancer and 1% of all cancer deaths for the most exposed generations in the 1950s and 1960s [52, 53]. A synergism between environmental pollution and tobacco smoking is also likely; consequently, smokers are at substantially higher risk for these carcinogens, too.

*Radiation*

This section includes ionising radiation, of cosmic and soil origin, as well as residual fallout of nuclear experiments in the atmosphere made in the 1950s and 1960s. Further, there are medical uses of radiation which have substantially improved over the last few years, but for which some further optimisation of use would be possible [26].

Moreover, there are non-ionising radiations, mainly sunshine and other sources of ultraviolet, which cause skin cancer—including melanomas—and which are responsible for up to 1% of cancer deaths in Europe.

Incidence and mortality from skin melanoma have substantially increased in all European countries between 1950 and 1990, and only over the last few years a levelling of trends became evident in younger generations, probably reflecting a more cautious pattern of ultraviolet exposure, and more widespread adoption of individual sun protection, as well as better surveillance and earlier diagnosis of skin lesions [54].

It is important, in any case, to avoid acute exposure to sunshine, mainly in the central hours of the day and particularly for children. The use of sunscreens effective against both UVA and UVB should be encouraged, while the use of ultraviolet for tanning purposes avoided.

*Infectious agents*

The most important infectious causes of cancer worldwide are hepatitis B and C viruses, which are strongly associated with liver cancer, the fifth most common cancer worldwide, accounting for 5% of cancers in both sexes [55]. Vaccination is available for hepatitis B and has been adopted in newborn babies and adolescents not only in Taiwan, but also in a few European countries, such as Italy, where liver cancer rates were, and still are, high. Only primary prevention is at present available for hepatitis C.

Human papilloma virus (HPV) is the major cause of cervical cancer, still a common neoplasm in women from developing countries, and may be related to oral, pharyngeal and laryngeal cancer, as well as to skin cancer too [56], although the evidence is still inconclusive [57].

*Helicobacter pylori* is a strong risk factor for gastric ulcer and, particularly when contracted early in life, may be associated with gastric cancer too [58].

Various viral agents have been sporadically related to lymphoid neoplasms, although they are still incompletely understood, apart from the association between Epstein–Barr virus and Burkitt's lymphoma and that between Herpes virus 8 and Kaposi's sarcoma [59].

These uncertainties notwithstanding, infectious agents account for a substantial proportion (which may well approach 15%) of all neoplasms worldwide. This proportion is probably lower in the Western world, including Europe.

## SCREENING AND EARLY DIAGNOSIS

Screening for cancer was reviewed by Jack Cuzick in an earlier Millennium Review [60], and only some main quantitative aspects will be mentioned here.

A more rational approach to cervical screening (Pap test) could further reduce the risk of this neoplasm and avoid up to 1% of cancer mortality in some areas of Europe.

It is also likely that rational indication of mammography can reduce breast cancer mortality by 20–30% in women aged 50–70 years. Early diagnosis and surveillance have been shown to be favourable in skin melanoma [61] and screening procedures have been suggested to reduce mortality from colorectal and prostate cancer. Data on these neoplasms, however, are at present inadequate to formulate actions at a public health level [62].

## POTENTIAL IMPACT OF NEWER THERAPIES ON THE PREVENTION OF CANCER DEATHS

It is difficult to understand and quantify the potential impact of newer treatment on cancer survival. For several of these neoplasms, there is little basis to suggest any material improvement, but even in the case of breast cancer, where a 10% improvement in survival may have been achieved [63, 64], this can easily be missed within the changes of incidence.

There are, however, a few selected neoplasms or groups of neoplasms for which the progress in therapy over the last few decades has been substantial, including lymphoid neoplasms and germ cell tumours. However, for these cancers, the availability and utilisation of efficacious therapies has not been uniform and timely across Europe.

In particular, in Western European countries, Hodgkin's disease mortality fell substantially, generally starting from the late 1960s or early 1970s. The overall decline was over 60% in both sexes. The decline in Hodgkin's disease mortality was not observed or much less consistent in most Eastern European countries. Assuming that trends comparable with those registered in Western Europe were observed in the East, this could lead to the avoidance of a further 1000 deaths per year [65].

With reference to leukaemias, the average decline in mortality rates for Western Europe over the last three decades has been over 35% in both sexes, corresponding to the avoidance of over 5000 deaths per year. These declines were greater in childhood, but were observed throughout young adulthood and middle age. Efficacious chemotherapy for leukaemias (particularly, acute lymphoblastic leukaemia) has been available since the early 1960s, and its impact on national mortality rates has been observed starting from the late 1960s or early 1970s. For leukaemias in those under the age of 65 years, some decline in mortality has been observed in most Eastern European countries too, starting in the 1980s, and led to the avoidance of approximately 800 deaths per year, a figure which could be raised up to 2-fold, assuming a generalised application of the best available treatments [66].

Childhood cancers also show major potentials for improvement. All Western European countries have shown substantial declines in mortality over the last few decades, with an average fall of over 50% in both sexes and an estimated total number of approximately 3000 avoided deaths. Favourable trends have also been observed in Eastern Europe, but the declines have been only approximately 30%, with an estimated number of approximately 1000 deaths

avoided per year. There is, therefore, scope and possibility for some further improvement in childhood cancer mortality through widespread adoption of currently available techniques, particularly since childhood cancer rates in North America have persistently been lower from the early 1970s onwards than those of Europe or other developed areas of the world [67].

In Western European countries, mortality rates from testicular cancer have been substantially declining in the last two decades. The average fall in rates has been over 50% in the whole of Western Europe, corresponding to the avoidance of approximately 800 deaths per year, if the rates of the late 1950s were applied to the population structure of the early 1990s. The progress may well have been larger, since incidence rates of testicular cancer have been rising in most developed countries over the last few decades. In Eastern Europe, where the impact of newer therapies has probably been limited, mortality rates increased by an average of approximately 60% and have not yet started to decline [12, 66].

Overall, the figures of cancer deaths avoidable through the development and implementation of newer therapies represent approximately 2% of the cancer deaths registered per year in Europe. The public health and social impact is, however, much larger than this crude figure, since most of these deaths avoided are in the young and middle-aged population and are consequently much more relevant in terms of years of life saved.

An estimation of any potential impact of therapies is difficult for other cancer sites. Mortality from cancers of the stomach and of the cervix uteri declined substantially, but these favourable trends cannot be attributed to therapy, nor to better control of identified risk factors, although at least part of the fall in cervical mortality is due to screening. It is none the less possible that some progress is concealed in the trends in mortality from a few common cancers, particularly breast cancer [68], and, even if limited in terms of the percentage decrease of mortality, this would have a major public health impact on account of the much higher incidence of those neoplasms.

For several reasons, therefore, the estimates given should be taken as a lower limit of the impact of the progress induced by anticancer drugs in Europe. This cannot eclipse, however, the second major message emerging from this report, that there is an appreciable scope for further improvement in cancer treatment in Europe and particularly Eastern Europe, through a more widespread and rational application of currently available treatments.

Finally, it is also possible that chemoprevention has some impact on avoiding cancer deaths over the next decade. This includes tamoxifen for breast cancer, aspirin and possibly selective cyclooxygenase-2 (COX-2) [69, 70] inhibitors, retinoids and perhaps other micronutrients, which are now being investigated on an experimental basis [71–74]. It is difficult, if at all possible, to provide an estimate of the number of deaths avoidable through chemopreventive interventions over the next few years.

It is clear, in any case, that primary prevention will remain the major available resource for cancer control over the next few years, allowing in principle to avoid up to 40% of cancer deaths, simply through rational implementation of available knowledge on a population level. Such progress has already been observed in middle-aged (35–64 years) males in Finland, whose total cancer mortality declined from 276.8/100 000 in 1955–1959 to 158.4/100 000 in 1990–1994 [5, 75].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