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Relationship between Diabetes and Risk of Second Primary Contralateral Breast Cancer

Christopher I. Li[1], **Janet R. Daling**[1], **Mei-Tzu C. Tang**[1], and **Kathleen E. Malone**[1]
[1] Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

Abstract

Breast cancer survivors have a substantially higher risk of developing a second primary contralateral breast cancer (CBC) compared to the risk of breast cancer among women in the general population. While data regarding the relationship between diabetes and breast cancer incidence are inconsistent, diabetes is more clearly linked to an elevated risk of all-cause mortality among breast cancer survivors. However, no prior studies have assessed its impact on CBC risk. We assessed the relationship between diabetes and CBC risk in a population-based nested case-control study consisting of women 40–79 years of age diagnosed with a first primary ER-positive invasive breast cancer. It included 322 women who developed a second primary CBC and 616 matched control women diagnosed only with a first breast cancer. We used conditional logistic regression to quantify associations between diabetes and CBC risk. Compared to women without a history of diabetes, diabetics had a 2.2-fold [95% confidence interval (CI): 1.3–3.6] increased risk of CBC. This risk was more pronounced among women diagnosed with their first breast cancer before age 60 years (odds ratio=11.5, 95% CI: 2.4–54.5), compared to those diagnosed at age 60 years or older (odds ratio=1.5, 95% CI: 0.8–2.7, p for interaction=0.011). Diabetics diagnosed with breast cancer appear to have an elevated risk of CBC. This is the first study to report this relationship, but if confirmed efforts to insure that diabetic breast cancer survivors are carefully screened for second breast cancers may be warranted.

Keywords

Breast cancer; diabetes; contralateral breast cancer

INTRODUCTION

Type 2 diabetes, which is characterized by hyperinsulinemia, insulin resistance, and hyperglycemia, is a weak to moderate risk factor for breast cancer with data from two recent meta-analyses finding that women with a history of diabetes have a 15–20% increased risk of breast cancer compared to women without diabetes.(1,2) In addition, breast cancer patients who are diabetics have been shown to have a 32% increased risk of chemotherapy related complications,(3) and two meta-analyses reported that they also have a 24–61% increased risk of all-cause mortality compared to breast cancer patients without diabetes.(2,4) The link between diabetes mellitus and breast cancer is complicated by obesity in that obesity is a well established risk factor for both diseases. However, it is biologically plausible that diabetes is related to breast cancer independent of obesity through the impact

Corresponding author: Christopher I. Li, MD, PhD, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., M4-C308, P.O. Box 19024, Seattle, WA 98109-1024, Telephone: 206.667.7444, Fax: 206.667.5948, cili@fhcrc.org.

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diabetes has on insulin levels. Elevated insulin can both directly promote breast cancer cell growth and proliferation, and indirectly through regulation of a variety of factors including insulin-like growth factors, sex hormones, and adipokines.(5)

While the literature supports a positive relationship between diabetes and breast cancer incidence and all cause mortality among breast cancer patients, no prior studies have evaluated the relationship between diabetes and risk of second primary contralateral breast cancer among breast cancer survivors. Contralateral breast cancer is an outcome of considerable concern to breast cancer survivors as they have a two to six times greater risk of developing a second primary contralateral breast cancer than women in the general population have of developing a first breast cancer.(6) While adjuvant hormonal therapy can reduce contralateral breast cancer risk by 47%,(7) little information on other factors that impact this risk are known. We evaluated the relationship between diabetes and risk of second primary contralateral breast cancer among survivors of invasive estrogen receptor positive (ER+) breast cancer. Identification of risk factors for second contralateral tumors is of clinical and public health importance given the ever growing number of breast cancer survivors.

METHODS

We conducted a population-based nested case-control study. Cases and controls were selected from the 17,628 women diagnosed with a first primary invasive, stage I to IIIB, ER + breast cancer at age 40 to 79 years in the four county Seattle-Puget Sound region (including King, Pierce, Snohomish, and Thurston counties) from January 1, 1990 to September 30, 2005 identified through the Cancer Surveillance System (CSS). CSS is the population-based cancer registry that serves western Washington and participates in the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) program.

Second primary invasive contralateral breast cancer cases were defined as women who developed invasive cancer in the breast contralateral to their first breast cancer six months or more after their first breast cancer diagnosis from July 1, 1990 to March 31, 2007 in our four county catchment area. Controls were individually matched 2:1 to cases on age, year, and county of first breast cancer diagnosis; race/ethnicity; SEER historic stage of first breast cancer (localized vs. regional); and survival without an ensuing contralateral breast cancer at least through the time their matched case was diagnosed with contralateral breast cancer. Controls were required to have an intact breast contralateral to their breast cancer at least through their matched case's second breast cancer diagnosis (those who had a prophylactic mastectomy on their contralateral breast were excluded). In addition, controls had to reside in their county of diagnosis from their breast cancer diagnosis to at least the duration between their matched case's first and second breast cancer diagnoses. Cases and controls who had an intervening recurrence of their first breast cancer were included, but those who had an intervening ipsilateral second primary breast cancer were excluded.

Potentially eligible participants were approached for this study through a letter describing the study's purpose and procedures followed several days later by a telephone call from a trained interviewer to answer questions and to either perform or schedule the study interview if the participant was willing. Eligible participants were included regardless of vital status, so deceased women were enrolled through a waiver of consent granted by the Fred Hutchinson Cancer Research Center's Institutional Review Board (n=246, 22% of the study population), and enrolled alive women all provided verbal informed consent. A total of 446 eligible cases were identified of which 369 (83%) were enrolled, and a total of 982 eligible controls were identified of which 734 (75%) were enrolled.

Data on history of diabetes and age at diagnosis was ascertained through a structured review of participant medical records focused on the time period between first breast cancer diagnosis and reference date (date of contralateral breast cancer diagnosis for cases, and date from breast cancer diagnosis through the interval between the date of their matched case's first and second breast cancers for controls). Records from multiple sources including hospitals, oncology practices, and primary care practices were abstracted. Additionally, data on breast cancer treatments, tumor characteristics, anthropometric characteristics, breast cancer risk factors, history of co-morbid conditions (hypertension, heart disease, and hypercholesterolemia), and body mass index were also abstracted from medical records and again focused on information prior to reference date. Data on factors such as race/ethnicity, family history of breast cancer, and use of menopausal hormone therapy were supplemented with self-reported information from structured telephone interviews. Information on history of diabetes and whether diabetics ever used any prescription medications to manage their diabetes was ascertained through the telephone interview, however data on use of specific types of medications for diabetes were not collected. For history of diabetes, data from the medical record review was treated as the "gold standard" of a clinical diagnosis of diabetes given that recall bias is a concern of the self-reported diabetes history data. So diabetes treatment information was only used for participants whose diagnosis of diabetes was confirmed through our medical record reviews.

Associations between diabetes history and risk of second primary contralateral breast cancer were estimated using conditional logistic regression. All analyses were conducted using Stata SE (College Station, TX). Conditional logistic regression was used to accommodate the individual matching of controls to cases on four factors, and so all models were implicitly adjusted for each of the matching variables (age, diagnosis year, county, and race). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as estimates of the relative risk. All statistical tests were two-sided. We systematically assessed a series of potential confounders including established breast cancer risk factors and breast cancer treatments (listed in Table 1). Only body mass index at first breast cancer (modeled as a categorical variable) and whether or not women had a screening mammogram in the year prior to reference date changed our risk estimates by greater than 10% when adjusted for in the statistical model, and so our final risk estimates were only additionally adjusted for these two variables. Our final analyses were therefore restricted to the 322 cases and 616 controls whose diabetes history, body mass index at first breast cancer diagnosis, and screening mammography history were known. Also excluded from our final analyses were the two participants diagnosed with diabetes before age 30 as a means of excluding women with type 1 diabetes since we did not distinguish between type 1 and type 2 diabetes in our medical record abstractions. We do however present risk estimates that are additionally adjusted for several other factors (including histology of the first cancer; radiation therapy, chemotherapy, and hormonal therapy for first breast cancer; and prior histories of hypertension, heart disease, and hypercholesterolemia) to clearly demonstrate the lack of impact adjusting for these factors had on our risk estimates. Age at diabetes diagnosis was treated as a categorical variable in the analysis with two groups, age <55 years and age ≥55 years as a proxy for diabetes that was diagnosed primarily premenopausally vs. diabetes that was diagnosed primarily postmenopausally. Years between diabetes diagnosis and reference date was also treated as a categorical variable divided into two groups based on this variable's median (six years). Age at first breast cancer diagnosis, age at reference date, and body mass index at first breast cancer diagnosis were each evaluated as potential effect modifiers of the relationship between diabetes history and contralateral breast cancer risk. P-values for interaction were calculated using likelihood ratio tests (α=0.05). Stratified analyses were presented for each of these variables where ages at first breast cancer diagnosis and reference date were dichotomized approximately to their respective median

ages (age 60 years and age 65 years, respectively), and BMI was dichotomized according to those who were obese (BMI≥30.0 kg/m^2) vs. not obese (BMI<30.0 kg/m^2).

RESULTS

Cases and controls were similar with respect to age at diagnosis, year of diagnosis, race/ethnicity, and treatment of their first breast cancers with radiation and chemotherapy (Table 1). Controls were somewhat more likely than cases to have had their first primary breast cancer treated with hormonal therapy, to not have a first degree family history of breast cancer, to have a BMI <25.0 kg/m^2, and to be current users of estrogen and progestin menopausal hormone therapy at first breast cancer diagnosis.

Breast cancer patients who had ever been diagnosed with diabetes had a 2.2-fold (95% CI: 1.3–3.6) increased risk of contralateral breast cancer compared to those never diagnosed with diabetes (Table 2). This risk did not vary by the timing of diabetes diagnosis relative to the first breast cancer diagnosis or the years between diabetes diagnosis and reference date. There was a suggestion that the elevation in risk was of a higher magnitude for women diagnosed with diabetes at <54 years of age compared to those diagnosed at ≥55 years of age, but the difference between these two risk estimates was not statistically significant (p=0.091). These results were all essentially unchanged when we additionally adjusted our analysis for histology of the first breast cancer, treatments women received for their first breast cancer (radiation, chemotherapy, and hormonal therapy), and co-morbid conditions (hypertension, heart disease, and hypercholesterolemia).

To assess the impact of use of prescription diabetes medications on the relationship between diabetes and contralateral breast cancer we conducted a sub-analysis using self-reported interview data on whether or not women with a history of diabetes ever used prescription medications to treat their diabetes. This analysis therefore excluded all women who were deceased at the time of enrollment. Diabetics who never used diabetes prescription medications had a 4.3-fold (95% CI: 0.99–18.4) increased risk of contralateral breast cancer compared to women without diabetes, and diabetics who have ever used diabetes prescription medications had a 2.7-fold (95% CI: 1.1–6.3) increased risk (p-value for difference between these two risk estimates = 0.567).

While body mass index was not an effect modifier of the relationship between diabetes and contralateral breast cancer risk (p for interaction=0.838), ages at first breast cancer diagnosis and reference date were (Table 3). Specifically, among women <60 years of age at first breast cancer diagnosis diabetes was associated with an 11.5-fold (95% CI: 2.4–54.5) increased risk of contralateral breast cancer, but diabetes history was not related to risk among women diagnosed with their first breast cancer at ≥60 years of age (p for interaction = 0.011). Similarly, among women <65 years of age at reference date diabetes was associated with a 8.0-fold (95% CI: 2.0–32.2) increased risk of contralateral breast cancer, but diabetes history was not related to risk among women who were ≥65 years of age at reference date (p for interaction = 0.021). Systemic treatments used to treat first breast cancers were also assessed as potential confounders, but neither hormonal therapy (p for interaction = 0.613) nor chemotherapy (p for interaction = 0.789) were found to be statistically significant effect modifiers.

DISCUSSION

This is the first study to evaluate the relationship between diabetes and risk of second primary contralateral breast cancer, and our results are consistent with a strong relationship between these two diseases, primarily for women diagnosed with their first breast cancer at

<60 years of age. This relationship was also independent of BMI, though there was a suggestion that the risk was higher among women who were not obese (had a BMI <30.0 kg/m^2). These results are consistent with the positive associations between diabetes and risk of incident breast cancer and all-cause mortality following breast cancer, though the magnitude of some of the increased risks observed (e.g., an 11.5-fold increased risk of contralateral breast cancer associated with diabetes among women diagnosed with their first breast cancer at <60 years of age), is substantially higher than those associated with breast cancer incidence (15–20% increases in risk)(1,2) and all-cause mortality (24–61% increases in risk).(2,4) However, an important limitation of our study was the lack of data on specific medications women used to treat diabetes. Recent data indicate that certain diabetes medications like metformin may be protective with respect to breast cancer risk, while other types are not,(8,9) but we could not assess the impact of these medications on second breast cancer risk in this study. However, the reasons why metformin is an effective treatment for diabetes is supportive of diabetes being potentially related to contralateral breast cancer risk. Among metformin's effects, it decreases circulating insulin levels and activates the adenosine mono-phosphate-activated protein kinase (AMPK) pathway. These effects are relevant to breast cancer in that insulin can promote cancer growth both directly and indirectly through modulators such as insulin-like growth factors, and AMPK activation can suppress several metabolic processes relevant to tumorigenesis.(8)

Potential biological mechanisms underlying the relationship between diabetes and contralateral breast cancer are likely similar to those underlying diabetes' relationship with breast cancer incidence and all-cause mortality among breast cancer survivors. Type 2 diabetes typically is characterized by insulin resistance and chronically elevated insulin secretion. Insulin is a breast mitogen,(10) and positive relationships between insulin and breast cancer risk have been observed in some(11,12) but not all studies.(13) Diabetics also have higher levels of endogenous estrogens and androgens,(14,15) both of which are strongly positively related to breast cancer risk.(16) Thus, diabetes could confer an elevated risk of second primary cancer through both insulin and steroid hormone pathways.

There is also some evidence to suggest that diabetic breast cancer patients are treated less aggressively and suffer more treatment related complications, particularly with respect to chemotherapy,(4) compared to non-diabetic patients.(17) However, the only treatments for a first breast cancer that can influence risk of developing contralateral breast cancer (other than bilateral mastectomy) are adjuvant hormonal therapy and chemotherapy since they are both systemic, and here we found no difference in the association between diabetes and contralateral breast cancer risk among never users of adjuvant hormonal therapy vs. ever users (p for interaction = 0.613) or among those who did vs. did not receive chemotherapy (p for interaction = 0.789). Thus, differences in treatment for first breast cancer are unlikely to account for the relationship between diabetes and contralateral breast cancer we observed.

With respect to the strengths and limitations of this study, a strength is that information on diabetes history and body mass index were all obtained from medical record reviews and not subject to the types of biases that are inherent to self-reported data. Also, eligible participants were included regardless of vital status reducing the impact of selection bias. A limitation though was a lack of information on severity of diabetes or detailed data on the types of treatments for diabetes women received (including duration and specific medications). We did conduct a sub-analysis based on self-reported history of ever taking prescription medication for diabetes and found no statistically significant difference in the relationship between diabetes and contralateral breast cancer risk among diabetics who have never or ever used prescription diabetes medications, though this study was not well powered to detect such a difference. Nevertheless, the substantial elevations in risk of breast cancer observed among both never and ever users of diabetes medications suggests that this

relationship is likely independent of the drugs used to treat diabetes. The diabetes medication data available was based on self-report, and therefore subject to recall bias. However, the extent of this bias is likely to be limited given that diabetes is a chronic disease, and so it is reasonable to assume that the majority of diabetics treated with medication prior to reference date were still using diabetes medications at the time of their interview. With respect to the generalizability of this study, it is important to note that this study was restricted to women with ER+ first breast cancer, so the relationship between diabetes and risk of second primary contralateral breast cancer among women whose first breast cancer is ER− could not be assessed.

Since this is the first study to evaluate the relationship between diabetes and risk of contralateral breast cancer it is important to confirm its results in additional studies. If it is confirmed that diabetic breast cancer survivors do have an appreciable increased risk of contralateral breast cancer, more frequent breast cancer screening, or screening with multiple complementary modalities, may be particularly warranted for these women.

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Table 1

Characteristics of controls and contralateral breast cancer cases

	Contralateral cases (n=322)		Controls (n=616)	
Characteristic	**n**	**%**	**n**	**%**
Demographic characteristics				
Age at 1st breast cancer diagnosis, yrs				
40–49	64	19.9	111	18.0
50–59	79	24.5	170	27.6
60–69	101	31.4	186	30.2
70–79	78	24.2	149	24.2
Age at reference date, yrs				
40–59	90	28.0	179	29.1
60–69	101	31.4	198	32.1
70–79	94	29.2	178	28.9
80–88	37	11.5	61	9.9
Year of 1st breast cancer diagnosis				
1990–1993	113	35.1	213	34.6
1994–1997	108	33.5	213	34.6
1998–2001	74	23.0	138	22.4
2002–2005	27	8.4	52	8.4
Months between 1st breast cancer diagnosis and reference date				
6–11	18	5.6	34	5.5
12–23	46	14.3	91	14.8
24–59	103	32.0	201	32.6
60–119	117	36.3	226	36.7
≥120	38	11.8	64	10.4
Race/ethnicity				
Non-Hispanic white	296	92.5	563	91.5
Asian	9	2.8	23	3.7
African American	8	2.5	17	2.8
Other	7	2.2	12	2.0
Missing	2		1	
Treatments for 1st primary breast cancer				
Radiation				
No	112	34.8	210	34.1
Yes	210	65.2	405	65.9
Missing			1	
Hormonal therapy				
No	117	36.4	167	27.2
Yes	204	63.6	448	72.8
Missing	1		1	
Chemotherapy				

	Contralateral cases (n=322)		Controls (n=616)	
Characteristic	**n**	**%**	**n**	**%**
No	236	73.8	442	71.9
Yes	84	26.3	173	28.1
Missing	2		1	
Characteristics of 1st breast cancer				
AJCC stage				
I	207	64.3	413	66.9
II or III	115	35.7	204	33.1
Histology				
Ductal	213	66.1	443	71.9
Lobular	83	25.8	94	15.3
Other	26	8.1	79	12.8
Patient characteristics				
First degree family history of breast cancer				
No	210	70.5	437	74.4
Yes	88	29.5	150	25.6
Missing	24		29	
BMI at 1st breast cancer diagnosis, kg/m^2				
<25.0	113	35.1	260	42.2
25.0–29.9	108	33.5	186	30.2
≥30.0	101	31.4	170	27.6
Menopausal hormone therapy use at 1st breast cancer diagnosis*				
Never	151	50.2	288	49.1
Former	38	12.6	65	11.1
Current E only user	64	21.3	121	20.6
Current E+P user	48	15.9	113	19.3
Missing	21		29	
Alcohol use at 1st breast cancer diagnosis, drinks/week				
None	108	46.6	228	48.3
<3.0	60	25.9	122	25.8
3.0–6.9	27	11.6	51	10.8
≥7.0	37	15.9	71	15.0
Missing	90		144	
Smoking at 1st breast cancer diagnosis				
Never	110	47.2	249	52.3
Former	82	35.2	154	23.4
Current	41	17.6	73	15.3
Missing	89		140	
Hypertension before reference date				
No	164	50.9	312	50.6
Yes	158	49.1	304	49.4

	Contralateral cases (n=322)		Controls (n=616)	
Characteristic	**n**	**%**	**n**	**%**
Heart disease before reference date				
No	252	78.3	465	75.6
Yes	70	21.7	150	24.4
Missing	0		1	
Hypercholesterolemia before reference date				
No	178	55.6	371	60.4
Yes	142	44.4	243	39.6
Missing	2		2	
Mammogram in year prior to reference date				
No	27	8.5	162	26.6
Yes	292	91.5	446	73.4

*E=unopposed estrogen, E+P=estrogen+progestin

Table 2

Relationship between diabetes and risk of contralateral breast cancer

	Contralateral Cases (n=322)		Controls (n=616)		Adjusted for body mass index and screening mammography		Multivariate adjusted‡	
	n	%	n	%	OR*	95% CI	OR*	95% CI
Ever clinically diagnosed with diabetes								
No	275	85.4	562	91.2	1.0	ref	1.0	ref
Yes	47	14.6	54	8.8	2.2	1.3–3.6†	2.3	1.3–3.9†
Age at diabetes diagnosis, yrs								
<54	19	5.9	10	1.6	7.0	1.7–29.0†	6.2	1.3–28.6†
≥55	23	7.1	36	5.8	1.9	1.1–3.5†	2.0	1.1–3.7†
	p for difference between risk estimates:					0.091		0.165
Timing of diabetes diagnosis								
Before first breast cancer diagnosis	19	5.9	23	3.7	2.4	1.1–5.3†	2.5	1.1–5.8†
After first breast cancer diagnosis	23	7.1	23	3.7	2.3	1.1–4.6†	2.2	1.1–4.7†
	p for difference between risk estimates:					0.905		0.848
Years between diabetes diagnosis and reference date, yrs								
<6	20	6.2	23	3.7	1.9	0.9–3.8	1.9	0.9–4.1
≥6	22	6.8	23	3.7	3.0	1.4–6.6†	3.0	1.3–6.9†
	p for difference between risk estimates:					0.354		0.414

*Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression and are implicitly adjusted for each of the matching variables (age and year of first breast cancer diagnosis, county, race/ethnicity, stage, and survival time until second cancer or reference date). In addition, all ORs are adjusted for body mass index at first breast cancer diagnosis and whether or not women had a screening mammogram in the year prior to reference date.

†p<0.05.

‡ORs additionally adjusted for histology of the first cancer; radiation therapy, chemotherapy, and hormone therapy for first breast cancer; and prior histories of hypertension, heart disease, and hypercholesterolemia.

Table 3

Relationship between diabetes and risk of contralateral breast cancer stratified by age and body mass index

	Contralateral Cases		Controls			
Ever clinically diagnosed with diabetes	**n**	**%**	**n**	**%**	**OR***	**95% CI**
<60 years of age at first breast cancer diagnosis						
No	127	88.8	273	96.5	1.0	ref
Yes	16	11.2	10	3.5	11.5	2.4–54.5†
≥60 years of age at first breast cancer diagnosis						
No	148	82.7	289	86.3	1.0	ref
Yes	31	17.3	46	13.7	1.5	0.8–2.7
					p for interaction = 0.011	
<65 years of age at reference date						
No	125	90.6	265	97.1	1.0	ref
Yes	13	9.4	8	2.9	8.0	2.0–32.3†
≥65 years of age at reference date						
No	150	81.5	297	86.1	1.0	ref
Yes	34	18.5	48	13.9	1.6	0.9–2.7
					p for interaction = 0.021	
BMI at first breast cancer diagnosis <30.0 kg/m²						
No	201	91.0	421	94.0	1.0	ref
Yes	20	9.0	27	6.0	2.4	1.0–5.8
BMI at first breast cancer diagnosis ≥30.0 kg/m²						
No	74	73.3	141	82.9	1.0	ref
Yes	27	26.7	29	17.1	1.3	0.4–3.6
					p for interaction = 0.838	

*Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression and are implicitly adjusted for each of the matching variables (age and year of first breast cancer diagnosis, county, race/ethnicity, stage, and survival time until second cancer or reference date). In addition, all ORs are adjusted for body mass index. and whether or not women had a screening mammogram in the year prior to reference date.

†p<0.05.