

# All-Cause Mortality and Cancer Incidence Among Adults Exposed to Blue Asbestos During Childhood

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**Background** *There are few data on the long-term health outcomes of exposure to asbestos in childhood. This study investigated cancer and mortality of adults exposed to blue asbestos as children.*

**Methods** *Data linkage to relevant health registries was used to identify cancers and mortality in a cohort of adults (n = 2,460) that had lived in an asbestos mining town during their childhood (<15 years).*

**Results** *There were 217 (93 female) incident cancers and 218 (70 female) deaths among the cohort. Compared with the Western Australian population females had elevated mesothelioma, ovarian and brain cancers, and increased "all cause" and "all cancer" mortality. Males had elevated mesothelioma, leukemia, prostate, brain, and colorectal cancers, and excess mortality from "all causes," "all cancers," circulatory disease, diseases of the nervous system, and accidents.*

**Conclusion** *Exposure to blue asbestos in childhood is associated with an increased risk of cancer and mortality in adults. Am. J. Ind. Med. © 2012 Wiley Periodicals, Inc.*

**KEY WORDS:** *crocidolite; asbestos; children; Wittenoom; cancer incidence; mortality*

## INTRODUCTION

Exposure to asbestos causes various malignant and non-malignant diseases including: malignant mesothelioma (MM) of the pleura and peritoneum, lung cancer, asbestosis, pleural effusion, diffuse pleural thickening (DPT), and rounded atelectasis [American Thoracic Society, 2004]. Various other diseases, such as laryngeal [Rafferty et al., 2001], gastrointestinal [Reid et al., 2004] and ovarian cancer [Reid et al., 2009; Camargo et al., 2011], as well as chronic obstructive pulmonary disease (COPD) [American Thoracic Society, 2004], ischemic heart disease [Sjogren, 2001], and auto-immune disorders [Noonan et al., 2006], have been associated with asbestos exposure although the data for these remain inconsistent. Most asbestos-related diseases (ARDs) have been caused by occupational asbestos exposure, particularly in men,

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although ARDs have been associated with non-occupational exposures as well [Goldberg and Luce, 2009]. Many people have been exposed to non-occupational levels of asbestos during childhood, either in public and domestic buildings [Landrigan, 1991] or from proximity to industrial [Magnani et al., 2001; Reid et al., 2007; Vinikoor et al., 2010] and natural [Metintas et al., 2002; Luo et al., 2003] sources.

Childhood exposure to asbestos has been reported as a cause for the subsequent development of MM [Marchevsky et al., 2006; Reid et al., 2007] but there are very few data on the subsequent development of other ARDs as a result of early life exposures [Anderson et al., 1979; Kilburn et al., 1985; Emri et al., 2002; Luo et al., 2003; Vinikoor et al., 2010]. Luo et al. [2003] reported increased risks of lung cancer, pleural plaques, and asbestosis, as well as MM, in Chinese villagers living near naturally occurring crocidolite. However, these villagers had been exposed continuously throughout their life and it is difficult to determine the effect of predominant childhood exposure. Similarly the prevalence of DPT and asbestosis is high in Turkish villagers living near naturally occurring asbestos and erionite deposits but again these people have had lifetime exposures [Emri et al., 2002]. Radiographic abnormalities [Anderson et al., 1979] and asbestosis [Kilburn et al., 1985] have been reported in adults who had been domestically exposed to asbestos as children of asbestos workers, while Vinikoor et al. [2010] found an increased prevalence for some respiratory symptoms in young adults who had childhood exposures to asbestos (tremolite, winchite, and ritcherite) contaminated vermiculite ore.

The township of Wittenoom, located in a remote part of Western Australia, was formed to support a crocidolite mine and mill which operated from 1943 to 1966. Although the town was situated about 12 km from the asbestos mine and mill, tailings from the mine were distributed widely around the town and all homes were constructed with asbestos cement sheets. Therefore, residents were exposed predominantly to crocidolite during their time at Wittenoom. In 1993, a cohort of former Wittenoom residents was established and the health outcomes of this cohort have been published previously [Hansen et al., 1993, 1998; Reid et al., 2007, 2008a]. Of the nearly 5,000 people in this cohort about half were children (<15 years old) when they were first exposed to asbestos. The former "Wittenoom children" are now at an age when chronic adult diseases are becoming more prevalent and many have died. Although they have been routinely included in the mortality and cancer incidence studies that have been reported for the whole cohort, apart from their risk of MM [Reid et al., 2007] they have not been studied separately as a group. The aim of this study, therefore, is to document the cancer incidence and

all-cause mortality of people exposed to blue asbestos as children.

## MATERIALS AND METHODS

### Wittenoom and the Wittenoom Residents' Cohort

Blue asbestos was mined and milled at Wittenoom between 1943 and 1966. The operation was owned by a single leaseholder the Australian Blue Asbestos company (ABA), which employed around 7,000 workers over that period. In 1946, the township of Wittenoom was built, originally only 1.6 km from the mine, but moved 12 km away from the mine in 1947 as the township grew in size [Layman, 1989]. Despite the distance from the mine, exposure to crocidolite in Wittenoom was a major problem as tailings from the mine, rich in crocidolite fibers, were used throughout the town to pave roads, footpaths, parking areas, the racecourse and school playgrounds, and for reducing dust in back-yards. The use of tailings in the town did not stop until the mid-1960s. From the late-1970s, successive State Governments adopted a policy of phasing down activity in the town but it was not officially degazetted until 2007.

The former residents' cohort consisted of the residents of the township of Wittenoom who had lived in the town but who had not worked for the asbestos company. A detailed description of how this cohort was established has been published previously [Hansen et al., 1993]. In summary, information was obtained from public records including: state primary school attendance lists, hospital and general practitioner records, the Western Australia electoral roll, birth and death records, non-mining employment lists and questionnaires sent to former Wittenoom mine and mill workers. Initially, a total of 18,853 records were collected identifying 5,097 individuals who were in Wittenoom but not directly employed by the Australian Blue Asbestos Company [Hansen et al., 1993, 1997, 1998]. Further work, including a questionnaire sent to all possible former residents who could be traced to an address in Australia, reduced the cohort to a total of 4,768 people (2,608 females) who had lived in Wittenoom for at least 1 month. This cohort only includes people who had lived in Wittenoom up until 1993 but very few people have lived there since that time: there were only 45 residents in the town in 1993.

### Children at Wittenoom

Over half of this cohort ( $n = 2,483$ ; 1,204 females) were "children" (aged <15 years) when they first arrived in Wittenoom. Four hundred and sixty-three (463) were born in Wittenoom and about 60% moved there before the

age of 5 years. Most (93.5%) of the former children had left before the age of 16 years, thereby only having exposure to asbestos during childhood.

## Asbestos Exposure Assessment

A full description of how the asbestos exposure measurements were undertaken has been published elsewhere [Armstrong et al., 1988; Hansen et al., 1997]. Briefly, between 1948 and 1958 there were several measurements of dust levels in the mine and mill taken by the Mines Department of WA using a konimeter. In 1966, the first fiber count of the mine and mill as well as the Wittenoom environment was undertaken using a Casella long running thermal precipitator. Further monitoring occurred in and around the township in 1973, 1977, 1978, 1980, 1984, 1986, and 1992 using a mixture of personal and fixed positional monitors. Between 1958 and 1966, when the mine closed, residents were assigned an intensity of exposure of 0.5 fiber/ml of air (f/ml), based on the monitoring done in 1966. In 1957, a new mill had been commissioned. Therefore, for the period 1943–1957 a level of 1.0 f/ml was assigned based on an estimate that fiber levels were approximately twice as high when the original mill was in operation. Interpolation between the dust surveys that used personal monitors allocated exposures from 0.5 f/ml in 1966 to 0.01 f/ml in 1992. Cumulative exposure was calculated for each individual resident by summing over all their years of residence the product of fiber concentration for each year and length of time spent in Wittenoom during that year. This figure was then adjusted by a factor of 4.2 ( $(24 \times 7)/(8 \times 5)$ ) to allow for a continuous 24-hr exposure rather than the 8-hr a day and 5 days a week measurement method used to determine occupational exposure levels [Hansen et al., 1997, 1998].

The estimates of asbestos exposure have been validated internally by showing agreement with lung fiber burdens [de Klerk et al., 1996]. Wittenoom exposures are comparable to exposures reported at other crocidolite mines [Hodgson and Darnton, 2000].

## Case Ascertainment

The cohort is periodically linked to various state and national cancer and death registries. These include the Western Australian Registrar General's Mortality Database, the National Death Index, the Western Australian Cancer Registry and its affiliated Mesothelioma Registry, and the National Cancer Statistics Clearing House. Coded cause of death was available from 1950 to the end of 2007, but dates (without coded causes) of death were available to the end of 2009. Cancer incidence was available from 1982 to the end of 2009. Cause of death as listed on the death certificate was defined using the

International Classification of Disease (ICD) Revisions 7–10 as appropriate for the time period. Cancers were defined using the ICD for Oncology, Second Edition.

This study had approval from both the Western Australian Department of Health and University of Western Australia Human Research Ethics Committees.

## Statistical Analysis

Expected numbers of deaths were estimated by applying age (5-year groupings), period, sex, and cause-specific mortality rates calculated for the Western Australian population in 5-year periods from 1970 to 2007 to the person-years accrued by the cohort in the same categories. Death rates for the period 1970–1974 were used to calculate expected deaths for the period 1950–1969 as specific death rates for that period were not calculated. Standardised Mortality Ratios (SMRs) were calculated, separately for males and females, as the ratio of observed deaths/expected deaths.

Similarly, the expected numbers of cancers were estimated using age, period, sex, and cancer-specific incidence rates calculated for the Western Australian population in 5-year periods from 1982 to 2009 by the Western Australian Cancer Registry; cancer data for the Western Australian population are only available from 1982. Standardised Incidence Ratios (SIRs) were calculated separately for males and females as the ratio of observed cancers/expected cancers. For both SMRs and SIRs 95% confidence intervals (95% CI) were assessed by treating the observed number as a Poisson count with expectation equal to the expected numbers. Dates of death (for non-coded deaths) in 2008 and 2009 were used to allocate correct follow-up time for the SIR analyses.

Western Australia has almost complete ascertainment of deaths and cancer incidence. For the analyses, all known cases were censored on either date of death (SMR) or cancer diagnosis (SIR). Approximately, 20% of the cohort has been lost to follow-up. Therefore, two methods were used to derive expected deaths and cancers to show a minimum and maximum estimate of effect, based on differing censoring dates. The first method (SMR/SIR1) assumed all subjects not known to be dead or to have developed a cancer or to have migrated were alive or cancer free at the end of 2007 or 2009, therefore, overestimating the number of person-years at risk and underestimating the SMR/SIR. The second method (SMR/SIR2) censored subjects lost to follow-up at their date last known to be alive therefore underestimating person-years at risk and overestimating the SMR/SIR. This second method underestimates person-years at risk because the majority of those censored in this way will still be alive in Australia (but lost); they would otherwise be contributing to person-years at risk. A few may have developed disease

but are most likely to be found once they die or get sick. Dates for when the individuals were last known to be alive have been collated from questionnaires sent to the Wittenoom cohorts, public records such as the Western Australian Electoral Roll, hospital records, or participation in an annual asbestos review program. In a few cases, records have not been able to be updated since the time they left Wittenoom.

Since smoking is a known risk factor for many of the disease outcomes adjustments were made, where appropriate, for SMRs/SIRs using the technique described by Axelson and Steenland [1988]. Information on smoking was available for the former Wittenoom children based on several questionnaires sent to all former Wittenoom workers and residents between 1979 and 2007, as well as information provided by participants in a cancer prevention program [Musk et al., 1998]. Smoking data were available for 885/1,204 females and 887/1,279 males. The prevalence of current and past smoking for the Australian population for a similar period was obtained from the Australian Institute for Health and Welfare (AIHW) [AIHW, 2007]. Risk ratios for smoking and the relevant diseases that were used for the calculation of the adjustments were obtained from the appropriate publications (see further details below). Adjustments were only made for diseases where SMR or SIR for the Wittenoom cohort was significantly elevated and where there is evidence that smoking is a risk for that disease.

Owing to the high occurrence rate of MM in the Wittenoom cohorts further analyses were conducted. Incidence rates (up to 2009) per 100,000 person-years at risk were derived for various categories of asbestos exposure and for males and females separately. These were calculated by dividing the number of cases in each exposure category by the number of person years at risk in the same exposure category and multiplied by 100,000. Subjects (non-cases) who were lost to follow-up were censored at their date last known to be alive. All analyses were undertaken using Stata 12.0 [StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP; 2011].

## RESULTS

### Former Wittenoom Children

Two thousand four-hundred and sixty children (1,191 girls and 1,269 boys) were documented to have been first exposed to blue asbestos at Wittenoom when they were aged <15 years, 63% of whom were exposed before the age of 5 years (Table I). The median age of first exposure was 3.1 years [interquartile range (IQR) 1–7 years]. The median duration of residence was 19 months (IQR 7–41 months) and ranged from 1 to 446 months. Estimated

cumulative exposure to asbestos fibers ranged from 0.1 to 64.4 f/ml year (median 3.3 f/ml year; IQR 1.4–7.5 f/ml year). The time since first exposure ranged between 24.5 and 68 years (median 49.6 years; IQR: 45.1–54.9 years). The mean age at the first censoring method (all those lost to follow-up censored at the end of follow-up) was 48.5 years [standard deviation (SD) 10.3], while for the second censoring method (all those lost to follow-up censored at their date last known to be alive) mean age was 42.4 years (SD 14.7; Table I). There were no significant differences between males and females for age at first exposure (medians 3.0 and 3.2 years, respectively), duration of residence (medians 18.0 and 20.0 months, respectively) and estimated cumulative exposure (medians 3.5 and 3.3 f/ml year, respectively).

To the end of 2009 there were 215 cases of cancer in 207 individuals (93 females). To the end of 2007, 228 (75 females) of the former Wittenoom children had died of any cause.

## Cancer Incidence and All Cause Mortality

### Females

**Cancer incidence** There were 95 cancers in 93 females. The first case was diagnosed in 1970. The most frequent cancers were breast ( $n = 28$ ), MM ( $n = 13$ ), melanoma ( $n = 11$ ), and ovarian ( $n = 6$ ; Table II). As expected, the incidence of MM was significantly elevated (Table II). Compared with the Western Australian female population the SIRs were elevated for “all cancers,” with and without MM and lung cancer included, and also for ovarian and brain cancers (Table II). However, these were only significantly elevated for SIR2.

As there is evidence of an association between smoking and ovarian cancer [Jordan et al., 2006] an adjustment was made for smoking. A relative risk (RR) of 2 was used for current smoking and an RR of 1 for both past and never smoking [Jordan et al., 2006]. Smoking rates for the former female Wittenoom children were 42.7% never smokers, 32.8% ex-smokers, and 24.5% current smokers. Age-relevant Australian data for females in 2006 were 57.5% never smokers, 23.6% ex-smokers, and 18.8% current smokers. The SIRs were adjusted by a factor of 1.05: SIR2 remained significant (3.55, 95% CI: 1.30–7.72). There is no consistent evidence for an association between smoking and brain cancers in adults [Wrensch et al., 2002]. As all subjects developed brain cancer in adulthood no adjustments for smoking were made. Smoking is not associated with MM [Mossman et al., 2011].

**Mortality** Seventy females who arrived at Wittenoom aged <15 years had died by 2007. Compared with the Western Australian female population girls from

**TABLE I.** Characteristics and Asbestos Exposure of Children at Wittenoom

Characteristic	Female	Male	Total
	(n = 1,191)	(n = 1,269)	(n = 2,460)
	n (%)	n (%)	n (%)
Age of arrival (years)			
<5	736 (62)	819 (65)	1,555 (63)
5 to 9	312 (26)	328 (26)	640 (26)
10 to <15	143 (12)	122 (10)	265 (11)
Year of arrival			
1943–1958	423 (36)	453 (36)	876 (36)
1959–1966	493 (41)	555 (44)	1,048 (43)
1967–1985	275 (23)	261 (21)	536 (22)
Length of stay (years)			
<2	652 (55)	697 (55)	1,349 (55)
2 to <5	337 (28)	355 (28)	692 (28)
5 to <10	120 (10)	126 (10)	246 (10)
10 to 37	75 (6)	84 (7)	159 (6)
Unknown	7 (1)	7 (1)	14 (1)
Cumulative exposure (f/ml year)			
<5	746 (63)	768 (61)	1,514 (62)
5 to <10	210 (18)	257 (20)	467 (19)
10 to 64	209 (18)	214 (17)	423 (17)
Unknown	26 (2)	30 (2)	56 (2)
Time to 2007 since first exposure (years)			
24–30	215 (18)	273 (22)	488 (20)
30–39	272 (23)	312 (25)	584 (24)
40–49	465 (39)	476 (38)	941 (38)
50–68	239 (20)	208 (16)	447 (18)
Ever smoked tobacco			
Yes	505 (42)	555 (44)	1,060 (43)
No	375 (31)	323 (25)	698 (28)
Unknown	311 (26)	391 (31)	702 (29)
	Mean (SD)	Mean (SD)	Mean (SD)
Age at censoring for method 1	49.1 (10.2)	48.0 (10.5)	48.5 (10.3)
Age at censoring for method 2	43.0 (14.9)	41.7 (14.5)	42.4 (14.7)

SD, standard deviation.

Wittenoom had a 20–47% greater risk of all cause mortality (Table III), depending on which censoring method was used. There were nine deaths due to MM by the end of 2007. SMRs for MM, based on data to 2007, ranged from 75.6 (95% CI: 34.6–143.6) and 100.0 (95% CI: 45.7–189.8). There was only one lung cancer death to the end of 2007 in this group. There were 20 deaths from neoplasms apart from MM and lung cancer. Of these the most frequent cancers causing death were breast (n = 5), brain (n = 3), and ovarian (n = 3). When MM and lung cancer were included, mortality from all cancers was greater than

**TABLE II.** Standardised Incidence Ratios (95% CI) Among Females Who First Arrived at Wittenoom Aged <15 Years, Compared With the Female - West Australian population

Cancer	N	SIR1 (95% CI) <sup>a</sup>	SIR2 (95% CI) <sup>a</sup>
All	93	1.12 (0.89–1.38)	<b>1.72 (1.38–2.12)</b>
Mesothelioma	13	<b>70.05 (36.20–122.37)</b>	<b>113.21 (58.49–197.75)</b>
Lung	5	1.47 (0.48–3.43)	2.57 (0.32–4.83)
All excl. MM and lung cancer	75	0.94 (0.74–1.19)	<b>1.35 (1.06–1.69)</b>
Breast	28	0.88 (0.58–1.28)	1.37 (0.90–2.00)
Brain	4	3.13 (0.85–8.00)	<b>4.43 (1.21–11.35)</b>
Colo-rectal	4	0.50 (0.10–1.46)	1.06 (0.29–2.70)
Leukemia	4	2.38 (0.49–6.96)	3.70 (0.76–10.82)
Ovarian	6	2.63 (0.97–5.73)	<b>4.14 (1.51–9.01)</b>
		2.50 <sup>b</sup> (0.92–5.46)	<b>3.55<sup>b</sup> (1.30–7.72)</b>
Uterine	2	0.79 (0.10–2.84)	1.31 (0.16–4.72)
Melanoma	11	0.87 (0.44–1.56)	1.22 (0.61–2.19)

SIR1, Standardised Incidence Ratio using censor method 1; SIR2, Standardised Incidence Ratio using censor method 2; CI, confidence intervals.

<sup>a</sup>All are unadjusted unless otherwise specified.<sup>b</sup>Adjusted for smoking.

Bolded values are statistically significant.

in the Western Australian female population irrespective of the censoring method but when these were excluded the SMR was only significantly elevated for SMR2 (Table III). There was increased mortality from diseases of uncertain diagnoses (signs/symptoms/ill defined conditions) for both censoring methods but no statistically significant increase in SMR for any of the specific disease groupings (Table III).

## Males

**Cancer incidence** There were 114 cancers in the former Wittenoom male children to the end of 2009. The most common cancers were MM (n = 29), melanoma (n = 17), prostate (n = 12), colorectal (n = 10), and leukemia (n = 7; Table IV). The former Wittenoom male children had increased incidence of “all cancers,” with and without the inclusion of MM and lung cancer, compared with the Western Australian male population (Table IV). Apart from MM, SIRs were also significantly elevated for leukemia (for both censoring methods), and prostate, brain, and colorectal cancer (SMR2 only).

Smoking has been associated with leukemia, specifically acute myeloid leukemia (AML), and colorectal cancer but not prostate cancer [Kuper et al., 2002]. Adjustments to the SIRs were, therefore, made for colorectal cancer and leukemia (although we had not confined this to cases of AML). The proportions of males in the cohort who were never, former and current smokers, based on a

**TABLE III.** Standardized Mortality Rates Among Females Who First Arrived at Wittenoom Aged <15 Years, Compared With the Female West Australian Population

Cause of death <sup>b</sup>	N	SMR1 (95% CI) <sup>a</sup>	SMR2 (95% CI) <sup>a</sup>
All causes	70	1.20 (0.93–1.51)	<b>1.47 (1.14–1.86)</b>
Neoplasms	30	<b>1.66 (1.12–2.37)</b>	<b>2.24 (1.51–3.20)</b>
<i>Mesothelioma</i>	9	<b>75.63 (34.58–143.57)</b>	<b>98.90 (45.22–189.75)</b>
<i>Lung cancer</i>	1	0.63 (0.02–3.49)	0.89 (0.02–4.95)
<i>Neoplasms excl. MM and lung cancer</i>	20	1.26 (0.77–1.94)	<b>1.69 (1.03–2.60)</b>
Infectious diseases	2	1.07 (0.13–3.86)	1.20 (0.15–4.33)
Nervous system	4	2.20 (0.60–5.63)	2.74 (0.75–7.01)
Circulatory system	5	0.97 (0.31–2.26)	1.31 (0.43–3.06)
Respiratory system	3	1.02 (0.21–2.99)	1.22 (0.25–3.58)
Symptoms/signs/ill defined	10	<b>4.83 (2.32–8.88)</b>	<b>5.46 (2.62–10.05)</b>
Accidents/injuries/poisonings	9	0.79 (0.36–1.51)	0.92 (0.42–1.75)
<i>Transport accidents</i>	5	0.92 (0.30–2.16)	1.04 (0.34–2.43)

SMR1, Standardised Mortality Ratio using censor method 1; SMR2, Standardised Mortality Ratio using censor method 2; CI, confidence intervals.

<sup>a</sup>All are unadjusted unless otherwise specified.

<sup>b</sup>Selected ICD disease chapters. Specific conditions (italicized) are reported where relevant.

Bolded values are statistically significant.

subset of the cohort, were 36.8%, 33.6%, and 29.7%, respectively. The proportions in the Australian population in 2006 were 48.2%, 29.2%, and 22.5%, respectively. Risk ratios for smoking and colorectal cancer used in the adjustments were 1.18 for ever smokers [Botteri et al., 2008]: for this analysis current and ex-smokers were

combined in both the Wittenoom and referent populations. For leukemia, the RR used was 1.3 for current smokers and 1.0 for past smokers [Kuper et al., 2002]. The adjustments were 1.02 for colorectal cancer and 1.16 for leukemia. SIRs remained significantly elevated for leukemia but not colorectal cancers after adjustment (Table IV). No adjustments were made for either MM or brain neoplasms.

**TABLE IV.** Standardised Incidence Rates (95% CI) Among Males Who First Arrived at Wittenoom Aged <15 Years, Compared With the Male West Australian Population

Cancer	N	SIR1 (95% CI) <sup>a</sup>	SIR2 (95% CI) <sup>a</sup>
All	114	<b>1.70 (1.40–2.05)</b>	<b>2.92 (2.40–3.51)</b>
Mesothelioma	29	<b>44.54 (29.83–63.98)</b>	<b>77.54 (51.93–111.36)</b>
Lung	3	0.68 (0.14–1.99)	1.24 (0.26–3.63)
All excl. MM and lung cancer	84	<b>1.33 (1.06–1.66)</b>	<b>2.04 (1.62–2.53)</b>
Bladder	3	1.81 (0.22–6.52)	3.21 (0.39–11.61)
Brain	5	2.73 (0.89–6.37)	<b>4.13 (1.34–9.63)</b>
Colo-rectal	10	1.23 (0.56–2.34)	<b>2.19 (1.00–4.16)</b>
Leukemia	7	1.21 <sup>b</sup> (0.55–2.29)	2.15 <sup>b</sup> (0.98–4.08)
<i>Leukemia</i>	7	<b>3.77 (1.52–7.77)</b>	<b>4.62 (1.86–9.53)</b>
<i>Leukemia</i>	7	2.27 <sup>b</sup> (0.91–4.67)	<b>2.66<sup>b</sup> (1.07–5.47)</b>
Prostate	12	1.04 (0.54–1.82)	<b>2.48 (1.28–4.33)</b>
Testis	5	1.81 (0.59–4.23)	2.42 (0.79–5.65)
Melanoma	17	1.25 (0.73–2.00)	1.37 (0.80–2.20)

SIR1, Standardised Incidence Ratio using censor method 1; SIR2, Standardised Incidence Ratio using censor method 2; CI, confidence intervals.

<sup>a</sup>All are unadjusted unless otherwise specified.

<sup>b</sup>Adjusted for smoking.

Bolded values are statistically significant.

**Mortality** By the end of 2007, 148 of the males who had lived at Wittenoom as children had died. Compared with the Western Australian male population, former Wittenoom male children had a 50–83% increased risk of all cause mortality (Table V), depending on which censoring method was used. There were 23 deaths from MM among the males with SMRs ranging between 56.5 (95% CI: 35.8–84.8) and 79.0 (95% CI: 50.1–118.6). As with the females there was only one case of lung cancer among the males and mortality from lung cancer was not increased. Mortality from all other cancers, excluding MM and lung cancer, was greater among the former Wittenoom male children than the WA male population using both censoring methods. The most frequent of the non-respiratory cancer deaths were colorectal (n = 6) and brain (n = 3) cancers, leukemia (n = 4), and melanoma (n = 3). Mortality from diseases of the circulatory system and accidents, injuries, and poisonings were increased compared with the WA male population but only when all those lost to follow-up were censored at their date last known to be alive (SMR2; Table V). Males who spent time in Wittenoom as children were also more likely than the WA male population to die of a diseases of the nervous system (Table V). Four nervous system deaths were

**TABLE V.** Standardized Mortality Rates Among Males Who First Arrived at Wittenoom Aged <15 Years, Compared With the Male West Australian Population

Cause of death <sup>c</sup>	N	SMR1 (95% CI) <sup>a</sup>	SMR2 (95% CI) <sup>a</sup>
All causes	148	<b>1.50(1.27–1.76)</b>	<b>1.83(1.55–2.15)</b>
Neoplasms	49	<b>3.08(2.28–4.07)</b>	<b>4.24(3.13–5.60)</b>
<i>Mesothelioma</i>	23	<b>56.52(35.83–84.82)</b>	<b>79.04(50.10–118.60)</b>
<i>Lung cancer</i>	1	0.58(0.01–3.24)	0.81(0.02–4.54)
<i>Neoplasms excl. MM and lung cancer</i>	25	<b>1.87(1.21–2.77)</b>	<b>2.53(1.64–3.74)</b>
Infectious diseases	1	0.44(0.01–2.45)	0.51(0.01–2.84)
Endocrine	2	0.90(0.11–3.27)	1.16(0.14–4.18)
Mental disorders	2	1.32(0.16–4.77)	1.63(0.20–5.87)
Nervous system	7	<b>2.58(1.04–5.32)</b>	<b>3.07(1.23–6.33)</b>
Circulatory system	17	1.53(0.89–2.45)	<b>2.12(1.24–3.40)</b>
		1.38 <sup>b</sup> (0.80–2.21)	<b>2.04<sup>b</sup>(1.20–3.21)</b>
Respiratory system	6	1.55(0.57–3.37)	1.81(0.67–3.95)
<i>Pneumoconiosis</i>	1	9.90(0.25–55.16)	10.53(0.27–58.65)
Digestive system	2	0.77(0.09–2.78)	1.06(0.14–3.84)
Symptoms/signs/ill defined	7	2.05(0.82–4.22)	2.38(0.96–4.44)
Accidents/injuries/poisonings	50	1.34(0.99–1.77)	<b>1.54(1.15–2.04)</b>
<i>Transport accidents</i>	25	1.41(0.91–2.08)	<b>1.57(1.02–2.32)</b>

SMR1, Standardised Mortality Ratio using censor method 1; SMR2, Standardised Mortality Ratio using censor method 2; CI, confidence intervals.

<sup>a</sup>All are unadjusted unless otherwise specified.

<sup>b</sup>Adjusted for smoking.

<sup>c</sup>Selected broad disease ICD chapters. Specific diseases (italicized) are reported where relevant.

Bolded values are statistically significant.

due to complications of epilepsy and three were caused by inflammatory diseases of the central nervous system (CNS).

Axelsson's adjustments were applied to SMRs for circulatory disease for males. Risk ratios for smoking and various circulatory diseases range between 1.5 and 4 and varies with age and consumption [Burns, 2003]. Although the risk decreases after smoking cessation it still may remain elevated for more than a decade after stopping [Burns, 2003]. For the current adjustment calculation, we used a RR for current smokers of 3 and 1.5 for former smokers. After adjustment, SMR2 for circulatory disease remained significant (2.04, 1.20–3.21; Table V).

**Mesothelioma rates** MM mortality and incidence rates followed similar patterns and data are presented for the incidence rates only (Table VI). There was evidence of an exposure–response relationship in that those who had a shorter duration of residence at Wittenoom and a lower cumulative asbestos exposure had a subsequent lower rate of MM. At all levels of exposure, MM rates were higher in former male than female Wittenoom children, although CIs crossed (Table VI). The incidence of MM increased with time since first exposure but there was no consistent trend on MM for age of arrival at Wittenoom (Table VI).

## DISCUSSION

Nearly 2,500 individuals were documented to have first been exposed to asbestos at Wittenoom when they were aged <15 years. After more than 30 years follow-up these “former Wittenoom children” have increased overall mortality and cancer incidence rates compared with the local population, predominantly but not solely due to MM. For females, the increases in mortality and cancer incidence were mostly due to MM, although there is some evidence that ovarian and brain cancers were increased. For males, overall cancer incidence, with and without MM, as well as MM, leukemia, colorectal, brain, and prostate cancer incidence were elevated. Cancer mortality, with and without MM, as well as deaths from circulatory diseases, accidents, and nervous disorders were also elevated. These data suggest that people who were exposed to blue asbestos in childhood have increased risk of death from both ARD and some non-ARDs.

The increased risk of MM has been reported previously in this cohort [Hansen et al., 1993; Reid et al., 2007]. The most recent analyses of the Wittenoom resident's cohort, prior to this study, had a follow-up to 2000 and showed that the MM mortality rate among those first exposed to environmental levels of asbestos when they were <15 years of age was less than half that of those

**TABLE VI.** Malignant Mesothelioma Incidence Rates Per 100,000 Person Years at Risk, by Categories of Asbestos Exposure, Among Former Children of Wittenoom, Calculated to the End of 2009

Characteristic	Female		Male		Total	
	N	Rate <sup>a</sup> (95% CI)	N	Rate <sup>a</sup> (95% CI)	N	Rate <sup>a</sup> (95% CI)
Total	13	28.1 (16.3–48.4)	29	60.4 (42.0–86.9)	42	44.6 (32.9–60.3)
Age of arrival (years)						
<5	7	23.9 (11.4–50.2)	17	60.3 (38.5–94.6)	26	42.8 (29.1–62.9)
5 to 9	5	42.6 (17.7–102)	7	58.9 (28.1–124)	12	50.8 (28.8–89.4)
10 to <15	1	19.0 (2.7–135)	3	65.4 (21.1–202)	4	40.6 (15.2–108)
Year of arrival						
1943–1958	8	41.3 (20.6–82.6)	16	79.7 (48.8–130)	24	60.8 (40.8–90.8)
1959–1966	4	21.1 (7.9–56.3)	11	53.8 (29.8–97.1)	15	38.1 (23.0–63.2)
1966–1985	1	12.6 (1.8–89.2)	2	26.8 (6.7–107)	3	19.5 (6.3–60.3)
Length of stay (years)						
<2	3	12.4 (4.0–38.4)	7	27.5 (13.1–57.8)	10	20.2 (10.8–37.5)
2 to <5	6	43.7 (19.6–97.4)	11	78.5 (43.5–142)	17	61.3 (38.1–98.6)
5 to <10	2	40.2 (10.1–161)	5	102.0 (42.5–245)	7	70.9 (33.8–149)
10–37	2	63.4 (15.9–254)	6	176.8 (79.4–394)	8	122.2 (61.1–244)
Cumexposure (f/ml year)						
<5	3	11.1 (3.6–34.5)	9	33.0 (17.2–63.5)	12	22.2 (12.6–39.0)
5 to <10	2	22.5 (5.6–90.2)	10	95.6 (51.4–178)	12	62.1 (35.3–109)
10–64	7	73.2 (34.9–154)	9	96.8 (50.4–186)	16	84.9 (52.0–139)
Unknown	1	108.9 (15.3–773)	1	103.2 (14.5–733)	2	106.0 (26.5–424)
Time since first exposure						
<30 years	2	6.2 (1.56–24.9)	1	2.93 (0.41–20.8)	3	4.53 (1.46–14.1)
30–39 years	5	57.7 (24.0–139)	8	91.8 (45.9–180)	13	74.8 (43.4–129)
40–49 years	3	64.0 (20.6–199)	14	313.9 (190–531)	17	185.9 (116–299)
50+ years	3	285.5 (92.1–885)	6	705.9 (320–1,600)	9	472.4 (246–908)

CI, confidence interval.

<sup>a</sup>Children lost to follow-up censored at date last known to be alive.

adults with similar (non-occupational) exposures who were first exposed aged >15 years (47 vs. 112 per 100,000 person years, respectively). Between 2000 and 2007, there were a further eight deaths from MM among the former Wittenoom children and the mortality rate was slightly less than previously reported (34 vs. 47 per 100,000 person years).

The reasons for the lower MM rates in those exposed as children are not known. Animal studies have also shown an increased MM incidence rate when rats are inoculated intrapleurally with asbestos at 10 compared with 2 months of age and it was proposed that the reason for the lower risk in the younger animals was due to them having more efficient defense mechanisms [Berry and Wagner, 1976]. This is not necessarily the cases in humans as the immune system is still developing throughout childhood [Branum et al., 2003]. Another possibility for age-related differences in risk is different patterns of fiber deposition and elimination in children compared with adults. Differences in airway geometry and ventilation

between children and adults can affect the pattern and total deposition of inhaled particles [Heyder et al., 1988]. Children have smaller lungs and higher respiratory minute ventilation relative to lung volume than adults and inhale a greater dose of particles per lung surface area than adults [Bennett and Zeman, 1998]. However, deposition models for particles suggest that children have greater deposition in the extra-thoracic and tracheo-bronchial regions and lower deposition in the intra-pulmonary airways compared with adults [Hofmann and Koblinger, 1989]. The deposition pattern may also affect the clearance of fibers, with fibers cleared much faster from the conducting airways than gas-exchanging air spaces [Eastern Research Group, 2003]. The retention of fibers is reliant on the clearance, or elimination, rate. An elimination rate of crocidolite fibers of between 10% and 15% a year has been calculated for occupationally exposed cohorts [Berry et al., 2003] but the elimination rate for children is not known. A greater understanding of age-related differences in asbestos fiber deposition,

elimination, and retention may help to explain the difference in mesothelioma rates between those exposed as either adults or children.

As has been regularly observed in adults both an exposure–response relationship [Hansen et al., 1993; Reid et al., 2007] and an increased risk of MM with time since first exposure [Berry et al., 2012] were observed. This study extended our earlier observations in this age group [Reid et al., 2007] by exploring in more detail the effect of age at first exposure on the risk of MM. Many organ systems undergo prolonged postnatal development during childhood and there may be critical windows of exposure for children's health [Selevan et al., 2000]. Although exposure in childhood seems to confer a lower risk for MM than exposure in adult years it remains possible that exposure at various developmental stages during childhood may affect the risk. In this study, this was not the case and mesothelioma incidence rates were similar for each of the age ranges. Age at first exposure does not seem to affect the risk of developing MM in adults [Doll and Peto, 1985] and understanding when the risk changes between childhood and adulthood exposure requires further investigation.

Males tended to have higher rates of MM than females at all levels of exposure. This pattern has been observed among the adults of the former Wittenoom resident's cohort, where for every level of cumulative asbestos exposure, duration of exposure and time since first exposure men had a higher MM mortality rate than women [Reid et al., 2007]. This difference may be an artifact of how the asbestos exposure measurements were calculated. Although the measures are assigned to each individual they were calculated, for the residents, on period and duration of residence at Wittenoom but not on activity patterns. Men and boys may have conducted more activities outside the home, thus exposing themselves to greater amounts of asbestos. There is no data on activity patterns of males and females during their residency at Wittenoom. The former Wittenoom male children were also more likely to have occupational exposures with about a third of the males ( $n = 9$ ), but none of the females, subsequently working in jobs with potential asbestos exposure. In most [Smith, 2002] but not all [Metintas et al., 1999, 2002] studies men have higher rates of MM than women and it is not known if differences are due to exposure or biology. Men and women also have different rates of survival once disease is established with women having on average higher survival rates than men [Musk et al., 2011]. Again the reason for this is not known but there may be biological differences in both susceptibility to- and progression of the disease.

The estimates of asbestos exposure in the Wittenoom cohorts have been criticized for being underestimates of the true exposure [Rogers and Major, 2002]. However, we

have demonstrated internal validity for these estimates by showing an agreement with lung fiber burdens [de Klerk et al., 1996], while clear dose–response relationships for various ARDs have been documented within the cohort [Armstrong et al., 1988; Hansen et al., 1998; Reid et al., 2007; Musk et al., 2008]. Furthermore, in a review of several studies assessing asbestos exposure and lung cancer risk, Hodgson and Darnton found the Wittenoom exposures comparable to exposures reported from other crocidolite mines, and in addition found the lung cancer risk ( $R_L$ ) similar to that from other studies [Hodgson and Darnton, 2000]. We accept that there are uncertainties in the exposure estimates, given the paucity of the dust measurements collected at Wittenoom, but recognizing their internal validity are confident of using them as a measure of quantified asbestos exposure. For this study, cumulative exposure assigned to each case was based on environmental levels of asbestos. Whether this was the main exposure route is uncertain. Some of the males had subsequent occupational exposure (see above) while the majority of the former Wittenoom children (35 of the 40 with known parentage) lived with an asbestos worker. Despite this, an exposure–response relationship based on assigned environmental levels was observed.

There was no increased lung cancer incidence or mortality in either the men or the women in these analyses. We have previously shown increased lung cancer incidence and mortality in both the Wittenoom workers' [Musk et al., 2008] and residents' [Reid et al., 2008a,b] cohorts but this is the first assessment of those whose exposure to environmental levels of crocidolite in Wittenoom was during their childhood. There are no data on the risk of lung cancer due to childhood exposures. Increased lung cancers have been observed in inhabitants of villages situated near natural outcrops of asbestos in both China [Luo et al., 2003] and Greece [Sichletidis et al., 2006] but, unlike the Wittenoom cohort, the villagers in these studies had had a lifetime of exposure. Other studies have not found an association between environmental exposures to asbestos and lung cancer [Hammond et al., 1979; Camus et al., 1998; Magnani and Leporati, 1998]. There was an increased incidence of lung cancer in women who had worked and/or lived in Wittenoom but elevated SIRs were greater for the workers than the residents.

Both smoking and asbestos exposure are risks for lung cancer and an interaction between the two is evident, although the degree of that interaction is uncertain [Reid et al., 2006]. Most data on smoking and asbestos derive from cohorts where the two occur simultaneously. Smoking rates in the former Wittenoom children's cohort are lower than in the older cohorts and, for most, any smoking would have started after their asbestos exposure and, therefore, the approximately multiplicative effect of

asbestos and smoking on lung cancer rates could be much lower. The latency period in this study, at least 24 and up to nearly 70 years, would be sufficient for the development of lung cancer but as most lung cancers are diagnosed after the age of 50 years [O'Rourke et al., 1987] the cohort may still be too young to observe differences.

For the women there was an increase in all cause mortality and both cancer incidence and mortality. These increases were mostly due to increased incidence and mortality from MM. However, deaths and incidence from all cancers were still elevated after MM was excluded, albeit only when using the second censoring method, which overestimates the SMRs and SIRs. Of the specific cancers, both ovarian and brain cancer incidence were increased. Both were based on a small number of cases and were only significant in the overestimated SIR. Ovarian cancer SIR remained significant after adjusting for smoking; there was no adjustment for brain cancer. The relationship between asbestos exposure and ovarian cancer remains controversial [Reid et al., 2011]. We had previously shown that when all Wittenoom women (workers and residents) were analyzed together there was no increase in the incidence of ovarian cancer compared with the Western Australian population [Reid et al., 2008b, 2009]. This study suggests early life exposure may increase the risk of ovarian cancer and this may become clearer as the cohort ages as the incidence of ovarian cancer increases with age after 40 years until about 75 years [Runnebaum and Stickeler, 2001].

Brain neoplasms were elevated for both females and males. A few studies have observed an association between occupational asbestos exposures and brain tumours [Bunderson-Schelvan et al., 2011]. As far as we are aware this is the first study to observe an association between non-occupational exposures and brain tumours. For both females and males, the number of cases was small and significance was only observed in the overestimated SIR. However, unlike other cancers it was observed in both sexes. There is still a poor understanding of environmental carcinogens and brain tumours [Wrensch et al., 2002].

For males both incidence and mortality from all cancers were significantly increased compared with the WA population even when asbestos-related respiratory cancers (MM and lung cancer) were excluded. Individual cancers that were significantly elevated in the males included leukemia (for both censoring dates), and prostate, brain, and colorectal cancers (for SIR2 only). All of these have previously been associated with asbestos exposure [Becker et al., 2001; Koskinen et al., 2003; Aliyu et al., 2005; Bunderson-Schelvan et al., 2011] but definitive cause and effect relationships have not been established. There are very few existing data for an association between these cancers and non-occupational exposure to asbestos and no data on predominant childhood exposure. Although in

some cases the relationships remained significant after adjusting, indirectly, for smoking other lifestyle factors could not be accounted for. Furthermore, as many of these boys grew up in mining families they may themselves have stayed in this industry and been exposed to other occupational carcinogens. There were insufficient numbers of any of these cancers to determine if there were exposure-response relationships, which would help to establish causality.

The male former Wittenoom children were also more likely than their peers to have increased mortality from non-cancer causes. Circulatory disease, accidents, and nervous system disorders were all significantly elevated, although apart from nervous system disorders these were only significant when overestimating the SMRs. Deaths from nervous system disorders included complications associated with epilepsy and inflammatory disorders of the CNS, predominantly meningitis. All the inflammatory disorders, and one of the epilepsy deaths, occurred in early childhood while the individuals were still living in Wittenoom. Although Wittenoom had a hospital the town was very remote and, therefore, the increased mortality rate may be due to the lack of adequate medical facilities to deal with these diseases.

Increased mortality from circulatory or coronary heart disease has been reported in occupationally asbestos-exposed cohorts [Sjogren, 2001]. In ex-Wittenoom workers, an association between pleuropulmonary abnormalities and cardiovascular mortality has also been observed [de Klerk et al., 1993]. There have been no reports of an association between circulatory disease and environmental asbestos exposure. In this study, the increased SMR for circulatory disease was only observed in males and there was no evidence of an exposure-response relationship (data not shown). Although SMR2 remained significant after adjusting for smoking, other behavioral or lifestyle factors may have contributed to this finding. These may relate particularly to the ongoing residence of the former Wittenoom children in remote and rural areas of Western Australia where death rates are higher than in major urban centres [AIHW, 2006].

Compared with the overall Western Australian population the former Wittenoom children are still more likely to live in rural or regional areas of the state. While 74% of the adult WA population reside in Perth, the main city, addresses for over 1,800 (nearly 75%) of the former Wittenoom children known to be alive since the year 2000 indicate that only 62% lived in Perth. Nearly, 15% live in the more remote northern towns of WA compared to 6.7% of the WA adult population. Compared with major cities, death rates in regional areas of Australia are 10–15% higher for males and 5–10% higher for females [AIHW, 2006]. One of the major causes of excess deaths in males living in regional areas is cardiovascular disease [AIHW,

2010]. There is also increased death from injury and poisonings as well as motor vehicle accidents in men living outside major cities [AIHW, 2010] and this may explain the increased mortality from accidents, particularly traffic accidents, in the male former Wittenoom children. Some of the causes of increased mortality in regional areas include greater socioeconomic disadvantage, health risk behaviors and barriers to accessing health services [AIHW, 2010].

Living in regional areas, however, may not explain the increased incidence of cancers in the males who had lived in Wittenoom. Indeed, men living outside of the major cities in Australia have a significantly lower incidence rate of prostate, lymphoma, stomach, kidney, lung, and colorectal cancer [AIHW, 2010]. Therefore, the SIRs for prostate and colorectal cancer in this cohort may actually have been higher if there was a direct comparison based on place of residence.

Although childhood exposure seems to be associated with lower risk of developing MM than exposure in adults, children are considered to be more susceptible than adults to the effects of environmental exposures and similar exposures at different developmental periods may cause a different spectrum of disease [Selevan et al., 2000]. There has been very little previous research, apart from the development of MM, published on the health outcomes of exposure to asbestos predominantly in childhood. A recent study investigated respiratory symptoms in children and young adults (age range 10–29 years old) who had lived in Libby, Montana, as children when a vermiculite mine (contaminated with amphibole asbestos) closed in 1990 [Vinikoor et al., 2010]. In this study various symptoms, such as cough, cough with bloody phlegm and dyspnoea on exertion were associated with vermiculite handling activities [Vinikoor et al., 2010]. That study has provided important data on potential health consequences of childhood exposure to asbestos. However, respiratory symptoms were self-reported and exposure was based on reported activities [Vinikoor et al., 2010]. The strengths of the current study were documented quantitative asbestos exposure measurements as well as long follow-up and good ascertainment of causes of death and cancer incidence.

The current study is the first to report on cancer incidence and mortality in adults exposed to asbestos as children. This is a unique cohort of nearly 2,500 children with quantitative measures of asbestos exposure, exposure to a known asbestos type (crocidolite) and good follow-up. Most of this cohort has now reached an age when chronic adult diseases are becoming more prevalent and potential associations between adult disease and childhood exposures can be explored. We observed an increase in overall cancer incidence and mortality as well as increased mortality for some specific non-cancer diseases. This was

more evident in the males than females. Some of these increases, particularly non-cancer mortality, may have been due to lifestyle and behavioral characteristics of the cohort and be influenced by where they currently live. However, a potential affect of early life asbestos exposure on cancer incidence cannot be discarded. The cohort will continue to be followed to investigate disease morbidity as well as continuing mortality and will provide important information on the long-term implications of exposure to asbestos in childhood.

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