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Analyzing a National Breast Cancer Registry Reveals Age-Related Variation in Lymph Node Metastases and Survival

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Abstract

Background: For several cancers, including those of the breast, young ageat diagnosis is associated with an adverse prognosis. Although this effect isoften attributed to heritable mutations such as BRCA1/2, the relationship between pathologic features, young age of onset, and prognosis for breastcancer remains unclear. In the present study, we highlight links between age-of-onset and lymph node metastasis (LNM) in US women with breastcancer.

Methods: Case listings from Surveillance, Epidemiology, and End Result(SEER) 18-population-based registry data for women with breast cancer, which include information on race, were used. LNM and its associated outcomes were evaluated for a subset of women with receptor subtype information and then compared against a larger, pre-subtype validationset of data from the same registry. Age of diagnosis was a 5-category variable; under 40 years, 40-49 years, 50-59 years, 60-69 years and 70+ years. Univariate and adjusted multivariate survival models were applied to both sets of data.

Results: As determined with adjusted logistic regression models, women under 40 years old at diagnosis had 1.55 times the odds of LNM as women60-69 years of age. The odds of LNM for (HR = hormone receptor) HR+/ HER2+, HR-/HER2+, and triple-negative breast cancer subtypes were significantly lower than those for HR+/HER2-. In subtype-stratified adjusted models, age of diagnosis had a consistent trend of decreasing oddsof LNM by age category, most noticeable for HR+ subtypes of luminal Aand B. Univariate 5-year survival by age was worst for women under 40 years, with LNM attributable for 49% of the hazard of death from cancer in adjusted multivariate models.

Conclusions: Lymph node metastasis is age-dependent, yet not all molecular subtypes are clearly affected by this relationship. For <40-yr- old women, LNM is a major cause for shorter survival. When stratifiedby subtype, the strongest associations were in HR+ groups, suggesting a possible hormonal connection between young age of breast cancer onset and LNM.

Keywords: Breast cancer, Nodal metastasis, early age of diagnosis, SEER cancer registry

Background

In 2020, an estimated 276,480 new cases of breast cancer were diagnosed in the United States https://seer.cancer.gov/statfacts/html/breast.html). Forwomen with breast cancer, the infiltration of tumor cells into surrounding lymph nodes is associated with a poor prognosis. Lymph node metastasis (LNM), a means for the regional and distant spread of tumor cells, has a considerable influence upon treatment options and patient survival. Approximately 60% of all newly diagnosed cases of breast cancer are localized (non-metastatic). However, one third of the patients with localized cancers will eventually develop metastatic disease [1]. Of all new cases of breast cancer, another third have regional LNM at the time of diagnosis [1]. Lymph nodes usually represent the first site of metastasis of breast cancer, and they initiate the process of metastasis of the disease.Breast cancer is distinctive among highly prevalent cancers in that women with a young age of onset oftenhave a more aggressive form of the disease. Although younger women are eligible for more intensive therapy, they nevertheless have, relative to older patients, worse survival and a higher recurrence rate [2,3]. Although links between molecular/receptor subtypes and disease progression (metastasis in particular) are commonplace

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[4–6], there has been little research into the durability of these relationships across age groups. Estrogen receptor-positive status has an unclear prognostic influence across ages [7–9]. However, *ERBB2+/HER2+* receptor status

seems to be more frequent and is associated with a lower survival of younger women [10]. A few negatively associated prognostic variables for early onset breast cancer are identified [11–13], yet the connection between patient characteristics and metastasis has not been fully assessed. In the present study, we used nation- wide data from Surveillance Epidemiology and End Result (SEER) cancer registries to gain a better understanding of the relationship between lymph node metastasis, receptor subtype, and age-dependent patient characteristics of breast cancer.

Materials and Methods

Study population data

The present analysis involved data from the SEER 18 (SEER*Stat8.3.8) database case listings. The data in SEER 18 represents 27.8% of the total US population and 18 cancer registries [14]. After excluding patients with non-ductal or lobular tumor histology, male gender, missing information onlymph node metastasis, and follow up of less than 6 months, our final sample consisted of 717,331 women diagnosed withbreast cancer from 1975 to 2017. Since SEER did not start recording information regarding the HER2 receptor subtype until 2010, we used a subset of the overall data that offered complete receptor subtype analysis. The receptor subtype set of data is made up of 223,986 cases of breast cancer with first and only primary tumor for patients diagnosed for the ~ 7 year period of 2010-2017.Study design

The present study used both case-control and follow-up designs. Cases were defined as breast cancer patients

with LNM at the time of diagnosis. Controls were patients

with no LNM at diagnosis. Data for all eligible patients were used, and no matching of controls to cases was done. A response variable of lymph node metastasis

was defined as a binary outcome using AJCC 7th edition tumor , nodes , and metastases (TNM) staging

[15]. This large data set with LNM information is consistent with AJCC 6th edition TNM staging [16]. All

nodes (N) values of N0 (including N0 (i-) and N0 (mol-)) were considered LNM negative, and any other N values (N1-N4) were considered positive. Othermetadata included were patient demographic measures of age and ethnicity as well as tumor differentiation and staging information. Breast cancer subtype was based on receptor status. The “HR” abbreviation for hormone receptor represents both estrogen (ER) and progesterone (PR) receptor status. HER2 indicates human epidermal growth factor 2 receptor status. Borderline information on HER2 status was excluded from analysis of SEER*Stat data queries [17]. Age-of-onset was considered as both a continuous and a categorical variable. Categories of age were based on preceding literature [8,18]: under 40 years, 40-49 years, 50-59 years, 60-69 years, and 70+ years. Additional survival analysis was accomplished with time to death from cancer as an outcome (Tables 1a and 1b).

Statistical analyses

In depicting the univariate relationship between LNM, receptor subtype, and individual covariates, we applied chi-square tests for categorical, and t-tests for continuous p-values. Logistic regression models were constructed for each variable to obtain univariate odds of LNM and 95% confidence intervals. To examine whether the effect of age upon odds of LNM was modified by receptor subtype, we performed 4 separate, adjusted logistic regression analyses stratified by subtype. Logistic regression modeling was also used to adjust for potential confounding variables, both for full data set and in receptor-based subtype subset analyses. Kaplan-Meier log-rank tests and Cox proportional hazard models were used to estimate the effect of age upon survivaland LNM. We measured 5-year survival for the similar age categories used in the analyses of Alteri et al. [19]. For 5 separate age category-stratified survival models, we calculated the proportion of hazard of death that was attributable to LNM (attributable fraction analysis) by comparing a counterfactual survival function (excluding LNM from baseline) to a factual survival function, including LNM [20,21]. In Cox models, variables adjusted for were LNM, race, size of tumor, and receptor subtype. All statistical analyses utilized R version 3.6.2 (2019-12-12) [22].

Table 1a: Clinical and demographic characteristics of US women with breast cancer by lymph node status (SEER, 2010-2017)

Lymph node metastasis (LNM)	**negative**	**positive**
Characteristics	**(N=151827)**	**(N=72159)**
Breast tumor by receptor subtype		
- HR-/HER2- (triple-negative)	18418 (12.1%)	9189 (12.7%)
- HR-/HER2+	6819 (4.5%)	4927 (6.8%)
- HR+/HER2-	110069 (72.5%)	47318 (65.6%)
- HR+/HER2+	16521 (10.9%)	10725 (14.9%)
Age (years)	60.5 ± 12.9	56.9 ± 13.3
Age categories		
- <40	7342 (4.8%)	6702 (9.3%)
- 40-49	25117 (16.5%)	15678 (21.7%)
- 50-59	38185 (25.2%)	19930 (27.6%)
- 60-69	42631 (28.1%)	16746 (23.2%)
- 70+	38552 (25.4%)	13103 (18.2%)
Cause of death		
- alive	142734 (94.0%)	60886 (84.4%)
- breast	4014 (2.6%)	8767 (12.1%)
- other	5079 (3.3%)	2506 (3.5%)
Race		
- White	120218 (79.2%)	54391 (75.4%)
- American Indian/Alaska Native	925 (0.6%)	512 (0.7%)
- Asian or Pacific Islander	14083 (9.3%)	6811 (9.4%)
- African American	15499 (10.2%)	10011 (13.9%)
- Unknown	1102 (0.7%)	434 (0.6%)
Metastasis (AJCC M 7th ed. 2010)		
- No distant metastasis	138047 (98.8%)	60336 (90.3%)
- Distant metastasis	1737 (1.2%)	6485 (9.7%)
Tumor size (AJCC T 7th ed.2010)		
- T1 (<2 cm)	98954 (71.7%)	22125 (33.8%)
- T2 (2 cm-5 cm)	33586 (24.3%)	29815 (45.6%)
- T3 (>5 cm)	3788 (2.7%)	7631 (11.7%)
- T4 (extension into chest wall/skin)	1727 (1.3%)	5798 (8.9%)
Grade		
- Well differentiated; Grade I	38066 (25.1%)	7535 (10.4%)
- Moderately differentiated; Grade II	63272 (41.7%)	29342 (40.7%)
- Poorly differentiated; Grade III	45972 (30.3%)	32305 (44.8%)
- Undifferentiated; anaplastic; Grade IV	340 (0.2%)	244 (0.3%)
- Unknown	4177 (2.8%)	2733 (3.8%)

Table 1b: Clinical and demographic characteristics of US women with breast cancer by lymph node status (SEER 1975-2017)

Lymph node metastasis (LNM)	**negative**	**positive**
Characteristics	**(N=459656)**	**(N=257675)**
Age (years)	60.7 ± 13.5	57.3 ± 13.8
Age categories		
- <40	24485 (5.3%)	24526 (9.5%)
- 40-49	80917 (17.6%)	57697 (22.4%)
- 50-59	110958 (24.1%)	67060 (26.0%)
- 60-69	112844 (24.5%)	54294 (21.1%)
- 70+	130452 (28.4%)	54098 (21.0%)
Cause of death		
- alive	332223 (72.3%)	141349 (54.9%)
- breast	36964 (8.0%)	77168 (29.9%)
- other	90469 (19.7%)	39158 (15.2%)
Race		
- White	378616 (82.4%)	204948 (79.5%)
- American Indian/Alaska Native	2316 (0.5%)	1514 (0.6%)
- Asian or Pacific Islander	35863 (7.8%)	19267 (7.5%)
- African American	40497 (8.8%)	30963 (12.0%)
- Unknown	2364 (0.5%)	983 (0.4%)
Grade		
- Well differentiated; Grade I	94056 (20.5%)	20760 (8.1%)
- Moderately differentiated; Grade II	174711 (38.0%)	87336 (33.9%)
- Poorly differentiated; Grade III	131972 (28.7%)	105851 (41.1%)
- Undifferentiated; anaplastic; Grade IV	4847 (1.1%)	4105 (1.6%)
- Unknown	54070 (11.8%)	39623 (15.4%)

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Results

Overall study population

Associations with LNM were consistent across overall

(1975-2017) and subset (2010—2017) analyses and showed that, at diagnosis, 32-36% of women had nodal metastasis of breast cancer. In follow up, women with LNM made up a larger proportion of breast cancer deaths, were more likely to be African American, had tumors of larger size at diagnosis, and had more distant metastases at diagnosis (Table 1a and 1b). Additional information unique to the test data set also showed higher grade/more poorly differentiated tumors for LNM cases. Women with nodal metastases were also younger than controls (non-LNM), with an average age at diagnosis of 57 years (61 years for controls). Lastly, a larger proportion of women had HR+/HER2+, triple-negative, and HR-/ HER2+

subtype cancers than controls. See Tables 1a and 1b

for a description of patient variables across nodal metastasis outcomes. In a subset analysis (data not shown) of women under 40 years in 1975-2017 data, no effect modification by age was found for the association between race, grade, and LNM.

Odds of Lymph nodal metastasis

The adjusted odds of LNM for common variables in bothdatasets were available for race, age, tumor size, and tumor grade. The relationship between age and the adjusted odds ofLNM had similar estimates for both sets of data. Among all age groups, women under 40 had the highest adjusted odds of LNM (1.55 in subset and 1.74 in overall data). Both sets of data confirmed tumor size as being strongly associated with LNM. Relative to Whites, African American women had higher adjusted odds of LNM (1.13 in subset and 1.23in overall data). Higher tumor grades were also positively associated with LNM, with the effect increasing parallel to the loss of differentiation. See Tables 2a and 2b for details ofunivariate and adjusted odds of LNM.

Receptor subtype

In receptor-stratified data, adjusted estimates of LNM bysubtype showed that TNBC cancers had lower odds of nodal metastasis relative to the HER2-/HR+ receptor subtype (OR 0.74, 95% CI 0.70-0.78) (Table 2b). There was, however, no significant increase in the odds of having LNM for either HER2+ subtypes of HER2+/ER+

or HER2+/ER- (Table 2a). There was a young-to-old gradient in the odds of LNM, whichis most apparent in for HR+ subtypes of tumors, HER2-/ER+and lHER2+/ER+ (Figure 1). In HR-/HER2+subtypes, age atdiagnosis had a similar trend in odds estimates per age group, but showed no significant difference between ages <40-59. In addition, triple-negative subtypes showed a slightly higher association with LNM for those younger than 60 but with noage gradient (Figure 1).

Survival analysis

For both subset and overall data, Kaplan-Meier analyses consistently showed women under 40 as sharing the worst survival outcomes with women aged 70 years and above. Although women 70 years and older had low survival, women under 40 years old began follow-up with survival

Table 2a: Odds of lymph nodal metastasis, unadjusted and adjusted models (SEER, 2010-2017)

Odds of lymph node metastasis (LNM)	**Unadjusted**			**Adjusted**	
Characteristics	**OR**	**95% CI**		**OR**	**95% CI**
Breast tumor by receptor subtype					
- HR-/HER2- (triple negative)	1.16	1.13-1.19		0.6	0.58-0.62
- HR-/HER2+	1.68	1.62-1.75		0.87	0.83-0.91
- HR+/HER2-	1	referent (ref.)		1	ref.
- HR+/HER2+	1.51	1.47-1.55		0.94	0.91-0.97
Age categories					
- <40	2.32	2.24-2.41		1.55	1.49-1.62
- 40-49	1.59	1.55-1.63		1.37	1.33-1.41
- 50-59	1.33	1.30-1.36		1.21	1.18-1.25
- 60-69	1	ref.		1	ref.
- 70+	0.87	0.84-0.89		0.8	0.77-0.82
Race					
- White	1	ref.		1	ref.
- American Indian/Alaska Native	1.22	1.10-1.36		1.08	0.95-1.23
- Asian or Pacific Islander	1.07	1.04-1.10		0.92	0.88-0.95
- African American	1.43	1.39-1.47		1.13	1.09-1.17
- Unknown	0.85	0.74-0.98		0.87	0.76-0.99
Metastasis (AJCC M 7th ed. 2010)					
- No distant metastasis	1	ref.		1	ref.
- Distant metastasis	8.54	8.10-9.02		3.68	3.46-3.91
Tumor size (AJCC T 7th ed. 2010)					
- T1 (<2 cm)	1	ref.		1	ref.
- T2 (2 cm-5 cm)	3.97	3.89-4.06		3.4	3.32-3.48
- T3 (>5 cm)	9.01	8.64-9.39		7	6.71-7.32
- T4 (extension into chest wall/skin)	15.02	14.21-15.88		9.91	9.34-10.51
Grade					
- Well differentiated; Grade I	1	ref.		1	ref.
- Moderately differentiated; Grade II	2.34	2.28-2.41		1.7	1.65-1.76
- Poorly differentiated; Grade III	3.55	3.45-3.65		2	1.94-2.08
- Undifferentiated; anaplastic; Grade IV	3.63	3.07-4.29		1.97	1.62-2.38
- Unknown	3.31	3.13-3.49		1.62	1.52-1.74

Table 2b: Odds of lymph nodal metastasis, unadjusted and adjusted models (SEER 1975-2017)

Odds of lymph node metastasis (LNM)	Unadjusted		Adjusted	
Characteristics	OR	95% CI	OR	95% CI
Age categories				
- <40	2.08	2.04-2.12	1.74	1.71-1.78
- 40-49	1.48	1.46-1.50	1.39	1.37-1.41
- 50-59	1.26	1.24-1.27	1.22	1.20-1.23
- 60-69	1	ref.	1	ref.
- 70+	0.86	0.85-0.87	0.87	0.85-0.89
Race				
- White	1	ref.	1	ref.

- American Indian/Alaska Native	1.21	1.13-1.28	1.14	1.06-1.21
- Asian or Pacific Islander	0.99	0.97-1.01	0.92	0.91-0.94
- African American	1.41	1.39-1.43	1.23	1.21-1.25
- Unknown	0.77	0.71-0.83	0.76	0.70-0.81
Grade				
- Well differentiated; Grade I	1	ref.	1	ref.
- Moderately differentiated; Grade II	2.26	2.23-2.30	2.2	2.17-2.24
- Poorly differentiated; Grade III	3.63	3.57-3.70	3.31	3.18-3.57
- Undifferentiated; anaplastic; Grade IV	3.84	3.67-4.01	3.53	3.38-3.69
- Unknown	3.32	3.25-3.39	3.23	3.17-3.30

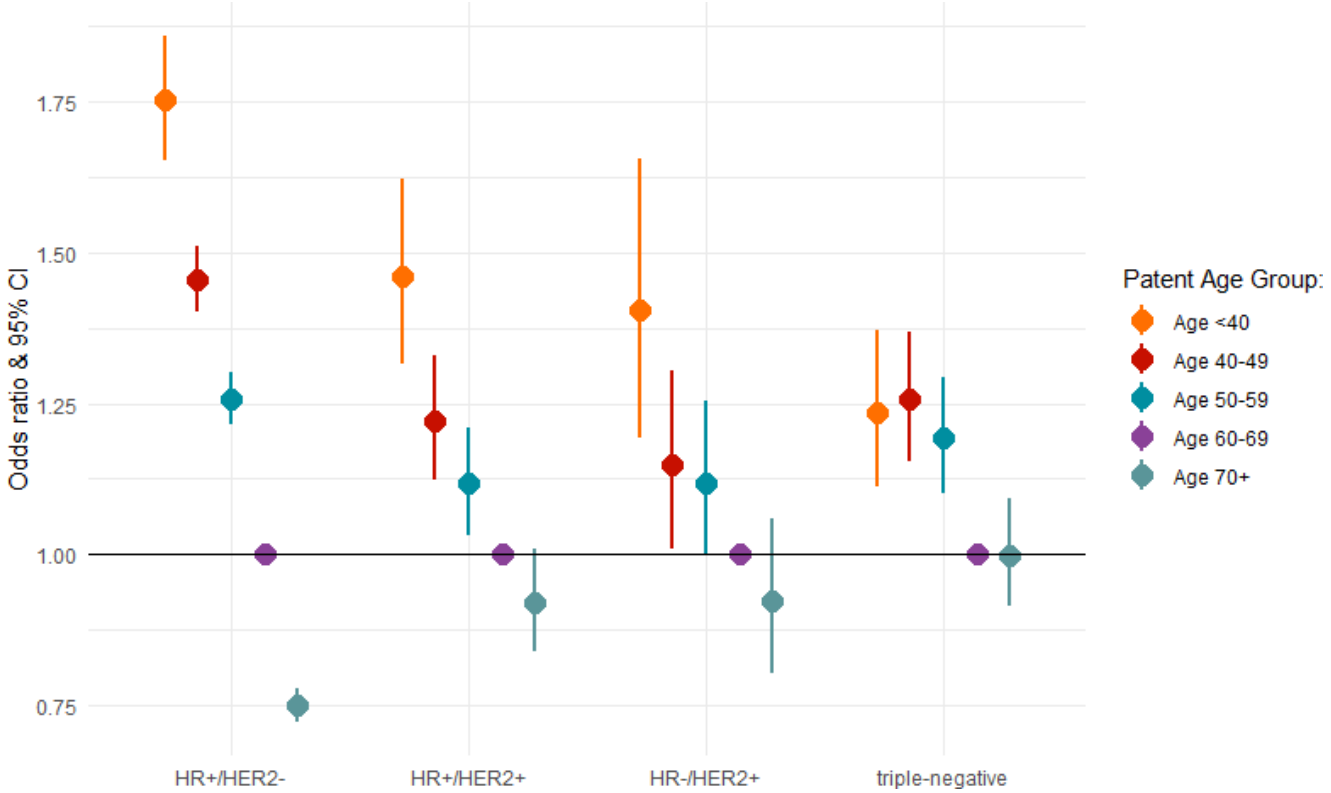

Figure 1: Comparison of adjusted (M stage, T stage, grade) odds of lymph nodal metastasis (LNM) by age, stratified by receptor subtype, SEER 2010-2017 (ref. group age 60-69 years). Adjusted for race and tumor size.

similarly high with other age categories (40-69 years), but there was a decline starting at ~15 months which surpassed 70-year-olds at ~22 months. Women under 40 years of age had the lowest probability of 5-year survival at 0.87, with age groups from 40-69 having similar 5-year survivals at approximately 0.91-0.93, with the value for the oldest group of women slightly decreasing to 0.89. As determined with adjusted Cox analyses, in both sets of data, women younger than 40 also had a higher fraction of hazard of death from cancer (~50% vs. ~37% at start) due to LNM than women 70years and above (Figure 2).

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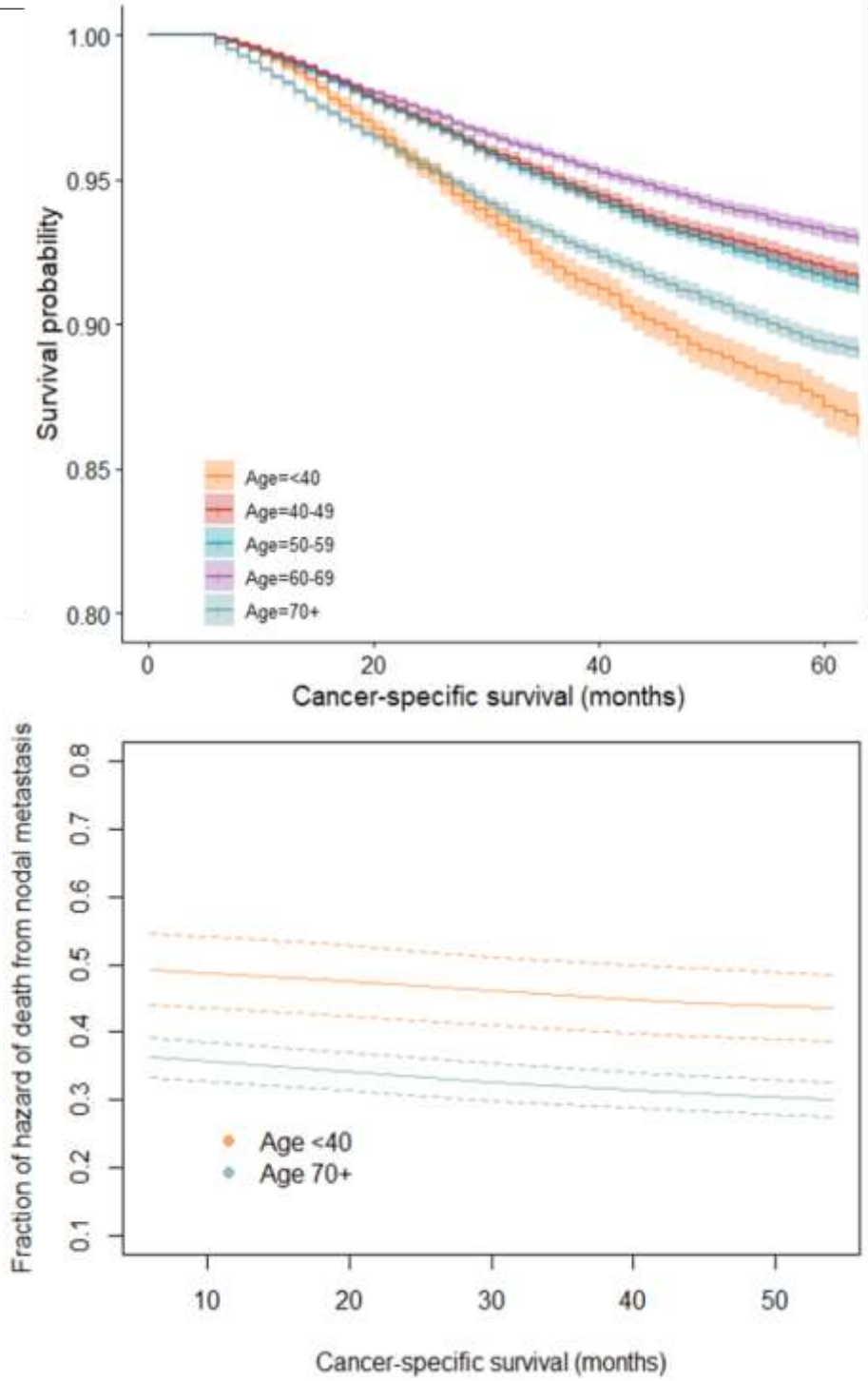

Figure 2: Univariate survival and LNM-attributable fraction from adjusted models by selected age groups. A) Kaplan-Meier plot of survival by age group, SEER 2010-2017; B) Fraction of hazard of death due to LNM for women under 40 years, and for women 70 years or more, SEER 2010-2017

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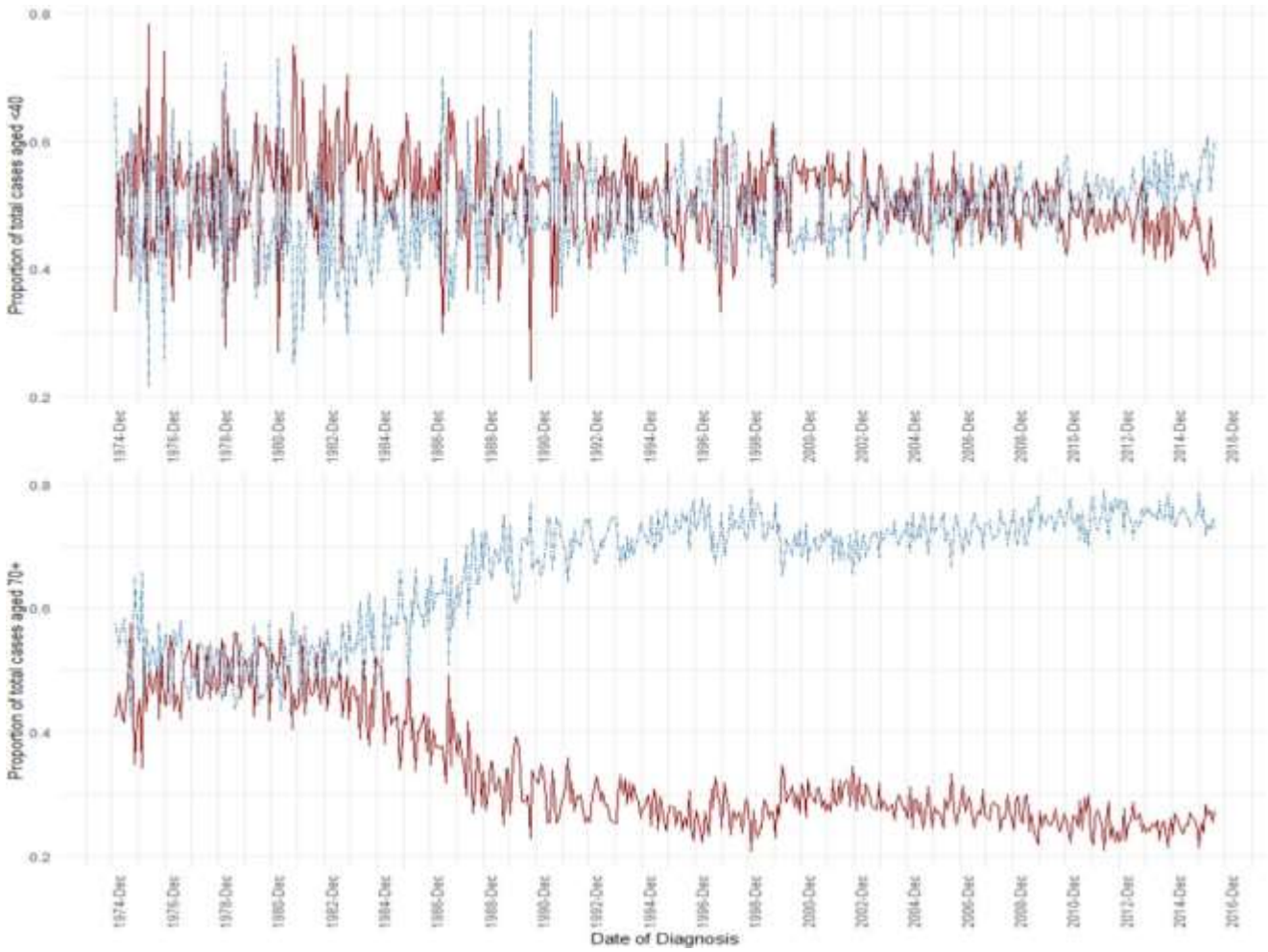

Figure 3: Lymph node metastasis (LNM) as a proportion of total cases by month from 1975-2017, for ages under 40 years (top) and 70 years or older (bottom)LNM in red, non-LNM in blue.

Discussion

In adult females younger than 40, there is considerable debate about whether breast cancer should be considered as a distinct disease. Women under 40 have consistently poor survival outcomes across various study populations [12,13,23–26] yet the reasons for this are not fully explained. The present study showed that the odds of LNM at diagnosis have a gradient relationship to patient age of onset. This age- decreasing slope is most prominent for hormone receptor- positive subtypes. Findings from survival analysis confirmed that women under 40 have a hazard of death from breast cancer equal to or greater than the next-poorest group, women 70 years or older. Furthermore, the hazard of death attributable to LNM was higher in women under 40 years, suggesting that LNM has a stronger causal role in breast cancer mortality for younger women as compared to late age of diagnosis survival factors.

Previous studies have suggested that a higher incidence of the HR-/HER2+ subtype for young women with breast cancer

partially explains their more aggressive disease [23–25]. Indeed, although our analysis showed a higher proportion of women under 40 years old having the HR-/HER2+ subtype, there was no significant difference in the odds of LNM and

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age among the HR-/HER2+, triple-negative and HR+ subtypes. However, a study, using a subset of the SEER data shows that, regardless of patients age, the HR+/HER2-breast cancer subtype has a higher rate of lymph node involvement at diagnosis than the triple-negative subtype [11]. From this study, LNM at diagnosis does not appear to be relatedto HR-/HER2+ aggressiveness in young age of diagnosis. Furthermore, this observation may be of importance in considering whether prior research examining the link between the HR-/HER2+ subtype and LNM was adequately controlled for age at diagnosis.

The level of generalizability of the SEER 2010-2017 receptor-only subset of data may be questioned as a liability for analysis. We evaluated how representative subset data was using the complete, 42-year data. For all the variables common between datasets, both measures of association and

measures of effect were consistent across data. Furthermore, we examined whether there was a time trend in proportion of LNM positive patients at diagnosis in relation to age group. Interestingly, we found that, for women <40 years, the proportion of LNM at diagnosis vs. non-LNM remained stable across time at approximately 50%. In women aged 70+, there was a marked split of LNM proportion from 50% starting in 1980, decreasing to ~25% by 2008 (Figure 3). The concordance of IHC-based receptor subtype with intrinsic molecular subtype has been shown to vary by subtype. Luminal B (HR+/HER2+) is the worst performing subtype in measures of both concordance and accuracy across several studies [27,28], suggesting that the relationship between young age of onset, LNM, and interplay between estrogen/ progesterone hormone receptors and HER2 should be studied further with a thorough consideration of molecular subtype classification. In contrast, previous research has shown the concordance and accuracy between both luminal A (HR+/ HER2-) and triple-negative (HR-/HER2-) to be the highest among subtypes [29], suggesting that the results found in our study for these subtypes are likely not due to misclassification.

Lastly, there is also a question of consistency in measurement of variables over time. Perhaps the phenomenon of aggressive disease for younger women with breast cancer is influenced by changes in screening and diagnostic practices. From the standpoint of the association between age of diagnosis and LNM, we included year of diagnosis as a predictor variable for both sets used for analysis. There was no confounding effect of the year of diagnosis upon the association between LNM and age of diagnosis.

Involvement of lymph nodes is a key component in decisions for postoperative therapy, particularly radiation therapy, because clinicians evaluate need for lymph node radiation to minimize toxicity of treatment. Therefore, our results showing that the higher incidence of LNM in young (<40 years) HR+ breast cancer groups (HR+/HER2- and HR+/HER2+) is clinically relevant. This relationship between LNM and age of diagnosis is clear in women with luminal tumors, and may explain observations from previous studies linking the luminal subtype, young age of diagnosis, and poor prognosis [8]. Thus, our findings may aid in identifyingaggressive disease in young women with luminal disease.

Conclusions

Our results suggest that a predisposition towards more severe breast cancer for women with younger age of diagnosis is driven in part by LNM. This relationship between LNM and age of diagnosis for women with luminal tumors is strong and may be related to a poor prognosis. These findings also have implications in identifying high-risk, young HR+ groups (HR+/HER2- and HR+/HER2+) of breast cancer patients foraggressive therapy.

List of abbreviations

LNM, lymph node metastasis; SEER, Surveillance, Epidemiology, and End Results; TNM, tumor, node, and metastasis; HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; ERBB2/HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; ref., referent.

Declarations

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Ethics approval and consent to participate

This study used publicly available data, thus these factorsare not applicable.

Consent for publication:

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' Contributions

UM and MB conceptualized the study; MB, SAD, PB, AE, FA, and H-GK collected the data. MB analyzed the data, and MB, SW, SS, and UM interpreted the data regarding breast cancer. MB was a major contributor for this study; all authors contributed to writing the manuscript. All authors read and approved the final manuscript.

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