Finding the Association between BMI and Risk of Subsequent Primary Cancer of the Breast, Lung, Colon, and Endometrium among Breast Cancer Survivors

Zahra Gohari

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Committee

Christopher Li

Amanda Phipps

Program Authorized to Offer Degree: Public Health Genetics

University of Washington

Abstract

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Zahra Gohari

Chair of the supervisory Committee:

Christopher Li

Department of Epidemiology

Introduction

There is a large population of breast cancer survivors at risk of developing second primary cancers. Most previous studies of second cancers have utilized data from cancer registries or medical records, with limited data on potential risk factors. We examined the association between body mass index (BMI) and risk of subsequent primary cancer of the breast, lung, colon, and endometrium after first primary breast cancer.

Methods

A population-based case-cohort study of women aged 20-74 diagnosed with a primary invasive breast cancer between 1986-2017 was conducted in Seattle, Washington. It consisted of 760 non-cases, 430 cases diagnosed with a second primary lung cancer, 527 cases with a second primary breast cancer, 212 cases with a second primary colon/rectum, and 250 cases with a second primary endometrial cancer. Multivariable-adjusted Cox proportional hazards regression was used to estimate hazard rations (HR) and 95% confidence intervals (CI) for the association of

BMI at the time of first breast cancer diagnosis with risk of second primary cancers at four anatomic sites.

Results

Compared to having a BMI of 18.5-24.9 kg/m^2 at the time of first primary breast cancer diagnosis, having a BMI of 25-29.9 kg/m^2 was associated with increased risk of second primary breast cancer (HR: 1.5; 95% CI: 1.2,1.9) and having a BMI ≥30 kg/m^2 was associated with increased risks of second primary endometrial and breast cancers (HR: 2.3; 95% CI: 1.7,3.2 and HR: 1.5; 95% CI: 1.2,1.9, respectively). BMI was not related to risks of second primary colorectal or lung cancers.

Conclusion

Our findings suggest that BMI may be positively associated with associated with certain forms of second primary cancers after first primary breast cancer and that women who are overweight or obese should be more closely monitored for development of certain second primary cancers.

Introduction

It is estimated that 3.8 million U.S. women are breast cancer survivors and based on the Surveillance, Epidemiology, and End Result (SEER) cancer registry network, 5-year relative survival for breast cancer is up to 90% (1,2) and with over 280,000 U.S. women predicted to be diagnosed with a first primary breast cancer in 2022 (2).

Based on data from the SEER cancer registry network from 2000-2009, 41% of second primary cancers in women were diagnosed in women with a first diagnosis of breast cancer. This statistic is much higher than the next most common first primary cancer site (i.e., colorectal cancer (13%)). Approximately 10% of breast cancer survivors are known to develop a second primary cancer (SEER data). This reflects both the high incidence and favorable survival of first primary breast cancer (3). Based on SEER data, the most common second primary cancers diagnosed among breast cancer survivors are cancers of the breast (35%), lung (17%), colon/rectum (10%), and endometrium (10%), together accounting for 72% of all second primary cancers diagnosed in breast cancer survivors.

Since the most common second primary cancer among breast cancer survivors is contralateral breast cancer (CBC), the most attention has been paid to this cancer type. Breast cancer survivors have a 60% higher risk of developing CBC compared to risk of women developing a first primary breast cancer (5). In a study by Li et al., obesity, regular alcohol consumption (≥7 alcoholic beverages/week), and current smoking were shown to be associated with 50%, 90%, and 120% increases in risk of CBC, respectively (6). In another study by Akdeniz et al., a meta-analysis was done to see the impact of lifestyle and reproductive factors on risk of CBC. They indicated that body mass index (BMI) (≥25 vs <25 kg/m^2 RR=1.22; 95% CI 1.01-1.47), alcohol use (ever vs never RR=1.25; 95% CI 1.01-1.47) and age at primiparity (≥25 vs <25 years RR=1.06; 95% CI 1.02-1.1) were associated with increased CBC risk. Additionally, they found no association between CBC and smoking (7). Druesne-Pecollo et.al. have also shown that BMI was associated with an increased risk of CBC (RR=1.40, 95% CI 1.2-1.57) (8).

Even though breast cancer survivors have a 22-52% excess risk of second primary lung, colorectal, and endometrial cancer compared to women in the general population (9,10), there has been a lack of research on the etiologies of these second primaries. Research on second primary lung cancer has focused primarily on radiation therapy and smoking. Breast cancer survivors who are smokers have a 6-fold increased risk of developing a subsequent lung cancer, and smokers who received radiation to treat their breast cancer had a 19-fold increased risk compared to non-smokers not treated with radiation (11). In another study by Li et al., radiotherapy alone was associated with elevated risk of second primary lung cancer after breast cancer (HR:1.11; P=0.045) (12). With respect to colorectal and endometrial cancer, most prior research has focused on obesity, and a meta-analysis of 13 studies found that, among breast cancer survivors, obesity was associated with increased risks of second primary colorectal (RR=1.89, 95% CI: 1.28-2.79) and endometrial (RR=1.96, 95% CI: 1.43-2.70) cancers (8). A population-based cohort from Wisconsin that included 132 women diagnosed with subsequent colorectal cancer and 113 with subsequent endometrial cancer among breast cancer survivors observed a positive association for second endometrial cancer with obesity ($p<0.01$) (13).

While more attention has been focused on CBC, and indeed risk factors have been identified, these findings need replication to clearly define potentially modifiable factors that can meaningfully reduce risk. Additionally, in-depth research on the etiologies of second primary lung, colorectal, and endometrial cancers following breast cancer is needed. Using our findings from this study, our aim is to add to the growing body of evidence that overweight and obesity may have an impact on the outcomes of breast cancer survivors. To fulfill our aim, we have included a larger sample size of all second primary cancer types compared to other studies and, to our knowledge, this study is the first study to look at all four second primary cancer sites in the same cohort.

Methods

The analysis was based on a case-cohort study design which was chosen to enhance efficiency compared to a full cohort study and improve flexibility over a nested case-control study. When there is a relatively large cohort and multiple rare outcomes of interest, this design is appropriate and advantageous because covariates only need to be evaluated for the cases of the second primary cancers and the common sub-cohort (not on the entire cohort). This reduces the costs of covariate collection (e.g., the number of interviews, medical record reviews, and tumor specimens obtained/tested) compared to the costs of collecting on the entire cohort while maintaining statistical power and allowing multiple outcomes to be assessed.

The population recruited was a randomly selected sub-cohort of breast cancer survivors among an underlying cohort of women diagnosed with a first primary invasive breast cancer between 1986-2017 between ages 20-74 years, while residing in the Seattle-Puget Sound region. This sub-cohort represents the distributions of age and diagnosis year of the full cohort. Specifically, cases are defined as women diagnosed with any of the four second primary cancers (including breast, lung, colorectal, and endometrium) after breast cancer; non-cases were women with a first primary invasive breast cancer who did not develop a second primary cancer at a site of interest. Overall, 800 non-cases, 621 cases of second primary lung cancer, 602 cases of CBC, 300 cases of second primary colon/rectum cancer and 307 cases of endometrial cancer were enrolled (total of 2,630 participants). Three primary sources of data used and obtained were participant interviews, medical records, and tumor tissue. Our exposure of interest was BMI at primary breast cancer diagnosis. The data included in this study was obtained from medical records obtained one year prior to first primary breast cancer diagnosis up to 3 months post-diagnosis of first primary breast cancer diagnosis; missing BMI values in medical records during this specified timeframe were filled in using available interview data where participants were asked to report their height and weight at primary breast cancer diagnosis. Based on this filter set on our data, as seen in table 1, 760 non cases, 527 cases of CBC, 426 cases of second primary lung cancer, 212 cases of second primary colon/rectum cancer and 250 cases of endometrial cancer were included in our analysis. The remaining participants with missing data were not included in this study.

Data analysis

Cox proportional hazards regression was used to calculate hazard ratios and 95% confidence intervals (assuming verification of the proportional hazards assumption). This method allows cases not included in the randomly sampled sub-cohort to be included in the analysis, but only in the risk set in which they fail and has been shown to produce less biased estimates than other methods in case-cohort studies with small sub-cohorts (<1% of full cohort) (14). Potential confounding variables included stage at diagnosis of first primary breast cancer (I–IV), definitive local treatment for first primary breast cancer (breast-conserving radiation), chemotherapy (yes, no),

race (Non-Hispanic, Hispanic, White, African American, Asian, American Indian/Alaska Native, and multiple), age categories at first primary and second primary cancer diagnosis, history of adjuvant hormonal therapy, year categories of primary and second primary cancer diagnosis, smoking status, family history of cancer, hormone receptor status (ER: estrogen receptor and PR: progesterone receptor from tumor samples), and alcohol consumption. The final models were adjusted for age at first primary cancer diagnosis, year of first primary cancer diagnosis, and race; second primary lung and endometrial cancer occurrence models were also adjusted for smoking status. All other variables did not change risk estimates by more than 10% and thus were not included in the final models. Effect modification was assessed by examining stratum-specific associations and by adding interaction terms to the Cox models.

Results

In this sample of lung, breast, and colon/rectum cancer cases, lung cancer cases were more likely to be older, have a later year of second cancer diagnosis, and more likely to be a current smoker compared to the sub-cohort (Table 1). Breast cancer cases were more likely than the overall sub-cohort to have a history of ER+/PR+ breast cancer subtype. Endometrial cancer patients were slightly less likely to be current alcohol users at the time of first primary breast cancer diagnosis. The age at primary breast cancer diagnosis, year of primary breast cancer diagnosis, and race distribution was similar between our sub-cohort and the second primary cancer group that was included in our analysis.

An increased risk of second primary endometrial cancer after breast cancer was associated with having a BMI ≥30 kg/m^2 (HR vs. <25 kg/m^2: 2.3; 95% CI: 1.7,3.2) (Table 2). BMI was also associated with an increased risk of second primary breast cancer in women with BMI 25-29.9 kg/m^2 (HR vs. <25 kg/m^2: 1.5; 95% CI: 1.2, 1.9) and BMI ≥30 kg/m^2 (HR vs. <25 kg/m^2: 1.5; 95% CI: 1.2,1.9). Second primary colorectal and lung cancers were not associated with BMI categories.

Discussion

In this analysis of second primary lung, breast, and colorectal cancers after first primary invasive breast cancer, our study suggests that obesity may primarily contribute to an increased risk of second primary breast and endometrial cancer. Our results agree with previous reports that suggest an increased risk of endometrial cancer among breast cancer survivors with greater BMI (8,13). Specifically, we found evidence that BMI ≥30 kg/m^2 (vs. <25 kg/m^2) was positively associated with risks of endometrial cancer.

Our results are also in agreement with reports that suggest an increased risk of CBC cancer among breast cancer survivors with greater BMI (6-8). Specifically having a BMI ≥30 kg/m^2 or 25-29.9 kg/m^2 (vs. <25 kg/m^2) at the time of first primary breast cancer diagnosis was positively associated with risk of second primary breast cancer. Based on previous studies, increased circulating levels of the hormone estrogen may explain the positive associations between excess body weight and risks of second primary breast and endometrial cancers. Mechanisms such as increased levels of other circulating hormones and growth factors or a low-grade chronic inflammatory state may also be involved (16,17).

Our study included a larger sample size of all second primary cancer types compared to other studies and, to our knowledge, is the first study to look at all four second primary cancer sites in the same cohort. Additionally, our data suggests that there is heterogeneity in the relationship between BMI and second primary cancer occurrence. Unlike the present analysis, some prior

studies have also suggested associations with second primary lung and colorectal cancers (8,12). However, there are also a number of studies that report similar findings to our results (13), suggesting that more research should be considered. We observed a suggested, but not statistically significant increased risk of second primary lung and colorectal cancer occurrence with greater BMI.

The finding that excess body weight was associated with increased risk of second primary cancers at sites where a relationship for first primary cancers is well established (15) suggests that this positive association seen in some second primary cancers may be due to a life-long exposure rather than a specific effect after the first breast cancer diagnosis. The mechanisms by which excess body weight increases the risk of developing first or second primary cancers are likely to be similar.

Our analysis is subject to some limitations due to available data. In particular, we were able to examine associations with BMI at first primary breast cancer diagnosis, which does not reflect BMI change or weight gain after cancer diagnosis in study participants. Additionally, although our population-based study reflects the demographic composition of breast cancer cases in the Seattle-Puget Sound region, it does not reflect the racial distribution of the broader United States; therefore, these results may not be generalizable to the U.S. population.

In conclusion, our findings suggest that BMI may be associated with risk of certain second primary cancers among women with a history of breast cancer. Additionally, they add to the growing body of evidence that overweight, and obesity may have an impact on the outcomes of breast cancer survivors. Obesity in women with breast cancer, as well as weight gain after a breast cancer diagnosis, has been linked to an increase in mortality. Physical activity, on the other hand, may improve the prognosis of breast cancer (8). Based on observational data, the American Cancer Society developed guidelines recommending that cancer patients and survivors achieve and maintain a healthy weight, engage in regular physical activity, and follow a diet rich in vegetables, fruits, and whole grains to improve cancer outcomes (18). Further clarifying the impact of potentially modifiable risk factors like BMI and alterations in regimens for obese breast cancer survivors could be an additional strategy to reduce risks of second cancers among these patients. Randomized clinical trials in overweight and obese breast cancer patients are needed to assess the effect of what is defined as normal BMI (18.5-24.9 kg/m^2) restoration through physical activity and/or dietary interventions on second primary cancer incidence and other breast cancer outcomes. At the very least, health care providers should encourage breast cancer patients to follow nutritional and physical activity guidelines.

Table 1 Distribution of patient characteristics and known cancer risk factors by cancer subtype.
*<5 counts are present in these groups
1.Non cases that developed a second primary cancer other than breast, lung, colorectal, and endometrial cancer were included, but censored from the analysis at time of second cancer diagnosis.

Risk factors and demographic characteristics	Non cases (n=760) n,%	Breast cancer (n=527) n,%	Lung cancer (n=430) n,%	Colorectal cancer (n=212) n,%	Endometrial cancer (n=250) n,%
Year of primary BC diagnosis Categories:					
1988-1994	22 (2.9)	57 (10.8)	10 (2.3)	6 (2.8)	4 (1.6)*
1995-1999	276 (36.3)	191 (36.2)	166 (38.6)	88 (41.5)	90 (36)
2000-2004	228 (30)	141 (26.7)	116 (27)	46 (21.7)	82 (32.8)
2005-2009	145 (19)	90 (17)	95 (22.1)	42 (19.8)	40 (16)
2010-2014	71 (9.3)	40 (7.6)	39 (9)	21 (9.9)	30 (12)
2015-2018	18 (2.5)	8 (1.7)	4 (1)*	9 (4.3)	4 (1.6)*
Age at primary BC diagnosis Categories:					
<40	36 (4.7)	48 (9.1)	8 (1.9)	7 (3.3)	7 (2.8)
40-49	123 (16.2)	97 (18.4)	51 (11.9)	18 (8.5)	65 (26)
50-59	228 (30)	170 (32.3)	127 (29.6)	49 (23.1)	83 (33.2)
60-69	294 (38.7)	152 (28.8)	185 (43)	87 (41.1)	75 (30)
70-79	79 (10.4)	60 (11.4)	59 (13.6)	51 (24)	20 (8)
≥80	0	0	0	0	0
Year of second primary cancer diagnosis Categories[1]:					
1988-1994	0	22 (4.2)	4 (0.9)*	1 (0.5)*	0
1995-1999	4	53 (10)	16 (3.7)	17 (8)	16 (6.4)
2000-2004	13	90 (17.1)	57 (13.2)	27 (12.7)	31 (12.4)
2005-2009	22	112 (21.3)	118 (27.4)	51 (24.1)	74 (29.6)
2010-2014	32	159 (30.2)	130 (30.3)	64 (30.2)	68 (27.2)
2015-2018	25	91 (17.2)	105 (24.5)	52 (24.5)	61 (24.4)
Age at second primary cancer diagnosis Categories[1]:					
<40	1	17 (3.2)	0	2 (0.9)*	0
40-49	6	46 (8.7)	11 (2.6)	8 (3.8)	15 (6)
50-59	14	104 (19.8)	57 (13.2)	26 (12.2)	74 (29.6)
60-69	31	196 (37.2)	153 (35.6)	60 (28.3)	87 (34.8)
70-79	40	135 (25.6)	169 (39.3)	83 (39.2)	61 (24.4)
≥80	4	29 (5.5)	40 (9.3)	33 (15.6)	13 (5.2)
Race/Ethnicity					
White	715 (94.3)	478 (90.7)	396 (92.1)	195 (92)	229 (91.6)
Black	20 (2.6)	18 (3.5)	11 (2.6)	4 (1.9)*	6 (2.4)

American Indian/Alaska Native	1 (0.1)*	5 (0.9)	7 (1.6)	3 (1.5)*	1 (0.4)*
Native Hawaiian or Pacific Islander	18 (2.3)	14 (2.6)	10 (2.3)	5 (2.3)	12 (4.8)
Asian	0	2 (0.4)*	0	0	0
Multiple	5 (0.6)	10 (1.9)	6 (1.4)	5 (2.3)	2 (0.8)*
(Missing)	1 (0.1)*	0	0	0	0
Hispanic ethnicity					
Yes	9 (1.2)	9 (1.7)	5 (1.2)	6 (2.8)	4 (1.6)*
No	751 (98.8)	518 (98.3)	425 (98.8)	206 (97.2)	246 (98.4)
First degree family history					
Yes	198 (26)	170 (32.2)	111 (25.8)	50 (23.6)	68 (27.2)
No	551 (72.5)	345 (65.5)	303 (70.5)	156 (73.6)	170 (68)
(Missing)	11 (1.5)	12 (2.3)	16 (3.7)	6 (2.8)	12 (4.8)
Alcohol use at diagnosis					
Never	215 (28.3)	103 (19.5)	50 (11.6)	46 (21.7)	72 (28.8)
Former	89 (11.7)	44 (8.4)	42 (9.8)	21 (9.9)	17 (6.8)
Current	411 (54)	293 (55.6)	247 (57.4)	110 (51.9)	120 (48)
Not current	41 (5.4)	78 (14.8)	64 (14.9)	29 (13.7)	36 (14.4)
(Missing)	4 (0.6)*	9 (1.7)	27 (6.3)	6 (2.8)	5 (2)
Smoking status at diagnosis					
Never	396 (52.1)	252 (47.9)	47 (10.9)	96 (45.3)	142 (56.8)
Former	258 (34)	166 (31.5)	142 (33.1)	76 (35.8)	86 (34.4)
Current	105 (13.8)	103 (19.5)	233 (54.2)	35 (16.5)	17 (6.8)
Not current	0	6 (1.1)	4 (0.9)*	5 (2.4)	5 (2)
(Missing)	1 (0.1)	0	4 (0.9)*	0	0
ER/PR status of primary breast cancer					
ER+/PR+	166 (21.8)	79 (5)	54 (12.5)	31 (14.6)	33 (13.2)
ER+/PR-	10 (1.3)	14 (2.7)	3 (0.7)*	1 (0.5)*	3 (1.2)*
ER-/PR+	74 (9.7)	45 (8.5)	39 (9)	15 (7.0)	20 (8.0)
ER-/PR-	473 (62.2)	368 (69.8)	311 (72.4)	160 (75.5)	185 (74)
(Missing)	37 (5.0)	21 (4.0)	23 (5.4)	5 (2.4)	9 (3.6)
History of adjuvant hormone therapy					
Yes	396 (52.1)	281 (53.3)	266 (61.9)	129 (60.9)	161 (64.4)
No	334 (43)	233 (44.2)	157 (36.5)	79 (37.2)	81 (32.4)
(Missing)	30 (4.9)	13 (2.5)	7 (1.6)	4 (1.9)*	8 (3.2)
History of breast-conserving radiation					
Yes	498 (65.5)	369 (70.1)	288 (67)	151 (71.2)	167 (66.8)
No	247 (32.5)	148 (28)	140 (32.5)	58 (27.4)	81 (32.4)
(Missing)	15 (2.0)	10 (1.9)	2 (0.5)*	3 (1.4)*	2 (0.8)*

Stage of primary breast cancer					
Local	279 (36.7)	164 (31.1)	115 (26.7)	61 (28.8)	62 (24.8)
Regional	481 (63.3)	363 (68.9)	315 (73.3)	151 (72.2)	188 (75.2)
BMI (kg/m^2) included in analysis					
<25	338 (44.4)	185 (35.2)	195 (45.3)	94 (44.3)	68 (27.2)
25-29.9	210 (27.6)	173 (32.8)	124 (28.8)	57 (26.9)	56 (22.4)
≥ 30	212 (28.0)	169 (32.0)	111 (25.9)	61 (28.8)	126 (50.4)

Table 2 Hazard rations and 95% confidence intervals for the risk of lung, breast, colorectal, and endometrial cancer reoccurrence among US women aged 20-74, 1986-2017

	Breast cancer HR (95% CI)	Lung cancer HR (95% CI)	Colorectal cancer HR (95% CI)	Endometrial cancer HR (95% CI)
BMI (kg/m^2)				
<25	Ref	Ref	Ref	Ref
25-29.9	1.5 (CI:1.2,1.9)*	1.1 (0.9,1.4)	1.1 (0.8,1.5)	1.4 (0.9,2.3)
≥ 30	1.5 (CI:1.2,1.9)*	1.0 (0.8,1.3)	1.0 (0.7,1.5)	2.3 (1.7,3.2)*

Abbreviations: HR: hazard ratio; CI: confidence interval, Ref: Reference
*Significant (p-value<0.01)

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