

Contribution of environmental factors to cancer risk

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Environmental carcinogens, in a strict sense, include outdoor and indoor air pollutants, as well as soil and drinking water contaminants. An increased risk of mesothelioma has consistently been detected among individuals experiencing residential exposure to asbestos, whereas results for lung cancer are less consistent. At least 14 good-quality studies have investigated lung cancer risk from outdoor air pollution based on measurement of specific agents. Their results tend to show an increased risk in the categories at highest exposure, with relative risks in the range 1.5–2.0, which is not attributable to confounders. Results for other cancers are sparse. A causal association has been established between exposure to environmental tobacco smoke and lung cancer, with a relative risk in the order of 1.2. Radon is another carcinogen present in indoor air which may be responsible for 1% of all lung cancers. In several Asian populations, an increased risk of lung cancer is present in women from indoor pollution from cooking and heating. There is strong evidence of an increased risk of bladder, skin and lung cancers following consumption of water with high arsenic contamination; results for other drinking water contaminants, including chlorination by-products, are inconclusive. A precise quantification of the burden of human cancer attributable to environmental exposure is problematic. However, despite the relatively small relative risks of cancer following exposure to environmental carcinogens, the number of cases that might be caused, assuming a causal relationship, is relatively large, as a result of the high prevalence of exposure.

Introduction

The concept of environment is often used with a broad scope in the medical literature, including all non-genetic factors such as diet, lifestyle and infectious agents. In this broad sense, the environment is implicated in the causation of the majority of human cancers¹. In a more specific sense, however, environmental factors include only the (natural or man-made) agents encountered by humans in their daily life, upon which they

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have no or limited personal control. The most important 'environmental' exposures, defined in this strict sense, include outdoor and indoor air pollution and soil and drinking water contamination.

In this review of the evidence linking exposure to selected (narrowly defined) environmental factors and risk of cancer, we consider the following sources of environmental exposure to possible carcinogens: asbestos, outdoor air pollution including residence near major industrial emission sources, environmental tobacco smoke (ETS), indoor radon, other sources of indoor air pollution, arsenic in drinking water, chlorination by-products in drinking water, and other drinking water pollutants. We do not consider agents whose exposure depends on lifestyle, such as solar radiation and food additives, nor agents occurring in the environment as a consequence of accidents or warfare. Whenever possible, we attempt a quantification of the burden of environmental cancer in the European Union, comprising 15 countries, as of 2003.

Cancer risk from environmental exposure to asbestos

Asbestos and asbestiform fibres are naturally occurring fibrous silicates with an important commercial use, mainly in acoustical and thermal insulation. They can be divided into two groups: chrysotile and the group of amphiboles, including amosite, crocidolite, anthophyllite, actinolite and tremolite fibres. Chrysotile is the most widely used type of asbestos. Although all types are carcinogenic to the lung and mesothelioma, the biological effects of amphiboles on the pleura and peritoneum seem to be stronger than those of chrysotile². The use of asbestos has been restricted or banned in many countries.

In contrast to the many epidemiological studies available on asbestos-exposed workers, there are few studies on the health effects of non-occupational (household and residential) exposure to asbestos. One type of household exposure concerns cohabitants of asbestos workers and arises from dust brought home on clothes. Other household sources of asbestos exposure are represented by the installation, degradation, removal and repair of asbestos-containing products. Residential exposure mainly results from outdoor pollution related to asbestos mining or manufacturing, in addition to natural exposure from the erosion of asbestos or asbestiform rocks. The assessment of non-occupational exposure to asbestos presents difficulties, since levels are generally low, and the duration and frequency of exposure and the type of fibre are seldom known with precision.

Table 1 summarizes the results of studies on risk of pleural mesothelioma and lung cancer from environmental (residential) exposure to asbestos. Studies were available from various countries and, in most cases, exposure was defined as residence near a mine or another major source of asbestos

Table 1 Studies of risk of mesothelioma and lung cancer from environmental exposure to asbestos

| Country | SD | TF | Source of exposure | Mesothelioma | | | Lung cancer | | | Reference |
|---------------------------|----|----|--|--------------|------|----------|-------------|-----|---------|--|
| | | | | Ca | RR | 95% CI | Ca | RR | 95% CI | |
| South Africa | Ec | A | Res. in mining area | 61 | 8.7 | 6.7–11.4 | 86 | 1.7 | 1.2–2.5 | Botha <i>et al</i> ^{3a} |
| South Africa | CC | A | Res. in mining areas | | | | 16 | 3.6 | 1.4–9.3 | Mzileni <i>et al</i> ^{4a} |
| Canada | Co | C | Res. in mining area | 7 | 1.3 | 0.5–3.0 | | | | Theriault and Grand-Bois ^{5a} |
| Canada | Ec | C | Res. in mining area | 7 | 7.6 | 3.4–14.9 | 71 | 1.1 | 0.9–1.4 | Camus <i>et al</i> ^{6b} |
| USA | CC | A | Res. near to asbestos plant | | | | 41 | 0.9 | 0.6–1.3 | Hammond <i>et al</i> ⁷ |
| Austria | Ec | A | Res. in polluted town | | | | 36 | 0.8 | 0.4–1.6 | Neuberger <i>et al</i> ^{8a} |
| Italy | Co | UM | Res. <1 km from asbestos cement plant | 36 | 6.6 | 4.1–11 | | | | Magnani <i>et al</i> ^{9a} |
| Italy | CC | UM | Res. in polluted city | 32 | 14.6 | 4.9–43.1 | | | | Magnani <i>et al</i> ^{10a} |
| Italy, Spain, Switzerland | CC | UM | Res. <2 km from potential source | 17 | 11.5 | 3.5–38.2 | | | | Magnani <i>et al</i> ¹¹ |
| UK | CC | A | Res. <0.5 miles from asbestos factory | 11 | 5.4 | 1.8–17 | | | | Newhouse and Thompson ¹² |
| UK | CC | A | Res. <0.5 km from potential source | 5 | 6.6 | 0.9–50 | | | | Howel <i>et al</i> ¹³ |
| China | CC | C | Res. >20 years <0.2 km from asbestos plant | NA | 182 | NA | 47 | 1.9 | 0.5–6.4 | Xu <i>et al</i> ^{14a} |
| China | Co | A | Res. in polluted area | | | | NA | 5.7 | NA | Luo <i>et al</i> ¹⁵ |
| New Caledonia | CC | A | Use of contaminated building materials | 14 | 40.9 | 5.1–325 | 56 | 0.9 | 0.6–1.3 | Luce <i>et al</i> ^{16a} |
| Australia | CC | A | Res. >5 years in mining area ^c | 14 | 6.7 | 2.0–22.2 | | | | Hansen <i>et al</i> ¹⁷ |

SD, study design: CC, case-control study; Co, cohort study; Ec, ecological study; TF, predominant type of fibre: A, amphiboles; C, chrysotile; UM, unspecified and mixed; Res., residence; Ca, number of exposed cases; RR, relative risk; CI, confidence interval.

^aResults derived from raw data reported in the publication.

^bWomen only.

^cCompared to residence <1 year.

exposure. A potential limitation of these studies, in particular those without assessments of exposure at the individual level ('ecological' studies), is possible concomitant occupational or household exposure to asbestos. The risk of mesothelioma was greatly increased in all but one study among individuals with environmental exposure to asbestos. Results for lung cancer, however, are less consistent, with an increased risk detected in studies from South Africa and China, but not in studies from Europe and North America. Imperfect control of confounding by smoking and other lung carcinogens may explain the lack of consistency.

According to a model used by WHO¹⁸, 5% of the European population experience residential exposure to asbestos. A meta-analysis estimated the relative risk (RR) of mesothelioma from environmental exposure to asbestos at 3.5 (95% confidence interval [CI] 1.8–7.0). The corresponding RR of lung cancer was 1.1 (95% CI 0.9–1.5)¹⁹. Combining these results with a prevalence of exposure of 5%, leads to estimated annual numbers of 425 mesotheliomas in men and 56 in women, and (if one assumes a causal association between environmental exposure to asbestos and lung cancer) of 771 lung cancers in men and 206 in women in the European Union. The figure of 5% might however over-estimate the prevalence of exposure to circumstances comparable to those investigated in the studies listed in Table 1. A conservative estimate of 1% of the exposed population leads to estimates of 92 mesotheliomas in men and 12 in women, as well as 153 lung cancers in men and 41 in women. It should be stressed that in specific areas, such as Casale Monferrato in Italy⁹ and Metsovo in Greece²⁰, the prevalence of heavy environmental exposure is relatively high, leading to a substantial burden of cancer.

Cancer risk from outdoor air pollution

Ambient air pollution has been implicated as a cause of various health effects, including cancer. Air pollution is a complex mixture of different gaseous and particulate components, and it is difficult to define an exposure measure of relevance when the biological mechanisms are largely unknown. The air pollution mix varies greatly by locality and time. In recent decades, emissions and air concentrations of traditional industrial air pollutants, such as SO₂ and smoke particles, have decreased, whereas there is an increasing or continued problem with air pollution from vehicles, with emissions of engine combustion products including volatile organic compounds, nitrogen oxides and fine particulates, as well as with secondarily increased ozone levels. There is biological rationale for a carcinogenic potential of numerous components of the air pollution mix, including benzo[a]pyrene, benzene, some metals, particles (especially fine particles) and possibly ozone.

Many definitions of outdoor air pollution exposure have been used in epidemiological studies. Earlier analytical studies generally compared residence in urban areas, where the air is considered more polluted, to residence in rural areas (for a review, see Katsouyanni and Pershagen²¹), sometimes providing limited data on the typical levels of some pollutants in the areas studied. Other studies have attempted to address exposure to specific components of outdoor air, providing risk estimates in relation to quantitative or semi-quantitative air pollution exposure assessments^{22–35} or, in some cases, to more qualitative exposure assessments^{14,36}. Another type of study has addressed residence in the proximity of specific sources of pollution, such as major industrial emission sources or heavy road traffic.

The evidence regarding outdoor air pollution and lung cancer has been the subject of several reviews^{21,37–40}. We do not further review the evidence from ecological studies, given the abundance of analytical studies. Eleven cohort studies of outdoor air pollution have been reported^{27,29,31,35,41–56}, as well as a number of case–control studies^{14,22–26,28,30,32–34,36,57–65}.

In these studies, most reported RRs were adjusted for age and active smoking, but generally information on other potential confounders, such as occupational exposure, radon, passive smoking and dietary habits, was lacking. Overall, the studies suggest RRs of up to about 1.5 for urban *versus* rural residence or high *versus* low estimated air pollution exposure. There is no clear indication if early or late exposure is more important, and data on possible interaction with smoking or occupational exposures are inadequate.

Among these studies, four cohort^{27,29,31,35,54–56} and 10 case–control^{22–26,28,30,32,34,65} studies were based on measurements of specific air components. Selected RR estimates from these studies, with the corresponding air pollution differentials, are presented in Table 2.

Although the results reported in Table 2 are not directly comparable, mainly because of differences in exposure assessment, they tend to show an increased risk of lung cancer in the categories at highest exposure, which does not seem to be attributable to confounding factors. The studies of lung cancer and air pollution, however, suffer from several weaknesses. Exposure measurements are often crude, and sometimes only represent urban/rural contrasts. Population exposure estimates suffer from measurement errors due to mobility, not only long-term residential but also short-term around the area of residence. Even when quantitative exposure assessments were attempted, limited air monitoring data were a problem. Another limitation of many studies is that the sufficiently exposed population is diluted by a considerable number of minimally exposed persons.

An apparent inconsistency is that cancer mortality rates are often highest in medium-sized cities and lower in larger agglomerations. An ecological analysis of environmental correlates and total cancer mortality in 98 US cities found that vehicle density was an excellent predictor⁶⁶.

Table 2 Relative risk of lung cancer and outdoor air pollution measurements in some studies with quantitative or semi-quantitative exposure assessment

| Location, study period | Reference | Sex | RR | 95% CI | Exposure contrast ^a | Basis for exposure assessment for individuals and/or areas | Comments |
|--------------------------------|--------------------------------------|-------|---------|---|---|--|---|
| Cohort studies USA, 1975–91 | Dockery <i>et al</i> ²⁹ | M + F | 1.37 | 0.81–2.31 | per 18.9 µg/m ³ PM _{2.5} | City of residence in 1975. Pollutant average 1979–85 | Study range 11–29.6 µg/m ³ PM _{2.5} across six studied cities |
| | Pope <i>et al</i> ⁵⁶ | M + F | 1.08 | 1.01–1.16 | per 10 µg/m ³ PM _{2.5} (1979–1983) | City of residence in 1982. Pollutant averages 1979–83, 1999–2000 or average of 1979–1983 and 1999–2000 | Mean (s.d.): 21.1 (4.6), 14.0 (3.0), 17.7 (3.7) for pollutant averages 1979–83, 1999–2000 or average of 1979–1983 and 1999–2000, respectively |
| USA, California, 1977–92 | Pope <i>et al</i> ³¹ | M + F | 1.13 | 1.04–1.22 | per 10 µg/m ³ PM _{2.5} (1999–2000) | | Study range roughly 10–30 or 5–20 µg/m ³ PM _{2.5} (1979–1983 and 1999–2000, respectively) |
| | | M | 1.14 | 1.04–1.23 | per 10 µg/m ³ PM _{2.5} (average of 1979–1983 & 1999–2000) | | |
| | Beeson <i>et al</i> ⁵³ | M + F | 1.36 | 1.1–1.7 | per 19.9 µg/m ³ SO ₄ | 1982–1989. City of residence in 1980 | Study range 3.6–23.5 µg/m ³ SO ₄ across 151 studied cities |
| | | M | 3.56 | 1.4–9.4 | per 556 h/year above 200 µg/m ³ O ₃ | Residential history 1973–92 and local monthly pollutant levels 1973–92 used to calculate individual subject averages over 1973–92 | Range 988 h over study subjects |
| | McDonnell <i>et al</i> ⁵⁴ | M | 5.21 | 1.9–14.0 | per 24 µg/m ³ PM ₁₀ | Residential history 1966–92 or 1973–92 (for PM _{2.5} and PM ₁₀ , respectively) and local monthly pollutant estimates based on airport visibility data 1966–92 (for PM _{2.5}) and TSP 1973–86 and measured PM ₁₀ 1987–1992 (for PM ₁₀) | Results for smaller sub-cohort of subjects living near an airport |
| M | | 2.66 | 1.6–4.4 | per 11 µg/m ³ SO ₂ (3.72 ppb) | | | |
| | | F | 2.14 | 1.4–3.4 | per 11 µg/m ³ SO ₂ (3.72 ppb) | | |
| | | M | 2.23 | 0.56–8.94 | per 24.3 µg/m ³ PM _{2.5} | | |

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Table 2 (continued from opposite page)

| | M | 1.84 | 0.59–5.67 | per 29.5 µg/m ³ PM ₁₀ | | Mean (S.D.) 59.2 (16.8) and 31.9 (10.7) for PM _{2.5} and PM ₁₀ , respectively over study subjects |
|-------------------------------|-------|------|-----------|---|--|--|
| Netherlands, 1986–94 | M + F | 1.06 | 0.4–2.6 | per 10 µg/m ³ Black Smoke | Residential history of last 1–4 residences up to 1986 matched by GIS to regional and urban background estimates from National Air Quality Monitoring Network 1987–1990 plus local exposure based on distance to major road | Estimated range 9.6–35.8 µg/m ³ Black Smoke and 14.7–67.2 µg/m ³ NO ₂ over study subjects |
| Case control studies | | | | | | |
| USA, Erie County, NY, 1957–65 | M | 1.7 | 1.0–2.9 | ≥50 years residence in areas with high (50–200 µg/m ³) TSP | Lifetime residential history. Pollutant average 1961–63 | Estimate for Erie county all-life residents |
| USA, Denver, 1979–82 | M | 1.66 | 0.7–4.2 | ≥100 exposure years versus 0–99 | Lifetime residential history. TSP measurements by census tract | Exposure-years = residential years weighted (multiplied) by ranking index (1–10) based on census tract TSP levels |
| Japan, Osaka, 1965 | F | 1.51 | | SPM 390 versus 190 µg/m ³ , BaP 79 versus 26 µg/m ³ | Present residence. Pollutant average 1965 | |
| Poland, Krakow, 1980–85 | F | 1.2 | P > 0.05 | TSP > 150 & SO ₂ > 104 versus TSP < 150 & SO ₂ < 104 | Last residence. Pollutant average 1973–80 | |
| | M | 1.46 | 1.1–2.0 | TSP > 150 or SO ₂ > 104 versus TSP < 150 & SO ₂ < 104 | | |
| Greece, Athens, 1987–89 | F | 0.81 | 0.7–2.0 | High versus low quartile, never-smokers | Lifetime residential and work address histories. Air pollution averages 1983–85 were used to classify areas into five categories. Range of BS from >400 in urban areas to <100 or less in rural areas | |

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Table 2 (continued) Relative risk of lung cancer and outdoor air pollution measurements in some studies with quantitative or semi-quantitative exposure assessment

| Location, study period | Reference | Sex | RR | 95% CI | Exposure contrast ^a | Basis for exposure assessment for individuals and/or areas | Comments |
|----------------------------------|------------------------------------|-----|------|---------|--|---|---|
| | | F | 1.35 | | Same, smokers 1–29 years | | |
| | | F | 2.23 | | Same, smokers 30+ years | | |
| Germany, 5 cities, 1984–88 | Jöckel <i>et al</i> ²⁸ | M | 1.16 | 0.6–2.1 | High versus low time-weighted semi-quantitative index | Lifetime residential history. BaP, TSP, SO ₂ data + local energy, SO ₂ and coal use and degree of industrialization 1900–1980 classified areas in 10-year intervals 1895–1984 | |
| | | M | 1.82 | | Same, using 20 years lag | | |
| Italy, Trieste, 1979–81, 1985–86 | Barbone <i>et al</i> ³⁰ | M | 1.4 | 1.1–1.8 | >294 µg/m ² /day versus <175 of particulate deposition | Last residence. Deposition measured 1972–77 | |
| Russia, Moscow, 1991–93 | Zaridze <i>et al</i> ³² | F | 2.6 | 1.2–5.6 | >200 SO ₂ , >60 NO ₂ , >2400 CO, >300 BS versus <50, <48, <1300, <60 | Final = 20 years of residential history. Pollutant average 1971–75 | Never-smokers only |
| Poland, Krakow, 1992–94 | Pawlega <i>et al</i> ³⁴ | M | 0.24 | 0.1–0.5 | TSP 142 & SO ₂ 110 versus 78 & 71 | Last residence. Pollutant average 1973–80 | Residual confounding by occupation possible despite some adjustment |
| Sweden, Stockholm, 1985–90 | Nyberg <i>et al</i> ³⁵ | M | 1.6 | 1.1–2.4 | NO ₂ ≥ 29.26 versus NO ₂ < 12.78 (Top decile versus lowest quartile) | 30-year residential history. NO ₂ estimates based on historical emission data and dispersion modelling (1960s, 70s and 80s) | |

^a µg/m³ if not otherwise indicated.

The authors noted that vehicle density generally levels off in more densely populated areas when other means of transportation are available, which might explain this inconsistency.

To pinpoint possible industrial emissions responsible for the suggested urban excess, populations living near point sources of air pollution have also been studied. Increased risks have been reported for living close to industries such as smelters, foundries, chemical industries, and others with various emissions^{14,30,32,67-69}, with up to doubled risk, although confidence intervals were mostly wide. Scottish ecological studies of residence near steel and iron foundries suggested a temporal relation between emission reductions and decreased lung cancer rates, with relatively short latency⁷⁰⁻⁷⁷. Other studies showed no relationship, however. For example, a recent epidemiological study could not show any association between heavy community exposure to sulphuric acid and lung cancer risk⁷⁸.

A number of studies concern sources of inorganic arsenic in air. Ecological studies suggested an increased lung cancer risk⁷⁹⁻⁸⁴, which three early US case-control studies of residential exposure failed to substantiate⁸⁵⁻⁸⁷. In two subsequent case-controls studies with better control for smoking and occupation^{88,89}, however, estimated RRs for living near the smelter were around 2 and statistically significant. In a third study, the RR in the top quintile of exposure was 1.6 (*P* value for trend 0.07)⁹⁰. Recent studies of 10 smelter towns in Arizona did not, however, observe any clear association or dose-response, but the arsenic content of the ore used was comparatively low^{91,92}.

The results of cohort and case-control studies regarding air pollution and lung cancer are too heterogeneous for a formal meta-analysis assessment of attributable cancers. The exposed proportion of the population in industrialized countries appears to lie in the range 15-75%, depending on the definition used⁹³⁻⁹⁵. As a conservative estimate, 20% of the population have low exposure (RR 1.1), 4% medium exposure (RR 1.3) and 1% high exposure (RR 1.5). In this scenario, the attributable proportion in the EU is approximately 3.6%, corresponding to some 7000 lung cancer cases per year.

Limited results are available for cancers other than the lung. In ecological studies, many individual cancers have shown elevated urban/rural ratios, including cancers of the mouth & throat, nasopharynx, oesophagus, stomach, colon, rectum, larynx, female breast, bladder and prostate^{96,97}. Stronger associations were often reported for smoking-related cancers such as oesophagus, larynx and bladder cancer. However, the urban/rural ratio is often higher in men, suggesting that residual confounding by smoking or occupational exposures may be involved. Other ecological studies have related cancer rates to air pollutant measurements, or emission indexes or figures for fuel consumption. For example, stomach cancer was related to SO₂, particulates or fuel consumption in several studies⁹⁸⁻¹⁰² but not all¹⁰³, and prostate cancer was associated with measured particulate air pollution

in two studies^{99,104}. Occupational benzene exposure is a recognized cause of leukaemia^{105,106}. A recent ecological study in 19 European countries found an inverse temporal association between gasoline use and leukaemia mortality or morbidity, but a weak positive spatial association¹⁰⁷. Overall, it was not very supportive of an association to environmental benzene exposure. Previous ecological and case-control studies also provide unclear evidence.

Two cohort studies also provided data on cancers in organs other than the lung. For major sites, a Swedish study⁴⁶ found significant urban/rural ratios only for cancers of the bladder and uterine cervix, among smokers and non-smokers. In a Finnish cohort⁵⁰, there was some excess, for leukaemia and prostate cancer in particular, in urbanized but not in lifetime-urban men (mainly unmarried)⁵⁰.

One case-control study¹⁰⁸ examined the relationship between air pollution and childhood cancer, using residential traffic density as exposure proxy. An odds ratio of 1.7 (95% CI 1.0–2.8) was found for total childhood cancers and an odds ratio of 2.1 (95% CI 1.1–4.0) for leukaemias in a comparison of high- and low-traffic density addresses.

In summary, evidence concerning adult cancers other than lung cancer comes mainly from ecological studies, is not consistent, and is insufficient to attempt any estimate of a possible cancer burden. Likewise, no conclusion is possible for childhood cancer.

Cancer risk from exposure to environmental tobacco smoke

Environmental tobacco smoke is composed of sidestream and mainstream smoke, in which known, probable or possible human carcinogens are present. The International Agency for Research on Cancer has evaluated the evidence of a carcinogenic risk from exposure to environmental tobacco smoke, and has classified it as an established human carcinogen¹⁰⁹. Confounding by dietary, occupational and social class-related factors can be reasonably excluded, and bias from misclassification of smokers is not likely to explain the results. On that occasion, a meta-analysis of epidemiological studies of lung cancer and adult exposure to environmental tobacco smoke was conducted, resulting in RRs of 1.22 (95% CI 1.12–1.32) in women and 1.36 (95% CI 1.02–1.82) in men from spousal exposure, and of 1.15 (95% CI 1.05–1.26) in women and 1.28 (95% CI 0.88–1.84) in men from workplace exposure. Other meta-analyses have reached very similar conclusions^{110,111}.

Table 3 presents our estimates of the numbers of lung cancers attributable to ETS exposure from the spouse and at the workplace in the European Union based on results of multicentre studies. In a study of lung cancer and ETS exposure, the proportion of never-smokers ever exposed to ETS

Table 3 Number of cases of lung cancer attributable to exposure to environmental tobacco smoke (ETS)

| Study | Men | | | | | Women | | | | |
|--------------------------------------|------|-------------------|------|----------------|-----|-------|-------------------|-----|----------------|-----|
| | RR | PE% | AF% | N ^a | NA | RR | PE% | AF% | N ^b | NA |
| Spousal ETS | | | | | | | | | | |
| EPA ¹¹² | 1.17 | 3.9 ^c | 0.66 | 4400 | 29 | 1.17 | 37.8 ^d | 6.0 | 7220 | 436 |
| Hackshaw <i>et al</i> ¹¹⁰ | 1.24 | | 0.93 | | 41 | 1.24 | | 8.3 | | 601 |
| Boffetta <i>et al</i> ¹¹³ | 1.47 | | 1.8 | | 79 | 1.11 | | 4.0 | | 288 |
| Workplace ETS | | | | | | | | | | |
| Boffetta <i>et al</i> ¹¹³ | 1.13 | 21.3 ^e | 2.7 | 4400 | 119 | 1.19 | 28.2 ^f | 5.1 | 7220 | 367 |

RR, relative risk from exposure to ETS; PE%, proportion of exposed cases; AF%, fraction of cases attributable to ETS; N, number of cases of lung cancer in the European Union in 1990; NA, number of cases attributable to ETS.

^a4400 = 3% of lung cancers.

^b7220 = 20% of lung cancers.

^c0.13 (from European study) \times 0.30 (prevalence of non-smokers).

^d0.63 (from European study) \times 0.60 (prevalence of non-smokers).

^e0.71 (from European study) \times 0.30 (prevalence of non-smokers).

^f0.47 (from European study) \times 0.60 (prevalence of non-smokers).

among controls was 13% in men and 63% in women for spousal ETS, and 71% in men and 47% in women for workplace ETS¹¹³. The average prevalence of never-smokers in Europe was estimated from a pooled analysis of case-control studies conducted in six European countries¹¹⁴: the overall prevalence among controls was 65% in women and 24% in men. Finally, from the same pooled analysis it was estimated that 29% of lung cancers in women and 2% in men occur among never-smokers¹¹⁴.

The annual number of cases attributable to spousal ETS is in the order of 50 in men and over 500 in women. The corresponding estimates for ETS exposure at the workplace are about 200 cases among men and 270 cases among women.

Estimates made by the US Environmental Protection Agency¹¹² for the US population, which considered spousal and background sources of ETS, resulted in 1930 cases among women and 1130 cases among men. With respect to previous estimates, our exercise has the advantage of being based on actual measurements of exposure and risk derived from European populations.

The evidence of a causal association between ETS exposure and cancers in organs other than the lung is inconclusive¹⁰⁹.

Cancer risk from residential radon exposure

The carcinogenicity of radon decay products has been widely studied in occupationally exposed populations, in particular underground miners. This agent causes lung cancer in humans, but the evidence for an effect

on other neoplasms is not conclusive¹¹⁵. The excess RR estimated from occupational cohorts, which included over 2500 cases of lung cancer occurring among over 60,000 miners, has been estimated in the order of 0.0049 per working level month of exposure¹¹⁶. Further refinements of this estimate took into account age at exposure and time since first exposure¹¹⁷ as well as smoking status, with a stronger effect being shown among never-smokers than among smokers.

Although exposure levels in the houses are one order of magnitude smaller than in underground mines, the duration of exposure and the number of exposed individuals stress the importance of residence as a source of exposure to radon decay products. Several case-control studies of lung cancer from residential radon exposure have been reported in the literature, and their results have been reviewed and summarized^{115,118,119}. A pooled RR of 1.06 (95% CI 1.01–1.10) has been calculated for individuals exposed at 100 Bq/m³ versus unexposed¹¹⁹, which is in agreement with the extrapolation from the results of occupationally exposed populations. Results of studies reported after these pooled analyses confirm these conclusions^{120–123}.

Most studies of residential radon rely on the historical reconstruction of exposure levels *via* household measurements. This approach is subject to substantial misclassification, most likely resulting in an underestimate of the risk. In a few studies, attempts were made to correct such biases, and the estimated RR increased by about 50%^{124,125}. Furthermore, in one study¹²⁶, in which cumulative radon exposure was estimated from surface monitors rather than measurement in houses, the RR was higher (1.63, 95% CI 1.07–2.93 for exposure at 100 Bq/m³).

Several estimates have been proposed of the number of lung cancers attributable to residential radon exposure. In one of the most detailed exercises, Darby and colleagues¹¹⁹ estimated that this agent is responsible for 6.5% of all deaths from lung cancer in the UK, including 5.5% attributable to the joint effect of radon and smoking and 1% to residential radon alone. The figure of 1% corresponds to 349 deaths in the UK in 1998, or 9.4% of lung cancer deaths not due to tobacco smoking. If these figures are applied to other European countries, the number of lung cancer cases attributable to indoor radon exposure is in the order of 2000 per year.

Cancer risk from other sources of indoor air pollution

Based on the observation of very high lung cancer rates in some regions of China and elsewhere among women who spend much of their time at home, exposure to indoor air pollution from combustion sources used for heating and cooking, as well as high levels of cooking oil vapours

resulting from some cooking methods, have been identified as risk factors for lung cancer. Table 4 presents a summary of results from relevant studies and illustrates the great variability in exposure measures across the case-control studies carried out in Asian populations.

Three main groups of factors influencing indoor air pollution ('smokiness') have been studied: (i) heating fuel: type of fuel, type of stove or central heating, ventilation, living area, subjective smokiness; (ii) cooking fuel: type of fuel, type of stove or open pit, ventilation of kitchen, location of cooking area in residence, frequency of cooking, smokiness; and (iii) fumes from frying oils: type of oil, frequency of frying, eye irritation when cooking. Many of the results are inconclusive, and the interpretation is difficult since the exposure measures used vary considerably. Nonetheless, strong and significant increases in risk have repeatedly been reported and merit consideration. In a recent review, it was concluded that the epidemiological findings regarding cooking oil vapours (group iii) from Chinese-style cooking are clearly suggestive of an effect and have some support from experimental data¹⁴⁰.

Limited data supporting a similar effect of exposure to cooking-derived indoor air pollution are available from other regions of the world. In a case control study from the Northern Province of South Africa⁴, the odds ratio of lung cancer among women using wood or coal as main fuel was 1.4 (95% CI 0.6–3.2). A study conducted among white women in Los Angeles in 1981–82 reported that coal use for cooking and heating in the home during childhood and adolescence was associated with an odds ratio of 2.3 (95% CI 1.0–5.5) for adenocarcinoma and 1.9 (95% CI 0.5–6.5) for squamous cell cancer¹⁴¹.

It appears plausible that indoor air pollution from combustion or cooking products (oil vapours in particular) could play a role in the causation of lung cancer. The relevance of the risks estimated in China for present-day conditions in Europe and North America is, however, somewhat questionable. Frying is less common in most parts of Europe than in China and kitchens are generally larger, better ventilated and separated from the living quarters. Central heating is increasingly common, and open combustion sources indoors are infrequent. However, given that lung cancer induction may span several decades, earlier living conditions may still play a role today in the risk of lung cancer among the middle-aged and older generations in Europe, although its importance should be waning.

Cancer risk from inorganic arsenic in drinking water

Inorganic arsenic causes cancer at various sites in humans¹⁰⁶. The main source of environmental exposure to arsenic for the general population

Table 4 Case-control studies in Asian women of lung cancer and indoor air pollution from cooking habits

| Study | Location ^a , years | Ca | Co | Exposure variable ^b | RR | 95% CI |
|---|------------------------------------|-----|-----|---------------------------------|------|-----------------|
| Sobue ¹²⁷ | Japan, Osaka, 1985 | 144 | 713 | Wood/straw for cooking | 1.8 | 1.1–2.9 |
| Koo and Ho ¹²⁸ | Hong Kong, 1981–83 | 200 | 200 | Combustion heating | 1.2 | 0.8–1.7 |
| Ko <i>et al</i> ⁶⁸ | Taiwan, Kaohsiung, 1992–93 | 105 | 105 | 41+ years of cooking | 0.4 | 0.1–1.0 |
| | | | | Coal/anthracite for cooking | 1.3 | 0.3–5.8 |
| | | | | Wood/charcoal for cooking | 2.7 | 0.9–8.9 |
| | | | | Kitchen fume extractor | 8.3 | 3.1–22.7 |
| Wu-Williams <i>et al</i> ²⁹ | Shenyang, 1985–87; Harbin, 1985–87 | 965 | 959 | 41+ years coal heating stoves | 1.3 | 1.0–1.7 |
| | | | | 50+ years kang use | 1.6 | 0.9–2.8 |
| Xu and co-workers ^{14,130,131} | Shenyang, 1985–87 | 520 | 557 | 50+ years coal heating stoves | 1.2 | <i>P</i> > 0.05 |
| | | | | 50+ years kang use | 3.4 | <i>P</i> < 0.05 |
| | | | | 20+ years direct burning kang | 2.3 | <i>P</i> < 0.05 |
| | | | | Indoor air pollution index | 1.5 | 1.0–2.4 |
| | | | | Subjective smokiness | 2.0 | 1.4–2.8 |
| Wang <i>et al</i> ¹³² | Shenyang, 1992–93 | 135 | 135 | Kang use | 1.0 | 0.6–1.5 |
| | | | | Coal for heating | 0.8 | 0.4–1.3 |
| | | | | Coal smoke when cooking | 2.4 | 1.4–3.9 |
| Dai <i>et al</i> ¹³³ | Harbin, 1992–93 | 120 | 120 | 30+ years coal stove in bedroom | 18.8 | 3.9–29 |
| | | | | 25+ years coal heating | 4.7 | 1.3–17 |
| He <i>et al</i> ¹³⁴ | Xuanwei, 1985–86 | 52 | 202 | 45+ years cooking | 8.4 | <i>P</i> < 0.05 |
| Lan <i>et al</i> ¹³⁵ | Xuanwei, 1988–90 | 139 | 139 | Use of smoky coal | 7.5 | 3.3–17.2 |
| Lan <i>et al</i> ¹³⁶ | Xuanwei, 1976–92 | 684 | N/A | Use of chimney instead of stove | 0.5 | 0.4–0.6 |
| Liu <i>et al</i> ¹³⁷ | Guangzhou, 1983–84 | 92 | 92 | No separate kitchen | 5.9 | 2.1–16 |
| Du <i>et al</i> ¹³⁸ | Guangzhou, 1985 | 283 | 283 | Coal fumes exposure | 2.2 | 1.2–4.2 |
| Gao <i>et al</i> ¹³⁹ | Shanghai, 1984–86 | 672 | 735 | Coal for cooking | 0.9 | 0.7–1.3 |
| | | | | Gas for cooking | 1.1 | 0.7–1.5 |
| | | | | Wood for cooking | 1.0 | 0.6–1.8 |
| | | | | Eye irritation | 1.6 | <i>P</i> < 0.05 |
| | | | | House smokiness | 1.6 | <i>P</i> < 0.05 |
| Zhong <i>et al</i> ¹⁴⁰ | Shanghai, 1992–94 | 504 | 601 | No separate kitchen | 1.24 | 0.94–1.62 |
| | | | | High smokiness | 2.36 | 1.53–3.62 |
| | | | | Frying | 1.79 | 0.94–3.41 |

Ca, number of cases; Co, number of controls; RR, relative risk; CI, confidence interval.

^aCountry is China if not otherwise specified.

^bReference category includes unexposed or low-exposure categories.

is through ingestion of contaminated water. A high level of arsenic in groundwater (up to 2–5000 µg/l) is found in areas of Argentina, Bangladesh, Bolivia, Chile, China (Xinjiang, Shanxi), India (West Bengal), Mexico, Mongolia, Taiwan, Thailand, the USA (Arizona, California, Nevada) and Vietnam. The most significant exposures, in terms of levels and populations, occur around the Gulf of Bengal, in South America and in Taiwan. In Europe, intermediate levels (not higher than 200 µg/l) are found in areas of Hungary and Romania in the Danube basin, as well as in Spain, Greece and Germany. There is strong evidence of an increased risk of bladder, skin and lung cancers following consumption of water with high arsenic contamination¹⁰⁹. The evidence for an increased risk of other cancers, such as those of the liver, colon and kidney, are weaker but suggestive of a systemic effect. Most of the available studies have been conducted in areas with elevated arsenic content (typically above 200 µg/l). The results of studies of bladder cancer conducted in areas with low or intermediate contamination are suggestive of a possible increased risk. In an ecological study from Finland, the RR for concentrations of arsenic above 0.5 µg/l *versus* less than 0.1 µg/l was 2.44 (95% CI 0.95–1.96) with 3–9 years of latency, and it was 1.51 (95% CI 0.67–3.38) with 10 or more years of latency¹⁴². In a study from the USA, the RR for a cumulative dose of 53 mg or more, compared to less than 19 mg, was 1.14 (95% CI 0.7–2.9) overall, but it was 3.3 (95% CI 1.1–10.3) among smokers¹⁴³. Very limited data are available on the risk of other neoplasms at low or intermediate exposure levels.

Few data are available on the proportion of the population in Europe exposed to arsenic in drinking water. In the study from Finland mentioned above¹⁴², 5% of the study population consumed water with concentrations above 5 µg/l, including 1% with concentrations above the WHO guideline of 10 µg/l.

Cancer risk from water chlorination by-products

Access to unpolluted water is one of the requirements of human health. Water quality is influenced by seasons, geology and discharges of agriculture and industry. Microbiological contamination of water is controlled by disinfection methods based on oxidants like chlorine, hypochlorite, chloramine, chlorine dioxine and ozone. Drinking water may contain a variety of potentially carcinogenic agents, including chlorination by-products¹⁴⁴. Showering and bathing represent another important source of exposure to chlorination by-products.

Chlorination by-products result from the interaction of chlorine with organic chemicals, whose level determines the concentration of the by-products. Among the many halogenated compounds that may be formed,

trihalomethanes are those most commonly found. Trihalomethanes include chloroform, bromodichloromethane, chlorodibromomethane and bromoform. Brominated by-products are formed from the reaction of chlorinated by-products with bromide, present at low levels in drinking water. Concentrations of trihalomethanes show a wide range, mainly as a result of the occurrence of water contamination by organic chemicals: average measurements from the USA¹⁴⁴ are in the order of 10 µg/l for chloroform, bromodichloromethane and chlorodibromomethane, whereas those for bromoform are close to 5 µg/l. In 1992, Morris and colleagues¹⁴⁵ carried out a meta-analysis of cancer risk from consumption of chlorinated drinking water. They estimated an RR of 1.21 (95% CI 1.09–1.34) for bladder cancer, based on seven studies. This estimate was not modified after adjusting for smoking. Two further studies of bladder cancer risk have been published^{146,147}, and their results are in line with the meta-analysis by Morris and colleagues. In three studies, information on duration of exposure was reported^{146–148}: a meta-analysis of the results for the category with longest exposure (more than 30 or 40 years, depending on the study) resulted in a pooled RR of 1.68 (95% CI 1.25–2.27). Results based on estimated intake of trihalomethanes and on other disinfection by-products are too sparse to allow a conclusion.

The interpretation of these data is complicated by several factors. The concentration of by-products in water varies depending on the presence of organic contaminants, which differs by geographical area and by season. In addition, people consume water outside their homes, which is seldom considered in the assessment of exposure in epidemiological studies. Furthermore, although the possible confounding effect of smoking has been taken into account in several studies, confounding by other risk factors such as diet remains a possibility. Despite the good consistency of the available studies on bladder cancer, the uncertainties in exposure assessment caution against the conclusion that a causal link has been established between consumption of chlorinated drinking water and increased risk of bladder cancer¹⁴⁹.

The evidence for an association between chlorination by-products and cancers in organs other than the bladder is inconclusive¹⁴⁹, although some of them are considered possible human carcinogens because of evidence of carcinogenicity in experimental systems¹⁰⁹.

Cancer risk from other drinking water pollutants

Several other groups of pollutants of drinking water have been investigated as possible sources of cancer risk in humans^{149,150}. They include organic compounds derived from industrial, commercial and agricultural activities, and in particular from waste sites, nitrites & nitrates,

Table 5 Epidemiological studies of nitrate in drinking water (NDW) and risk of stomach cancer

| Country | Period | Design | Exposure | Results | Study |
|----------|---------|--------|------------------------------------|------------------|--|
| Colombia | 1968–72 | CC, I | NDW in areas of residence | + | Cuello <i>et al</i> ¹⁵¹ |
| Hungary | 1960–79 | E, I | NDW and soil type in a county | + | Juhasz <i>et al</i> ¹⁵² |
| UK | 1969–73 | E, Mo | NDW in 32 rural districts | + Male; – Female | Fraser and Chilvers ¹⁵³ |
| Denmark | 1943–72 | E, I | NDW in two towns | + | Jensen ¹⁵⁴ |
| Italy | 1976–79 | E, I | NDW (20+ mg/l) in 1199 communities | + | Gilli <i>et al</i> ¹⁵⁵ |
| UK | 1969–73 | E, Mo | NDW of 253 urban areas | – | Beresford ¹⁵⁶ |
| USA | 1982–85 | E, Mo | NDW in Wisconsin areas | – | Rademacher <i>et al</i> ¹⁵⁷ |

CC, case-control study; E, ecological study; I, incidence; Mo, mortality.

radionuclides and asbestos. Most of the studies were based on ecological comparisons and did not provide a quantitative risk estimate. Several cancer sites were analysed in these studies and selective reporting of positive results, resulting in an over-estimate of the risk, is a possibility.

Despite these limitations, three sets of results are particularly interesting. Firstly, an increased risk of stomach cancer has been repeatedly reported in areas with high nitrate levels in drinking water (Table 5). However, the two most recent studies did not confirm these findings^{156,157}.

Secondly, two studies are available on the association between nitrate level in drinking water and risk of non-Hodgkin lymphoma in the USA. Weisenburger¹⁵⁸ found a higher rate of lymphoma in eastern counties of Nebraska with more than 20% of wells with nitrate levels exceeding the standard, as compared to counties with less than 10% of such wells. In a case-control study in the same region, Ward *et al*¹⁵⁹ found an increased risk for high cumulative intake of nitrates in drinking water. A further case-control study of bladder cancer reported an association with high nitrate level in drinking water¹⁶⁰.

Finally, two ecological studies from the USA reported an increased risk of leukaemia in adults among residents in areas with elevated levels of radium in drinking water^{161,162}. A third study reported a similar association between radon levels and childhood leukaemia¹⁶³.

Conclusions

A number of circumstances of environmental exposure to carcinogens has definitely been linked with an increased risk of cancer in humans. For some of them, the available data allow an attempt to quantify the burden of cancer. Uncertainties in all the components of such quantifications, however, suggest great caution in their interpretation: they should be considered as indicating the likely order of magnitude of the risk based on current knowledge.

It is noteworthy, however, that despite the relatively small relative risks of cancer following exposure to environmental carcinogens, the number of cases that might be caused, assuming a causal relationship, is relatively large, as a result of the high prevalence of exposure. This emphasizes the need for a better understanding of the actual risk of cancer posed by environmental factors, and of the effect of measurements aimed at controlling exposure to environmental carcinogens.

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