

Risk for Colorectal Cancer after Gynecologic Cancer

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Background. Studies have suggested that women with previous diagnoses of gynecologic cancer (cervical, endometrial, or ovarian) have an increased risk for colorectal cancer.

Objective: To quantify risk for colorectal cancer after gynecologic cancer, both overall and for subgroups defined by age at diagnosis, cancer stage at diagnosis, ethnicity, and duration of follow-up.

Design: Retrospective cohort analysis of the Surveillance, Epidemiology, and End Results (SEER) program database from 1974 through 1995.

Setting: U.S. cancer registry.

Patients: 21 222 patients with cervical cancer, 51 680 patients with endometrial cancer, and 28 832 patients with ovarian cancer.

Measurements: Standardized incidence ratios (SIRs) were calculated for each gynecologic cancer site and for subgroups to represent the relative risk for colorectal cancer in women with previously diagnosed gynecologic cancer compared with women without gynecologic cancer. Poisson regression methods adjusting simultaneously for all study variables were used to estimate relative risks for colorectal cancer across subgroups with each gynecologic cancer.

Results: Overall, risk for colorectal cancer was elevated among women with previous ovarian cancer (SIR, 1.36 [95% CI, 1.21 to 1.53]). Risk was greatest in women who received a diagnosis before 50 years of age (SIR, 3.67 [CI, 2.74 to 4.80]) but was also elevated in women who received a diagnosis between 50 and 64 years of age (SIR, 1.52 [CI, 1.25 to 1.83]). The risk for colorectal cancer after endometrial cancer was also elevated substantially if endometrial cancer was diagnosed before the age of 50 (SIR, 3.39 [CI, 2.73 to 4.17]). No apparent risk elevation was associated with previous cervical cancer.

Conclusions: Previous endometrial or ovarian cancer, particularly when diagnosed at an early age, increases subsequent risk for colorectal cancer. Greater emphasis on colorectal cancer screening in these populations may be necessary.

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Colorectal cancer is the second leading cause of death from cancer among women in the United States. Previous epidemiologic studies have identified a 1.5- to 3-fold increased risk for colorectal cancer in women with previous ovarian or endometrial cancer (1, 2).

In this study, we quantified risk for colon and rectal cancer after gynecologic cancer (ovarian, endometrial, and cervical) for cases initially reported to the Surveillance, Epidemiology, and End Results (SEER) program from 1974 through 1995. We examined risk in subgroups defined by age, ethnicity, and stage of gynecologic cancer at the time of diagnosis. Evidence that risk for colorectal cancer is elevated for some or all women with previous gynecologic cancer would have implications for colorectal cancer screening recommendations.

Methods

Participants were all women in whom incident, invasive epithelial cancer of the uterine cervix, uterine corpus, or ovary had been diagnosed between 1974 and 1995 and who were reported to a SEER registry. The SEER program is a network of nine population-based cancer registries whose catchment area includes approximately 10% of the U.S. population. Of these 118 505 women, we excluded those in whom cancer was diagnosed on autopsy or death certificate ($n = 725$), those with no follow-up time ($n = 2436$), those whose ethnicity was not white or black ($n = 6670$), those whose age at diagnosis was less than 25 years ($n = 1016$), and those with unknown cancer stage at diagnosis ($n = 5924$). After these exclusions, 101 734 women remained: 21 222 women with cervical cancer, 51 680 women with endometrial cancer, and 28 832 women with ovarian cancer.

Using the unique identifier assigned to these gynecologic cancer cases, we again searched the database for records of subsequent incident, invasive colon or rectal cancer. The rate of colon or rectal cancer among women with gynecologic cancer was then compared to the standard rates in the general female population (derived from the special public-use tape of the SEER program for 1973 to 1995).

Rates were compared by calculating standardized incidence ratios of observed to expected cases on

Table 1. Frequency Distribution of Patient Characteristics of Women Reported to Surveillance, Epidemiology, and End Results Registries, 1974–1995, with Incident Gynecologic Cancer and the Subcohort with Subsequent Incident Colorectal Cancer

Characteristic	Cervical Cancer		Endometrial Cancer		Ovarian Cancer	
	Full Cohort (n = 21 222)	Colorectal Cancer Subgroup (n = 193)	Full Cohort (n = 51 680)	Colorectal Cancer Subgroup (n = 1018)	Full Cohort (n = 28 832)	Colorectal Cancer Subgroup (n = 300)
	← n (%) →					
Age at diagnosis of gynecologic cancer						
25–49 years	10 788 (50.8)	34 (17.6)	5202 (10.1)	90 (8.8)	6550 (22.7)	52 (17.3)
50–64 years	5573 (26.3)	70 (36.3)	22 530 (43.6)	406 (39.9)	10 205 (35.4)	111 (37.0)
≥65 years	4861 (22.9)	89 (46.1)	23 948 (46.3)	522 (51.3)	12 077 (41.9)	137 (45.7)
Ethnicity						
White	17 765 (83.7)	160 (82.9)	49 591 (96.0)	968 (95.1)	27 190 (94.3)	284 (94.7)
Black	3457 (16.3)	33 (17.1)	2089 (4.0)	50 (4.9)	1642 (5.7)	16 (5.3)
Gynecologic cancer stage						
Local	12 152 (57.3)	118 (61.1)	42 512 (82.3)	874 (85.9)	7164 (24.9)	138 (46.0)
Regional	7215 (34.0)	68 (35.2)	5530 (10.7)	99 (9.7)	3638 (12.6)	47 (15.7)
Distant	1855 (8.7)	7 (3.6)	3638 (7.0)	45 (4.4)	18 030 (62.5)	115 (38.3)
Duration of follow-up						
0–18 months	5276 (24.9)	55 (28.5)	7915 (15.3)	162 (15.9)	12 303 (42.7)	136 (45.3)
19–66 months	6143 (29.0)	40 (20.7)	13 396 (25.9)	303 (29.8)	9527 (33.0)	58 (19.3)
≥67 months	9803 (46.2)	98 (50.8)	30 369 (58.8)	553 (54.3)	7002 (24.3)	106 (35.3)

the basis of age-, ethnicity-, and calendar year-specific standard rates. Therefore, standardized incidence ratios are interpreted as the age-, ethnicity-, and calendar year-adjusted relative risks for colorectal cancer in women with diagnosed gynecologic cancer compared with women without these diagnoses. Standardized incidence ratios were calculated separately for each gynecologic cancer site, as well as for subgroups within each site defined by age at gynecologic cancer diagnosis, cancer stage (local, regional, and distant), ethnicity, and duration of follow-up. Poisson regression methods incorporating external standard rates were used to estimate relative risks for colon or rectal cancer across subgroups of women with each gynecologic cancer, adjusting simultaneously for all study variables (3). These adjustments revealed little difference in the patterns across subgroups; thus, only person-year standardized incidence ratios are presented. Because separate analyses of colon and rectal cancer rates resulted in standardized incidence ratio trends similar to an aggregate end point of colorectal cancer, only the latter is presented.

Results

Table 1 displays frequency distributions of select characteristics for the full study cohort and the subgroup that developed invasive colorectal cancer. The median age at diagnosis of gynecologic cancer was 49 years for cervical cancer, 63 years for endometrial cancer, and 61 years for ovarian cancer. Incident colorectal cancer cases included a much smaller proportion of women younger than 50 years of age; this reflects the comparative deficit of young-

er women with endometrial cancer. The cervical cancer group had a greater proportion of black women, a finding consistent with the known ethnic disparity in the incidence of this tumor (4). Women with a diagnosis of local-stage ovarian cancer disproportionately accounted for incident cases of colorectal cancer; this probably reflects the poor prognosis of nonlocal ovarian cancer. Women with ovarian cancer had shorter observed follow-up (median, 2 years) than women with cervical cancer (median, 5 years) or endometrial cancer (median, 7 years). These results are also probably a function of the worse prognosis of this tumor.

Table 2 reports unadjusted colon cancer incidence rates in each cohort, both overall and stratified by age at gynecologic cancer diagnosis, ethnicity, gynecologic cancer stage, and duration of follow-up. This table also shows the standardized incidence ratios for each cohort and for cohort subgroups. Women who received a diagnosis of endometrial cancer before 50 years of age were more than three times more likely than women without endometrial cancer to have subsequent colorectal cancer (standardized incidence ratio, 3.39 [95% CI, 2.73 to 4.17]). In the ovarian cancer group, this younger age group also seemed to be at particular risk for colorectal cancer (standardized incidence ratio, 3.67 [CI, 2.74 to 4.80]). Women who were 50 to 64 years of age when ovarian cancer was diagnosed were also significantly more likely to develop colorectal cancer than like-aged counterparts without ovarian cancer (standardized incidence ratio, 1.52 [CI, 1.25 to 1.83]).

Black women with endometrial cancer seem to have a higher than expected risk for colorectal cancer (standardized incidence ratio, 1.81 [CI, 1.35 to 2.39]), as do women whose endometrial cancer is

diagnosed at a distant stage (standardized incidence ratio, 1.44 [CI, 1.05 to 1.92]). The subgroup of women with ovarian cancer at a distant stage is the only stage subgroup without evidence of excess risk for colorectal cancer, perhaps because of the limited survival in this group.

Regardless of gynecologic site, patients tended to have a higher than expected incidence of colorectal cancer in the first 6 months after diagnosis of the gynecologic tumor. Stratification by duration of follow-up is commonly used to determine whether heightened medical surveillance after a first cancer explains enhanced detection of second cases of cancer (5). Women with new gynecologic cancer are likely to receive comprehensive medical evaluations

around the time of diagnosis, suggesting a possible contribution of surveillance bias. However, in Poisson regression models (not shown) that simultaneously adjusted for length of follow-up and other variables, the associations for age, ethnicity, and stage persisted. This finding suggests that the excess colorectal cancer risk associated with endometrial and ovarian cancer in young age groups is valid. This is further supported by estimation of standardized incidence ratios after simultaneous stratification by age and duration of follow-up. Young women with endometrial and ovarian cancer had excess risk for colorectal cancer in all follow-up periods. Finally, analyses stratifying by duration of follow-up also showed that patients with ovarian

Table 2. Incidence of Invasive Colon Cancer and Standardized Incidence Ratios for Women Reported to Surveillance, Epidemiology, and End Results Registries, 1974–1995, with a Diagnosis of Gynecologic Cancer

Variable	Colon Cancer Incidence per 100 000 Person-Years (95% CI)	Standardized Incidence Ratio (95% CI)*
Patients with cervical cancer	115.02 (99.39–132.44)	1.08 (0.93–1.24)
Age at diagnosis		
25–49 years	35.45 (24.58–49.46)	1.23 (0.86–1.72)
50–64 years	155.64 (121.40–196.55)	1.10 (0.86–1.39)
≥65 years	330.65 (265.67–406.77)	1.02 (0.82–1.25)
Ethnicity		
White	112.16 (95.49–130.95)	1.09 (0.93–1.27)
Black	131.25 (90.45–183.98)	1.03 (0.71–1.44)
Cancer stage at diagnosis		
Local	100.03 (82.83–119.77)	1.11 (0.92–1.33)
Regional	153.01 (118.89–193.88)	1.05 (0.82–1.33)
Distant	130.11 (52.31–263.67)	0.91 (0.36–1.84)
Duration of follow-up		
0–6 months	160.21 (73.33–205.03)	1.69 (0.77–2.17)
7–18 months	107.86 (66.87–164.27)	1.15 (0.71–1.75)
19–66 months	76.10 (54.42–103.49)	0.80 (0.57–1.09)
≥67 months	131.48 (106.79–160.20)	1.08 (0.88–1.32)
Patients with endometrial cancer	203.96 (191.63–216.89)	0.98 (0.92–1.04)
Age at diagnosis		
25–49 years	163.39 (131.45–200.78)	3.39 (2.73–4.17)
50–64 years	152.85 (138.36–168.47)	0.93 (0.84–1.02)
≥65 years	292.57 (268.03–318.79)	0.91 (0.83–0.99)
Ethnicity		
White	199.51 (187.15–212.48)	0.96 (0.90–1.02)
Black	372.74 (276.88–490.97)	1.81 (1.35–2.39)
Cancer stage at diagnosis		
Local	196.33 (183.54–209.80)	0.95 (0.89–1.01)
Regional	253.46 (206.09–308.51)	1.15 (0.94–1.40)
Distant	302.11 (220.56–403.81)	1.44 (1.05–1.92)
Duration of follow-up		
0–6 months	216.72 (104.23–250.65)	1.31 (0.63–1.51)
7–18 months	102.43 (76.09–134.92)	0.59 (0.44–0.78)
19–66 months	198.46 (176.77–222.12)	1.07 (0.95–1.19)
≥67 months	224.84 (206.51–244.39)	0.94 (0.87–1.03)
Patients with ovarian cancer	206.37 (183.70–231.10)	1.36 (1.21–1.53)
Age at diagnosis		
25–49 years	114.82 (85.82–150.44)	3.67 (2.74–4.80)
50–64 years	195.03 (160.51–234.83)	1.52 (1.25–1.83)
≥65 years	317.36 (266.53–375.13)	1.03 (0.86–1.22)
Ethnicity		
White	205.90 (182.68–231.30)	1.36 (1.20–1.52)
Black	215.05 (123.12–347.31)	1.49 (0.85–2.40)
Cancer stage at diagnosis		
Local	221.49 (186.14–261.66)	1.54 (1.29–1.82)
Regional	232.67 (171.10–309.09)	1.50 (1.10–1.99)
Distant	182.93 (151.08–219.54)	1.16 (0.96–1.39)
Duration of follow-up		
0–6 months	336.43 (161.16–393.31)	2.20 (1.06–2.58)
7–18 months	165.35 (117.70–225.73)	1.15 (0.82–1.57)
19–66 months	122.40 (93.01–158.12)	0.88 (0.67–1.14)
≥67 months	232.62 (190.53–281.30)	1.38 (1.13–1.67)

* Standardized incidence ratios were adjusted for age, ethnicity, and year. Ratios stratified by any one of these variables are adjusted for the other two.

cancer, in addition to having excess risk soon after diagnosis, also had greater than expected colorectal cancer rates in the longest follow-up period (standardized incidence ratio, 1.38 [CI, 1.13 to 1.67]).

Discussion

A woman's lifetime risk for colorectal cancer is approximately 5% (6). Greater elevations in risk are seen in other settings, such as in women with a family history of colorectal cancer or polyps or those with a preexisting illness (such as inflammatory bowel disease). Our analysis suggests that endometrial cancer at 50 years of age or younger or ovarian cancer at 64 years of age or younger should also be considered major risk factors. Elevated risks for colorectal cancer in women younger than 50 years of age with endometrial or ovarian cancer are similar in magnitude to the risk conferred by having a first-degree relative with colorectal cancer. Previous cervical cancer does not appear to pose equivalent concerns.

Our analysis is not the first to suggest an elevated risk for colorectal cancer after gynecologic cancer (1, 2). The association is strengthened by studies demonstrating a reciprocal relation of elevated risk for ovarian or endometrial cancer after colorectal cancer (7). Relatives of women with ovarian cancer have elevated rates of death from colorectal cancer (8), and the risk for colorectal cancer is higher in women reporting endometrial or ovarian cancer in a first-degree relative (9).

The specific risk factors shared among these cancers are unknown. Hormonal modulation is one explanation. Colorectal cancer incidence rates in women lag approximately 5 years behind those in men, and the rates in both sexes converge after age 60 years (4). Decreased exposure to unopposed estrogen seems to protect against colorectal, endometrial, and ovarian cancer (10–12). In addition, dietary factors and obesity have been implicated in colorectal and ovarian or endometrial cancer (10). Elevated estrogen levels are typically observed in obese persons, suggesting a common mediating factor (13).

Hereditary nonpolyposis colorectal cancer is a familial colorectal cancer syndrome notable for the early development of colorectal and extraintestinal cancer, particularly endometrial and ovarian cancer. Colorectal cancer typically develops by 45 years of age. Endometrial cancer is the second most common type of cancer, affecting 40% of women with hereditary nonpolyposis colorectal cancer. Ovarian cancer risk is elevated fourfold over that in normal women, involving 10% of women with hereditary nonpolyposis colorectal cancer (14).

Shared genetic abnormalities may contribute to the association of endometrial or ovarian cancers and colorectal cancer. Although faulty mismatch repair mechanisms underlie most colorectal tumors associated with hereditary nonpolyposis colorectal cancer, they occur infrequently in endometrial cancer associated with hereditary nonpolyposis colorectal cancer, even for women who receive a diagnosis before 45 years of age (15). The molecular genetics of ovarian carcinoma are incompletely understood, although mismatch repair genes may be less important than susceptibility genes, such as *BRCA1* and *BRCA2* (16).

Our analysis could not determine the relative contribution of primary cancer therapy to secondary cancer development. Although we did not see any increased risk for rectal cancer after cervical cancer, this association has been reported (17). We did not attempt to control for treatment because data collected by SEER are incomplete (4).

The SEER database provides a large number of patients and a population-based control group; these characteristics minimize selection bias. Nearly all cancers are histologically confirmed, and this reduces the risk that metastatic gynecologic cancer was misdiagnosed as colorectal cancer. Although second cancers for persons who migrate out of the SEER database or who die of other causes with subclinical cancer may be underreported, this would reduce the magnitude of colorectal cancer incidence. We excluded many cases of gynecologic cancer reported to SEER. Although we believe that our findings apply to most women in whom gynecologic cancer was diagnosed, we are less certain that they apply to excluded groups (for example, women who received a diagnosis of gynecologic cancer before age 25 years).

We observed some excess risk for colorectal cancer during the first 6 months of follow-up for all types of gynecologic cancer. As mentioned, neither adjustment for length of follow-up nor calculation of standardized incidence ratios with simultaneous stratification for length of follow-up and age at diagnosis of gynecologic cancer support surveillance bias as a viable explanation for our other findings.

Our results underscore the importance of age at diagnosis of endometrial and ovarian cancer and subsequent risk for colorectal cancer. The possibility of hereditary nonpolyposis colorectal cancer should be considered in this setting. Other associations, including elevated risk for colorectal cancer among black women with endometrial cancer, require further study. Of note, our analysis was limited to patients who developed colorectal cancer after gynecologic cancer. Published recommendations for the follow-up of persons with hereditary nonpolyposis colorectal cancer emphasize screening for gynecologic

colorectal cancer after the development of colorectal cancer, not the converse (18). Little emphasis has been placed on colorectal cancer awareness for women with gynecologic cancers in their 40s and 50s.

A popular misconception is that women are not affected by colorectal cancer. Although screening reduces mortality rates, primary colorectal cancer screening for women and men is infrequent in the United States (19). Furthermore, reports suggest that women with preexisting comorbid conditions participate less in cancer screening programs than healthy women (20). Greater colorectal cancer risk after endometrial or ovarian cancer emphasizes the importance of colorectal cancer screening in this group. Whether more aggressive colonoscopy-based screening is appropriate for certain subgroups (that is, women who receive a diagnosis at young ages) or whether women who were previously given a diagnosis of endometrial or ovarian cancer will find colorectal cancer screening tenable requires further study.

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