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ORIGINAL PAPER

Breast cancer mortality in relation to receipt of screening mammography: a case–control study in Saskatchewan, Canada

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Abstract
Purpose The efficacy of screening mammography in reducing breast cancer mortality continues to be controversial. In addition, few data exist on the efficacy of screening mammography in women 70 years of age or older. An organized screening mammogram program has existed in Saskatchewan since the mid-1990s. It offers mammography every 2 years to women ≥50 years of age.
Methods We conducted a population-based case–control study to evaluate the efficacy of screening mammography, as practiced in Saskatchewan, Canada. Cases ($n = 501$) were women who died of breast cancer during 1995–2008 and were at least 52 years of age at the time of their diagnosis. Controls ($n = 5{,}009$) were matched to cases on birth year and duration of healthcare coverage prior to the cases' breast cancer diagnosis date. In cases and controls, receipt of screening mammography during the several years up to and including the date of the case's diagnosis of breast cancer was ascertained from the records of the screening program.
Results Receipt of a screening mammogram in the preceding 2 years was more common among controls (53 %) than cases (37 %), OR 0.51 (95 % CI 0.42–0.62). A decreased risk was observed among women in all age groups, including those 70–79 years (OR 0.40; 95 % CI 0.27–0.60).
Conclusion Our findings suggest that receipt of screening mammography among women in Saskatchewan has been associated with a decreased risk of death from breast cancer.

Keywords Mammography · Screening · Breast cancer · Mortality · Case–control study

Background

The efficacy of screening mammography in reducing breast cancer mortality has been demonstrated in randomized trials: The summary relative risk of breast cancer mortality among women 50 years of age or older was 0.78 (95 % credible interval 0.70–0.87) based on the results of seven trials [1]. The ability of screening mammography to reduce breast cancer mortality within a given community may differ, however, for a variety of reasons, including differences between the community and trial setting in terms of the proficiency of persons who perform and interpret the mammograms, the completeness of follow-up of women with a positive mammogram, and treatment practices [2].

In Canada, breast cancer screening programs exist in all ten provinces and in two territories and are organized at the provincial or territorial level [3]. Yet, there is a paucity of evidence on the efficacy of screening mammography—as practiced within the setting of these programs—at reducing breast cancer mortality. The Screening Program for Breast Cancer (SPBC) has existed in the province of Saskatchewan since the early 1990s [4]. It offers biennial screening mammography to eligible women 50 years of age or older [3, 5]. Herein, we report the results of a case–control study

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to evaluate the efficacy of screening mammography, as practiced in Saskatchewan during 1995–2008. We also present an estimate specific to women 70 years of age or older, a group for which—in any setting— the evidence on the efficacy of screening mammography at reducing breast cancer mortality is sparse [6, 7].

Methods

Setting

Saskatchewan has a universal healthcare system which is funded by the provincial government. More than 99 % of the population is eligible for health benefits (about 1 million persons) [8]. Eligible individuals receive a unique lifetime health services number which enables an individual's records to be linked across various provincial health services databases [8]. Approximately 91 % of those eligible for healthcare benefits are also eligible for outpatient prescription drug benefits through the Saskatchewan Drug Plan; persons not eligible are primarily First Nation peoples, who receive prescription drug benefits through a federal program [8]. The cases and controls in the present analyses were part of a larger population-based case–control study in which the primary exposure under study was menopausal hormone therapy [9]. Therefore, the underlying population from which cases and controls were drawn included only women eligible for the Drug Plan.

The SPBC began in selected regions of Saskatchewan in 1990, and since 1993, it has been present in all regions. It offers mammography every year to women with a first-degree family history of breast cancer and mammography every 2 years to those without a family history [4]. Therefore, as of 1995, all women in the province who were eligible to receive a screening mammogram during the preceding 2 years would have had the opportunity to be screened at least once. Eligible women are $\geq$50 years of age, do not have symptoms of breast cancer such as breast lumps, and do not have breast implants [4, 10]. Women 50–69 years of age are identified from the population registry and are mailed a letter of invitation to receive a screening mammogram (women $\geq$70 years of age may attend, but they are not mailed a letter of invitation) [4, 10]. Screening mammograms are provided at fixed sites in urban areas and mobile sites in rural areas [4, 10].

Case and control ascertainment

Women who died of breast cancer at 50–79 years of age during 1990–2008 and who had continuous Saskatchewan healthcare coverage for at least 5 years prior to their first primary breast cancer diagnosis (index date) were identified from the vital statistics death registry of Saskatchewan and the Saskatchewan Cancer Agency's cancer registry ($n = 1{,}565$). We excluded women who did not have a record of a breast cancer diagnosis in the cancer registry ($n = 29$), women who were not at least 50 years of age 2 years prior to their index date ($n = 329$), and women who were diagnosed before 1995 ($n = 912$). A total of 501 case women remained.

For privacy reasons, our de-identified data only included a woman's year of birth—day and month of birth were not present. We imputed December 31 as the month and day of birth for all women to ensure that we only included women who were at least 50 years of age during the entire 2-year period prior to their index date.

Controls were enumerated from the population registry after excluding women not eligible for the Drug Plan. For each case, 15 potential controls were randomly sampled, with replacement, among women with the same birth year and the same duration of continuous health coverage as the case prior to the cases' breast cancer diagnosis date (index date). The potential controls were assigned the index date of their matched case. Controls with a breast cancer diagnosis prior to the index date, ascertained from the cancer registry, were excluded from the control pool. Then, for each case, ten controls were randomly sampled from the remaining pool of controls.

Exposure and covariate ascertainment

Dates of receipt of screening mammography prior to (and including) the index date (date of breast cancer diagnosis in the cases and comparable date in controls) were ascertained from the SPBC database.

Receipt of menopausal hormone therapy prescriptions dispensed to cases and controls prior to the index date was ascertained from the Drug Plan database. The database includes most outpatient prescriptions dispensed for drugs listed on the Saskatchewan Formulary since September 1975. Unopposed estrogen hormone therapy (EHT) and combined hormone therapy (CHT) comprised prescriptions for oral or transdermal patch estrogens and progestogens. Ever use was defined as $\geq$2 prescriptions for the specified hormone therapy (HT) within a 6-month period. Current users were defined as women who had a prescription for the specified HT within the 6 months prior to the index date.

Demographic information from the index year was ascertained from the population registry (residence, marital status and receipt of income security benefits). Receipt of a hysterectomy prior to the index date was ascertained from the hospital services and physician services databases. The hospital services database dates back to 1970 and includes procedure and diagnosis codes for all hospital inpatient

Table 1 Characteristics of women who died of breast cancer (cases) and control women

	Cases ($n = 501$)		Controls ($n = 5,009$)	
	n	%	*n*	%
Duration of continuous healthcare coverage prior to index date (years)[a,b]				
5–19	30	6.0	300	6.0
20–29	238	47.5	2,379	47.5
30–39	233	46.5	2,330	46.5
Mean (standard deviation)	28.6 (5.2)		28.6 (5.2)	
Median (interquartile range)	29.0 (26.0–32.2)		29.0 (26.0–32.2)	
Index year[a]				
1995–1999	266	53.1	2,659	53.1
2000–2004	177	35.3	1,770	35.3
2005–2008	58	11.6	580	11.6
Age in index year (years)[a]				
52–59	129	25.8	1,290	25.8
60–69	216	43.1	2,159	43.1
70–79	156	31.1	1,560	31.1
Year of breast cancer death				
1995–1999	101	20.2	n/a	n/a
2000–2004	212	42.3	n/a	n/a
2005–2008	188	37.5	n/a	n/a
Age in year of breast cancer death (years)				
52–59	68	13.6	n/a	n/a
60–69	195	38.9	n/a	n/a
70–79	238	47.5	n/a	n/a
Residence in the index year[a]				
Urban (population > 100,000)	203	40.5	1,845	36.8
Small urban[c]	68	13.6	655	13.1
Rural	230	45.9	2,509	50.1
Marital status in index year[a]				
Single, never married	29	5.8	173	3.5
Married or common law	295	58.9	3,340	66.7
Divorced, separated, widow, or other	177	35.3	1,496	29.9
Receipt of government income security benefits in index year[a,d]				
None	358	71.5	3,984	79.5
Any	143	28.5	1,025	20.5
Receipt of hysterectomy prior to index date[a,e]	129	25.8	1,359	27.1
Cancer diagnoses prior to index date[a,f]				
None	432	86.2	4,494	89.7
Any	69	13.8	515	10.3
Use of hormone therapy (HT) prior to index date[g]				
Never[h]	229	45.7	2,075	41.4
Current combined therapy (CHT)[i]				
<5 years	13	2.6	187	3.7
≥5 years	17	3.4	124	2.5
Current unopposed estrogen therapy (EHT)[j]				
<5 years	19	3.8	210	4.2
≥5 years	31	6.2	314	6.3

Table 1 continued

	Cases ($n = 501$)		Controls ($n = 5,009$)	
	n	%	*n*	%
Former CHT or EHT[k]	108	21.6	1,135	22.7
Ever use of other HT only[l]	84	16.8	964	19.3

[a] The index date/year is the date of the first primary breast cancer diagnosis for cases and the comparable date for controls

[b] The start date for healthcare coverage was the initiation of Saskatchewan healthcare coverage or 1 January 1970, whichever occurred later

[c] Includes communities with a regional hospital

[d] Includes various income security programs for low-income families and individuals (including programs for seniors)

[e] Ascertained from: (1) procedure codes from hospital inpatient stays and day surgeries as of 1970 or initiation of healthcare coverage, whichever occurred later; and (2) Saskatchewan physician billing codes as of 1975 or initiation of healthcare coverage, whichever occurred later

[f] Ascertained from the Saskatchewan Cancer Agency's cancer registry going back to 1970 (the earliest year in which automated data were available). By design no case or control had a breast cancer diagnosis prior to the index date

[g] CHT and EHT include oral and transdermal patch EHT and CHT prescriptions only

[h] Women who never had a prescription for any menopausal hormone therapy

[i] Includes 16 women who were also current users of EHT, and 111 women who were former users of EHT

[j] Includes 108 women who were former users of CHT

[k] Includes 0 women who were current users of EHT or CHT

[l] Includes women whose only use of menopausal hormone therapy did not include use of oral or transdermal patch EHT or CHT (e.g., includes women whose only use of hormone therapy was estrogen vaginal creams)

stays and day surgeries for Saskatchewan beneficiaries. The physician services database includes physicians' claims for payment since 1975 (most Saskatchewan physicians are paid on a fee-for-service basis). We were unable to specifically ascertain receipt of bilateral oophorectomy because not all codes distinguished unilateral from bilateral oophorectomy. A diagnosis of cancer prior to the index date was ascertained from the cancer registry, going back to 1970 (the earliest year with automated data).

Statistical analysis

We compared cases and controls for a history of receipt of a screening mammogram during the period prior to diagnosis when we would expect that a breast tumor could be detected by mammography [11]. We present an analysis which assumes a 2-year interval and a separate one which assumes a 3-year interval. For all analyses, this interval includes the index date (date of diagnosis in cases and comparable date in controls). We used conditional logistic regression to compute odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between receipt of a screening mammogram during the 2-year (or 3-year) period prior to the index date and risk of death from breast cancer, implicitly adjusting for matching factors: year of birth, index year, and duration of continuous healthcare coverage prior to the index date. We also evaluated the following variables (categorized as shown in Table 1) for potential confounding, but none met our threshold ($a \geq 10$ % change in the odds ratio) and thus were not included in the final models: residence in the index year, marital status in the index year, receipt of government income security benefits in the index year, receipt of hysterectomy prior to the index date, a diagnosis of cancer prior to the index date (by design no case or control had a breast cancer diagnosis prior to the index date), and history of use of EHT and CHT.

Results

A total of 501 case women and 5,009 control women were identified. Among the cases, 53 % were diagnosed with a first primary breast cancer during 1995–1999, 35 % during 2000–2004, and 12 % during 2005–2008. When they died from breast cancer, 14 % of case women were 52–59 years of age, 39 % were 60–69 years, and 48 % were 70–79 years.

Cases were slightly more likely than controls to have lived in an urban area in the index year, to not be married in the index year, to have received government income security benefits in the index year, to have been previously diagnosed with cancer (by design no case or control had a prior breast cancer diagnosis), and to have been a current user of CHT for ≥5 years (Table 1). A similar proportion of cases and controls were current users of EHT for ≥5 years (Table 1).

Receipt of a screening mammogram within the 2 years prior to the index date was more common among controls (53 %) than cases (37 %), OR 0.51 (95 % CI 0.42–0.62)

Table 2 Risk of fatal breast cancer in relation to receipt of screening mammography prior to and including the index date

Receipt of a screening mammogram	Cases		Controls		OR[a] (95 % CI)
	n	%	*n*	%	
Within the 2 years prior to and including the index date					
No	315	62.9	2,362	47.2	1.00 (Ref.)
Yes	186	37.1	2,647	52.8	0.51 (0.42–0.62)
Within the 3 years prior to and including the index date[b]					
No	239	57.3	1,697	40.7	1.00 (Ref.)
Yes	178	42.7	2,473	59.3	0.49 (0.40–0.61)

[a] Conditional logistic regression; cases were matched to controls on year of birth, index date, and duration of continuous healthcare coverage prior to index date

[b] Restricted to women who were at least 50 years of age 3 years prior to the index date and had an index date of 1996 or later (417 cases and 4,170 controls)

(Table 2). We observed an association of similar magnitude when the time frame for ascertainment of receipt of screening mammography was extended to include the 3-year period prior to the index date (OR 0.49; 95 % CI 0.40–0.61) (Table 2). A decreased risk was observed in women 52–59 years of age (OR 0.65; 95 % CI 0.45–0.94), 60–69 years of age (OR 0.50; 95 % CI 0.37–0.66), and 70–79 years of age (OR 0.40; 95 % CI 0.27–0.60) (Table 3).

Discussion

We found that screening mammography, as practiced in Saskatchewan during 1995–2008, was associated with about a 50 % decrease in breast cancer mortality. Further, a decrease was observed among women aged 52–59, 60–69, and 70–79 years. There are several reasons to believe that our study may have underestimated the efficacy of screening mammography in reducing breast cancer mortality in Saskatchewan during this period. First, although women with symptoms of breast cancer were not eligible to receive a mammogram through the SPBC, it is possible that some women received one even though it was symptom-initiated. To the degree that this occurred, the ORs reported herein are falsely high (meaning the ORs underestimate any true decrease in risk) because it is more likely that cases—women who died of breast cancer—received a mammogram in response to symptoms than did controls.

Second, we assumed that a breast tumor would be detectable by mammography 2 or 3 years prior to diagnosis [11]. However, if the true interval was shorter or longer than 2–3 years, the exposure status of some proportion of cases and controls would have been misclassified. Misclassification resulting from either overestimating or underestimating the interval during which the tumor could be detected would likely lead to a falsely low estimate of the efficacy of screening [12].

Third, we did not have information on family history of breast cancer, which has been found to be relatively more common in women who receive screening mammography [13, 14]. To the degree that high risk women in our study were more likely to receive a screening mammogram, our ORs would again be underestimates of any true decrease in risk.

Fourth, some women in our study who did not receive a screening mammogram may have received a clinical breast examination—a variable on which we did not have information—at their physician's office during the 2- or 3-year period prior to the index date. We would not expect there to be more than a modest benefit of screening mammography on breast cancer mortality beyond that due to clinical breast examination [15]. Therefore, our ability to detect an association was diminished to the extent that this was occurring in our study population.

Fifth, although the SPBC is intended to be the mechanism by which women receive screening mammograms in Saskatchewan, if some women were receiving screening mammograms outside of the SPBC our ability to detect an association would again be diminished as our "unexposed" group would have included some women who did receive a screening mammogram.

Another consideration when interpreting our results is that we relied in part on death certificates to ascertain women who died of breast cancer. However, in comparison to medical records, underascertainment of breast cancer deaths from death certificates has been found to be small (4 %) [16]. If underascertainment occurred to the same degree in women who did and did not receive a screening mammogram, we would not expect our risk estimates to be biased [17]. On the other hand, if it was related to receipt of

Table 3 Risk of fatal breast cancer in relation to receipt of screening mammography prior to and including the index date, by age

Receipt of a screening mammogram within the 2 years prior to and including the index date	Cases		Controls		OR[a] (95 % CI)
	n	%	*n*	%	
52–59 years					
No	71	55.0	572	44.3	1.00 (Ref.)
Yes	58	45.0	718	55.7	0.65 (0.45–0.94)
60–69 years					
No	126	58.3	887	41.1	1.00 (Ref.)
Yes	90	41.7	1,272	58.9	0.50 (0.37–0.66)
70–79 years					
No	118	75.6	903	57.9	1.00 (Ref.)
Yes	38	24.4	657	42.1	0.40 (0.27–0.60)

[a] Conditional logistic regression; cases were matched to controls on year of birth, index date, and duration of continuous healthcare coverage prior to index date

screening mammography, our ORs may be over- or underestimates.

There are several strengths of this study. Selection bias is unlikely because all of the eligible cases, identified from the cancer registry and vital statistics death registry, and all sampled eligible controls, identified from the population registry (and representing the underlying population from which the cases arose) were included. Screening history prior to the index date was ascertained using prospectively recorded data, and therefore, it was not subject to errors in recall. Potential confounding by recency and duration of use of EHT and CHT was evaluated using detailed, prospectively recorded data on dispensed prescriptions from the population-based Drug Plan database. We did not have information on access to breast cancer diagnostic services or access to breast cancer treatment, which may have been related to the likelihood that a woman received a screening mammogram. However, we did have information on potential proxies of these variables including rural residence and receipt of government income security benefits—a measure of socioeconomic status—but neither was found to be a confounder.

There are other potential confounders on which we did not have information. However, not adjusting for a fatal breast cancer risk factor that was more common in women who received mammography screening (as we might expect with a family history of breast cancer [13, 14], for example) would yield ORs that underestimate any true benefit of screening mammography. The lack of adjustment for other risk factors that may have been less common in women who received mammography screening (e.g., cigarette smoking and obesity) is unlikely to substantially explain the decrease in risk that we observed [18, 19]. Nickson et al. [18, 19] conducted a sensitivity analysis that addressed this point. Their computations show that for example, a risk factor present in 20 % of screened women and 30 % of unscreened women would have to be associated with a tenfold increase in risk to explain an observed unadjusted OR of 0.48 associated with receipt of screening when adjustment for the factor would have yielded an OR of 0.80 [18, 19]. A factor associated with a more modest twofold increase in risk (smoking and obesity have been associated with a 1.3- to 1.6-fold increased risk of fatal breast cancer [20, 21]) would have to be present in 90 % of unscreened women and 20 % of screened women to explain the same change in the OR—from 0.48 before adjustment to 0.80 after adjustment [18, 19].

Our overall findings from Saskatchewan are in line with prior results from case–control studies of the efficacy of screening mammography at reducing breast cancer mortality. In a recent meta-analysis, receipt of a screening mammogram was associated with a 49 % lower risk of death from breast cancer (OR 0.51; 95 % CI 0.46–0.55; 10 case–control studies) [18]. Most of the studies in the meta-analysis included women no younger than 50 years of age [18, 22–28]; two included women as young as 40 years of age [29, 30]. Only three studies included women older than 70 years of age, but in none of them was a risk estimate specific to women in this age group reported [23–25]. The US Preventive Services Task Force concluded that data are lacking on whether screening mammography reduces breast cancer mortality in women 70 years of age or older [7]. In our study, receipt of a screening mammogram in the 2-year period prior to the index date was associated with a 60 % decreased risk of breast cancer mortality among women 70–79 years of age (OR 0.40; 95 % CI 0.27–0.60; Table 3).

In summary, we observed a decreased risk of breast cancer mortality associated with receipt of screening mammography in Saskatchewan during 1995–2008 among women 52–79 years of age. A decreased risk was present not only among women in their 50s and 60s, but also among women in their 70s.

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Conflict of interest The authors declare that they have no conflict of interest.

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