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Asbestos, Asbestosis, Smoking and Lung Cancer: New Findings from the North American Insulator Cohort

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Asbestos, Asbestosis, Smoking and Lung Cancer:

New Findings from the North American Insulator Cohort

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Abstract

Rationale

Asbestos, smoking, and asbestosis increase lung cancer risk in incompletely elucidated ways. Smoking cessation among asbestos-exposed cohorts has been little studied.

Objectives

To measure the contributions of asbestos exposure, asbestosis, smoking and their interactions to lung cancer risk in an asbestos-exposed cohort, and to describe their reduction in lung cancer risk when they stop smoking.

Methods

We examined lung cancer mortality obtained through the National Death Index for 1981-2008 for 2,377 male North American insulators for whom chest x-ray, spirometric, occupational and smoking data were collected in 1981- 1983 and for 54,243 non-asbestos exposed blue collar male workers from Cancer Prevention Study II for whom occupational and smoking data were collected in 1982.

Measurements and Main Results

Lung cancer caused 339 (19%) insulator deaths. Lung cancer mortality was increased by asbestos exposure among non-smokers [rate ratio = 3.6 (95% CI: 1.7-7.6)], by asbestosis among non-smokers [rate ratio = 7.40 (95% CI, 4.0-13.7], and by smoking without asbestos exposure [rate ratio = 10.3 (95% CI, 8.8-12.2)]. The joint effect of smoking and asbestos alone was additive [rate ratio = 14.4 (95% CI, 10.7-19.4)] and with asbestosis, supra-additive [rate ratio = 36.8 (95% CI, 30.1-46.0)]. Insulator lung cancer mortality halved within 10 years of smoking cessation and converged with that of never-smokers 30 years following smoking cessation.

Conclusions Asbestos increases lung cancer mortality among non-smokers. Asbestosis further increases the lung cancer risk and, considered jointly with smoking, has a supra-additive effect. Insulators benefit greatly by quitting smoking.

Abstract word count: 246 words

Key words: interaction, smoking cessation

Introduction

The classic multiplicative interaction between asbestos exposure and smoking in raising lung cancer risk was first identified by Hammond and Selikoff[1] and has been variably duplicated by others.[2,3] Substantial uncertainty remains, however, due to small numbers of lung cancers among non-smokers; inadequate control for asbestos exposure; failure to identify asbestosis in study cohorts; and limited study of smoking cessation.

We employ and extend the approach of Hammond and Selikoff by comparing the lung cancer mortality experience of a large group of insulators first studied in the 1980s with a contemporaneous blue collar control group from the Cancer Prevention Study II.

Methods

Study populations and baseline data

The asbestos-exposed group consists of 2,377 long-term North American insulators who underwent physical examinations, chest radiographs, spirometry, and smoking, occupational and medical histories between 1981 and 1983. [4-6] The insulators were ≥ age 40, had worked as insulators for ≥ 20 years at baseline examination, and had an adequate chest x-ray and spirometry.

In 1967, Selikoff and colleagues enrolled a cohort of 17,800 insulators.[1] As of July 1, 1981, 5,391 insulators who had reached ≥ 30 years from onset of work as insulators were still alive and were invited for clinical examination in 1981. Approximately 40% underwent clinical examination; most of the non-participants cited reasons other than health (personal or logistic) for not participating in the clinical examination.[4] In addition, there were a limited number of insulators with < 30 years from onset of insulation work who were examined. Chest radiographs were interpreted by a NIOSH B reader according to the International Classification of Radiographs of the Pneumoconioses 1980.[7] Pulmonary function was assessed by spirometric testing adhering to contemporaneous guidelines.[8] Low FEV_1/FVC was defined as < 65% and low FVC as < 80% predicted for all ages.

The group unexposed to asbestos was a blue collar subset of 54,243 men of the Cancer Prevention Study II (CPS II).[9,10] This group reported no history of exposure to asbestos and had not worked > 1 year in an asbestos factory, shipyard, in construction, or in automobile repair.

Smoking information for both groups included current smoking status, age of smoking initiation, age stopped (if applicable), and average number of cigarettes smoked per day.

Mortality follow-up

The National Death Index provided underlying causes of death from 1981 (or 1982 in CPS II cohort) through 2008. ICD-9 code 162 (1981-1998) and ICD-10 codes C-33 and C-34 (1999-2008) were used for primary cancer of the lung and trachea. All insulators not identified as being deceased by NDI were assumed to be alive as of December 31, 2008.

For the CPS II blue collar cohort, the American Cancer Society provided aggregate rate data, including number of people and person-years of follow-up by five year age categories (age 40 through $\geq$ age 85 years), smoking status (current, former, never), pack-years categories (0-9 through 80-89 pack-years), years since quitting for former smokers (five year categories: 0-4 through 35-39 years), and number of lung cancer deaths, 1982-2008.

Statistical analysis

Basic descriptive data of the insulator cohort included age, duration of work and duration from onset of work as an insulator, smoking history, parenchymal asbestosis (4 point and 11 point ILO scales), asbestos-related pleural fibrosis (present, absent), and low FEV_1/FVC (<65%).

The number of person-years contributed by each subject was calculated as the time interval between the date of examination for each insulator or 1982 for the CPS II cohort and the date of death or, for surviving study participants, December 31, 2008.

Death rates were calculated as the number of lung cancer deaths divided by the number of person-years for each group for any selected time period. The lung cancer death rate for each year between 1982 and 2008 was calculated as the number of lung cancer deaths that occurred in that year divided by the number of person-years contributed during that year by the people who were alive on January 1 of the same year.

Poisson regression modeling was used for all comparisons of CPS II cohort to the insulator cohort. Cox proportional hazard modeling was used for all within insulator cohort analyses. The assumption of hazard proportionality across values of relevant covariates (smoking pack-years and duration of work as an insulator) during the follow-up period was found to be met using the ASSESS option of the PHREG procedure in SAS.[11]

Crude lung cancer rate ratios were calculated for each potential covariate, including age, duration of work as an insulator, smoking histories (current, former, never), pack-years; and years since quitting smoking, parenchymal asbestosis (4 point and 11 point ILO scales), pleural asbestos-related fibrosis, and low FEV1/FVC. Cox proportional hazard analysis was used to calculate these same rate ratios adjusted for age as a continuous variable.

The full insulator study group and insulators without and with parenchymal asbestosis were compared to the CPS II blue collar cohort by obtaining age-adjusted rate ratios and 95% confidence intervals (CI's) of: a) non-smokers without asbestos exposure (CPS II: reference group), b) non-smokers with asbestos exposure (insulators), c) smokers without asbestos exposure (CPS II), and d) smokers with asbestos exposure (insulators).

The joint effect of asbestos exposure (with or without asbestosis) and cigarette smoking was considered additive if the rate ratio associated with both exposures was equal to the sum of the rate ratios associated with each individual exposure minus 1. The joint effect of asbestos exposure (with or without asbestosis) and cigarette smoking was considered multiplicative if the rate ratio associated with both exposures was equal to the product of the rate ratios associated with each individual exposure.

We formally tested whether the joint effect of asbestos and former smoking among insulators departed from a multiplicative model by using a Poisson model that included age, pack-years, group (insulator versus CPS II), smoking score, and a product term for smoking score and group.

SAS/PC for Windows was used to perform all statistical procedures.[11]

IRB Review

The study was ruled exempt from review by the Institutional Review Boards of the Mount Sinai School of Medicine and Queens College, City University of New York.

Results

Baseline characteristics

Insulators were slightly younger and smoked more frequently than did the CPS II blue collar cohort (Table 1). The majority of insulators (58.8%) who ever smoked had quit by study onset. Two-thirds of insulators had worked 30-39 years as insulators. 61.4% of insulators had parenchymal asbestosis on chest x-ray. Two-thirds (65.2%) of ever smokers had parenchymal asbestosis, whereas, 45.9% of never-smoking insulators had parenchymal asbestosis ($p < 0001$).

Asbestos exposure as measured by duration of work as an insulator was similar for non-smoking insulators without asbestosis (mean=32.7 years, sd=5.6 years) versus non-smoking insulators with asbestosis (mean=34.9 years, sd=6.6 years) and also for smoking insulators without asbestosis (mean=32.2 years, sd=5.4 years) versus smoking insulators with asbestosis (mean=33.5 years, sd=5.7 years). Smoking (number of pack-years) was also similar among smoking insulators without asbestosis (mean= 32.7, sd=5.6) versus smoking insulators with asbestosis (mean=34.9, sd=6.6).

Mortality follow-up

Three-quarters (n=1,786) of insulators died during the 28 year follow-up period. The mean age at death was 72.6 years (s.d. = 8.7 years). Cancers caused 45.7% of deaths, principally lung cancer (19.0%, or 339 deaths). Among 121 insulators who died in their 50's, nearly one-third (30.6%) died from lung cancer. This dropped to 25.1% of 525 insulators who died in their 60's and to 15.0% among 1,136 insulators who died at ≥ 70 years of age. Lung cancer caused 23.9%, 19.6% and 13.6% of deaths during the 1981-1989, 1990-1999, and 2000-2008 periods, respectively. Eighteen lung cancer deaths occurred among never-smoking insulators, including 11 insulators who had parenchymal asbestosis.

Asbestosis or other pulmonary fibrosis caused 122 deaths (6.8%) during the follow-up period. The cumulative risk of dying from asbestosis among insulators without asbestosis on chest x-ray at study onset was 1.3% during 1981-2008 versus 7.3% of insulators who had radiographic asbestosis.

Risk factors for lung cancer among insulators

Within the insulator cohort, the age-adjusted lung cancer mortality increased with increasing parenchymal asbestosis (the 4 point and the 11 point ILO scales of parenchymal asbestosis), low FEV1/FVC, and smoking (online supplemental Table 1). As expected, lung cancer risk dropped with added time following cessation of smoking.

Separate and joint effects of smoking, asbestos, and asbestosis

Figure 1 and Table 2 show rate ratios for lung cancer, comparing non-smoking controls (CPS II), non-smoking insulators, smoking controls (CPS II), and smoking insulators. The mortality rate among non-smoking non-asbestos exposed workers was 40 per 100,000. Asbestos exposure increased the lung cancer rate ratio 5.2-fold (based on 18 lung cancer deaths), smoking 10.3-fold, and the two exposures combined, 28.4-fold. The joint effect of the two exposures is more than additive (additive effect = 5.2 + 10.3 – 1 = 14.5) but less than multiplicative (multiplicative effect = 5.2 * 10.3 = 53.6). This analysis was repeated for current and former smokers and by smoking intensity ($<$ or $\geq$ 40 pack-years) with similar results (online supplemental Table 2).

Asbestos exposure in the absence of asbestosis increased the lung cancer rate ratio (RR= 3.6; 95% CI, 1.7-7.6) among non-smokers (Figure 1 and Table 2). Smoking in the absence of asbestos exposure is associated with a lung cancer rate ratio of 10.3 (95% CI, 8.8-12.2). Asbestos exposure (in the absence of asbestosis) and smoking in combination are associated with a lung cancer rate ratio of 14.4 (95% CI, 10.7-19.4), which represents a joint effect that is additive (additive effect = 3.6 + 10.3 – 1=12.9; multiplicative effect = 3.6*10.3 = 37.1). By contrast, when insulators had asbestosis, their lung cancer ratio increased to 7.4 (95% CI, 4.0-13.7) among non-smokers, and, jointly with cigarette smoking, to 36.8 (95% CI, 30.1-46.0). This joint effect is, like the overall group of insulators, supra-additive (additive effect = 7.4+10.3-1=16.7; multiplicative effect = 7.4*10.3=76.2).

Effect of smoking cessation on lung cancer risk

Former smokers among the CPS II cohort had similar smoking habits to insulators, having quit smoking a mean of 16.4 years before baseline, but had a slightly heavier history of smoking than insulators: 35.4 pack-years versus 32.6 pack-years, respectively.

Figure 2 portrays adjusted lung cancer death rate ratios by smoking status and years since quitting smoking for insulators and the CPS II cohort, using CPS II non-smokers as a reference. The lung cancer mortality rate ratio among insulators dropped steeply during the first 10 years after quitting smoking, from 53.7 to 26.6, and the lung cancer mortality rate dropped from 177 deaths per 10,000 among current smokers to 90 per 10,000 among quitters < 10 years following cessation.

The lung cancer rate ratio for insulators with ≥ 30 years since quitting (rate ratio = 5.8, 95% C.I., 2.2-11.4), based on 6 lung cancer deaths, was similar to the lung cancer rate ratio among never-smoking insulators (rate ratio = 5.3).

Overall, the joint effect of asbestos exposure and former smoking at < 30 years since quitting was greater than additive and less than multiplicative (Figure 2).

Figure 3 illustrates that lung cancer mortality clearly differs according to whether insulators had asbestosis (panel 2) or not (panel 1). The lung cancer rate ratios of insulators without asbestosis diminished in parallel with the CPS II former smokers, supporting an additive joint effect (Figure 3, panel 1). By contrast, when asbestosis is present, the joint effect of asbestos and former smoking was supra-additive, though not multiplicative (Figure 3, panel 2).

Using a Poisson model and a product term for smoking score and exposure group, we found a statistically significant negative interaction between smoking and asbestos exposure (insulator group), i.e., on a multiplicative scale (p=.004). This result confirms that the lung cancer decline among insulators shown in Figure 2 was supra-additive, but not multiplicative.

Discussion

Lung cancer remains the dominant cause of death among insulators, killing one in five over the past three decades, and disproportionately killed younger insulators, even though the majority of smoking insulators (59%) had already quit at study onset.

We confirmed the five-fold elevation in lung cancer mortality among non-smoking insulators previously documented by Hammond and Selikoff based on 4 lung cancer deaths.[1] Our finding of a lung cancer mortality rate ratio of 5.2 (95% C.I., 1.3-3.2) based on 18 deaths among 468 never smoking insulators, is the largest number of lung cancer deaths among non-smoking asbestos-exposed workers ever reported.

Asbestos exposure without radiographic evidence of asbestosis and without smoking raised the risk of lung cancer by 3.6-fold (95% CI, 1.7-7.6). This finding improves on previous studies, in which adjustment for smoking and asbestos exposure was limited. [12-15]

Asbestosis further doubled the lung cancer mortality risk, both among non-smokers and smokers. Importantly, this added risk of lung cancer conferred by asbestosis was not due to additional exposure to asbestos. The study group of insulators, unlike most asbestos-exposed groups studied to date, had reasonably homogeneous exposure to asbestos, as measured by the duration of insulation work or based on the nature of their work with asbestos-containing products such as cement, pipe covering, or insulation spray from the 1950s through the 1970s. Prior studies had limited ability to control for asbestos exposure due to inclusion of a wide range of occupations (i.e., case-control studies) [14] or to large variation in work with asbestos-containing materials among trades such as carpenters or sheet metal workers (i.e., cohort studies). [16,17]

We found that the overall combined effect between asbestos and smoking in raising lung cancer risk was supra-additive, not multiplicative as previously documented.[1] A possible partial explanation is that the prevalence of asbestosis among insulators in the current study was lower than among insulators in the prior study, in which asbestosis was not studied.[1] Additionally, Hammond et al studied insulators with a mean age of 45.2 years at study onset versus 58.1 years in the current study.[1] Interaction between asbestos and smoking could vary by age. Finally, in the prior study, the lung cancer mortality rate ratio estimate for non-smoking insulators was based on 4 deaths and, therefore, had limited precision.[1]

Do insulators with heavy long-term asbestos exposure experience the benefit of smoking cessation? Lung cancer mortality among insulators dropped precipitously following smoking cessation and proportionate to that of smokers who were unexposed to asbestos. Secondly, though based on a small number of lung cancer deaths (n=6), the lung cancer rate ratio for insulators who had quit smoking at least 30 years previously was similar to that of the insulator who had never smoked. Other studies have found a persistence of lung cancer risk following smoking cessation among asbestos-exposed workers ranging from 1.9 (95% CI, 0.50, 7.2) at ≥ 20 years since quitting smoking[18] to 1.6 (95% CI, 0.9, 2.9) among workers ≥ 40 years since quitting smoking.[19]

This is the first study that examines the impact of asbestosis versus asbestos exposure alone in lung cancer mortality following smoking cessation. Asbestos alone raises lung cancer risk among formerly smoking insulators and having superimposed asbestosis further raises that risk. The latter does so in a supra-additive fashion that differs from the pattern seen among insulators without asbestosis. The asbestosis-dependent interaction may explain some of the variation in joint effects of smoking and asbestos found in previous studies.

Our study findings - the differential lung cancer risk associated with asbestos exposure alone versus asbestosis and the different pattern of interaction between asbestos and smoking depending upon the presence of asbestosis - provide strong epidemiological support for the existence of multiple mechanisms through which asbestos causes cancer. The similarity of the interaction between asbestos and smoking among both active and former smokers suggests that the mechanism(s) underlying lung cancer development in both active and former smokers are the same. These findings may thus be helpful in sorting out the timing and relative importance of competing mechanistic explanations for the interaction of asbestos and smoking in causing lung cancer.[20-22]

Study strengths include use of a study group with homogeneous exposure to asbestos, a large sample size, long-term follow-up, and use of the National Death Index for follow-up. We replicated the earlier asbestos-smoking study approach of Hammond and Selikoff by using a contemporaneous blue collar referent cohort with both occupational and smoking information.[1] This approach reduces the confounding influences of other occupational lung carcinogens and unmeasured differences in smoking between blue collar and general populations.

This study has some notable limitations. Smoking status in insulator and CPS II cohorts and the presence of parenchymal asbestosis among insulators were evaluated only once (1981-1983), and they may have changed in subsequent years, resulting in exposure misclassification. However, the mean duration from onset of insulation work at examination in 1981-1983 was 35.7 years, and it is unlikely that many insulators would have first developed asbestosis after that period.[23] Differential change in smoking status between study groups may have occurred, but the smoking quit rate would have to be significantly different between the two groups to affect the relative risk.

A second limitation is misclassification of asbestosis, since asbestosis can exist without parenchymal disease on chest x-ray.[24,25] However, few insulators (1.3%) without radiographic asbestosis subsequently died from asbestosis during 1981-2008 versus insulators with asbestosis (7.3%), suggesting limited misclassification. Thirdly, some members of the control group might have been exposed to asbestos, albeit short-term (≤ one year by cohort definition). If so, our estimate of the mortality rate ratio of lung cancer due to asbestos would underestimate the true mortality rate ratio of lung cancer with regard to asbestos exposure.

This study evaluated the effects of fairly uniform long-term heavy exposure to asbestos. The narrow range of exposure increased internal study validity, but limited its generalizability about risks from lower exposure to asbestos.

In conclusion, asbestos exposure without associated asbestosis raises the relative risk of lung cancer among non-smokers and is additive to the risk of smoking. Asbestosis further increases the lung cancer risk and, considered jointly with smoking, has a supra-additive effect on lung cancer risk. This differential pattern of risk dependent upon the absence or presence of asbestosis continues with smoking cessation. The risk of lung cancer death among insulators who had quit smoking at least 30 years previously converges with that of never-smoking insulators.

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Legends

Figure 1. Lung cancer mortality rate ratios (95% C.I.) by asbestos, asbestosis and smoking status. North American Insulators vs. Cancer Prevention Study II, 1981-2008.

Figure 2. Decline in lung cancer mortality rate ratios with smoking cessation: North American Insulators versus Cancer Prevention Study II, 1981-2008. Rate ratios are adjusted for age categories and pack-years. The reference group is Cancer Prevention Study II, never smokers.

Figure 3, Panel 1. Decline in lung cancer mortality rate ratios with smoking cessation: North American Insulators without asbestosis versus Cancer Prevention Study II, 1981-2008. Rate ratios are adjusted for age categories and pack-years. The reference group is Cancer Prevention Study II, never smokers.

Figure 3, Panel 2. Decline in lung cancer mortality rate ratios with smoking cessation: North American Insulators with asbestosis versus Cancer Prevention Study II, 1981-2008. Rate ratios are adjusted for age categories and pack-years. The reference group is Cancer Prevention Study II, never smokers.

Table 1. Baseline characteristics of Insulators (1981-1983) and Cancer Prevention Study II blue collar cohort (1982)

Variable	CPS II* (n=54,243)		All insulators (n=2,377)		Insulators [redacted] (n=918)		Insulators [redacted] (n=1,459)	
	n	%	n	%	n	%	n	%
Age: mean (interquartile range), years	59.6	(52.5-67.5)	58.1	(53-62)	56.3	(52-60)	59.2	(54-64)
40-49 years	9,153	16.9	232	9.8	136	14.8	96	6.6
50-59 years	19,877	36.6	1257	52.9	513	55.9	744	51.0
60-69 years	17,761	32.7	698	29.4	234	25.5	464	31.8
≥70 years	7,452	13.7**	190	8.0	35	3.8**	155	10.6
Cigarette smoking history								
Never	18,843	34.7	468	19.7	253	27.6	215	14.7
Former (years since quitting)	20,043	37.0	1,123	47.2	438	47.7	685	46.9
Mean (interquartile range), years	16.4	(8-23)	16.4	(8-23)	16.9	(9-23)	16.1	(8-22)
>0-9 years	6,309	31.5	304	27.1	110	25.1	194	28.3
10-19 years	7,003	34.9	403	35.9	156	35.6	247	36.1
20-29 years	4,294	21.4	274	24.4	115	26.3	159	23.2
≥ 30 years	2,437	12.2	142	12.6	57	13.0	85	12.4
Current	15,357	28.3	786	33.1	227	24.7	559	38.3
Mean (interquartile range), pack-years	48.8	(35-65)	50.1	(35-64)	46.5	(32-58)	51.7	(36-66)
0-9 pack-years	814	5.3	19	2.4	9	4.0	10	1.8
10-19 pack-years	1,068	7.0	35	4.5	15	6.6	20	3.6
20-29 pack-years	1,557	10.1	61	7.8	23	10.1	38	6.8
≥30 pack-years	11,918	77.6***	671	85.4	180	79.3***	491	87.8
Duration of exposure to asbestos								
Mean (interquartile range), years	-	-	33.2	(30-36)	32.3	(29-35)	33.7	(30-37)
20-29 years	-	-	518	21.8	239	26.0	279	19.1
30 - 39 years	-	-	1,523	64.1	582	63.4	941	64.5
≥ 40 years	-	-	336	14.1	97	10.6	239	16.4
Radiographic abnormalities								
Parenchymal opacities (ILO profusion)								
Category 0	-	-	918	38.6	918	100.0	0	0.0
Category 1	-	-	1,125	47.3	0	0.0	1,125	77.1
Category 2	-	-	259	10.9	0	0.0	259	17.8
Category 3	-	-	75	3.2	0	0.0	75	5.1
Pleural abnormalities								
Absent	-	-	621	26.1	348	37.9	273	18.7
Present	-	-	1,756	73.9	570	62.1	1,186	81.3

*CPS II = Cancer Prevention Study II

**Age (insulators without asbestosis vs. CPS II): Chi-square = 173; p<0.0001

***Smoking (insulators without asbestosis vs. CPS II): Chi-square=58; p<0.0001

Table 2. Age-adjusted lung cancer mortality rate ratios, by smoking, asbestos, and asbestosis status, Insulators versus Cancer Prevention Study II blue collar cohort, 1981-2008

Variable	Number of people	Number of lung cancer deaths	Number of person-years	Number lung cancer deaths/ person-years x 10^4	Rate ratio	Poisson regression	
						Age-adjusted rate ratio	Age-adjusted rate ratio 95% CI**
A. CPS II (n=54,243) vs All insulators (n=2,377)							
a. CPS II, non-smokers	18,843	151	377,396	4.00	1.00	1.00	reference
b. Insulators, non-smokers	468	18	8,706	20.68	5.17	5.20	3.19, 8.48
c. CPS II, smokers	35,400	2,540	652,533	38.93	9.73	10.31	8.74, 12.15
d. Insulators, smokers	1,909	321	29,950	107.18	26.79	28.36	23.36, 34.44
B. CPS II (n=54,243) vs. Insulators without asbestosis (n=918)							
a. CPS II, non-smokers	18,843	151	377,396	4.00	1.00	1.00	reference
b. Insulators without asbestosis, non-smokers	253	7	5,205	13.45	3.36	3.55	1.66, 7.58
c. CPS II, smokers	35,400	2,540	652,533	38.93	9.73	10.31	8.75, 12.15
d. Insulators without asbestosis, smokers	665	62	12,057	51.42	12.85	14.44	10.74, 19.43
C. CPS II (n=54,243) vs. Insulators with asbestosis (n=1,459)							
a. CPS II, non-smokers	18,843	151	377,396	4.00	1.00	1.00	reference
b. Insulators with asbestosis, non-smokers	215	11	3,501	31.42	7.85	7.40	4.01, 13.65
c. CPS II, smokers	35,400	2,540	652,533	38.93	9.73	10.29	8.73, 12.13
d. Insulators with asbestosis, smokers	1,244	259	17,893	144.75	36.18	36.79	30.08, 44.99

*CPS II = Cancer Prevention Study II

**CI = Confidence interval

Figure 1.

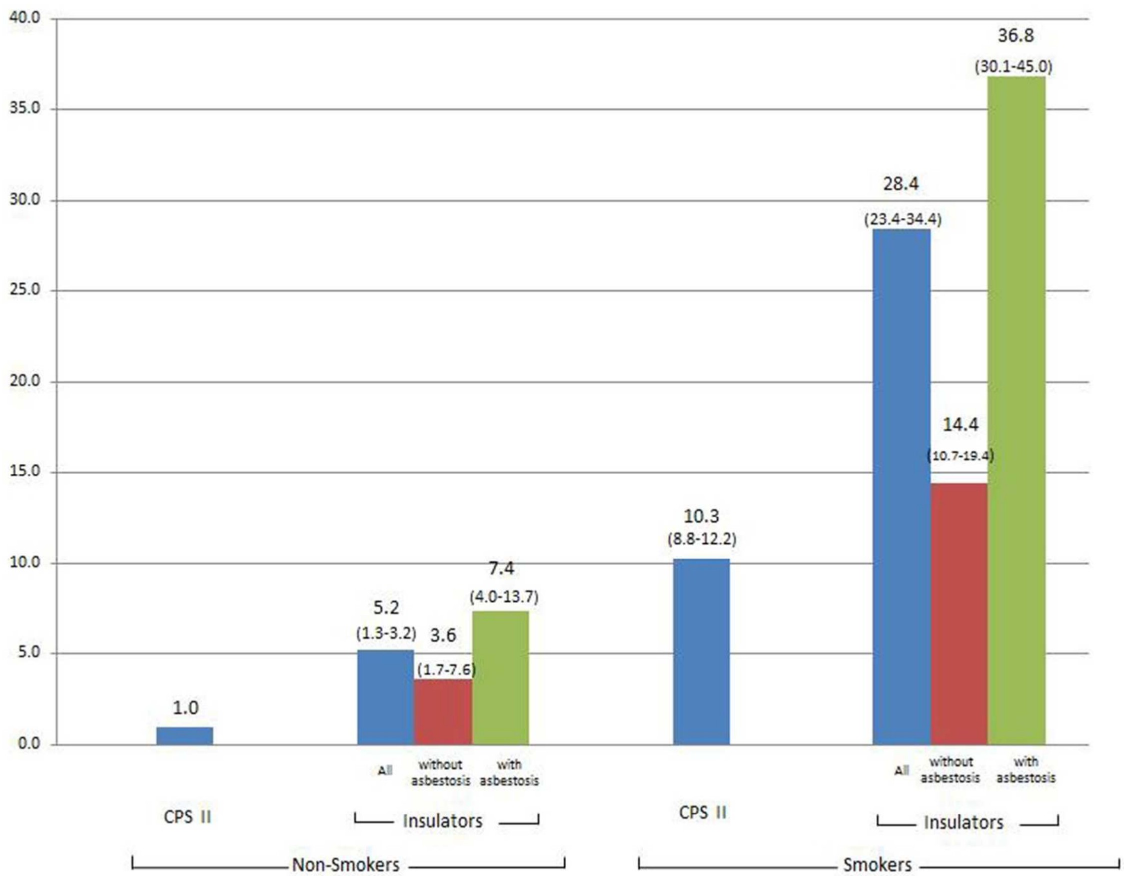

40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
1.0
5.2
(1.3-3.2)
3.6
(1.7-7.6)
7.4
(4.0-13.7)
10.3
(8.8-12.2)
28.4
(23.4-34.4)
14.4
(10.7-19.4)
36.8
(30.1-45.0)
All
without asbestosis
with asbestosis
All
without asbestosis
with asbestosis
CPS II
Insulators
CPS II
Insulators
Non-Smokers
Smokers

Figure 2.

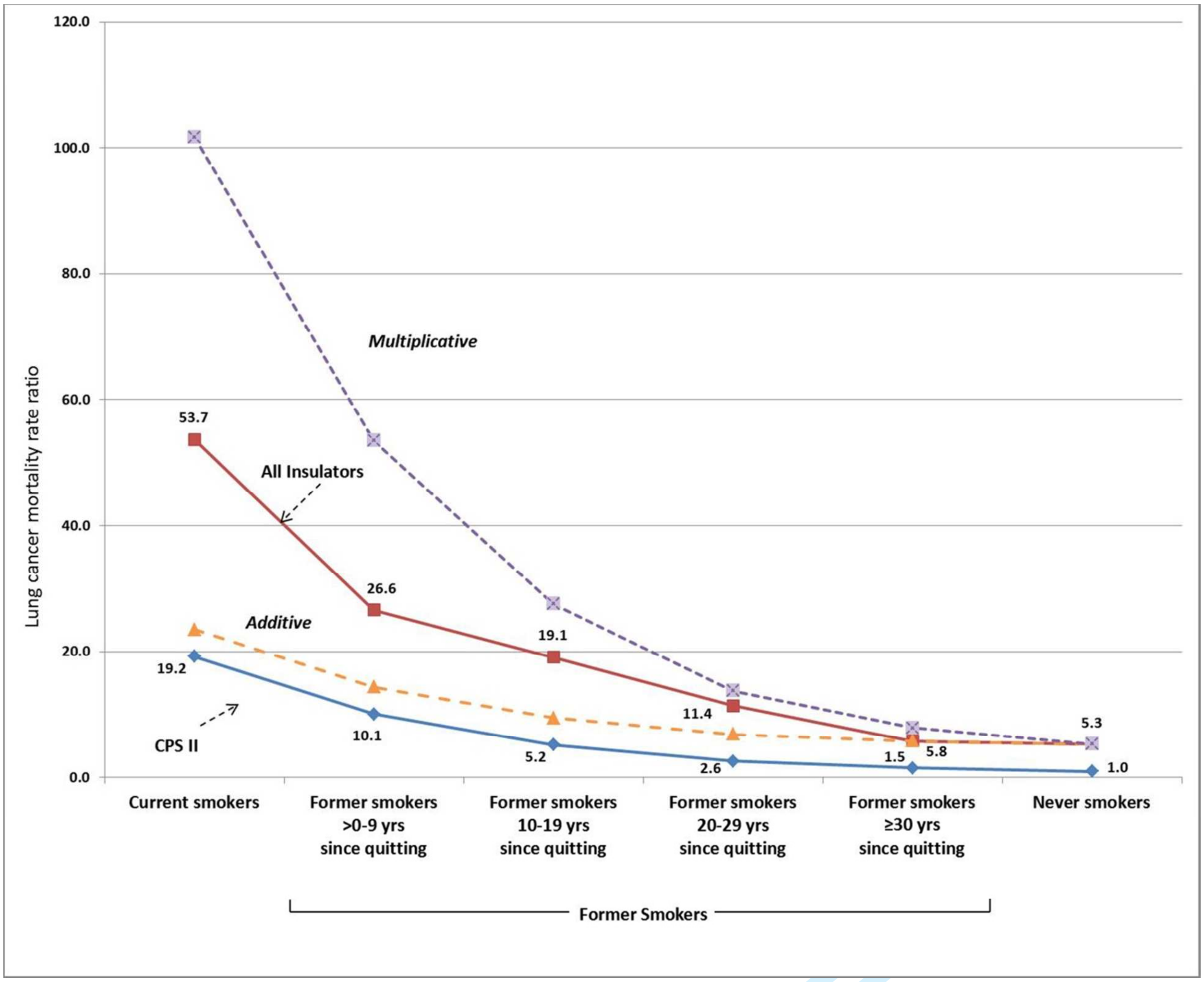

120.0
100.0
80.0
60.0
40.0
20.0
0.0
Lung cancer mortality rate ratio
Multiplicative
All Insulators
Additive
CPS II
53.7
26.6
19.1
11.4
5.8
5.3
19.2
10.1
5.2
2.6
1.5
1.0
Current smokers
Former smokers >0-9 yrs since quitting
Former smokers 10-19 yrs since quitting
Former smokers 20-29 yrs since quitting
Former smokers ≥30 yrs since quitting
Never smokers
Former Smokers

Figure 3.

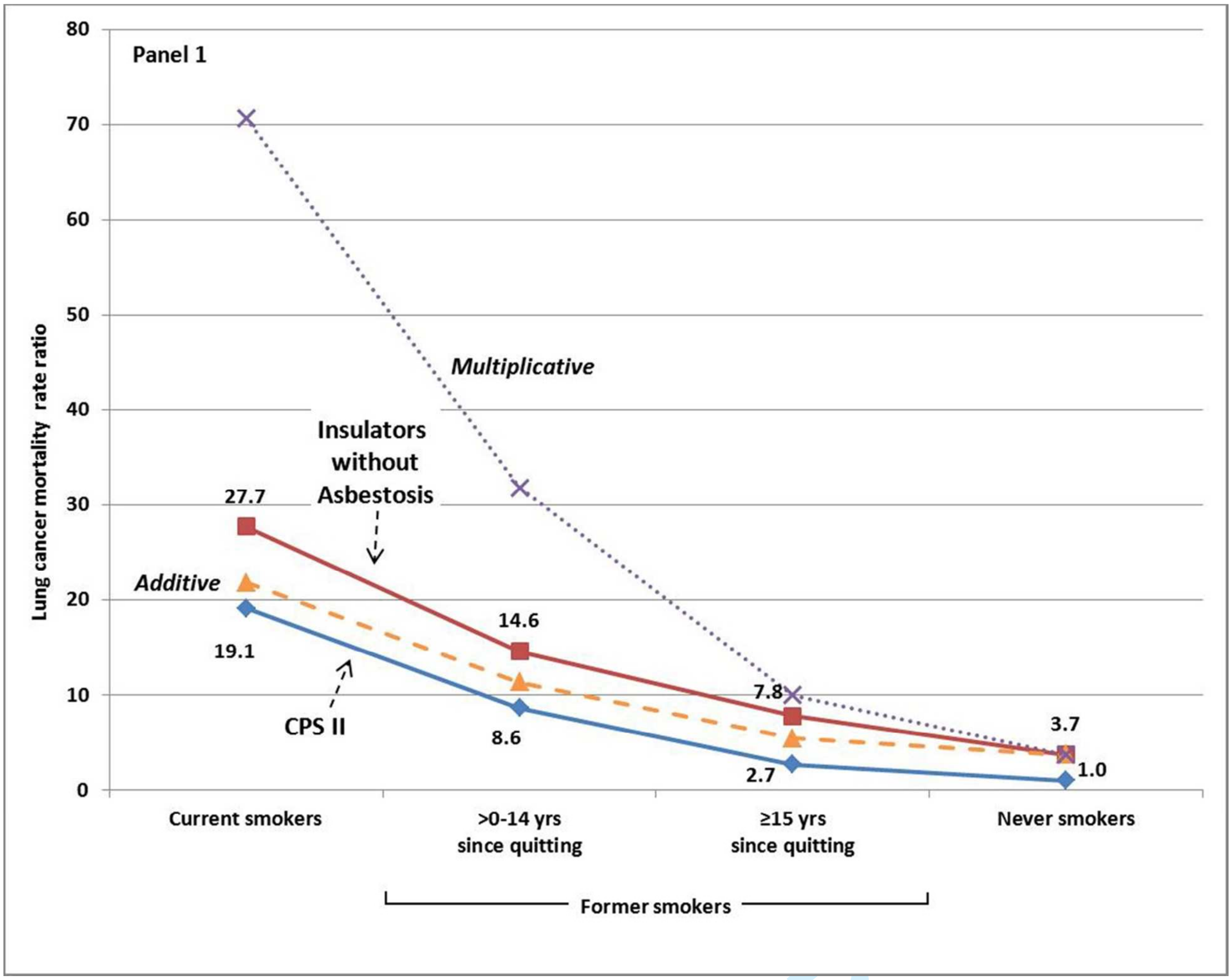
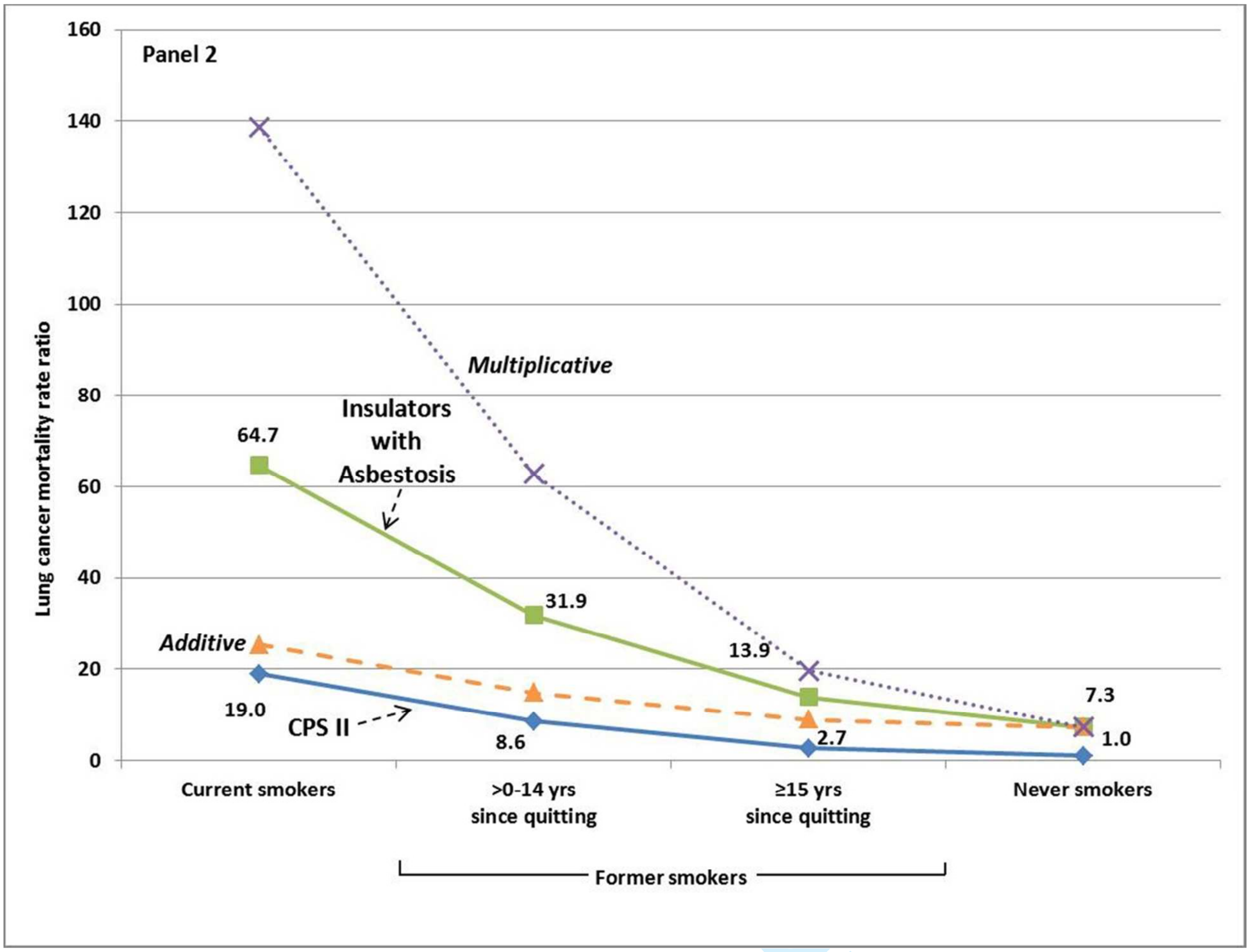

Panel 1
Lung cancer mortality rate ratio
80
70
60
50
40
30
20
10
0
Multiplicative
Insulators without Asbestosis
Additive
CPS II
27.7
19.1
14.6
8.6
7.8
2.7
3.7
1.0
Current smokers
>0-14 yrs since quitting
≥15 yrs since quitting
Never smokers
Former smokers

Figure 3 continued.



Supplemental Table 1. Rates of lung cancer death by risk factor, Insulators (n=2,377)								
Risk factor	Number of people	Total deaths	Number of lung cancer deaths	Person-years	Number lung cancer deaths/ person-years x 10^4	Crude rate ratio	Age-adjusted rate ratio*	95% Confidence interval
Total								
	2,377	1,786	339	38,655	87.70		-	
Age (Years) at baseline exam								
40-49	232	99	20	5,039	39.69	1.00	-	reference
50-59	1,257	876	184	22,432	82.03	2.07	-	1.07, 2.69
60-69	698	624	110	9,422	116.75	2.94	-	1.14, 2.94
≥70	190	187	25	1,762	141.88	3.58	-	0.85, 2.75
Duration of work as insulator								
<30 years	518	320	63	9,637	65.37	1.00	1.00	reference
30-39 years	1,523	1,158	231	24,787	93.19	1.43	1.21	0.91, 1.60
≥40 years	336	308	45	4,231	106.36	1.63	0.99	0.65, 1.49
Parenchymal asbestosis (4 ILO categories)								
Category 0	918	591	69	17,262	39.97	1.00	1.00	reference
Category 1	1,125	874	177	18,180	97.36	2.44	2.11	1.60, 2.79
Category 2	259	248	75	2,669	281.00	7.03	3.93	2.81, 5.49
Category 3	75	73	18	544	330.88	8.28	3.27	1.93, 5.52
Pleural disease								
absent	621	424	91	11,088	82.07	1.00	1.00	reference
present	1,756	1,362	248	27,567	89.96	1.10	0.94	0.73, 1.19

FEV_1/FVC**								
Normal	2,009	1,462	254	33,812	75.12	1.00	1.00	reference
Low (<65%)	368	324	85	4,843	175.51	2.34	1.80	1.41, 2.31
Cigarette smoking								
Never	468	309	18	8,706	20.68	1.00	1.00	reference
Former (years since quitting)								
(total)	1,123	824	117	18,413	63.54	3.07	2.72	1.65, 4.47
>0-9 years	304	222	43	4,796	89.66	4.34	3.90	2.25, 6.77
10-19 years	403	300	47	6,723	69.91	3.38	3.11	1.80, 5.35
20-29 years	274	189	21	4,775	43.98	2.13	2.00	1.07, 3.75
≥30 years	142	113	6	2,119	28.32	1.37	0.95	0.38, 2.40
Current smoker								
(total)	786	653	204	11,536	176.84	8.55	7.30	4.50, 11.85
<20 pack-years	54	41	12	877	136.83	6.62	6.75	3.25, 14.11
20-39 pack-years	227	179	59	3,571	165.22	7.99	7.48	4.64, 13.51
≥40 pack-years	505	433	133	7,088	187.64	9.08	7.45	4.45, 11.95

*Adjusted through use of Cox proportional hazards regression

** FEV_1 = Forced expiratory volume in 1 second

FVC = Forced vital capacity

Supplemental Table 2. Lung cancer mortality rate ratios by level of smoking, Insulators versus Cancer Prevention Study II blue collar cohort, 1981-2008

Variable	Number of people	Number of lung cancer deaths	Number of person-years	Number lung cancer deaths/ person-years x 10^4	Rate ratio	Poisson Regression: Age-adjusted rate ratio	Poisson Regression: Age-adjusted rate ratio 95% CI
1. Current Smokers CPS II (n=34,200)							
versus All insulators (n=1,254)							
a. CPS II, non-smokers	18,843	151	377,396	4.00	1.00	1.00	reference
b. Insulators, non-smokers	468	18	8,706	20.68	5.17	5.23	3.21, 8.53
c. CPS II, current smokers	15,357	1,740	275,480	63.16	15.79	18.38	15.55, 21.73
d. Insulators, current smokers	786	204	11,537	176.82	44.19	50.83	41.09, 62.87
2. Former Smokers CPS II (n=38,886)							
versus All insulators (n=1,591)							
a. CPS II, non-smokers	18,843	151	377,396	4.00	1.00	1.00	reference
b. Insulators, non-smokers	468	18	8,706	20.68	5.17	5.35	3.28, 8.73
c. CPS II, former smokers	20,043	800	377,053	21.22	5.30	5.39	4.53, 6.42
d. Insulators, former smokers	1,123	117	18,414	63.54	15.88	16.95	13.30, 21.61
3. Light Smokers CPS II (n=38,070)							
versus All insulators (n=1,525)							
a. CPS II, non-smokers	18,843	151	377,396	4.00	1.00	1.00	reference
b. Insulators, non-smokers	468	18	8,706	20.68	5.17	5.25	3.22, 8.57
c. CPS II, smokers < 40 pack-years	19,227	787	384,375	20.47	5.12	5.62	4.71, 6.69
d. Insulators, smokers < 40 pack-years	1,057	125	17,874	69.93	17.48	18.95	14.92, 24.07
4. Heavy Smokers CPS II (n=35,031)							
versus All insulators (n=1,320)							
a. CPS II, non-smokers	18,843	151	377,396	4.00	1.00	1.00	reference
b. Insulators, non-smokers	468	18	8,706	20.68	5.17	5.19	3.19, 8.47
c. CPS II, smokers ≥40 pack-years	16,188	1,753	268,380	65.32	16.32	16.56	14.02, 19.55
d. Insulators, smokers ≥40 pack-years	852	196	12,077	162.29	40.56	41.73	33.72, 51.65

*CPS II = Cancer Prevention Study II

** Light smoker = < 40 pack-years

Heavy smoker = ≥ 40 pack-years