CHAPTER 13. COMBINED EFFECT OF AIR POLLUTION WITH OTHER AGENTS

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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

Table 13.1 Levels of interaction between smoking and other agents

Exposure	• Work assignments of smokers and nonsmokers differ • Absenteeism rates differ for smokers and nonsmokers
Exposure–dose relationships	• Patterns of physical activity and ventilation differ for smokers and nonsmokers • Exposures of smokers and nonsmokers differ in activity size distribution • Patterns of lung deposition and clearance differ in smokers and nonsmokers • Morphometry of target cells differ in smokers and nonsmokers
Carcinogenesis	• Alpha particles and tobacco smoke carcinogens act at the same or different steps in a multistage carcinogenic process

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

Table 13.2 Proportion of lung cancer attributable to the joint effect of air pollution and tobacco smoking

Reference	Air pollution	Measure of smoking	Rate ratios relative to nonsmoking residents of low-pollution areas		Proportion attributable to joint exposure
			Air pollution	Air pollution/ smoking	(EFI)[a]
Stocks and Campbell (1955)	Urban residents	1 pack per day	9.3	21.2	0.31
Haenszel *et al.* (1962)	Male residents of urban counties	> 1 pack per day	1.1	5.7	0.30
Vena (1982)	Lifetime residents of high- and medium-pollution areas	≥ 40 pack-years	1.1	4.7	0.45
Jedrychowski *et al.* (1990)	Residents of high-pollution areas	Ever-smokers	1.1	6.7	0.27
Barbone *et al.* (1995)	Residence in areas with high levels of particulate deposition (> 0.298 g/m²/day)	≥ 40 cigarettes per day	3.7	59.6	0.21

[a] 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.

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/m³ $PM_{2.5}$ 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/m³ increment) but not with $PM_{2.5}$ (RR, 1.03; 95% CI, 0.80–1.33 for a 24.5 μg/m³ 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/m³ 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

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

Alberg AJ & Samet JM (2003). Epidemiology of lung cancer. *Chest*, 123: Suppl: 21S–49S. PMID:12527563

Barbone F, Bovenzi M, Cavallieri F, Stanta G (1995). Air pollution and lung cancer in Trieste, Italy. *Am J Epidemiol*, 141: 1161–1169. PMID:7771454

Dockery DW, Pope CA 3rd, Xu X *et al.* (1993). An association between air pollution and mortality in six U.S. cities. *N Engl J Med*, 329: 1753–1759. doi:10.1056/NEJM199312093292401 PMID:8179653

Doll R (1971). The age distribution of cancer: implications for models of carcinogenesis. *J R Stat Soc [Ser A]*, A134: 133–166.

Haenszel W, Loveland DB, Sirken MG (1962). Lung-cancer mortality as related to residence and smoking histories. I. White males. *J Natl Cancer Inst*, 28: 947–1001. PMID:13903525

IARC (1977). Asbestos. *IARC Monogr Eval Carcinog Risk Chem Man*, 14: 1–106. PMID:863456

IARC (1988). Man-made mineral fibres and radon. *IARC Monogr Eval Carcinog Risks Hum*, 43: 1–300.

IARC (2004). Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum*, 83: 1–1438. PMID:15285078

Jedrychowski W, Becher H, Wahrendorf J, Basa-Cierpialek Z (1990). A case-control study of lung cancer with special reference to the effect of air pollution in Poland. *J Epidemiol Community Health*, 44: 114–120. doi:10.1136/jech.44.2.114 PMID:2370498

Krewski D, Burnett RT, Goldberg MS *et al.* (2000). Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. Investigators' Reports Parts I and II. Cambridge, MA: Health Effects Institute.

Lewtas J (2007). Air pollution combustion emissions: characterization of causative agents and mechanisms associated with cancer, reproductive, and cardiovascular effects. *Mutat Res*, 636: 95–133. doi:10.1016/j.mrrev.2007.08.003 PMID:17951105

Pope CA 3rd (2000). Particulate matter-mortality exposure-response relations and threshold. *Am J Epidemiol*, 152: 407–412. doi:10.1093/aje/152.5.407 PMID:10981452

Pope CA 3rd, Burnett RT, Thun MJ *et al.* (2002). Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA*, 287: 1132–1141. doi:10.1001/jama.287.9.1132 PMID:11879110

Pope CA 3rd, Thun MJ, Namboodiri MM *et al.* (1995). Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am J Respir Crit Care Med*, 151: 669–674. doi:10.1164/ajrccm/151.3_Pt_1.669 PMID:7881654

Rothman KJ, Greenland S (1998). *Modern Epidemiology*, 2nd ed. Philadelphia: Lippincott-Raven.

Samet JM, Cohen AJ (2006). Air pollution. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*, 3rd ed. New York: Oxford University Press, pp. 355–381.

Samet JM, Cohen AJ (1999). Air pollution and lung cancer. In: Holgate ST, Samet JM, Koren HS, Maynard RL, eds. *Air Pollution and Health*. San Diego, CA: Academic Press, pp. 841–864.

Stocks P & Campbell JM (1955). Lung cancer death rates among non-smokers and pipe and cigarette smokers. An evaluation in relation to air pollution by benzo[a] pyrene and other substances. *BMJ*, ii: 923–929. doi:10.1136/bmj.2.4945.923

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

exposures, smoking, and lung cancer. *Am J Ind Med*, 13: 131–147. doi:10.1002/ajim.4700130109 PMID:3344752

Turner MC, Krewski D, Pope CA 3rd *et al.* (2011). Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. *Am J Respir Crit Care Med*, 184: 1374–1381. doi:10.1164/rccm.201106-1011OC PMID:21980033

Vena JE (1982). Air pollution as a risk factor in lung cancer. *Am J Epidemiol*, 116: 42–56. PMID:7102655

Walker AM (1981). Proportion of disease attributable to the combined effect of two factors. *Int J Epidemiol*, 10: 81–85. doi:10.1093/ije/10.1.81 PMID:7239766

Whittemore AS (1977). The age distribution of human cancer for carcinogenic exposures of varying intensity. *Am J Epidemiol*, 106: 418–432. PMID:920729