Asbestos Exposure and Gestational Trophoblastic Disease: A Hypothesis

Alison Reid,1,2 Jane Heyworth,1,3 Nick de Klerk,1,4 and A.W. Musk1,5

1School of Population Health, 2Centre for Medical Research, 3Faculty of Medicine, Dentistry and Health Science, and 4Telethon Institute for Child Health Research and Centre for Child Health Research, University of Western Australia; and 5Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

Abstract

Among 2,968 women and girls exposed to crocidolite (blue asbestos) at Wittenoom, three cases of choriocarcinoma and three cases of hydatidiform mole have been identified (crude incidence rate of 9.9 per 1000 women and 1.7 per 1000 deliveries for choriocarcinoma and hydatidiform mole, respectively). The women with chorio-carcinoma were resident at Wittenoom at the time of disease development, whereas hydatidiform mole occurred much later in women who had first been exposed to asbestos as young girls. Four of the six cases were known to have lived with asbestos company work-ers who brought their dusty work-clothes home for washing. Asbestos fibers have been reported in the lung, the pleural and peritoneal mesothelium, and the human ovary. They have also been detected in placental digests of live and stillborn infants. This cluster of gestational trophoblastic diseases has some biological plausibility for asbestos causation. Taking an occupa-tional and residential history and examining pathologic specimens for asbestos fibers or bodies may prove use-ful in patients with gestational trophoblastic disease. (Cancer Epidemiol Biomarkers Prev 2009;18(11):2895–8)

Background

Gestational trophoblastic disease (GTD) collectively names a spectrum of disorders of abnormally proliferat-ing trophoblasts from benign hydatidiform moles to ma-lignant choriocarcinoma (cancer of the placenta). Most commonly, they occur after a pregnancy (1). They are very rare. In Australia in 2003, there were six cases of chorio-carcinoma recorded nationally (2). In 2003 to 2004, there were 540 reported hospital separations with the principal diagnosis of hydatidiform mole (3).

Known risk factors for GTD include maternal age (those ages <20 and >40 years experiencing the highest risk), having a history of hydatidiform mole, and using oral contraceptives (the risk increasing with the duration of use). The incidence of these diseases is highest in Asia (excepting Japan), South America, Africa, and the Middle East and lowest in Oceania, Japan, and southern, western, and northern Europe (4).

Almost 3,000 women and girls (41% were ages <15 years on first arrival) lived and worked at Witte-noom, a crocidolite (blue asbestos) mining and milling town in remote Western Australia, between 1936 and 1992. Between 1943 and 1966, the principal mining leases were operated by the Australian Blue Asbestos (ABA). Two thousand five hundred fifty-two women lived in the town (∼12 km from the mine and mill) but did not work for the asbestos company, whereas a further 416 were ABA employees (mostly in the company shop, offices, and hotel). The mine-site and township were heavily polluted with asbestos and tailings from the mine were distributed around the town (5). These women have been followed up since 1973 at national and state death and cancer registries as well as frequent questionnaires to ascertain smoking histories and demo-graphic information. Their mortality and cancer incidence have been reported elsewhere (6–8). The studies have ethics approval from the University of Western Australia Human Research Ethics Committee.

A disease cluster is an occurrence of a greater than ex-pected number of cases of a particular disease within a group of people, delineated in time and/or space. The aim of this short report is to describe a possible cluster of GTD that occurred among women exposed to blue as-bestos at Wittenoom.

Choriocarcinoma

Three cases of choriocarcinoma were brought to our at-tention following publicity about our study examining the health of the women from Wittenoom. A survivor of choriocarcinoma (case 1, Table 1) contacted one of us (A.R.) and gave details of her hospital admission and treatment in 1963. She mentioned two other Wittenoom women being treated for the same condition at the same hospital at the time she was treated. She named one whose death certificate and pathology specimens have subsequently been traced. She was unable to name the second case but was definite that her disease was the same and that she had worked in the ABA company of-fices at Wittenoom.

Our records show that there were 302 women of repro-ductive age (ages 15–54 years) in Wittenoom at some point in 1963. Therefore, the crude incidence rate for cho-riocarcinoma among the Wittenoom women was 3/302 = 9.9 per 1,000 women of reproductive age (or 993 per
Using direct standardization and applying the Wittenoom age-adjusted rates for the three choriocarcinoma cases in 1963 to the Australian female population of reproductive age gives an age-adjusted comparable incidence ratio of 258.9 (95% confidence interval, 53-757).

### Hydatidiform Moles

Linking our cohort to the Hospital Morbidity Data Collection for Western Australia (a record of all Western Australia hospital separations), from 1970 to the end of 2005, identified three different cases of hydatidiform mole (International Classification of Diseases, Eighth Edition code 634.2 and International Classification of Diseases, Ninth Edition code 630) among the 63% of women who were known to have resided in Western Australia subsequent to leaving Wittenoom. Our records show that there were 1,741 deliveries at hospitals in Western Australia between 1970 and 2005 among the former Wittenoom women resident in Western Australia. Therefore, the crude incidence rate for hydatidiform mole in this population was 3/1741 = 1.7 per 1,000 deliveries (or 172 per 100,000 deliveries).

### Asbestos Exposure Characteristics

All three choriocarcinoma cases were living at Wittenoom at the time they developed the disease (Table 1). Two died from the condition (cases 2 and 3), although we could only trace one death certificate (case 2). All worked for ABA: case 1 in the shop in town, whereas case 2 was listed as “casual” in her employment records. Case 1 was exposed to asbestos for 2 years before her diagnosis of choriocarcinoma, which occurred after a period of incessant heavy bleeding following the birth of her second child. Her father worked underground for ABA and her mother and sisters all had periods of working for ABA. ABA workers brought their dusty work-clothes home for washing. Both parents died of lung cancer and one sister died of pleural mesothelioma. Case 2 came to Wittenoom first when she was 3 years old and lived most of her life there. Her father worked in the mill, whereas her brother was a mechanic located in the townsite. She was also resident in Wittenoom at the time when the “old mill” was in operation and the town was much dustier (5). She developed choriocarcinoma 13 years after first exposure to asbestos. She was diagnosed with choriocarcinoma following a 2-month history of lower abdominal pain, which was thought to have been a left ectopic pregnancy. We have limited anecdotal information on case 3. She worked in the mine office, which was heavily polluted, with asbestos dust being located downwind from the mill (9). She miscarried while living at Wittenoom immediately before her diagnosis of choriocarcinoma (Table 1).

All three women who subsequently developed a hydatidiform mole had been born at Wittenoom (Table 1). The father of case 4 worked for ABA as an underground miner and her mother worked in the shop and hotel in town. The father of case 5 worked as an underground miner for ABA and her mother worked at the Wittenoom hospital. Case 6 was born at Wittenoom after the closure of the asbestos mine and mill but lived in the town for 20 years. Her father was a miner but he did not work for ABA. Time since first exposure to asbestos was shorter...
among the women who developed choriocarcinoma than among the women who developed a hydatidiform mole (Table 1).

**Pathologic Findings**

Pathology specimens were obtained for one case of choriocarcinoma and two cases of hydatidiform mole. The choriocarcinoma, in addition to a malignant mixed germ cell tumor (dysgerminoma and choriocarcinoma), showed a component of gonadoblastoma. Gonadoblastomas are almost exclusively (96%) found in patients with gonadal dysgenesis (10), so it is unlikely that asbestos caused this particular choriocarcinoma.

The hydatidiform moles showed fragments of decidua and gestational-type endometrium admixed with chorionic villi. Immunostaining showed the loss of staining in the villous trophoblast in one (an early complete hydatidiform mole) and no loss of staining in the other (a partial hydatidiform mole).

**Discussion**

The incidence of hydatidiform moles varies geographically, with Indonesia reported to have the highest rates at 1 in 57 deliveries. In general, the rate appears higher in Asian, and particularly Southeast Asian, women. Population-based studies among Asian populations suggest that the incidence is declining (11). In 2004 to 2005 in Australia, there were 164 hospital separations with classic hydatidiform mole as the principal diagnosis, 252 with incomplete and partial hydatidiform mole, and 146 with hydatidiform mole unspecified (3).

Choriocarcinoma is a very rare cancer that makes epidemiologic investigation difficult. In Europe and North America, 1 in 30,000 to 40,000 pregnancies and 1 in 40 molar pregnancies are affected. This increases to 1 in every 500 to 3,000 pregnancies in Southeast Asia (11). In Australia, there were 6 choriocarcinoma cases in 2004 (2). The risk of choriocarcinoma is 1,000 times higher following a hydatidiform mole than following other types of pregnancy (12).

Differences in the reported incidence rates of these diseases, nationally and internationally, can be explained to some extent by some studies using hospital-based live births, pregnancies, or deliveries as denominators rather than census-based denominators. In addition, until recently, there was no uniform classification of these disorders.

The crude incidence rate of choriocarcinoma for Australia in 1982 (the first year for which there were computerized records) was 0.1 per 100,000 women (2). Similarly, an early study of cases of GTD in Sydney from 1950 to 1966 reported an incidence of hydatidiform moles and choriocarcinomas of 1.962 and 1:12,705 confinements, respectively (13). This gives a crude incidence rate of 1.04 per 1,000 confinements for hydatidiform moles and 0.08 per 1,000 confinements for choriocarcinoma. This was much lower than our estimated rate for choriocarcinomas among the women from Wittenoom, which was 993 per 100,000 women, although it must be acknowledged that the Steigrad (13) study used confinements as their denominator, whereas the rates for the Wittenoom women used number of women of reproductive age in Wittenoom in 1963 as the denominator for the choriocarcinomas. Among the Wittenoom women, the crude incidence rate of hydatidiform moles is somewhat greater at 1.7 compared with that earlier study, and in this case, the denominators used in both groups are similar (deliveries and confinements).

It is biologically plausible that asbestos exposure could be associated with these uncommon diseases. Asbestos fibers have been reported in the placental digest of live and stillborn infants (14-16) of women who were not specifically asked about asbestos exposure. The fiber burden was higher in the infants of employed mothers. The mean placental asbestos fiber count was 52,894 fibers/g (range, 12,000-252,000 fibers/g). A statistically significant association was found between the presence of fibers and placental diseases (odds ratio, 2.8; 95% confidence interval, 1.0-7.8; P = 0.041; ref. 15). Haque et al. found that the number of fibers present in the stillborn placenta were similar to the number present in the stillborn fetal tissue and that placental and fetal liver digestes had higher fiber burdens than fetal lung and muscle digestes, suggesting that the fibers were blood-borne. This suggests that transplacental transfer of fibers occurs via the maternal circulation (15). In support of this theory, chrysotile (white asbestos) fibers have been observed in newborn mice following gavage feeding of their pregnant mothers, suggesting that the fibers can pass across the placental barrier (17, 18). The placental fiber burden may be greater among women with known, heavy asbestos exposure, such as occurred among the women at Wittenoom (7). Asbestos fibers or asbestos bodies have been found in the lung, pleural and peritoneal mesothelium, the spleen, and the ovary many years after exposure to asbestos (19, 20). We were not able to examine for asbestos fibers or bodies in the specimens obtained on the Wittenoom women.

The rate of GTD increased sharply during the 1970s and 1980s in the Ho Chi Minh City (Saigon) area of Vietnam, which was heavily bombed and targeted with herbicides and pesticides during the Vietnam war. The effects of Agent Orange and dioxin contaminants and incidence of GTD has been investigated and no increased risk of GTD found, although the exposure levels were measured indirectly (4). Vietnam imported asbestos from Russia, Canada, and China for use in the manufacture of asbestos cement roofing tiles from the 1970s (21). It is likely that asbestos was released into the environment as a result of the bombing of Ho Chi Minh City and therefore may have contributed to the observed increase in GTD incidence. Among the Wittenoom women, the choriocarcinomas occurred when the women were living at Wittenoom and may have been a more immediate response to asbestos exposure. The hydatidiform moles occurred years later in women who had been very young girls at Wittenoom possibly as a result of the prolonged presence of asbestos in ovarian tissue.

It was possible to obtain documentary evidence on only one of the cases of choriocarcinoma. The treating hospital had destroyed records before 1966 and the treating physician had died. The Hospital Morbidity Data Collection did not commence before 1970 and the Western Australian Cancer Registry did not commence until the early 1980s. Hydatidiform mole information is further limited because our search of the Hospital Morbidity Data Collection was restricted to those women still...
residing in Western Australia or being admitted to hospital in Western Australia. This could underestimate the incidence of choriocarcinoma and hydatidiform moles in this cohort.

**Conclusion**

This cluster of GTD, with some rationale for asbestos causation, warrants further research. Taking an occupational and residential history and examining pathologic specimens for asbestos fibers or bodies may prove useful in patients with GTD.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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