JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Subtype-Dependent Relationship Between Young Age at Diagnosis and Breast Cancer Survival

Ann H. Partridge, Melissa E. Hughes, Erica T. Warner, Rebecca A. Ottesen, Yu-Ning Wong, Stephen B. Edge, Richard L. Theriault, Douglas W. Blayney, Joyce C. Niland, Eric P. Winer, Jane C. Weeks,† and Rulla M. Tamimi

Ann H. Partridge, Melissa E. Hughes, Erica T. Warner, Eric P. Winer, Jane C. Weeks, and Rulla M. Tamimi, Dana-Farber Cancer Institute and Brigham and Women's Hospital; Erica T. Warner, Harvard T.H. Chan School of Public Health, Boston, MA; Rebecca A. Ottesen and Joyce C. Niland, City of Hope Comprehensive Cancer Center, Duarte; and Douglas W. Blayney, Stanford Cancer Institute, Palo Alto, CA; Yu-Ning Wong, Fox Chase Cancer Center, Philadelphia, PA; Stephen B. Edge, Baptist Cancer Center, Memphis, TN; and Richard L. Theriault, The University of Texas MD Anderson Cancer Center, Houston, TX.

†Deceased.

Published online ahead of print at www.jco.org on August 1, 2016.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Ann H. Partridge, MD, MPH, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02115; e-mail: ahpartridge@partners.org.

0732-183X/16/3499-1/$20.00

DOI: 10.1200/JCO.2015.65.8013

ABSTRACT

Purpose
Young women are at increased risk for developing more aggressive subtypes of breast cancer. Although previous studies have shown a higher risk of breast cancer recurrence and death among young women with early-stage breast cancer, they have not adequately addressed the role of tumor subtype in outcomes.

Methods
We examined data from women with newly diagnosed stage I to III breast cancer presenting to one of eight National Comprehensive Cancer Network centers between January 2000 and December 2007. Multivariable Cox proportional hazards models were used to assess the relationship between age and breast cancer–specific survival.

Results
A total of 17,575 women with stage I to III breast cancer were eligible for analysis, among whom 1,916 were ≤ 40 years of age at diagnosis. Median follow-up time was 6.4 years. In a multivariable Cox proportional hazards model controlling for sociodemographic, disease, and treatment characteristics, women ≤ 40 years of age at diagnosis had greater breast cancer mortality (hazard ratio [HR], 1.4; 95% CI, 1.2 to 1.7). In stratified analyses, age ≤ 40 years was associated with statistically significant increases in risk of breast cancer death among women with luminal A (HR, 2.1; 95% CI, 1.4 to 3.2) and luminal B (HR 1.4; 95% CI, 1.1 to 1.9) tumors, with borderline significance among women with triple-negative tumors (HR, 1.4; 95% CI, 1.0 to 1.8) but not among those with human epidermal growth factor receptor 2 subtypes (HR, 1.2; 95% CI, 0.8 to 1.9). In an additional model controlling for detection method, young age was associated with significantly increased risk of breast cancer death only among women with luminal A tumors.

Conclusion
The effect of age on survival of women with early breast cancer seems to vary by breast cancer subtype. Young age seems to be particularly prognostic in women with luminal breast cancers.

J Clin Oncol 34. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Although approximately 6% to 7% of women diagnosed with breast cancer each year in the United States are 40 years of age or younger, breast cancer is the leading cause of cancer-related deaths in this population. Moreover, the 5-year relative survival rate for women diagnosed with breast cancer before age 40 years is 85%, compared with 90% among women diagnosed at age 40 or older.[1] Prior research has revealed that young age is a risk factor for breast cancer recurrence and death, despite the more intensive treatment that young women conventionally receive compared with older women.[2] This seeming contradiction may be related to differences in tumor biology and/or host differences between younger and older women.

Breast cancer is phenotypically diverse in prognosis and response to treatment. This diversity has resulted in the delineation of a molecular taxonomy of the disease. In 2000, gene expression profiling in 65 breast cancer and normal breast samples identified a set of 496 intrinsic genes that clustered breast tumor profiles into four groups: basal-like, ERBB2 positive (human epidermal growth factor receptor 2 [HER2] positive), normal-breast–like,

and luminal epithelial/estrogen receptor (ER) positive.[3] More recent work integrating clinicopathologic and gene expression data has revealed that receptor phenotype and grade can be used as surrogates for the main molecular subtypes.[4] Numerous studies, including expression profiling, array comparative genomic hybridization, and proteomic analyses, have confirmed the distinct molecular subtypes of breast cancer, which in turn are associated with differing risks of early disease recurrence, sites of metastases, response to therapy, and overall survival.[5-8] The identification of molecular subtypes has aided in the development and validation of treatments for breast cancer that have improved prognosis for particular subgroups of patients. In particular, there has been great success with endocrine therapy for estrogen-responsive tumors.[9,10]

Numerous studies have documented that young women are more likely to develop more aggressive subtypes of breast cancer with unfavorable prognostic features, as well as present with more advanced disease stage.[11-13] A majority of tumors in all age groups are hormone receptor positive and ERBB2 (HER2) negative, but compared with tumors in older women, those in young women are more likely to be high grade, be hormone receptor–negative, have high proliferation fraction, and exhibit lymphovascular invasion. Accumulating evidence suggests that young women are more likely to develop more aggressive tumor molecular subtypes, including a greater proportion of triple-negative or ERBB2 overexpressing tumors.[14-16] The few studies to date that have evaluated the effect of age on disease outcome when considering modern tumor subtypes have suggested that the effect of age on outcomes may vary by tumor phenotype.[17-21] However, studies have been limited by small sample size and tumor subtyping availability, as well as a lack of robust outcome data, particularly regarding mortality. In an effort to assess the role of tumor subtype on outcome disparities by age, we evaluated the effect of age on breast cancer mortality using a longitudinal cohort study, the National Comprehensive Cancer Network (NCCN) Breast Cancer Outcomes Database Project. The NCCN Database is one of the few large data sets to have collected tumor characteristics, including receptor status, such as ER, progesterone receptor (PR), and HER2, and to have tracked disease recurrence and survival.

METHODS

Participants

The study cohort consisted of women with newly diagnosed stage I, II, and III (*AJCC* [American Joint Committee on Cancer] *Cancer Staging Manual*, 5th and 6th editions) breast cancer who received their primary cancer care at one of the eight institutions participating in the NCCN Breast Cancer Outcomes Database Project between January 1, 2000, and December 31, 2007. The eight institutions were The Ohio State University Comprehensive Cancer Center–James Cancer Hospital and Solove Research Institute, Columbus, OH; City of Hope Comprehensive Cancer Center, Duarte, CA; Dana-Farber Cancer Institute, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; The University of Texas MD Anderson Cancer Center, Houston, TX; Roswell Park Cancer Institute, Buffalo, NY; and University of Michigan Comprehensive Cancer Center, Ann Arbor, MI. Each center is an academic comprehensive cancer center at which the majority of surgical and medical oncologists treating breast cancer devote most or all of their clinical effort to breast cancer care. The institutional review board at each center approved the study, data collection process, data transmission methods, and data storage protocols. Patients presenting for second opinions and those receiving no primary therapy at the NCCN institution were excluded from the database.

We identified 20,025 stage I, II, and III patients who presented with a new diagnosis of unilateral breast cancer and received primary therapy at one of the NCCN institutions between January 1, 2000, and December 31, 2007 (Fig 1). We excluded those who had a previous cancer diagnosis (n = 1,572), as well as those missing ER, PR, or HER2 status (n = 854) and those with no follow-up information (n = 24). Our final sample included 17,575 women.

Data Sources

The NCCN Breast Cancer Outcomes Database Project collected data prospectively on sociodemographic, tumor, and treatment characteristics, as well as outcomes on newly diagnosed patients with breast cancer at participating NCCN institutions from 1997 to 2012. The database contained tumor information on size, nodal status, histologic grade, hormone receptor status, and HER2 status, as abstracted from pathology reports, and detailed treatment information on surgical, chemotherapy, immunotherapy, and endocrine therapy, as abstracted from medical records.[22,23] HER2 status by immunohistochemistry was added to the NCCN data as a routinely collected data element in 1999; HER2 status by fluorescent in situ hybridization was added in 2001. In addition, patient-reported sociodemographic elements were collected via survey on first presentation at most centers. The survey collected information on race/ethnicity, employment status at diagnosis, educational status at presentation to the NCCN center (defined as the highest level of education completed), and menopausal status. Vital status and cause of death were abstracted by annual chart review through 2012, with a secondary search of the Social Security Death Index and the National Death Index, current as of December 31, 2009. This was then coded in the database using International Classification of Diseases (9th revision, clinical modification) codes. Rigorous data quality assurance processes as previously documented were in place for the study.[23,24]

Variable Definitions

For HER2 status classification, fluorescent in situ hybridization result was used, if available. If only immunohistochemistry was available, 3+, high positive, or positive/not otherwise specified were considered HER2 positive, whereas 2+, 1+, and 0 or negative were considered HER2 negative. For molecular subtype classification, patients were classified into four subtype groups: luminal A (ER positive and/or PR positive, HER2 negative, and low/intermediate grade); luminal B (ER positive and/or PR positive and HER2 positive; or ER positive and/or PR positive and HER2 negative and high grade); HER2 (ER negative, PR negative, and HER2 positive); and triple negative (ER negative, PR negative, and HER2 negative).

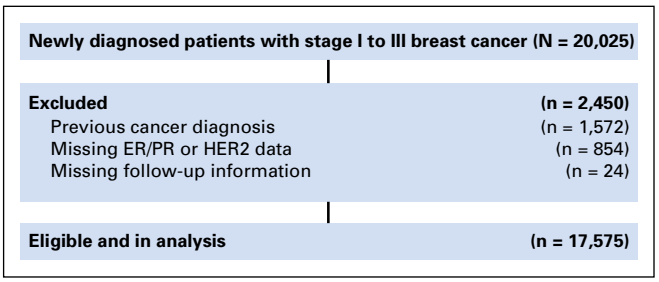

Fig 1. Flow diagram of participants. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

Analyses

We summarized patient and clinical characteristics at the time of first presentation to the NCCN institution, stratified by age at diagnosis (≤ 40, 41 to 50, 51 to 60, 61 to 70, and > 70 years). *P* values in Table 1 were obtained from χ^2 tests. We used the 51- to 60-year-old age group as the reference category because it had the greatest number of people and allowed us to examine the association among both younger and older populations. Follow-up was defined as time in years from breast cancer diagnosis to date of death or last date of NCCN follow-up. Breast cancer–specific survival was determined by identifying breast cancer as the cause of death using International Classification of Disease codes 174 and 174.9. We used multivariable Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% CIs for the relationship between age group and breast cancer–specific survival. Visual assessment of Kaplan-Meier curves suggested no violation of the proportional hazards assumption. We assessed the association overall and stratified by breast cancer subtype.

We conducted multivariable analyses with stepwise adjustment, beginning with sociodemographic characteristics, including race/ethnicity (categorical), insurance type (Medicare, Medicaid, managed care, indemnity, or other/unknown/uninsured), educational attainment (high school or less, some college, college graduate, graduate school), employment status (employed or student; homemaker or retired; or unable to work, unemployed, or other), and NCCN center. Next, we also accounted for tumor characteristics and treatment: stage at diagnosis, tumor grade (high-grade or low/intermediate), year of diagnosis (continuous), receipt of adjuvant chemotherapy (yes/no), endocrine therapy (yes/no), or trastuzumab (yes/no). We then conducted separate analyses within each breast cancer subtype (luminal A, luminal B, HER2, and triple-negative). For covariates that had missing data, we included a missing category that was included in the analysis.

All statistical tests were two-sided, and *P* values < .05 were considered statistically significant. Analyses were conducted using SAS (version 9.2, SAS Institute, Cary, NC).

RESULTS

Patient and tumor characteristics and treatments by age at diagnosis are presented in Table 1. Among 17,575 women with breast cancer eligible for analysis, 1,916 were ≤ 40 years of age at diagnosis, with a mean age of 35 years; the mean age of women > 40 years of age was 57 years. Median follow-up time was 6.42 years overall. This ranged from 6.21 years for HER2-type tumors to 6.45 years for luminal A tumors. Compared with older women, younger women were more likely to be nonwhite, premenopausal, more educated, and employed or in school ($P < .001$). Younger women also were more likely to have higher-stage and higher-grade disease, and their tumors were more likely to be of luminal B, triple-negative, or HER2 subtype ($P < .001$). In addition, younger women were more likely to receive chemotherapy compared with the older group ($P < .001$).

Relationship Between Younger Age and Breast Cancer Mortality

In a multivariable model controlling for demographic characteristics, we found that women ≤ 40 years old were 90% more likely to die of breast cancer than were women ages 51 to 60 years at diagnosis (HR, 1.9; 95% CI, 1.6 to 2.3; Table 2). Additional adjustment controlling for treatment, stage at diagnosis, tumor grade, and year of diagnosis attenuated the association, and women ≤ 40 years old were 50% more likely to die of their breast cancer than were women ages 51 to 60 (HR, 1.5; 95% CI, 1.3 to 1.8). After adjusting for tumor molecular subtype and detection method (symptomatic or screen), the association was further attenuated; however, women ≤ 40 years old remained 30% more likely to die of their breast cancer than were women ages 51 to 60 years (HR, 1.3; 95% CI, 1.1 to 1.5). In fully adjusted models, there was no difference in survival among women ages 41 to 50 years (HR, 0.9; 95% CI, 0.8 to 1.1), 61 to 70 years (HR, 0.8; 95% CI, 0.7 to 1.0), or >70 years (HR, 1.0; 95% CI, 0.7 to 1.4) compared with women ages 51 to 60 years.

Stratification by Tumor Subtype

We examined the association between age group and breast cancer mortality, stratifying by tumor subtype (Table 3). Among women with luminal A disease (n = 7,738), when controlling for patient, disease, and treatment factors, women ≤ 40 years of age at diagnosis were more than twice as likely to die of breast cancer compared with women ages 51 to 60 years (HR, 2.1; 95% CI, 1.4 to 3.2). In women with luminal B disease, the younger women also had greater breast cancer mortality (HR, 1.4; 95% CI, 1.1 to 1.9), and for women with triple-negative disease, young age was associated with borderline increased risk (HR, 1.4; 95% CI, 1.0 to 1.8). In contrast, among women with HER2-positive disease, young age was not significantly associated with breast cancer–specific mortality when controlling for other prognostic factors (HR, 1.2; 95% CI, 0.8 to 1.9). Furthermore, in subset analysis of the luminal B group (data not shown), the increased risk demonstrated seemed to be largely due to the HER2-negative subgroup. When we controlled for detection method, these relationships were attenuated, and poor prognostic effect of young age on mortality was seen primarily in women with luminal A disease.

DISCUSSION

Young age at diagnosis has long been considered a poor prognostic factor, because young women, on average, have an increased risk of disease recurrence and decreased survival.[12,13,25] In recent years, however, with improved understanding of tumor biology, this assertion has been challenged with increased recognition of the prognostic and predictive role of tumor subtype and awareness that young women are more likely to develop more aggressive phenotypes.[14,16,26,27] Our study expands on this work to demonstrate that in a large national sample where control of tumor subtype is possible, young age is a prognostic factor in certain breast cancer subtypes, but not others.

In women with HER2-positive disease, prior analysis in a clinical trial population receiving modern therapy demonstrated that young age was neither prognostic nor predictive of short-term outcome among women treated with chemotherapy, whether followed by trastuzumab or not.[18] In the setting of triple-negative breast cancer, the risk of recurrence also seems to be similar in older women compared with younger women when controlling for other conventional prognostic factors.[27,28] In this report, we found that in women with HER2-type or triple-negative breast cancer, there was no clear increased risk of breast cancer mortality among women ≤ 40 years of age compared with women 51 to 60 years of age.

Table 1. Descriptive Characteristics of 17,575 Patients With Stage I, II, and III Breast Cancer According to Age at Diagnosis

	Age at Diagnosis (years)					
	≤ 40 (n = 1,916)	41-50 (n = 4,654)	51-60 (n = 5,249)	61-70 (n = 3,477)	> 70 (n = 2,279)	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	*P**
Race/ethnicity						< .001
White non-Hispanic	1,407 (73.4)	3,666 (78.8)	4,295 (81.8)	2,937 (84.5)	1,963 (86.1)	
Hispanic	208 (10.9)	341 (7.3)	347 (6.6)	198 (5.7)	82 (3.6)	
Black non-Hispanic	172 (9.0)	395 (8.5)	393 (7.5)	215 (6.2)	170 (7.5)	
Asian/Pacific Islander non-Hispanic	97 (5.1)	177 (3.8)	141 (2.7)	77 (2.2)	41 (1.8)	
Other	17 (0.89)	40 (0.86)	39 (0.74)	25 (0.72)	9 (0.39)	
Unknown	15 (0.78)	35 (0.75)	34 (0.65)	25 (0.72)	14 (0.61)	
Educational status						< .001
Grade school/high school	365 (19.1)	930 (20.0)	1,188 (22.6)	1,156 (33.3)	947 (41.6)	
Some college	445 (23.2)	1,112 (23.9)	1,221 (23.3)	649 (18.7)	383 (16.8)	
College graduate	512 (26.7)	1,081 (23.2)	1,012 (19.3)	516 (14.8)	278 (12.2)	
Graduate school	282 (14.7)	747 (16.1)	906 (17.3)	454 (13.1)	183 (8.0)	
Unknown/missing	312 (16.3)	784 (16.9)	922 (17.6)	702 (20.2)	488 (21.4)	
Insurance status						< .001
Managed	1,525 (79.6)	3,812 (81.9)	4,244 (80.9)	1,676 (48.2)	116 (5.1)	
Medicaid	196 (10.2)	311 (6.7)	316 (6.0)	158 (4.54)	24 (1.1)	
Indemnity	82 (4.3)	267 (5.7)	369 (7.0)	183 (5.3)	15 (0.7)	
Medicare	20 (1.0)	86 (1.9)	144 (2.7)	1,368 (39.34)	2,095 (91.9)	
Other/unknown/uninsured	93 (4.6)	178 (3.8)	176 (3.4)	92 (2.7)	29 (1.3)	
Employment status						< .001
Employed/student	1,183 (61.7)	3,070 (66.0)	3,145 (59.9)	1,077 (31.0)	154 (6.8)	
Homemaker/retired	407 (21.2)	783 (16.8)	1,198 (22.8)	1,870 (53.8)	1,868 (82.0)	
Unable to work/unemployed/other	326 (17.0)	801 (17.2)	906 (17.3)	530 (15.2)	257 (11.3)	
Detection method						< .001
Screening	194 (10.1)	1,543 (33.2)	2,536 (48.3)	1,964 (56.4)	1,292 (56.7)	
Symptomatic	1,639 (85.5)	2,931 (63.0)	2,507 (47.8)	1,390 (40.0)	907 (40.0)	
Unknown	83 (4.3)	180 (3.9)	206 (3.9)	123 (3.5)	80 (3.5)	
Stage at diagnosis						< .001
I	547 (28.6)	1,770 (38.0)	2,367 (45.1)	1,744 (50.2)	1,247 (54.7)	
II	973 (50.8)	2,116 (45.5)	2,077 (39.6)	1,304 (37.5)	793 (34.8)	
III	396 (20.7)	768 (16.5)	805 (15.3)	429 (12.3)	239 (10.5)	
Histologic grade						< .001
High	1,211 (63.2)	2,302 (49.46)	2,265 (43.2)	1,332 (38.3)	804 (35.3)	
Low/intermediate	629 (32.8)	2,171 (46.65)	2,749 (52.4)	1,972 (56.7)	1,323 (58.1)	
Unknown/other	76 (4.0)	181 (3.9)	235 (4.5)	173 (5.0)	152 (6.7)	
ER status						
Positive	1,188 (62.0)	3,395 (73.0)	3,875 (73.8)	2,734 (78.6)	1,926 (14.7)	
Negative	728 (38.0)	1,259 (27.1)	1,374 (26.2)	743 (21.4)	353 (15.4)	
PR status						
Positive	1,018 (53.1)	3,017 (64.8)	3,197 (60.9)	2,198 (63.2)	1,534 (67.3)	
Negative	898 (46.9)	1,637 (35.2)	2,052 (39.1)	1,279 (36.8)	745 (32.7)	
HER2 status						< .001
Positive	466 (24.3)	899 (19.3)	926 (17.6)	456 (13.1)	282 (1.6)	
Negative	1,450 (75.7)	3,755 (80.7)	4,323 (82.4)	3,021 (86.9)	1,997 (87.6)	
Molecular subtype						< .001
Luminal A†	510 (26.6)	1,871 (40.2)	2,391 (45.6)	1,779 (51.2)	1,187 (52.1)	
Luminal B‡	698 (36.4)	1,514 (32.5)	1,428 (27.2)	875 (25.2)	634 (27.8)	
HER2 type§	189 (9.9)	343 (7.4)	410 (7.8)	203 (5.8)	98 (4.3)	
Triple negative‖	478 (24.9)	818 (17.6)	861 (16.4)	495 (14.2)	234 (10.3)	
Unknown	41 (2.1)	108 (2.3)	159 (3.0)	125 (3.6)	126 (5.5)	
Treatment						< .001
Chemotherapy and hormones	824 (43.0)	2,102 (45.2)	1,954 (37.2)	938 (27.0)	229 (10.0)	
Chemotherapy only	617 (32.2)	1,023 (22.0)	1,063 (20.3)	543 (15.6)	169 (7.4)	
Hormones only	107 (5.6)	699 (15.0)	1,296 (24.7)	1,371 (39.4)	1,304 (57.2)	
Chemotherapy, hormones, trastuzumab	144 (7.5))	262 (5.6)	202 (3.8)	77 (2.2)	30 (1.3)	
Trastuzumab only	2 (0.10)	0 (0)	0 (0)	0 (0)	2 (0.09)	
Hormones and trastuzumab	0 (0)	4 (0.09)	1 (0.02)	1 (0.03)	6 (0.26)	
Chemotherapy and trastuzumab	106 (5.5)	188 (3.1)	211 (4.0)	100 (2.9)	33 (1.4)	
Missing/untreated	116 (6.1)	376 (8.1)	522 (9.9)	447 (12.9)	506 (22.2)	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.
*P value from χ^2 test.
†ER positive and/or PR positive, HER2 negative/low grade.
‡ER positive and/or PR positive, HER2 positive; or ER positive and/or PR positive, HER2 negative/high grade.
§ER negative, PR negative, and HER2 positive.
‖ER negative, PR negative, and HER2 negative.

Table 2. Hazard Ratios and 95% CIs for Breast Cancer Mortality According to Age at Diagnosis

Age at Diagnosis (years)	No. of Patients	Breast Cancer Deaths, No. (%)	HR (95% CI)*	HR (95% CI)†	HR (95% CI)‡	HR (95% CI)§
≤ 40	1,916	242 (12.6)	1.9 (1.6 to 2.3)	1.5 (1.3 to 1.8)	1.4 (1.2 to 1.7)	1.3 (1.1 to 1.5)
41-50	4,654	321 (6.9)	1.1 (0.9 to 1.2)	1.0 (0.9 to 1.2)	1.0 (0.8 to 1.2)	0.9 (0.8 to 1.1)
51-60	5,249	343 (6.5)	1.0 (REF)	1.0 (REF)	1.0 (REF)	1.0 (REF)
61-70	3,477	164 (4.7)	0.7 (0.6 to 0.9)	0.9 (0.7 to 1.1)	0.9 (0.7 to 1.1)	0.8 (0.7 to 1.0)
> 70	2,279	112 (4.9)	0.7 (0.5 to 1.0)	1.2 (0.8 to 1.6)	1.1 (0.8 to 1.5)	1.0 (0.7 to 1.4)

Abbreviations: HR, hazard ratio; REF, reference.
*Adjusted for race/ethnicity, insurance, employment, center, and education.
†Adjusted for race/ethnicity, insurance, employment, center, education, treatment (hormone [yes/no], chemotherapy [yes/no], trastuzumab [yes/no]), stage at diagnosis, grade, and year of diagnosis.
‡Adjusted for race/ethnicity, insurance, employment, center, education, treatment (hormone [yes/no], chemotherapy [yes/no], trastuzumab [yes/no]), stage at diagnosis, grade, year of diagnosis, and molecular subtype.
§Adjusted for race/ethnicity, insurance, employment, center, education, treatment (hormone [yes/no], chemotherapy [yes/no], trastuzumab [yes/no]), stage at diagnosis, grade, year of diagnosis, molecular subtype, and detection method (symptomatic or screen).

This growing body of evidence suggests that in these two more aggressive phenotypes, outcomes are similar regardless of age at diagnosis, although the incidence of these more aggressive tumors in young women is higher. The finding that among women with luminal breast cancer, age seems to remain an independent prognostic factor has been observed previously and merits further consideration.[12,27]

Luminal A and B subtypes are characterized by the expression of hormone receptors and potential sensitivity to endocrine manipulations, and benefit from adjuvant endocrine therapy or the chemoendocrine effect of chemotherapy in premenopausal women. There are several potential mechanisms by which young women may not get the same benefits as older women. In older series, tamoxifen was not commonly administered to young women; therefore, they would not have received the potential benefits in terms of risk reduction. Chemotherapy-related amenorrhea, which is associated with improved outcomes, particularly in women with endocrine sensitive tumors, is less likely to occur in younger women.[29,30] Young age also is a predictor of decreased adherence with adjuvant endocrine therapy, associated with increased mortality.[31-35] Hershman et al[32] reported that women ≤ 40 years were 40% more likely to be nonadherent than were those ages 50 to 65 years ($P < .001$). Similarly, Huiart et al[34] found that 40% of women with early breast cancer with a mean age younger than 40 years had discontinued tamoxifen after 3 years of

Table 3. Age and Breast Cancer Mortality According to Breast Cancer Subtype

Breast Cancer Subtype and Age (years)	No. of Breast Cancers	Breast Cancer Deaths, No. (%)	HR (95% CI)*	HR (95% CI)†	HR (95% CI)‡
Luminal A					
≤ 40	510	38 (7.5)	2.7 (1.8 to 4.1)	2.1 (1.4 to 3.2)	1.7 (1.1 to 2.7)
41-50	1,871	40 (2.1)	0.9 (0.6 to 1.3)	0.8 (0.5 to 1.2)	0.7 (0.5 to 1.1)
51-60	2,391	58 (2.4)	1.0 (REF)	1.0 (REF)	1.0 (REF)
61-70	1,779	36 (2.0)	0.8 (0.5 to 1.3)	1.0 (0.6 to 1.6)	0.9 (0.6 to 1.5)
> 70	1,187	29 (2.4)	0.9 (0.5 to 1.8)	1.5 (0.8 to 3.1)	1.5 (0.7 to 3.0)
Luminal B					
≤ 40	698	85 (12.2)	1.6 (1.2 to 2.2)	1.4 (1.1 to 1.9)	1.2 (0.9 to 1.7)
41-50	1,514	102 (6.7)	0.9 (0.7 to 1.12)	0.8 (0.6 to 1.1)	0.7 (0.6 to 1.0)
51-60	1,428	106 (7.4)	1.0 (REF)	1.0 (REF)	1.0 (REF)
61-70	875	44 (5.0)	0.7 (0.5 to 1.0)	0.7 (0.5 to 1.1)	0.7 (0.5 to 1.0)
> 70	634	37 (5.8)	1.0 (0.6 to 1.7)	1.2 (0.7 to 2.1)	1.0 (0.6 to 1.8)
HER2 type					
≤ 40	189	30 (15.9)	1.2 (0.7 to 1.8)	1.2 (0.8 to 1.9)	1.1 (0.7 to 1.7)
41-50	343	29 (8.5)	0.6 (0.4 to 1.0)	0.6 (0.4 to 1.0)	0.6 (0.3 to 0.9)
51-60	410	59 (14.4)	1.0 (REF)	1.0 (REF)	1.0 (REF)
61-70	203	23 (11.3)	0.9 (0.5 to 1.5)	1.2 (0.7 to 2.0)	1.0 (0.5 to 1.8)
> 70	98	11 (11.2)	1.1 (0.4 to 2.7)	1.6 (0.6 to 4.0)	1.2 (0.4 to 3.2)
Triple negative					
≤ 40	478	88 (18.4)	1.4 (1.1 to 1.9)	1.4 (1.0 to 1.8)	1.3 (0.9 to 1.7)
41-50	818	146 (17.9)	1.4 (1.1 to 1.8)	1.3 (1.0 to 1.7)	1.3 (1.0 to 1.7)
51-60	861	115 (13.4)	1.0 (REF)	1.0 (REF)	1.0 (REF)
61-70	495	53 (10.7)	0.7 (0.5 to 1.0)	0.8 (0.5 to 1.1)	0.7 (0.5 to 1.1)
> 70	234	28 (12.0)	0.7 (0.4 to 1.2)	0.7 (0.4 to 1.3)	0.7 (0.4 to 1.2)

Abbreviation: HER2, human epidermal growth factor receptor 2; REF, reference.
*Adjusted for race/ethnicity, insurance, employment, center, and education.
†Adjusted for race/ethnicity, insurance, employment, center, education, treatment, stage at diagnosis, grade, and year of diagnosis.
‡Adjusted for race/ethnicity, insurance, employment, center, education, treatment, stage at diagnosis, grade, year of diagnosis, and detection method (symptomatic or screen).

treatment. Adherence in this population is a critical issue that needs to be addressed, given the demonstrated efficacy of endocrine therapy in reducing the risk of recurrence and death among women with luminal disease. Uptake in clinical practice of recent findings demonstrating incremental benefits from combined ovarian suppression and either tamoxifen or an aromatase inhibitor in young women may help to reduce disparities by age among those with higher-risk luminal tumors in particular.[36,37]

It also is possible that tumors arising in young women have different biologic characteristics than do those that arise in older women, even within tumor subtypes. Younger women are more likely to harbor a *BRCA1*, *BRCA2*, or other cancer-related genetic-associated tumor.[38] Yet, it is not clear whether this factor negatively affects survival, particularly if women are given chemotherapy.[39,40] Tumors in young women have lower mRNA expression of ER-alpha, ER-beta, and PR, with higher HER2 and epidermal growth factor receptor expression.[41] Although these differences diminish when considering differences in molecular subtype distribution by age, there may be residual age-related differences in gene expression beyond subtype. Azim et al[16] demonstrated that tumors in young women were enriched with phosphatidylinositol 3-kinase, extracellular signal–related kinase-related genes, and genes for mammary stem cells, luminal progenitor cells, *c-kit*, and receptor activator of nuclear factor kappa-B ligand, while accounting for subtype distribution. Lastly, younger women are more likely to have pregnancy-associated breast cancer (disease diagnosed in the 1 to 5 years after a pregnancy), which is correlated with poor prognosis and enriched tumor expression of genes in several cancer pathways.[19,42] Future research is warranted to determine whether these biologic differences in tumors of young women contribute to subtype-specific survival differences.

To our knowledge, this study was the largest comprehensive evaluation to date to assess the relationship between patient age and breast cancer mortality while controlling for modern tumor subtyping, including HER2 status. A major strength of the study was the availability of detailed patient, tumor, and treatment information in a large, diverse, multicenter observational cohort of women with breast cancer. However, our results should be considered in light of the possible limitations of this research. The NCCN database enrolled patients only from large comprehensive cancer centers and is not population based; therefore, the experiences of women in this study may not be generalizable to all women with breast cancer. It is possible that younger women with more aggressive cancers preferentially choose to come to these centers and therefore may bias these results. We ascertained tumor characteristics and subtypes from medical records, thus using hormone receptor status and grade from medical records as surrogates for determination of molecular subtype. However, at least for ER status, pathology reports are a demonstrated reasonable alternative to central laboratory testing.[43] Lastly, because we lacked information on cytokeratin 5/6 and epidermal growth factor receptor, we could not precisely identify basal-like subtypes.

Nevertheless, this study supports the growing evidence that the relationship between age at diagnosis and breast cancer–specific survival varies by tumor subtype, which has implications for both treatment decisions and future research directions. Young age does not seem to be an independent predictor of outcome when controlling for other factors in women with triple-negative and HER2 subtype tumors. However, in women with luminal disease, younger age does have a substantial prognostic role, which may reflect inadequate therapy, including lower treatment efficacy and less therapeutic adherence and persistence, as well as residual differences in tumor biology. In a previous study that was based on this data set, we demonstrated similar persistent disparities among black women with luminal tumors, suggesting that targeted interventions for young and black women with these tumors is an important step toward reducing age and race-related disparities in breast cancer.[44] Research on improving outcomes should focus on disease, treatment, access, and behavioral issues in an effort to reduce mortality. The effect of age on survival of women with early breast cancer seems to vary by breast cancer subtype, and age seems to be particularly prognostic in women with luminal A and luminal B, HER2-negative breast cancer. Further research to elucidate differences in breast cancer biology and efficacy of therapy among young women with luminal breast cancer by age may identify targets to improve outcomes in this higher-risk population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Ann H. Partridge, Rebecca A. Ottesen, Joyce C. Niland, Jane C. Weeks
Financial support: Ann H. Partridge
Administrative support: Ann H. Partridge, Jane C. Weeks
Provision of study materials or patients: Yu-Ning Wong, Stephen B. Edge, Richard L. Theriault, Douglas W. Blayney, Eric P. Winer, Jane C. Weeks
Collection and assembly of data: Melissa E. Hughes, Yu-Ning Wong, Stephen B. Edge, Richard L. Theriault, Douglas W. Blayney, Jane C. Weeks
Data analysis and interpretation: Ann H. Partridge, Melissa E. Hughes, Erica T. Warner, Rebecca A. Ottesen, Stephen B. Edge, Joyce C. Niland, Eric P. Winer, Jane C. Weeks, Rulla M. Tamimi
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. American Cancer Society: Breast Cancer Facts & Figures 2013-2014. Atlanta, GA, American Cancer Society, 2013. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-042725.pdf
2. Narod SA: Breast cancer in young women. Nat Rev Clin Oncol 9:460-470, 2012
3. Perou CM, Sørlie T, Eisen MB, et al: Molecular portraits of human breast tumours. Nature 406: 747-752, 2000
4. Desmedt C, Haibe-Kains B, Wirapati P, et al: Biological processes associated with breast cancer clinical outcome depend on the molecular subtypes. Clin Cancer Res 14:5158-5165, 2008
5. Engstrøm MJ, Opdahl S, Hagen AI, et al: Molecular subtypes, histopathological grade and survival in a historic cohort of breast cancer patients. Breast Cancer Res Treat 140:463-473, 2013

6. Kennecke H, Yerushalmi R, Woods R, et al: Metastatic behavior of breast cancer subtypes. J Clin Oncol 28:3271-3277, 2010

7. Voduc KD, Cheang MC, Tyldesley S, et al: Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 28:1684-1691, 2010

8. Carey LA, Dees EC, Sawyer L, et al: The triple negative paradox: Primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 13:2329-2334, 2007

9. Burstein HJ, Temin S, Anderson H, et al: Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol 32:2255-2269, 2014

10. Arteaga CL, Sliwkowski MX, Osborne CK, et al: Treatment of HER2-positive breast cancer: Current status and future perspectives. Nat Rev Clin Oncol 9:16-32, 2011

11. Colleoni M, Rotmensz N, Peruzzotti G, et al: Role of endocrine responsiveness and adjuvant therapy in very young women (below 35 years) with operable breast cancer and node negative disease. Ann Oncol 17:1497-1503, 2006

12. Ahn SH, Son BH, Kim SW, et al: Poor outcome of hormone receptor-positive breast cancer at very young age is due to tamoxifen resistance: Nationwide survival data in Korea–a report from the Korean Breast Cancer Society. J Clin Oncol 25:2360-2368, 2007

13. Anders CK, Johnson R, Litton J, et al: Breast cancer before age 40 years. Semin Oncol 36:237-249, 2009

14. Collins LC, Marotti JD, Gelber S, et al: Pathologic features and molecular phenotype by patient age in a large cohort of young women with breast cancer. Breast Cancer Res Treat 131:1061-1066, 2012

15. Keegan TH, DeRouen MC, Press DJ, et al: Occurrence of breast cancer subtypes in adolescent and young adult women. Breast Cancer Res 14:R55, 2012

16. Azim HA Jr, Michiels S, Bedard PL, et al: Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clin Cancer Res 18:1341-1351, 2012

17. Arvold ND, Taghian AG, Niemierko A, et al: Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. J Clin Oncol 29:3885-3891, 2011

18. Partridge AH, Gelber S, Piccart-Gebhart MJ, et al: Effect of age on breast cancer outcomes in women with human epidermal growth factor receptor 2-positive breast cancer: Results from a herceptin adjuvant trial. J Clin Oncol 31:2692-2698, 2013

19. Blows FM, Driver KE, Schmidt MK, et al: Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: A collaborative analysis of data for 10,159 cases from 12 studies. PLoS Med 7:e1000279, 2010

20. Loibl S, Jackisch C, Gade S, et al: Neoadjuvant chemotherapy in the very young 35 years of age or younger. Cancer Res 72:96s, 2012 (24, suppl)

21. Loibl S, Jackisch C, Lederer B, et al: Outcome after neoadjuvant chemotherapy in young breast cancer patients: A pooled analysis of individual patient data from eight prospectively randomized controlled trials. Breast Cancer Res Treat 152: 377-387, 2015

22. Niland JC: NCCN Internet-based data system for the conduct of outcomes research. Oncology (Williston Park) 12(11A):142-146, 1998

23. Niland JC: NCCN outcomes research database: Data collection via the Internet. Oncology (Williston Park) 14(11A):100-103, 2000

24. Partridge AH, Hughes ME, Ottesen RA, et al: The effect of age on delay in diagnosis and stage of breast cancer. Oncologist 17:775-782, 2012

25. Fowble BL, Schultz DJ, Overmoyer B, et al: The influence of young age on outcome in early stage breast cancer. Int J Radiat Oncol Biol Phys 30:23-33, 1994

26. Azim HA Jr, Partridge AH: Biology of breast cancer in young women. Breast Cancer Res 16:427, 2014

27. Sheridan W, Scott T, Caroline S, et al: Breast cancer in young women: Have the prognostic implications of breast cancer subtypes changed over time? Breast Cancer Res Treat 147:617-629, 2014

28. Anders CK, Deal AM, Miller CR, et al: The prognostic contribution of clinical breast cancer subtype, age, and race among patients with breast cancer brain metastases. Cancer 117:1602-1611, 2011

29. Walshe JM, Denduluri N, Swain SM: Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. J Clin Oncol 24: 5769-5779, 2006

30. Swain SM, Jeong JH, Geyer CE, Jr, et al: Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. N Engl J Med 362:2053-2065, 2010

31. Partridge AH, Wang PS, Winer EP, et al: Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol 21: 602-606, 2003

32. Hershman DL, Kushi LH, Shao T, et al: Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol 28:4120-4128, 2010

33. Hershman DL, Shao T, Kushi LH, et al: Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 126:529-537, 2011

34. Huiart L, Bouhnik AD, Rey D, et al: Early discontinuation of tamoxifen intake in younger women with breast cancer: Is it time to rethink the way it is prescribed? Eur J Cancer 48:1939-1946, 2012

35. Huiart L, Ferdynus C, Giorgi R: A meta-regression analysis of the available data on adherence to adjuvant hormonal therapy in breast cancer: Summarizing the data for clinicians. Breast Cancer Res Treat 138:325-328, 2013

36. Pagani O, Regan MM, Walley BA, et al: Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 371:107-118, 2014

37. Francis PA, Regan MM, Fleming GF, et al: Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 372:436-446, 2015

38. Greenup R, Buchanan A, Lorizio W, et al: Prevalence of BRCA mutations among women with triple-negative breast cancer (TNBC) in a genetic counseling cohort. Ann Surg Oncol 20:3254-3258, 2013

39. Wang C, Zhang J, Wang Y, et al: Prevalence of BRCA1 mutations and responses to neoadjuvant chemotherapy among BRCA1 carriers and noncarriers with triple-negative breast cancer. Ann Oncol 26:523-528, 2015

40. Rennert G, Bisland-Naggan S, Barnett-Griness O, et al: Clinical outcomes of breast cancer in carriers of BRCA1 and BRCA2 mutations. N Engl J Med 357: 115-123, 2007

41. Anders CK, Acharya CR, Hsu DS, et al: Age-specific differences in oncogenic pathway deregulation seen in human breast tumors. PLoS One 3: e1373, 2008

42. Azim HA, Jr., Santoro L, Russell-Edu W, et al: Prognosis of pregnancy-associated breast cancer: A meta-analysis of 30 studies. Cancer Treat Rev 38: 834-842, 2012

43. Collins LC, Marotti JD, Baer HJ, et al: Comparison of estrogen receptor results from pathology reports with results from central laboratory testing. J Natl Cancer Inst 100:218-221, 2008

44. Warner ET, Tamimi RM, Hughes ME, et al: Racial and ethnic differences in breast cancer survival: Mediating effect of tumor characteristics and sociodemographic and treatment factors. J Clin Oncol 33:2254-2261, 2015

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Subtype-Dependent Relationship Between Young Age at Diagnosis and Breast Cancer Survival

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Ann H. Partridge
Consulting or Advisory Role: Pfizer

Melissa E. Hughes
No relationship to disclose

Erica T. Warner
No relationship to disclose

Rebecca A. Ottesen
No relationship to disclose

Yu-Ning Wong
Research Funding: Pfizer (Inst), Tokai Pharmaceuticals (Inst), PhRMA (Inst)
Travel, Accommodations, Expenses: Tokai Pharmaceuticals

Stephen B. Edge
No relationship to disclose

Richard L. Theriault
Patents, Royalties, Other Intellectual Property: UpToDate royalties

Douglas W. Blayney
Consulting or Advisory Role: Clinical Oncology Advisory Group, Physician Resource Management, Bristol-Myers Squibb, Carevive Systems, Oncothyreon
Research Funding: Amgen (Inst)
Travel, Accommodations, Expenses: BeyondSpring Pharmaceuticals

Joyce C. Niland
No relationship to disclose

Eric P. Winer
No relationship to disclose

Jane C. Weeks
No relationship to disclose

Rulla M. Tamimi
No relationship to disclose

Acknowledgment

In memoriam: This article is dedicated to the memory of Jane C. Weeks, MD, MSc, who established and led the National Comprehensive Cancer Network Breast Cancer Outcomes Database. She died on September 10, 2013, after a long illness.