Breast cancer survival by molecular subtype in Ontario: A population-based analysis of cancer registry data

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Abstract

Background: Incidence and survival has been shown to vary by molecular subtype (hormone receptor and human epidermal growth factor receptor 2 status) in other jurisdictions but little information is available on the Canadian population.

Methods: 29,833 breast cancers diagnosed from 2010 to 2012 were extracted from the Ontario Cancer Registry. Associations between molecular subtype and predictor variables were estimated using a Cox proportional hazards model. A separate model was fitted for each of the four subtypes and likelihood ratio testing was used to evaluate the significance of differences in mortality risk.

Results: Luminal A was the most commonly diagnosed subtype and in a univariate model it had the highest survival while Triple Negative had the poorest. In the multi-variate model a dose-response effect was observed with age for all subtypes, with the greatest effect of increased age found for Luminal B (HR=11.5, 95% CI 9.9-13.4). For all subtypes advanced stage (III or IV) increased the risk of mortality, however the greatest effect was seen for HER2 Enriched (HR=15.1, 95% CI 12.8-20.0). Moderate co-morbidities were associated with decreased survival for Triple Negative cancers (HR=2.6 95% CI 1.5-4.0) while severe co-morbidities decreased survival for all subtypes.

Interpretation: This study indicates a need to address outcomes related to the treatment and/or detection of hormone receptor negative cancers for which survival lags behind hormone receptor positive cancers. Survival was also associated with stage, age, histology and co-morbidities, although the effect varied by subtype.

Introduction

Breast cancer remains the most commonly diagnosed cancer and the second most common cause of cancer-related death among women in Ontario. More than 10,000 cases of breast cancer 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] Hormone receptive positive tumours can be sensitive to exposure to either estrogen (estrogen receptor positive or ER+) or progesterone (progesterone receptor positive or PR+) or not sensitive to either hormone (hormone receptor negative or ER- or PR-). Tumours that are HER2 positive (HER2+) overproduce the HER2 protein that stimulates uncontrolled breast cell proliferation. Four breast cancer molecular subtypes have been identified: Luminal A (ER+/PR+/HER2-); Luminal B (ER+PR+/HER2+); HER2 Enriched (ER-/PR-/HER2+); and Triple Negative (ER-/PR-/ HER2-). These molecular subtypes have been shown to affect survival, patients with hormone receptor negative tumours tend to have greater mortality and lower survival than those with hormone receptor positive tumours.[3-5]

While the relationship between breast cancer molecular subtype and survival has been studied in other jurisdictions, little information is available on the Canadian population. The goal of this study was to determine how breast cancer molecular subtype impacts survival among Ontario women and how this relationship may be modified by selected demographic and tumour-based characteristics.

Methods

Data sources

The data for this study were extracted from the July 2016 version of the Ontario Cancer Registry (OCR), a population-based database of new cancer cases. Demographic and tumour

characteristics of interest were age and residence at time of diagnosis, tumour histology, stage at diagnosis, molecular subtype, and comorbidities.

Breast cancer incident cases and deaths were classified as C50 according to the International Classification of Diseases for Oncology – Third Edition (ICD-O-3)[6] and the International Statistics Classification of Diseases and Related Health Problems – 10th Revision (ICD-10).[7] The study population included all cases of invasive carcinoma of the breast diagnosed in females aged 15 years and over in Ontario between January 1, 2010 and December 31, 2012, resulting in a sample of 29,833 cases. This time period was chosen as data on molecular subtype was unavailable for cases diagnosed prior to 2010 and data on mortality was unavailable for cases diagnosed after 2012.

Stage at diagnosis was classified using the Collaborative Stage (CS) method of staging.[8] Information on molecular subtype was collected from coded synoptic pathology reports, which are submitted electronically to the OCR by public and private laboratories. Data on co-morbidities was extracted from the Canadian Institute of Health Information's Discharge Abstract Database (DAD) and linked using OHIP card number. Co-morbidities were organized according to the Charlson Co-morbidity Index (CCI).[9] Co-morbidity categories are weighted from 1 to 6 with a score of zero indicating no co-morbid conditions. Residence at the time of diagnosis (either rural or urban) was determined using the Postal Code Conversion File Plus (PCCF+) package.[10]

Analysis

The survival analysis started with 29,833 cases which represented 26,538 individual women. From these patients, 223 were excluded from the analysis because their breast carcinomas were diagnosed only by autopsy or death certificate, and 4,143 women were excluded due to missing health card number, stage at diagnosis or receptor status. This resulted in a final sample of 22,538 women who were included in the survival analysis.

Survival time was calculated as the time (in days) between the subject's date of diagnosis and one of the following, whichever occurred first: (a) date of death, (b) date last known to be alive, or (c) the most recent follow-up cut-off date (December 31, 2012). The outcome of interest was death due to breast cancer, deaths from other causes were censored at their date of death.

The statistical software SAS (version 9.4) was used to perform the analysis.[11] Associations between molecular subtype and the predictor variables were estimated using the Cox proportional hazards model. Four separate models were fitted for each molecular subtype and the association with predictors were investigated within each model. No interactions between variables were found in any model. The proportionality assumption was investigated 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 1,000 simulated residual patterns. With the exception of the stage at diagnosis variable, none of the variables in the models violated the proportionality assumption. In order to make the stage variable satisfy the proportionality assumption the variable was regrouped dichotomously (stage I and II vs. stage III and IV). Likelihood ratio testing was used to evaluate whether the variations in the mortality risk by different levels of a variable were statistically significant.

Results

Incidence counts and rates

Table 1 presents the incidence of breast cancer cases for each molecular subtype by age group for the years 2010 to 2012 combined. The Luminal A subtype was the most commonly diagnosed, representing 59.1% of all cases at a rate of 103.3 per 100,000, followed Triple Negative (15.1 per 100,000), Luminal B (13.5 per 100,000) and HER2 Enriched (7.0 per 100,000).

For the most common subtype, Luminal A, the incidence rate peaked in the 70-79 year age group (262.1 per 100,000). The rate of Luminal B cancers by age was much more evenly distributed than for Luminal A, with similar rates among women aged 50 to 79. The rate of HER2 Enriched cancers peaked in women aged 50-59 (12.9 per 100,000). Among all the subtypes, the HER2 Enriched distribution was most skewed towards the younger age groups and in women aged 50 and older the rate decreased with age. Triple Negative cancers skewed more towards the oldest age groups, with the highest rates found among those aged 60 and older.

Survival

Table 2 presents the number of patients and observed deaths for each molecular subtype by the variables used in the Cox regression analysis. Regardless of molecular subtype, the crude mortality rates were higher among patients with more advanced age, severe comorbidity (CCI≥3), advanced stage at diagnosis (stage III-IV), lobular carcinoma and who lived in an urban area.

A univariate model was performed to compare overall survival among the molecular subtypes. The results shown in Figure 1 show significant differences in survival among the subtypes (p <0.0001). Pairwise comparisons using log-rank tests also showed that survival differed significantly between each molecular subtype with Luminal A patients experiencing the highest survival followed by Luminal B and HER2 Enriched. The poorest survival was observed in Triple Negative patients.

A multivariate Cox model was performed separately for each molecular subtype. For all subtypes, age at diagnosis, histology (except for HER2 Enriched), stage at diagnosis and comorbidity index were the significant contributors to the hazard of death (Table 3).

Age

Age at diagnosis was significantly associated with mortality for all subtypes. For all subtypes, there was a dose-response relationship with age, with the mortality hazard increasing with increasing levels of age, although significance differed by subtype.

Among those with Luminal A cancer, increasing age was associated with increased risk of death for women aged 60 and older. For those with Luminal B cancers however, increased risk over the reference level was only found in those aged 60-69 and 80 and over. Of all the subtypes, age had the greatest effect on the mortality hazard for Luminal B cancers, with women aged 80 and over having 11.5 times the risk compared to women aged 15-49.

Among women with HER2 Enriched cancers, the hazard was significantly increased for those aged 60 and over with women aged 80 and over having 8 times the risk of those aged 15-49. For Triple negative cancers, the hazard was only increased for women aged 70 and over. Age at diagnosis had the smallest effect on Triple Negative cancers, compared to the other subtypes, with women aged 80 and over having only a 2 fold increase in the risk of death compared to women 15-49.

Histology

Histology was a significant predictor of survival for all subtypes except HER2 Enriched. There was no significant difference in risk between ductal and lobular carcinomas regardless of molecular subtype. However, those patients with cancers classified as ‘other’ had increased survival compared to ductal carcinomas in all molecular subtypes other than HER2 Enriched. The greatest increase in survival for ‘other’ histologies was seen in Luminal A cancers, with these patients having less than a quarter the mortality risk of those with ductal cancers.

Stage

For all subtypes stage at diagnosis was the strongest predictor of survival. Across all subtypes women diagnosed in the two highest stages had a significantly increased mortality

hazard compared to those diagnosed in stages I or II. The greatest increase was in HER2 Enriched cancers where women diagnosed in stages III or IV had 15 times the risk of death compared to women diagnosed in lower stages.

Co-morbidities

Women with moderate (one or two) co-morbidities and Luminal A, Luminal B or HER2 Enriched cancers had no increase mortality risk compared to women with no co-morbidities. Triple negative cancers expressed a dose-response relationship with the number of co-morbidities; women with one or two co-morbidities had 2.6 times the mortality risk of those with no co-morbidities, while women with severe (three or more) co-morbidities had 3.5 times the risk. Severe co-morbidities increased the risk of mortality for all subtypes with the greatest effect found in Luminal B cancers where they increased the risk of mortality 7.7 times, more than twice the effect seen in the other three subtypes.

Residence

Urban or rural residence had no effect on survival regardless of subtype.

Interpretation

This analysis illustrates the heterogeneous nature of female breast cancer with regard to molecular subtype in Ontario women. The majority of female breast cancers in Ontario diagnosed between 2010 and 2012 were Luminal A cancers, the subtype with the greatest overall survival. However the second most common type was Triple Negative, the subtype with the worst overall survival. Age, histology, stage and co-morbidities were all found to affect survival although the effect varied by subtype. Stage was the strongest predictor of survival with later stage diagnosis increasing the risk of mortality from 8 to 15 fold depending on the subtype. Any number of co-morbidities increased the mortality risk for Triple Negative cancers, while for

the other three subtypes an increased mortality risk was only associated with three or more co-morbidities.

This analysis confirmed the findings found in other studies that the risk of molecular subtype varies by age. Previous analyses have found that the incidence of hormone receptor negative cancers tends to peak before menopause, while hormone receptor positive cancers are more common after menopause.[12-14] While the incidence of Luminal A, Luminal B and HER2 Enriched cancers in the Ontario population generally conformed to these findings, Triple Negative cancers did not. The rate of Triple Negative cancers (ER-/PR-/HER2-) peaked in women who tend to be post-menopausal (aged 60 and older).

Overall survival in Ontario was highest for Luminal A followed by Luminal B cancers, confirming the better outcomes in hormone receptor positive cancers reported in other studies.[15-18] However, adjustment for age, residence at diagnosis (urban vs. rural), histology, co-morbidity and stage at diagnosis, showed no significant difference in survival between Luminal A and Luminal B cancers. As Luminal A cancers were more likely to be diagnosed at stage I or II than Luminal B cancers (Table 2), this may partially account for the survival advantage in Luminal A cancers in the unadjusted model.

This analysis found no difference in survival between lobular and ductal histologies among any of the molecular subtypes, despite the fact that lobular cancers tend to be associated with better prognosis.[19-21]

The results also showed no difference in survival between urban and rural residents regardless of molecular subtype. This is despite the fact that rural Canadians often lag behind urban Canadians in many health indicators such as life expectancy.[22] The absence of a difference in survival between rural and urban women is a positive sign of equity in breast cancer outcomes in Ontario. However, this analysis only considered residence by a single breakdown of rural versus urban, future analyses may find differences by examining the relationship using different geographic breakdowns.

This analysis confirmed the importance of co-morbidities on cancer survival. A moderate number of co-morbidities (1 or 2 co-morbid conditions) was associated with decreased survival for those with Triple Negative cancers. As three in five Canadians aged 20 and over are estimated to have at least one chronic condition, this indicates that a considerable proportion of women with Triple Negative cancers are at an increased risk of mortality due to co-morbidity.[23] The presence of three or more co-morbidities was associated with lower survival across all subtypes, although the effect was greatest for Luminal B cancers, with the risk more than twice that of other subtypes. While these results support the importance of severe co-morbidities to survival from breast cancer regardless of subtype, it emphasizes the greater risk to women with Luminal B cancers and may support the need for increased co-morbidity management among women with this subtype.

There are a number of variables that have been associated with the risk of some of the subtypes that we were unable to examine in this analysis. These include: race, which has been shown to affect the risk of hormone receptor negative cancers (black women have a higher risk)[24, 25] and survival within subtypes;[26-28] obesity, which has been linked with an increased risk of hormone receptor positive cancers;[29-31] and reproductive factors such as age at menarche, parity, oral contraceptive use and breast feeding history which have also been show to affect the risk of hormone receptor positive cancers.[29, 32]

To our knowledge, this is the first population-based study of breast cancer survival by molecular subtype using Ontario data. This is a considerable strength of this study as the use of a population-based cancer registry allowed for the complete enumeration of breast cancer cases during the study period. Once more data are available further analysis on this topic will be possible, including trends over time. This could be a fruitful area of investigation as other jurisdictions have found that survival has improved more for estrogen positive tumours than other subtypes.[33-37]

This study represents a first step in understanding the unique burden of breast cancer by molecular subtype in Ontario. Survival for female breast cancer in Ontario was found to vary considerably by molecular subtype. The results of this study indicate a need to address outcomes related to the treatment and/or detection of hormone receptor negative cancers whose survival lags behind hormone receptor positive cancers. The prognosis and treatment of breast cancer patients may be improved by also taking into account age, stage and co-morbidities in relation to their tumour hormone status.

References:

1. Ontario CC. Ontario Cancer Statistics Cancer Care Ontario 2016.
2. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol. 2011;22(8):1736-47.
3. Grann VR, Troxel AB, Zojwalla NJ, Jacobson JS, Hershman D, Neugut AI. Hormone receptor status and survival in a population-based cohort of patients with breast carcinoma. Cancer. 2005;103(11):2241-51.
4. Ravdin PM, Green S, Dorr TM, McGuire WL, Fabian C, Pugh RP, et al. Prognostic significance of progesterone receptor levels in estrogen receptor-positive patients with metastatic breast cancer treated with tamoxifen: results of a prospective Southwest Oncology Group study. J Clin Oncol. 1992;10(8):1284-91.
5. Shek LL, Godolphin W, Spinelli JJ. Oestrogen receptors, nodes and stage as predictors of post-recurrence survival in 457 breast cancer patients. Br J Cancer. 1987;56(6):825-9.
6. International Classification of Diseases for Oncology, Third Edition. Geneva: World Health Organization; 2000.
7. Organization WH. International Statistical Classification of Diseases and Related Health Problems: 10th revision (ICD-10). Geneva: World Health Organization 2004.
8. Edge SB, DR. Compton, CC. Fritz, AG. Greene, FL. Trotti, A. , editor. AJCC cancer staging manual. . New York: Springer-Verlag; 2010.
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
10. Postal Code Conversion File Plus - Version 6A. Statistics Canada; 2015.
11. SAS - Version 9.4. Gary, NC: SAS Institute 2013.
12. Anderson WF, Chu KC, Chatterjee N, Brawley O, Brinton LA. Tumor variants by hormone receptor expression in white patients with node-negative breast cancer from the surveillance, epidemiology, and end results database. J Clin Oncol. 2001;19(1):18-27.
13. Yasui Y, Potter JD. The shape of age-incidence curves of female breast cancer by hormone-receptor status. Cancer Causes Control. 1999;10(5):431-7.
14. Cadoo KA, Fornier MN, Morris PG. Biological subtypes of breast cancer: current concepts and implications for recurrence patterns. Q J Nucl Med Mol Imaging. 2013;57(4):312-21.
15. Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, et al. Metastatic behavior of breast cancer subtypes. J Clin Oncol. 2010;28(20):3271-7.
16. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007;109(9):1721-8.

17. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006;295(21):2492-502.
18. Yang XR, Sherman ME, Rimm DL, Lissowska J, Brinton LA, Peplonska B, et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. Cancer Epidemiol Biomarkers Prev. 2007;16(3):439-43.
19. Wasif N, Maggard MA, Ko CY, Giuliano AE. Invasive lobular vs. ductal breast cancer: a stage-matched comparison of outcomes. Ann Surg Oncol. 2010;17(7):1862-9.
20. Toikkanen S, Pylkkanen L, Joensuu H. Invasive lobular carcinoma of the breast has better short- and long-term survival than invasive ductal carcinoma. Br J Cancer. 1997;76(9):1234-40.
21. Dian D, Herold H, Mylonas I, Scholz C, Janni W, Sommer H, et al. Survival analysis between patients with invasive ductal and invasive lobular breast cancer. Arch Gynecol Obstet. 2009;279(1):23-8.
22. Kondro W. Health of rural Canadians lags behind urban counterparts. CMAJ. 2006;175(10):1195.
23. Betancourt MT, Roberts KC, Bennett TL, Driscoll ER, Jayaraman G, Pelletier L. Monitoring chronic diseases in Canada: the Chronic Disease Indicator Framework. Chronic Dis Inj Can. 2014;34 Suppl 1:1-30.
24. Li CI, Malone KE, Daling JR. Differences in breast cancer hormone receptor status and histology by race and ethnicity among women 50 years of age and older. Cancer Epidemiol Biomarkers Prev. 2002;11(7):601-7.
25. Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. J Natl Cancer Inst. 2005;97(6):439-48.
26. Sparano JA, Wang M, Zhao F, Stearns V, Martino S, Ligibel JA, et al. Race and hormone receptor-positive breast cancer outcomes in a randomized chemotherapy trial. J Natl Cancer Inst. 2012;104(5):406-14.
27. Tao L, Gomez SL, Keegan TH, Kurian AW, Clarke CA. Breast Cancer Mortality in African-American and Non-Hispanic White Women by Molecular Subtype and Stage at Diagnosis: A Population-Based Study. Cancer Epidemiol Biomarkers Prev. 2015;24(7):1039-45.
28. Sullivan HC, Oprea-Ilies G, Adams AL, Page AJ, Kim S, Wang J, et al. Triple-negative breast carcinoma in African American and Caucasian women: clinicopathology, immunomarkers, and outcome. Appl Immunohistochem Mol Morphol. 2014;22(1):17-23.
29. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev. 2004;13(10):1558-68.
30. Dolle JM, Daling JR, White E, Brinton LA, Doody DR, Porter PL, et al. Risk factors for triple-negative breast cancer in women under the age of 45 years. Cancer Epidemiol Biomarkers Prev. 2009;18(4):1157-66.
31. Huang WY, Newman B, Millikan RC, Schell MJ, Hulka BS, Moorman PG. Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. Am J Epidemiol. 2000;151(7):703-14.
32. Cotterchio M, Kreiger N, Theis B, Sloan M, Bahl S. Hormonal factors and the risk of breast cancer according to estrogen- and progesterone-receptor subgroup. Cancer Epidemiol Biomarkers Prev. 2003;12(10):1053-60.
33. Giordano SH, Buzdar AU, Smith TL, Kau SW, Yang Y, Hortobagyi GN. Is breast cancer survival improving? Cancer. 2004;100(1):44-52.
34. Holleczek B, Brenner H. Trends of population-based breast cancer survival in Germany and the US: decreasing discrepancies, but persistent survival gap of elderly patients in Germany. BMC Cancer. 2012;12:317.
35. Jatoi I, Chen BE, Anderson WF, Rosenberg PS. Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. J Clin Oncol. 2007;25(13):1683-90.
36. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res. 2007;9(1):R6.
37. Ademuyiwa FO, Groman A, Hong CC, Miller A, Kumar S, Levine E, et al. Time-trends in survival in young women with breast cancer in a SEER population-based study. Breast Cancer Res Treat. 2013;138(1):241-8.

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

Molecular subtype	All ages (15+)		Age group (years) 15-49		50-59		60-69		70-79		80+	
	Count (Col %)	Rate	Count (Col %)	Rate	Count (Col %)	Rate	Count (Col %)	Rate	Count (Col %)	Rate	Count (Col %)	Rate
Luminal A	17598 (59.1)	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 (11.9)	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	**29833**	**175.1**	**5939**	**60.7**	**7033**	**243.3**	**7675**	**369.2**	**5452**	**420**	**3734**	**382.7**

Note: Luminal A=ER+/PR+/HER2-; Luminal B=ER+/ER+/HER2+; HER2 Enriched=ER-/PR-/HER2+; Triple Negative=ER-/PR-/HER2-

Table 2. Number of breast cancer patients and deaths, Cox regression cohort, Ontario, 2010-2012

Variable	Level	Luminal A (ER+/ER/HER2-) No. of Cancer Patients (n=16761)	Luminal A (ER+/ER/HER2-) No. of Cancer Deaths (n=361)	Luminal B (ER+/PR+/HER2+) No. of Cancer Patients (n=2200)	Luminal B (ER+/PR+/HER2+) No. of Cancer Deaths (n=74)	HER2 Enriched (ER-/PR-/HER2+) No. of Cancer Patients (n=1154)	HER2 Enriched (ER-/PR-/HER2+) No. of Cancer Deaths (n=68)	Triple Negative (ER-/PR-/HER2-) No. of Cancer Patients (n=2423)	Triple Negative (ER-/PR-/HER2-) No. of Cancer Deaths (n=208)
Age (years)									
	15-49	3157	36	681	12	333	12	648	50
	50-59	3943	55	640	14	361	15	599	35
	60-69	4559	78	470	18	253	15	560	35
	70-79	3187	83	262	7	127	8	368	47
	≥ 80	1915	109	147	23	80	18	248	41
Residence at Diagnosis									
	Urban	14795	325	1961	68	1008	61	2131	185
	Rural	1966	36	239	6	146	7	292	23
Histology									
	Ductal	10663	268	1468	58	859	55	1744	161
	Lobular	2105	64	165	7	35	3	42	9
	Other	3993	29	567	9	260	10	637	38
Stage at Diagnosis									
	I-II	14046	100	1579	16	745	7	1866	66
	III-IV	2715	261	621	58	409	61	557	142
Charlson comorbidity index (CCI)									
	0	15493	243	2021	39	1028	43	2238	163
	1≤ CCI ≤2	550	20	46	5	34	4	76	14
	CCI ≥ 3	718	98	133	30	92	21	109	31

Figure 1. Kaplan-Meier plot of overall breast cancer survival by molecular subtype, Ontario, 2010-2012

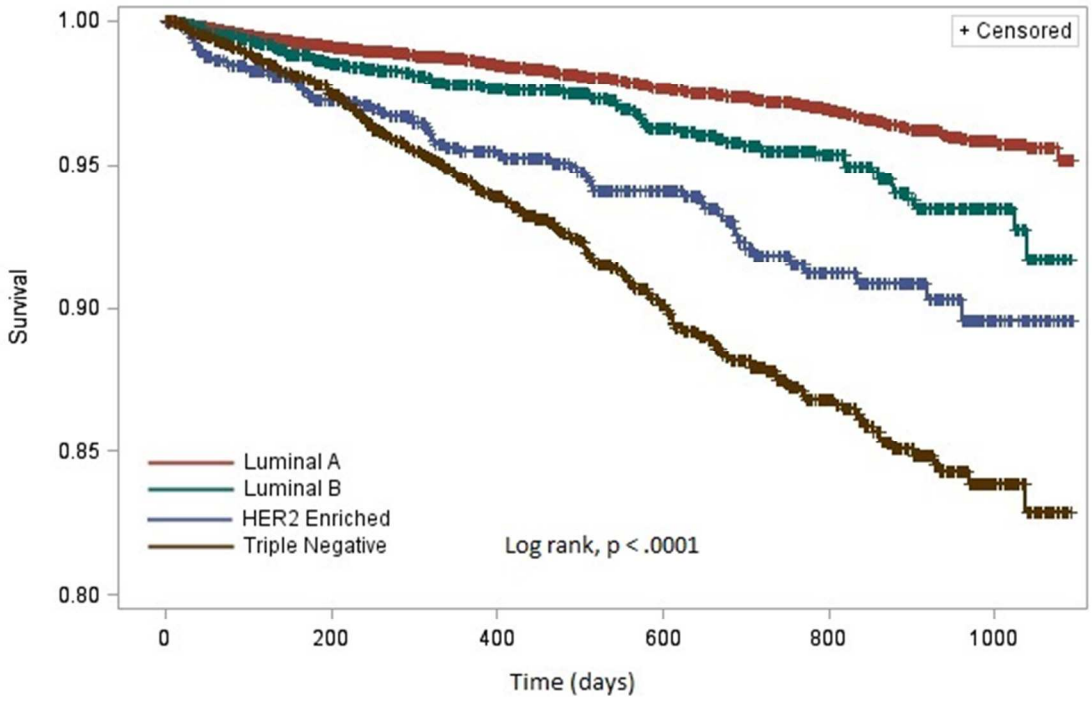

Table 3. Breast cancer survival hazard ratios, by molecular subtype and patient characteristics, Ontario, 2010-2012

Variable	Level	Luminal A (ER+/PR+/HER2-)		Luminal B (ER+/PR+/HER2+)		HER2 Enriched (ER-/PR-/HER2+)		Triple Negative (ER-/PR-/HER2-)	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)			<.0001		<.0001		<.0001		<.0001
	15-49	REF	-	REF	-	REF	-	REF	-
	50-59	1.38 (0.92, 2.11)	0.12	1.25 (0.57, 2.28)	0.31	1.17 (0.68, 2.25)	0.26	0.88 (0.53, 1.28)	0.48
	60-69	1.97 (1.32, 2.72)	<0.01	2.63 (1.26, 4.32)	0.01	2.21 (1.04, 3.88)	0.04	0.91 (0.58, 1.40)	0.65
	70-79	2.39 (1.68, 3.56)	<.0001	1.33 (0.42, 2.27)	0.50	2.46 (1.74, 3.64)	0.04	1.94 (1.29, 2.92)	<0.01
	≥80	3.91 (3.16, 4.73)	<.0001	11.45 (9.86, 13.39)	<.0001	8.07 (6.75, 10.15)	<.0001	2.04 (1.36, 3.11)	<0.01
Residence at Diagnosis			0.39		0.44		0.86		0.85
	Urban	REF	-	REF	-	REF	-	REF	-
	Rural	0.89 (0.63, 1.26)	0.39	1.40 (0.59, 2.30)	0.45	0.95 (0.42, 1.74)	0.86	0.97 (0.63, 1.51)	0.85
Histology			<.0001		0.02		0.13		0.02
	Ductal	REF	-	REF	-	REF	-	REF	-
	Lobular	1.35 (0.60, 2.04)	0.09	1.05 (0.17, 1.62)	0.08	1.21 (0.32, 2.57)	0.15	1.79 (0.92, 2.66)	0.11
	Other	0.22 (0.15, 0.32)	<.0001	0.40 (0.19, 0.83)	0.01	0.64 (0.31, 1.31)	0.21	0.68 (0.48, 0.98)	0.04
Stage at Diagnosis			<.0001		<.0001		<.0001		<.0001
	I-II	REF	-	REF	-	REF	-	REF	-
	III-IV	12.98 (10.21, 16.50)	<.0001	7.75 (5.38, 9.96)	<.0001	15.08 (12.78, 19.55)	<.0001	8.31 (6.15, 11.21)	<.0001
Charlson comorbidity index (CCI)			<.0001		<.0001		<.0001		<.0001
	0	REF	-	REF	-	REF	-	REF	-
	1 ≤ CCI ≤ 2	1.49 (0.94, 2.38)	0.08	2.07 (0.77, 4.17)	0.14	1.73 (0.66, 3.14)	0.23	2.64 (1.50, 3.95)	<0.01
	CCI ≥ 3	3.54 (2.78, 4.52)	<.0001	7.67 (5.45, 9.74)	<.0001	3.25 (1.85, 4.81)	<.0001	3.46 (2.65, 4.917)	<.0001