Second Malignant Neoplasms among Long-Term Survivors of Ovarian Cancer

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ABSTRACT

Second malignant neoplasms were evaluated among 32,251 women with ovarian cancer, including 4,402 10-year survivors, within the nine population-based registries of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (1973–1992) and the Connecticut Tumor Registry (1935–1972). Overall, 1,296 second cancers occurred against 1,014 expected (observed/expected (O/E), 1.28; 95% confidence interval (CI), 1.21–1.35). Sites contributing 25 or more excess cancers included leukemia (O/E, 4.17; CI, 1.11–4.53) and malignancies of colon (O/E, 1.33; CI, 1.15–1.54), breast (O/E, 1.18; CI, 1.04–1.30), and bladder (O/E, 2.07; CI, 1.65–2.52). Ocular melanoma (O/E, 4.45; CI, 1.92–8.77) was also significantly increased. Second cancer risk was high during all follow-up intervals, and cumulative risk at 20 years was 18.2%, compared with a population expected risk of 11.5%. Statistically significant relationships existed between serous adenocarcinoma of the ovary and breast cancer (O/E, 1.29; CI, 1.06–1.56) and mucinous ovarian adenocarcinoma and rectal cancer (O/E, 1.95; CI, 1.09–3.22). Secondary leukemia appeared linked with antecedent chemotherapy, whereas radiotherapy was associated with cancers of connective tissue, bladder, and possibly pancreas. Genetic and reproductive factors predisposing to ovarian cancer may have contributed to the elevated risk of breast and colorectal neoplasms and possibly ocular melanoma. Thus, excess malignancies following ovarian cancer represent complications of curative therapies and/or underlying susceptibility states that have etiological and clinical ramifications.

INTRODUCTION

Cancer of the ovary is the second most common gynecological malignancy in the United States, with an estimated 26,600 cases expected to develop in 1995 (1). Survival for women with ovarian cancer has improved significantly within recent decades (2), such that the occurrence of late effects has gained increasing clinical importance (3). Previous investigations have addressed the risk of subsequent neoplasms by type of primary treatment (4, 5) and histology of ovarian cancer (6). Leukemia has been convincingly linked with prior chemotherapy regimens for ovarian cancer (7, 8), but more recent treatment options have not been evaluated. Although an excess risk of breast and colorectal neoplasms seemed associated with histological type of ovarian cancer in one series (6), sparse numbers limited interpretation. In the current study, we quantify the risk of second malignancies among 32,251 women with ovarian cancer, including 4,402 10-year survivors, reported to selected population-based registries within the United States.

MATERIALS AND METHODS

We evaluated all women diagnosed with invasive ovarian cancer as a first primary malignancy who were reported to one of nine population-based registries of the SEER2 program of the National Cancer Institute (1973–1992) or to the CTR (1935–1972).3 In addition to Connecticut, SEER areas include Hawaii, Iowa, New Mexico, Utah, and the metropolitan regions of Atlanta (1975–1992), Detroit, San Francisco and Oakland, and Seattle and Puget Sound (1974–1992), which together constitute ~10% of the U.S. population. Information routinely collected by all SEER registries includes patient demographic data, tumor histology, and vital status. Active tracing of all living patients involving patient or physician contact and data linkage with files that provide information on vital status are standard follow-up procedures.

SEER and CTR files also typically record from hospital charts the first course of treatment administered to patients, based on one of several broad designations. We used this information to identify ovarian cancer patients treated with chemotherapy and/or radiotherapy. The SEER Program and CTR do not record therapy given after the initial course. Neither is information available with regard to the specific drugs or dose schedules administered. Treatment of ovarian cancer typically includes surgical resection followed by chemotherapy and/or local radiation, depending on disease stage and site of involvement (9). Surgical management varies from unilateral oophorectomy or bilateral salpingo-oophorectomy and hysterectomy with omentectomy to pelvic exenteration (10). In the 1960s, adjuvant chemotherapy frequently consisted of treatment with single alkylating agents, such as chlorambucil, cyclophosphamide, melphalan, or thiopentene-thiophosphoramide (thiotepa) (10), with treatment commonly continued until relapse. Melphalan was widely used throughout the 1970s, with combination chemotherapy regimens employing cyclophosphamide, Adriamycin, and cisplatin introduced in the latter part of the decade. By the early 1980s, platinum-based regimens were considered optimal chemotherapy. External beam radiotherapy was used for decades as either an adjuvant to surgery, treatment for nonresectable disease, or palliation of advanced ovarian cancer (10). Postoperative irradiation for ovarian cancer has generally consisted of pelvic or whole abdominopelvic radiotherapy (11), in which fields extend from above the diaphragm to below the pelvic floor.

Intraperitoneal instillation of radiocolloids has also been used (12).

SEER and CTR incidence files were searched for second malignant neoplasms that developed at least 2 months after a diagnosis of invasive ovarian cancer. Subsequent diagnoses of female genital tract tumors were not included in any analyses. Second cancer sites were grouped according to the WHO International Classification of Diseases for Oncology (13). The risk of second cancers of the breast, colon, and rectum were stratified by histological categories of ovarian adenocarcinoma specified by Percy et al. (14) and Platz and Benda (15). For secondary colorectal cancer, latter analyses were limited to 1-year survivors of ovarian carcinoma, given possible misclassification with mucin-producing adenocarcinomas during the patient’s early course.

To estimate risk of second cancer, person-years of observation were compiled according to age and calendar periods from 2 months after diagnosis of ovarian cancer to date of last follow-up evaluation, date of death, date of diagnosis of second cancer, or end of study (December 31, 1992), whichever occurred first. By close of study, 65% of the women had died, 29% remained alive, and 6% were lost to follow-up. Cancer incidence rates specific for age (within 5 years), sex, and 5-year calendar year intervals were multiplied by the accumulated person-years at risk to estimate the number of cancer cases expected. Statistical tests and 95% CIs were based on the assumption that the

Received 11/27/95; accepted 2/12/96.

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The abbreviations used are: SEER, Surveillance, Epidemiology, and End Results; CTR, Connecticut Tumor Registry; CI, confidence interval; O/E, observed/expected; ALL, acute lymphoblastic leukemia; ANLL, acute nonlymphocytic leukemia; NOS, not otherwise specified.

Women diagnosed with ovarian carcinoma within selected SEER registries (1980–1982) were included in a prior case-control study (see Ref. 36). Patients reported to the CTR were included in previous reports (see Refs. 4 and 31), with follow-up extended for the current survey.

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SECOND MALIGNANT NEOPLASMS AFTER OVARIAN CANCER

Table 1 Characteristics of women with ovarian cancer reported to the CTR (1935–1972) or to the SEER program (1973–1992)

All patients were diagnosed with ovarian cancer as a first primary cancer and survived ≥2 months. The cohort consisted of 4,742 subjects reported to the CTR (1935–1972) and 27,509 subjects reported to the SEER program (1973–1992). Follow-up of the cohort ended December 31, 1992.

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of patients</th>
<th>Average age (yr)</th>
<th>Person-years of follow-up</th>
<th>Average follow-up (yr)</th>
<th>No. of second primary cancersa</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ovarian cancer</td>
<td>32.251</td>
<td>58.8</td>
<td>133,098</td>
<td>4.1</td>
<td>1,296</td>
</tr>
<tr>
<td>Carcinoma, all</td>
<td>30.254</td>
<td>59.7</td>
<td>120,191</td>
<td>4.0</td>
<td>1,218</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>27.887</td>
<td>59.3</td>
<td>113,844</td>
<td>4.1</td>
<td>1,160</td>
</tr>
<tr>
<td>Serous</td>
<td>7.692</td>
<td>59.2</td>
<td>29,940</td>
<td>3.9</td>
<td>310</td>
</tr>
<tr>
<td>Mucinous</td>
<td>3.424</td>
<td>56.1</td>
<td>21,479</td>
<td>6.3</td>
<td>226</td>
</tr>
<tr>
<td>Endometroid</td>
<td>2.279</td>
<td>58.0</td>
<td>10,812</td>
<td>4.7</td>
<td>129</td>
</tr>
<tr>
<td>Other specified types</td>
<td>9.777</td>
<td>58.6</td>
<td>39,795</td>
<td>4.1</td>
<td>372</td>
</tr>
<tr>
<td>NOS†</td>
<td>4.805</td>
<td>63.8</td>
<td>11,818</td>
<td>2.5</td>
<td>123</td>
</tr>
<tr>
<td>Carcinoma, other/NOS</td>
<td>2.367</td>
<td>64.5</td>
<td>6,346</td>
<td>2.7</td>
<td>58</td>
</tr>
<tr>
<td>Noncarcinoma</td>
<td>1.997</td>
<td>44.6</td>
<td>12,907</td>
<td>6.5</td>
<td>78</td>
</tr>
</tbody>
</table>

a Numbers exclude all female genital sites.


d ICD-0 morphology codes 8441 and 8460–8461.

e ICD-0 morphology codes 8470–8471 and 8480–8481.


The observed numbers of second tumors were distributed as a Poisson variable. Tests for homogeneity and linear trend were conducted using methods described by Breslow et al. (16). All P values are two sided.

RESULTS

Average age at diagnosis for 32,251 women with invasive ovarian cancer was 58.8 years, and average follow-up was 4.1 years (Table 1). Approximately 4,400 women survived 10 or more years. Second cancers occurred in 1,296 patients (4%). Diagnoses were microscopically confirmed in 98% and 97% of initial and subsequent tumors, respectively. Adenocarcinomas constituted 87% of the ovarian cancers, with the growth patterns of 7,602 tumors characterized as serous in morphology.

Altogether, 1,296 women developed subsequent cancers, compared with 1,013.85 expected (O/E, 1.28; 95% CI, 1.21–1.35; Table 2). The risk of second cancer was slightly higher in the CTR, 1935–1972 (O/E, 1.38), than in the SEER Program, 1973–1992 (O/E, 1.25). Significantly increased risks were observed for all solid tumors.
combined and for cancers of the colon, rectum, breast, bladder, and eye. All ocular tumors, which occurred an average of 6.7 years after ovarian cancer, were unilateral, histologically confirmed malignant melanomas. Seven- to 9-fold risks were seen for ALL and ANLL. Nonsignificant 2-fold excesses were noted for chronic granulocytic leukemia and connective tissue cancer.

The risks of all solid tumors and cancers at selected sites are presented in Table 3 according to primary treatment and time since diagnosis of ovarian cancer. Significantly elevated risks of solid tumors developed 1 year after diagnosis of ovarian cancer and persisted throughout the follow-up period (P trend > 0.05). Fifteen-year survivors experienced significant excesses of cancers of the pancreas, bladder, and connective tissue. The cumulative risk of all second malignancies two decades after diagnosis of ovarian cancer was 18.2%, compared with a population expected risk of 11.5% (Fig. 1).

Temporal patterns of solid tumor risk differed according to primary treatment for ovarian cancer. Following radiotherapy alone, excesses of solid tumors increased with time to reach almost 2-fold among long-term survivors (P trend = 0.07); an additional 88 solid tumors (O/E, 1.42; 95% CI, 1.14–1.75) occurred after ≥20 years of follow-up. Although risk of solid tumors after any chemotherapy was elevated within the 5–9-year interval after ovarian cancer, nonsignificant excesses occurred in later intervals.

More than 400 second cancers occurred in the breast, with the distribution of histological types similar to general patterns within the SEER and CTR data bases. Significantly elevated risks were noted within 10 years after diagnosis of ovarian cancer but decreased to below expectation after 15 years of follow-up.

Of 188 colon cancers, 98% were microscopically confirmed. Over-all, a 30% excess of second primary colon tumors was observed, with increased risks 5–14 years after ovarian cancer. Four tumors occurred

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**Table 3 Selected second malignant neoplasms by site, treatment, and time since diagnosis of ovarian cancer**

<table>
<thead>
<tr>
<th>Time since diagnosis (yr)</th>
<th>1–4</th>
<th>5–9</th>
<th>10–14</th>
<th>15+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients (all entering interval)</strong></td>
<td>22,248</td>
<td>8,396</td>
<td>4,402</td>
<td>2,147</td>
</tr>
<tr>
<td><strong>Radiotherapy only</strong></td>
<td>2,796</td>
<td>1,439</td>
<td>1,000</td>
<td>650</td>
</tr>
<tr>
<td><strong>Any chemotherapy</strong></td>
<td>11,581</td>
<td>3,041</td>
<td>1,139</td>
<td>316</td>
</tr>
<tr>
<td><strong>Person-years</strong></td>
<td>51,920</td>
<td>30,704</td>
<td>15,851</td>
<td>12,805</td>
</tr>
<tr>
<td><strong>Radiotherapy only</strong></td>
<td>7,467</td>
<td>6,004</td>
<td>4,101</td>
<td>4,294</td>
</tr>
<tr>
<td><strong>Any chemotherapy</strong></td>
<td>22,709</td>
<td>9,644</td>
<td>3,370</td>
<td>714</td>
</tr>
</tbody>
</table>

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**SECOND MALIGNANT NEOPLASMS AFTER OVARIAN CANCER**

- All solid tumors:
  - Observed: 375
  - O/E: 1.12
  - Person-years: 11,41

- Radiotherapy only:
  - Observed: 51
  - O/E: 1.33
  - Person-years: 112

- Any chemotherapy:
  - Observed: 164
  - O/E: 1.04
  - Person-years: 112

- Colon, all:
  - Observed: 52
  - O/E: 1.07
  - Person-years: 48

- Radiotherapy only:
  - Observed: 9
  - O/E: 1.63
  - Person-years: 10

- Any chemotherapy:
  - Observed: 20
  - O/E: 0.93
  - Person-years: 22

- Rectum:
  - Observed: 25
  - O/E: 1.35
  - Person-years: 21

- Radiotherapy only:
  - Observed: 3
  - O/E: 1.29
  - Person-years: 2

- Any chemotherapy:
  - Observed: 11
  - O/E: 1.33
  - Person-years: 5

- Pancreas, all:
  - Observed: 13
  - O/E: 1.07
  - Person-years: 11

- Radiotherapy only:
  - Observed: 3
  - O/E: 2.28
  - Person-years: 1

- Any chemotherapy:
  - Observed: 8
  - O/E: 1.44
  - Person-years: 4

- Breast, all:
  - Observed: 164
  - O/E: 1.32
  - Person-years: 104

- Radiotherapy only:
  - Observed: 20
  - O/E: 1.35
  - Person-years: 22

- Any chemotherapy:
  - Observed: 78
  - O/E: 1.30
  - Person-years: 44

- Kidney, all:
  - Observed: 9
  - O/E: 1.21
  - Person-years: 4

- Radiotherapy only:
  - Observed: 2
  - O/E: 2.45
  - Person-years: 2

- Any chemotherapy:
  - Observed: 1
  - O/E: 0.28
  - Person-years: 2

- Bladder, all:
  - Observed: 21
  - O/E: 1.93
  - Person-years: 10

- Radiotherapy only:
  - Observed: 2
  - O/E: 1.72
  - Person-years: 2

- Any chemotherapy:
  - Observed: 8
  - O/E: 1.59
  - Person-years: 3

- Connective tissue, all:
  - Observed: 0
  - O/E: 0
  - Person-years: 0

- Radiotherapy only:
  - Observed: 0
  - O/E: 0
  - Person-years: 0

- Any chemotherapy:
  - Observed: 0
  - O/E: 0
  - Person-years: 0

- Leukemia, all:
  - Observed: 66
  - O/E: 7.01
  - Person-years: 32

- Radiotherapy only:
  - Observed: 5
  - O/E: 4.67
  - Person-years: 2

- Any chemotherapy:
  - Observed: 44
  - O/E: 10.53
  - Person-years: 25

- Acute lymphoblastic leukemia, all:
  - Observed: 4
  - O/E: 11.00
  - Person-years: 2

- Radiotherapy only:
  - Observed: 1
  - O/E: 23.05
  - Person-years: 0

- Any chemotherapy:
  - Observed: 3
  - O/E: 18.47
  - Person-years: 2

- Acute nonlymphocytic leukemia, all:
  - Observed: 56
  - O/E: 16.67
  - Person-years: 25

- Radiotherapy only:
  - Observed: 3
  - O/E: 7.96
  - Person-years: 2

- Any chemotherapy:
  - Observed: 39
  - O/E: 25.53
  - Person-years: 18

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*Includes women who received radiotherapy alone as primary treatment for ovarian cancer. Patients may have subsequently been given chemotherapy, but these data are not collected by the SEER program.

*Includes women whose primary treatment for ovarian cancer included chemotherapy alone (n = 10,677 1-year survivors) or chemotherapy and radiotherapy (n = 904 1-year survivors).

*Number of person-years within interval.

Number of person-years within interval.

One hundred sixty-four solid tumors (O/E, 1.04) occurred 2 months–1 year after diagnosis of ovarian cancer.
The distribution of histological types of bladder cancer (54 transitional cell carcinoma, 5 squamous cell cancer, and 6 other or not specified) was evident within most follow-up periods. Increased risks of rectal cancer, all microscopically verified, were evident within most follow-up periods.

A 2-fold risk of bladder cancer was evident 1–4 years following diagnosis of ovarian tumors and increased to 4-fold among 15-year survivors (P trend = 0.01). Significant excesses of bladder cancer were associated with radiotherapy for ovarian cancer, with 6–7-fold risks evident ≥10 years after primary treatment (P trend = 0.03). Risk among patients initially given any chemotherapy was not significantly elevated. The distribution of histological types of bladder cancer (54 transitional cell carcinoma, 5 squamous cell cancer, and 6 other or not specified) was similar to general patterns within SEER and CTR files.

Most (86%) renal cancers were diagnosed during life. The 29 cancers consisted of 19 renal cell carcinomas, 3 carcinomas NOS, and 7 transitional cell carcinomas of the renal pelvis (n = 3) or ureter (n = 4), a pattern similar to de novo cancers in the general population.

Of 45 pancreas cancers, 40 (89%) were microscopically confirmed. Risk was significantly increased among 15-year survivors of ovarian cancer (P trend = 0.04). Although late excesses of pancreatic cancer seemed confined to ovarian carcinoma patients initially treated with radiotherapy, expected numbers within the chemotherapy group were quite small (0.25).

Risk of connective tissue cancer was almost 5-fold among 15-year survivors of ovarian carcinoma (P trend = 0.04). Six sarcomas (fibrosarcoma, clear cell sarcoma, malignant fibrous histiocytoma, hemangiosarcoma, leiomyosarcoma, and rhabdomyosarcoma) developed ≥1 year after any treatment which included radiotherapy; three of these cancers occurred within soft tissues likely to be in the treatment field, i.e., abdomen, lower limb, or hip.

Of the 111 leukemias, 84 were ANLL. Significant excesses of ANLL were evident in the 1–4- and 5–9-year intervals after ovarian cancer. Significant 60-fold risks for ANLL in the 1–4- and 5–9-year periods followed combined modality therapy (data not shown). Among subjects given chemotherapy alone, risk of secondary ANLL 1–9 years after treatment was 39.58 (O, 19; 95% CI, 23.82–61.82) and 17.22 (O, 26; 95% CI, 11.25–25.23), respectively, for those diagnosed with ovarian cancer in the 1970s or 1980–1992. No secondary ANLL was reported after treatment with chemotherapy alone among ovarian cancer patients diagnosed in the 1960s. Median survival after ANLL was 2 (range, 0–19) months.

Significantly increased risks for secondary ALL, all of which were histologically confirmed, were apparent in the 1–4- and 5–9-year intervals after diagnosis of ovarian cancer. Significant excesses of ALL were restricted to patients initially given any chemotherapy. Survival after ALL was generally poor (median, 4 months; range, 0–72 months).

Risks of second cancers of breast, colon, and rectum are stratified by histological type of ovarian adenocarcinoma in Table 4. A significantly increased risk of breast cancer occurred among women with serous adenocarcinoma of the ovary (O/E, 1.29), with nonsignificant excesses following endometrioid ovarian tumors (O/E, 1.32). Elevated risks of colon cancer occurred after all specified types of ovarian adenocarcinoma. Significantly increased 2-fold risks of rectal cancer developed among women with mucinous ovarian adenocarcinoma.

The large number of second breast cancers permitted further evaluation of risk by histological type of ovarian adenocarcinoma and patient age (Table 5). Significantly increased risks of breast cancers occurred among women diagnosed with ovarian adenocarcinoma before age 50 years (O/E, 1.37) or between 50 and 60 years (O/E, 1.28) but not at age 60 years or older (O/E, 1.04). Patients diagnosed with serous adenocarcinoma of the ovary prior to age 50 years demonstrated a significant 80% excess of breast cancer, with much smaller risks noted among older women. Less striking age patterns of breast cancer excesses were associated with endometrioid ovarian adenocarcinoma, with nonsignificant 1.3- to 1.5-fold risks present within all categories.

**DISCUSSION**

Using registry-based information, 32,251 women with ovarian cancer, including large numbers of long-term survivors, were evaluated for second cancer risk by primary therapy. An important finding is the significantly elevated risk of solid tumors among 15-year survivors of ovarian cancer, particularly those initially given radiotherapy, with no evidence of a diminution in risk with time. Based on our results, about one in five women with ovarian cancer would be expected to develop a new malignancy within two decades, including a variety of solid.
containing regimens became more widely used. Because details of chemotherapy during the later years of our survey, when cisplatin-common use of melphalan. a well-established leukemogen (7, 8, 19).

Breast cancer risk was associated with family history of breast cancer (36). In a case-control study of carcinoma (O, 54; O/E, 1.23; P > 0.05).4 In a case-control study of ovarian adenocarcinoma (87 cases), a significant 2-fold risk was associated with family history of breast cancer (36).

In our cohort, elevated risks of breast cancer were confined to women diagnosed with ovarian adenocarcinoma before age 60 years, which may reflect the greater contribution of genetic factors to tumors of early onset (38). Young women were especially prone to breast cancer after serous ovarian adenocarcinoma, similar to findings reported by Shah et al. (6). In our series, there was no clear age effect on breast cancer risk among women with endometrioid ovarian adenocarcinoma.

**Colorectal Cancer.** High-dose radiation for cancer and other diseases has induced colon cancer in some (39), but not all (40), patient populations. Although excesses of colon cancer were linked with prior radiotherapy in one survey of ovarian cancer patients (31), the pattern of elevated risks in our cohort seemed more consistent with the influence of shared etiological factors. In support of this hypothesis is the reciprocal finding that significant excesses of ovarian cancer (O, 250; O/E, 1.49) follow colon cancer in the SEER and CTR files.4 Some investigators have suggested that nutritional and hormonal interactions may contribute to the occurrence of multiple primary cancers, including colon, ovary, breast, and uterine corpus (41, 42). Ovarian tumors are also associated with hereditary nonpolyposis colorectal cancer, suggesting that genetic determinants may influence the constellation of ovarian and colon cancers (43). Whether defects in mismatch repair genes described in hereditary nonpolyposis colorectal cancer (44) contribute to elevated risks of colon cancer after radiotherapy for ovarian cancer (31) should be explored. Excess risks of colon cancer were seen after all cell types of ovarian cancer except the serous type. In several clinical surveys, a relation has been described between mucinous ovarian and appendiceal tumors (45–48), typically among patients with pseudomyxoma peritonei, a diagnostic entity not included in our study base. However, Shah et al. (6) found significantly elevated risks of colorectal carcinoma (n = 10) after serous ovarian tumors but not mucinous or endometrioid types.

Although we did not find a persuasive relationship between radiotherapy and the risk of rectal cancer, a significant association between radiation dose and rectal cancer has been reported following cervical cancer (40). In our study, the risk of rectal cancer seemed greater among women with mucinous ovarian adenocarcinoma, but CIs were wide, and misclassification may have affected the pattern seen.

**Pancreatic Cancer.** The pancreas is considered relatively insensitive to the carcinogenic effects of ionizing radiation (39); however, very high doses may induce cancers at this site (49). The excess seen among long-term survivors in our survey suggested a late effect of treatment, but the number of cases was small. The pancreas may receive radiation exposure during whole abdominopelvic radiotherapy

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**Table 5 Risk of second breast cancer by patient age and histology of first primary ovarian adenocarcinoma**

<table>
<thead>
<tr>
<th>Histology of ovarian adenocarcinoma</th>
<th>No. of patients</th>
<th>O</th>
<th>O/E</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All histologic types</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;50 yr</td>
<td>2,159</td>
<td>98</td>
<td>1.37*</td>
<td>1.11–1.67</td>
</tr>
<tr>
<td>Age 50-59 yr</td>
<td>6,651</td>
<td>110</td>
<td>1.28*</td>
<td>1.05–1.55</td>
</tr>
<tr>
<td>Age ≥60 yr</td>
<td>14,077</td>
<td>152</td>
<td>1.04</td>
<td>0.88–1.22</td>
</tr>
<tr>
<td>Serous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;50 yr</td>
<td>1,856</td>
<td>27</td>
<td>1.83*</td>
<td>1.21–2.67</td>
</tr>
<tr>
<td>Age 50-59 yr</td>
<td>1,891</td>
<td>28</td>
<td>1.20</td>
<td>0.80–1.74</td>
</tr>
<tr>
<td>Age ≥60 yr</td>
<td>3,855</td>
<td>50</td>
<td>1.15</td>
<td>0.86–1.52</td>
</tr>
<tr>
<td>Endometrioid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;50 yr</td>
<td>669</td>
<td>10</td>
<td>1.51</td>
<td>0.72–2.78</td>
</tr>
<tr>
<td>Age 50-59 yr</td>
<td>614</td>
<td>12</td>
<td>1.27</td>
<td>0.65–2.21</td>
</tr>
<tr>
<td>Age ≥60 yr</td>
<td>996</td>
<td>19</td>
<td>1.27</td>
<td>0.76–1.98</td>
</tr>
</tbody>
</table>

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*Includes all patients with ovarian adenocarcinoma (n = 27,887). Risk is also presented for histologic types of adenocarcinoma (serous and endometrioid) for which excess second primary breast cancers were noted (Table 4).

Refer to Table 1 for ICD-0 codes.

P < 0.05.

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for ovarian carcinoma, but SEER and CTR data do not permit correlation of second cancer risk with a specific regimen.

Bladder Cancer. The temporal pattern and distribution of excess bladder cancers among treatment groups in our survey suggest a radiogenic effect, particularly since pelvic irradiation for ovarian cancer delivers a high dose (~20–60 Gy) to the bladder (5). Comparable doses to this organ during treatment for cervical cancer resulted in an overall 4-fold risk of bladder neoplasia, with a 6-fold risk 15 years after therapy (40), consistent with our results. In addition, nonsignificant excesses of bladder cancer followed chemotherapy for ovarian cancer in our survey, perhaps due to the common use of cyclophosphamide, an established bladder carcinogen, in treatment regimens. Cyclophosphamide has been linked with bladder cancer among ovarian cancer patients (50), and a strong dose-response relationship has been reported following treatment for non-Hodgkin’s lymphoma (51).

Connective Tissue Cancer. The pattern of excess risks for connective tissue cancers also supports a radiogenic effect. Our findings are consistent with a follow-up of cervical cancer patients, documenting 3-fold excess risks of connective tissue cancer among 10-year survivors given radiation doses of >10 Gy (40).

Ocular Melanoma. Increased risks observed for ocular melanoma following ovarian cancer have not been seen previously and deserve further investigation, particularly to clarify the possible role of genetic (52) and hormonal (53) factors that may be shared by these tumors. Although statistically nonsignificant, an excess of ovarian cancer is seen after ocular melanoma in the SEER and CTR data bases (O/E, 1.34; P > 0.05). Ocular melanoma has been described occasionally in families prone to breast cancer, particularly in association with the susceptibility gene BRCAl (54, 55). Unlike BRCAl, however, this gene has not been clearly linked with ovarian carcinoma (54). There have been case reports suggesting an association between bilateral uveal melanoma and other cancers, including ovarian cancer (56), but further studies are needed to clarify the risks and mechanisms involved.

Comment. Various strengths and weaknesses of data on multiple primary tumors reported to cancer registries must be considered in interpreting our results. The SEER Program and CTR together provide large numbers of subjects and population-based data which minimize the bias due to selection or referral patterns in clinical or hospital series. The large sample size also permits quantification of second cancer risk by site. Because a very high percentage of all cancers in our series was histologically confirmed, it is unlikely that metastatic ovarian cancer was mistakenly diagnosed as a secondary malignancy. Because underreporting of second cancers may occur among long-term survivors migrating from areas included in the SEER Program or CTR, however, our estimates of increased risk may be conservative. In surveys of multiple primary cancers, one should be mindful that the large number of comparisons will generate some statistically significant associations by chance alone.

In our study, classification of ovarian tumors preceded the development of second malignancies, so that risk estimates for second cancer by cell type of ovarian tumor should not be biased. Furthermore, nondifferential misclassification between designated histological types of ovarian adenocarcinoma (57), if present, would dampen differences in risk (58). There was no evidence that associations of second cancer risk with patient age and histological type of ovarian adenocarcinoma were confounded by treatment.

Nevertheless, our data provide a reasonable estimate of the overall risk of second cancers among women with invasive ovarian cancer. Significant excesses of subsequent malignancies were evident in all time intervals after diagnosis of ovarian cancer and persisted among long-term survivors, suggesting the need for lifelong medical surveillance. Further epidemiological and laboratory studies are needed to clarify the carcinogenic risks associated with modern therapies for ovarian cancer and with shared susceptibility mechanisms, including genetic and reproductive factors. The multiple tumor complexes associated with ovarian cancer need further histological and molecular studies in efforts to elucidate etiological mechanisms and to develop targeted screening programs. Meanwhile, in proposing recommendations for the follow-up and management of women with ovarian cancer (59), it is important to recognize their long-term predisposition to an array of second cancers.

ACKNOWLEDGMENTS

We are indebted to George Giese and Dennis Buckman for computer support, to Denise Nguy for typing assistance, and to Rebecca Albert and Debra Reames for clerical services.

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Second Malignant Neoplasms among Long-Term Survivors of Ovarian Cancer

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