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Research

Breast cancer survival by molecular subtype: a population-based analysis of cancer registry data

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Abstract

Background: The relation between breast cancer molecular subtype and survival has been studied in several jurisdictions, but limited information is available for Ontario. The aim of this study was to determine breast cancer survival by molecular subtype and to assess the effect on survival of selected demographic and tumour-based characteristics.

Methods: We extracted 29 833 breast cancer cases (in 26 538 girls and women aged ≥ 15 yr) diagnosed between 2010 and 2012 from the Ontario Cancer Registry. Cancers were categorized into 4 molecular subtypes: 1) luminal A (estrogen-receptor–positive and/or progesterone-receptor–positive [ER+ and/or PR+] and negative for human epidermal growth factor receptor 2 [HER2–]), 2) luminal B (ER+ and/or PR+/HER2+), 3) HER2-enriched (ER– and PR–/HER2+) and 4) triple-negative (ER– and PR–/HER2–). We estimated associations with predictor variables (age, stage at diagnosis, histologic type, comorbidity and place of residence [urban or rural]) using a multivariate Cox proportional hazards model. Likelihood ratio testing was used to evaluate differences in risk of death.

Results: Luminal A was the most commonly diagnosed subtype (59.0%) and had the greatest survival, whereas triple-negative had the poorest survival. For all subtypes, a dose–response effect was observed between the hazard of death and age and stage at diagnosis, with the greatest effect found for the HER2-enriched subtype (age: hazard ratio [HR] 7.87 [95% confidence interval (CI) 3.68–11.81]; stage at diagnosis: HR 37.71 [95% CI 34.64–41.27]). Moderate comorbidity (Charlson Comorbidity Index score 1 or 2) was associated with increased risk of death for triple-negative cancers (HR 2.42 [95% CI 1.36–4.31]), and severe comorbidity (Charlson Comorbidity Index score ≥ 3) increased the risk for all molecular subtypes.

Interpretation: The results indicate the importance of including molecular subtype, along with age, stage at diagnosis and comorbidity, in assessing breast cancer survival. They highlight the need to address outcomes related to hormone-receptor–negative cancers, for which survival lags behind that for hormone-receptor–positive cancers.

Breast cancer is the most commonly diagnosed cancer and the second most common cause of cancer-related death among women in Ontario.[1] More than 10 000 cases are diagnosed each year in the province.[1] Several molecular subtypes of breast cancer have been identified based on hormone receptor and human epidermal growth factor receptor 2 (HER2) status.[2] These molecular subtypes have been shown to affect survival: patients with hormone-receptor–negative tumours tend have greater mortality and lower survival than those with hormone-receptor–positive tumours.[3–5]

Although the relation between breast cancer molecular subtype and survival has been studied in other jurisdictions, including British Columbia,[6,7] limited information is available for Ontario. The goal of this study was to determine how breast cancer molecular subtype affects survival among Ontario women and how survival for each subtype varies by selected demographic and tumour-based characteristics.

Methods

Setting and study population

The study population included all cases of malignant breast cancer diagnosed in girls and women aged 15 years or more in Ontario between Jan. 1, 2010, and Dec. 31, 2012. We chose this period because data on molecular subtype were unavailable for cases diagnosed before 2010, and mortality data were unavailable for cases diagnosed after 2012.

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Data sources and definitions

The data for this study were extracted from the July 2016 version of the Ontario Cancer Registry, a population-based database of new cancer cases. The registry covers the entire population of Ontario and includes information about all cases of invasive neoplasia diagnosed in the province since 1964 except for basal cell and squamous cell skin cancers. Quality measures for the 2012 diagnosis year with the data-quality standard of the North American Association of Central Cancer Registries were as follows: completeness of case ascertainment (94.8%), missing age and missing sex (0%), cases with death certificate only (1.8%) and passing North American Association of Central Cancer Registries edit checks (100%).[8] Breast cancer incident cases and deaths were classified as C50 according to the International Classification of Diseases for Oncology, 3rd edition[9] and the International Statistical Classification of Diseases and Related Health Problems, 10th revision.[10]

Predictor variables of interest were age, histologic type, stage at diagnosis, comorbidity and residence at diagnosis. Histologic type was defined as ductal (histology codes 8201, 8230, 8401, 8500–8504, 8507, 8508, 8523, 8541, 8543), lobular (histology codes 8520–8522, 8524) or other. We classified stage at diagnosis using the Collaborative Staging method, which incorporates information on tumour size, lymph node involvement and metastases.[11] Information on molecular subtype was collected from coded synoptic pathology reports, which are submitted electronically to the Ontario Cancer Registry by public and private laboratories. We extracted data on comorbidities from the Canadian Institute for Health Information's Discharge Abstract Database and linked them using health card number. Comorbidities were organized according to the Charlson Comorbidity Index.[12] Comorbidity categories are weighted from 1 to 6, with a score of 0 indicating no comorbid conditions. We determined residence (rural or urban) at the time of diagnosis using the Postal Code Conversion File Plus package.[13]

Molecular subtypes

We categorized breast cancer cases into 4 molecular subtypes based on hormone receptor and HER2 status. Hormone-receptive–positive tumours can be sensitive to exposure to either estrogen (estrogen-receptor–positive [ER+]) or progesterone (progesterone-receptor–positive [PR+]) or not sensitive to either hormone (hormone-receptor–negative [ER– or PR–]). Tumours that are HER2-positive (HER2+) overproduce the HER2 protein that stimulates uncontrolled breast cell proliferation. This results in 4 molecular subtypes: luminal A (ER+ and/or PR+/HER2–), luminal B (ER+ and/or PR+/HER2+), HER2-enriched (ER– and PR–/HER2+) and triple-negative (ER– and PR–/HER2–).

Statistical analysis

We calculated survival as the time (in days) between the patient's date of diagnosis and 1 of the following, whichever occurred first: 1) date of death, 2) date last known to be alive or 3) the most recent follow-up cut-off date (Dec. 31, 2012). The outcome of interest was death due to breast cancer; deaths from other causes were censored at the date of death.

We used SAS statistical software (version 9.4) (SAS Institute) to perform the analysis. A univariate model was performed to compare survival among the molecular subtypes. We estimated associations between molecular subtype and the predictor variables using the Cox proportional hazards model. Four separate multivariate Cox models were fitted for each molecular subtype, and the association with predictors was investigated within each model. No interactions between variables were found in any model. We investigated the proportionality assumption for each variable through the log-log survival function as well as the computed p value of a Kolmogorov-type supremum test based on a sample of 1000 simulated residual patterns. With the exception of stage at diagnosis, none of the variables in the models violated the proportionality assumption. To make stage at diagnosis satisfy the proportionality assumption, we regrouped the variable (stage I and II v. stage III v. stage IV). We used likelihood ratio testing to evaluate whether the variations in risk of death by variable were statistically significant.

Ethics approval

Because this was secondary analysis of data, no ethics approval was sought.

Results

Incidence counts and rates

A total of 29 833 cases of breast cancer (in 26 538 individual girls and women) were included in the incidence analysis. Table 1 presents the incidence counts and rates for each molecular subtype by age group. The luminal A subtype was the subtype most commonly diagnosed, accounting for 59.0% of all cases, with a rate of 103.3 per 100 000, followed by triple-negative (15.1 per 100 000), luminal B (13.5 per 100 000) and HER2-enriched (7.0 per 100 000).

The incidence rate of the luminal A subtype peaked among patients aged 70–79 years (262.1 per 100 000). The incidence of luminal B cancers was much more evenly distributed, with similar rates among patients aged 50–59, 60–69 and 70–79. The rate of HER2-enriched cancers peaked among those aged 50–59 (12.9 per 100 000), and the distribution was most skewed toward the younger age groups. For triple-negative cancers, the distribution was skewed more toward the oldest age groups, with the highest rates found among those aged 60 or more.

Survival

Of the 26 538 patients, 4000 were excluded from the survival analysis: 3777 had multiple primary cancers or were missing health card number, stage or receptor status, and 223 had an autopsy or death certificate only. This resulted in a final sample of 22 538 patients in whom breast cancer was diagnosed for the first time between 2010 and 2012.

Table 2 presents the number of patients and observed breast cancer deaths for each molecular subtype by the variables used in the Cox regression analysis. Regardless of molecular subtype, mortality was higher among patients with more advanced age, severe comorbidity (Charlson Comorbidity

Index score ≥ 3), advanced stage at diagnosis (stage III or IV), lobular carcinoma and urban residence.

Univariate analysis showed significant differences in survival between the molecular subtypes ($p < 0.001$) (Figure 1). Pairwise comparisons using log-rank tests also showed that survival differed significantly between each molecular subtype, with patients with the luminal A subtype experiencing the longest survival, followed by those with the luminal B and HER2-enriched subtypes. The poorest survival was observed among patients with the triple-negative subtype.

Cox regression analysis showed that, for all molecular subtypes, age at diagnosis, histologic type (except for HER2-enriched), stage at diagnosis and comorbidity were the significant contributors to the hazard of death (Table 3).

Age at diagnosis

Age at diagnosis was significantly associated with death for all molecular subtypes. For all subtypes, there was a dose–response relation with age, with the hazard of death increasing with increasing age, although which age groups had significantly higher hazard of death differed by subtype. Among patients with luminal A cancer, increasing age was associated with increased risk of death for women aged 60 or more. Among those with luminal B or HER2-enriched cancers, however, increased risk over the reference level was found only for those aged 80 or more. Age had the greatest effect on the hazard of death for HER2-enriched cancers, with patients aged 80 or more having almost 8 times the risk of those aged 15–49. For triple-negative cancers, the hazard of death was increased for women aged 70 or more. Age at diagnosis had the smallest effect on triple-negative cancers, with patients aged 80 or more having only a twofold increase in the risk of death compared to those aged 15–49.

Histologic type

Histologic type was a significant predictor of survival for all molecular subtypes except HER2-enriched. There was no significant difference in risk of death between ductal and lobular carcinoma regardless of molecular subtype. However, for the luminal A, luminal B and triple-negative subtypes, patients with cancers classified as "other" had increased survival compared to those with ductal carcinomas. The greatest increase in survival in the "other" group was seen for patients with luminal A cancer, who had less than a quarter the risk of death of those with ductal cancers.

Stage at diagnosis

For all molecular subtypes, stage at diagnosis was the strongest predictor of survival. Across all subtypes, patients with stage III or IV cancer had a significantly increased hazard of death compared to those with stage I or II disease. For all subtypes, there was a dose response–relation with stage at diagnosis, with the hazard of death increasing with increasing stage. The greatest increase in the hazard of death was observed for HER2-enriched cancers: patients with stage III cancer had almost 8 times the risk of death of those with stage I or II cancer, while women with stage IV disease had almost 38 times the risk.

Comorbidity

For the luminal A, luminal B and HER2-enriched molecular subtypes, patients with moderate comorbidity (Charlson Comorbidity Index score 1 or 2) had no increase in risk of death compared to those with no comorbid conditions. For the triple-negative subtype, a dose–response relation with level of comorbidity was observed: patients with moderate comorbidity had 2.2 times the risk of death of those with no comorbid conditions, and patients with severe comorbidity (Charlson Comorbidity Index score ≥ 3) had 3.4 times the risk. Severe comorbidity increased the risk of death for all molecular subtypes, with the greatest effect found for luminal B cancers, for which the risk was 6 times higher (twice the effect seen for the other 3 subtypes).

Table 1: Breast cancer cases and age-specific incidence rates (per 100 000) by molecular subtype, Ontario, 2010–2012

	Age group, yr											
	All ages		15–49		50–59		60–69		70–79		≥ 80	
Molecular subtype	Count (%)	Incidence rate per 100 000	Count (%)	Incidence rate per 100 000	Count (%)	Incidence rate per 100 000	Count (%)	Incidence rate per 100 000	Count (%)	Incidence rate per 100 000	Count (%)	Incidence rate per 100 000
Luminal A	17 598 (59.0)	103.3	3238 (54.5)	33.1	4085 (58.1)	141.3	4789 (62.4)	230.4	3403 (62.4)	262.1	2083 (55.8)	213.5
Luminal B	2308 (7.7)	13.5	704 (11.8)	7.2	660 (9.4)	22.8	494 (6.4)	23.8	287 (5.3)	22.1	163 (4.4)	16.7
HER2-enriched	1193 (4.0)	7.0	337 (5.7)	3.4	372 (5.3)	12.9	261 (3.4)	12.6	137 (2.5)	10.6	86 (2.3)	8.8
Triple-negative	2574 (8.6)	15.1	669 (11.3)	6.8	638 (9.1)	22.1	606 (7.9)	29.2	386 (7.1)	29.7	275 (7.4)	28.2
Unknown	6160 (20.6)	36.2	991 (16.7)	10.1	1278 (18.2)	44.2	1525 (19.9)	73.4	1239 (22.7)	95.4	1127 (30.2)	115.5
Total	29 833	175.1	5939	60.7	7033	243.3	7675	369.2	5452	420	3734	382.7

Note: HER2 = human epidermal growth factor receptor 2.

Table 2: Number of patients with breast cancer and deaths from breast cancer, multivariate model, Cox regression cohort

Variable	Molecular subtype							
	Luminal A		Luminal B		HER2-enriched		Triple-negative	
	No. of deaths/ no. of patients	Cancer deaths, %	No. of deaths/ no. of patients	Cancer deaths, %	No. of deaths/ no. of patients	Cancer deaths, %	No. of deaths/ no. of patients	Cancer deaths, %
Age, yr								
15–49	36/3157	1.1	12/681	1.8	12/333	3.6	50/648	7.7
50–59	55/3943	1.4	14/640	2.2	15/361	4.2	35/599	5.8
60–69	78/4559	1.7	18/470	3.8	15/253	5.9	35/560	6.2
70–79	83/3187	2.6	7/262	2.7	8/127	6.3	47/368	12.8
≥ 80	109/1915	5.7	23/147	15.6	18/80	22.5	41/248	16.5
Residence at diagnosis								
Urban	325/14 795	2.2	68/1961	3.5	61/1008	6.0	185/2131	8.7
Rural	36/1966	1.8	6/239	2.5	7/146	4.8	23/292	7.9
Histologic type								
Ductal	268/10 663	2.5	58/1468	4.0	55/859	6.4	161/1744	9.2
Lobular	64/2105	3.0	7/165	4.2	3/35	8.6	9/42	21.4
Other	29/3993	0.7	9/567	1.6	10/260	3.8	38/637	6.0
Stage at diagnosis								
I–II	100/14 046	0.7	16/1579	1.0	7/745	0.9	66/1866	3.5
III	93/2080	4.5	12/480	2.5	23/304	7.6	81/440	18.4
IV	168/635	26.4	46/141	32.6	38/105	36.2	61/117	52.1
Charlson Comorbidity Index score								
0	243/15 493	1.6	39/2021	1.9	43/1028	4.2	163/2238	7.3
1–2	20/550	3.6	5/46	10.9	4/34	11.8	14/76	18.4
≥ 3	98/718	13.6	30/133	22.6	21/92	22.8	31/109	28.4
Total	361/16 761	2.2	74/2200	3.4	68/1154	5.9	208/2423	8.6

Note: HER2 = human epidermal growth factor receptor 2.

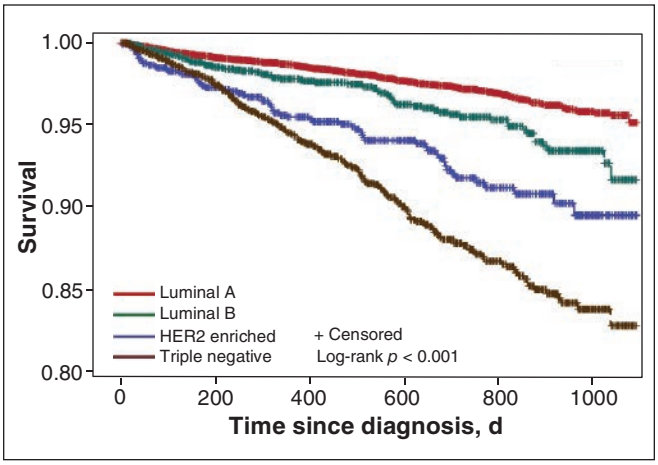

Figure 1: Kaplan–Meier plot of overall breast cancer survival by molecular subtype, Ontario, 2010–2012. Note: HER2 = human epidermal growth factor receptor 2.

Interpretation

This analysis illustrates the heterogeneous nature of female breast cancer with regard to molecular subtype in Ontario. Most female breast cancers diagnosed between 2010 and 2012 were luminal A cancers, the subtype with the greatest survival. However, the second most common type was triple-negative, the subtype with the poorest survival. Age, histologic type, stage at diagnosis and comorbidity were all found to affect survival. Stage at diagnosis was the strongest predictor of survival, with patients with stage IV disease having a 27- to 38-fold increase in risk of death, depending on the molecular subtype, compared to those with stage I–II disease.

In this analysis, luminal A cancers accounted for 59.0% of all breast cancers. This is higher than the proportion found in other Canadian studies, 41%–44%.[6,7] Previous analyses have shown that the incidence of hormone-receptor–negative cancers tends to peak before menopause, whereas hormone-receptor–positive cancers are more common after menopause.[14–16] The incidence

of triple-negative cancers in our study did not conform to these findings, peaking in postmenopausal women (aged ≥ 60).

We found that survival was highest for patients with luminal A cancers, followed by those with luminal B cancers. This confirms the better outcomes in hormone-receptor–positive cancers reported in other jurisdictions.[6,7,17–19] We found no difference in survival between lobular and ductal histologic types among any of the molecular subtypes, despite the fact that lobular cancers tend to be associated with better prognosis.[20–22] We also found no difference in survival between urban and rural residents, regardless of molecular subtype, even though rural Canadians often lag behind urban Canadians in many health indicators, such as life expectancy.[23] This result is similar to that in a previous study of breast cancer outcomes in BC, which showed no difference between rural and urban women in either breast cancer or overall survival.[24] However, as postulated in the BC study, the length of follow-up in the current analysis may not have been sufficient to detect significant differences. Nevertheless, the absence of a difference in survival between rural and urban residents is a positive sign of equity in breast cancer outcomes in Ontario.

Limitations

There are several possible confounders that we were unable to include in this analysis because data were not available. These include race, which has been shown to affect the risk of hormone-receptor–negative cancers[25,26] and survival within subtypes;[27–29] tobacco use, which has been associated with increased risk of hormone-receptor–negative cancers in postmenopausal women;[30] obesity, which has been linked with an increased risk of hormone-receptor–positive cancers[31–33] and, for premenopausal women, triple-negative cancers;[34,35] and reproductive factors such as age at menarche, parity, oral contraceptive use and breastfeeding history, which have also been shown to affect the risk of hormone-receptor–positive cancers.[30,31] Including these variables in our analysis may have adjusted the hazard ratios. In addition, data on treatment were not included in the analysis, as concerns about the quality of the treatment data currently available in Ontario meant that the possible informative value of the data did not outweigh the possible bias they may have introduced. Other investigators used additional molecular subtypes;[6] however, identification of these additional subtypes was not possible in the current analysis, as

Table 3: Breast cancer survival hazard ratios, multivariate model, by molecular subtype and patient characteristics

	Molecular subtype; HR (95% CI)			
Variable	Luminal A	Luminal B	HER2-enriched	Triple-negative
Age, yr				
15–49	Reference	Reference	Reference	Reference
50–59	1.33 (0.87–2.03)	1.24 (0.56–2.73)	1.54 (0.72–3.33)	0.77 (0.50–1.20)
60–69	1.81 (1.21–2.68)	1.91 (0.89–3.27)	1.82 (0.844–3.93)	0.73 (0.46–1.13)
70–79	2.29 (1.54–3.41)	1.05 (0.402–2.73)	2.04 (0.77–4.41)	1.73 (1.11–2.70)
≥ 80	4.13 (2.81–6.07)	6.34 (2.88–11.06)	7.87 (3.68–11.81)	1.77 (1.18–2.65)
Residence at diagnosis				
Urban	Reference	Reference	Reference	Reference
Rural	0.85 (0.60–1.21)	1.34 (0.57–3.14)	0.91 (0.40–1.64)	0.97 (0.63–1.51)
Histologic type				
Ductal	Reference	Reference	Reference	Reference
Lobular	0.83 (0.63–1.09)	0.46 (0.19–1.09)	1.27 (0.34–3.21)	1.84 (0.92–2.67)
Other	0.22 (0.15–0.33)	0.42 (0.21–0.87)	0.61 (0.29–1.24)	0.68 (0.47–0.97)
Stage at diagnosis				
I–II	Reference	Reference	Reference	Reference
III	6.52 (4.89–8.69)	2.14 (1.02–4.58)	7.86 (4.33–11.52)	5.49 (3.93–7.66)
IV	27.05 (24.41–31.29)	34.32 (30.48–39.73)	37.71 (34.64–41.27)	27.02 (24.76–28.82)
Charlson Comorbidity Index score				
0	Reference	Reference	Reference	Reference
1–2	1.59 (0.98–2.54)	1.37 (0.49–3.17)	1.84 (0.62–3.51)	2.42 (1.36–4.31)
≥ 3	2.54 (1.98–3.27)	5.94 (3.48–8.13)	2.54 (1.47–4.44)	3.41 (2.61–4.62)

Note: CI = confidence interval, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio.

the data did not allow for the inclusion of Ki-67, epidermal growth factor receptor or cytokeratin 5/6 status. We had to use a broad age range for the younger patients (15–49 yr), as the case counts were too low to allow for smaller groups. Finally, the length of follow-up (3 yr) may be considered short. However, as the goal was to present current survival, not to predict future survival, we believe the follow-up period was adequate.

Conclusion

Survival among girls and women with breast cancer in Ontario was found to vary considerably by molecular subtype. The results indicate a need to address outcomes related to the treatment and/or detection of hormone-receptor–negative cancers, for which survival lags behind that for hormone-receptor–positive cancers. The prognosis and treatment of patients with breast cancer may be improved by also taking into account age, stage at diagnosis and comorbidity in relation to their tumour hormone status. Once more data are available, further analysis on this topic, including trends over time, will be possible. This could be a fruitful area of investigation, as other jurisdictions have found that survival has improved more for estrogen-positive tumours than for other subtypes.[36–40]

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