Asbestos and Gastrointestinal Cancer

A Review of the Literature

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Exposure to asbestos is among several factors cited as possible causes of esophageal, gastric and colorectal cancer. More than 45 published studies have presented mortality data on asbestos-exposed workers. For each cohort, we listed the observed and expected rates of deaths from types of gastrointestinal cancer based on the latest published follow-up. Summary standardized mortality ratios (SMRs) were then derived. Finally, we calculated summary SMRs for total gastrointestinal tract cancer for three occupational groups: asbestos factory workers, insulators/shipyard workers and asbestos miners.

Statistically significant elevations in summary SMRs were found for esophageal, stomach and total gastrointestinal tract cancer in all asbestos-exposed workers. Esophageal cancer summary SMR remained significantly elevated when data were reanalyzed to include only those cohorts with death certificate diagnoses for cause of observed deaths. However, summary SMRs were not statistically significant for stomach and total gastrointestinal tract cancer after reanalysis. Summary SMRs by occupational group showed a significant elevation for total gastrointestinal cancer in insulators/shipyard workers. The elevation was not significant after reanalysis.

Based on the results after reanalysis, the elevations in summary SMRs for stomach and total gastrointestinal tract cancer are of a magnitude that could result from diagnostic and investigator error. We conclude that more studies are required before stomach and colorectal cancers are documented as asbestos-related diseases.

(Morgan RW, Foliart DE, Wong O: Asbestos and gastrointestinal cancer—A review of the literature. West J Med 1985 Jul; 143:60-65)

What causes gastrointestinal cancer is far from clear. Cited as possible causes are factors as diverse as diet, race, blood group, alcohol intake and exposure to asbestos. This review will examine the relationship of occupational asbestos exposure to the risk of developing carcinoma of that portion of the gastrointestinal tract including the esophagus, stomach and colon-rectum. The association of asbestos and peritoneal mesothelioma is well documented, does not involve the gastrointestinal tract and will not be reviewed here.

Esophageal cancer is a relatively uncommon cancer for which death rates have remained stable over time: 4.1/100,000 in 1955 and 4.3/100,000 in 1975, for US white men. Higher death rates have been reported in areas of Africa and Eastern Europe. In the United States, esophageal cancer is found predominantly in men and is associated with cigarette smoking and alcohol intake.

Gastric cancer is a slightly more common disease of considerable geographic variation, with some countries, notably Japan, having rates significantly higher than those of the United States. Dietary factors have been implicated in the pathogenesis of the disease. In the United States both mortality and incidence of stomach cancer in white men have fallen consistently and dramatically over a 20-year period. For example, the mortality rate dropped from 17.2/100,000 in 1955, to 8.2/100,000 in 1975.

Colorectal cancer presents an etiologic puzzle distinguished more by the number of hypotheses than by discovery of causative agents. In addition to asbestos, associations are postulated for intake of fiber, fat and specific foodstuffs. For US white men, death rates for colorectal cancer were 23.4/100,000 in 1955 and 24.4/100,000 in 1975.

Attempts to study the relationship of asbestos to gastroin-

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ABBREVIATIONS USED IN TEXT

AR = attributable risk
SMR = standardized mortality ratio

testinal cancer are frustrated by a number of factors. First, for any specific site (for example, stomach), the disease is sufficiently uncommon that few work forces can be expected to account for enough cases from which to draw conclusions. Perhaps more important, there is considerable opportunity for misdiagnosis or inaccurate certification of death, in that some gastrointestinal tract cancers will be certified as mesothelioma, and vice versa. This question has been addressed by both Newhouse [1] and Selikoff [2] in their examinations of death certificate accuracy in asbestos workers' deaths. In the Newhouse series, half of the deaths certified as gastrointestinal cancer were actually due to mesotheliomas. In Selikoff's series, only 24 deaths were originally certified as peritoneal mesotheliomas; after examining further clinical and pathologic evidence from other deaths in the cohort, investigators classified 112 deaths as due to that cause, with a pronounced reduction in number of deaths due to "all other cancer" and "all other causes."

Although diagnostic inaccuracy is troubling, it is not easily remedied. Selikoff has used "best evidence" from numerous sources, rather than the certified cause of death, to calculate standardized mortality ratios (SMRs). However, "best evidence" data cannot properly be compared with national mortality statistics, which are derived solely from death certificates. Unless one can also correct the statistics from the US reference population, comparisons are invalid because of the underlying principle that both study and reference populations should have similar ascertainment and classification of death. Another statistically questionable practice is attributing to cancer those deaths previously certified as due to a cause other than cancer, but where cancer was present (Selikoff communication quoted by Miller[3]). Again, without a similar mechanism for including cancer as a contributing cause of death in the national mortality statistics, such comparisons will either create an apparent excess of cancer in the study population or will exaggerate any excess already there.

Most of the evidence concerning asbestos and disease comes from the retrospective cohort mortality studies of asbestos-exposed workers. In all of these studies, a cohort exposed to asbestos has been identified from employment, union or other existing records and then followed prospectively over time to compare their rate and pattern of mortality with a reference population with presumably no exposure or less exposure. The reference population is frequently that of county, state or country. In general, national statistics are used because of availability and the stability imparted by large numbers. Smaller jurisdictions tend to produce statistics that can be heavily influenced by relatively few deaths, including those occurring in the work force under study.

Methods

To determine the role of occupational asbestos exposure in the risk of gastrointestinal cancer, we attempted to identify all relevant publications from the indexed literature. From each report, we extracted the details concerning cohort definition, exposure of concern and gastrointestinal cancer deaths (both observed and expected). We did not include any judgment concerning scientific merit in selecting papers to be included.

A summary of published studies of asbestos-exposed workers is presented in Table 1. Some 45 publications have described about 22 different cohorts, although within them there is some overlap. Deciphering the interwoven cohorts is complicated because in many cases a single data set has been repeatedly published, sometimes for an alternative analysis. In other cases, there appears to be no clear reason for the republication. Further confusion is introduced when papers do not specify that the data, or portions thereof, were previously reported. Some of the cohort studies reported do not mention gastrointestinal cancer, let alone specific sites, so contribute little to a quantitative analysis.

Table 2 summarizes the results of those studies which are informative as to the possible relationship of asbestos to gastrointestinal cancer. Studies were included in Table 2 when the number of gastrointestinal tract cancer deaths was available and the cohort discrete. Because of the problem of data overlap, we have used the latest published follow-up of each cohort rather than numbers from earlier papers. When available, observed deaths based on death certificates, rather than "best evidence," are presented in Table 2. Several of the studies[24,28,38] in Table 2 grouped deaths from peritoneal mesotheliomas with gastrointestinal cancers. When the actual numbers of mesotheliomas were given in the text, we deleted these from "observed" deaths. One report[33] grouped esophageal and stomach cancer deaths together for analysis. This report was not included in the calculations for those sites.

In order to provide a quantitative summary risk index for gastrointestinal cancers based on the studies reviewed, we have examined a number of statistical procedures. One procedure is the combination of relative risks based on the variance-weighted logarithms of the relative risk.[56-58] In this procedure, we can treat each cohort as a 2×2 table and the SMR as a special type of relative risk.[59] The unexposed group in the 2×2 table would be a sample of the standard population, whose sample size is the same as that of the exposed study group. This procedure, however, presents some difficulties because the number of person-years is not always presented in every study reviewed.

Another procedure of combining the risk estimates from these studies is the indirect standardization. We can view each cohort as a separate stratum; within each, certain characteristics are homogeneous (for example, study design, length of follow-up and exposure). This view is similar to that in calculating SMR within a cohort, where the strata are homogeneous with respect to age, race, sex and so forth. In the direct standardization only the observed and expected deaths are needed for the calculation. The summary SMR can be calculated as follows:

$$\text{Summary SMR} = \frac{\text{Sum of Observed Deaths}}{\text{Sum of Expected Deaths}} \times 100.$$

In essence, the summary SMR is weighted by the number of expected deaths, which is the reciprocal of the variance of the individual SMR.[58] Thus, this method is, to some extent, similar to the one based on the logarithm of the relative risks.

Needless to say, this application of the indirect standardization in summarizing SMRs from different studies is subject to the same criticisms that are often raised in summarizing

age-sex-race-specific rates in a single study. On the other hand, we know of no way to overcome the bias due to the fact that negative studies were less likely to result in published SMRs or observed and expected values, although even studies with negative findings in gastrointestinal cancer but with positive findings in respiratory tract cancer would still have a high likelihood of being published.

We have also derived summary SMRs for three major occupations: asbestos factory workers, insulators/shipyard workers and miners. In the follow-up of the New York-New Jersey cohort of insulation workers to 1976,[2] only "best evidence" calculations of observed deaths are presented (Table 3). Due to the limitations of "best evidence" data, summary SMRs were also calculated after deleting observed deaths in this cohort.

Results

Summary SMRs and confidence intervals for esophageal, stomach, colorectal and total gastrointestinal tract cancer appear in Table 3. Significant elevations in summary SMRs

TABLE 1.—*Summary of Studies of Asbestos-Exposed Workers*

Authors	Published: First	Published: Follow-up	Date Republished	Cohort Description and Comments
Doll	1955 (9)*	...	...	Asbestos textile factory workers
Knox et al	...	1965 (10)	...	Followed through 1961
		1968 (11)	...	Followed through 1966
Peto et al	...	1977 (12)	...	Followed through 1974
Braun and Truan	1958 (14)	...	...	Canadian asbestos miners followed 1950-55
Dunn et al	1960 (15)	...	...	Multiple occupational groups studied 1954-62
		1965 (16)	...	Follow-up through 1962
Mancuso et al	1963 (17)	...	...	Factory workers followed 1938-60
	1967 (18)	...	...	Same cohort?
Elwood et al	1964 (19)	...	...	Asbestos sheeting factory workers followed 1936-62
Selikoff et al	1964 (5)	...	1979 (2)	New York-New Jersey insulators followed through 1962
		1968 (6)	...	Followed through 1964
		1974 (4)	...	Followed through 1971
		1979 (2)	1981 (52)	Followed through 1976
Selikoff et al	1972 (20)	...	...	Asbestos insulation workers, including NY-NJ cohort survivors, followed through 1971
		1979 (2)	1979 (50)	Followed to 1976
			1981 (52)	...
Selikoff et al	1972 (21)	...	...	Amosite factory workers through 1971
		1979 (49)	1980 (22)	Followed through 1977
			1981 (51)	...
Selikoff et al	1979 (7)	...	...	Shipyard workers from 1967-76, a subcohort of 1972a study
Selikoff et al	1979 (8)	...	...	Chrysotile miners from Quebec
Enterline	1965 (23)	...	...	Asbestos products workers 1948-51, followed through June 1963
	1967 (24)	...	...	Asbestos products workers to 6/30/63, some from previous cohort
Kleinfeld et al	1967 (25)	...	...	PMR study of asbestos workers
Newhouse et al	1969 (1)	...	...	Asbestos factory men
	1972 (26)	...	...	Asbestos factory women employed 1936-1942, followed through 1968
	1973 (27)	...	...	Follow-up of above 2 cohorts to 1970
	1979 (28)	...	...	Follow-up to 1975
Elmes and Simpson	1971 (29)	...	...	170 Shipyard workers through 1966
		1977 (30)	...	Followed through 1975
McDonald et al	1971 (31)	...	...	Quebec miners followed to 11/1/66
		1974 (32)	...	Followed through 1969 with different analysis
		1980 (33)	...	Followed through 1975
	1978 (34)	...	...	199 Exposed to crocidolite traced through 1975
Enterline	1972 (35)	...	...	Retirees from asbestos mfg followed through 1969
			1973 (36)	Retirees presumed identical to the above
			1973 (37)	Reanalysis of previous two papers
		1979 (38)	...	Retirees followed through 1973
Meurman et al	1974 (39)	...	...	Case-control study of anthophyllite miners
Weiss	1977 (40)	...	...	Chrysotile factory workers 1935-54 followed through 1974
Rubino et al	1979 (41)	...	...	Miners followed through 1974
Gillam et al	1979 (42)	...	...	Gold miners exposed to asbestiform rock followed through 1973
Kolonel et al	1980 (43)	...	...	Shipyard workers followed through 1969
Jones et al	1980 (44)	...	...	Gas mask workers followed through 1978
Hobbs et al	1980 (45)	...	...	Crocidolite miners followed through 1978
Rossiter and Coles	1980 (46)	...	...	Dockyard workers 1947-78
Hughes and Weill	1980 (13)	...	...	Factory workers followed through 1974
Newhouse and Berry	1982 (47)	...	...	Asbestos (mainly chrysotile) friction material workers, 1942-79
		1983 (48)	...	Followed through 1980
Acheson et al	1982 (53)	...	...	Female gas mask workers, 40-year follow-up

PMR=proportionate mortality ratio

*Numbers in parentheses ( ) = reference numbers.

were found for esophageal (SMR=214) and gastric (SMR=183) cancer. Although summary SMRs for these sites were based on data from four studies, numbers were small and the 95% confidence intervals were wide. The slight excess in SMR for colorectal cancer (SMR=113) was not statistically significant. The SMR for total gastrointestinal tract cancer (SMR=108) was minimally but significantly elevated.

Table 4 presents site-specific summary SMRs after "best evidence" data are deleted. Esophageal cancer remains elevated (SMR=238, $P<.05$).

Total gastrointestinal tract cancer deaths and summary SMRs for three exposure categories are presented in Table 5. Of the three occupational groups, only insulators/shipyard workers had a significant elevation in total gastrointestinal tract cancer (SMR=132). Total gastrointestinal tract cancer was not significantly elevated in insulators when "best evidence" data were removed.

Discussion

The strongest evidence linking asbestos to esophageal and gastric cancer is a series of studies of the New York-New Jersey (NY-NJ) and US-Canadian insulation workers.[2,4-6] The summary SMR for esophageal cancer was significantly

TABLE 2.—*Summary of SMRs from Various Cohort Studies*

Author (Date)/Comments (Ref. No.)	Cohort Size	Person-Years	Standard Population	Esophageal Cancer			Stomach Cancer			Colorectal Cancer			Total GI Cancer		
				SMR	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp
Peto et al (1977) (12) Asbestos factory workers	1,106	16,072	Brit Natl	...	...	...	...	...	...	...	...	...	102	16	15.7
Selikoff et al (1979) (2) NY-NJ insulators to 1976 ("best evidence" used)	632	13,925	US	71	1*	1.4	352	19*	5.4	277	23*	8.3	285	43*	15.1
Selikoff et al (1979) (2) US-Canada insulators	17,800	166,853	US	253	18	7.1	127	18	14.2	152	58	38.1	158	94	59.4
Selikoff et al (1980) (22) Amosite factory workers	582	6,311	New Jersey	125	1	0.8	200	4	2.0	212	11	5.2	200	16	8.0
Selikoff et al (1979) (7) Shipyard workers	389	...	US	...	...	...	...	...	...	...	...	...	97	3	3.1
Nicholson et al (1979) (8) Chrysotile mining and milling	544	7,408	Canada Natl	...	...	...	...	...	...	...	...	...	105	10	9.5
McDonald et al (1980) (33) Chrysotile miners, 20 or more years after 1st employment; stomach/esophageal deaths analyzed together	11,379	...	Quebec	127	130*	102.0	127	130*	102.0	78	79	101.0	103	209	202.9
Newhouse and Berry (1979) (28) Rates exclude mesotheliomas	5,522	...	Brit	...	...	...	...	...	...	...	...	...	136	60*	44.2
Enterline and Kendrick (1967) (24) Various exposures (bldg, friction/textile products), rate includes malignant mesotheliomas	21,755	...	US	...	...	...	...	...	...	...	...	...	106	83	78.2
Henderson and Enterline (1979) (38) Rates include mesotheliomas	1,348	...	US	...	...	...	...	...	...	...	...	...	138	110	79.7
Meurman et al (1974) (39) Anthophyllite miners	1,092	...	Finland	...	...	...	...	...	...	...	...	...	47	7	14.9
Weiss (1979) (40) Chrysotile miners; stomach & colorectal cancers combined to calculate GI cancer SMR	264	...	US	...	...	...	...	...	...	...	...	...	105	4	3.8
Rubino et al (1979) (41) Chrysotile miners	952	21,459	Italy	...	...	...	...	...	...	...	...	...	98	19	19.4
Jones et al (1980) (44) Gas mask workers	951	...	Brit	...	...	...	...	...	...	...	...	...	49	10	20.4
Rossiter and Coles (1980) (46) Shipyard workers	6,292	...	Engl/Wales	...	...	...	...	...	...	...	...	...	83	63	75.9
Hughes and Weill (1980) (13) Factory workers	5,645	...	US	...	...	...	...	...	...	...	...	...	50	25	50.0
Mancuso and Coulter (1963) (17) Factory workers	1,495	23,257	US	200	1	0.5	107	2	1.9	145	5	3.5	135	8	5.9
Berry and Newhouse (1983) (48) Asbestos friction materials (mainly chrysotile) workers	11,182	163,009	Engl/Wales	...	...	...	...	...	...	...	...	...	98	132	134.6

GI=gastrointestinal, SMR=standardized mortality ratio

*See comment in Author (Date)/Comments column

elevated even after "best evidence" data on observed deaths in the New York-New Jersey cohort were removed. Gastric cancer in the NY-NJ cohort contributed 19 observed deaths of 43 deaths in the calculation of the summary SMR. For the NY-NJ cohort, unfortunately, causes of death used in analysis were obtained not only from death certificates but from "best evidence." The authors did not present the number of observed deaths derived solely from death certificate information. The gastric cancer summary SMR was not significantly elevated when "best evidence" data were deleted. The same researchers found no excess of gastrointestinal cancer in either shipyard workers[7] or chrysotile miners.[8] One of the best-performed and longest-term cohort studies[9-12] has found no increase of gastrointestinal cancers of any type after more than 50 years of meticulous follow-up from first exposure.

Most of the evidence favoring an association between asbestos and gastrointestinal cancer comes from a series of studies by one group of investigators; these results must withstand critical review if a causal relationship is to be accepted. The fallacy of using "best evidence" for the cause of death has been discussed above, as a bias that inflates SMRs. In addition, repeated publishing of the same results may have created the illusion of more positive evidence than actually exists. Four cohorts have resulted in at least 14 publications (see Table 1). The original table describing the original New York-New Jersey cohort, first published in 1964, was republished in 1979 without incorporating the follow-up that had been accomplished and published in the interim. The 1976 follow-up was published in both 1979 and 1981. The 1976 follow-up of the US-Canadian cohort was published twice in 1979 and the amosite cohort follow-up of 1977 was published in 1979, 1980 and 1981. The negative studies[7,8] have not been republished.

In an earlier review, Miller[3] came to the conclusion that asbestos and gastrointestinal malignant conditions were causally related, although he did not attempt to calculate a summary risk estimate. Most of his conclusions were based upon the work of Selikoff and the review did not have the later negative studies coming from Peto,[12] Hughes[13] and Selikoff's associates.[7,8] Miller also failed to appreciate the error involved in the practice of using "best evidence" rather than the certificated cause of death for comparison with national statistics. Finally, although the review paper acknowledges the work by Newhouse in showing the extent of cause-of-death

TABLE 3.—*Summary SMRs*

Site of Cancer	*Observed*	*Expected*	*SMR*	*95% Confidence Interval**	*References*
Esophagus	21	9.8	214†	132.6-327.6	2‡,17,22
Stomach	43	23.5	183†	132.4-246.5	2‡,17,22
Colorectal	176	156.4	113	96.5-130.4	2‡,17,22,33
Total gastrointestinal tract	912	840.9	108†	101.5-115.7	2‡,7,8,12,13,17,22,24,28,33,38,41,44,46,48

SMR=standarized mortality ratio

*Reference 54.
†$P < .05$.
‡NY-NJ cohort and US-Canadian cohort.

TABLE 4.—*Summary SMRs Deleting 'Best Evidence' Data*

Site of Cancer	*Observed*	*Expected*	*SMR*	*95% Confidence Interval**	*References*
Esophagus	20	8.4	238†	145-368	2‡,17,22
Stomach	24	18.1	133	85-197	2‡,17,22
Colorectal	153	148.1	103	88-121	2‡,17,22,33
Total gastrointestinal tract	869	825.8	105†	98-113	2‡,7,8,12,13,17,22,24,28,33,38-41,44,46,48

SMR=standardized mortality ratio

*Reference 54.
†$P < .05$.
‡US-Canadian cohort; NY-NJ cohort excluded.

TABLE 5.—*Summary SMRs By Occupation for Total Gastrointestinal Tract Cancer*

Occupation	*Observed*	*Expected*	*SMR*	*95% Confidence Interval**	*References*
Asbestos factory workers	460	436.9	105	95.9-115.4	12,13,17,22,24,28,38,44,48
Insulators/shipyard workers	203	153.5	132†	114.7-151.7	2‡,7,46
Insulators/shipyard workers deleting "best evidence" data	160	138.4	116	98.0-135.0	2§,7,46
Asbestos miners	249	250.5	99	87.4-112.5	8,33,39,40,41

SMR=standardized mortality ratio

*Reference 54.
†$P < .05$.
‡NY-NJ cohort and US-Canadian cohort.
§US-Canadian cohort;NY-NJ cohort excluded.

misclassification, there was little attention paid to its potential impact on study results.

Conclusion

Malignant lesions of the lung, pleura and peritoneum have been clearly linked with exposure to asbestos. Some studies of cohorts occupationally exposed to asbestos have also found elevations in incidence of gastrointestinal cancer, while other reports have not found excesses after years of follow-up.

In an effort to summarize the available studies of gastrointestinal cancers in asbestos-exposed workers, we have calculated summary SMRs for esophageal, gastric, colorectal and total gastrointestinal tract cancer. In addition, we have derived total gastrointestinal tract cancer summary SMRs for workers exposed to asbestos in three specific capacities: factory work, shipyard/insulation work and mining.

Although there are statistically significant elevations of SMR for esophageal and gastric cancer for all groups and for total gastrointestinal tract cancer for insulators and shipyard workers, we are not convinced of the relationship to asbestos exposure, especially for stomach cancer, where the finding is inconsistent and possibly erroneous in the largest positive study. For colorectal cancer, at this time there is no discernible relationship to asbestos exposure. We hope that the occupationally exposed cohorts now under study will provide more conclusive evidence soon—refuting or supporting such an association.

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