

AERODIGESTIVE AND GASTROINTESTINAL TRACT CANCERS AND EXPOSURE TO CROCIDOLITE (BLUE ASBESTOS): INCIDENCE AND MORTALITY AMONG FORMER CROCIDOLITE WORKERS

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The objective of this article was to assess the association between the incidence and mortality from aerodigestive cancers and exposure to crocidolite (blue asbestos). Our study is a cohort study of former workers of the now-defunct crocidolite mining and milling operation at Wittenoom, Western Australia, who have been followed up since 1979 and on whom asbestos exposure and smoking information was known. Standardised mortality and incidence rates were used to compare former workers with the Western Australian male population. Cases were matched with up to 10 randomly assigned controls, and conditional logistic regression was used to examine the relationship between asbestos exposure, smoking status and cancer incidence. There were 129 incident cases from all cancers of interest and 57 deaths. Former workers had a significantly higher risk of mortality from upper aerodigestive cancers than the Western Australian male population. The incidence of upper and lower aerodigestive cancers was higher in the Wittenoom cohort but not significantly so. Cumulative exposure to asbestos did not appear to be associated with the incidence of stomach cancer, colorectal cancer or upper aerodigestive cancers. Smoking status was strongly associated with the incidence of upper aerodigestive cancers, with current smokers experiencing the greatest risk. Our study with longer and more complete follow-up, smoking information and a stronger study design does not show an association between cumulative asbestos exposure and stomach cancer or other gastrointestinal cancers. The excess mortality from upper aerodigestive cancers seen in this cohort of former asbestos workers compared to the Western Australian male population does not appear to be associated with exposure to crocidolite.

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Key words: crocidolite; Wittenoom; smoking; cancer; asbestos

Rates of malignant pleural and peritoneal mesothelioma and lung cancer are consistently higher in subjects exposed to asbestos of various varieties.^{1–4} The association between asbestos exposure and cancers of the upper (lip, mouth, tongue, pharynx, larynx and maxillary sinus) and lower (oesophagus, stomach and colon and rectum) aerodigestive tract is less certain. Evidence for an association has been found by some authors^{5–8,9–12} but no association has been reported by others.^{7,11,13–15} Meta analyses also provide conflicting results; an association between cancer of the larynx and asbestos exposure has been reported by some^{16,17} and not others.^{18–22} Similarly, conflicting results have been reported in meta analyses of cancer of the colon and asbestos exposure.^{17,23–25}

Between 1943 and 1966, 6,493 males and 415 females were employed in the Wittenoom crocidolite industry, by the now-defunct Australian Blue Asbestos Company. Their median duration of employment was less than 4 months and the median cumulative exposure to crocidolite was 6 f/ml-years.² Our study is unique because the workers were only exposed to crocidolite and not other forms of asbestos. Mortality studies of this cohort have shown increased death rates from malignant mesothelioma, lung cancer and asbestosis, as well as smoking and alcohol related diseases.^{1,26} The aims of our study were to examine the incidence and mortality rates of aerodigestive cancers in a subset of the Wittenoom workforce who were alive and contacted in 1979, from whom smoking history was obtained by questionnaire and for

whom complete follow-up was available, and to relate these rates to cumulative crocidolite exposure, duration of crocidolite exposure and to tobacco smoking.

METHODS

Subjects

Australian Blue Asbestos (ABA), a subsidiary of CSR Limited, employed 6,908 workers in the crocidolite mining industry at Wittenoom in Western Australia (WA) between 1943 and 1966 when the industry was closed for financial reasons. In 1979, 2,928 were traced and 2,400 (37%) men and 149 (36%) women replied to a questionnaire on smoking and occupational histories. A second smoking questionnaire was sent out in 1985 and a further 2 questionnaires in the 1990s. Five hundred thirty-five new responses were received from these subsequent questionnaires, providing direct data on 45% of the original workforce (the smoking data subset). Because of the small number of women workers, this analysis is restricted to men.

Periodically, between 1948 and 1958, measurements of dust concentrations were taken in the mine and the mill by the Mines Department of Western Australia using a konimeter.² Often the upper measurement limit of 1,000 particles per cubic centimetre was exceeded. These measurements suggest that there was little change in the concentrations of total dust over this period, at least until a new mill was commissioned in September 1957. In 1966, the concentrations of airborne respirable fibres greater than 5 microns in length were measured in various workplaces.²⁷ These measurements and the employment records provided by CSR enabled the calculation of each subject's cumulative exposure in fibre years per ml, by adding over all their jobs the product of their estimated fibre concentration and the length of time in the job.

Certified causes of death were obtained from all states of Australia up until the end of September 2000, via the National Death Index at the Australian Institute of Health and Welfare (AIHW). Incident cases of cancer were available at the WA, and Tasmanian Cancer Registries until December 1999, Northern Territory until December 1998 and other states until December 1997, through the National Cancer Statistics Clearing House at the AIHW. Incident cancers and deaths were matched to our cohort using date of birth, surname, first name, middle name, address and previous name (if any).

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Received 26 March 2003; Accepted after revision 25 February 2004

DOI 10.1002/ijc.20313

Published online 20 May 2004 in Wiley InterScience (www.interscience.wiley.com).

Age and calendar period standardised incidence and mortality rates were calculated using Stata 7.0²⁸ to compare the incidence and mortality of aerodigestive cancers in the whole former Wittenoom workers cohort, and those former workers traced from 1979 (the smoking data subset), to the Western Australian male population. Incident cancers were defined using the International Classification of Diseases (ICD) Volume O, Second Edition;²⁹ mortality was defined using ICD volumes Eight,³⁰ Nine³¹ and Ten³² (Table I). The number of person-years for calculating expected cancer incidence and expected deaths were estimated assuming that those who had not died and who were not traced at the cancer registries, and who were not known to have migrated, were alive at the end of the study period. Expected numbers of cancer cases were calculated separately for each state. Subjects were censored at September 30, 2000 and those without a death record were assumed deceased if aged greater than 85 years on this date ($N=10$).^{33,34} Subjects who were known to have departed from Australia were censored at their departure date, excepting Italians who returned to Italy and who have been followed up in Italy.³⁵

Subjects from the smoking data subset with aerodigestive cancer, cases, were matched randomly with up to 10 controls using the STATA 7.0 statistical package.²⁸ Controls were selected if they were not known to have developed cancer of these sites by the year of diagnosis of the case, who were the same age as the case and who were known to be alive at the time of diagnosis of the case. Subjects could be controls for more than 1 case and cases could be controls in years prior to the onset of their disease.

Incident cancer cases were available in Western Australia until the end of 1999, whilst some other states were available only until the end of 1997. Including the additional cases from Western Australia increased our incident cancer cases by 12. In order to reduce the potential bias resulting from the differing dates of cancer registration received from each state, control subjects were restricted to those followed up in Western Australia. Smoking status was compiled from questionnaires completed in 1979, 1985, 1990 and 1994. If a subject answered more than 1 questionnaire, the most recent data was used to categorise him according to smoking status. Twenty-eight percent of the workers subset answered the 1979 questionnaire as their final questionnaire, with a further 24% responding for the last time in 1994. A derived variable, consisting of current smoker, past smoker and never smoked, was created. Fifty percent of the workers subset were past smokers and 31% were current smokers at the time they answered their last smoking questionnaire.

After log transformation, comparisons were made between cases and controls from the smoking data subset only, using conditional logistic regression³⁶ (in Stata 7.0), for cumulative crocidolite exposure (fibre per ml-year), time since first crocidolite exposure and

year of starting work at Wittenoom, before or after 1957 (as the new "cleaner" mill was introduced in 1957) and smoking status. The models were repeated including place of birth as a categorical variable (Australian/British, Continental European and Other).

RESULTS

There were 196 incident cases from all cancers of interest and 115 deaths in the whole cohort of former Wittenoom workers. Of those traced from 1979 (the smoking data subset), there were 129 incident cases from all cancers of interest and 57 deaths. Mortality from upper aerodigestive cancers was twice that expected for the whole worker's cohort when compared to the Western Australian male population (p -value<0.001). Mortality from lower aerodigestive cancers for the whole worker's cohort was not significantly higher than that observed in the Western Australian male population. The incidence of upper aerodigestive cancers was higher in the Wittenoom cohort, particularly cancers of the pharynx (p -value=0.01) and larynx (p -value<0.005). The incidence of lower aerodigestive cancers for the whole worker's cohort was not significantly higher than that observed in the Western Australian male population (Table I). Mortality was higher (p -value=0.05) for the smoking data subset for upper aerodigestive cancers but not lower aerodigestive cancers when compared to the Western Australian male population. The incidence of upper and lower aerodigestive cancers was higher in the smoking data subset but not significantly so (Table I).

There was an association (p -value=0.057) between cancer of the stomach and cumulative exposure to asbestos (Table II). Time since first asbestos exposure (OR 0.58 95% CI 0.05–7.56) and year of starting work at Wittenoom (OR 1.80 95% CI 0.62–5.26) were unrelated to cancer of the stomach. Smoking status was associated with cancer of the stomach, but not significantly (p -value = 0.61). Including place of birth as a categorical variable in the model attenuated the association between cancer of the stomach and cumulative exposure to asbestos (OR 1.28 95%CI 0.94–1.76); although place of birth was not itself significantly associated with cancer of the stomach, continental Europeans had a higher risk than other ethnic groups (OR 2.03 95%CI 0.68–6.04).

Smoking status was strongly associated with upper aerodigestive cancers, with current smokers experiencing the greatest risk (Table III). There was no association between cumulative exposure to asbestos and upper aerodigestive cancers. There was no association with time since first exposure to asbestos (OR 0.34 95% CI 0.06–1.92) or year of starting work at Wittenoom (OR 1.32 95% CI 0.61–2.88). Including place of birth as a categorical variable in the models slightly attenuated the association between current smoking and upper aerodigestive cancers (OR 7.25 95%CI 0.91–

TABLE I—STANDARDISED INCIDENCE AND MORTALITY RATES 1979–2000¹

Incidence Cancer	ICD code ²	Whole cohort				Smoking data subset			
		Observed	Expected ³	SIR	(95% CI)	Observed	Expected ³	SIR	(95% CI)
Upper aerodigestive	C000–C148 C300–C329	71	45	158	(126–200)	39	29	132	(96–180)
Lip	C00.0–C00.9	15	11	142	(85–235)	10	7	140	(75–259)
Tongue	C01.9–C02.9	8	5	149	(75–298)	5	3	141	(59–339)
Mouth	C04.0–C09.9	13	8	164	(95–282)	6	5	115	(52–255)
Pharynx	C09.0–C14.8	16	9	188	(115–307)	9	6	159	(83–306)
Larynx	C32.0–C32.9	19	10	182	(116–285)	9	7	131	(68–252)
Lower aerodigestive									
Oesophagus	C15.0–C15.9	10	9	111	(60–207)	7	6	101	(45–224)
Stomach	C16.0–C16.9	27	22	131	(82–175)	19	14	131	(83–205)
Colon/rectum	C18.0–C20.9	88	84	105	(85–129)	64	53	105	(81–135)
Mortality									
Upper aerodigestive	1400–1499 1600–1619	37	15	251	(182–346)	16	9.5	163	(100–267)
Oesophagus	1500–1509	8	9	89	(44–178)	3	5.7	50	(16–155)
Stomach	1510–1519	21	15	139	(91–214)	12	9	124	(70–218)
Colon/rectum	1530–1541	49	37	131	(99–174)	26	23.2	106	(72–155)

¹Cancer Incidence until 1999 only. ²Incidence, International Classification of Diseases for Oncology, 2nd edition. Mortality, International Classification of Diseases, vol. 9. ³WA Population Rates only available from 1982/3 onwards; therefore 1982–1983 rates used for 1979–1983

TABLE II—INCIDENCE OF CANCER OF THE STOMACH, CUMULATIVE EXPOSURE TO CROCIDOLITE AND SMOKING HABIT (19 CASES AND UP TO 10 WESTERN AUSTRALIAN CONTROLS PER CASE; 158 CONTROLS IN TOTAL)

	Odds ratio	95% CI	p-value
Cumulative exposure Crocidolite exposure (fibre/ml year)	1.38	(.99–1.92)	.057
	$p = .0480^*$		
Smoking status			
Never	1.00		
Past	2.20	(.27–18.1)	.46
Current	2.81	(.30–25.9)	.36
	$p = .6058^*$		

* p value for removal of exposure term from full model.

TABLE III—INCIDENCE OF UPPER AERODIGESTIVE CANCERS, CUMULATIVE EXPOSURE TO CROCIDOLITE AND SMOKING HABIT (39 CASES AND UP TO 10 WESTERN AUSTRALIAN CONTROLS PER CASE; 326 CONTROLS IN TOTAL)

	Odds ratio	95% CI	p-value
Cumulative exposure Crocidolite exposure (fibre/ml-year)	1.02	(.85–1.22)	.84
	$p = .6101^*$		
Smoking status			
Never	1.00		
Past	4.84	(.63–37.5)	.13
Current	8.31	(1.04–66.2)	.04
	$p = .0282^*$		

* p value for removal of exposure term from full model.

TABLE IV—INCIDENCE OF CANCER OF THE COLON AND RECTUM, CUMULATIVE EXPOSURE TO CROCIDOLITE AND SMOKING HABIT (58 CASES AND UP TO 10 WESTERN AUSTRALIAN CONTROLS PER CASE; 466 CONTROLS IN TOTAL)

	Odds ratio	95% CI	p-value
Cumulative exposure Crocidolite exposure (fibre/ml-year)	.97	(.84–1.12)	.69
	$p = .6903^*$		
Smoking status			
Never	1.00		
Past	.66	(.31–1.39)	.27
Current	.62	(.25–1.54)	.30
	$p = .5221^*$		

* p value for removal of exposure term from full model

57.57), although place of birth was not itself significantly associated with upper aerodigestive cancers.

Cumulative asbestos exposure and smoking status were not associated with cancer of the colon and rectum (Table IV). Year of starting work at Wittenoom (OR 1.01 95% CI .54–1.86) and time since first asbestos exposure (OR 0.68 95% CI 0.15–3.03) were unrelated to cancer of the colon and rectum. Including place of birth in the models did not impact upon the results reported.

Neither duration of asbestos exposure nor intensity (fibre per ml) of exposure changed any of the outcomes when added separately to the models.

DISCUSSION

Our study has shown that the asbestos-exposed cohort of former Wittenoom workers has higher rates of upper and lower aerodigestive cancer incidence and mortality than the West Australian male population. These excess risks were not statistically significant except for upper aerodigestive cancer mortality. This excess risk does not appear to be related to asbestos exposure. Smoking

status was associated with upper aerodigestive cancers but was not significantly associated with colon, rectum or stomach cancers.

A potential limitation of our study is that the analysis exploring the association between crocidolite exposure and cancer incidence was conducted on a subset of the original Wittenoom worker's cohort who were contacted in 1979. This smoking data subset consists of 45% of the original workforce and has approximately half the deaths of the whole worker's cohort. It has the advantages of almost complete follow-up and information on smoking. This subset is quite different from the whole workers cohort; for example, there were more foreign-born subjects in the whole cohort than have been traced in the subset. Workers who were at Wittenoom for only a very short period were more likely to have not been traced and were therefore not included in the subset. Given these differences, it is therefore not feasible to generalise the results of our study to the whole cohort of former Wittenoom workers. It is reasonable to surmise that the within-group associations between asbestos exposure and cancer incidence would be similar for both groups.

Smoking information was collected at various times from 1979. The smoking status assigned in our study is taken from the most recent questionnaire that the respondent answered. Cases and controls were matched on their age and time in the study and not on smoking status. A weakness of this method is that the assigned smoking status may have been different at the time that the case and control were designated. Current smokers may have been past smokers at the time the case or control status was designated or past smokers may have been current smokers. However, this is unlikely to have been a differential bias and should not therefore grossly over or under estimate the impact of smoking on upper aerodigestive cancers.

We assumed former workers were dead if they were without a death record or had not been otherwise traced at the age of 85.^{33,34} There were only 10 such subjects who were so treated in our study. Excluding this small number of subjects from the study should not have any implications for the results presented.

In order to increase the number of incident cancers for this analysis, cancers were identified at the Western Australian cancer registry until 1999, although they were not available beyond 1997 for the most populous Australian states. In an attempt to reduce any potential bias from having more cases from Western Australia than other states, we restricted our control subjects to only Western Australian residents. One possible bias of this restriction could be an under representation of particular ethnic subgroups in Western Australia. Therefore place of birth was included in the models and the significant association between stomach cancer and cumulative asbestos exposure attenuated, although place of birth itself was not associated with stomach cancer. An excess of stomach cancer among migrants from continental Europe has been found earlier in this cohort.² This suggests the importance of migration status for this cohort rather than a bias introduced by restricting our controls to Western Australian residents. A hierarchy of worksites existed at Wittenoom, with newer migrants more likely to be placed in the dirtier, dustier jobs.³⁷ Eighty-one percent of the smoking data subset (cases and controls) are residents of Western Australia. In addition only 7 potential controls were excluded for non-Western Australian residence from the stomach cancer examination. It therefore seems unlikely that our control restriction would substantially bias this analysis.

The majority of literature reviews and meta-analyses attempting to answer the question concerning an association between exposure to asbestos and gastrointestinal cancer have in the main been inconclusive^{38–40} or found no association.^{15,17,25,41} Doll and Peto¹³ opined that the positive association found in many studies, in particular those with high estimated risks of lung cancer, was due to misdiagnosis of mesothelioma and lung cancer to gastrointestinal cancers. Homa⁶ suggested that exposure to amphibole asbestos may be associated with colorectal cancer but that these

results could also reflect an artefact of cause of death misclassification.

Published case control and cohort studies assessing asbestos exposure and cancers of the gastrointestinal tract report mixed results. Newhouse *et al.*⁴² reported convincing evidence of a dose-response relationship between exposure to asbestos and gastrointestinal cancer in East London factory workers. This cohort was further analysed for all cancer mortality and found an exposure-related excess of mortality for colon cancer.¹¹ The authors suggest that this excess may have been due to peritoneal mesotheliomas being certified as cancer of the colon. Kang¹⁰ found a positive association between asbestos exposure and some gastrointestinal cancers; however cases were identified from occupations with elevated proportionate mortality ratios (PMRs) for mesothelioma and it is again possible that peritoneal mesotheliomas were misclassified as gastrointestinal cancers. Several other studies have not found any association between exposure to asbestos and gastrointestinal cancers^{43,44} and some studies that report an excess risk fail to report a dose-response relationship.^{5,45}

Laryngeal cancer is known to be strongly associated with smoking and alcohol consumption^{46,47} and many older studies examining asbestos exposure and laryngeal cancer have not adjusted for these factors.^{48,49} Reviews and meta-analyses, addressing the same case control and cohort studies, come to differing conclusions. Some conclude that the evidence does not indicate that asbestos exposure increases the risk of laryngeal cancer,^{14,18,19,21,22,50} whilst others conclude that it does.^{16,17} Smith *et al.*¹⁶ selected those cohorts with a relative risk for lung cancer greater than 2, before adjusting for smoking. This procedure could have biased the result in favour of cohorts who smoked more than their control populations.

Significantly increased risks for laryngeal cancer and evidence of dose-response relationships have been found in several studies. Among chrysotile miners in Italy, those with the longest duration of asbestos exposure showed the highest risk of laryngeal cancer, although increasing duration did not show a statistically significant trend. The authors suggested that high alcohol consumption in their cohort could explain some of the excess.⁵¹ Evidence of both

a dose-response relationship and increased risk of laryngeal cancer was found in a community-based case referent study conducted in Sweden assessing various occupational exposures.⁹ Our study adjusted for both alcohol and tobacco consumption. A case-control study of incident laryngeal cancer on the Gulf coast of Texas found that when asbestos was categorised by intensity of exposure, a significant positive gradient was found.⁵² This analysis controlled for confounding by cigarette smoking and alcohol consumption.

Several other studies have found no association between asbestos exposure and laryngeal cancer^{11,20,53} including Hutchings *et al.*⁷ who assessed more than 57,000 asbestos workers in England, Scotland and Wales.

The excess mortality from upper aerodigestive cancers seen in the whole Wittenoom cohort and the smoking data subset compared to the Western Australian male population does not appear to be associated with crocidolite exposure. The excess incidence of cancers of the mouth, pharynx and larynx is associated with smoking status and the high rates of current and past smokers in the subset probably explains some of the high mortality from these cancers. Earlier work has shown an excess of deaths from cirrhosis of the liver and alcoholism² and immoderate alcohol consumption may also have contributed to the high mortality rate in these cancers: we have collected information on alcohol intake in this cohort only recently. Earlier analysis of the Wittenoom workers has previously shown no dose-response effect of exposure to crocidolite on stomach cancer, no excess risk of other gastrointestinal cancers and no evidence of diagnostic transfer between mesothelioma or lung cancer to gastrointestinal cancers in particular.^{2,26} Our study with longer and more complete follow-up, smoking information and a stronger study design does not show an association between cumulative asbestos exposure and stomach cancer or other gastrointestinal cancers.

ACKNOWLEDGEMENTS

The authors thank N. Olsen, P. Etherington, Emeritus Professor G. Berry, JEM Fund, National Health and Medical Research Council, The Wittenoom Workers, Western Australian Cancer Registry and Asbestos Diseases Society of Western Australia.

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