Gynecologic and Breast Cancers in Women After Exposure to Blue Asbestos at Wittenoom

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Abstract

Introduction: **Animal studies have suggested an association between asbestos and ovarian cancer, and asbestos fibers have been detected in human ovaries. Sexual intercourse may introduce asbestos fibers into the vagina and to the cervix and ovaries. Occupational cohorts have reported excess mortality from reproductive cancers, but exposure-response relationships are inconsistent. We examine the incidence and exposure-response relationships of these cancers among 2,968 women and girls exposed to blue asbestos at Wittenoom, Western Australia.**

Methods: **2,552 women were residents of the town and 416 worked for the asbestos company (Australian Blue Asbestos). Standardized incidence ratios compared the Wittenoom women with the Western Australian population. A nested case-control design and conditional logistic regression examined exposure-response relationships.**

Results: **Ovarian (standardized incidence ratio, 1.27), cervical (standardized incidence ratio, 1.44), and uterine cancer (standardized incidence ratio, 1.23) increased but not statistically significantly among the Wittenoom women compared with the Western Australian population. Among the Australian Blue Asbestos workers, cervical cancer was twice that of the Western Australian population (standardized incidence ratio, 2.38), but ovarian cancer was less (standardized incidence ratio, 0.65). Women who first arrived at Wittenoom aged ≥40 years had an odds ratio of 13.9 (95% confidence interval, 2.2-90.2) for cervical cancer compared with those aged <15 years at first arrival. Women who lived with or washed the clothes of an Australian Blue Asbestos worker did not have an increased risk for any of the gynecologic or breast cancers.**

Discussion: **There is no consistent evidence of an increased risk for gynecologic and breast cancers among the women from Wittenoom. Ovarian cancers and peritoneal mesotheliomas were not misclassified in this cohort.** (Cancer Epidemiol Biomarkers Prev 2009;18(1):140–7)

Introduction

Mortality studies among women exposed occupationally to various types of asbestos have reported increased risks for ovarian (1-5) and cervical (2, 6) cancers. Excess mortality has also been reported for uterine cancer, wherein corpus and cervix were not differentiated (7-9). The number of cases of each cancer was small in most cohorts and exposure-response relationships were generally not shown. Examination of pathologic material, where undertaken, found that some of the ovarian cancers were malignant mesotheliomas of the peritoneum that had been misdiagnosed (1, 5). Excess breast cancer mortality has also been reported among female asbestos textile factory workers with severe exposure lasting >2 years (10). No studies have examined incidence of these cancers among women with asbestos exposure.

Asbestos fibers have been found in the ovaries of women whose household contacts worked with asbestos and among Norwegian paper and pulp workers (11, 12). The mechanism of transportation of asbestos fibers to the ovary is not clearly understood. One hypothesis suggests passive transfer of fibers via the vaginal canal (11) because the transfer of pathogens from the lower to the upper genital tract has been shown to occur this way (13). This route may also explain any association between asbestos exposure and cancer of the cervix and uterus. To further support this argument, tubal ligation has been found to reduce the risk for ovarian cancer in several studies (14), including a Danish population based study that followed up 65,000 sterilized women. Compared with the Danish population, tubally sterilized women have a lower risk for ovarian cancer [standardized incidence ratio, 0.82; 95% confidence interval (95% CI), 0.6-1.0]. There was no effect on cervical cancer in this study (15). Alternatively, fibers could penetrate to the ovary and other genital organs through the mesothelium.

Whatever their method of distribution, once the fibers have reached the specific organ, disease initiation may occur in the same way as for the other asbestos-related diseases. These include mechanical irritation from the fiber leading to scarring or cancer (16) and ''frustrated phagocytosis'' whereby the macrophage is unable to fully digest the whole asbestos fiber because of its long length resulting in an incessant production of hydroxyl radicals and reactive oxygen species, which induce cell

Received 8/12/08; revised 10/8/08; accepted 10/14/08.

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doi:10.1158/1055-9965.EPI-08-0746

injury (17, 18). Generation of hydroxyl radicals may be particularly relevant for asbestos carcinogenesis because these molecules can modify and damage cellular DNA. Inadequate repair of this oxidative damage may lead to mutations or DNA strand breaks (19, 20).

The aims of this study were (*a*) to determine if there were excess risks for cancer of the ovary, cervix, uterine corpus, and breast among 3,000 women and girls exposed to blue asbestos at Wittenoom; and (*b*) to examine the potential for disease misclassification by reviewing pathologic material on ovarian, colon, and peritoneal cancers.

Materials and Methods

Women and Girls at Wittenoom. Almost 3,000 women and girls were documented to have lived and worked at the crocidolite (blue asbestos) mining and milling town of Wittenoom in remote Western Australia over the period of 1943 to 1992. Forty-six per cent were <15 y when they first arrived (21). The Australian Blue Asbestos company operated the principal leases and mined and milled crocidolite between 1943 and 1966 when the industry closed for economic reasons. Four hundred and sixteen women worked for Australian Blue Asbestos, mostly in the company offices, hotel, and shop, whereas the remaining 2,552 women were wives and daughters of Australian Blue Asbestos workers or were there as government service workers, teachers, and nurses. Tailings from the mine site, rich in crocidolite fibers, were distributed around the town in an attempt to contain the red dust, and this process did not cease until 1966.

The Wittenoom workers' and residents' cohorts (22, 23) and the women's cohort (21) have been described elsewhere. Employment records provided by Australian Blue Asbestos identified 416 women (6% of the workforce) and their dates and places of employment. For the residents' cohort, the following public records were searched (with the percentage of people they identified in parentheses): state primary school records (22%), general practitioner and Wittenoom hospital records (20%), the state Electoral Roll for the Pilbara region (12%), questionnaires sent to former Australian Blue Asbestos workers (14%), and participants in a cancer prevention program (18%; refs. 24, 25). Table 1 shows in detail the establishment of the residents' cohort. Briefly, 5,097 residents who had lived at Wittenoom but who did not work for the asbestos company were identified (23, 26, 27). The residents' cohort was considered complete when it corresponded with the population of Wittenoom recorded at various population census dates (23).

All former residents traced to an address in Australia (n = 3,244, 64%) were sent a questionnaire in 1993, except 641 (13%), who were participating in the cancer prevention program and on whom the information was already available (24, 25). The questionnaire ascertained their asbestos exposure experience including place and dates of residence at Wittenoom, whether they lived with and/or washed the clothes of an Australian Blue Asbestos worker, as well as demographic characteristics. Upon receipt of questionnaires, 438 were deleted from the cohort because they denied living at Wittenoom or there were no details on date of birth or duration of residence at Wittenoom. As of the end of 1993, 2,814 (61%) had returned a questionnaire or were participating in the cancer prevention program, 460 (10%) were dead, 51 (1%) had permanently departed from Australia, 784 (17%) had not returned a questionnaire, and 549 (11%) were not traced beyond the date they left Wittenoom (Table 1).

Table 1. Establishment of Wittenoom resident cohort (23, 26-28)

5,097 Residents identified from 18,553 records collected
3,885 (76.2%) Traced to an address in Australia between 1991 and 1993
3,244 (63.6%) Sent a questionnaire in 1993
641 (12.6%) Participating in cancer prevention program (not sent a questionnaire as information already obtained)
460 (9.0%) Dead
51 (1%) Permanently departed overseas
701 (13.8%) Untraced
Following receipt of questionnaires
438 Deleted from cohort
209 (47.7%) Denied living at Wittenoom
22 (5%) Lived at Wittenoom <1 mo
152 (34.7%) No details on date of birth or period of residence
55 (12.6%) Duplicate records
4,659 Cohort total and status as of 1993
2,173 (46.6%) Returned a questionnaire
641 (13.8%) Participating in cancer prevention program
460 (9.9%) Dead
51 (1.1%) Permanently departed overseas
401 (8.6%) Questionnaire not returned
383 (8.2%) Questionnaire returned to sender
549 (11.8%) Whereabouts unknown

People who were related to an Australian Blue Asbestos worker but were dead, untraced, or did not respond were assumed to have stayed at the same place and for the same period as the worker. For those unrelated to an Australian Blue Asbestos worker, dates of residence were assumed the same as other family members providing that at least one family member had completed a questionnaire providing this information. For all other residents, dates of residence were assumed identical to those listed on the public records used to identify the residents. If the wife of an Australian Blue Asbestos worker who was known to have lived with that worker at Wittenoom remained untraced, it was assumed that she washed his clothes.

The residents' cohort has been continually updated since 1993, and this reflects any difference in numbers shown here from previous reports (23, 26-28). As of 2000, there were 2,160 male and 2,608 female former residents of Wittenoom (29).

Asbestos Exposure Measurements. Several surveys of dust counts were undertaken by the Mines Department of Western Australia between 1948 and 1958 using a konimeter. In 1966, airborne respirable fibers >5 μm in length were measured in a survey using a Casella long-running thermal precipitator at the mine site and in the town (22). Seven more surveys to gauge environmental levels using personal and fixed positional monitors were undertaken in and around the town from 1973 to 1992, when the town was officially closed (26). Based on the results from these surveys, former residents were assigned an exposure intensity of 1.0 fibers per milliliter

(f/mL) of air between 1943 and 1957, when a cleaner mill was built, and 0.5 f/mL for the period 1958 to 1966, when the mine and mill closed. Assigned values ranged from 0.5 f/mL in 1966, reducing to 0.010 f/mL in 1992 based on interpolation from surveys using personal monitors. Cumulative exposure (f/mL-y) for each resident was calculated by summing the product of fiber concentration for each year and length of time spent at Wittenoom over the years of residence at Wittenoom, and adjusted by a factor of 4.2 [= (24 * 7) / (8 * 5)] to allow for environmental exposure occurring over 24 h/d rather than the 8-h working shift, which was used to determine the fiber levels (26). Cumulative exposure was calculated for the former Australian Blue Asbestos workers by summing the product of estimated fiber concentration and length of time spent in the job, for all their jobs (22). An additional amount was added to reflect 16 more hours of daily residential exposure and a 2-d weekend.

Follow-Up and Case Ascertainment. Follow-up of the women from Wittenoom and case ascertainment have been previously described (21). All women not known to be dead and not participating in the cancer prevention program (24, 25) were searched for in the Marriage Register of Western Australia from their date last known to be alive to ascertain any possible change of name. In addition, birth, death, and marriage certificates of spouse or offspring were also sought in an attempt to obtain the wife or mothers' date of birth and maiden name. Two hundred and thirty-five women (7% of those previously lost to follow-up) were traced by this process. Fifty-six women were excluded from the data set because they were resident at Wittenoom for <1 mo or because of insufficient identifying information. The final cohort consisted of 2,968 women (416 former Australian Blue Asbestos workers and 2,552 former residents). At the end of 2004, 556 (19%) were dead, 1,762 (59%) were alive, and 650 (22%) were lost to follow-up.

Incident gynecologic and breast cancers were obtained from the Western Australian Cancer Registry for the period of 1982 to 2006. Cancers diagnosed between 1960 and 1982 were obtained by manually searching printed computer records of all cancer registrations in Western Australia, as well as hospital admission records at all public hospitals in Australia. Pathologists throughout Australia and state and territory cancer registries were sent a list of names of all cohort members and asked to search their records. The completeness of cancer registrations for cancers diagnosed before 1982 is not known; therefore, cancers before 1982 have not been included in the standardized incidence ratios. Incident cancers for women not resident in Western Australia were obtained from every State and Territory Cancer Registry via the National Cancer Statistics Clearing House to the end of 2002, except the state of Victoria, which had data available only to the end of 1997. Cancers were defined using the International Classification of Diseases for Oncology, Second Edition (30).

Verification of Diagnosis. The Western Australian Cancer Registry was searched for pathology reports on all women from Wittenoom identified as being diagnosed with or dying from cancer of the ovary and colon and peritoneal mesothelioma. Forty reports were reviewed by a pathologist (A. Segal). Histologic sections were not reviewed in cases described as conventional adenocarcinomas arising within the colon (n = 25). Where the report stated ovarian tumor, peritoneal fluid, or colonic resection with unusual features, histologic sections were retrieved and reviewed and additional stains were done as necessary. Sections were reviewed in 15 cases, 9 ovarian tumors, 2 peritoneal biopsies, 2 peritoneal fluids, 1 case of peritoneal mesothelioma, and 1 adenocarcinoma of the colon extending into ovary.

Statistical Analysis. Standardized incidence ratios were calculated as the ratio of observed to expected cancers. Expected cancers were calculated in 5-y periods using age, period, and cause-specific cancer incidence rates provided by the Western Australian Cancer Registry for the period of 1982 to 2006. Expected cancers were calculated two ways to derive minimum and maximum estimates because of lost to follow-up among these women and the almost complete ascertainment of cancers in Western Australia (22). To create the minimum estimate, all women not diagnosed with a cancer and not known to be dead or to have migrated were assumed cancer-free at the end of 2006, or if they were residents of another Australian state or territory to the end of 2002 (except the state of Victoria to the end of 1997). This method overestimates person-years at risk. To create the maximum estimate all women not known to be diagnosed with a cancer, dead, or migrated were assumed cancer-free at their date last known to be alive. This method underestimates person-years at risk. Both methods censored women at the age of 85 y if they were not known to have a cancer or to have died before reaching that age. Ninety-five percent confidence intervals were calculated assuming a Poisson distribution of the observed cases.

A nested case-control design was used to examine exposure-response relationships between asbestos exposure and cancer incidence with all available matching controls who were born in the same 5-y period and who were at risk at the time the case was diagnosed. Conditional logistic regression was done to investigate the association between asbestos exposure and cancer incidence. All gynecologic and breast cancers diagnosed between 1960 and 2006 were included in this analysis, which was undertaken using Stata 9.0 (31).

Results

Pathologic Review. Among the nine ovarian tumors, the original diagnosis of ovarian serous carcinoma was confirmed in five cases, all of which showed negative staining for the mesothelial marker calretinin. Of the remaining four cases originally diagnosed as ovarian tumor, one showed serosal involvement of the colon by a serous carcinoma of ovarian origin, one was confirmed as a borderline ovarian mucinous tumor, one was a bilateral ovarian borderline serous tumor, and one was a malignant Brenner tumor. The two peritoneal biopsy specimens showed features of adenocarcinoma, consistent with an ovarian primary. One other case showed extension of a primary cecal adenocarcinoma into adherent ovarian tissue. In the remaining three cases, two cases were of peritoneal fluid only, both showing metastatic adenocarcinoma that could not be further

Table 2. Characteristics of cancer cases and noncases among women from Wittenoom for all cancers diagnosed between 1960 and 2006

ICDO-2 code	Ovarian cancer C560-C569	Cervical cancer C530-C539	Uterine cancer C540-C549	Breast cancer C500-C509	Noncases
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Year of arrival at Wittenoom					
1940s	0	0	2 (14)	6 (6)	109 (4)
1950s	7 (44)	8 (42)	7 (50)	39 (41)	1,030 (36)
1960s	8 (50)	10 (53)	4 (29)	42 (44)	1,257 (45)
1970s	1 (6)	1 (5)	1 (7)	8 (8)	402 (14)
Unknown	0	0	0	1 (1)	25 (1)
Age of arrival at Wittenoom (y)					
<15	3 (19)	2 (11)	2 (14)	25 (26)	1,190 (42)
15 to <40	4 (25)	10 (53)	11 (79)	61 (64)	1,329 (47)
≥40	9 (56)	7 (37)	1 (7)	9 (9)	269 (10)
Unknown	0	0	0	1 (1)	35 (1)
Duration of exposure (y)					
<1	11 (69)	12 (63)	9 (64)	45 (47)	1,261 (45)
1 to <3	3 (19)	2 (11)	4 (29)	20 (21)	752 (27)
3 to <5	1 (6)	2 (11)	1 (7)	18 (19)	430 (15)
≥5	1 (6)	3 (16)	0	13 (14)	350 (12)
Unknown	0	0	0	0	30 (1)
Cumulative exposure (f/mL-y)					
0-9.9	15 (94)	16 (84)	12 (86)	75 (78)	2,345 (83)
10-19.9	1 (6)	3 (16)	2 (14)	16 (17)	289 (10)
20-29.9	0	0	0	2 (2)	96 (3)
30.0-39.9	0	0	0	3 (3)	36 (1)
40+	0	0	0	0	26 (1)
Unknown	0	0	0	0	31 (1)
Cohabit with asbestos worker (residents only)					
Yes	7 (54)	7 (54)	10 (83)	54 (68)	1,559 (64)
No	6 (46)	6 (46)	2 (17)	25 (32)	823 (34)
Unknown	0	0	0	0	52 (2)
Wash clothes of asbestos worker (residents only)					
Yes	3 (23)	6 (46)	4 (33)	25 (32)	528 (22)
No	5 (38)	5 (38)	4 (42)	33 (42)	1,242 (51)
Unknown	5 (38)	2 (15)	3 (25)	21 (27)	664 (27)
Former ABA worker	3 (19)	6 (32)	2 (14)	16 (17)	389 (14)
Total	16	19	14	96	2,823

Abbreviations: ICDO-2, International Classification of Diseases for Oncology, Second Edition; ABA, Australian Blue Asbestos.

typed. There was one case of mesothelioma in an abdominal wall biopsy, confirmed by immunohistochemistry and electron microscopy; in this case, it was difficult to determine whether the tumor was arising in the pleural or peritoneal cavity. In short, none of the specimens had been misclassified and the original diagnosis was confirmed in all instances. The borderline ovarian tumors were included as ovarian cancers in the statistical analysis.

Cancer Incidence. There were 145 incident cases of breast or gynecologic cancer among the 2,968 Wittenoom women between 1960 and 2006 (Table 2). There was no difference between cases and noncases in terms of decade of arrival at Wittenoom, but 56% of subsequent ovarian cancer cases and 37% of cervical cancer cases were 40 years or older when they first arrived compared with 10% of noncancer cases. Duration of residence at Wittenoom differed between women with >60% of ovarian, cervical, and uterine cases staying for ≤1 year compared with 47% of breast cancer cases or 45% of noncases. Most women had an estimated cumulative asbestos exposure of <10 f/mL-y. Of those women who were former residents, 83% of uterine, 54% of ovarian, and cervical and 68% of breast cancer cases compared with 64% of noncases were known to have lived with an Australian Blue Asbestos worker. Forty-six percent of cervical cancer cases among former residents reported washing the clothes of an Australian Blue Asbestos worker.

Among all Wittenoom women and the former residents, the incidence of gynecologic cancers, but not breast cancer, was slightly higher than that of the Western Australian female population, irrespective of which censoring method used (Table 3). However, none of these findings were significantly different from the Western Australian female population rates. The incidence of breast cancer was similar to that observed in the Western Australian female population.

Among former Australian Blue Asbestos workers the incidence of ovarian cancer was less than half of that of the Western Australian female population. The incidence of cervical cancer was between 85% and 240% greater than that of the Western Australian population, but this increase was not statistically significant and was based on only three cases. The incidence of uterine and breast cancers among former Australian Blue Asbestos worker was similar to that of the Western Australian population.

Exposure-response relationships between characteristics of asbestos exposure and the four sites of incident cancer are shown in Table 4. For all sites, the risk

decreased with categories of time since first exposure. Those women who had ≥40 years time since first exposure had a statistically significant lower risk for all cancer sites, except uterine cancer, than those who had <20 years time since first exposure.

The risk for cervical cancer increased 2-fold among those with the age of 15 to 40 years compared with those with the age of <15 years when first exposed to asbestos, but this increase was not statistically significant. However, women aged ≥40 years at first exposure had a statistically significant 14-fold risk for cervical cancer ($P < 0.01$) compared with those aged <15 years when first exposed to asbestos. Similarly, among women first exposed to asbestos aged 40 years or older, the risk for ovarian cancer was increased, but not statistically significantly. There was a >2-fold increased risk for cervical cancer among women who were former Australian Blue Asbestos workers compared with those who were former residents and a slight increase (30%) among those who reported washing the clothes of an Australian Blue Asbestos asbestos worker, but neither of these increases was statistically significant. There was an inverse relationship with intensity of exposure and cervical cancer risk, with the risk being 70% lower among those who had an intensity of ≥2 f/mL compared with those with an intensity of <2 f/mL, (Table 3). Except time since first exposure, ovarian, uterine, and breast cancer were not associated with any other measure of asbestos exposure.

Discussion

In this study the incidence of gynecologic cancer among the former Wittenoom women and girls has tended to be higher than among those in the Western Australian female population. In particular, cancer of the cervix was two times greater among the former Australian Blue Asbestos workers than among the Western Australian female population. However, these excesses were not statistically significant. None of the ovarian, colon, or peritoneal cancer specimens available for examination had been misclassified, and the original diagnosis was confirmed in all instances. Examination of exposure-response relationships showed that the risk for ovarian, cervical, and breast cancer were inversely related to time since first exposure.

Excess mortality from ovarian cancer has been reported in earlier studies on women occupationally exposed to asbestos, although exposure-response relationships have been inconsistent. Two cohort studies on World War II gas mask workers in England exposed to crocidolite showed excess mortality from ovarian cancer (1, 2). The excess was greatest among those heavily exposed (standardised mortality ratio, 1,481; $P < 0.001$; ref. 1). Another cohort of gas mask workers exposed to chrysotile reported non-significant excesses of ovarian cancer mortality (2). Studies on women exposed to asbestos in textile factories or asbestos cement manufacturing reported a statistically significant excess mortality from ovarian cancer but no consistent relationship with asbestos exposure (3-5, 10). Female Australian Blue Asbestos workers at Wittenoom mostly worked in the company offices, shop, and hotel. Their occupational exposure was unlikely to have been as high as that reported for women in the earlier cohorts, which may explain why no excess risk for ovarian cancer was observed.

Mesothelioma has until relatively recently been difficult to diagnose, and it was particularly difficult to distinguish between peritoneal mesothelioma and ovarian serous carcinoma (32). Peritoneal mesotheliomas have also been reported in several of the studies that reported excess mortality from ovarian cancer. Among East London factory workers, a review of pathology showed that one peritoneal mesothelioma had been misclassified as an ovarian carcinoma (5). Misclassification of peritoneal mesotheliomas as ovarian cancers in these studies with so few cases of ovarian cancer would overestimate any reported effect of asbestos exposure. Possible misclassification of peritoneal mesotheliomas as ovarian cancers may explain why these earlier studies reported excess mortality from ovarian cancer. In this present study, we reviewed all pathology specimens of ovarian and colon cancer and peritoneal mesothelioma and failed to find any misclassification. If misclassification of peritoneal mesothelioma as ovarian cancers

Table 3. Observed cases and standardized incidence ratios (95% CI) for gynecologic and breast cancers in Wittenoom women, 1982 to 2006

Cancer incidence	Ovarian cancer	Cervical cancer	Uterine cancer	Breast cancer
ICDO-2 code	C560-C569	C530-C539	C540-C549	C500-C509
All women				
Observed	11	13	13	88
SIR 1* (95% CI)	1.05 (0.43-1.67)	1.21 (0.55-1.86)	1.01 (0.46-1.56)	0.90 (0.73-1.10)
SIR 2† (95% CI)	1.27 (0.52-2.02)	1.44 (0.66-2.22)	1.23 (0.56-1.90)	1.10 (0.87-1.33)
ABA workers				
Observed	1	3	2	14
SIR 1* (95% CI)	0.49 (0.01-2.74)	1.85 (0.38-5.41)	0.79 (0.10-2.84)	0.82 (0.39-1.25)
SIR 2† (95% CI)	0.65 (0.02-3.64)	2.38 (0.49-6.96)	1.04 (0.13-3.74)	1.07 (0.51-1.62)
Residents				
Observed	10	10	11	74
SIR 1* (95% CI)	1.18 (0.45-1.91)	1.10 (0.42-1.78)	1.07 (0.44-1.70)	0.92 (0.71-1.13)
SIR 2† (95% CI)	1.40 (0.53-2.28)	1.28 (0.49-2.08)	1.27 (0.52-2.03)	1.11 (0.86-1.36)

Abbreviation: SIR, standardized incidence ratio.
*Minimum estimate censored at the earliest of date of diagnosis, date of death, date at the age of 85 y, or end date of State Cancer Registry follow-up.
†Maximum estimate censored at the earliest of date of diagnosis, date of death, date at the age of 85 y, or date last known to be alive.

Table 4. Characteristics of asbestos exposure and cancer incidence, 1960 to 2006, among the former Wittenoom women

Time since first exposure (y)	<20	20 to <30	30 to <40	40+ y
Ovarian cancer	1.00	0.12 (0.02-0.67)*	0.22 (0.06-0.77)*	0.02 (0.01-0.10)†
Cervical cancer	1.00	0.44 (0.15-1.26)	0.07 (0.02-0.27)†	0.01 (0.00-0.06)†
Uterine cancer	1.00	0.32 (0.02-5.08)	0.68 (0.08-5.84)	0.24 (0.03-1.99)
Breast cancer	1.00	0.86 (0.41-1.88)	0.56 (0.27-1.16)	0.10 (0.04-0.21)†
Intensity of exposure	<2 f/mL	2+ f/mL		
Ovarian cancer	1.00	0.66 (0.24-1.81)		
Cervical cancer	1.00	0.29 (0.12-0.72)†		
Uterine cancer	1.00	2.43 (0.54-10.9)		
Breast cancer	1.00	0.93 (0.60-1.45)		
Year of arrival	1940/50s	1960s	1970/80s	
Ovarian cancer	1.00	1.84 (0.66-5.13)	1.43 (0.17-11.9)	
Cervical cancer	1.00	1.61 (0.63-4.14)	0.84 (0.10-6.83)	
Uterine cancer	1.00	0.68 (0.21-2.21)	1.09 (0.14-8.69)	
Breast cancer	1.00	1.22 (0.79-1.88)	1.15 (0.51-2.55)	
Age of first exposure	<15	15-40	40+ y	
Ovarian cancer	1.00	0.27 (0.05-1.41)	1.90 (0.35-10.5)	
Cervical cancer	1.00	2.53 (0.53-12.1)	13.9 (2.2-90.2)†	
Uterine cancer	1.00	0.40 (0.07-2.14)	0.11 (0.01-1.44)	
Breast Cancer	1.00	0.49 (0.29-0.83)	0.24 (0.10-0.59)	
Duration of exposure	<1 y	1 to <3 y	3+ y	
Ovarian cancer	1.00	1.46 (0.13-1.66)	0.27 (0.06-1.20)	
Cervical cancer	1.00	0.26 (0.06-1.17)	0.61 (0.21-1.73)	
Uterine cancer	1.00	0.75 (0.23-2.42)	0.17 (0.02-1.33)	
Breast cancer	1.00	0.79 (0.46-1.34)	1.15 (0.72-1.84)	
Live with asbestos worker‡	No	Yes		
Ovarian cancer	1.00	0.38 (0.13-1.15)		
Cervical cancer	1.00	0.39 (1.13-1.17)		
Uterine cancer	1.00	1.55 (0.34-7.08)		
Breast cancer	1.00	0.77 (0.48-1.27)		
Wash clothes‡	No	Yes	Unknown	
Ovarian cancer	1.00	0.40 (0.09-1.75)	1.30 (0.37-4.57)	
Cervical cancer	1.00	1.28 (0.37-4.41)	0.72 (0.14-3.76)	
Uterine cancer	1.00	0.43 (0.11-1.62)	0.73 (0.17-3.06)	
Breast cancer	1.00	0.66 (0.39-1.14)	1.01 (0.58-1.77)	
Former ABA worker	No	Yes		
Ovarian cancer	1.00	1.01 (0.29-3.55)		
Cervical cancer	1.00	2.30 (0.87-6.11)		
Uterine cancer	1.00	0.64 (0.14-2.87)		
Breast cancer	1.00	0.86 (0.49-1.50)		

NOTE: Nested case control, cases, and noncases matched on age. Odds ratio (95% CI).
*$P < 0.05$.
†$P < 0.01$.
‡Residents only.

occurred in those earlier studies that reported excess mortality from ovarian cancer, our not finding any misclassification of peritoneal mesotheliomas may contribute to why we also failed to find any excess risk for ovarian cancer in this cohort.

Experimental studies have shown that injection of asbestos fibers (tremolite) into the peritoneal cavity produced epithelial changes in the ovaries of guinea pigs and rabbits, similar to those seen in early ovarian cancer patients (33). Heller et al. (11) found significant numbers of asbestos fibers in the ovaries of 9 of 13 women with household asbestos exposure. Three women had asbestos fiber counts over 1 million fibers per gram wet weight. Six of 17 women with no reported history of asbestos exposure had significant amounts of asbestos fiber detected in their ovaries. The authors concluded that particulate matter can reach the peritoneal cavity via the transvaginal route and that sexual contact with a male contaminated with asbestos fibers may introduce those fibers into the vagina and subsequently to the

ovaries (11). However, this sexual contact hypothesis has generally not been supported by the results shown here from the Wittenoom women. Women who reported washing the clothes of an Australian Blue Asbestos worker were more likely to be sexual partners of Australian Blue Asbestos workers. No particular excesses for any of the cancers examined were observed among this group or among those who reported living with an Australian Blue Asbestos worker.

Occupational exposure to asbestos has also been associated with excess mortality from cervical cancer. Cervical cancer mortality was increased, but not statistically significantly, among World War II gas mask workers (1, 2). Another cohort of gas mask workers exposed to chrysotile reported nonsignificant excesses of cervical cancer mortality (2), and nonstatistically significant excesses of cervical cancer have also been reported among asbestos textile and cement manufacturers but again with no consistent association with asbestos exposure (6, 10). Among women compensated for asbestosis in Italy there was an increased risk for uterine cancer, but the authors did not distinguish between cervix and corpus and could not examine exposure-response relationships (7). The present study has the advantage of examining cancer incidence rather than mortality, with mortality reflecting risk and survival, whereas incidence reflects the risk for disease. A nonstatistically significant excess incidence of cervical cancer among former Australian Blue Asbestos workers has been found in the present study, but this was based on only three cases. Former Australian Blue Asbestos workers had a 2-fold risk for cervical cancer compared with former residents.

Excess mortality from breast cancer has not been found in most of the studies that examined the mortality of women occupationally exposed to asbestos (1, 2, 4, 7). The only study to suggest any association found a nonsignificant excess ($P = 0.08$) among women factory workers with severe exposure of $\geq$2 years' duration (10). Consistent with this, excess incidence of breast cancer has not been found among the former Wittenoom workers, and except an inverse relationship with time since first exposure, no other exposure-response relationships were confirmed.

Among women exposed environmentally or domestically to asbestos, only a few studies have reported mortality or incidence from causes other than mesothelioma or lung cancer (34). Excess mortality (but not significant statistically) from ovarian cancer was reported among the wives of asbestos factory workers. Reduced risks for uterine and breast cancer were also reported (35). The associations did not change with longer follow-up (36). Crude death rates were similar for breast and cervical cancer mortality among residents of Da-yao, China, exposed to surface crocidolite and a comparison group located 200 km away. Ovarian cancer was not examined (37). Among the former Wittenoom residents, there was no statistically significant excess incidence of ovarian, cervical, or breast cancer.

The women from Wittenoom had a lower risk for ovarian cancer and a higher cervical cancer risk compared with the Western Australian population. Wittenoom was an isolated mining town, working and living conditions were hard, and its population was largely transient. Sociodemographic factors such as low socioeconomic status and related lifestyle risk factors of parity, number of sexual partners, age at first childbirth, tobacco smoking, and human papilloma virus may be largely responsible for the cancer incidence patterns observed in this cohort (38-40).

Twenty-two percent of the women were lost to follow-up, most from the time they left Wittenoom. Western Australian marriage, birth, and death records were searched to identify any name changes and to improve follow-up. However, follow-up was more difficult among women who were not living in Western Australia subsequent to leaving Wittenoom. Cancer incidence was available to the end of 2006 for women in Western Australia, but only until 1997 for Victoria, the second most populous Australian state, or 2002 for the remaining states and territories. In the same vein, we do not know how complete our cancer records are before 1982 when the cancer registries were established. In addition, former male Australian Blue Asbestos workers who returned to Italy have been traced but not their wives or families (41, 42). Consequently the results of this study may underestimate the number of gynecologic and breast cancers that have occurred among the Wittenoom women.

A further limitation of this study was its inability to account for individual and lifestyle factors that may influence the incidence of gynecologic cancers. Follow-up of the Wittenoom women was passive via cancer and mortality registers and does not provide any information about childbearing, use of oral contraceptives, age of menarche or menopause, tubal ligation, or presence of human papilloma virus. These factors are not confounders as they are unlikely to be associated with asbestos exposure, although they are independent risk factors. These factors have not been adjusted for in the creation of the expected rates using the Western Australian age-adjusted female population, so lacking this information should not overestimate our risk estimates.

Conclusion. Among the Wittenoom women there was no consistent evidence of an increased risk for gynecologic and breast cancers compared with the Western Australian population. Ovarian cancers and peritoneal mesotheliomas have not been misclassified in this cohort.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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We thank Janice Hansen, Tim Threlfall of the Western Australian Cancer Registry, Jan Sleith, Nola Olsen, and Robin Mina.

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