Synergy between Asbestos and Smoking on Lung Cancer Risks

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We have examined data from 12 epidemiologic studies for quantitative evidence of biologic synergy between asbestos and smoking on lung cancer risks. Estimates of the effect associated with joint exposure to the two agents exceeded the sum of their separate effects in each study. We explored the variations in the strength of the synergistic effect across the studies using three indices: the ratio of the combined effects to the sum of the separate effects of smoking and asbestos (S), the relative excess risk due to interaction (RERI), and the attributable proportion of risk due to interaction (AP). The weighted average of S across all studies was 1.64 (95% confidence interval = 1.33–2.03). The attributable proportion associated with this average S was estimated as 33%, that suggests that one-third of cancer cases among smokers who were exposed to asbestos can be attributed to the synergistic behavior of the two carcinogens, as distinct from their separate effects and those attributable to other ("background") factors. (Epidemiology 1999;10:405–411)

Keywords: synergy, asbestos, smoking, lung neoplasm, meta-analysis, biologic interaction.

Following seminal reports published during the 1950s and 1960s,[1,2] epidemiological studies have confirmed that both tobacco smoke and asbestos fibers are potent human carcinogens. In 1968, Selikoff *et al*[3] noted that the combined exposure to both of these agents appeared to be associated with more lung cancer cases than expected from the sum of estimates of their separate effects. Rothman *et al*[4,5] have suggested that this type of phenomenon may be interpreted as biologic interaction, or synergy, and that it can be quantified by an index, S, defined as the ratio of the observed effects of joint exposure to the two agents to the sum of estimates of the separate effects of each. Greenland and Rothman[6] review varying interpretations of "interactions" in epidemiologic data and distinguish between (1) the purely statistical use of the word, which has to be interpreted in the context of the scale of measurement used to represent the response variable; (2) interactions that might be interpreted as implying differences in biologic mechanisms depending on whether the suspect etiologic factors are acting singly or in combination; and (3) the public health implications of any such interactions. Various numerical measures that reflect these different ideas are also described.[6]

This paper focuses primarily on the biologic significance of apparent departures from a simple additive model of the effects of exposure to asbestos and smoking on lung cancer risks. In this paper, we ask the following: *Is the available evidence from different studies regarding such biologic synergy qualitatively consistent? What factors might be responsible for observed variations among studies? Is it possible to estimate, quantitatively, the overall magnitude of such synergy?* We chose S as a convenient statistic to explore these questions. We also record two other indices, the relative excess risk due to interaction (RERI) and the attributable proportion of risk due to interaction (AP), the latter being helpful for an assessment of the public health implications of the findings.

Subjects and Methods

Data Sources

We searched the MEDLINE reference base (1966–1996) and found three reviews[7–9] and 17 research papers[3,10–25] that provided quantitative information about occupational exposures to asbestos, smoking habits, and the separate and combined associations of these factors with lung cancer risks. We selected studies for inclusion in the analyses reported here by verifying that sufficient data were available in the reports to estimate relative risks of lung cancer, and the corresponding standard errors, for "smokers" and for "nonsmokers" (as defined below), among both those exposed and those not exposed or minimally exposed to asbestos (Table 1.).

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TABLE 1. Selected Studies for the Analyses of Lung Cancer Risks in Relation to Occupational Asbestos Exposure and Smoking

Design, Location	Source Population	Study Subjects	Comparison Group	First Named Author
Cohort, England	Employed at an asbestos factory in London; men, since 1933, and women, 1936–1942	1,300 men, 480 women; study period, 1960–1970	SMR, using general population death rates adjusted for residence in Greater London and for observed smoking habits	Berry[10]
Case-referent, England	Men admitted to a TSC during 1 year	201 cases, 201 matched referents	Admission to TSC 1972–1973	Martischnig[12]
Case-referent, United States	Residents of coastal Georgia; catchment in four local hospitals	458 male cases, 553 referents	Referents from four regional hospitals and from death certificates	Blot[13]
Cohort, United States and Canada	Entire membership of the insulation workers' union (United States and Canada)	12,051 workers with at least 20 years of asbestos exposure; study period, 1967–1976	External: 73,763 men of similar social class selected from an ACS study	Hammond[14]
Cohort, United States	933 amosite asbestos workers who began work from 6/1941 through 12/1945 in Paterson, NJ	582 men; follow-up from 1961 through 1977	External: white men with matching smoking history from the ACS study	Selikoff[15]
Case-referent, United States	Mortality listing during 1976 from Virginia	336 male cases, 492 matched referents	Deaths in Virginia in 1976	Blot[17]
Nested case-referent, Canada	Birth cohort of ~30,000 past and present employees of the Quebec chrysotile production industry	223 male cases, 715 matched referents	Surviving members of same cohort	Liddell[18]
Case-referent, Italy	Male workers in industrialized Lombardy region during 1976 and 1979	204 cases, 351 matched referents	Men from the study area	Pastorino[20]
Cohort, England	Employees at an asbestos factory in London; men, since 1933, and women, 1936–1942	1,250 men, 420 women; follow-up from 1971 through 1980	SMR, using sex-, age- and period-specific death rates for England and Wales	Berry[21]
Case-referent, Norway	Medical wards of Telemark and Vestfold County Hospital during 1979 and 1983	176 male cases, 176 referents	Medical wards of Telemark and Vestfold County Hospital	Kjuus[23]
Nested case-referent, Australia	6,500 persons employed in the Wittenoom asbestos industry between 1943 and 1966	40 male cases, 1,799 matched referents	Surviving members of the same cohort	de Klerk[24]
Cohort, China	Workers employed in the Tianjin asbestos factory on January 1, 1972	662 men and 510 women	3,219 workers not exposed to asbestos, dust, fumes, or vapor	Cheng[25]

SMR = standardized mortality ratio; TSC = thoracic surgical center; ACS = American Cancer Society.

From this list of 17 reports, we omitted 2,[3,11] because a later paper,[14] which is included, describes a larger cohort of insulation workers over a longer, overlapping follow-up period. We also did not include the report on Canadian chrysotile production workers,[16] because the nested case-referent study by Liddell and colleagues,[18] which is included, is based on that cohort and uses improved, less ambiguous classification of smoking habits. We also excluded the report from Acheson *et al*,[19] because the expected number of lung cancer deaths was reported without correction for smoking. Finally, we excluded the Hilt *et al*[22] report, because there were no lung cancer cases recorded among nonsmokers. We therefore used 12 reports for our analyses.

Berry *et al*[10,21] described lung cancer mortality in the same cohort in two papers. Data from both are included in the analyses described here because they refer to distinct, nonoverlapping follow-up periods. The later paper,[21] published in 1985, includes revised estimates of effects reported earlier.[10] We used those revised estimates in the calculations described here.

TABLE 2. Summary of Information about Smoking and Exposure to Asbestos in 12 Selected Reports, and Criteria Used for Definition of Exposure Dichotomies in this Review

Information on Asbestos Exposure	Information on Smoking Habits	Asbestos/No Asbestos Definition Used Here	Smoker/Nonsmoker Definition Used Here	First Named Author
Occupational history extracted from the personnel records at the factory; mixed asbestos	Questionnaire or interview on smoking habits for those alive in 1971; for deceased: medical records, family doctor, relatives	Severe exposure *vs* external comparison population	Men, smokers *vs* never-smoked; women, smoked at some time *vs* never smoked	Berry[10]
Assessment of the occupational history when admitted to the TSC; any asbestos	Assessment when admitted to TSC	Exposed *vs* not exposed	At least 15 cigarettes/day *vs* 0–14 cigarettes/day	Martischnig[12]
Occupational history assessed through interviews with cases and referents or their next of kin; unspecified asbestos	Personal interviews of patients and referents; for deceased, next of kin	Ever employed in shipbuilding, yes *vs* no	Heavy or moderate smoker *vs* nonsmoker, light smoker, or stopped smoking	Blot[13]
Membership in the International Association of Heat and Frost Insulators and Asbestos workers; chrysotile, amosite	Questionnaire on lifetime smoking habits (recorded in 1966)	Asbestos workers (when at least 20 years exposed) *vs* external comparison population	History of cigarettes *vs* never smoked regularly	Hammond[14]
Work at the factory during 1941–1954; confirmation of predominant use of amosite in the asbestos factory	Ascertainment of smoking habits 20 years after start of employment (1961–1965)	Amosite asbestos worker *vs* external comparison population	History of cigarette smoking *vs* never smoked regularly	Selikoff[15]
Occupational history assessed through personal interviews with next of kin of cancer patients and referents; unspecified asbestos	Personal interviews with next of kin of cancer patients and referents	Employed in shipyards before 1950, yes *vs* no	Heavy or moderate smoker *vs* never smoked, light smoker, or long-term ex-smoker	Blot[17]
Assessment of average dust concentrations at specific jobs based on measurements, approximations and interviews; chrysotile	Questionnaire responses on smoking habits as in 1970 for those alive or from relatives or friends of those who died after 1950	Exposure to ≥100 fibers *vs* <100 fibers	At least 1 pack-year *vs* 0 pack-years	Liddell[18]
Assessment of occupational history in interviews with cases and referents or their next of kin; any asbestos	Interviews with cases and referents or their next of kin	Exposed (probably) *vs* not exposed	At least 10 cigarettes/day *vs* 0–9 cigarettes/day	Pastorino[20]
See Berry et al.[10]	Questionnaire or interview on smoking habits in 1971	Severe asbestos exposure *vs* external comparison population	Men, smokers *vs* never smoked; women, smokers *vs* never smoked	Berry[21]
Asbestos history through personal interview and questionnaire for cases and referents; any asbestos	Personal interview and questionnaire for cases and referents	Grade 2–3, moderate or heavy exposure *vs* grade 0–1, no, uncertain, light/sporadic exposure	At least 10 cigarettes/day *vs* 0–9 cigarettes/day	Kjuus[23]
Occupational exposure from employment records; crocidolite	Questionnaire in 1979	High exposure *vs* low exposure	Smokers *vs* nonsmokers (includes cessation for >10 years)	de Klerk[24]
Detailed work history from employment card; unspecified asbestos	Smoker's history was determined by number of cigarettes/day, beginning smoking age, number of years smoked	Asbestos exposure, yes *vs* no	Men and women (≥1 cigarette/day for at least 1 year): Yes *vs* no	Cheng[25]

TSC = thoracic surgical center.

Exposure Classification

Table 2 summarizes the information about exposure to asbestos and smoking habits from the reports and indicates how we used this information in this review. We defined a "no-exposure" category of smoking behavior to include nonsmokers or all of those in the lowest smoking category described in the paper concerned. We excluded ex-smokers from the analysis where possible, on the grounds that lung cancer risks decrease gradually after cessation of smoking.[26] We also excluded those who

TABLE 3. Standardized Estimates of Relative Lung Cancer Risks Associated with Separate and Joint Exposures to Smoking and Asbestos, and Three Indices of Synergy (S, RERI, AP)*

Lung Cancer Risk Ratio Estimates by:							
	Asbestos						
Smoking	No	Yes	S	95% CI	RERI	AP	First Named Author
No	1	5.0	2.30	0.94–5.60	19.5	0.55	Berry[10]†
Yes	12.1	35.5					
No	1	1.1	5.30	0.93–30.15	3.71	0.67	Martischnig[12]
Yes	1.8	5.6					
No	1	1.3	1.65	0.98–2.78	2.60	0.34	Blot[13]
Yes	4.7	7.6					
No	1	5.2	3.73	1.71–8.11	38.22	0.72	Hammond[14]
Yes	10.9	53.2					
No	1	25	1.25	0.58–2.68	7.94	0.20	Selikoff[15]
Yes	8.7	40.6					
No	1	1.9	1.30	0.68–2.48	0.88	0.18	Blot[17]
Yes	3.1	4.9					
No	1	3	1.22	0.78–1.91	1.29	0.16	Liddell[18]
Yes	4.9	8.2					
No	1	2.8	1.41	0.55–3.63	2.57	0.26	Pastorino[20]
Yes	5.5	9.9					
No	1	11.5	1.45	0.70–3.01	9.57	0.30	Berry[21]†
Yes	11.8	31.9					
No	1	2.4	3.24	1.15–9.12	13.04	0.66	Kjuus[23]
Yes	5.4	19.9					
No	1	2.2	2.33	0.75–7.27	4.89	0.51	de Klerk[24]
Yes	3.4	9.6					
No	1	5.4	1.54	0.74–3.15‡	2.71	0.31	Cheng[25]
Yes	1.6	8.7					

* S = synergy index; RERI = relative excess risk due to interaction; AP = attributable proportion of risk due to interaction.
† Men and women combined.
‡ These confidence limits were not calculable directly from the data reported.[25] Regression of the estimated standard errors (SEs) of ln(S) from the other 11 studies on the corresponding values of S provided a convincing fit (variance accounted for = 60.2%). The fitted linear equation was used to estimate SE(lnS), and thus the 95% CI, for S = 1.54.

reported smoking a "pipe and/or cigar only" from the analysis.

For occupational exposure to asbestos, we defined a no-exposure category that included all of those in the lowest exposure category from each paper. We classified all others as "exposed."

Analysis

We estimated the relative risks of lung cancer associated with smoking, with exposure to asbestos, and with simultaneous exposure to both for each of the 12 reports. For each cohort study, we calculated the relative risk as $RR_{ij} = (R_{ij}/R_{00})$, where i and j index respectively the presence (1) and absence (0) of exposure to tobacco smoke and to asbestos, as defined above. R_{i1} was calculated as x_{i1}/PYR_{i1}, and R_{i0} was estimated by y_{i0}/PYR_{i1}, where x_{i1} refers to number of reported lung cancer cases, y_{i0} to number of cases expected on the basis of age-specific lung cancer death rates in the external comparison population involved, and PYR_{i1} to number of person-years at risk, for $i = 0,1$.

For case-referent studies, we estimated the relative risks by odds ratios (OR), as follows: $OR_{ij} = (c_{ij}/r_{ij})/(c_{00}/r_{00})$, where c_{ij} and r_{ij} refer to cases and referents, respectively, with exposure combination ij.

We then calculated excess relative risks, ERR_{ij}, for effects associated with smoking and exposure to asbestos, singly and in combination, by subtracting unity from the estimates of relative risk. This calculation allowed us to derive three indices of synergy for each study: the synergy index, S[27] [$S = ERR_{11}/(ERR_{10} + ERR_{01})$]; the relative excess risk due to interaction,[28] RERI [$RERI = ERR_{11} - (ERR_{10} + ERR_{01})$]; and the attributable proportion of risk due to interaction,[29] AP {$AP = [ERR_{11} - (ERR_{10} + ERR_{01})]/(ERR_{11} + 1)$}. AP is that fraction of total lung cancer risk among those exposed to both factors in the population concerned (including the background risk in the absence of the two factors) that is attributable to the combined (as distinct from the separate) effects of the two factors.

The standard errors of the natural logarithms of S were estimated from the formulae for cohort and case-referent studies proposed by Rothman[27] and were used to approximate to 95% confidence limits for S by exponentiating the limits for ln(S). Values of S from selected groups of studies were pooled to produce weighted averages, S_P [and their approximate 95% confidence intervals (CIs)], where $S_p = \exp\{[\Sigma w \bullet \ln(S)]/(\Sigma w)\}$; the summation is over the different studies; and the weighting

factors, w, are the reciprocals of the estimated variances of the ln(S).[30]

Results

Table 3 shows that for each study, the combined effects of smoking and asbestos (ERR_{11}) were greater than the sums of the estimated separate effects ($ERR_{10} + ERR_{01}$). Values of S ranged from 1.2 to 5.3 (coefficient of variation, CoV = 57%). The *differences* between the combined and the sum of the two separate excess relative risks (RERI) ranged from 0.9 to 38.2 (CoV = 117%). The fraction of total lung cancer risk attributable to the biologic interaction among those exposed to both agents (AP) ranged from 16 to 72% (CoV = 52%).

Although the 12 estimates of S and of their confidence limits vary, there was no suggestion of systematic study design-associated variation in S. Of the two highest values of S, one was from a case-referent study,[12] and the other was from a cohort study.[14] The other four values of S from cohort studies[10,15,21,25] were not conspicuously different from those calculated from most of the case-referent data. In seven of the studies, however, including four of the five cohort studies,[10,14,15,21] estimates of the asbestos-associated risks for smokers were less than those for nonsmokers; for the other cohort study,[25] these risks were almost identical.

The rank correlation between S and AP was high (Spearman's $r_S = 0.98$). The rank correlation between S and RERI was not as high, although it was still positive ($r_S = 0.59$). This lower correlation reflects the relatively low value of RERI in the Martischnig *et al* study,[12] despite the high values of S and AP, and also the converse pattern in results from workers exposed to amosite asbestos.[15]

A test of the homogeneity of S from 11 studies that provided information allowing direct estimation of the variances of the corresponding ln(S) did not contraindicate pooling the data concerned ($\chi^2_{10} = 11.48$; $P \approx 0.32$). The weighted summary value of S based on those 11 studies (that is, omitting the study by Cheng and Kong[25]) was 1.66 (95% CI = 1.33–2.06). This weighted average is not overly dependent on just one or two high values of S, because the latter are associated with relatively wide CIs. Inclusion of results from the 12th study[25] in the weighted average, using an additional approximation to the variance of ln(S), also made little difference to the estimate of S_r (it was 1.64).

Discussion

Results from the 12 reviewed studies consistently indicated that the joint effect on lung cancer risks of smoking and occupational exposure to asbestos was greater than the sum of the separate effects. The consistency might be artifactual in part, because choice of studies for inclusion in meta-analyses is always subject to a possible bias arising from the reluctance of authors (and some editors) to publish negative results. In the present case, such "publication bias" would probably be relatively mild with respect to the main issue, the postulated *synergy* between asbestos and smoking on lung cancer risks. Absence of evidence supporting the idea of synergy between these two agents is unlikely, on its own, to have disqualified otherwise interesting results from publication.

It was necessary, for inclusion in this review, that reports contain sufficient detail for estimation of both the separate and the combined effects of asbestos and smoking. This requirement may have influenced the pattern of results obtained. Nevertheless, we believe that it is reasonable to conclude that the findings provide a fairly clear-cut answer to the first of the three questions posed in the introduction to this paper. Epidemiologic evidence accumulated over some 30 years is consistent, in broad qualitative terms, with the observation by Selikoff *et al*,[3] in 1968, of a potentiating biologic interaction (synergy) between the effects of asbestos and smoking on lung cancer risks. The other two questions prefacing this paper, about variability between the studies and quantitative generalizability, require more detailed consideration.

Variability between Studies

Indices of synergy derived from five cohort studies did not differ systematically from those based on case-referent data (Table 3). Moreover, results from the three hospital-based case-referent studies[12,13,23] were typical of the ranges recorded from all 12 studies. The overall pattern of variability in results is therefore not explicable simply in terms of study design-related factors.

The follow-up periods in the five cohort studies were similar, between 10 and 16 years, but the criteria for inclusion in the study of North American insulation workers[14] were unusual in that these criteria required that all of the individuals involved had been exposed to asbestos for at least 20 years. It is conceivable that this could have resulted in a pattern of response different from that recorded in the other four cohort studies, in which less demanding exposure criteria were used to define the study groups. Suppose that the 20-year minimum exposure criterion determined that some of these men had also experienced nontrivial exposures to occupational carcinogens other than asbestos. (McDonald *et al*[31] have speculated that exposure to materials other than asbestos may be one possible explanation for the apparently higher asbestos-associated cancer risk among these insulation workers as compared with that found in Canadian chrysotile miners and millers.[15,31]) Suppose additionally that the carcinogenic potential in the lung of such other material is enhanced in the presence of tobacco fumes. This scenario would not affect the asbestos-specific effect as estimated for this review (ERR_{21}), but it would inflate the effects apparently associated with smoking, nominally "on its own" (ERR_{12}) and in combination with exposure to asbestos (ERR_{11}). The results calculated from the study by Hammond *et al*[14] follow this pattern. The ERR_{21} (4.2) is the fourth highest of the 12 values calculated but close to the arithmetic mean (4.6). The ERR_{12} (9.9) and ERR_{11} (52.2) are both

well above the corresponding means (5.2 and 18.6, respectively.) Thus, the postulated exposure of the insulation workers to at least one lung carcinogen other than asbestos that potentiates (or is potentiated by) tobacco smoke could partially explain the relatively high synergy indices calculated from those data.[14]

Sophistication in assessments of exposures to asbestos varied across the studies, from "ever employed in ship building" (mostly during World War II)[13] to estimates of individuals' working-life cumulative exposures to asbestos.[18] We used the dichotomy exposed/not exposed in an attempt to place the available data on an approximately common scale. This simplification implies loss of power to identify a possible asbestos dose-related variation in any synergy with smoking. But if the relatively crude exposure gradient defined by the dichotomy does suggest a synergistic effect (as it does here), then there should be a compensatory increase in confidence that the apparent effect is real rather than artifactual, provided that errors in exposure classifications are random. The limits of that confidence are quantified approximately in Table 3 as 95% CIs, on the assumption of no classification bias. That assumption is not necessarily valid, particularly for hospital-based case-referent studies, but a possible asbestos exposure classification bias would have had to be substantial to have affected the overall pattern of results.

Three of the studies[15,18,24] allow us to consider variation in synergistic effects relative to the type of asbestos involved. Estimates of the three synergy indices for the Australian workers who were exposed "almost exclusively" to crocidolite[24] are all higher than the corresponding results from the Canadian chrysotile miners and millers.[18] But the lower 95% confidence limit for S based on the Australian data (0.75) is almost the same as that calculated from the Canadian results (0.78). The RERI among factory workers who were described as having been exposed almost exclusively to amosite[15] is higher than those found for the other two specifically differentiable fiber types,[18,24] but this RERI (7.94) ranks as only the fifth highest among those from all 12 studies, and the corresponding values of S and AP are both low. Thus, the available data do not convince us that there is a difference in the synergistic potentials of different types of asbestos.

We also used a dichotomy to summarize the varying representations of exposure to tobacco smoke that are recorded in Table 2. The convention that we adopted was arbitrary and may have further reduced power to detect a real synergistic effect. But again, because a synergistic effect was detectable using this crude classification of smoking habits, we think it even more likely that the effect would have been found if it had been possible to quantify exposure to tobacco smoke more precisely, provided also that there was no differential misclassification of smoking habits between those with and those without lung cancer.

How Strong Is the Synergistic Effect?

We believe that the robustness of our estimate of S_p, and the homogeneity of the contributing sets of data, justify the following generalizations. The excess lung cancer risk arising from simultaneous exposures to particular levels of asbestos and tobacco smoke is higher than the sum of the two separate excess risks by a factor of about 1.64. The 95% CI associated with this estimate is approximately 1.33–2.03.

Public health implications of these findings can be assessed by noting that the 12 AP indices that we calculated for this review are very closely related to the corresponding values of S. A fitted quadratic in S accounted for 98.7% of the variability across the APs. The estimated value of AP, given $S_p = 1.64$, was 33%. Estimates of AP corresponding to the approximate 95% confidence limits for S_p are 22% and 45%. The results therefore suggest that, among smokers who are also exposed to asbestos, some 33% of lung cancer cases can be attributed to the synergistic behavior of the two carcinogens, as distinct from their separate effects and from those arising from other ("background") factors.

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