Diabetes and Breast Cancer Among Women With *BRCA1* and *BRCA2* Mutations

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BACKGROUND: Hyperinsulinemia and the metabolic syndrome are both risk factors for breast cancer. It is not clear if diabetes is associated with the risk of breast cancer in women with a *BRCA1* or *BRCA2* mutation. **METHODS:** The authors reviewed the medical histories of 6052 women with a *BRCA1* or *BRCA2* mutation, half of whom had been diagnosed with breast cancer. They estimated the odds ratio for breast cancer, given a self-report of diabetes. They then estimated the hazard ratio for a new diagnosis of diabetes associated with a history of breast cancer. **RESULTS:** There was no excess of diabetes in the period before the diagnosis of breast cancer, compared with controls with no diagnosis of breast cancer. The risk of diabetes was doubled among *BRCA* carriers in the 15-year period after the diagnosis of breast cancer (relative risk, 2.0; 95% confidence interval [CI], 1.4-2.8; *P* = .0001), compared with carriers without cancer. The risk was particularly high for women with a body mass index (BMI) >25.0 kg/m^2 (odds ratio, 5.8; 95% CI, 4.0-8.6; *P* = .0001). **CONCLUSIONS:** After a diagnosis of breast cancer, women with a *BRCA1* or *BRCA2* mutation face a 2-fold increase in the risk of diabetes, which is exacerbated by a high BMI.

KEYWORDS: BRCA1, BRCA2, breast cancer, diabetes.

Women with a *BRCA1* or *BRCA2* mutation face a high lifetime risk of breast cancer.[1] It is important to identify risk factors for breast cancer among genetically predisposed women, to devise strategies to minimize the risk. Several lines of evidence link diabetes and breast cancer.[2,3] Insulin resistance and hyperinsulinemia, which predispose to diabetes, may increase the risk of breast cancer in the general population,[4] and hyperinsulinemia may promote the growth of pre-existing breast neoplasms.[5] Furthermore, a high body mass index (BMI) is a risk factor for both breast cancer recurrence and for insulin resistance.[6-8] It is also of interest to establish whether diabetes (or any of the drugs used to treat diabetes) influences the risk of breast cancer in *BRCA* carriers.

The risk of future diabetes may also be increased in women after a diagnosis of breast cancer.[9] This risk may be mediated by common risk factors, such as high BMI or insulin resistance, or diabetes may be a late effect of breast cancer treatment. It is important to explore the impact of these factors on the risk of diabetes in women with *BRCA* mutations. In this cohort of *BRCA* carriers, we sought to determine whether diabetes increases the risk of breast cancer in *BRCA* carriers, and to identify risk factors for diabetes in this high-risk population.

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MATERIALS AND METHODS

Study Population

Eligible subjects are women who carry a pathogenic mutation in either the *BRCA1* or the *BRCA2* gene or both. Information on study subjects was submitted from 57 participating centers in 7 countries. All study subjects provided written informed consent for genetic testing. The study was approved by the ethics committees of all participating centers. In most cases, genetic testing was offered initially to women who were affected by either breast or ovarian cancer. Mutations in the *BRCA1* or *BRCA2* genes were detected using a range of techniques, and all abnormal nucleotide sequences were confirmed by direct DNA sequencing. A subject was eligible for the current study if the molecular analysis confirmed that she was a carrier of a pathogenic *BRCA* mutation. Most (>95%) of the mutations identified in the study subjects were either nonsense mutations, deletions, insertions, or small frameshifts, which resulted in premature termination of protein translation. When a *BRCA1* or *BRCA2* mutation was detected in an affected individual (proband), genetic testing was offered to other unaffected and affected women in the family. In a few families (<10% of the total), only unaffected carriers were identified.

Case and Control Subjects

All study subjects completed a baseline questionnaire that asked for information regarding family history, reproductive and medical histories, weight at ages 18, 30, and 40 years, height, the diagnosis of breast cancer and other illnesses including diabetes, and the use of medications (over-the-counter and prescription). This information was updated every 2 years by a mailed follow-up questionnaire. The follow-up questionnaire asked about new diagnoses of cancer and of nonmalignant diseases. Not all subjects completed a follow-up questionnaire; for those who did not, information was derived from the baseline questionnaire only.

In total, 8472 women with mutations were eligible for the study. Potential subjects were excluded if pertinent information was missing, such as date of birth, breast cancer diagnosis, *BRCA* mutation, and year of prophylactic mastectomy (n = 141). After exclusions, there was a total of 8268 eligible women.

Two case-control studies were conducted, the first compared women with and without breast cancer; the second was restricted to women with breast cancer and compared those with and without diabetes. In the first study,

potential case subjects were women with a diagnosis of invasive breast cancer. Potential control subjects were women who never had breast cancer and who were also carriers of a mutation in *BRCA1* or *BRCA2*. A single control subject was selected for each case subject, matched according to mutation in the same gene (*BRCA1* or *BRCA2*), year of birth (within 1 year), and country of residence. This matching resulted in 3026 case-control pairs. If the control had a prophylactic mastectomy, the date of prophylactic mastectomy was later than the date of cancer for the matched case. A matched case-control analysis was performed to evaluate the association between a history of diabetes and the diagnosis of breast cancer. Diagnoses of diabetes that occurred before and after the diagnosis of breast cancer were analyzed separately. Student *t* test was used to compare continuous variables, and the chi-square test was used to test for differences in categorical variables. We evaluated the annual risk of diabetes in cases and controls according to BMI at age 40 years (≤ 25 kg/m^2 or >25 kg/m^2). Conditional logistic regression was used to estimate the univariate odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer associated with a history of diabetes and with BMI.

In the second case-control study, we examined risk factors for the development of diabetes after the diagnosis of breast cancer. Women with a diagnosis of breast cancer who developed diabetes were matched to patients with breast cancer who did not develop diabetes. They were matched according to mutation in the same gene (*BRCA1* or *BRCA2*), year of birth (within 1 year), age of diagnosis, and country of residence. Conditional logistic regression was used to estimate the univariate and multivariate ORs and 95% CIs for selected variables identified as significant between subjects with breast cancer, with and without diabetes. All *P* values were 2-tailed. Analyses were conducted using the SAS statistical package, version 9.13 (SAS Institute, Cary, NC).

RESULTS

A total of 3026 matched pairs were included in the analysis. Case and control subjects were similar with respect to year of birth, year of baseline questionnaire, year of completion of most recent questionnaire, country of residence, and *BRCA* gene (Table 1). Cases and controls were similar with regard to BMI and weight at age 30 years (Table 1). The majority (63%) of the cases and controls resided in North America. The mean age of breast cancer diagnosis in the case subjects was 42.2 years (range, 19-80 years).

Table 1. Characteristics of Control and Case Subjects

Variables	Controls, n = 3026	Cases, n = 3026	P^a
Year of birth, mean (range)	1953.9 (1908-1981)	1953.7 (1909-1981)	.36
Year of baseline questionnaire, mean (range)	2002.6 (1992-2009)	2002.4 (1982-2009)	.01
Year of last contact, mean (range)	2005.9 (1990-1909)	2006.0 (1980-1909)	.17
Age of breast cancer diagnosis, mean y (range)	NA	42.2 (19-80)	NA
Year of breast cancer diagnosis, mean (range)	NA	1995.3 (1940-2009)	NA
Mutation, No. (%)			Matched
BRCA1	2255 (74.5%)	2255 (74.5%)	
BRCA2	770 (25.5%)	770 (25.5%)	
BRCA1&2	1 (0.1%)	1 (0.1%)	
Country of residence, No. (%)			Matched
USA	952 (31.5%)	1221 (31.5%)	
Canada	958 (31.7%)	890 (31.7%)	
Israel	155 (5.1%)	155 (5.1%)	
Poland	848 (28.0%)	848 (28.0%)	
Other	113 (3.7%)	113 (3.7%)	
BMI at age 30 y	22.4 (13.8- 59.3)	22.5 (13.3-56.7)	.59
Weight at age 30 y	132.1 (83.0-425.0)	131.9 (68.0-373.7)	.81

NA indicates not applicable; BMI, body mass index.
Weight and BMI at age 30 years were based on the means for those cases and controls whereby the case was diagnosed with breast cancer at age 30 years or older.
[a] The t test to compare means and chi-square test to compare frequencies.

Table 2. Frequency of Reporting of Diabetes Medication by Case and Control Subjects

Variables	Controls, n = 3026	Cases, n = 3026	P
History of diabetes, No. (%)			
No	2941 (97.2)	2895 (95.7)	
Yes	85 (2.8)	131 (4.3)	.001
Timing of diabetes in relation to breast cancer, No.			
Before breast cancer	23	17	.37
At or after (same time) breast cancer	62	114	<.0001

Table 3. Rate of Diabetes by 5-Year Interval After a Diagnosis of Breast Cancer

Time From Breast Cancer Diagnosis in Case, y	0-5	6-10	≥10	Total
Controls				
Person-years	12,612	8055	9407	30,073
New cases	24	16	22	62
Annual rate, %	0.19	0.20	0.23	0.21
Cases				
Person-years	12,784	7965	9417	30,165
New cases	44	26	44	114
Annual rate, %	0.34	0.33	0.47	0.38

On average, 10.7 years had elapsed from the diagnosis of breast cancer to the date of the most recent follow-up.

A diagnosis of diabetes was self-reported for 131 (4.3%) case subjects and for 85 (2.8%) control subjects. The mean reported age of diabetes diagnosis was 54.0 years (range, 13-81 years) in case subjects and 51.1 years (range, 4-75 years) in control subjects ($P = .10$).

For 17 case subjects, diabetes preceded the diagnosis of breast cancer, and for 114 case subjects, the diabetes followed the breast cancer diagnosis (Table 2). There was no excess of diabetes observed in cases versus controls before the year of diagnosis of breast cancer. However, a significant increase in the number of new-onset diabetes cases was reported at, or after, the diagnosis of breast cancer, compared with controls (OR, 2.0; 95% CI, 1.4-2.8; P = .0001). The distribution of new cases of diabetes by 5-year interval after the diagnosis of breast cancer is reported in Table 3. For each 5-year interval, the reported risk of diabetes was higher for cases than for controls. The highest risk of new-onset diabetes was in the interval 10 or more years after the diagnosis of breast cancer.

We also examined the annual risk of diabetes in cases and controls, based on BMI at age 40 years (≤25 kg/m^2 or >25 kg/m^2) (Table 4). The analysis shows an increase in the annual risk of diabetes in subjects with BMI >25 kg/m^2, for both cases and controls. For each category of BMI, the annual risk of diabetes was higher for cases than for controls.

Table 4. Annual Risk for Diabetes After Diagnosis Based on BMI at Age 40 Years

BMI at Age 40 Years	Total Subjects	Diabetes Cases	Person-Years	Annual Risk, %
Cases				
≤25 kg/m^2	1349	32	15,240	0.21
>25 kg/m^2	621	65	6650	0.98
Missing BMI	1033	17	8275	0.21
Total	3003	114	30,165	0.38
Controls				
≤25 kg/m^2	1387	19	15,024	0.13
>25 kg/m^2	637	31	6542	0.47
Missing BMI	958	10	8507	0.14
Total	3009	57	30,073	0.21

BMI indicates body mass index.

Table 5. Relative Risk of Diabetes by History of Breast Cancer and BMI at Age 40 Years

Variables	Univariate, RR (95% CI)	P	Multivariate, RR (95% CI)	P
Breast cancer				
No	1.0		1.0	
Yes	1.8 (1.4-2.5)	.0001	1.9 (1.3-2.6)	.0003
BMI at age 40 years				
<25	1.0		1.0	
>25	4.4 (3.1-6.2)	<.0001	4.2 (3.0-6.0)	.0001

BMI indicates body mass index; RR, relative risk; CI, confidence interval.

In a multivariate analysis, the relative risk (RR) for diabetes was associated both with a history of breast cancer (RR, 1.9; 95% CI, 1.3-2.6; $P = <.0003$) and BMI >25kg/m^2 (RR, 4.2; 95% CI, 3.0-6.0; $P < .0001$) (Table 5). For women with both a diagnosis of breast cancer and BMI >25 kg/m,^{2} the risk of new-onset diabetes was 5.8 (95% CI, 4.0-8.6; $P < .0001$).

To identify risk factors for diabetes among women with breast cancer, we compared BRCA carriers affected with breast cancer with and without (postcancer) diabetes. A matched analysis was performed, matching for year of birth, age of breast cancer diagnosis, country of residence, and BRCA mutation type. Of the 3 breast cancer treatments evaluated in the analysis (radiotherapy, chemotherapy, and tamoxifen use), only chemotherapy was associated with new-onset diabetes; 77.2% of the cases with diabetes received chemotherapy, versus 64.3% of cases without diabetes (OR, 2.2; $P = .01$). BMI at age 40 years, weight (at age 30 and at age 40 years), and weight gain were also significant predictors of new-onset diabetes (Table 6). In a multivariate analysis, the risk of diabetes in BRCA carriers affected with breast cancer was related both to BMI at age 40 years (OR, 6.3; 95% CI, 3.5-11.2; $P <$

.0001) and chemotherapy (OR, 2.4; 95% CI, 1.2-2.9; $P = .01$). There were 213 women with breast cancer who had a BMI >25 kg/m^2 and who were treated with chemotherapy; of these, 48 (22.5%) developed diabetes after a mean of 8.6 years of follow-up.

DISCUSSION

We observed an increased rate of diabetes in the 15-year period after a diagnosis of breast cancer in a population of BRCA carriers. Among those who developed breast cancer, the risk was particularly high for women who were overweight at the time of breast cancer diagnosis (BMI >25 kg/m^2) and who were treated with chemotherapy. In this subgroup, the annual incidence of diabetes was 2.4% per year. This risk was substantially higher than the risk of diabetes in women with breast cancer, but who did not have chemotherapy and who were not overweight (OR, 13.3; 95% CI, 4.6-38.1).

A high BMI is a well-established risk factor for diabetes in the general population, particularly for women.[10,11] It now appears that obesity and a high BMI are also strong risk factors for diabetes in BRCA mutation carriers. Insulin resistance is also a risk factor for breast cancer.[3,4] It is possible that insulin resistance is the common mechanism, but we did not see an excess of diabetes before the diagnosis of breast cancer.

A history of breast cancer was a risk factor for diabetes in our patient population, and this association was independent of BMI. In particular, women who were treated with chemotherapy were at increased risk for diabetes. To date, there is little evidence to support a link between adjuvant chemotherapy and the long-term risk of diabetes. Several studies have shown that women with breast cancer who receive adjuvant chemotherapy are

Table 6. Predictors of Diabetes in *BRCA* Mutation Carriers With a History of Breast Cancer

Variables	Diabetes, n = 101	No Diabetes, n = 731	P
Date of birth, mean (range)	1946.7 (1927-1964)	1946.6 (1928-1964)	.96
Year of last contact, mean (range)	2006.4 (1999-2009)	2006.6 (1997-2009)	.64
Age of breast cancer diagnosis, mean y (range)	46.3 (25-75)	46.4 (26-74)	.95
Year of breast cancer diagnosis, mean y (range)	1992.5 (1960-2006)	1992.5 (1961-2005)	.99
Mutation, No. (%)			.06
BRCA1	79 (78.2%)	640 (87.6%)	
BRCA2	19 (21.8%)	91 (12.5%)	
Country of residence, No. (%)			
USA	18 (17.8%)	129 (17.7%)	
Canada	41 (40.6%)	223 (30.5%)	
Israel	6 (5.9%)	15 (2.1%)	
Poland	36 (35.6%)	364 (49.4%)	
Oophorectomy, No. (%)	55 (54.5%)	385 (52.6%)	.93
Chemotherapy, No. (%)	78 (77.2%)	470 (64.3%)	.03
Radiotherapy, No. (%)	45 (44.6%)	406 (55.6%)	.27
Tamoxifen, No. (%)	59 (58.4%)	386 (52.8%)	.58
Weight at age 18 years, pounds (range)	123.0 (75-180)	119.5 (99-143)	.15
Weight at age 30 years, pounds (range)	143.5 (88-260)	128.9 (102-155)	<.0001
Weight at age 40 years, pounds (range)	162.1 (95-300)	138.2 (107-169)	<.0001
Weight gain ages 18 to 40 years	38.8 (−9 to 150)	19.5 (−13 to 49)	<.0001
BMI at age 40 years, kg/m^2	28.0 (18-47)	23.8 (18-29)	<.0001
Height, inches	63.9 (58-70)	64.0 (56-71)	.91

BMI indicates body mass index.
For women with no diabetes history, mean of set means were used to compare the matched case.

more likely to gain weight after treatment than are women who do not receive chemotherapy.[12,13] Weight gain may contribute to the risk of diabetes associated with chemotherapy. We did not measure weight gain after treatment; further studies are needed to explore this possibility. Glucocorticoids are often used in conjunction with chemotherapy in the treatment of breast cancer, and these drugs may cause acute hyperglycemia in predisposed individuals.[14] However, this effect is believed to be acute, transient, and reversible, and steroids have not been shown to impact on glycemic control in the long term.

Estrogen suppression may also promote diabetes.[15,16] Menopause, which is often induced by chemotherapy, is associated with an increased risk of the metabolic syndrome,[15] and postmenopausal hormone replacement therapy has been shown to lower the risk of diabetes.[17,18] We did not find an association between either oophorectomy or tamoxifen treatment and diabetes in our study.

Our data are consistent with a large population-based study showing that women with diabetes were 22% more likely to have a previous diagnosis of breast cancer compared with women without diabetes.[9] These findings suggest that breast cancer is a risk factor for future diabetes, possibly mediated through the effects of chemotherapy

and/or weight gain. In some women, insulin resistance and hyperinsulinemia might contribute to an excess risk of both breast cancer and diabetes. Insulin resistance and hyperinsulinemia usually precede the onset of diabetes by 10 to 20 years[19-21]; the effects of insulin resistance on breast carcinogenesis may occur before clinical diabetes develops. Thus, insulin-resistant women may present with breast cancer with a high insulin level, but before the onset of frank diabetes.[6] This suggests that it may be prudent to screen *BRCA1*-positive women for serum insulin at the time of their diagnosis, in particular if they have a high BMI. Other studies found an elevated risk of breast cancer among women with conditions that carry a high risk of future diabetes, such as gestational diabetes[22] and polycystic ovarian syndrome.[23,24] These syndromes are generally characterized by insulin resistance and hyperinsulinemia, but not necessarily with frank diabetes.

The results of this study do not suggest that diabetes is a risk factor for breast cancer among women with *BRCA1* and *BRCA2* mutation. Although diabetes has been associated with a small but significant increased risk of incident breast cancer in the general population,[2,3] the lack of association in our study may reflect differences in the study populations. The average age of breast cancer diagnosis in the *BRCA* mutation carriers in our study is 42.2

years, and this is younger than in the general population. The prevalence of diabetes in our study sample before diagnosis was only 2.9%. The association between diabetes and breast cancer risk in the general population appears to be limited to postmenopausal women.[2,3] Women with a *BRCA1* or *BRCA2* mutation are likely to be premenopausal at the time of breast cancer diagnosis. In our study, 53% of the breast cancer cases were premenopausal at the time of diagnosis. Cancers in *BRCA1* carriers are predominantly estrogen receptor (ER)-negative, and cancers related to diabetes may be more likely to be ER-positive.[25]

Our study has several limitations. Detailed information about diabetes treatment was not systematically collected, and therefore we were unable to evaluate breast cancer risk according to the type of treatment. We did not measure insulin or its metabolites; therefore, we can only speculate regarding the roles of hyperinsulinemia and insulin resistance. It is possible that the risk of diabetes is correlated with the extent of weight gain experienced after cancer therapy. We did not have details of weight before and after therapy, and this will be the topic of a future analysis. We relied on self-reported data, which were based on diabetes requiring medical treatment. This may have led to an under-reporting of diabetes and its treatment, in particular for mild (untreated) cases. Details regarding the type of chemotherapy were not available. The role of specific chemotherapies in diabetes risk warrants further investigation. It is possible that the diagnosis of breast cancer precipitated close clinical follow-up, including blood tests, but in many cases the diagnosis of diabetes was well after the diagnosis of breast cancer. The number of women with a *BRCA2* mutation was small, and we are unable to confirm whether this association was present among carriers of *BRCA2* mutations. Finally, we cannot exclude the impact of a survival bias in our findings, as patients with breast cancer may be less likely to live long enough to develop diabetes.

In conclusion, in this study of women with *BRCA1* and *BRCA2* mutation, we observed a significant increase in the risk of developing diabetes after a breast cancer diagnosis. We observed this association within a *BRCA*-positive population, and it is not clear to what extent this association is present in a population of women treated for breast cancer who did not have a *BRCA* mutation. We also found that the risk was compounded by a high BMI and the use of chemotherapy. These intriguing findings warrant further investigation in carriers and in noncarriers.

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