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Geographic co-occurrence of mesothelioma and ovarian cancer incidence

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Abstract

Background: Asbestos is an established cause of several cancers, including mesothelioma and ovarian cancer. Incidence of mesothelioma, the sentinel asbestos-associated cancer, varies by state, likely reflecting different levels of asbestos exposure. We hypothesized that states with high mesothelioma incidence may also have high ovarian cancer incidence.

Materials and Methods: Using data from the Centers for Disease Control and Prevention National Program for Cancer Registries and the National Cancer Institute Surveillance, Epidemiology and End Results program, we examined the geographic co-occurrence of mesothelioma and ovarian cancer incidence rates by U.S. state for 2003–2015.

Results: By state, mesothelioma incidence ranged from 0.5 to 1.3 cases per 100,000 persons and ovarian cancer incidence ranged from 9 to 12 cases per 100,000 females. When states were grouped by quartile of mesothelioma incidence, the average ovarian cancer incidence rate was 10% higher in states with the highest mesothelioma incidence than in states with the lowest mesothelioma incidence. Ovarian cancer incidence tended to be higher in states with high mesothelioma incidence (Pearson correlation r=0.54; P<0.0001).

Conclusions: Data from state cancer registries show ovarian cancer incidence was positively correlated with mesothelioma incidence, suggesting asbestos may be a common exposure.

Impact: The potential for asbestos exposure has declined since the 1970s because fewer products contain asbestos; however, some products, materials, and buildings may still release asbestos and thousands of workers may be exposed. Ensuring that people are protected from exposure to asbestos in their workplaces, homes, schools, and communities may reduce the risk of several cancers.

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Keywords

mesothelioma; ovarian cancer incidence; epidemiology; surveillance; National Program of Cancer Registries; U.S. Cancer Statistics

Introduction

Ovarian cancer is one of the most common cancers among women in the United States[1] with about 21,000 cases reported in 2015.[2] The etiology of ovarian cancer is not well understood although there is a strong association with family history, and some ovarian cancers are related to genetic mutations including BRCA1, BRCA2, and Lynch syndrome.[3] Beyond tubal ligation and oral contraceptive use, both which reduce risk, and excess body weight, which increases risk, few modifiable risk factors associated with ovarian cancer have been identified.[4] In 2009, the International Agency for Research on Cancer concluded there was sufficient evidence that all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite) cause ovarian cancer.[5]

Evidence from multiple studies indicate that women who have been exposed to asbestos have a higher risk of ovarian cancer than women who are not exposed.[5] This association is supported by the observation that asbestos fibers don’t degrade and accumulate in such tissues as the ovarian epithelium.[5] Women can be exposed to asbestos through occupational exposure on their jobs;[6] through household exposure by living with someone who is occupationally exposed to asbestos, living in buildings with deteriorating asbestos construction materials, or using asbestos-containing commercial products;[7] or through environmental exposure by living in a community with industrial asbestos contamination[8] or close to geologic formations that include asbestos.[9] A meta-analysis of 18 cohort studies of women occupationally exposed to asbestos reported a 77% increased risk of ovarian cancer mortality[6], and a meta-analysis of 14 cohort and 2 case-control studies of women exposed to asbestos in their jobs or from their general environment reported a 75% increased risk of ovarian cancer.[10]

Exposure to asbestos is known to increase the risk of several cancers other than ovarian cancer, including laryngeal cancer, lung cancer, and mesothelioma.[5] Because asbestos is the only established cause of mesothelioma, it can be considered a sentinel occupational or environmental event.[5] In the United States, variations in mesothelioma incidence by state likely reflect different levels of exposure to asbestos.[11,12] Asbestos exposure can vary geographically because of proximity to geologic formations that include asbestos or the distribution of asbestos-related industries such as textile manufacture, mining, cement production, or asbestos-related occupations, such as shipbuilding.[6,13] The U.S. Occupational Safety and Health Administration estimated in 1986 that about 568,000 workers in production and services industries and 425,000 to 1.4 million workers in construction industries were potentially exposed to asbestos; current estimates for U.S. workers are not available.[14] Ongoing occupational and environmental exposure to asbestos in the United States is indicated by a recent study that observed mesothelioma deaths during 1999 to 2015 among persons <55 years.[15]

Since asbestos contributes to the development of both mesothelioma and ovarian cancer, we hypothesized that states with high mesothelioma incidence may also have high ovarian cancer incidence. To examine the geographic co-occurrence of ovarian cancer and mesothelioma, we used data from U.S. Cancer Statistics, which includes population-based cancer registry data from the Centers for Disease Control and Prevention (CDC) National Program for Cancer Registries (NPCR) and the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results Program (SEER).[2]

Methods

Cancer incidence

Cancer incidence data in this report come from the U.S. Cancer Statistics (USCS) dataset, the official federal statistics on cancer.[2] In each state and the District of Columbia (DC), all new diagnoses of cancer from patient records at such medical facilities as hospitals, physicians' offices, therapeutic radiation facilities, freestanding surgical centers, and pathology laboratories are reported annually to NPCR or SEER central cancer registries. The central cancer registries collate these data and use state vital records and the National Death Index to collect information about any cancer deaths that were not reported as cases and then consolidate information about each cancer case into a single record. These data are submitted to CDC or NCI and combined into one dataset. Cancer registries demonstrated that cancer incidence data were of high quality by meeting USCS publication criteria.[2] Data from registries in DC and all states met USCS publication criteria each year during 2003–2015 and covered 100% of the U.S. population.

Cases were first classified by anatomic site using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), then by histology.[16] This analysis includes cases classified as ovarian cancer (ICD-O-3 C56.9, excluding histology codes 9590–9992, 9050–9055, and 9140) or as mesothelioma (any ICD-O-3 anatomic site code with histology codes 9050–9055). Only invasive cases were included in this analysis. Cases were further restricted to those that were microscopically confirmed (92% of ovarian cancers and 94% of mesotheliomas). Ovarian cancer cases were classified by histologic type: serous (ICD-O-3 histology codes 8441, 8460, 8461, 9014), mucinous (8243, 8470, 8471, 8480–8482, 9015), endometrioid (8380–8383, 8560, 8570, 8930, 8933, 8950–8951, 8980), clear cell (8310, 8313), other epithelial (8010–8015, 8020–22, 8030–8033, 8035, 8041–8042, 8045,8050,8052,8070–8074, 8120, 8130, 8140–8141, 8144, 8160, 8201, 8230–8231, 8244, 8249–8250, 8255, 8260, 8262–8263, 8320, 8323, 8330, 8340, 8401, 8430, 8440, 8450, 8490, 8503–8504, 8562, 8572, 8574–8575, 9000), stromal tumors (8590, 8600, 8620–8621, 8623, 8630–8631, 8632, 8634, 8640, 8670, 8810), and germ cell tumors (8240, 8245–8246, 9060, 9064–9065, 9070–9072, 9080–9085, 9090–9091, 9100–9101, 9105, 9364, 9392, 9473).[17] Mesothelioma cases were classified by anatomic site: pleura (ICD-O-3 anatomic site code C38.4), peritoneum (ICD-O-3 C48), and other mesothelioma (all other ICD-O-3 anatomic site codes).

Population estimates

Population estimates for rate denominators were a modification of annual county population estimates by age, sex, bridged-race, and ethnicity produced by the U.S. Census Bureau in collaboration with CDC's National Center for Health Statistics and with support from NCI.[18] The modified county-level population estimates were summed to the state and national levels.[18]

Statistical analysis

Average annual rates for 2003–2015 per 100,000 population were age-adjusted (using 19 age groups) by the direct method to the 2000 U.S. standard population.[19] Corresponding 95% confidence intervals (CIs) were calculated as modified gamma intervals.[20] State-specific age-adjusted ovarian cancer and mesothelioma incidence rates were mapped using quartiles as cutpoints, and the average rate for each quartile was calculated. The average ovarian cancer rate for states grouped by quartile of mesothelioma incidence was calculated. Because stromal tumors and germ cell tumors may have different etiology than other ovarian tumors; these histologic types were excluded in a sensitivity analysis. The Pearson correlation was used as a measure of the association between incidence rates of mesothelioma and ovarian cancer (overall and by ovarian histologic type) within states, weighted by the inverse variance of the mesothelioma incidence rate. In a sensitivity correlation analysis, mesothelioma cases were restricted to the pleura. All statistical tests were 2-sided.

Results

During 2003 to 2015, there were 19,830 microscopically confirmed invasive ovarian cancers (11.2 cases per 100,000 females) reported on average each year in the United States (Table 1). Almost half (45%) were serous carcinomas and 13% were endometrioid carcinomas (Table 1). About 90% of ovarian cancer cases were diagnosed between ages 45 to 84 years, with the highest incidence observed among those 75 to 84 years (43 cases per 100,000 females). Ovarian cancer incidence rates by state ranged from about 9 to 12 cases per 100,000 females (Figure 1A).

During 2003 to 2015, there were 3,200 new cases of invasive mesothelioma reported on average each year in the United States; 3,043 of these were microscopically confirmed (0.94 cases per 100,000 persons) (Table 1). Mesothelioma incidence rates were higher among males (1.7 cases per 100,000 males) than females (0.4 cases per 100,000 females) (Table 1). Eighty-two percent of mesotheliomas were found in the pleura and 10% in the peritoneum. Mesothelioma occurred among persons of all ages, with rates ranging from 0.01 cases per 100,000 persons among those <25 years up to 7.9 cases per 100,000 persons among those 75 to 84 years; almost half of mesothelioma cases were diagnosed in those 75 years or older. Mesothelioma incidence rates by state ranged from 0.5 to 1.3 cases per 100,000 persons (Figure 1B).

When states were grouped by quartile of mesothelioma incidence, the average ovarian cancer incidence rate was 10% higher in states with the highest mesothelioma incidence than in states with the lowest mesothelioma incidence (Figure 2). In a sensitivity analysis excluding stromal tumors and germ cell tumors, which may not be related to asbestos exposure, ovarian cancer incidence rates were 6% lower in each category. However, a similar relationship between ovarian cancer and mesothelioma incidence was observed (data not shown).

Ovarian cancer incidence tended to be lower in states with low mesothelioma incidence and higher in states with high mesothelioma incidence (Pearson correlation $r=0.54$; $P<0.0001$) (Figure 3). A similar correlation was observed when restricted to pleural mesothelioma (Pearson correlation $r=0.54$; $P<0.0001$) (data not shown). Significant positive correlations with mesothelioma incidence were observed for endometrioid carcinoma (Pearson correlation $r=0.55$; $P<0.0001$), clear cell carcinoma (Pearson correlation $r=0.51$; $P=0.0002$), and serous carcinoma (Pearson correlation $r=0.48$; $P=0.0004$) but not for stromal tumors (Pearson correlation $r=0.10$; $P=0.4644$) or germ cell tumors (Pearson correlation $r=0.13$; $P=0.3585$) (data not shown).

Discussion

This ecologic analysis shows moderate geographic co-occurrence of two asbestos-related cancers, mesothelioma and ovarian cancer. We found that the rate of ovarian cancer was 10% higher among states with the highest rates of mesothelioma than among states with the lowest rates of mesothelioma. One possible explanation for this association may be common exposure to asbestos. Although studies have conclusively shown a link between asbestos exposure and increased risk of ovarian cancer, less is known about the association with histologic subtypes.[5] We found positive correlations between mesothelioma and incidence of several histologic subtypes including endometrioid carcinoma, clear cell carcinoma, and serous carcinoma, but no correlation with stromal tumors or germ cell tumors, which may be related more to stromal growth factors or genetic factors than to environmental exposures.[3,4] Better understanding the underlying biologic mechanism linking asbestos exposure to ovarian cancer may help develop and evaluate prevention, diagnostic, and treatment strategies for women who may have been exposed to asbestos.[21]

Early detection of cancer can lead to improved survival; however, ovarian cancer screening is not recommended for asymptomatic women who are not known to have a high-risk hereditary cancer syndrome.[22] Consequently, the greatest impact to reduce ovarian cancer incidence may come from cancer control efforts directed at primary prevention of established risk factors. Asbestos exposure is one of the few modifiable risk factors for ovarian cancer. A recent report estimated that 54% of ovarian cancers among women occupationally exposed to asbestos (attributable fraction) were due to asbestos exposure.[23] Based on limited data, studies estimate that <1% to 3% of ovarian cancers among women (population attributable fraction) in Argentina, Brazil, Colombia, Mexico, Korea, and France may be due to occupational asbestos exposure; estimates for the United States were not reported.[24–26] Although the population attributable fraction of ovarian cancers attributable to occupational asbestos exposure may be low, it represents cancers that could have been avoided by following occupational safety and health rules to reduce exposure to asbestos in the workplace or by eliminating the use of asbestos.[27,28] Occupational safety and health rules might also reduce household exposures from living with workers exposed to asbestos.

This study also found that 3200 new cases of mesothelioma were diagnosed each year on average during 2003 to 2015.[29] The time between first exposure to asbestos and mesothelioma is generally 20 to 40 years,[30] so many recent mesothelioma cases were probably caused by exposure to asbestos many years ago. The potential for asbestos exposure in the United States peaked in the 1970s and has since declined with the closing of U.S. asbestos mines and the reduction of asbestos-containing products and materials from the market.[29] The decline in exposure is reflected, about 30 years later, by declines in mesothelioma incidence and death rates.[11,15] However, new cases may occur if workplace and other regulations to protect people from asbestos are not adequately followed. Furthermore, products, materials, and buildings that contain asbestos may release asbestos into the environment.[31] A recent report found that U.S. adults aged <55 years were continuing to die from mesothelioma in 2015, suggesting ongoing occupational and environmental exposure to asbestos.[15] From the early 1900s through the 1980s, asbestos was widely used in fireproof textiles, paper, plastics, asbestos-cement pipe and sheet, roofing products, friction products, packing and gaskets, coatings and compounds, and electrical and thermal insulation, potentially exposing the entire U.S. population.[29,31] Asbestos was banned from flooring felt, rollboard, and corrugated, commercial, or specialty paper and from new commercial uses introduced after 1989 in the United States by the U.S. Environmental Protection Agency (EPA).[32] Many aspects of this ban were set aside by the U.S. Fifth Circuit Court of Appeals in 1991; however, U.S. manufacturers did discontinue the use of asbestos in several product categories including adhesives, sealants, and roof and non-roof coatings; arc chutes; beater-add gaskets; extruded sealant tape and other tape; filler for acetylene cylinders; high-grade electrical paper; millboard; missile liner; pipeline wrap; reinforced plastics; roofing felt; separators in fuel cells and batteries; vinyl-asbestos floor tile; and any other building material (other than cement).[33] While asbestos is no longer mined nor manufactured in the United States, about 300 metric tons were imported in 2017[34] and 750 metric tons in 2018, and asbestos is currently used in several products manufactured or imported into the United States.[35] Nearly all asbestos recently imported into the United States was used by the chloralkali industry to manufacture semipermeable diaphragms.[34,35] In addition, an unknown number of manufactured products containing asbestos were imported including brake linings and pads and gaskets.[34,35] In April 2019, the EPA finalized a rule that would allow the use of discontinued, and potentially new, uses of asbestos and asbestos-containing products upon review and approval by the EPA.[33,36]

Evidence from case-control and cohort studies also suggest an association between the use of cosmetic talc in the perineal area (e.g., to sanitary napkins, underwear, contraceptive devices, or directly to body) and increased risk of ovarian cancer.[37–39] A decade ago, the International Agency for Research on Cancer concluded that there was sufficient evidence that talc containing asbestiform fibers (referring to the mineral growth, not to the presence of asbestos) was a carcinogen, limiting the outcomes to mesothelioma and lung cancer,[40] and that there was limited evidence for the carcinogenicity of perineal use of talc-based body powder and classified it as Group 2B, possibly carcinogenic to humans.[5] Suggested potential carcinogenic mechanisms include chronic inflammation or contamination of talc with asbestos.[5,38]

This study is subject to at least the following limitations. Because of migration, state-specific cancer incidence rates may not reflect past asbestos exposure because the cancer may not have been diagnosed in the state where the asbestos exposure occurred, particularly given the long latency period between exposure and disease. Second, while ovarian cancer incidence was significantly positively correlated with mesothelioma incidence in this ecologic analysis, a causal association with asbestos exposure cannot be inferred.[41] Third, cancer rates in this report were based on state populations; analyses based on smaller geographic regions may find a stronger, or different, association. However, because mesothelioma is relatively rare, county-level analyses often have insufficient data for analysis—and counties that do have sufficient cases for analysis may do so because of large populations and not necessarily because of high mesothelioma burden. Finally, women with ovarian cancer and peritoneal mesothelioma often present with similar clinical symptoms, such as ascites, abdominal distention, and abdominal pain.[42] However, the possibility of misdiagnosis is low because current standards recommend that a malignant mesothelioma diagnosis be confirmed by biopsy and immunohistochemistry. Nevertheless, some peritoneal mesothelioma tumors may be misdiagnosed as ovarian cancer or some ovarian cancers may be misdiagnosed as mesothelioma.[5] To minimize misclassification, we restricted our analysis to microscopically confirmed cases.

Conclusion

This study found that within U.S. states, the incidence of ovarian cancer was positively correlated with the incidence of mesothelioma, a sentinel asbestos-related cancer. Controlling or eliminating asbestos exposure is considered an optimal approach to preventing mesothelioma.[43] The risk of ovarian cancer might also be reduced by ensuring that people are protected from exposure to asbestos in their workplaces, homes, schools, and communities. As long as there is ongoing use of asbestos-containing products, providing information about the relationship between asbestos and cancer may help people make informed choices about reducing their exposure to asbestos. Finally, more research could further the understanding of the pathogenesis and biology of ovarian cancer histologic subtypes.

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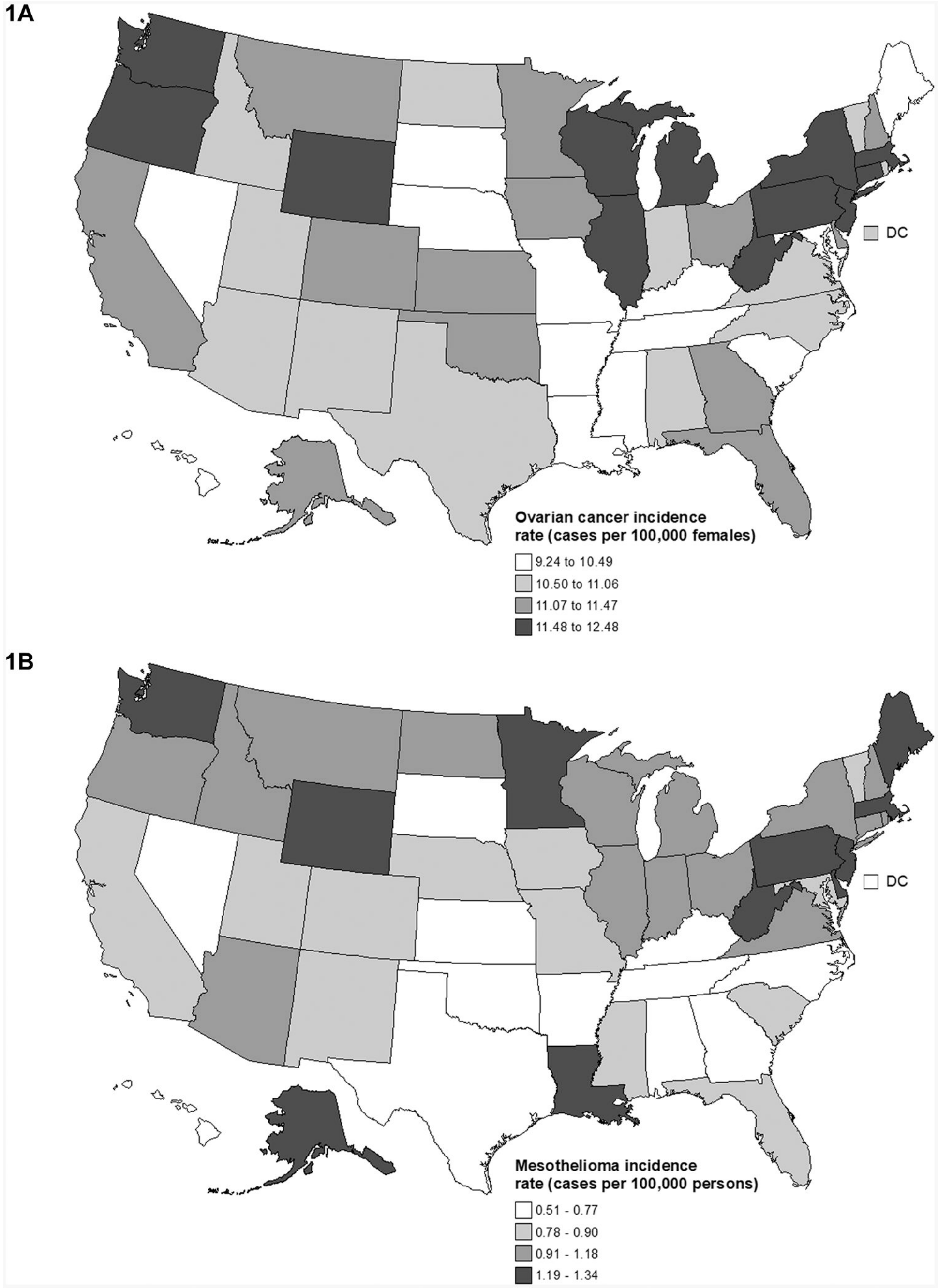

Figure 1.

Geographic distribution of incidence rates of ovarian cancer (Figure 1A) and mesothelioma (Figure 1B), United States, 2003 to 2015. Rates were the average annual number of microscopically confirmed cases per 100,000 persons, age-adjusted to the 2000 U.S. standard population. Data are from cancer registries participating in CDC's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results program.

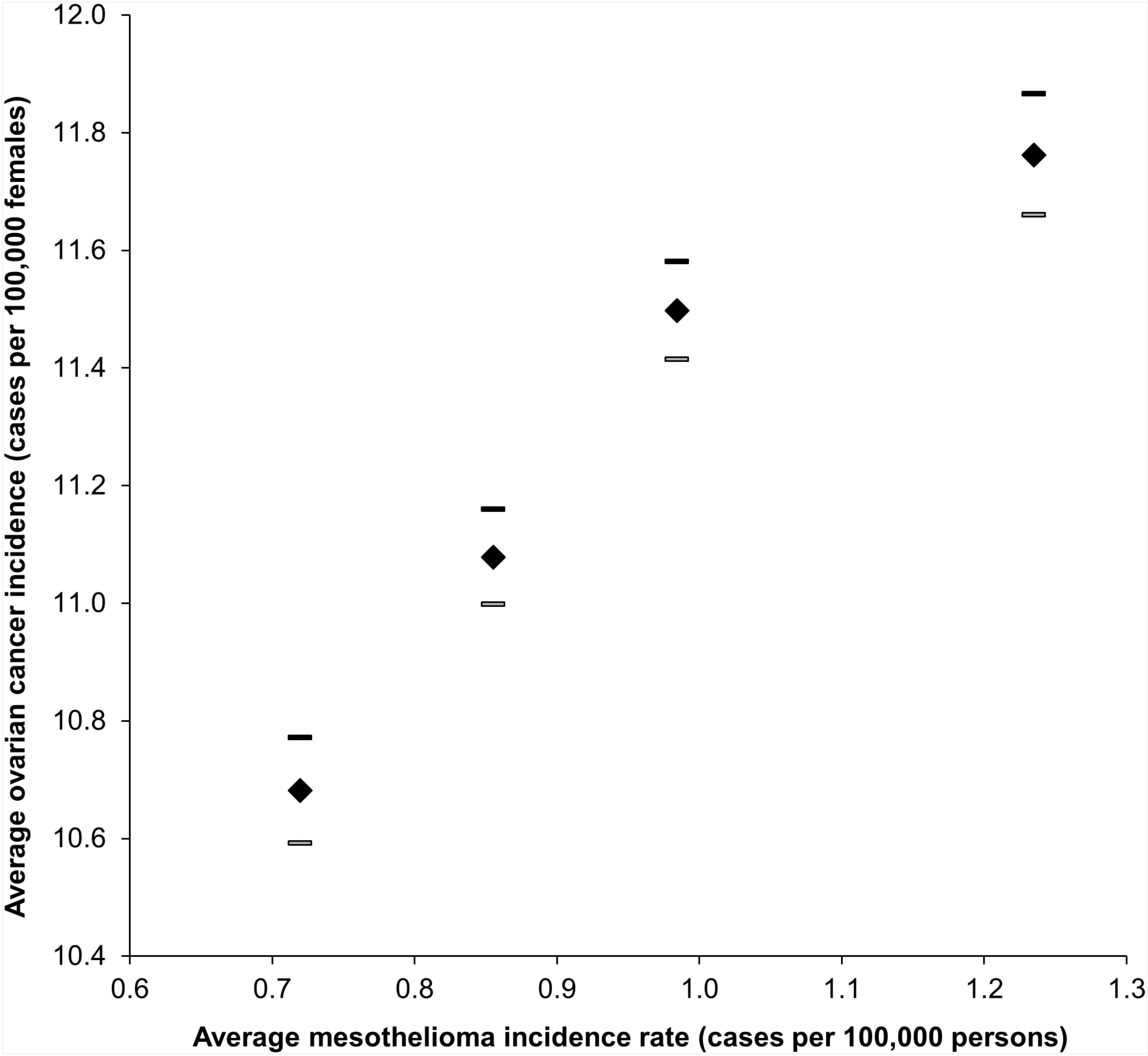

Figure 2.

Average ovarian cancer incidence in states ranked in quartiles by magnitude of mesothelioma incidence, United States, 2003 to 2015. Rates were the average annual number of microscopically confirmed cases per 100,000 persons, age-adjusted to the 2000 U.S. standard population. Diamonds represent the rate and horizontal bars represent lower and upper 95% confidence limits for the rate. States with average mesothelioma incidence=0.72 include Alabama, Arkansas, District of Columbia, Georgia, Hawaii, Kansas, Kentucky, Nevada, North Carolina, Oklahoma, South Dakota, Tennessee, and Texas; states with average mesothelioma incidence=0.86 include California, Colorado, Florida, Iowa, Maryland, Mississippi, Missouri, Nebraska, New Mexico, South Carolina, Utah, and Vermont; states with average mesothelioma incidence=0.98 include Arizona, Connecticut, Idaho, Illinois, Indiana, Michigan, Montana, New York, North Dakota, Ohio, Oregon, Rhode

Island, and Virginia; states with average mesothelioma incidence=1.23 include Alaska, Delaware, Louisiana, Maine, Massachusetts, Minnesota, New Hampshire, New Jersey, Pennsylvania, Washington, West Virginia, Wisconsin, and Wyoming. Data are from cancer registries participating in CDC's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results program.

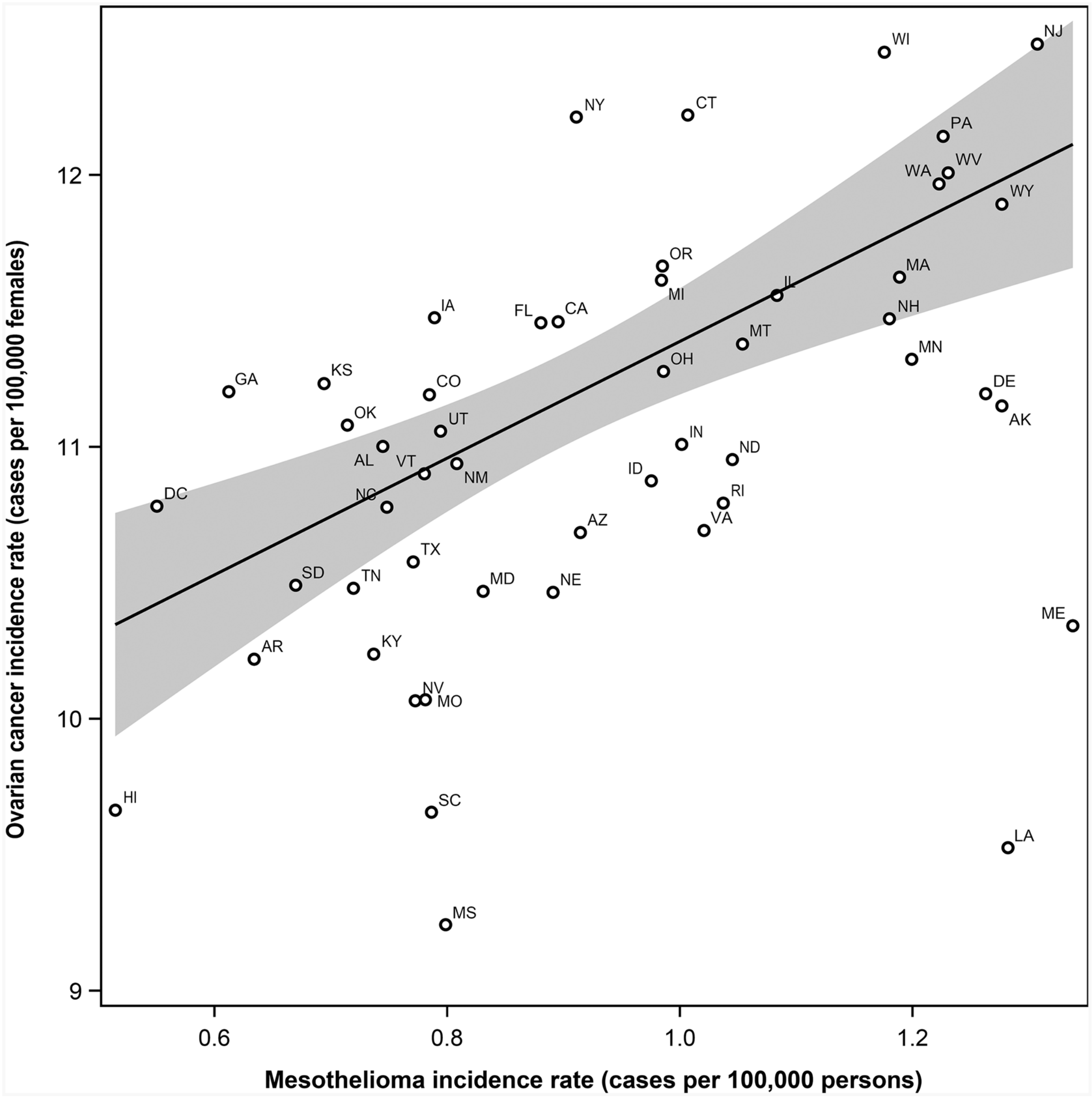

Figure 3.

Linear association between ovarian cancer incidence and mesothelioma incidence within states, United States, 2003 to 2015 (Pearson correlation r = 0.54; P < .0001). The estimated regression line is shown as a straight line with 95% confidence limits as shaded area. Analyses were weighted by the inverse variance of the mesothelioma incidence rate. Rates were the average annual number of microscopically confirmed cases per 100,000 persons, age-adjusted to the 2000 U.S. standard population. Data are from cancer registries participating in CDC's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results program.

Table 1.

Characteristics of mesothelioma and ovarian cancer incidence, United States, 2003 to 2015[1]

	Average annual cases	(%)[2]	Average annual rate[3]	95% Confidence Interval
Ovarian Cancer				
Overall	21,617	(100)	12.16	(12.12 to 12.21)
Microscopic confirmation				
Yes	19,830	(92)	11.24	(11.19 to 11.28)
No	1,787	(8)		
Histologic type[4]				
Serous carcinoma	8,984	(45)	5.77	(5.74 to 5.81)
Mucinous carcinoma	1,124	(6)	0.72	(0.71 to 0.73)
Endometrioid carcinoma	2,523	(13)	1.62	(1.60 to 1.64)
Clear cell carcinoma	989	(5)	0.64	(0.62 to 0.65)
Other epithelial tumors	4,794	(24)	3.08	(3.06 to 3.11)
Stromal tumors	411	(2)	0.26	(0.26 to 0.27)
Germ cell tumors	606	(3)	0.39	(0.38 to 0.40)
Age at diagnosis (years)				
<25	419	(2)	0.82	(0.80 to 0.85)
25–34	555	(3)	2.72	(2.66 to 2.79)
35–44	1,412	(7)	6.71	(6.61 to 6.80)
45–54	3,721	(19)	16.83	(16.68 to 16.98)
55–64	4,890	(25)	26.91	(26.70 to 27.12)
65–74	4,453	(22)	38.01	(37.70 to 38.32)
75–84	3,306	(17)	42.95	(42.55 to 43.36)
≥85	1,073	(5)	29.62	(29.13 to 30.11)
Mesothelioma				
Overall	3,253	(100)	1.00	(0.99 to 1.01)
Microscopic confirmation				
Yes	3,043	(94)	0.94	(0.93 to 0.95)
No	210	(6)	0.06	(0.06 to 0.07)
Sex				
Female	716	(24)	0.40	(0.39 to 0.40)
Male	2,327	(76)	1.68	(1.66 to 1.70)
Anatomic site[5]				
Pleura	2,506	(82)	0.77	(0.76 to 0.78)
Peritoneum	316	(10)	0.10	(0.09 to 0.10)
All other sites	221	(7)	0.07	(0.07 to 0.07)
Age at diagnosis (years)				
<25	7	(<1)	0.01	(0.01 to 0.01)
25–34	21	(1)	0.05	(0.05 to 0.06)
35–44	57	(2)	0.13	(0.12 to 0.14)

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	Average annual cases	(%)[2]	Average annual rate[3]	95% Confidence Interval
45–54	174	(6)	0.39	(0.38 to 0.41)
55–64	480	(16)	1.36	(1.33 to 1.40)
65–74	896	(29)	4.19	(4.11 to 4.26)
75–84	1,050	(35)	7.91	(7.77 to 8.04)
≥85	358	(12)	6.67	(6.48 to 6.86)

[1] Data are from cancer registries participating in CDC’s National Program of Cancer Registries and the National Cancer Institute’s Surveillance, Epidemiology, and End Results program.

[2] Percentages may not sum to 100% because of rounding.

[3] Rates were the average annual number of cases per 100,000 persons, age-adjusted to the 2000 U.S. standard population.

[4] Ovarian histologic types include: serous (ICD-O-3 histology codes 8441, 8460, 8461, 9014), mucinous (8243, 8470, 8471, 8480–8482, 9015), endometrioid (8380–8383, 8560, 8570, 8930, 8933, 8950–8951, 8980), clear cell (8310, 8313), other epithelial (8010–8015, 8020–22, 8030–8033, 8035, 8041–8042, 8045,8050,8052,8070–8074, 8120, 8130, 8140–8141, 8144, 8160, 8201, 8230–8231, 8244, 8249–8250, 8255, 8260, 8262–8263, 8320, 8323, 8330, 8340, 8401, 8430, 8440, 8450, 8490, 8503–8504, 8562, 8572, 8574–8575, 9000), stromal tumors (8590, 8600, 8620–8621, 8623, 8630–8631, 8632, 8634, 8640, 8670, 8810), and germ cell tumors (8240, 8245–8246, 9060, 9064–9065, 9070–9072, 9080–9085, 9090–9091, 9100–9101, 9105, 9364, 9392, 9473). Other histologic types were included in the overall rate but not examined separately.

[5] Mesothelioma anatomic sites include: pleura (ICD-O-3 anatomic site code C38.4), peritoneum (C48), other mesothelioma (all other ICD-O-3 anatomic site codes).