Second Primary Ovarian Cancer Among Women Diagnosed Previously with Cancer

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Abstract
This study assessed the risk of second primary ovarian cancer among United States women diagnosed previously with invasive cancer. We analyzed data from cancer registries participating in the Surveillance, Epidemiology, and End Results program for women diagnosed with invasive cancer between 1973 and 1996. We calculated the risk [observed (O)/expected numbers (E)] of second primary ovarian cancer by cancer site and age at diagnosis of first primary cancer (<50 years and ≥50 years), race (all, white, and black), and years since first cancer (0–4, 5–9, 10–14, and 15–24 years). Statistical tests and 95% confidence intervals (CI) assumed a Poisson distribution. A significantly increased risk of ovarian cancer was found for women who were aged <50 years at diagnosis with melanoma (O/E = 3.5, 95% CI = 2.1–5.5) or cancer of the breast (O/E = 6.0, 95% CI = 4.9–7.2), cervix (O/E = 4.2, 95% CI = 2.6–6.3), corpus uteri (O/E = 11.9, 95% CI = 7.3–18.4), colon (O/E = 17.9, 95% CI = 11.1–27.3), or ovary (O/E = 4.9, 95% CI = 2.7–8.2). No increased risk was found for women aged ≥50 years. Ovarian cancer risk remained elevated after these first primary cancers 5–9 years after diagnosis; for breast and colon cancer, risk remained elevated 15–24 years after diagnosis. Women ≥50 years at diagnosis with melanoma or cancer of the cervix, corpus uteri, ovary, rectum, or lung and bronchus were at a decreased risk for second primary ovarian cancer. Ovarian cancer risk is higher than expected for women who were diagnosed with certain types of cancer at <50 years of age.

Introduction
Ovarian cancer is the second most common gynecological cancer in the United States, with 23,100 new cases and 14,000 deaths expected in 2000 (1). Five-year relative survival is 95% for cases diagnosed at localized stage (25% of ovarian cancers), 79% for cases diagnosed with regional disease (9% of ovarian cancers), and 28% for those with distant disease at diagnosis (60% of ovarian cancers; Ref. 2). Currently, screening tests that would detect ovarian cancer at an early stage and thus decrease mortality are not available.

Risk factors for ovarian cancer include older age (≥50 years), never having had any children, never having used oral contraceptives, and having a family history of breast or ovarian cancer (1, 3, 4). Evidence also suggests that women with certain types of first primary cancers have a higher risk of ovarian cancer, a second primary cancer. Increased risk of second primary ovarian cancer has been found after first primary cancers of the breast, uterine corpus, colon, rectum or small intestine, lymphoma, and melanoma (5–13). Among women with first primary breast cancer, the risk of second primary ovarian cancer appeared to be confined to women who were of premenopausal age at the time of diagnosis of the first primary cancer (9, 14). The potential effects of age and time since diagnosis of the first primary cancer have not been assessed for all sites potentially associated with second primary ovarian cancer. Differences by race in risk for second primary ovarian cancer have also not been investigated.

This study was conducted to determine the risk of ovarian cancer among United States women who have had cancer and to determine differences in risk by race, age at diagnosis of first primary cancer, site of first primary cancer, and time since diagnosis of the first primary cancer.

Materials and Methods
We used data from cancer registries participating in the SEER2 program of the National Cancer Institute to identify women diagnosed with cancer between 1973 and 1996 (15). The SEER program covers ~14% of the United States population. All cases diagnosed in Connecticut, Hawaii, Iowa, New Mexico, and Utah and the metropolitan areas of Atlanta, Detroit, San Francisco and Oakland, and Seattle and Puget Sound were included in the study. Follow-up information for cancer cases is obtained by SEER registries through linkage with files containing information on vital status and by contact with patients and physicians.

The information we obtained from the SEER files included the site of the first primary cancer, age at diagnosis of the first primary cancer, vital status, years of follow-up, sex, race, diagnostic confirmation of first and second primary cancers, and histology of the ovarian cancers (i.e., the second cancer). We classified histology according to the WHO Classification of malignant ovarian tumors (16). Similar to the

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methods used in previous studies (10, 17), person-years of observation were accumulated from 2 months after diagnosis of the first primary cancer to the date of diagnosis of ovarian cancer, death, loss to follow-up, or end of follow-up (i.e., December 31, 1996). Of 911,667 women diagnosed with invasive cancer, 111,405 were excluded because they survived <2 months or because the second primary ovarian cancer was diagnosed ≤2 months after initial cancer diagnosis, and 14,185 were excluded because follow-up information was not available. Women with first primary in situ cancers were also excluded, except for women with in situ breast cancer (n = 25,039), for whom we also assessed the risk of subsequent ovarian cancer. The number of records available for analysis for each cancer site is shown in Table 1.

The expected number of cases was obtained by multiplying 5-year age and calendar year interval-specific ovarian cancer incidence rates, based on SEER data, by the accumulated person-years at risk (18). We calculated the risk (O/E) and 95% CIs assuming a Poisson distribution (5).

**Results**

Between 1973 and 1996, 1,751 of 786,077 women diagnosed with an invasive first primary cancer during that time period experienced a second primary ovarian cancer. The average follow-up time ranged from 2.3 years for women with cancers of the digestive tract, other than those of the colon or rectum, to 8.9 years for women with cancer of the corpus uteri (Table 1). The average age at diagnosis of the first primary cancer ranged from 57.7 years for cancer of the cervix to 75.6 years for cancers of the bladder or colon. The percentage of cases microscopically confirmed was >95% for most of the first primary cancers, with the exception of cancers of other digestive sites (94%), lung and bronchus (89.5%), leukemia (92.9%), and multiple myeloma (88.9%). The majority of the second primary ovarian cancers was epithelial tumors (97%); ~1% were either stromal cell or other unspecified tumors, and <1% were germ cell tumors. Most (95.9%) of the second primary ovarian cancers was histologically confirmed.

Risk of second primary ovarian cancer varied by age at diagnosis of the first primary cancer. A significantly increased risk of ovarian cancer was observed for women aged <50 years at diagnosis of first primary cancer for women with melanoma or cancer of the breast, cervix, corpus uteri, ovary, colon, or digestive tract sites other than colon or rectum (Table 2). No significantly increased risk of ovarian cancer was found for any of the cancer sites among women aged ≥50 years at the last diagnosis. In fact, decreased risk of second primary ovarian cancer was found for women diagnosed previously with melanoma or cancer of the cervix, corpus uteri, ovary, rectum, or lung and bronchus.

Among women aged <50 years when diagnosed with first primary cancer of the cervix or ovary, the risk of second primary ovarian cancer remained significantly elevated 5–9 years after diagnosis of their first primary cancer (Table 2). Few or no second primary ovarian cancers were observed for these women after that time. For women with melanoma, risk of second primary ovarian cancer remained elevated 10–14 years after diagnosis, and for women with breast and colon cancer, this risk remained elevated 15–24 years after diagnosis.

Among black women <50 years at diagnosis of their first primary cancer, second primary ovarian cancers occurred only among those with cancer of the breast (n = 8), cervix (n = 3), colon (n = 3), or lymphoma (n = 1). Among women with first primary breast cancer, the risk of second primary ovarian cancer was 6.24 (95% CI = 5.11–7.63; P < 0.01) among white women and 6.89 (95% CI = 2.97–13.57; P < 0.01) among black women. However, because of their small numbers, the estimates for black women had wide CIs, and no clear difference was found between the risk estimates for black and white women with the CIs overlapping. For both white and black women, there was no increased risk of second primary ovarian cancer among those aged ≥50 years at diagnosis of their first primary cancer (data not shown).

Finally, there were 25,039 women diagnosed with in situ breast cancer; 58 of these women developed ovarian cancer. No
Discussion

In this study, we found that women aged <50 years when diagnosed with melanoma or cancer of the breast, cervix, corpus uteri, ovary, or colon or digestive cancers other than colon or rectum were at increased risk for developing a second primary ovarian cancer. No increased risk of ovarian cancer was found among women aged ≥50 years at diagnosis of their first primary cancer. In fact, for these women, a reduced risk of second primary ovarian cancer was found for those with melanoma or cancer of the cervix, corpus uteri, ovary, rectum, or lung and bronchus.

Our results confirm earlier findings of an increased risk of ovarian cancer among women with cancer of the breast (9, 11–13), uterine corpus (7), and colon (11, 12). Some of these earlier studies used data from the Connecticut tumor registry (9, 12), which is part of the SEER program. This is the first study using data from all SEER areas to assess second primary ovarian cancer risk.

Several factors may explain the increased risk for second primary ovarian cancer among these women. Familial cancer syndromes, such as the familial breast-ovarian cancer syndrome or the hereditary nonpolyposis colorectal cancer syndrome, point to a hereditary susceptibility to multiple primary cancers of the ovary, breast, endometrium, and colon, as well as other cancers (3, 5, 19). Hereditary nonpolyposis colorectal cancer, characterized by germline mutations in DNA mismatch repair genes and autosomal dominant genetic transmission, predisposes to early onset cancers (19). Carriers of susceptibility alleles for breast or ovarian cancers (e.g., BRCA1) are especially at risk for early onset cancers of the ovary and breast, and the genetic attributable risk is higher for younger women (20). Future studies may assess familial predisposition to cancer and specific cancer genes, such as BRCA1, among women with multiple primary cancers. However, other factors must contribute to inherited susceptibility to develop cancer (20).

Endocrine factors might also explain the relations between multiple primary cancers of the ovary, breast, corpus uteri, and
colon (12). Factors that reduce gonadotropin release, such as oral contraceptive use and increased parity, are associated with lower risk of ovarian and endometrial cancers (4, 21). Shared risk factors for breast and ovarian cancer, such as low parity, also support a hormonal etiology, and these risk factors are more strongly associated with disease among premenopausal women (5, 21).

A common etiology is additionally supported by bi-directional associations between multiple cancers, such as the higher risk of ovarian cancer after an initial breast cancer and a higher risk of breast cancer after an initial ovarian cancer, or the bi-directional association between colon and ovarian cancers (12, 17). Other shared risk factors for cancer of the ovaries, breast, and colon may include dietary intake, such as consumption of high dietary fat or low consumption of vegetable fiber (4). With regard to possible iatrogenic effects from previous cancer treatments, evidence suggests that the risk of developing subsequent cancers from therapy of initial cancers is small (9, 22).

Our results are also in agreement with an earlier study that found a higher risk for subsequent cancer of the ovary after initial melanoma (11). This association, however, may be less easily explained than those discussed previously. Possibly, these cancers share an etiology influenced by hormones, similar to that which may explain the association found between breast cancer and melanoma (23).

If detection of second primary cancer is attributable to increased medical surveillance, then it would be most likely that the second cancer would be detected soon after diagnosis of the initial cancer (5). However, the risk of ovarian cancer among women aged <50 years remained elevated beyond 4 years after diagnosis of the initial cancers and 15–24 years for cancers of the breast and colon. Our findings are consistent with earlier reports of a risk that remained elevated among long-term survivors of breast cancer (9). Among women ≥50 years, the reduced risk is unlikely to be related to early detection of precursors to ovarian cancer, as no screening methods have been shown to be effective.

Similar to earlier results using data from the Connecticut tumor registry (9) and a case-control study in North Carolina (14), we found that risk of ovarian cancer among women with breast cancer was limited to premenopausal women (i.e., women <50 years of age at diagnosis of the first primary breast cancer). In addition, we found that the increased risk of ovarian cancer among women with cancers at other sites was also limited to women aged <50 years at diagnosis of their initial cancer. This finding is not likely to be attributable to a difference in survival time, because we found the average survival times to be similar for younger and older women. Although women aged ≥50 years generally have a higher incidence of ovarian cancer than women <50 years (the average annual incidence/100,000 women for 1992–1996 was 5.2 for women <50 years and 43.8 for women ≥50 years), factors that may be related to developing multiple primary cancers, such as a family history of cancer, are also related to the early onset of cancer.

The reasons for the decreased risk of second primary ovarian cancer among women aged ≥50 years at diagnosis of certain first primary cancers are unclear. An earlier study of women with first primary breast cancer found a downward trend of second primary cancer risk by age at diagnosis of the first primary cancer for ovarian as well as other cancers (9) but not a reduced risk among older age groups. Risk factors such as genetic predisposition or parity are also risk factors for older women, although the associations are not as strong as for younger women, and women with early first primary cancer are no longer susceptible to a first cancer later in life. Fewer women aged ≥50 years at the time of diagnosis of the first primary cancer may be at risk for ovarian cancer. Future studies may investigate whether the lower risk of second ovarian cancer among women aged ≥50 years may be related to hysterectomy rates, as ovarian cancer risk is reduced after hysterectomy or unilateral oophorectomy (24). Recent national survey results show that <23% of women aged ≥18 years have had a hysterectomy, with higher prevalence rates among older women (38% among women aged 50–59 years and 45% among women aged ≥65 years). The proportion of hysterectomies with concomitant oophorectomy also increases with age (25). Treatment for gynecologic cancer also may include bilateral oophorectomy, which would reduce the risk of ovarian cancer, e.g., breast cancer treatment may include hysterectomy or removal or radiation ablation of ovaries, thereby reducing the risk of subsequent ovarian cancer (9). Such treatment may be more common among women beyond child-bearing age.

The strengths of this study include the availability of population-based data from cancer registries with high-quality data collection and processing. SEER covers ~14% of the United States population, but the population it covers is more affluent, has lower unemployment, and is more urban than the population living elsewhere in the United States (26).

Possible errors in studies of multiple primary cancers might occur when metastatic disease is misclassified as second primary cancer, especially among tumors in close anatomical or temporal proximity, e.g., cancer of the colon may spread to the ovaries. However, metastatic disease is unlikely to explain our findings as 95.9% of the second primary ovarian cancers were histologically confirmed. A bias may arise when second primary cancer is detected because of increased medical surveillance among cancer patients. We were not able to assess the extent of this bias, because ovarian cancer screening is not common. The power to detect associations may be limited as stratification by ≥4 variables may result in a low number of expected cases and wide CIs. Finally, in studies of multiple primary cancers, multiple comparisons are made that increase the possibility of detecting spurious associations. Studies such as ours are therefore important to confirm findings of earlier studies.

In summary, this study described the risk of second primary ovarian cancer among women diagnosed previously with invasive cancer. We found that women <50 years at age of diagnosis with certain initial cancers had an increased risk for ovarian cancer, and women ≥50 years with certain initial cancers had a reduced risk. Women <50 years who are diagnosed with melanoma or cancers of the breast, corpus uteri, cervix, ovary, colon, or of the digestive tract other than colon or rectum appear to be at increased risk for developing a subsequent ovarian cancer. The relations between some of these cancers suggest that future research should focus on common etiologies and biomarkers. This may eventually lead to a screening device that could reduce mortality from this most serious cancer.

References
3. Internet address: http://apps.nccd.cdc.gov/brfss/.


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