

Risk of Breast Cancer After Onset of Type 2 Diabetes

Evidence of detection bias in postmenopausal women

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OBJECTIVE—To examine the risk of breast cancer in pre- and postmenopausal women with type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS—This was a population-based retrospective cohort study. Cox regression, stratified by pre- (<55 years) and postmenopausal (≥55 years) status, was used to estimate hazard ratios (HRs) for breast cancer, during earlier (0–3 months) and later (3 months to 10 years) time windows after diabetes index date.

RESULTS—Compared with women without T2D, HRs for breast cancer were 0.95 (95% CI 0.48–1.86; $P = 0.88$) and 1.31 (0.92–1.86; $P = 0.14$) in pre- and postmenopausal women with T2D, respectively, in the early time window, and 0.92 (0.75–1.13; $P = 0.45$) and 1.00 (0.90–1.11; $P = 0.93$) in pre- and postmenopausal women with T2D, respectively, in the later time window.

CONCLUSIONS—We observed a trend toward an increased risk of breast cancer in postmenopausal women with T2D, but only in the time period immediately after diabetes index date.

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Previous epidemiologic research suggests a modestly elevated risk of breast cancer in women with type 2 diabetes (T2D), particularly after menopause (1). However, it is unclear whether this increased risk is related to a potential detection bias or increased mammography screening surrounding diabetes onset (2,3). Women with a new diagnosis of T2D may have the advantage of increased screening opportunities, which could transpire into more cases of breast cancer being diagnosed in this population. Therefore, we examined the risk of breast cancer in pre- and postmenopausal women with incident T2D, during earlier and later time windows after diabetes index date.

RESEARCH DESIGN AND METHODS

Study design

The dataset used for this study has been described in detail previously (4). In brief,

this was a population-based retrospective cohort study, using the British Columbia Linked Health Databases (BCLHD) from British Columbia, Canada.

Women who were likely to have a clinical diagnosis of diabetes were identified based on the established case definition for the Canadian National Diabetes Surveillance System. The index date for diabetes was defined as the first of 1) a hospital admission for diabetes (ICD-9 code 250) or 2) the second of two medical fee-for-service claims coded ICD-9 250 within a 2-year period. Physician visits and hospital admissions were classified according to ICD-9. Women with claims for gestational diabetes (ICD-9 648.8) were excluded.

From 1 April 1996 to 31 March 2006, we identified women with incident T2D as those 30 years or older and meeting the definition of diabetes after 2 consecutive years of not meeting the criteria ($N = 84,506$). Nondiabetic women registered

for health coverage on the diabetes index date were then matched, with replacement, on age and index year. After a minimum 2-year cancer washout period prior to index date, first breast cancers were identified prospectively in both cohorts, via linkage to the British Columbia Cancer Agency database. Censoring occurred at death, departure from British Columbia, or 31 March 2006, whichever was earliest.

Statistical analyses

Incident rates and 95% CIs were determined for breast cancer using Poisson regression. Cox regression was then used to estimate the hazard ratios (HRs) and 95% CIs for the association between incident diabetes and breast cancer. We stratified this analysis, using age as a proxy, for pre- (<55 years) and postmenopausal (≥55 years) status. We split the follow-up time into earlier (0–3 months) and later (3 months to 10 years) intervals, after diabetes index date, to account for time-varying HRs. SAS version 9.2 (SAS Institute, Inc., Cary, NC) was used for analyses and R version 2.8 (Wien, Austria) for plotting.

RESULTS—There were 84,506 women in each of the incident diabetes and matched nondiabetes cohorts, and the mean (SD) age was 61.8 (14.2) years. The mean cancer-free period before index was 6.9 (2.9) and 7.1 (2.9) years, and the mean (SD) follow-up was 4.4 (2.9) and 4.5 (2.9) years for the diabetes and nondiabetes cohorts, respectively.

There were 2,381 incident breast cancer cases identified throughout the full follow-up period. Incidence rates (per 1,000 person-years) for breast cancer were 1.83 (1.61–2.08) and 1.92 (1.68–2.21) for premenopausal women with and without T2D, and 4.02 (3.77–4.29) and 3.89 (3.62–4.19) for postmenopausal women with and without T2D, respectively (Table 1).

During the first 3 months after diabetes index date, we observed a trend toward an increased risk of breast cancer in postmenopausal women with T2D (HR 1.31; 95% CI 0.92–1.86; $P = 0.14$), compared with women without T2D (Table 2).

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Table 1—Incidence rates for breast cancer in the T2D and control cohorts, stratified by pre- and postmenopausal status

| | Incident breast cancers (N) | Incidence rate (per 1,000 person years) | 95% CI |
|--|-----------------------------|---|-----------|
| Incident T2D cohort (N = 84,506) | 1,178 | 3.23 | 3.05–3.42 |
| Matched nondiabetes cohort* (N = 84,506) | 1,203 | 3.22 | 3.02–3.43 |
| Postmenopausal women (≥55 years) | | | |
| With diabetes (N = 1,893) | | | |
| 0–3 months follow-up | 72 | 5.33 | 4.23–6.72 |
| >3 months to 10 years follow-up | 866 | 3.94 | 3.69–4.21 |
| 0–10 years follow-up | 938 | 4.02 | 3.77–4.29 |
| Without diabetes (N = 1,893) | | | |
| 0–3 months follow-up | 55 | 4.03 | 3.09–5.25 |
| >3 months to 10 years follow-up | 900 | 3.83 | 3.56–4.13 |
| 0–10 years follow-up | 955 | 3.89 | 3.62–4.19 |
| Premenopausal women (<55 years) | | | |
| With diabetes (N = 488) | | | |
| 0–3 months follow-up | 17 | 2.46 | 1.53–3.96 |
| >3 months to 10 years follow-up | 223 | 1.80 | 1.57–2.05 |
| 0–10 years follow-up | 240 | 1.83 | 1.61–2.08 |
| Without diabetes (N = 488) | | | |
| 0–3 months follow-up | 17 | 2.46 | 1.53–3.96 |
| >3 months to 10 years follow-up | 231 | 1.88 | 1.63–2.17 |
| 0–10 years follow-up | 248 | 1.92 | 1.68–2.21 |

*Matched on birth year with replacement.

Relative risk of breast cancer in premenopausal women with T2D during this earlier time period was 0.95 (0.48–1.86; $P = 0.88$). In the later time window of 3 months to 10 years after diabetes index, the risks of breast cancer were 0.92 (0.75–1.13; $P = 0.45$) and 1.00 (0.90–1.11; $P = 0.93$) in pre- and postmenopausal women with T2D, respectively, compared with women without T2D (Table 2).

CONCLUSIONS—Our observation of a trend toward an elevated risk of breast cancer among postmenopausal women with T2D is consistent with previously published studies (1). However, there is little evidence in the literature examining detection bias as a possible explanation for the observed association between T2D and breast cancer (2). Therefore, previous epidemiologic associations of breast cancer risk in women with

diabetes may have been overestimated, if they did not take into consideration this initial detection bias at the time of diabetes diagnosis.

Strengths of this study include the use of a very large population-based dataset, linkage with the BC Cancer Registry, matching our cohorts to balance potential confounders, and examining risk of breast cancer during different time windows after diabetes index date to address potential detection bias. The main limitation to our research surrounds the potentially tenuous index date assigned to diabetes onset. Although it is possible for a clinical diagnosis of diabetes to have preceded the case date in the BCLHD, it is less likely that a cancer diagnosis would have actually preceded the clinical diagnosis of diabetes, particularly given the minimum 2-year cancer-free period we imposed prior to index date, which coincided with the same time window for the diabetes case definition. In previous validation studies of the diabetes case definition, ~85–90% of case subjects were identified through physician services claims. Furthermore, the median duration between qualifying physician visits is only 39 days (interquartile range 12–150 days; unpublished data).

In summary, we observed a trend toward an increased risk of breast cancer, but only in postmenopausal women with T2D. As well, these findings were restricted to the time period immediately after diabetes index date, reflecting a potential detection bias. Perhaps screening initiatives for breast cancer in women with T2D should focus on postmenopausal women in this earlier time period after a diagnosis of diabetes. Additional research is required to further explore this potential for detection bias in different patient populations.

Table 2—HRs for breast cancer in the T2D cohort, stratified by pre- and postmenopausal status

| | Adjusted HR* | 95% CI | P value |
|--|--------------|-----------|---------|
| Incident T2D cohort (N = 84,506) | 1.00 | 0.92–1.10 | 0.93 |
| Postmenopausal women with diabetes (≥55 years) (N = 1,893) | | | |
| 0–3 months follow-up | 1.31 | 0.92–1.86 | 0.14 |
| >3 months to 10 years follow-up | 1.00 | 0.90–1.11 | 0.93 |
| 0–10 years follow-up | 1.01 | 0.92–1.21 | 0.79 |
| Premenopausal women with diabetes (<55 years) (N = 488) | | | |
| 0–3 months follow-up | 0.95 | 0.48–1.86 | 0.88 |
| >3 months to 10 years follow-up | 0.92 | 0.75–1.13 | 0.45 |
| 0–10 years follow-up | 0.93 | 0.76–1.13 | 0.93 |

*Adjusted for age, socioeconomic status, number of physician visits, and year of diagnosis; matched nondiabetes cohort is reference group.

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S.L.B. conceived of the study, planned the data analysis, prepared a first draft, and edited subsequent versions of the manuscript. K.R. conducted the data analysis and contributed to the writing of the manuscript. C.A.M. obtained the data from the BCLHD and British Columbia Cancer Agency database and edited subsequent versions of the manuscript. J.A.J. obtained funding, planned the data analysis, and edited subsequent versions of the manuscript.

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