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ORIGINAL CONTRIBUTION

Secondary Breast, Ovarian, and Uterine Cancers After Colorectal Cancer: A Nationwide Population-Based Cohort Study in Korea

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BACKGROUND: The risk of a second primary cancer has increased along with the increasing life expectancies of colorectal cancer survivors.

OBJECTIVE: We aimed to evaluate the incidence rate and risk factors of breast and gynecological (ovarian, uterine cervix/corpus) cancers among female colorectal cancer survivors.

DESIGN: This is a retrospective population-based cohort study.

SETTINGS: This study used data from the National Health Insurance Corporation of Korea.

PATIENTS: Each patient with colorectal cancer diagnosed from 2007 to 2012 was followed until 2015 and compared with age-matched women without colorectal cancer at a 1:5 ratio.

MAIN OUTCOME MEASURES: The primary outcome was de novo breast/gynecological cancer. Patients with available medical checkup data were included in an additional analysis.

RESULTS: We analyzed 56,682 patients with colorectal cancer and 288,119 age-matched noncolorectal cancer controls. The risk of breast/gynecological cancer was higher among patients with colorectal cancer than among controls (HR, 2.91; $p < 0.001$). The association with colorectal cancer was the highest for ovarian cancer (HR, 6.72), followed by uterine corpus cancer (HR, 3.99), cervical cancer (HR, 2.82), and breast cancer (HR, 1.85). This association remained consistent in the subgroup analysis of medical checkup data (14,190 patients with colorectal cancer, 71,933 controls). Among patients with colorectal cancer, those aged <55 years had a higher risk of breast/gynecological cancers than those aged >55 years (HR, 3.51 vs 2.59), and those with dyslipidemia had a higher risk of breast cancer than those without dyslipidemia (HR, 2.66 vs 2.06).

LIMITATIONS: This was a retrospective, population-based study. A prospectively designed study is needed to validate our conclusions.

CONCLUSIONS: Compared with the general population, patients with colorectal cancer carry a higher risk of developing secondary breast, ovarian, and uterine cancers. See **Video Abstract** at http://links.lww.com/DCR/A731.

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Patients who have cancer often develop synchronous or metachronous double or multiple malignancies, with 13.1% of male and 13.7% of female patients with cancer experiencing multiple primary tumors. In addition, cancer survivors have a 2-fold increased risk of developing a new second primary cancer even after previously achieving a cancer-free status.[1,2] The co-occurrence of multiple malignancies may be attributable to common risk factors for carcinogenesis.

Women are most often affected by cancers of the breast, colon, endometrium, lung, cervix, skin, and ovaries.[3] Breast cancer is the second most common cancer overall and is undoubtedly the most common cancer in women, with an estimated 1.7 million new cases (25% of all incident cancer cases) reported worldwide in 2012.[4] In addition, the comprehensive global statistics regarding gynecological cancers (eg, cervical, endometrial, and ovarian cancers) from the International Agency for Research on Cancer indicate that 19% of the 5.1 million estimated new cancer cases, 2.9 million cancer deaths, and 13 million 5-year prevalent cancer cases reported among women in 2002 could be attributed to these malignancies.[5] Interestingly, colorectal cancer (CRC) is the second most common cancer in women, with an estimated 614,000 new cases in women worldwide in 2012 (9.2% of all incident cancer cases in women).[4] South Korea has reported one of the greatest increases in the prevalence of CRC, with an incidence exceeding that reported in the United States.[6–10] Notably, CRC is the most common cancer affecting women in Korea.

Increasing evidence suggests that patients with CRC may have a greater risk of developing other types of cancer in comparison with the general population.[10–12] This incidence of second primary cancer development is expected to increase as the development of treatment and screening strategies leads to increases in the average life expectancies of CRC survivors. In South Korea, gynecological and breast cancers account for 28.8% (29,702/103,153) of the total cancer incidence and 15.8% (4881/30,822) of all cancer-related deaths.[7] Against this background, the present study aimed to evaluate the site-specific risks of second primary malignancies of the breast and female reproductive organs (ovary, uterine cervix, and uterine endometrium) among survivors of CRC.

MATERIALS AND METHODS

Data Source

This study used data from patients enrolled in the National Health Insurance Corporation (NHIC) database between 2007 and 2012 and whose diagnoses were based on codes from the *International Classification of Diseases, 10th Revision* (ICD-10). The NHIC is operated by the Korean government. The National Health Insurance Scheme is a social welfare program that aims to prevent bankruptcy due to high medical fees by mandating individuals to contribute regularly throughout their lives. More than 97% of Korean residents have been covered by this medical health insurance law since the 1963 reform. A diagnosis of any type of cancer received by an insured individual is automatically registered with the NHIC as a relevant code. The provision of NHIC data for medical research purposes allows researchers to obtain relatively accurate data regarding factors such as age, sex, smoking, and alcohol consumption statuses, accompanying diseases, drug prescription registry information, incidence, and mortality rate of diseases. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and national research committees, as well as the 1964 Declaration of Helsinki and later amendments or comparable ethical standards. The study was based on routinely collected data, and therefore informed consent was not specifically obtained. The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (X-1608/360–904).

Study Population and Design

The incidence of breast and gynecological (ovarian, uterine cervical, and uterine corpus) cancers among women diagnosed with CRC (ICD-10 codes C18, C19, and C20) was compared with the incidence among controls. Control group subjects were randomly selected from the general population of non-CRC patients in the NHIC database and were matched with patients with cancer in a 1:5 ratio by age and year of breast/gynecological cancer diagnosis. The primary outcome was a diagnosis of breast/gynecological cancer (ICD-10 codes: C50 for breast cancer, C53–55 for uterine cancer, and C56 for ovarian cancer) after a diagnosis of CRC. To exclude the possibility of synchronous or metastatic CRC, patients who received a diagnosis of female cancer within a latency period of 1 year after a CRC diagnosis were excluded. Patients who had previously been diagnosed with cancers other than CRC were also excluded. Information about the previous CRC diagnosis date, latency period, type of secondary cancer (breast/gynecological), annual income, and comorbidities (diabetes mellitus, hypertension, and dyslipidemia) was extracted from the database. Blood glucose, total cholesterol, and blood pressure data were also obtained.

An additional subgroup analysis of patients who had undergone a medical health checkup within 1 year before the diagnosis of CRC was performed. In addition, the BMI (additive effect) and information about lifestyle factors such as smoking, alcohol drinking, and exercise were obtained. Patients with CRC and available medical checkup data were compared with controls matched for age, BMI, smoking, alcohol use, exercise, income, and underlying disease.

Definition

Diabetes mellitus was defined as a fasting blood glucose level ≥126 mg/dL, a 2-hour plasma glucose level ≥200 mg/dL during an oral glucose tolerance test, or the use of antidiabetic medication.[11] Hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of an antihypertensive drug.[12] Dyslipidemia was defined as any one of the following: total cholesterol level ≥240 mg/dL, triglyceride level ≥150 mg/dL, low-density lipoprotein cholesterol level ≥140 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL, or the use of a lipid-lowering drug.[13] Participants with incomes <20% of the mean of the total population were classified as having a low household income. Residential areas were divided into urban or rural, with an urban area defined as a metropolitan city with a population exceeding 1 million residents. The ever-smoker group included ex-smokers and current smokers and was defined as patients who had smoked at least 5 packs of cigarettes in their lifetimes. Patients were further categorized by alcohol intake as nondrinkers and alcohol drinkers; the latter were defined as those who consumed alcohol at least once per week. Regular exercise was defined as the performance of physical activity for >20 minutes more than 3 times per week. The BMI was calculated by dividing the body weight by the height squared; overweight and obesity were defined as a BMI >23 kg/m^2 and >25 kg/m^2. Blood samples were collected after patients had fasted for at least 8 hours.

Statistical Analyses

Propensity score methods were used to generate the control group. Continuous variables with normal distributions were analyzed using the Student *t* test. Hazard ratios and 95% CIs were calculated via statistical analysis using Cox regression models after controlling for age, sex, BMI, smoking, alcohol consumption, exercise, diabetes mellitus, hypertension, dyslipidemia, and income. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria; http://www. R project. org). A 2-sided p value <0.05 was considered statistically significant.

RESULTS

Characteristics of the Study Population

In this study, we identified 56,682 individuals who had been newly diagnosed with primary CRC between 2007 and 2012. These patients with CRC were compared with 288,119 age-matched controls (Fig. 1). Table 1 shows the demographic characteristics of the study population. All included subjects were female, and the 2 groups did not differ significantly in terms of age ($p = 0.11$); approximately 25% and 75% of the subjects were younger than 55 years and older than 55 years. Compared with the control group, the CRC group included a significantly larger proportion of diabetic patients (16.89% vs 12.48%; $p < 0.001$) and patients with hypertension (41.7% vs 36.97%; $p < 0.001$).

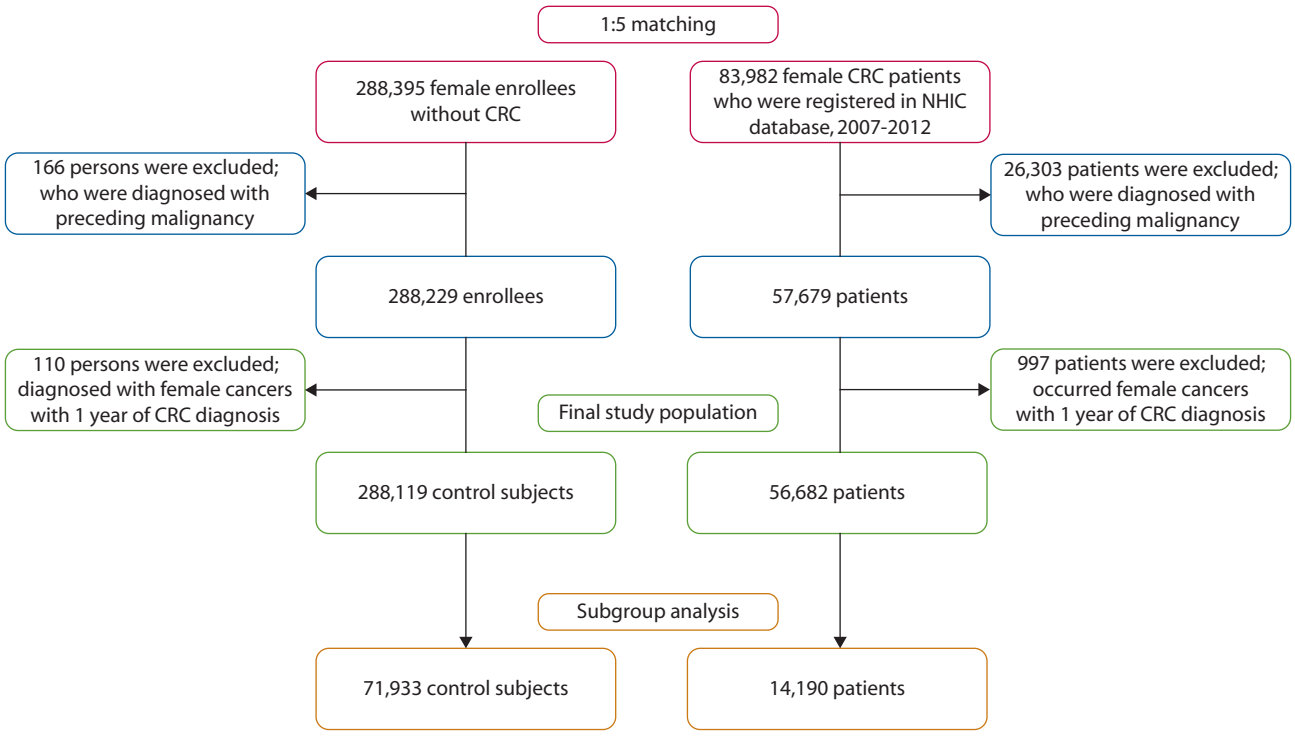

FIGURE 1. CONSORT flow diagram of patient recruitment. CRC = colorectal cancer; NHIC = National Health Insurance Corporation.

TABLE 1. Baseline characteristics of the population of the colorectal cancer (n = 56,682) and control group (n = 288,119)

Variables	*Control group (n = 288,119)*	*Colorectal cancer group (n = 56,682)*	*p value*
Female sex, n (%)	288,119 (100)	56,682 (100)	1.00
Age <55 y, n (%)	72,073 (25.02)	13,997 (24.69)	0.11
Age ≥55 y, n (%)	216,046 (74.98)	42,685 (75.31)	
Diabetes mellitus, n (%)	35,966 (12.48)	9574 (16.89)	<0.001
Hypertension, n (%)	106,520 (36.97)	23,634 (41.7)	<0.001
Dyslipidemia, n (%)	54,209 (18.81)	10,860 (19.16)	0.06
Low household income, n (%)[a]	77,779 (27)	14,151 (24.97)	<0.001
City (urban) residents, n (%)[b]	126,948 (44.38)	25,832 (45.99)	<0.001

The values represent the number and proportion of patients in each group.
[a] The low household income refers to those who are in the bottom 20% of the total population.
[b]City residents refer to people living in metropolitan areas with a population of over 1 million.

Dyslipidemia was also slightly more common in the CRC group, although this difference was not statistically significant (19.16% vs 18.81%; $p = 0.06$). A low household income was significantly more common in the control group (24.97% vs 27%; $p < 0.001$). A significantly higher proportion of patients in the CRC group lived in urban areas (45.99% vs 44.38% for controls; $p < 0.001$).

Risk of Breast/Gynecological Cancer Development in Patients With CRC

Table 2 lists the HRs for breast/gynecological cancers during the follow-up period after treatment for CRC. Patients were followed for a total of 330,442 person-years (mean: 5.83 years/person) in the CRC group and 1,691,937 person-years (mean: 5.87 years/person) in the general population. Overall, 949 of 56,682 patients with CRC (1.67%) and 1675 of 288,119 in the general population (0.58%) developed breast/gynecological cancer (HR, 2.91; 95% CI, 2.69–3.15; $p < 0.001$; incidence ratio, 2.87 vs 0.99 per 100,000 person-years).

The HRs for the development of site-specific breast/gynecological cancers were higher among CRC survivors than among control subjects. This increased risk was most prominent for ovarian cancer, followed by uterine corpus cancer, cervical cancer, and breast cancer (ovarian cancer: HR, 6.72; 95% CI, 5.72–7.91; $p < 0.001$; uterine corpus cancer: HR, 3.99; 95% CI, 3.21–4.96; $p < 0.001$; cervical cancer: HR, 2.82; 95% CI, 2.34–3.40; $p < 0.001$; breast cancer: HR, 1.85; 95% CI, 1.64–2.08; $p < 0.001$).

The risk of female cancer was higher among CRC patients younger than 55 years (HR, 3.51; 95% CI, 3.09–3.98; $p < 0.001$) than among those older than 55 years (HR, 2.59; 95% CI, 2.34–2.87; $p < 0.001$).

Figure 2 shows the cumulative incidence of breast/gynecological cancer in each group over time. The incidence of these cancers was concentrated within the first 5 years after the diagnosis of CRC. However, the risk of all breast/gynecological cancers remained higher among patients with CRC relative to the general population, even after 5 years, with annual averages of 0.99 and 2.87 breast/gynecological cancer diagnoses per 1000 women in the control group and the CRC patient group.

Subgroup Analysis Using BMI and Health Behavior Data

A total of 14,190 women with CRC and 71,933 women without CRC who had undergone a health checkup within 1 year of CRC diagnosis were included in an additional subgroup analysis (Supplementary Table 1, http://links.lww.com/DCR/A732). Patients with diabetes mellitus, hypertension, or dyslipidemia were significantly more common in the CRC group than in the control group. However, smoking, alcohol consumption, and BMI did not significantly differ between the 2 groups.

In this subgroup analysis, 210 of 14,190 patients with CRC (1.48%) and 372 of 71,933 subjects in the general population (0.52%) were diagnosed with breast/gynecological cancer (adjusted HR, 2.88; 95% CI, 2.43–3.41; $p < 0.001$) (Supplementary Table 2, http://links.lww.com/DCR/A733). Even after adjusting for BMI and health behavior data in addition to demographic differences and comorbidities, the risks of breast, ovarian, and uterine cancer were higher in the CRC group than in the general population.

We next conducted a multivariable analysis of CRC survivors to evaluate potential risk factors for secondary breast/gynecological cancer development (Table 3). In this analysis, BMI, alcohol consumption, physical exercise, income, and the status of hypertension or diabetes mellitus were not associated with the risk of secondary breast/gynecological cancer among CRC survivors. However, current smoking was associated with an increased risk of developing ovarian and uterine cervical cancers (HR, 1.62; 95% CI, 1.05–2.5 and HR, 1.54; 95% CI, 1.07–2.22), whereas dyslipidemia was associated with an increased risk of breast cancer (HR, 1.40; 95% CI, 1.10–1.79).

We additionally evaluated the possible combined effect of CRC and dyslipidemia on the development of secondary breast/gynecological cancers (Table 4). Among non-CRC subjects, dyslipidemia was associated with an increased risk of breast cancer (HR, 1.45; 95% CI, 1.09–

TABLE 2. The risks for secondary female cancers in colorectal cancer group and control group

Cancer type	*Group*	*Number (%)*	*Duration*[a]	*IR*[b]	*HR (95% CI)*[c]	*p value*	*Age <55*	*p value*	*Age ≥55*	*p value*
Overall	Control (n = 288,119)	1675 (0.58)	1,691,937.05	0.99	1 (reference)	<0.001	1 (reference)	<0.001	1 (reference)	<0.001
	Colorectal cancer (n = 56,682)	949 (1.67)	330,442.72	2.87	2.91 (2.69–3.15)		3.51 (3.09–3.98)		2.59 (2.34–2.87)	
Breast	Control (n = 288,119)	1053 (0.37)	1,693,030.43	0.62	1 (reference)	<0.001	1 (reference)	<0.001	1 (reference)	<0.001
	Colorectal cancer (n = 56,682)	382 (0.67)	332,416.90	1.15	1.85 (1.64–2.08)		2.02 (1.68–2.42)		1.75 (1.50–2.04)	
Ovarian	Control (n = 288,119)	258 (0.09)	1,694,569.7	0.15	1 (reference)	<0.001	1 (reference)	<0.001	1 (reference)	<0.001
	Colorectal cancer (n = 56,682)	338 (0.60)	332,293.59	1.02	6.72 (5.72–7.91)		10.14 (7.78–13.22)		5.11 (4.15–6.31)	
Cervix uteri	Control (n = 288,119)	307 (0.11)	1,694,431.9	0.18	1 (reference)	<0.001	1 (reference)	<0.001	1 (reference)	<0.001
	Colorectal cancer (n = 56,682)	170 (0.30)	332,909.17	0.51	2.82 (2.34–3.40)		3.22 (2.25–4.62)		2.67 (2.14–3.33)	
Corpus uteri	Control (n = 288,119)	184 (0.06)	1,694,661.01	0.11	1 (reference)	<0.001	1 (reference)	<0.001	1 (reference)	<0.001
	Colorectal cancer (n = 56,682)	146 (0.26)	333,081.38	0.44	3.99 (3.21–4.96)		5.43 (3.73–7.91)		3.40 (2.60–4.45)	

IR = incidence rate.
[a]The unit of duration is person-year.
[b]Incidence rate refers to the number of female cancer patients per 1000 people.
[c]Hazard ratio was adjusted for age, sex, income, and diabetes mellitus.

1.92 in dyslipidemic subjects). Among CRC patients, the incidence of breast/gynecological cancer was significantly higher among those with dyslipidemia (HR, 2.66; 95% CI, 1.78–3.98; $p < 0.001$) than among those without dyslipidemia (HR, 2.06; 95% CI, 1.52–2.78; $p < 0.001$) (Table 4). In other words, dyslipidemia is an additional contributor to the development of secondary breast cancer.

DISCUSSION

In this nationwide population-based cohort study of CRC survivors, we have identified an increased risk of breast and gynecological (ovarian, uterine cervix, and uterine corpus) cancers in comparison to age- and sex-matched non-CRC controls. Several studies have addressed the risk of second primary malignancies as the life expectancies of patients with CRC continue to increase.[14–19] However, few studies have focused on breast and gynecological cancers among CRC survivors. Lee et al[19] reported 2-fold and 3.2-fold increases in the risks of ovarian and uterine cancers among patients with CRC relative to the general population. Hemminki et al[17] reported higher risks of breast, ovarian, and uterine cancer among patients with CRC than among the general population, in particular, within 1 year after the diagnosis of CRC. Although the present study showed an increased risk of all site-specific breast/gynecological cancers in the CRC group, Yang et al[14] reported a higher incidence of uterine corpus cancer, but not of ovarian and breast cancers, among survivors of CRC than in the general population. Furthermore, Yang and colleagues[14,15] observed an increased risk of second primary malignancies within 5 years after the diagnosis of CRC. Although the reasons underlying the variable risks of breast and gynecological cancers among studies remain unclear, ethnic variation is likely a major contributor. In previous studies, the incidence of malignancy was found to vary according to differences in racial background and accessibility to medical services.[20,21]

In the present study, the risk of breast/gynecological cancer was higher among patients who were younger than 55 years at the first CRC diagnosis (HR, 3.51), compared with those aged 55 years or older (HR, 2.59). Other studies have similarly reported a higher risk of secondary malignancy in patients initially diagnosed with CRC at a younger age.[10,11,16] In summary, a lower age at CRC diagnosis corresponds to a higher probability of early breast/gynecological cancer detection during surveillance tests.

The occurrence of a second primary malignancy may be associated with genetic susceptibility, cancer-related treatment, environmental exposures, or hormonal effects. Currently, the most common and well-known syndromes are hereditary breast and ovarian cancer and hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome). Mutations in mismatch repair genes (*MLH1*,

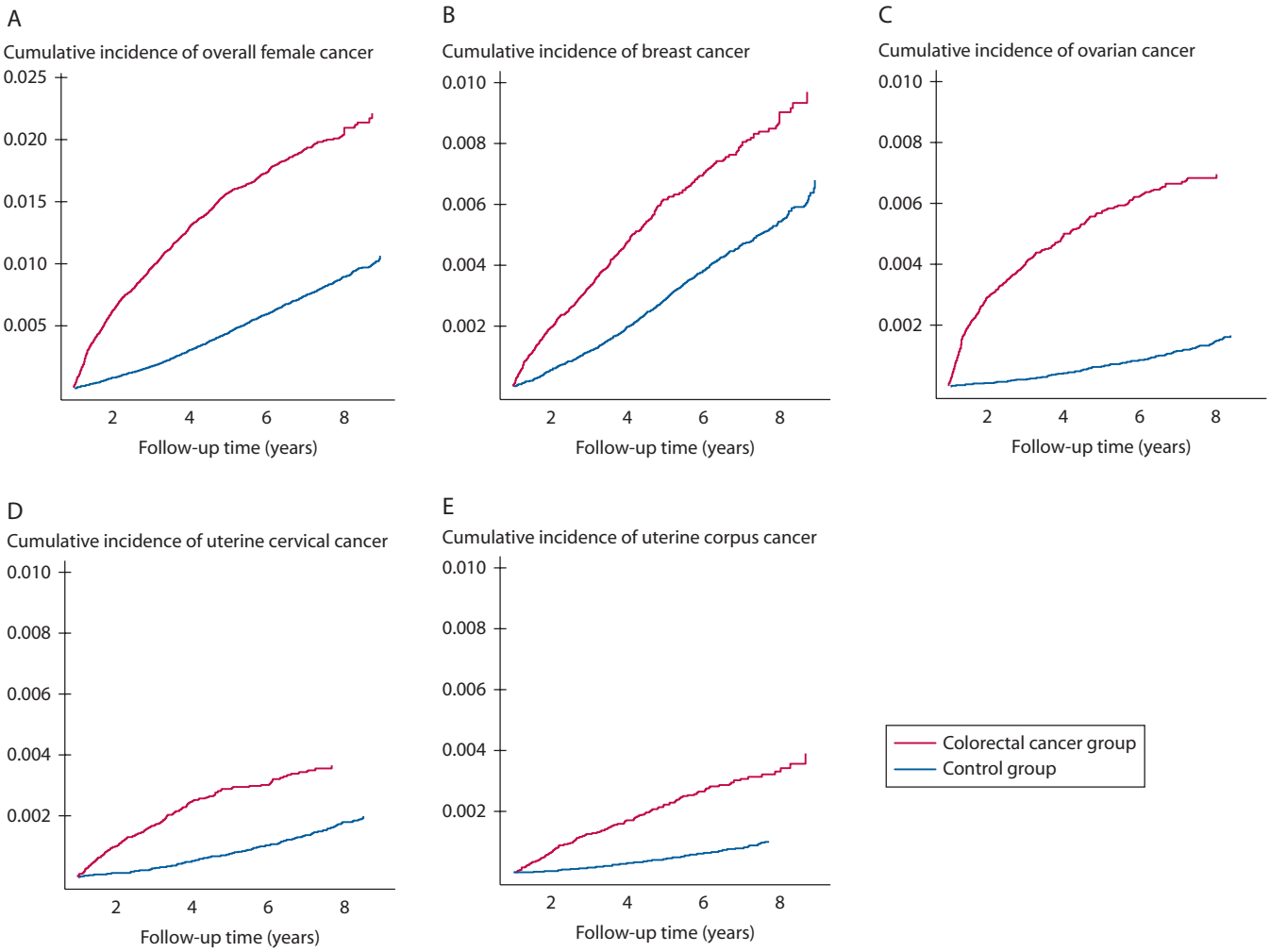

FIGURE 2. Cumulative incidence of breast and gynecological cancers over time.

MSH2, *PMS1*, and *MSH6*) can cause both CRC and gynecological (ovarian, breast, and endometrial) cancers at a young age.[22] However, HNPCC is a very rare disease, accounting for <1% of all CRC cases.[23] Evans et al[16] reported that patients with HNPCC had a 0.2% to 2% risk of developing primary carcinomas, with the exception of ovarian cancer. Women harboring a deleterious mutation in *BRCA1* or *BRCA2*, which encodes tumor suppressors, have an elevated risk of developing breast or ovarian cancer, as well as an elevated risk of CRC.[24] However, women harboring a *BRCA* mutation have only a slight overall increased risk of non-breast or -ovarian malignancies.[24] HNPCC and *BRCA* mutations are rare, and therefore cannot account for most of the secondary breast/gynecological cancers in patients with CRC. Genetic susceptibility to therapeutic agents is thought to correlate with the development of secondary cancers. Because individuals harbor genetic differences (ie polymorphisms) related to drug metabolism (eg, glutathione transferase), patients who are more sensitive to drugs have a higher risk of developing secondary cancers.[25]

Environmental and lifestyle factors such as smoking, excess alcohol intake, and dietary patterns also affect secondary cancer development.[26] Until recently, smoking was not considered a risk factor for breast/gynecological cancers, and studies of this issue were very limited. In 2009, the International Association for Cancer Research added ovarian cancer to the list of cancers caused by smoking.[27] Although smoking may not directly cause uterine cervical cancer, it appears to accelerate the damage to cervical tissues caused by the human papillomavirus or an otherwise unhealthy lifestyle.[28] In this study, we showed that current smoking is associated with an increased risk of secondary ovarian and cervical cancer development. However, whether a history of CRC might increase susceptibility to tobacco-related breast/gynecological carcinogenesis remains to be determined.

The other factor that may contribute to the association between CRC and uterine corpus cancer is the influence of

TABLE 3. Multivariable analysis for factors potentially affected secondary female cancers

Variables (reference)	*Overall, HR (95% CI)*	*Cancer type*			
		Breast, HR (95% CI)	*Ovarian, HR (95% CI)*	*Cervix uteri, HR (95% CI)*	*Corpus uteri, HR (95% CI)*
BMI <18.5 kg/m^2	1.12 (0.81–1.56)	1.32 (0.8–2.01)	1.14 (0.51–2.54)	1.82 (0.85–3.90)	0.63 (0.19–2.07)
BMI 18.5–23 kg/m^2	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
BMI 23–25 kg/m^2	0.87 (0.7–1.09)	0.91 (0.67–1.23)	1.01 (0.6–1.71)	0.68 (0.41–1.12)	0.75 (0.39–1.46)
BMI 25–30 kg/m^2	0.9 (0.73–1.11)	0.91 (0.68–1.20)	0.77 (0.44–1.32)	1.05 (0.7–1.59)	0.96 (0.54–1.71)
BMI ≥30 kg/m^2	1.33 (0.94–1.89)	1.23 (0.76–2.00)	1.82 (0.85–3.90)	1.12 (0.51–2.46)	1.52 (0.59–3.92)
Age, per 1 y	0.97 (0.96–0.98)	0.97 (0.96–0.97)	1.00 (0.98–1.01)	0.97 (0.95–0.98)	0.98 (0.97–1.00)
Smoking (no)	1.17 (0.98–1.4)	0.99 (0.77–1.27)	1.62 (1.05–2.5)	1.54 (1.07–2.22)	1.19 (0.71–1.98)
Drinking (no)	0.94 (0.78–1.12)	0.94 (0.74–1.2)	0.81 (0.52–1.26)	0.94 (0.65–1.35)	1.38 (0.84–2.29)
Exercise (no)	0.98 (0.8–1.19)	1.07 (0.82–1.39)	0.84 (0.5–1.4)	0.80 (0.52–1.25)	1.01 (0.58–1.77)
Low income[a]	0.87 (0.72–1.05)	0.76 (0.58–1.00)	0.98 (0.62–1.54)	1.01 (0.68–1.49)	0.92 (0.53–1.59)
Diabetes mellitus (no)	0.98 (0.79–1.22)	1.03 (0.77–1.38)	0.63 (0.35–1.13)	1.19 (0.77–1.85)	0.90 (0.48–1.68)
Hypertension(no)	1.10 (0.92–1.32)	1.27 (0.99–1.61)	0.93 (0.6–1.44)	0.86 (0.59–1.26)	0.92 (0.55–1.55)
Dyslipidemia (no)	1.22 (1.02–1.47)	1.40 (1.1–1.79)	1.4 (0.9–2.17)	0.94 (0.62–1.41)	1.33 (0.79–2.24)

Hazard ratio was adjusted for age, BMI, smoking, alcohol drinking, income, diabetes mellitus, and hypertension.
[a]The low household income refers to those who are in the bottom 20% of the total population.

hormones. Notably, nulliparous women have a higher risk of uterine corpus cancer.[29] In addition, nulliparous women with a family history of CRC had a risk ratio of 2.38 for CRC, compared with a risk ratio of 1.21 among women who bore more than 4 children.[30]

Interestingly, the present study found an increased risk of secondary breast cancer development among CRC survivors with that dyslipidemia. An elevated cholesterol level is a risk factor for breast cancer, although the mechanism by which this occurs is not well understood.[31] It is possible that dyslipidemia increases the cholesterol contents of cell membranes, which affects membrane fluidity and subsequent signaling. Moreover, the metabolite 27-hydroxycholesterol can function as an estrogen, thus increasing the proliferation of estrogen receptor-positive breast cancer cells.[31] In the present study, the CRC survivors with dyslipidemia had a synergistically elevated risk for developing breast cancers in comparison with CRC survivors without dyslipidemia. Further studies are needed to determine the mechanism of increased risk of breast cancer in patients with CRC who have dyslipidemia.

This study had several limitations. First, because this study was based on claims data, disease stage data were not available; in addition, we could not discern locally advanced and recurrent CRCs affecting female organs from true second primary cancers. Second, information related to other confounding factors, including parity, age of first menstruation and menopause, history of breastfeeding, and hormone therapy, was not available. Third, although hereditary CRC is rare, it could not be excluded because information about family histories or genetic testing was not available. Despite these limitations, this population-based study sourced data from a nationwide database compiled by the NHIC program, in which more than 97% of Koreans are obliged to participate. Because a biopsy confirmation is required for all patients registered for cancer, the cancer diagnoses were exhaustive and reliable. Moreover, studies evaluating the association between CRC and cancers of female organs are limited.

CONCLUSION

The risk of developing breast, ovarian, and uterine (including cervix and corpus) cancers is higher among patients with CRC than in the non-CRC population. Further causal and mechanistic studies are warranted.

TABLE 4. The relationship between dyslipidemia and breast cancer

Group	*Number*	*Breast cancer (%)*	*Duration[a]*	*IR[b]*	*Adjusted HR (95% CI)[c]*	*p value*
Dyslipidemia(–) CRC(–)	50,692	149 (0.29)	227,935.7	0.65	1 (reference)	NA
Dyslipidemia(–) CRC(+)	9842	60 (0.61)	43,997.49	1.36	2.06 (1.52–2.78)	<0.001
Dyslipidemia(+) CRC(–)	21,241	79 (0.37)	92,888.53	0.85	1.45 (1.09–1.92)	0.01
Dyslipidemia(+) CRC(+)	4348	30 (0.69)	18,951.55	1.58	2.66 (1.78–3.98)	<0.001

The subjects of this analysis are those who have health checkup data before and after diagnosis of colorectal cancer.
IR = incidence rate; NA = not available; CRC = colorectal cancer.
[a]The unit of duration is person-year.
[b]Incidence rate refers to the number of female cancer patients per 1000 people.
[c]Hazard ratio was adjusted for age, BMI, smoking, alcohol drinking, income, diabetes mellitus, and hypertension.

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REFERENCES

1. Rheingold SR, Neugut AI, Meadows AT. Secondary cancers: incidence, risk factors, and management. In: Bast Jr RC, Kufe DW, Pollock RE, Weichselbaum RR, Holland JF, Frei 3rd E, eds. *Holland-Frei Cancer Medicine*, 6th ed. Hamilton (ON): BC Decker; 2003. Available at: https://www.ncbi.nlm.nih.gov/books/NBK12712/ Accessed September 15, 2017.
2. Kufe DW, Pollock RE, Weichselbaum RR, Bast Jr RC, Gansler TS. Cancer Medicine 6 Review: A Companion to Holland-Frei Cancer Medicine 6. Hamilton (ON): BC Decker, 2003.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66:7–30.
4. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359–E386.
5. Sankaranarayanan R, Ferlay J. Worldwide burden of gynaecological cancer: the size of the problem. *Best Pract Res Clin Obstet Gynaecol*. 2006;20:207–225.
6. Oh CM, Won YJ, Jung KW, et al; Community of Population-Based Regional Cancer Registries. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2013. *Cancer Res Treat*. 2016;48:436–450.
7. Jung KW, Won YJ, Oh CM, Kong HJ, Lee DH, Lee KH. Prediction of cancer incidence and mortality in Korea, 2017. *Cancer Res Treat*. 2017;49:306–312.
8. Shin A, Kim KZ, Jung KW, et al. Increasing trend of colorectal cancer incidence in Korea, 1999-2009. *Cancer Res Treat*. 2012;44:219–226.
9. Shin CM, Han K, Lee DH, et al. Association among obesity, metabolic health, and the risk for colorectal cancer in the general population in Korea using the National Health Insurance Service-National Sample Cohort. *Dis Colon Rectum*. 2017;60:1192–1200.
10. Jung KW, Won YJ, Kong HJ, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2012. *Cancer Res Treat*. 2015;47:127–141.
11. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37(suppl 1):S81–S90.
12. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507–520.
13. Teramoto T, Sasaki J, Ishibashi S, et al. Diagnostic criteria for dyslipidemia. *J Atheroscler Thromb*. 2013;20:655–660.
14. Yang J, Li S, Lv M, et al. Risk of subsequent primary malignancies among patients with prior colorectal cancer: a population-based cohort study. *Onco Targets Ther*. 2017;10:1535–1548.
15. Guan X, Jin Y, Chen Y, et al. The incidence characteristics of second primary malignancy after diagnosis of primary colon and rectal cancer: a population based study. *PLoS One*. 2015;10:e0143067.
16. Evans HS, Møller H, Robinson D, Lewis CM, Bell CM, Hodgson SV. The risk of subsequent primary cancers after colorectal cancer in southeast England. *Gut*. 2002;50:647–652.
17. Hemminki K, Li X, Dong C. Second primary cancers after sporadic and familial colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2001;10:793–798.
18. Lee JW, Kim JW, Kim NK. Clinical characteristics of colorectal cancer patients with a second primary cancer. *Ann Coloproctol*. 2014;30:18–22.
19. Lee YT, Liu CJ, Hu YW, et al. Incidence of second primary malignancies following colorectal cancer: a distinct pattern of occurrence between colon and rectal cancers and association of co-morbidity with second primary malignancies in a population-based cohort of 98,876 patients in Taiwan. *Medicine (Baltimore)*. 2015;94:e1079.
20. Silber JH, Rosenbaum PR, Ross RN, et al. Racial disparities in colon cancer survival: a matched cohort study. *Ann Intern Med*. 2014;161:845–854.
21. Gill AA, Enewold L, Zahm SH, et al. Colon cancer treatment: are there racial disparities in an equal-access healthcare system? *Dis Colon Rectum*. 2014;57:1059–1065.
22. Seppälä T, Pylvänäinen K, Renkonen-Sinisalo L, et al. [Diagnosis and treatment of Lynch syndrome]. *Duodecim*. 2016;132:233–240.
23. Chika N, Eguchi H, Kumamoto K, et al. Prevalence of Lynch syndrome and Lynch-like syndrome among patients with colorectal cancer in a Japanese hospital-based population. *Jpn J Clin Oncol*. 2017;47:108–117.
24. Thompson D, Easton DF; Breast Cancer Linkage Consortium. Cancer incidence in BRCA1 mutation carriers. *Obstet Gynecol Surv*. 2013;58:27–28.
25. Wood ME, Vogel V, Ng A, Foxhall L, Goodwin P, Travis LB. Second malignant neoplasms: assessment and strategies for risk reduction. *J Clin Oncol*. 2012;30:3734–3745.
26. Curtis RE, Freedman DM, Ron E, et al, eds. New malignancies among cancer survivors: SEER Cancer Registries, 1973–2000. Bethesda, MD: National Cancer Institute; 2006. NIH Publ. No. 05-5302.
27. Secretan B, Straif K, Baan R, et al; WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens–Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol*. 2009;10:1033–1034.
28. Fonseca-Moutinho JA. Smoking and cervical cancer. *ISRN Obstet Gynecol*. 2011;2011:847684.
29. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol*. 1995;85:304–313.
30. Newcomb PA, Taylor JO, Trentham-Dietz A. Interactions of familial and hormonal risk factors for large bowel cancer in women. *Int J Epidemiol*. 1999;28:603–608.
31. Nelson ER, Chang CY, McDonnell DP. Cholesterol and breast cancer pathophysiology. *Trends Endocrinol Metab*. 2014;25:649–655.