Air pollution has been linked to several malignancies, including lung cancer, urinary bladder cancer, and acute leukaemia; the evidence is most abundant for lung cancer, for which several causal factors are well established (Samet and Cohen, 2006). Worldwide, tobacco use, and in particular cigarette smoking, is the dominant cause of lung cancer and accounts for the majority of cases; in fact, most cases in many countries (IARC, 2004). Other well-characterized causes of lung cancer include occupational agents and indoor radon (Alberg and Samet, 2003). When considering air pollution and its sources in the causation of lung cancer, its combined effects with these other causes of lung cancer are inevitably an issue. At present in the USA and some other developed countries, the relative risk of lung cancer in regular smokers compared with never-smokers ranges from 10 to > 20. These extremely high relative risk values indicate a need to consider the potential modification by tobacco smoking of the risk of lung cancer (and possibly other cancers) associated with air pollution, and to assess the potential for residual confounding by tobacco smoking to explain risks associated with air pollution in epidemiological studies. In addition, information on tobacco smoking and cancer is relevant to the collective body of evidence for an evaluation of air pollution by the International Agency for Research on Cancer (IARC), since some specific carcinogens in air pollution are also found in tobacco smoke, which similarly to ambient and indoor air pollution, is a complex mixture that contains a multitude of carcinogens, and, similarly to ambient air pollution, elicits an inflammatory response in the lung and systemically (Lewtas, 2007).

Conceptual issues

The combined effects of particular carcinogens with other carcinogens have been addressed in previous IARC Monographs, including those that covered asbestos (IARC, 1977), radon (IARC, 1988), man-made fibres (IARC, 1988), and tobacco smoking (IARC, 2004). The Monograph on tobacco smoking provides an extended conceptual framework, which is summarized below.

For many cancers, including lung cancer, multiple causal factors are relevant. Persons who are exposed to more than one risk factor may experience risks that differ from those anticipated from the effects of the individual agents when they act alone. Epidemiologists refer to effect modification when effects of multiple agents are interdependent; the pattern of effect...
modification is termed synergistic when positive and antagonistic when negative. Statistical models test whether there is an interaction between independent determinants of cancer risk, and model-derived estimates of the degree of interaction are interpreted within the epidemiological framework. In the Monograph on tobacco smoking (IARC, 2004), standardization of the concepts and terminology of effect modification was introduced. Interdependence of effects was termed effect modification, and synergism and antagonism were used to describe the consequences of the interdependence of risk for disease when both factors are present (Rothman and Greenland, 1998). Interaction was a term reserved for the statistical approach of testing whether effect modification occurs.

In considering air pollution with other risk factors and the risk of cancer, many potential stages exist at which the biological consequences of other risk factors could affect a response to air pollution. Following a toxicological paradigm that extends from exposure through to dose and finally to biological effects, several different stages in the sequence exist at which tobacco smoking or other risk factors might influence the effect of an air pollutant or air pollution in general (Table 13.1). The levels of potential interaction between the agents are multiple and range from molecular to behavioural. Some of the likely points of interaction could have an impact on the level of exposure; others, including an exposure–dose relationship, could affect the dose–response relationship of exposure with risk, either for tobacco smoking or for air pollution. In assessing the presence of synergism or antagonism, a model is assumed to predict the combined effect from the individual effects. However, due to the lack of sufficient biological understanding to be certain of the most appropriate model, the choice is often made by convention or convenience.

Of interest is effect modification, which is reviewed and considered in IARC Monographs because of its implications for disease prevention and insights into mechanisms of carcinogenesis. In a multistage formulation of carcinogenesis, inferences as to the stages at which agents act can be made based on patterns of effect modification, particularly if data are available on the timing of the exposures (Doll, 1971; Whittemore, 1977; Thomas and Whittemore, 1988). In general, agents that act at the same step would be anticipated to have additive combined effects, whereas those that act at different steps are anticipated to have synergistic effects. While simplistic, this formulation offers a useful framework for considering joint exposures to air pollutant mixtures that have many of the components of tobacco smoke.

### Epidemiological studies

In most epidemiological studies of air pollution and lung or other cancers, tobacco smoking has been treated as a potential confounding factor that has been controlled through stratification or

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**Table 13.1 Levels of interaction between smoking and other agents**

<table>
<thead>
<tr>
<th>Exposure</th>
<th><em>Work assignments of smokers and nonsmokers differ</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure–dose relationships</td>
<td><em>Patterns of physical activity and ventilation differ for smokers and nonsmokers</em></td>
</tr>
<tr>
<td></td>
<td><em>Exposures of smokers and nonsmokers differ in activity size distribution</em></td>
</tr>
<tr>
<td></td>
<td><em>Patterns of lung deposition and clearance differ in smokers and nonsmokers</em></td>
</tr>
<tr>
<td></td>
<td><em>Morphometry of target cells differ in smokers and nonsmokers</em></td>
</tr>
<tr>
<td>Carcinogenesis</td>
<td><em>Alpha particles and tobacco smoke carcinogens act at the same or different steps in a multistage carcinogenic process</em></td>
</tr>
</tbody>
</table>
modelling (Samet and Cohen, 2006). Only a few studies provide information on effect modification, since most do not have a sufficient sample size to estimate rates of lung cancer in smokers and never-smokers. In addition, some of the major cohort studies that provide relevant data have obtained information on smoking only at enrolment; therefore, misclassification of smoking over follow-up most likely occurred as some smokers successfully quit.

The American Cancer Society’s Cancer Prevention Study II (CPS-II) is one of the few studies with sufficient data to assess the modification by cigarette smoking of the risk of lung cancer associated with air pollution. The cohort was established in 1982, and risks for mortality in relation to air pollution were described in two reports that were based on follow-up through 1989 (Pope et al., 1995) and through 1998 (Pope, 2000). Pope et al. (2002) described risks for lung cancer in approximately 500,000 of the 1.2 million participants in relation to exposure to fine particles (particulate matter < 2.5 µm in diameter [PM$_{2.5}$]). Overall, mortality from lung cancer was estimated to increase by 14% (relative risk [RR], 1.14; 95% confidence interval [CI], 1.04–1.23) per 10 µg/m$^3$ PM$_{2.5}$ from enrolment through 1998. The authors presented the effect of PM$_{2.5}$ on mortality from lung cancer by smoking status in their Figure 4, which showed an increment in effect from current to former to never-smokers. Formal tests for effect modification were not provided. The picture of risk of lung cancer by smoking stratum was less clear in the earlier follow-up (Pope et al., 1995); risk of lung cancer was increased in association with ambient concentrations of sulfate (RR, 1.36; 95% CI, 1.11–1.66 for a 19.9 µg/m$^3$ increment) but not with PM$_{2.5}$ (RR, 1.03; 95% CI, 0.80–1.33 for a 24.5 µg/m$^3$ increment). Turner et al. (2011) followed the American Cancer Society cohort through 2008 and reported relative risks of lung cancer mortality of 1.15–1.27 for a 10 µg/m$^3$ increment in PM$_{2.5}$ among 188,000 never-smokers.

The Harvard Six Cities Study of Air Pollution and Mortality included a much smaller population (n = 8111) (Dockery et al., 1993). A report on the re-analysis (Krewski et al., 2000) included

<table>
<thead>
<tr>
<th>Reference</th>
<th>Air pollution</th>
<th>Measure of smoking</th>
<th>Rate ratios relative to nonsmoking residents of low-pollution areas</th>
<th>Proportion attributable to joint exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Air pollution</td>
<td>Air pollution/smoking</td>
</tr>
<tr>
<td>Stocks and Campbell (1955)</td>
<td>Urban residents</td>
<td>1 pack per day</td>
<td>9.3</td>
<td>21.2</td>
</tr>
<tr>
<td>Haenszel et al. (1962)</td>
<td>Male residents of urban counties</td>
<td>&gt; 1 pack per day</td>
<td>1.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Vena (1982)</td>
<td>Lifetime residents of high- and medium-pollution areas</td>
<td>≥ 40 pack-years</td>
<td>1.1</td>
<td>4.7</td>
</tr>
<tr>
<td>Jedrychowski et al. (1990)</td>
<td>Residents of high-pollution areas</td>
<td>Ever-smokers</td>
<td>1.1</td>
<td>6.7</td>
</tr>
<tr>
<td>Barbone et al. (1995)</td>
<td>Residence in areas with high levels of particulate deposition (&gt; 0.298 g/m$^2$/day)</td>
<td>≥ 40 cigarettes per day</td>
<td>3.7</td>
<td>59.6</td>
</tr>
</tbody>
</table>

* The EFI (etiological fraction due to interaction) provides an estimate of the proportion of disease among those exposed to both high air pollution and smoking (either former or current) that is attributable to their joint effect.
estimates of the effect of air pollution for ever- and never-smokers. The relative risk estimates for a PM$_{2.5}$ concentration difference of 18.6 µg/m$^3$ were 3.88 (95% CI, 0.44–34.18) for never-smokers and 1.40 (95% CI, 0.80–2.46) for ever-smokers.

Samet and Cohen (1999) made estimates of the effect of joint exposure to ambient air pollution and cigarette smoking based on several studies that provided the requisite data (Table 13.2). Although the studies were limited in scope, the results indicated that the joint contribution may be substantial.

Conclusions

Assessment of the relatively modest effects of air pollution on risk of cancer has long been complicated by the high prevalence of tobacco smoking and the powerful effect that smoking has to increase the risk of cancer. To the extent possible, IARC Monographs on air pollutants will need to assess studies carefully with regard to their approach to tobacco smoking, to the potential for residual confounding, and also to an evaluation of any effect modification. Synergism of air pollution with smoking would indicate that the burden of cancer associated with smoking may be far greater than that indicated by the estimated risk for smoking alone.

References


Thomas DC & Whittemore AS (1988). Methods for testing interactions, with applications to occupational
Air pollution and cancer


