A population-based analysis of breast cancer incidence and survival by subtype in Ontario women

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ABSTRACT

Background Breast cancer (BCa) is the type of cancer most frequently diagnosed among women in Canada. Breast cancer is categorized into various molecular subtypes by the expression of estrogen receptor (ER), progesterone receptor (PgR), and HER2 (human epidermal growth factor receptor 2). Currently, Canada has no national cancer registry with epidemiology data by subtype. Thus, we conducted a study to determine incidence, survival, and clinicopathologic characteristics by BCa subtype [triple negative breast cancer (TNBC); HER2+; and hormone receptor-positive (HR+), HER2-] in Canadian women newly diagnosed with BCa.

Methods Female patients diagnosed between 1 April 2012 and 31 March 2016 (fiscal 2012–2015) were identified in the Ontario Cancer Registry, and individual patient data were linked to data in provincial health administrative databases. Descriptive statistics and Kaplan–Meier curves were generated.

Results In this cohort, 3277 women (9.5%) had TNBC, 4902 (14.3%) had HER2+ BCa, and 22,247 (64.8%) had HR+, HER2- breast cancer. The annual incidence was 15 per 100,000 for the TNBC group, 21–23 per 100,000 for the HER2+ group, and 97–105 per 100,000 for the HR+, HER2- group. The lowest median overall survival (mos) of 8.9 months was observed in women with clinical stage IV TNBC. In comparison, the mos was 37.3 months in those with HER2+ disease and 35.2 months in those with and HR+, HER2- metastatic BCa.

Conclusions In the present study, the most recent and largest administrative database analysis of a Canadian population to date, we observed a subtype distribution consistent with previously reported data, together with comparable annual incidence and overall survival patterns.

Key Words Breast cancer, subtypes; incidence; overall survival; epidemiology

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INTRODUCTION

For women in Canada, breast cancer (BCa) is the most frequently diagnosed type of cancer (excluding non-melanoma skin cancers). In 2017, an estimated 26,300 Canadian women were diagnosed with BCa, and an estimated 4900 died of the disease¹. Breast cancer is routinely categorized into a number of different molecular subtypes that are identified by gene expression profiling^{2,3} and immunohistochemistry⁴. In the literature, BCa is commonly divided into the luminal A, luminal B, HER2 (human epidermal growth factor receptor 2)-enriched, and basal types. Given that

Ki-67, epidermal growth factor receptor, and cytokeratin 7 testing are not routinely used in Canada and many other countries around the world, the BCa subtypes are generally categorized as hormone receptor positive (HR+), based on expression of estrogen receptor (ER) or progesterone receptor (PgR), or both^{5–7}; HER2-positive (HER2+), regardless of HR status; or triple-negative (TNBC), lacking expression of HER2, ER, and PgR. Those subtypes of BCa each have distinct biologic and clinical characteristics, including differences in risk factors, disease management, recurrence rates, and survival outcomes^{8,9}. A personalized treatment approach is required based on the patient's specific BCa subtype^{10–12}.

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Approximately 15%–20% of BCa is triple-negative and 20% is HER2+; most are HR+, HER2–^{13–16}. Historically, longer survival has been reported for patients with HR+, HER2– BCa than for those with TNBC or HER2+ disease^{17–19}. However, a recent study of almost 160,000 U.S. patients diagnosed with BCa between 2010 and 2013 found that median overall survival (mos) was longer for those with metastatic HER2+ BCa than for those with HR+, HER2– disease (44 months vs. 36 months); patients with metastatic TNBC had the shortest mos, at 13 months²⁰. The superior outcomes of patients with metastatic HER2+ BCa in that study can be explained by the availability of very effective HER2-targeted therapies, including trastuzumab and pertuzumab (in combination with taxanes in the first-line metastatic setting), trastuzumab emtansine, and lapatinib plus capecitabine²¹. However, with the recent introduction of inhibitors of cyclin-dependent kinases 4 and 6 for patients with metastatic HR+, HER2– BCa, it is possible that those trends will change in the near future. In contrast, patients with metastatic TNBC have consistently been reported to have a shorter life expectancy, largely because of the lack of targeted and effective systemic therapies.

To date, population-based epidemiologic studies of BCa subtypes have largely focused on small observational cohorts or particular geographic regions, mostly outside of Canada^{22–24}. From a Canadian perspective, studies of incidence and survival in women by BCa subtype have been limited^{1,25}. The objective of the present study was to determine the clinicopathologic characteristics, incidence, and overall survival (OS) of women newly diagnosed with BCa in Ontario during fiscal years 2012–2015, based on BCa subtype.

METHODS

Study Design and Setting

This population-based retrospective study identified women newly diagnosed with BCa in Ontario between 1 April 2012 and 31 March 2016 (fiscal years 2012–2015) through the Ontario Cancer Registry (OCR). All data, including OCR data, were obtained from data holdings at ICES (formerly the Institute for Clinical Evaluative Sciences). The not-for-profit ICES research institute encompasses a community of research, data, and clinical experts, and holds a secure and accessible array of Ontario's health-related data. Research ethics approval for this study was granted by Advarra's Canadian institutional review board.

Patient Cohort

Ontario has a resident population of 14.2 million and provides publicly funded health care services through OHIP, the Ontario Health Insurance Plan. To conduct analyses of real-world data, ICES combines OHIP with other population-level health information based on encrypted patient identifiers.

For the present study, women with an initial primary diagnosis of BCa were identified in the OCR using the *International Statistical Classification of Diseases and Related Health Problems* (10th revision) diagnosis code C50x (female, right and left breasts). Women whose information was available within the follow-up period (until 31 March 2017) were included in the study cohort. Exclusion criteria

included a concurrent cancer diagnosis, previous diagnosis of any other cancer, diagnosis of malignant lymphoma of the breast, non-Ontario resident, male or missing sex, missing age, age less than 18 or greater than 105 years, and BCa diagnosis after the date of death because of entry error. The BCa subtype, tumour size, and grade were characterized from the OCR. The BCa subtypes analyzed in this study were defined as follows: TNBC (ER–, Pgr–, HER2–); HER2+ (HR+ or HR–); and HR+, HER2–. We did not discriminate between weak ER+ or Pgr+ compared with less than 1% ER or Pgr expression because the latter was the “gold standard”²⁶ for the diagnosis of TNBC at the time of data collection between 2012 and 2016. Further, that definition of TNBC (<1% ER or Pgr expression, and HER2– status) still applies today.

Statistical Analysis

Descriptive statistics (means, medians, standard deviations, interquartile ranges) were used to evaluate the study cohort by subtype, but *t*-tests were not conducted to determine statistical significance. The results are reported at an aggregate level and tabulated. Demographic characteristics, including neighborhood income quintile, were obtained using the Registered Persons Database. Score on the Charlson comorbidity index²⁷ was calculated using inpatient admission records, with a lookback period of 2 years before the BCa diagnosis. Annual incidence of BCa was calculated by dividing the number of newly diagnosed BCa cases in the OCR for each fiscal year by the number of adult Ontario women at risk (excluding women previously diagnosed with BCa) based on an ICES-derived cohort of approximately 5–6 million women who were alive and eligible to receive health insurance through OHIP, and who experienced at least 1 encounter during the follow-up period (supplemental Table 1). Thus, annual incidence is reported per 100,000 women at risk. For survival outcomes, 1-year follow-up was used (survival rates and mos); OS was defined as time from diagnosis to date of death (for women with a known date of death). Women alive or lost to follow-up at the end of the study period (31 March 2017) were censored. Kaplan–Meier curves were generated to present median, 1-year, and 5-year OS rates for each BCa subtype. The SAS Enterprise Guide software application (version 7.15; SAS Institute, Cary, NC, U.S.A.) was used in this analysis.

RESULTS

Baseline Patient and Tumour Characteristics

During fiscal years 2012–2015, 34,340 women (“all cases”) diagnosed with BCa met the study inclusion criteria (Table 1). In that cohort, the distribution by BCa subtype was 64.8% HR+, HER2–; 14.3% HER2+; and 9.5% TNBC. In 11.4%, subtype was unknown, and so that group of women was excluded from further analyses.

Mean age at diagnosis was similar regardless of BCa subtype, although women with HER2+ BCa were slightly younger (57.8 years) than those with TNBC (59.1 years) and those with HR+, HER2– BCa (62.1 years). Most women were diagnosed with stage I or II disease (78.0%); however, at diagnosis, tumours tended to be larger in women with TNBC and HER2+ BCa (>3 cm: 41.9% and 38.9% respectively) than in those with HR+, HER2– BCa (25.4%). In addition,

presentation with stage IV disease was slightly more likely in women with HER2+ BCa (7.2%) than in those with TNBC (5.8%) or HR+, HER2- BCa (3.7%). Tumours were also more likely to be lymph node-positive in women with HER2+ BCa

(42.6%) than in those with TNBC (33.0%) or HR+, HER2- BCa (32.2%). Interestingly, presentation with lymph node-positive tumours was more likely among younger women (<65 years: 44.9% HER2+; 37.2% HR+, HER2-; 34.7% TNBC) than

TABLE I Baseline patient and disease characteristics

Characteristic	Disease subtype			
	Overall	TNBC	HER2+	HR+, HER2-
Patients (<i>n</i>)	34,340 ^a	3,277	4,902	22,247
Mean age (years)	61.5±13.8	59.1±14.6	57.8±13.5	62.1±13.2
Age group [<i>n</i> (%)]				
18–34 Years	684 (2.0)	140 (4.3)	157 (3.2)	291 (1.3)
35–49 Years	6,295 (18.3)	729 (22.2)	1,249 (25.5)	3,727 (16.8)
50–64 Years	13,027 (37.9)	1,196 (36.5)	1,986 (40.5)	8,485 (38.1)
65–74 Years	8,247 (24.0)	700 (21.4)	904 (18.4)	5,798 (26.1)
75–84 Years	4,217 (12.3)	367 (11.2)	445 (9.1)	2,854 (12.8)
≥85 Years	1,870 (5.4)	145 (4.4)	161 (3.3)	1,092 (4.9)
Disease stage [<i>n</i> (%)]				
0	86 (0.3)	0 (0.0)	0 (0.0)	1–5 ^b
I	13,989 (40.7)	910–914 ^b	1,412 (28.8)	10,469 (47.1)
II	12,819 (37.3)	1,608 (49.1)	2,107 (43.0)	8,232 (37.0)
III	4,508 (13.1)	559–563 ^b	1,016 (20.7)	2,657–2,662 ^b
IV	1,673 (4.9)	190 (5.8)	354 (7.2)	813 (3.7)
Unknown	1,265 (3.7)	6 (0.2)	13 (0.3)	71 (0.3)
Score on the CCI				
Mean	0.64±1.20	0.60±1.18	0.61±1.22	0.61±1.15
Median	0	0	0	0
IQR	0–1	0–1	0–1	0–1
CCI score group [<i>n</i> (%)]				
0–5	10,708 (31.2)	993 (30.3)	1,353 (27.6)	6,927 (31.1)
6–10	187 (0.5)	16 (0.5)	31 (0.6)	92 (0.4)
Missing	23,445 (68.3)	2,268 (69.2)	3,518 (71.8)	15,228 (68.4)
Tumour size category [<i>n</i> (%)]				
No mass found	70 (0.2)	11 (0.3)	13 (0.3)	14 (0.1)
<1 cm	4,822 (14.0)	231 (7.0)	542 (11.1)	3,451 (15.5)
1 cm to <2 cm	10,264 (29.9)	775 (23.6)	1,133 (23.1)	7,907 (35.5)
2 cm to <3 cm	7,404 (21.6)	825 (25.2)	1,195 (24.4)	4,989 (22.4)
3 cm to <4 cm	3,850 (11.2)	568 (17.3)	736 (15.0)	2,325 (10.5)
4 cm to <5 cm	1,916 (5.6)	302 (9.2)	371 (7.6)	1,124 (5.1)
≥5 cm	3,710 (10.8)	503 (15.3)	800 (16.3)	2,195 (9.9)
Other ^c	2,304 (6.7)	62 (1.9)	112 (2.3)	242 (1.1)
Nodal status [<i>n</i> (%)]				
Positive	10,787 (31.4)	1,082 (33.0)	2,087 (42.6)	7,153 (32.2)
Negative	18,637 (54.3)	1,941 (59.2)	2,442 (49.8)	13,248 (59.5)
Unknown	4,916 (14.3)	254 (7.8)	373 (7.6)	1,846 (8.3)
Follow-up time (months)				
Median	33.1	30.7	32.5	33.9
IQR	21.6–46.1	19.4–44.7	21.5–45.8	22.4–46.5

^a The “Overall” group includes 3914 patients with breast cancer of an unknown subtype; the sum of the 3 known breast cancer subtypes will not equal 34,340.

^b Small-cell suppression or number ranges that contain values subject to small-cell suppression (required to prohibit “back calculation”).

^c Includes “other,” “unknown,” “missing.”

TNBC = triple-negative breast cancer; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; CCI = Charlson comorbidity index; IQR = 25%–75% interquartile range.

TABLE II Survival rates and median overall survival by breast cancer subtype and known stage

Subtype	Cases	Stage	Survival (% alive) at ...		Median overall survival	
			1 Year	5 Years	Months	95% CI
TNBC	3,277	I	98.8	93.3	—	6.7 to 11.1
		II	97.6	78.9	—	
		III	90.2	47.2	—	
		IV	41.1	7.4	8.9	
HER2+	4,902	I	99.6	96.5	—	28.0 to 43.0
		II	98.6	87.5	—	
		III	96.4	79.9	—	
		IV	74.6	36.6	37.3	
HR+	22,247	I	99.4	94.7	—	32.4 to 41.5
		II	98.7	88.1	—	
		III	96.0	72.9	—	
		IV	80.4	24.0	35.2	
All cases	32,989	I	99.3	94.1	—	26.2 to 30.9
		II	98.3	86.3	—	
		III	95.0	70.8	—	
		IV	70.7	23.4	28.6	

CI = confidence interval; TNBC = triple-negative breast cancer; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

among older women (≥ 65 years: 37.4% HER2+; 25.7% HR+, HER2–; 30.2% TNBC; supplemental Table 2). Comorbidity was difficult to assess because scores on the Charlson comorbidity index were missing in most patients for each subtype (>68%). Median follow-up ranged from 30.7 months to 33.9 months for the various subtypes.

Incidence

For fiscal years 2012–2015, 30,426 women with BCa of a known subtype constituted the denominator for calculating the annual incidence (BCa cases per 100,000 women at risk) in Ontario for the cohort overall and by subtype (Figure 1). As expected, the incidence rate was highest for the HR+, HER2– subtype (97–105 per 100,000), followed by HER2+ (21–23 per 100,000) and TNBC (15 per 100,000). The incidence was generally consistent over the timeframe examined.

FIGURE 1 Annual breast cancer incidence per 100,000 women, by subtype. TNBC = triple negative breast cancer; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

Overall Survival

The 34,340 women with BCa in fiscal years 2012–2015 were used to determine survival estimates for the subtypes overall; the 32,989 women with BCa of a known subtype were used to determine survival as stratified by disease stage (I–IV) at diagnosis (Figure 2), thus excluding the 1351 women with either stage 0 or unknown-stage disease. Kaplan–Meier survival curves for each subtype [Figure 2(A–C)] consistently showed that more advanced stages of disease were associated with worse long-term outcomes. In addition, relative to the HER2+ and HR+, HER2– cohorts [Figure 2(B,C)], the TNBC cohort [Figure 2(A)] showed more pronounced differences in survival outcomes for the various stages.

For each BCa subtype, the 1-year and 5-year survival rates were both associated with disease stage (Table II). The mos was available only for women with metastatic or stage IV disease and not for those with early-stage BCa (I–III). Women with stage IV TNBC had the lowest mos (8.9 months vs. 37.3 months for HER2+ BCa and 35.2 months for HR+, HER2– BCa).

DISCUSSION

This retrospective, population-level study identified a cohort of 34,340 women diagnosed with BCa in Ontario during fiscal years 2012–2015, among whom 30,426 had a known BCa subtype. The distribution by subtype was 64.8% HR+, HER2–; 14.3% HER2+; and 9.5% had TNBC. The subtype for remaining 11.4% was unknown. A study by Fallahpour and colleagues²⁸ reported similar subtype distributions (59.0% HR+, HER2–; 11.7% HER2+; and 8.6% TNBC) in Ontario between 2010 and 2012, but the proportion of patients with an unknown BCa subtype in their study (20.6%) was higher than that reported here. Other epidemiologic studies from England (5.3% TNBC)²⁹, France (66.8% HR+, HER2–; 10.0% HER2+; 6.3% TNBC; 14.0% unspecified)³⁰, and the United

FIGURE 2 Kaplan–Meier survival estimates overall and by subtype for cases of breast cancer with a known stage. TNBC = triple negative breast cancer; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

States (66.6% HR+, HER2–; 14.0% HER2+; 10.8% TNBC; 8.7% unspecified)³¹ also yielded similar subtype distributions. Thus, the distribution of BCa subtypes observed in the present study is similar to those in other real-world epidemiology studies. Similarly, the incidence per 100,000 by BCa subtype reported here is consistent with other smaller Canadian cohort studies^{28,32} and a study conducted in England³³.

Our study revealed poor survival for women with high-stage TNBC, as did an analysis by Dent and colleagues³⁴. However, variation in recurrence and survival outcomes by stage for patients with TNBC has been reported in the literature. For example, a large retrospective study ($n = 1879$) of surgical patients with BCa, which had a median follow-up of 73.3 months, observed no relationship between TNM staging and recurrence-free survival for patients with TNBC³⁵. Reddy and colleagues³⁶ recently reported on the risk of late recurrence in 873 patients with early stage TNBC who were disease-free at least 5 years after diagnosis, with a median follow-up of 8.3 years. In that group, the 10-year recurrence-free survival was 91%. The natural history of TNBC thus differs significantly from that of HR+ BCa, which portends a persistent risk of recurrence up to 20 years after diagnosis despite adjuvant endocrine therapy^{37–39}.

Patients with metastatic TNBC have consistently been shown to experience survival inferior to that experienced by patients with other metastatic BCa subtypes^{20,36,40–44}. Of 7578 women in the Surveillance, Epidemiology, and End Results database study²⁰ diagnosed with stage IV BCa between 2010 and 2013, 13.2% had TNBC and experienced a

mos of 13.0 months (95% confidence interval: 12.2 months to 13.8 months). The younger median age of the patients and the inclusion of those with prior early (nonmetastatic) BCa might explain the slightly longer mos in the Surveillance, Epidemiology, and End Results cohort compared with our cohort. We acknowledge, however, that some Canadian data suggest longer mos for patients with *de novo* metastatic TNBC than for those with metastatic relapse⁴⁰ (11 months vs. 8 months, $p = 0.02$). Kassam and colleagues⁴¹ also conducted a retrospective cohort study of 111 patients with metastatic TNBC at 3 University of Toronto–affiliated institutions between January 2003 and December 2006; the mos in that cohort was 13.3 months (range: 0.8–99.8 months). Inherent bias toward the selection of generally healthy patients who present for treatment to a cancer centre likely resulted in longer mos, albeit the very small sample size that represented a limitation in that retrospective study. A different distribution of molecular TNBC subtypes in the various studies (something that was not assessed in our study) might also contribute to differences in reported clinical outcomes⁴⁵.

The poor survival of patients with metastatic TNBC might be attributable to biologically aggressive disease, with a propensity for metastases to visceral organs and the central nervous system^{46–48}. A lack of effective and targeted treatment options also contributes to poor outcomes for women with metastatic TNBC. However, immunotherapy⁴², poly-ADP ribose polymerase inhibitors^{49,50}, the AKT inhibitors ipatasertib⁵¹ and capivasertib⁵², and antibody–drug conjugates such as sacituzumab govitecan-hziy⁵³

in development for metastatic TNBC all hold promise for improved outcomes in that subgroup.

In our study, the mos was longest among women with HER2+ metastatic breast cancer (37.3 months), which is shorter than the mos of 56.5 months observed in the first-line trial of paclitaxel and trastuzumab with or without pertuzumab⁵⁴. Our shorter os might reflect the inclusion of women in the “real world” setting and the limited use of trastuzumab emtansine in the second-line setting in the cohort (approved by Health Canada in 2013 and funded as of May 2014); however, treatment patterns are beyond the scope of this manuscript.

Finally, the mos for women with HR+, HER2– metastatic BCa was 35.2 months at a time when single-agent endocrine therapy was typically used in the first-line metastatic setting. It is likely that the outcomes of women with HR+, HER2– breast cancer will improve over time with the increasing uptake of inhibitors of cyclin-dependent kinases 4 and 6 and of PI3K, which have been associated with a clinically meaningful benefit in this subtype^{55–57}.

Whether patients with HR+, HER2+ BCa as opposed to HR–, HER2+ BCa have superior outcomes has been debated, with several studies reporting conflicting clinical results^{58,59}. We did not distinguish between HR+ and HR– status for the population of women with HER2+ tumours; that difference could be explored in future publications.

The present Canadian cohort study is one of the largest to date spanning multiple years, allowing 30,426 women with BCa of a known subtype to be analyzed for annual incidence and 32,989 women with BCa of known disease stage at diagnosis to be analyzed for os. The study has some limitations, such including only women resident in Ontario, excluding the 11% of women with an unknown BCa subtype, incomplete assessment of performance status, and lack of other biomarker results (Ki-67, epidermal growth factor receptor, cytokeratin 7). In addition, mos could be calculated only for women with stage IV disease and those for whom relapse or recurrence could not be assessed. Given the variation in the natural history of BCa, it would be of great interest to examine, at a future date, early and late recurrence by disease subtype in Canadian women^{24,44–46}.

CONCLUSIONS

This retrospective, population-based study of 30,426 women with BCa is the largest Canadian BCa cohort to date, revealing a subtype distribution consistent with previously reported data, together with comparable patterns of annual incidence and os. The significantly shorter survival observed for women with advanced disease, particularly metastatic TNBC, highlights the pressing need to provide better treatment options. Future work will include an examination of treatment patterns and resource costs associated with each BCa subtype to better understand disease management and the impact of BCa in Canada.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: SJS declares consultancies through the HOPE Research Centre, a group that consults to the pharmaceutical industry. Medical writing support was received from Hoffmann–La Roche Limited. BP, KEF, and MC are employees of Hoffmann–La Roche Limited. KJJ declares consultancies with Esai, Genomic Health Inc., Novartis, Purdue Pharma, Pfizer, and Roche. She has also received grants or research support from AstraZeneca and speaker fees from Apobiologix, Novartis, and Purdue Pharma.

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