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A M E R I C A N C O L L E G E O F



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Age and Sex Differences in Malignant Mesothelioma After Residential Exposure to Blue Asbestos (Crocidolite)*

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Background: Blue asbestos was mined and milled at Wittenoom, Western Australia, from 1943 until 1966. Various public records were used to establish a cohort of residents of the nearby township. Mine tailings were distributed throughout the town.

Aims: To report the incident number of malignant mesotheliomas that have occurred in residents of the town who did not work at the mine or mill; and to determine if female subjects are more susceptible to asbestos exposure than male subjects, and if children are more susceptible than adults.

Subjects and methods: A total of 4,768 residents of the town of Wittenoom have been followed up in cancer and death registries.

Results: There were 67 cases of mesothelioma, and 64 deaths with mesothelioma to the end of 2002. The mortality rate with mesothelioma increased with increasing residence duration, time since first exposure, and estimated cumulative exposure. The mesothelioma mortality rate was consistently lower for female subjects when compared with male subjects, but the dose-response curve was steeper for female subjects. The rate was lower in those first exposed as children compared with those first exposed at ≥ 15 years of age. The dose-response slope for asbestos exposure and mortality from mesothelioma was not different between those who were first exposed as children than those who were first exposed at ≥ 15 years of age.

Conclusions: Former residents of a crocidolite mining town have a high rate of mesothelioma. The rate is higher in male subjects and those ≥ 15 years of age at first exposure, but women have a steeper dose-response curve. (CHEST 2007; 131:376–382)

Key words: asbestos; crocidolite; mesothelioma; Wittenoom

Abbreviations: ABA = Australian Blue Asbestos Company; CI = confidence interval; f/mL = fibers per milliliter

Crocidolite (blue) asbestos was mined and milled at Wittenoom Gorge, Western Australia, by the Australian Blue Asbestos Company (ABA) between

1943 and 1966. Originally, the residential area was in the Wittenoom Gorge, 1 km from the mine; but in 1947, a new town was established 12 km from the mine, on the flats of the Fortescue River. In 1957 a

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new mine and mill were established in a nearby gorge (Colonial Gorge). Tailings from the mining operation containing residual crocidolite fiber were used throughout the town for paving roads, parking areas, the school playground, and the race course, and was spread on the yards of houses to suppress

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the red dust and mud.^{1,2} Asbestos was trucked through the town past the primary school and houses, and the workers took their dusty work clothes home for washing. Hansen and colleagues reported 24 cases of mesothelioma to 1992 in a cohort of 4,890 residents of the town who had never worked for the mining company,³ and 27 cases in 4,659 former residents to the end of 1993.⁴

Greater standardized mortality ratios for mesothelioma have been reported for women than men in various studies^{5,6}; among factory workers in East London followed up for > 20 years, 1.5% of women compared with 1% of men died from a mesothelial tumor.⁷ Other studies^{8,9} have reported greater disease rates in women than men at lower levels of exposure, leading to the suggestion that women may be more susceptible to mesothelioma than men.¹⁰

We present the results of a further follow-up to the end of 2000 among the former residents of Wittenoom, not employed in the milling and mining industry, and to determine if women are more susceptible to mesothelioma than men. Since the previous articles,^{3,4} work has gone into further development of the cohort and into reducing the amount of missing information, and this accounts for any difference in numbers of subjects from those earlier reports. The Wittenoom studies are unique because the exposure of asbestos was exclusively to crocidolite for defined periods of time, exposures have been characterized, and follow-up rates are relatively high when compared with studies performed elsewhere.

MATERIALS AND METHODS

Resident Cohort

Residents were defined as those who were documented to have lived in the town for at least 1 month and who had not been exposed to asbestos occupationally either at the Wittenoom mine or mill, or elsewhere.³ The cohort was established using information from numerous sources. These included the local school register (n = 835); electoral roll (n = 616); Wittenoom hospital records (n = 838); Vitamin A Cancer Prevention Programme^{11,12} (n = 819); publicity and questionnaires (n = 570); Registrar General birth certificates (n = 207) and death certificates (n = 15, from workers' questionnaires (n = 157); from parent or guardian (n = 212); the Asbestos Diseases Society of Western Australia (n = 131); public hospital referrals in Perth (n = 86);

interview (n = 58); company employment records (n = 41); and other (n = 183). The resident cohort consisted of 4,768 people (2,608 female and 2,160 male subjects). The residents included spouses and children of mine and mill workers, government employees (teachers, hospital staff, police, and local government workers), those who worked for other mining companies using Wittenoom as a base camp for exploration in the surrounding area, and those providing services in the town.

Ascertainment of Cases

Reporting of cases of mesothelioma is mandatory in Australia. Cases were ascertained from various sources throughout Australia: the National Death Index, Cancer Statistics Clearing House, Australian Mesothelioma Surveillance Programme, and the Western Australian Cancer Registry, Mesothelioma Registry, and Registrar General.

Asbestos Exposure Assessment

It was assumed that the exposure began when the subjects first became residents, excepting those who were residents before 1943; exposure was then assumed to have started in 1943. It is possible that some of these exposures took place a few years earlier because there was some asbestos extraction and hand cobbing from the 1930s. Based on surveys of airborne fiber (threads or filaments forming textile substances) counts conducted in the township itself and performed periodically by the Health Department of Western Australia and the Mines Department of Western Australia, former residents of the township of Wittenoom not working directly with asbestos were assigned an intensity of exposure of 1.0 fibers (> 5 μm long) per milliliter (f/mL) of air from 1943 to 1957 (when the new mill was commissioned), and then 0.5 f/mL between 1958 and 1966, when the mining operations ceased. Interpolation between surveys using personal monitors assigned exposures from 0.5 f/mL in 1966 to 0.01 f/mL in 1992. Exposures were based on measurement methods developed in an occupational setting, a time-weighted average over an 8-h working day, 5 d/wk. Consequently, they represented only 40 of a 168 h/wk exposure. To adjust for this and produce more accurate estimates of total exposure, the cumulative exposure figures were multiplied by 4.2 (*ie*, 168/40) to represent 24 h, 7 d/wk residential exposure.

Duration of residence was extracted from a questionnaire sent to each subject, or was taken from the information contained in various sources: state primary school records, admission and outpatient records from the hospital, the State Electoral Roll for the Pilbara district, and information supplied by others who returned completed questionnaires. Mesothelioma death rates per 100,000 person-years were calculated with a latency of 20 years by dividing the number of mesothelioma deaths by the person-years of follow-up from 20 years after first exposure to the end of 2000. Those not known to be dead were assumed to be alive at the end of 2000, and were censored at an age of 85 years.

Proportional hazards survival models with a Weibull distribution for the hazards were used to examine the slope of the dose-response relationship between asbestos exposure and death from mesothelioma in different age and sex groups. Analysis was performed using statistical software (Stata Statistical Software, Release 9; StataCorp; College Station, TX).

RESULTS

Population

The number of Wittenoom residents fluctuated with the expansion and contraction of the asbestos

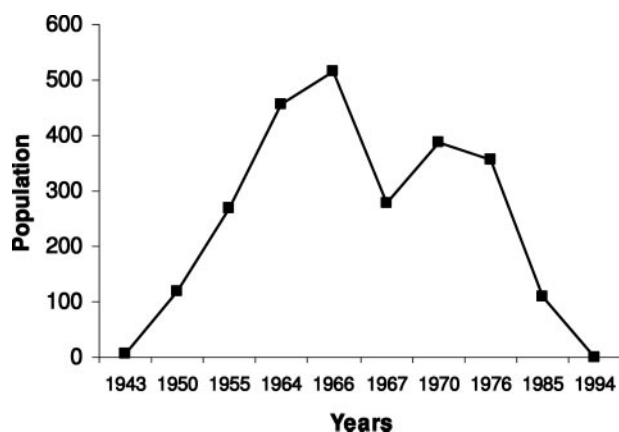


FIGURE 1. Population of residents at Wittenoom, 1943–1994.

mining and milling operation. The residents population peaked in 1964 and declined quickly after December 1966 with the closure of the mine and mill (Fig 1). However, numbers increased again after this period as new people moved into the vacated accommodation. From 1994, the state government decided to phase out the town, and buildings were demolished and services withdrawn.

Most residents moved to the town during the 1950s and 1960s, the mean year of arrival being 1962. Ten

percent of residents were born at Wittenoom, with 61% of males compared with 46% of females being there when they were < 15 years old. The median duration of residence was 20 months with 35% staying for < 1 yr. More women than men lived with a worker employed by ABA. The mean cumulative exposure to asbestos was 5.5 fibers/mL-years, with females having a greater mean exposure than males (Table 1). More men than women arrived at Wittenoom after the mine and mill had closed, when the (assigned) asbestos exposures were lower; therefore, men had greater cumulative days of asbestos exposure but a lower mean cumulative dose (Table 1).

Mesotheliomas

By the end of 2002, there were 67 known cases of mesothelioma in former residents, 36 in male subjects and 31 in female subjects. Sixty-two cases were pleural, 3 were peritoneal, and the site was not stated for 2 cases. Mortality from mesothelioma and residence with an asbestos worker were significantly associated for women ($p = 0.01$). Twenty-seven of the 31 female subjects lived with an asbestos miner or miller. This association did not hold for men: 13 subjects had lived with an ABA worker. Sixty-four of the mesothelioma subjects had died. The mortality rate and incidence rates are therefore very similar.

Table 1—Residential Characteristics of the Former Wittenoom Residents Cohort*

Characteristics	Female Residents	Male Residents	Total	p Value
Subjects, No.	2,608	2,160	4,768	
Year of first residence				
<1943	8 (0)	25 (1)	1	< 0.001
1943–1949	110 (4)	78 (4)	4	
1950s	929 (36)	619 (29)	32	
1960s	1,136 (44)	929 (43)	43	
1970s	374 (14)	432 (20)	17	
1980s	39 (1)	48 (2)	2	
Unknown	12 (0)	29 (1)	1	
Age at first residence, yr				
Born at Wittenoom	220 (8)	250 (12)	10	< 0.001
< 5	549 (21)	601 (28)	24	
5–14	449 (17)	438 (21)	18	
15–39	1,148 (44)	610 (28)	37	
≥ 40	197 (8)	183 (8)	8	
Unknown	57 (2)	91 (4)	3	
Length of residence, yr				
< 1	911 (35)	764 (35)	35	0.5514
1 to < 3	806 (31)	598 (28)	29	
3 to < 5	356 (14)	277 (13)	13	
≥ 5	437 (17)	368 (17)	17	
Unknown	98 (4)	153 (7)	5	
Lived with an ABA worker	1,711 (66)	968 (45)	2,679 (56)	< 0.001
Asbestos Exposure				
Mean year of arrival	1961 ± 8	1963 ± 9	1962 ± 9	
Mean No. of days of residential exposure	1,018 ± 1,380	1,962 ± 1,434	1,007 ± 1,404	
Mean cumulative exposure, f/mL-yr	5.9 ± 8	4.9 ± 7	5.5 ± 8	< 0.001

*Data are presented as No. (%) or mean ± SD.

Table 2—Mesothelioma Death Rate by Number of Years Resident at Wittenoom*

Years of Residence	Female Subjects		Male Subjects		Total	
	Deaths	Death Rate	Deaths	Death Rate	Deaths	Death Rate
<1	1	7	5	47	6	23
1–2	6	43	2	21	8	34
3–4	7	109	6	134	13	119
5–9	5	101	5	155	10	122
10–19	4	177	4	223	8	197
20–45	1	195	1	142	2	164
Unknown	1	96	6	403	7	277
Total	25	57	29	91	54	71

*Per 100,000 person-years from 20 yr after first exposure.

The mortality rate with mesothelioma increased with increasing length of residence (Table 2), cumulative exposure (Table 3), and latency period (Table 4). The mesothelioma mortality rate was consistently lower for female when compared with male subjects.

Age at First Residence

There was some evidence that children < 15 years of age had lower rates of mortality with mesothelioma than those ≥ 15 years old at first exposure (Table 5). These two groups had similar mean residence times in Wittenoom, cumulative exposures, and lengths of follow-up. The relative risk in those exposed at older ages was 2.4 (95% confidence interval [CI], 1.4 to 4.2). However the slope of the dose-response relationship between mesothelioma and cumulative asbestos exposure was not different between those first exposed at < 15 years of age and those first exposed at ≥ 15 years of age (not shown).

Susceptibility

Adjusting for cumulative asbestos exposure and age at first residence, men had an overall higher rate of mesothelioma than women (Table 6). However, the second part of Table 6 shows that the interaction between asbestos exposure, mesothelioma, and sex was statistically significant, indicating that the slope of the dose-response relationship differed between

women and men (Table 6; Fig 2). Women have a steeper dose-response slope than men ($p = 0.047$). The sex-specific dose-response slopes, with and without the interaction, for malignant mesothelioma and cumulative asbestos exposure, derived from Table 6, show that women had a steeper dose-response slope than men but their overall risk is lower than that for men (Fig 2).

DISCUSSION

In this cohort study of the former residents of Wittenoom, women had a lower mesothelioma mortality rate when compared with men at each level of cumulative exposure, lag period, and number of years of residence at Wittenoom. The slope of the dose-response relationship was different between women and men, showing women had a significantly steeper dose-response slope than men. Children who were at Wittenoom aged < 15 years had a lower rate of mesothelioma than those aged ≥ 15 years, but there was no difference in the dose-response slope between these two groups.

The shortest lag period between first known exposure to crocidolite and diagnosis with mesothelioma was 24 years for women compared with 19 years in men. The shortest lag time between first known exposure and death with mesothelioma was 20 years for residents compared with 13 years in the former

Table 3—Mesothelioma Death Rate by Cumulative Exposure (f/mL-Years)*

Cumulative Exposure, yr	Female Subjects		Male Subjects		Total	
	Deaths	Death Rate	Deaths	Death Rate	Deaths	Death Rate
<10	10	30	13	53	23	40
10–24.9	8	107	6	132	14	116
25–49.9	4	173	4	274	8	212
≥ 50	1	384	0	0	1	321
Unknown	2	197	6	409	8	323
Total	25	57	29	91	54	71

*Per 100,000 person-years from 20 yr after first exposure.

Table 4—Mesothelioma Death Rate by Latency From First Exposure*

Lag Time, yr	Female Subjects		Male Subjects		Total	
	Deaths	Death Rate	Deaths	Death Rate	Deaths	Death Rate
<10	0	0	0	0	0	0
10–19	0	0	0	0	0	0
20–29	4	18	6	35	10	25
30–39	12	75	10	91	22	82
≥ 40	9	165	13	351	22	240
Total	25	26	29	40	54	32

*Per 100,000 person-years.

workers.¹³ The longer lag time in women and residents is consistent with their lower risk. Thereafter, the rates continue to increase with increasing lag time and, as would be expected, increased with increasing exposure in the Wittenoom township.

The mesothelioma rate in those first exposed as children (≤ 15 years) was approximately 40% that of those first exposed at older ages, and approximately 25% after adjusting for exposure and sex. This is a larger difference than in reports from earlier work⁴ that showed a lower risk for those first exposed as children at < 10 years of age (relative risk, 0.7; 95% CI, 0.3 to 1.5). Those first exposed as children have more years left to live, so their lifetime risk may not be lower than the group exposed when older. No mesothelioma cases were diagnosed in children, as the youngest age at diagnosis was 26 years. A similar finding was found after environmental exposure to erionite in three villages in Turkey, where the youngest patients of 135 mesothelioma cases were 26 and 27 years old.¹⁴ An animal study¹⁵ has shown that the incidence rate of mesothelioma was significantly higher in rats inoculated intrapleurally with asbestos at age 10 months compared to rats inoculated at age 2 months. The relative rate was estimated to be approximately four. The asbestos started its effect soon after injection, but the size of the effect was dependent on age. The authors¹⁵ suggest that the reason for the lower risk in the younger rats could be due to their having a more efficient defense mechanism. Our results are in the same direction and magnitude as this study. The reduced risk of mesothelioma in children exposed to asbestos at Witte-

noom could be explained by their having a more efficient defensive mechanism than older persons.

In this cohort of former residents of Wittenoom who did not work in asbestos mining or milling, men had an overall greater rate of mesothelioma than women. However, the significant interaction between asbestos exposure, mesothelioma, and sex suggests that the slope of the dose-response relationship is different for women and men. Women have a steeper dose-response slope than men, but the risk was greater in men for exposures of ≤ 50 f/mL-years, which covers $> 99\%$ of the residents. Greater disease rates among women at lower levels of exposure have been reported in other studies, particularly peritoneal mesothelioma, but only three of the mesotheliomas in the residents were peritoneal, all in males. Peritoneal mesothelioma usually occurs in persons who have received high levels of asbestos exposure.¹⁶ The presence of asbestos fibers in peritoneal tumors has been reported in seven women in the United States with peritoneal mesothelioma, who were not knowingly exposed to asbestos.⁸ This suggests that peritoneal mesothelioma may develop at low exposure levels in women, although this study did not report results for non-mesothelial peritoneal tumors, so possible sample contamination cannot be dismissed.

The increased susceptibility of women to asbestos exposure is further supported with work by Metintas et al,⁵ who report observed/expected = 52.63 (95% CI, 29.9 to 92.6) for males and observed/expected = 143.9 (95% CI, 81.8 to 253.4) for females among a cohort of asbestos-exposed villagers in Turkey after

Table 5—Mesothelioma Death Rate by Age at First Exposure in Former Residents*

Age at First Exposure, yr	Residents, No.	%	Residents With Mesothelioma, No.	Residents With Mesothelioma, %	Mesothelioma Death Rate
< 15	2,491	52.2	24	1.0	47
≥ 15	2,154	45.2	43	2.0	112
Unknown	123	2.6	0	0	
Total	4,768	100.0	67	1.4	71

*Per 100,000 person-years

Table 6—Sex, Age at First Residence, Cumulative Asbestos Exposure, and Malignant Mesothelioma Dose-Response Slopes Among Former Wittenoom Residents

Variables	Hazard Ratio	95% CI	p Value
Base model			
Cumulative exposure, log f/mL-yr	1.39	1.11–1.75	0.005
Females	1.00		
Males	2.37	1.39–4.05	0.002
First residence at Wittenoom aged < 15 yr	1.00		
First residence at Wittenoom aged ≥ 15 yr	3.88	2.22–6.78	0.000
Base model with interaction			
Cumulative exposure, log f/mL-yr*	1.81	1.27–2.57	0.001
Females	1.00		
Males†	4.08	1.87–8.93	< 0.001
First residence at Wittenoom aged < 15 yr	1.00		
First residence at Wittenoom aged ≥ 15 yr	3.83	2.19– 6.71	< 0.001
Male × cumulative exposure	0.63	0.40–0.99	0.047

*For female subjects; the slope for male subjects is the female slope multiplied by the interaction = 1.14.

†At the mean value of log f/mL-years of 0.93; the male effect declines with increasing levels of exposure.

10 years of follow-up. The Turkish study does not possess quantitative asbestos exposure measurements; therefore, differential asbestos exposure between women and men may explain the observed differences.

The steeper dose-response slope for women than men in our study could have a biological or physiologic explanation. For pleural mesothelioma: women have smaller lung volume but a higher forced expiratory flow rate and a higher ratio of FEV₁ to FVC than men.¹⁷ This may lead to greater alveolar fiber deposition and greater fiber retention than in men with larger lungs.¹⁰

The greater prevalence of mesotheliomas in men than women at the same level of exposure is possibly because of greater exposure measurement error in men than in women. Men, for example, may have had exposure to asbestos in other occupations prior or subsequent to living at Wittenoom. Differences in behavior that could have led to different individual exposure patterns between females and males may also account for some of the observed differences.

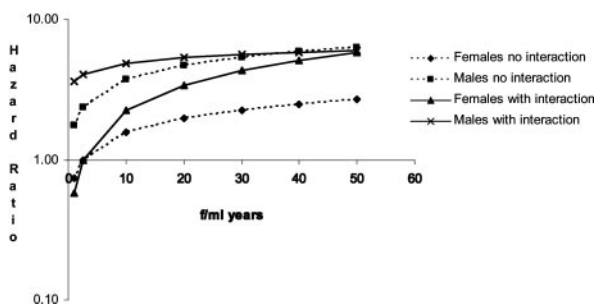


FIGURE 2. Cumulative asbestos exposure and dose-response slopes for former female and male residents of Wittenoom (derived from Table 6).

For example, in Turkey, sweeping and cleaning done more by women could be the chief exposure routes, whereas in Wittenoom it could have been gardening or casual laboring done more by men. However, more women residents lived with an asbestos miner or miller than did male residents and so may have been exposed to asbestos fibers in their homes, from work clothes being taken home for washing. Both the former workers' and residents' exposures are based on the interpolation of environmental measures and not individual data.

CONCLUSION

The township of Wittenoom has proved to be an area of high environmental exposure to crocidolite asbestos, and the consequence is a high mortality rate from malignant mesothelioma. The rate is higher in male subjects and those ≥ 15 years old at first exposure, although women have a steeper dose-response slope than men.

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