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Breast Cancer Screening, Incidence, and Mortality in Women Treated With Maintenance Dialysis: A Population-Based Cohort Study in Ontario, Canada

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INTRODUCTION

Cancer and cancer-related mortality incidence is approximately 1.5 times higher in patients with kidney failure compared to the age and sex-matched general population. The increased incidence is dependent on the type of cancer.[1] For example, for cancers known to cause kidney dysfunction, such as urinary tract cancer and multiple myeloma, the risk is almost 10 times higher in patients with kidney failure compared to the general population, whereas the incidence of lung cancer, colorectal cancer, and Kaposi's sarcoma is 2 to 3 times higher among patients with chronic kidney disease.[2] In contrast, the risk of developing breast and prostate cancer is similar between patients with kidney failure and those without kidney disease.[1,2] The postulated pathogenic mechanisms leading to increased cancer development with kidney dysfunction include alteration in DNA repair, impairment of immune function leading to reduced immune surveillance, reduction in antioxidant defense, chronic inflammation, and cumulative exposure to carcinogenic agents such as long-term immunosuppression.[3]

Although the risk of breast cancer may not be increased in women receiving dialysis, the prognosis of women with breast cancer treated with dialysis is poor. Data from Australia and New Zealand Dialysis and Transplant Registry indicated that the standardized mortality ratio for breast cancer in women treated with maintenance dialysis was 2.3, compared to women in the general population.[4] Similar observations were made among women with breast cancer and moderate-stage chronic kidney disease. The risk of breast cancer death was increased by 1.5 times in women with an estimated glomerular filtration rate <60 ml/min per 1.73 m^2 compared to women with an estimated glomerular filtration rate >60 ml/min per 1.73 m^2.[1]

Screening for breast cancer with mammography reduces the risk of death from breast cancer and is widely implemented globally. Large-scale randomized controlled trials have shown that mammographic screening for breast cancer in women aged 50 to 70 years is associated with a relative reduction in breast cancer death by 20%.[5] However, screening is not without potential harm. One of the concerns associated with population-based screening is over-diagnosis.[6] Over-diagnosis refers to screen-detected breast cancer that would not have progressed to a clinical presentation during the individual's lifetime and would not have caused the individual any harm.[5,6] This is particularly relevant for women between 50 and 75 years, treated with maintenance dialysis, whose years of life lost is 10-7-

23.4 years, and a projected life expectancy is at least 70% less than the general population.[7] A modeled economic evaluation of annual mammographic screening (compared with no screening) in women on dialysis found that the overall survival gains were small (absolute gain of less than 0.1% compared with no screening) and the incremental cost-effectiveness ratio was over US $100,000 per life-year saved.[8] However, these findings relied primarily on effectiveness data extrapolated from the general population. Comparative data on the benefits of routine mammographic screening in women treated with maintenance dialysis are lacking. In this study, we used data from Ontario, Canada, held at ICES (formerly known as the Institute for Clinical Evaluative Sciences) and a multistate diagram[S3] to estimate the risks of breast cancer, breast cancer-specific and nonbreast cancer-related deaths in women treated with maintenance dialysis who were either up-to-date or not-up-to-date with breast cancer screening (based on clinical guideline recommendations).

METHODS

Using the various administrative databases held at ICES, we conducted a retrospective population-based cohort study from July 1, 2002, to December 31, 2018, in all women between 50 to 74 years with kidney failure initiated on maintenance dialysis therapy. Full details of the methods are reported in Supplementary Methods.

RESULTS

Between July 1, 2002 and December 31, 2018, a total of 18,842 women with kidney failure initiated treatment with maintenance dialysis in Ontario, Canada. Of these, 22 had a recorded death date on or before the index date (i.e., dialysis initiation date), 13 were non-Ontario residents, 717 had undergone kidney transplantation on or before the index date, 8667 women were either less than 50 years or were 75 years or more on the index date, 112 had breast cancer screening before 50 years of age, 467 had a history of breast cancer or mastectomy on or before the index date, 465 were previously on dialysis before the index date, and 6 women had breast cancer-related death without breast cancer diagnosis or kidney transplantation after the diagnosis of breast cancer. After the exclusions mentioned above, the final cohort included 8373 women (Supplementary Figure S1).

Based on their participation in mammographic screening, women were divided into 2 states: screening "up-to-date" and screening "not-up-to-date" states. During the observation period, these women transitioned between these 2 screening states, and to the other states, such as the state of breast cancer diagnosis, breast cancer and nonbreast cancer death, and kidney transplantation. Details of the states and transitions are shown in Figure 1 and Supplementary Table S1.

Within the included cohort, 6370 women on maintenance dialysis entered the screening "not-up-to-date"

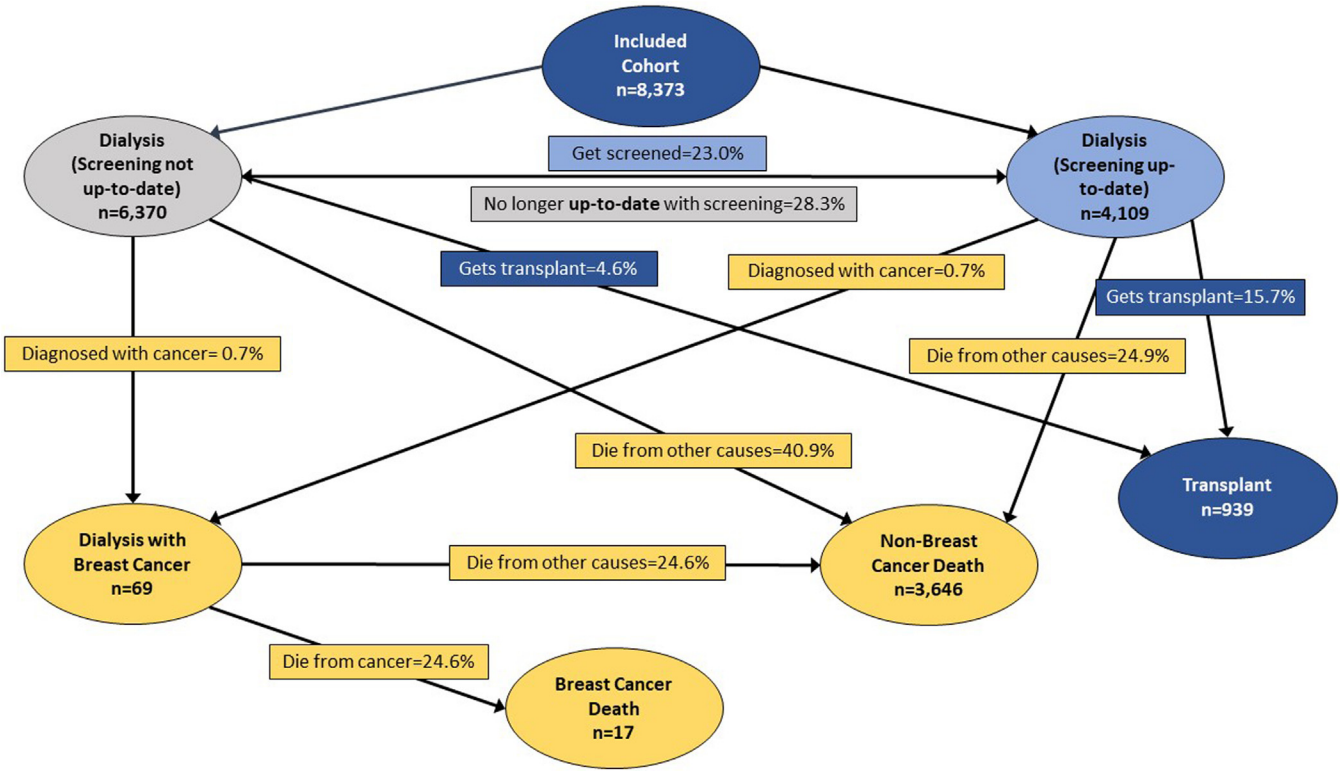

Figure 1. Multistate transition diagram of women on dialysis and moving through different transition states.

state, and 4109 entered the screening "up-to-date" state at least once during the follow-up period of 24,457 patient-years. At the end of follow-up, 23.0% of women transitioned from the screening "not-up-to-date" state to the screening "up-to-date" state and 28.3% transitioned from the screening "up-to-date" state to the screening "not-up-to-date" state. Among 8373 women included in the final cohort, 69 had breast cancer (0.8%), 17 (0.2%) had a breast cancer-related death, 3646 (43.5%) had a nonbreast cancer death, and 939 (11.2%) received a kidney transplant (Supplementary Table S2).

Baseline Characteristics of the Study Cohort

In Table 1, we show the baseline characteristics of the study cohort of women treated with dialysis stratified by cancer status and screening states. The mean (SD) age of all enrolled women was 63.8 (6.8) years, and the mean Charlson comorbidity index (SD) was 3.25 (2.25). Most women were hypertensive (90.9%), 65.2% had diabetes mellitus, 46.3% had cardiovascular disease, and most were on hemodialysis (78.6%). Compared to the earlier era (2002 to 2007), the proportion of the times women entering the screening "up-to-date" states appeared to be higher in the most recent era (2013 to 2018), increased from 23.0% to approximately 47.7% for women who did not develop breast cancer. Over the observation period (from the latest of the 50th birthday or 3 years before the index date to the end of follow-up), the mean (SD) number of screening events per individual was 1.2 (1.7), and the mean (SD) time a woman spent in the screening "up-to-date" and "not-up-to-date" states were 2.2 (1.9) and 2.4 (2.3) years, respectively.

Breast Cancer Incidence, Breast Cancer, and NonBreast Cancer Mortality Rates Between the Screening "Up-To-Date" And "Not Up-To-Date" States

Breast cancer incidence per 1000 patient-year (95% confidence interval) was 3.01 (2.06–4.39) among those in the screening "up-to-date" state and 2.75 (2.03–3.72) among women within the screening "not up-to-date" state. For women aged 50 to 59 years, the breast cancer incidence rate (95% confidence interval) was 3.64 (2.11–6.26) per 1000 patient-years in the screening "up-to-date" state and 2.37 (1.38–4.09) per 1000 patient-years in the screening "not-up-to-date" state. In the 60- to 74-years age category, the breast cancer incidence (95% confidence interval) in the screening "up-to-date" and "not-up-to-date" states were 2.60 (1.54–4.38) and 2.96 (2.05–4.25) per 1000 patient-years, respectively. Among women diagnosed with breast cancer ($n = 69$), 17 (25%) died due to breast cancer, and the incidence rate for breast cancer death (per 1000 patient-year) was 0.70 (0.43–1.12). This incidence rate was numerically lower among those women who were "up-to-date" with their cancer screening than those "not up-to-date" with breast cancer screening (Table 2). The incidence rate (95% confidence interval) for nonbreast cancer death was 149 (144–154) per 1000 patient-years. Across all age groups, the incidence of nonbreast cancer death was numerically lower among women in the screening "up-to-date" state than among women who were "not-up-to-date" with screening.

DISCUSSION

Using data from a very large population-based cohort in Ontario, Canada, we have shown a low overall incidence rate of breast cancer and breast cancer-related deaths among women receiving maintenance dialysis. Breast cancer incidence may be numerically higher among women in the screening "up-to-date" states than the screening "not-up-to-date" states, and breast cancer deaths may be lower in the screening "up-to-date" states than the screening "not-up-to-date" states. On the contrary, the incidence of nonbreast cancer-related death is very high in this dialysis cohort and may be higher in women within the screening "not-up-to-date" states than those in the screening "up-to-date" states.

Trial-based evidence in the general population has shown a relative risk reduction in breast cancer mortality by almost 20% with screening compared to no screening.[5,8] These survival benefits predominate for women aged 50 to 69 years who are attending organized mammographic screening programs. However, there is a delay in benefits. On average, it may take up to 10 years for 1 in 1000 women (0.1%) screened to avoid 1 breast cancer death. In women treated with maintenance dialysis, the benefits of routine screening are uncertain because of the lower life expectancy related to noncancer-related deaths. Moreover, mammographic screening may be less accurate in patients receiving dialysis because soft tissue calcification, secondary to kidney disease and hyperparathyroidism, may mimic malignant disease.[S6,S4] False-positive mammography findings can lead to harm associated with unnecessary diagnostic tests such as biopsies and the psychological stress of a potential cancer diagnosis.[5,8,S5] Prior research highlights the merits of an individualized approach to breast cancer screening in women on dialysis; however, previous work has not provided reliable estimates of breast cancer incidence and deaths in screened and unscreened populations to support this approach.[9] Given the higher competing risks of noncancer-related deaths in patients on dialysis, this current

Table 1. Baseline characteristics of the study cohort

Variable Description	All (N = 8373)	Women without breast cancer at baseline			Women who developed breast cancer during follow-up		
		Screening not up to date (n = 6370)	Screening up-to-date (n = 4109)	Std. Diff	Screening not up to date (n = 42)	Screening up-to-date (n = 27)	Std. diff
Age (years, mean ± SD)	63.78 ± 6.81	63.84 ± 6.93	63.27 ± 6.39	0.09	66.10 ± 5.80	62.81± 6.40	0.54
Median (IQR)	64 (58–70)	65 (58–70)	64 (58–69)	0.10	67 (61–72)	62 (57–69)	0.51
Income quintile, *n* (%)							
1 (Lowest)	2426 (29.0)	1920 (30.1)	1126 (27.4)	0.06	12 (28.6)	6 (22.2)	0.15
2	1902 (22.7)	1467 (23.0)	917 (22.3)	0.02	7 (16.7)	1–5[c]	0.05–0.44
3	1597 (19.1)	1208 (19.0)	791 (19.3)	0.01	11 (26.2)	1–5[c]	0.18–0.66
4	1344 (16.1)	970 (15.2)	691 (16.8)	0.04	2–10	1–5[c]	0.01–0.61
5 (Highest)	1054 (12.6)	764 (12.0)	562 (13.7)	0.05	1–5[c]	7 (25.9)	0.36–0.72
Missing	50 (0.6%)	41 (0.6)	22 (0.5%)	0.01	1–5[c]	0	0.22–0.52
Rurality, *n* (%)	1121 (13.4)	809 (12.7)	562 (13.7)	0.03	7 (16.7)	1–5[c]	0.05–0.44
Calendar year, *n* (%)							
2002–2007	2386 (28.5)	2018 (31.7)	603 (14.7)	0.41	9 (21.4)	7 (25.9)	0.11
2008–2012	2271 (27.1)	1764 (27.7)	1146 (27.9)	0.00	14 (33.3)	6 (22.2)	0.25
2013–2018	3716 (44.4)	2588 (40.6)	2360 (57.4)	0.34	19 (45.2)	14 (51.9)	0.13
[a]Primary care physician visits (Mean ±SD)	14.00 ± 15.84	14.17 ± 17.13	12.63 ± 14.57	0.10	9.17 ± 9.35	12.7 ±18.7	0.24
[a]Outpatient nephrology visits (Mean ± SD)	2.92 ± 5.92	2.45 ± 6.27	2.65 ± 6.67	0.03	0.57 ± 2.50	0.81 ± 2.04	0.11
[a]Hospitalizations (Mean ± SD)	1.10 ± 1.46	1.17 ± 1.48	0.96 ± 1.39	0.15	0.88 ± 1.17	0.59 ± 1.08	0.26
[b]Cancer screening (≤3 years), *n* (%)	886 (10.6)	0	1877 (45.7)	1.30	0	14 (51.9)	1.47
(>3 years), *n* (%)	3059 (36.5)	1942 (30.5)	2232 (54.3)	0.50	9 (21.4)	13 (48.1)	0.58
Never	4428 (52.9)	4428 (69.5)	0	2.14	33 (78.6)	0	2.71
Charlson Comorbidity Index (Mean ± SD)	3.25 ± 2.25	3.50 ± 2.30	3.22 ± 2.10	0.13	4.81 ± 1.78	4.48 ± 2.33	0.16
Causes of kidney failure, *n* (%)							
GN/ Autoimmune	817 (9.8)	572 (9.0)	493 (12.0)	0.10	1–5[c]	1–5[c]	0.01–0.55
Cystic kidney disease	421 (5.0)	286 (4.5)	273 (6.6)	0.09	1–5[c]	1–5[c]	0.01–0.55
Diabetes mellitus	3517 (42.0)	2873 (45.1)	1531 (37.3)	0.16	18 (42.9)	8 (29.6)	0.28
Renal vascular disease	1038 (12.4)	791 (12.4)	493 (12.0)	0.01	1–7	1–5[c]	0.01–0.55
Other/Unknown	2580 (30.8)	1848 (29.0)	1319 (32.1)	0.07	15 (35.7)	8 (29.6)	0.13
Coexisting comorbidities, *n* (%)							
Bowel cancer	215 (2.6)	151 (2.4)	117 (2.8)	0.03	0	1–5[c]	0.28–0.67
Lung cancer	170 (2.0)	131 (2.1)	88 (2.1)	0.01	0	1–5[c]	0.28–0.67
CVD	3878 (46.3)	3115 (48.9)	1884 (45.9)	0.06	27 (64.3)	13 (48.1)	0.33
PVD	533 (6.4)	507 (8.0)	276 (6.7)	0.05	9 (21.4)	1–5[c]	0.07–0.55
Diabetes mellitus	5456 (65.2)	4304 (67.6)	2527 (61.5)	0.13	34 (81.0)	18 (66.7)	0.33
Chronic liver disease	935 (11.2)	694 (10.9)	488 (11.9)	0.03	1–5[c]	1–5[c]	0.01–0.55
Chronic lung disease	1649 (19.7)	1305 (20.5)	725 (17.6)	0.07	9 (21.4)	1–5[c]	0.07–0.55
Hypertension	7607 (90.9)	5794 (91.0)	3786 (92.1)	0.04	41 (97.6)	27 (100)	0.22
Stroke	1364 (16.3)	1133 (17.8)	600 (14.6)	0.09	11 (26.2%)	1–5[c]	0.18–0.66
Dialysis modality, *n* (%)							
Hemodialysis	6578 (78.6)	5103 (80.1)	3046 (74.1)	0.14	37–41 (88.1–97.6)	18 (66.7)	0.53–0.88
Peritoneal dialysis	1795 (21.4)	1267 (19.9)	1063 (25.9)	0.14	1–5[c]	9 (33.3)	0.53–0.88

CVD, cardiovascular disease; GN, glomerulonephritis; IQR, interquartile range; No., number; PD, peritoneal dialysis; PVD, peripheral vascular disease; Std. Diff, Standardized difference.
[a]visits per month.
[b]time defined as before the index date.
[c]Cells with <6 patients were suppressed due to ICES privacy policies.

study raises an important question of whether routine breast cancer screening will incur any significant survival gains in women on dialysis. Current guidelines recommend a shared-decision approach to cancer screening, considering the individuals' breast cancer risk, life expectancy, potential harms, values, and preferences.[9] Although breast cancer deaths may be uncommon in women on dialysis, other factors such as age, transplant listing status, and genetic factors are important elements to consider when discussing screening strategies and options. Our study findings suggest that a "one-size-fits all" approach to cancer screening is probably inappropriate for women treated with maintenance dialysis. Implementation of routine

Table 2. Overall and age-based stratification of breast cancer incidence, breast cancer, and nonbreast cancer mortality event

Age strata based on index date	Strata	Number of events	Total patient-years of follow-up	Incidence per 1000 patient-yrs (95% CI)
Incident breast cancers				
	All	69	24,261.3	2.84 (2.25–3.60)
All ages	Screening not-up-to-date	42	15,291.7	2.75 (2.03–3.72)
	Screening up-to-date	27	8969.6	3.01 (2.06–4.39)
	All	26	9052.5	2.87 (1.96–4.22)
50–59 yrs	Screening not-up-to-date	13	5477.9	2.37 (1.38–4.09)
	Screening up-to-date	13	3574.6	3.64 (2.11–6.26)
	All	43	15,208.8	2.83 (2.10–3.81)
60–74 yrs	Screening not-up-to-date	29	9813.8	2.96 (2.05–4.25)
	Screening up-to-date	14	5395.0	2.60 (1.54–4.38)
Breast cancer deaths				
	All	17	24,457.4	0.70 (0.43–1.12)
All ages	Screening not-up-to-date	12–16	15,394.6	0.78–1.04 (N/A–N/A)
	Screening up-to-date	1–5[a]	9062.8	0.11–0.55 (N/A–N/A)
Nonbreast cancer deaths				
	All	3646	24,457.4	149.08 (144.31–153.99)
All ages	Screening not-up-to-date	2615	15,394.6	169.86 (163.48–176.50)
	Screening up-to-date	1031	9062.8	113.76 (107.03–120.92)
	All	1027	9151.0	112.23 (105.57–119.31)
50–59 yrs	Screening not-up-to-date	751	5524.7	135.93 (126.55–146.01)
	Screening up-to-date	276	3626.3	76.11 (67.64–85.64)
	All	2619	15,306.4	171.10 (164.68–177.79)
60–74 yrs	Screening not-up-to-date	1864	9869.9	188.86 (180.47–197.63)
	Screening up-to-date	755	5436.5	138.88 (129.32–149.14)

CI, confidence interval.
N/A – due to the very small number in these cells, we could only provide a range of the highest and lowest possible values for the point estimate of the incidence rate (not the 95% CI) due to ICES privacy policies.
[a]Cells with <6 patients were suppressed due to ICES privacy policies.

breast cancer screening in women on dialysis requires careful evaluation of the accuracy of the screening tools, screening frequency, patients' choices, cost-benefits, and the benefits-to-harm ratios, limited not only to the screening tests, but also the downstream consequences of the diagnostic tests and treatments.

Our study has several strengths. It is a large population-based cohort study of over 8000 women aged 50 to 74 years treated with dialysis. This study is sufficiently large to evaluate the incidence of breast cancer and deaths using observational data. However, we acknowledge that statistical inferences could not be made given the low event rates for both breast cancer incidences and deaths across the entire cohort. A randomized controlled trial comparing the benefits and harms of screening with no screening in women on dialysis would require a very large sample size, with sufficient power to detect a clinical and statistical difference between the 2 arms and is unlikely to be feasible within the dialysis population (and is unlikely ever to be done). Using state-transition techniques, we followed-up with the participants over time as they moved through screened and unscreened states with minimal attrition rates. Our outcomes, breast cancer incidence and deaths, were defined using a validated algorithm[S7]; therefore, misclassifying outcomes was unlikely. This study has several limitations. It is an observational study, which is subjected to potential confounding and selection biases. Despite our best efforts to only include women presented for screening mammography, it is possible that we may have included women with signs and symptoms of breast cancer in the analyses due to the potentially suboptimal accuracy of administrative health data. Details of harms associated with screening and the transplant wait-list status of the cohort were not available. Women who remained in the screening "up-to-date" states may be healthier and were more likely to be listed on the transplant waiting list, because adherence to routine cancer screening is a key criterion for transplant listing. Nonetheless, findings from this study will pave the way for policymakers to consider the benefit-to-harm ratio associated with screening and implement a personalized and risk-based approach to breast cancer screening in women on maintenance dialysis.

DISCLOSURE

The authors have declared no conflicting interest.

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Western site. This document used data adapted from the Statistics Canada Postal Code^{OM} Conversion File, which is based on data licensed from Canada Post Corporation, and/or data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under license from Canada Post Corporation and Statistics Canada. We thank IQVIA Solutions Canada Inc. for use of their Drug Information File. Parts of this material are based on data and information compiled and provided by: Ontario Ministry of Health, Ministry of Long-Term Care, Ontario Health, Canadian Institutes for Health Information; and on death information from Ontario Registrar General, the original source of which is ServiceOntario. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. Flow chart displaying study cohort selection based on the eligibility criteria.

Table S1. Description of transitions between states.

Table S2. Number of patients included in each state and duration of follow-up state.

Record Checklist.

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