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Age-Specific Changes in Intrinsic Breast Cancer Subtypes: A Focus on Older Women

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Gene microarray • Breast cancer • Age • Elderly

ABSTRACT

Purpose. Breast cancer (BC) is a disease of aging and the number of older BC patients in the U.S. is rising. Immunohistochemical data show that with increasing age, the incidence of hormone receptor-positive tumors increases, whereas the incidence of triple-negative tumors decreases. Few data exist on the frequency of molecular subtypes in older women. Here, we characterize the incidence and outcomes of BC patients by molecular subtypes and age.

Patients and Methods. Data from 3,947 patients were pooled from publicly available clinical and gene expression microarray data sets. The PAM50 algorithm was used to classify tumors into five BC intrinsic subtypes: luminal A, luminal B, HER2-enriched, basal-like, and normal-like. The association of age and subtype with recurrence-free survival (RFS), overall survival, and disease-specific survival (DSS) was assessed.

Results. The incidence of luminal (A, B, and A+B) tumors increased with age ($p < .01$, $p < .0001$, and $p < .0001$, respectively), whereas the percentage of basal-like tumors decreased ($p < .0001$). Among patients 70 years and older, luminal B, HER2-enriched, and basal-like tumors were found at a frequency of 32%, 11%, and 9%, respectively. In older women, luminal subtypes had better outcomes than basal-like and HER2-enriched subtypes. After controlling for subtype, treatment, tumor size, nodal status, and grade, increasing age had no impact on RFS or DSS.

Conclusion. More favorable BC subtypes increase with age, but older patients still have a substantial percentage of high-risk tumor subtypes. After accounting for tumor subtypes, age at diagnosis is not an independent prognostic factor for outcome.

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Implications for Practice: Breast cancer incidence increases dramatically with age, and the number of older patients is increasing worldwide. Estrogen receptor, progesterone receptor, and HER2 expression remain the cornerstones for selecting adjuvant systemic therapy, but an expanding body of knowledge suggests that making decisions on the basis of the genetic characteristics of the breast cancer (molecular subtypes) may ultimately improve on current treatment outcomes. Our data suggest that although increasing age is associated with more favorable breast cancer biology, within subtypes outcomes are similar for all age groups. Also, after accounting for breast cancer subtypes, age alone was not related to outcome.

INTRODUCTION

The incidence of breast cancer increases dramatically with age, and the majority of women who die of breast cancer are older than 65 years [1]. Although older patients are more likely to present with tumors that are hormone receptor (HR)-positive and HER2-negative when compared with younger patients, many older patients present with more aggressive triple-negative and HER2-positive phenotypes [2, 3]. These findings have broad implications, because many older women have estimated survivals exceeding 5 years, and those with high-risk triple-negative and HER2-positive breast cancers are most likely to relapse within 5 years of diagnosis [4]; optimizing treatment for such patients is a major consideration. PAM50 is a 50-gene expression-based predictor that classifies breast cancers into four intrinsic subtypes of prognostic significance [5]: luminal A, luminal B, HER2-enriched (HER2-E), or basal-like [6]. The PAM50 assay has been shown to provide more precise prognostic information than immunohistochemical (IHC)-based subtyping and can be performed using paraffin-embedded tissues [6–8].

Molecular subtypes of breast cancer have been well-defined in younger women [9], but to our knowledge, no large-scale, genomic-based studies have determined the distribution of molecular subtypes in older women. Although intrinsic subtypes are not yet widely used in clinical practice, this is likely to change as clinical trial data showing the superiority of these analyses compared with IHC assays in predicting treatment benefit mature [10, 11]. Moreover, exciting recent data suggest that molecular subtypes differ substantially in

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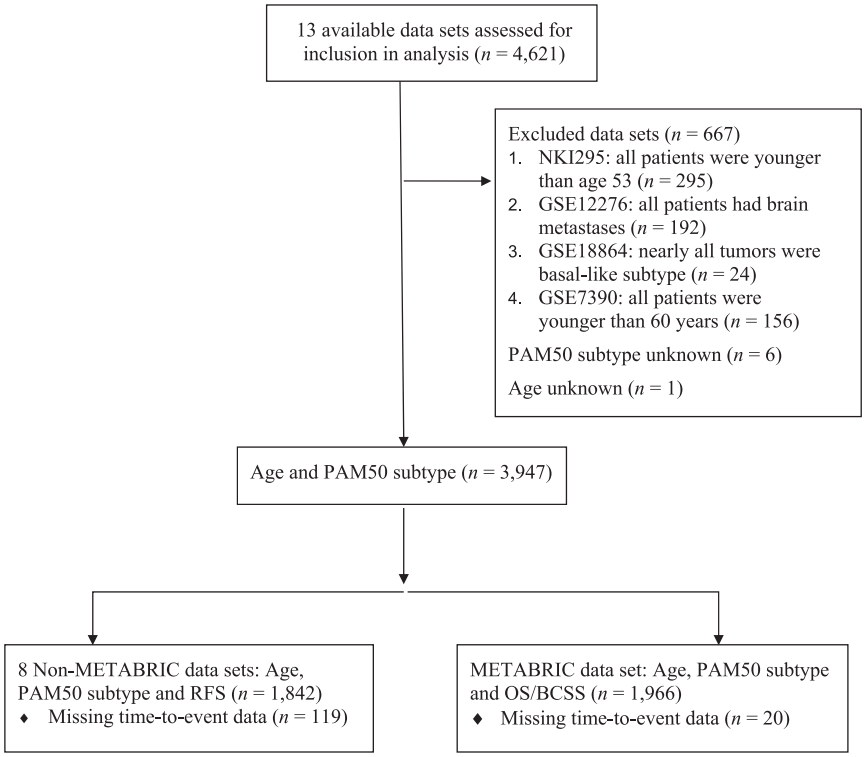

Figure 1. CONSORT diagram of publicly available gene array data sets used to define breast cancer subtypes using the PAM50 model [6]. Abbreviations: BCSS, breast cancer-specific survival; OS, overall survival; RFS, recurrence-free survival.

the intracellular pathways responsible for cell growth and metastatic spread, suggesting a wide array of potential molecular targets for drug development [12, 13]. In this study, we characterize breast cancer molecular intrinsic subtypes by age and focus on the implications of these subtypes in older women. In addition, we explore the association of age on recurrence-free survival (RFS), overall survival (OS), and disease-specific survival (DSS) after accounting for intrinsic subtype, clinical-pathological characteristics, and adjuvant treatment.

Patients and Methods

Thirteen publicly available microarray data sets were pooled for a total of 4,621 breast cancer samples. Samples from patients in these data sets were collected from as early as 1980 and as recent in 2010, with time frames varying greatly among different data sets. Four data sets were excluded because of a lack of representation of older patients or particularly poor outcomes (Fig. 1). All patients had potentially curable breast cancer and were without metastases. Tumor size was available for 97% of patients, nodal status was available for 98% of patients, and tumor grade was available for 83% of patients. Adjuvant treatment data were available for 90% of patients and included chemotherapy, endocrine therapy, both chemotherapy and endocrine therapy, and no adjuvant treatment (Table 1). Specific details regarding adjuvant chemotherapy, such as regimens used and years of administration, were not available. Complete IHC data (at least estrogen receptor [ER] and HER2) were available for 49% of samples. In the large Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) data set, OS and DSS (breast cancer-specific survival) were used and available for 99% of patients. Among the eight non-METABRIC data sets, RFS (or DFS) was used in four data sets and distant disease-free survival (or distant RFS) was used in four data sets to identify associations of each variable with outcome and was available for 94% of patients (Fig. 1). Relapse-free survival and distant relapse-free survival were combined for this analysis. All specimens were analyzed before systemic treatment. To our knowledge, none of the patients with HER2-positive tumors received trastuzumab.

All tumors, except for the GSE18229 and METABRIC data sets, in which we used the already reported PAM50 subtype calls [21], were assigned to one of five molecular subtypes of breast cancer: luminal A, luminal B, HER2-enriched, basal-like, or normal-like, using the PAM50 subtype predictor [23]. Prior to subtyping, each individual data set was properly normalized as previously described [21, 24, 25].

χ^2 tests were used to compare differences in proportions. RFS was censored at 7 years because the GSE25066 [18] data set has a maximum follow-up of 7.4 years. The Kaplan-Meier method was used to evaluate the association of categorical variables with RFS, OS, and DSS. Cox regression models were used to evaluate the association of age, alone and while controlling for other covariates, with RFS, OS, and DSS. Because of missing data, sample sizes for multivariable models with different covariates varied. The results are presented for models using all possible data (i.e., different sample sizes), but similar results were seen when running all models only on patients with complete data. All statistical analyses were conducted using SAS statistical software v9.3 (SAS Institute, Inc., Cary, NC, http://www.sas.com).

Table 1. Patient and tumor sample characteristics

Variable	All patients	Age cohort				
		21–39 years	40–49 years	50–59 years	60–69 years	70–93 years
Pam50 subtype	$n = 3,947$	$n = 335$	$n = 841$	$n = 956$	$n = 1,013$	$n = 802$
Basal-like (%)	21	44	26	22	16	9
Her2-enriched (%)	13	15	12	16	14	11
Luminal A (%)	33	18	32	33	32	39
Luminal B (%)	22	12	15	17	28	32
Normal (%)	11	11	15	12	10	9
T size[a] ($n = 3,838$)[b]		$n = 325$	$n = 813$	$n = 932$	$n = 987$	$n = 781$
T0[c]/T1 (%)	38	30	38	39	43	34
≥T2 (%)	62	70	62	61	57	66
Nodal status ($n = 3,856$)[d]		$n = 320$	$n = 810$	$n = 933$	$n = 1,003$	$n = 790$
Negative (%)	55	44	56	54	60	54
Positive (%)	45	56	44	46	40	46
Grade[e] ($n = 3,278$)[f]		$n = 283$	$n = 680$	$n = 812$	$n = 842$	$n = 661$
1 (%)	11	2	12	15	10	11
2 (%)	39	28	37	39	40	46
3 (%)	50	70	51	46	50	43
Adjuvant treatment ($n = 3,546$)[g]		$n = 285$	$n = 735$	$n = 858$	$n = 941$	$n = 727$
None (%)	32	29	38	30	32	30
Endocrine therapy (%)	36	5	14	31	48	63
Chemotherapy (%)	16	41	25	19	10	3
Both (%)	15	25	23	20	10	4
Data set by GSE series		$n = 335$	$n = 841$	$n = 956$	$n = 1,013$	$n = 802$
GSE22219 [14][h]	6%	5	6	7	7	2
GSE7849 [15][h]	2%	2	2	2	3	1
GSE2034 [16][h]	7%	9	11	6	7	5
GSE4922 [17][i]	6%	5	4	5	6	11
GSE25066 [18][h]	15%	27	24	18	10	3
GSE2603 [19][i]	2%	2	3	2	1	2
GSE2990 [20][i]	5%	4	5	5	5	3
GSE18229 [21][i]	7%	10	8	7	4	7
Total non-METABRIC (%)	50%	64	64	53	43	34
METABRIC [22] (%)	50%	36	36	47	57	66

All numbers in table are percentages unless otherwise specified. More information is available from the GEO Omnibus (http://www.ncbi.nlm.nih.gov/geo/).
[a]T1 tumors measure ≤20 mm in greatest dimension. ≥T2 tumors measure >20 mm.
[b]97% of total patients.
[c]Proportion of T0 (in situ carcinomas) is unknown.
[d]98% of total patients.
[e]Grade 1, well-differentiated; grade 2, moderately differentiated; grade 3, poorly differentiated.
[f]83% of total patients.
[g]90% of total patients.
[h]Distant disease-free (or relapse-free) survival.
[i]Disease-free (or relapse-free) survival.
Abbreviation: METABRIC, Molecular Taxonomy of Breast Cancer International Consortium.

Results

Subtype Distribution by Age

The distribution of intrinsic subtypes by age group is shown in Figure 2. The incidence of luminal tumors (luminal A and luminal B combined) increased with age ($p < .0001$), whereas the incidence of basal-like tumors decreased ($p < .0001$). In the oldest age cohort (70–93 years), basal-like and HER2-enriched, the subtypes with the worst prognosis historically among all age groups, were represented in 9% and 11% of patients, respectively. Intrinsic subtypes were compared with IHC phenotypes, and our results are consistent with previously published reports showing a modest association [6, 26]. Of the 1,940 patients with complete immunohistochemical data for ER, progesterone receptor (PR), and HER2 (Fig. 3), 76% of tumors that were triple-negative on clinical assays for ER, PR,

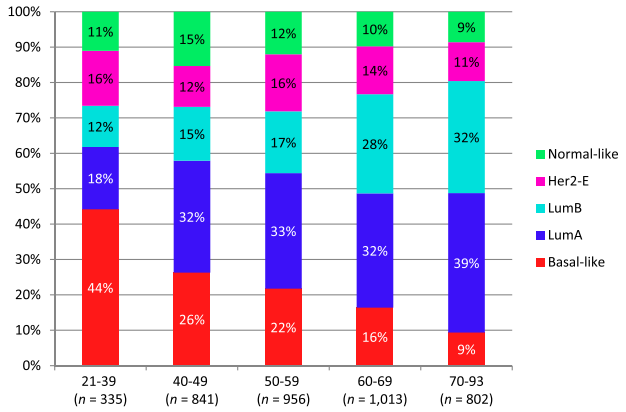

Figure 2. PAM50 intrinsic subtypes by age. The sum of the first column is 101% because of rounding.

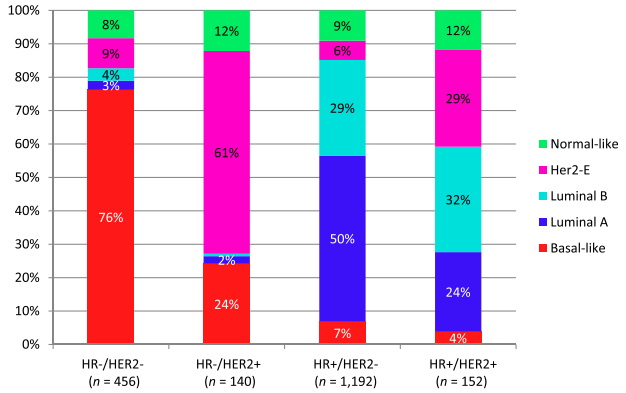

Figure 3. PAM50 intrinsic subtypes by immunohistochemical molecular subtypes for all patients. The sums of the third and fourth columns are 101% because of rounding.

and HER2 (triple-negative breast cancer [TNBC]) were basal-like. Of all the HR+/HER2− patients, 50% were luminal A and 29% were luminal B with the percentages varying across age groups ($p = .006$); 67% in the youngest age group were luminal A/B compared with 86% in the oldest age group (Fig. 4A). Conversely, the percentage of TNBC patients who were basal-like decreased with age ($p = .003$; Fig. 4B), from approximately 80% for those younger than 60 years to 70% for those 60–69 years and 57% for those 70 years and older. Of HR−/HER2+ patients, 61% were HER2-enriched and 24% were basal-like, and no differences were seen within age groups ($p = .37$). Overall, 32% of HR+/HER2+ were luminal B, and this percentage varied from approximately 20% in patients of less than 60 years to approximately 50% in patients aged 60 years and older ($p = .03$; Fig. 4C).

Outcome by Subtype and Age

Relapse-free survival was available from the eight non-METABRIC data sets, and OS and DSS were available from the large METABRIC data set (Fig. 1). RFS (Fig. 5A, 5B) and OS and DSS (Fig. 5C–5F) were examined according to subtype and age. As anticipated, the luminal A subtype had a better outcome than the other subtypes, particularly when compared with basal-like and HER2-E subtype; this relationship remained statistically significant in the 70–93-year age cohort (Fig. 5B, 5D, 5F).

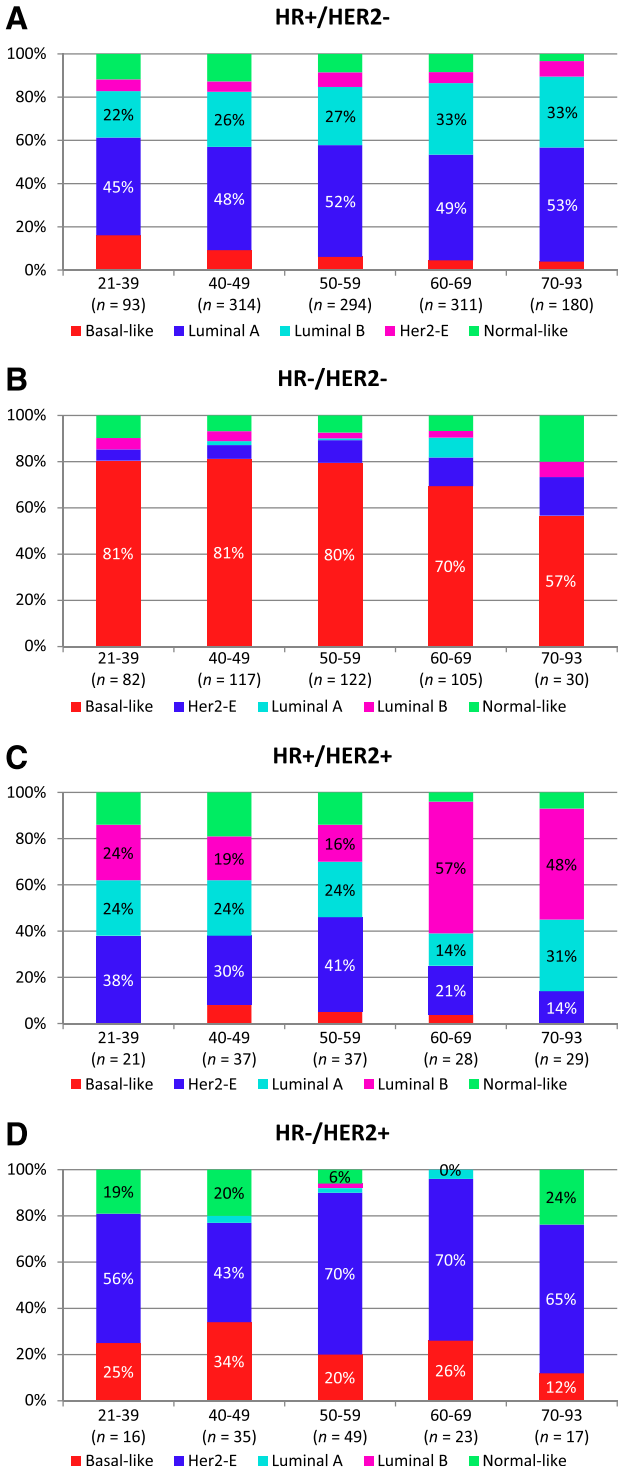

Figure 4. PAM 50 subtypes by age according to HR and HER2 phenotype. **(A):** HR+/HER2−. **(B):** HR−/HER2− ("triple-negative"). **(C):** HR+/HER2+. **(D):** HR−/HER2+.

Independent Impact of Age on Breast Cancer Outcomes

Multivariable analysis was performed using Cox regression modeling. RFS was used for identifying associations of each variable with outcome in the non-METABRIC data sets (Table 2). Age was not significantly associated with RFS after controlling for intrinsic subtype ($p = .66$); this remained true after controlling for adjuvant treatment, tumor size, nodal status, and grade as well ($p = .47$). In the METABRIC data set,

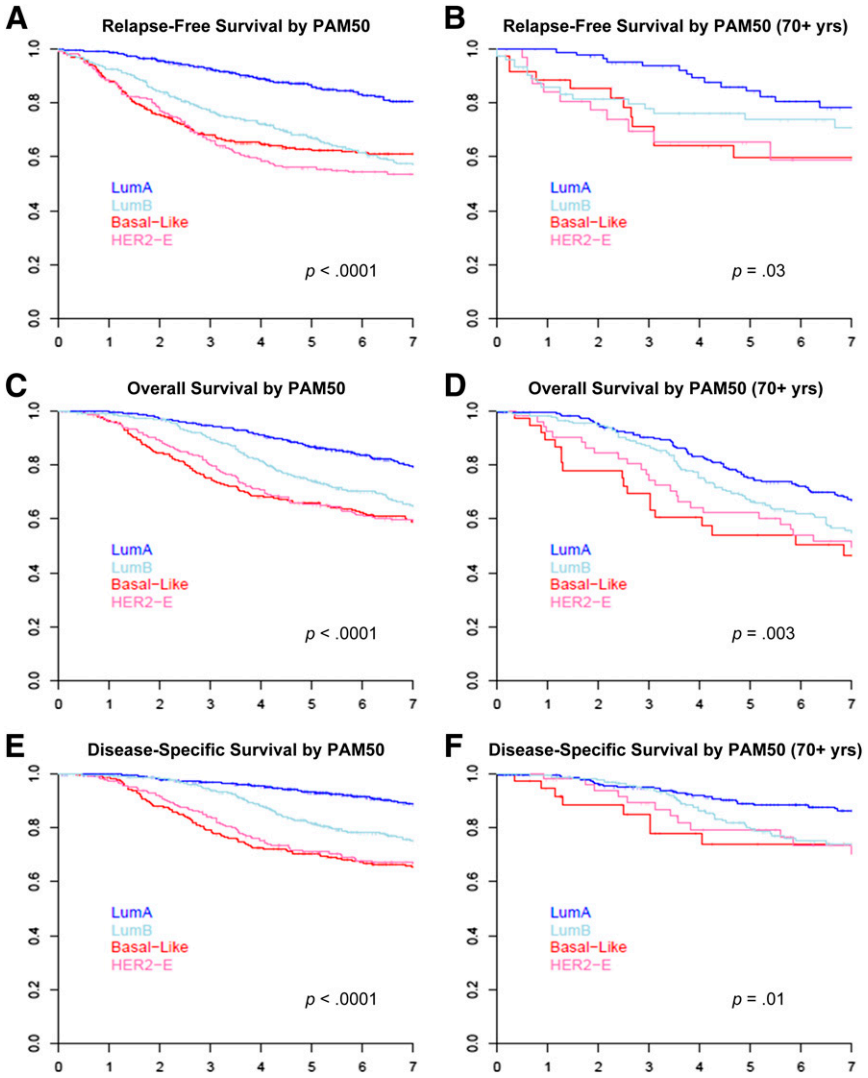

Figure 5. Outcomes according to subtype and age. Recurrence-free survival (RFS) was used as a surrogate for outcome in the non-Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) data sets. Overall survival (OS) and disease-specific survival (DSS) were used as surrogates for outcome in the METABRIC data set (see Fig. 1). Normal-like samples were excluded. **(A):** RFS by PAM50 for all age cohorts. **(B):** RFS by PAM50 for 70–93-year age cohort. **(C):** OS by PAM50 for all age cohorts. **(D):** OS by PAM50 for 70–93-year age cohort. **(E):** DSS by PAM50 for all age cohorts. **(F):** DSS by PAM50 for 70–93-year age cohort.

OS and DSS were used to identify associations of age, subtype, adjuvant treatment, tumor size, nodal status, and grade with outcome. Age was significantly associated with OS (all $p < .0001$) but not with DSS (all $p > .07$) in all models. After controlling for subtype, adjuvant treatment, tumor size, nodal status, and grade, increasing age was associated with worse OS (10-year HR 1.36 [1.25–1.48], $p < .0001$), but not DSS ($p = .21$). The significant association of age with OS persisted when similar models were run within each subtype for all but the HER2-enriched subtype ($p = .3$). The adjusted hazard ratios for death were basal-like: 1.24 (95% confidence interval [CI]: 1.05–1.46), HER2-enriched: 1.11 (95% CI: 0.91–1.37), luminal A: 1.78 (95% CI: 1.49–2.11), and luminal B: 1.29 (95% CI: 1.09–1.52).

Discussion

The incidence of more favorable subtypes as defined by PAM50 increases with age and is similar to changes in phenotype with age shown by IHC [27, 28]. In this series, luminal A tumors accounted for 40% of breast cancers in patients older than 70 years of age, whereas basal-like and HER2-enriched subtypes were the least common (9% and 11%, respectively). The 20% of elders in this series with basal-like and HER2-enriched subtypes indicates that many elders have aggressive breast cancers as defined by the PAM50 subtype predictor. As expected, the luminal A subtype had better outcomes than the more aggressive luminal B, basal-like and HER2-enriched subtypes among all age groups, as well as in the elderly population (Fig. 5). Of note, compared with younger patients, older patients with triple-negative breast cancer determined by IHC were less likely to have the basal-like subtype, whereas those older patients with HR+/HER2+ (triple-positive) cancer determined by IHC were much more likely to have tumors with luminal B subtypes. This may prove to have major implications for treatment selection in older patients as more trials of subtype and outcomes with adjuvant therapy are reported.

Table 2. Multivariable time to event analyses for the relationship of age with RFS, OS, and DSS, controlling for covariates

	Model covariates		
Variable	**Age, subtype**	**Age, subtype, adjuvant treatment**	**Age, subtype, adjuvant treatment, T size, nodal status, grade**
RFS (non-METABRIC)			
Number of patients	1,842	1,464	886
HR (95% CI)	0.98 (0.92–1.06)	1.01 (0.93–1.10)	1.05 (0.92–1.19)
p value	.66	.86	.47
OS (METABRIC)			
Number of patients	1,965	1,965	1,856
HR (95% CI)[a]	**1.22 (1.14–1.32)**	**1.41 (1.30–1.53)**	**1.36 (1.25–1.48)**
p value[a]	**<.0001**	**<.0001**	**<.0001**
DSS (METABRIC)			
Number of patients	1,965	1,965	1,856
HR (95% CI)	0.95 (0.87–1.04)	1.09 (0.99–1.21)	1.07 (0.97–1.18)
p value	.24	.07	.21

The age variable used for multivariable analysis is continuous, and the unit of each hazard ratio is 10 years (i.e., for each 10-year increase in age).
[a]Bold type indicates $p < .05$.
Abbreviations: CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; METABRIC, Molecular Taxonomy of Breast Cancer International Consortium; OS, overall survival; RFS, recurrence-free survival.

Age was not significantly associated with RFS or DSS, but it was associated with OS. This relationship between advancing age and poorer OS is almost certainly caused by women dying of non-breast cancer-related causes [29]. Similar findings were noted in a retrospective analysis of four large cancer and leukemia group B randomized adjuvant chemotherapy trials in women with breast cancer in which relapse-free survival benefits were similar among age groups but overall survival was poorer as age increased; older patients were more likely to die of non-breast cancer-related causes [30]. The available data suggest that tumor biology and treatment, as driven by intrinsic subtype and not age, is the main determinant of outcome. In the future, genomic subtyping may better define cancer prognosis and potential treatment benefit. Interestingly and at the other end of the age spectrum, this finding is consistent with previously published reports from our group illustrating that age alone does not appear to provide an additional layer of biologic knowledge above that of breast cancer subtype and grade among young women diagnosed with breast cancer [31].

Although tumor subtypes as defined by gene expression are still are not widely used to select treatment, an increasing number of assays based on tumor profiling are now commercially available and can be helpful in treatment selection [32, 33]. The PAM50 gene signature assay used in this analysis has now been approved by the Food and Drug Administration as a prognostic indicator for 10-year distant recurrence-free survival in postmenopausal women with hormone receptor-positive stage I and II breast cancer or patients with involvement of one to three lymph nodes who are to be treated with adjuvant endocrine therapy (Prosigna; NanoString Technologies, Seattle, WA, http://www.nanostring.com). As yet, none of these assays provide treatment recommendations based on genetically defined subtypes, but it is likely that clinical trials will soon show that treatment choices based on intrinsic subtypes will prove superior to decisions based on hormone receptor and HER2 status [33–37]. A French trial, ASTER 70s for women aged 70 and older and currently in progress, is using high genomic grade as a basis for randomization for chemotherapy or not (ERICO11/PACS10-NCT01564056).

A major limitation of this study is the heterogeneity of the patients in the different data sets, which may limit how representative these patients are of the general population. However, the large number of patients among the various subtypes suggest that our findings are likely to be confirmed as newer and larger data sets become available. Another major limitation of this study is the lack of treatment detail, such as endocrine or chemotherapy type, schedule, and duration; however, the data are still provocative in that age had no significant effect on either RFS or DSS once we controlled for subtype. However, our results, based on a large sample size, strongly suggest that irrespective of age, patients with similar intrinsic subtypes have similar RFS and DSS survival outcomes. This has major clinical implications and suggests that elders with high-risk intrinsic subtypes, with a lack of significant comorbidities, and with an estimated survival exceeding 5 years should be considered for standard-of-care therapies that would typically include chemotherapy—and for some chemotherapy and anti-HER2-directed therapy [38].

Conclusion

Although comorbidities and performance status are important considerations in treatment planning, the aging process is heterogeneous, and an individualized approach is necessary in elderly patients. Estimated survival, and not chronological age, should be the major factor for clinicians to consider when recommending systemic and local treatments to older patients. Tools are now available to help treating physicians accurately estimate life expectancy to help guide these important treatment decisions (see http://www.eprognosis.org and [39]). Finally, given the underrepresentation of elders in clinical trials [40], older women with breast cancer should be included in studies exploring the role of breast cancer subtypes

on treatment selection and outcomes, so that this large and increasing segment of the breast cancer population can reap the rewards of ongoing, cutting-edge research.

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Final approval of manuscript: Emily O. Jenkins, Allison M. Deal, Carey K. Anders, Charles M. Perou, Lisa A. Carey, Hyman B. Muss

Disclosures

Carey K. Anders: Merrimack, Sanofi, Bipar, GERON, to-BBB, Genentech/Roche (C/A), Novartis, BiPAR, Sanofi, BMS, GERON, to-BBB (RF); **Aleix Prat:** Nanostring Technologies (C/A); **Charles M. Perou:** Bioclassifier LLC and University Genomics (E, IP, OI); **Lisa A. Carey:** GSK, Genentech (RF). The other authors indicated no financial relationships.

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References

1. Altekruse SFKC, Krapcho M, Neyman N et al. SEER Cancer Statistics Review, 1975–2007. Bethesda, MD: National Cancer Institute, 2010.

2. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst 2000;92:550–556.

3. Durbecq V, Ameye L, Veys I et al. A significant proportion of elderly patients develop hormone-dependant "luminal-B" tumours associated with aggressive characteristics. Crit Rev Oncol Hematol 2008;67:80–92.

4. Walter LC, Covinsky KE. Cancer screening in elderly patients: A framework for individualized decision making. JAMA 2001;285:2750–2756.

5. Bastien RR, Rodriguez-Lescure A, Ebbert MT et al. PAM50 breast cancer subtyping by RT-qPCR and concordance with standard clinical molecular markers. BMC Med Genomics 2012;5:44.

6. Nielsen TO, Parker JS, Leung S et al. A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. Clin Cancer Res 2010;16: 5222–5232.

7. Prat A, Cheang MC, Martin M et al. Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal a breast cancer. J Clin Oncol 2013;31: 203–209.

8. Ellis MJ, Suman VJ, Hoog J et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: Clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype–ACOSOG Z1031. J Clin Oncol 2011; 29:2342–2349.

9. Anders CK, Hsu DS, Broadwater G et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. J Clin Oncol 2008;26: 3324–3330.

10. Dowsett M, Sestak I, Lopez-Knowles E et al. Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. J Clin Oncol 2013;31:2783–2790.

11. Cheang MC, Voduc D, Bajdik C et al. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res 2008;14:1368–1376.

12. Ellis MJ, Ding L, Shen D et al. Whole-genome analysis informs breast cancer response to aromatase inhibition. Nature 2012;486:353–360.

13. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61–70.

14. Buffa FM, Camps C, Winchester L et al. MicroRNA-associated progression pathways and potential therapeutic targets identified by integrated mRNA and microRNA expression profiling in breast cancer. Cancer Res 2011;71: 5635–5645.

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

16. Wang Y, Klijn JG, Zhang Y et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. Lancet 2005;365: 671–679.

17. Ivshina AV, George J, Senko O et al. Genetic reclassification of histologic grade delineates new clinical subtypes of breast cancer. Cancer Res 2006; 66:10292–10301.

18. Hatzis C, Pusztai L, Valero V et al. A genomic predictor of response and survival following taxane-anthracycline chemotherapy for invasive breast cancer. JAMA 2011;305:1873–1881.

19. Minn AJ, Gupta GP, Siegel PM et al. Genes that mediate breast cancer metastasis to lung. Nature 2005;436:518–524.

20. Sotiriou C, Wirapati P, Loi S et al. Gene expression profiling in breast cancer: Understanding the molecular basis of histologic grade to improve prognosis. J Natl Cancer Inst 2006;98: 262–272.

21. Prat A, Parker JS, Karginova O et al. Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. Breast Cancer Res 2010;12:R68.

22. Curtis C, Shah SP, Chin SF et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature 2012;486:346–352.

23. Parker JS, Mullins M, Cheang MC et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol 2009;27:1160–1167.

24. Perou CM, Parker JS, Prat A, Ellis MJ, Bernard PS. Clinical implementation of the intrinsic subtypes of breast cancer. Lancet Oncol 2010;11:718–719.

25. Prat A, Parker JS, Fan C, Perou CM. PAM50 assay and the three-gene model for identifying the major and clinically relevant molecular subtypes of breast cancer. Breast Cancer Res Treat 2012;135: 301–306.

26. Prat A, Perou CM. Deconstructing the molecular portraits of breast cancer. Mol Oncol 2011;5: 5–23.

27. Morrison DHRD, Rahardja D, King E et al. Tumour biomarker expression relative to age and molecular subtypes of invasive breast cancer. Br J Cancer 2012;107:382–387.

28. Ihemelandu CULL, Leffall LD Jr., Dewitty RL et al. Molecular breast cancer subtypes in premenopausal and postmenopausal African-American women: Age-specific prevalence and survival. J Surg Res 2007;143:109–118.

29. Ring A, Sestak I, Baum M et al. Influence of comorbidities and age on risk of death without recurrence: A retrospective analysis of the arimidex, tamoxifen alone or in combination trial. J Clin Oncol 2011;29:4266–4272.

30. Muss HB, Woolf S, Berry D et al. Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. JAMA 2005;293: 1073–1081.

31. Anders CKFC, Fan C, Parker JS et al. Breast carcinomas arising at a young age: Unique biology or a surrogate for aggressive intrinsic subtypes? J Clin Oncol 2011;29:e18–e20.

32. Paik S, Tang G, Shak S et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24:3726–3734.

33. Drukker CA, van Tinteren H, Schmidt MK et al. Long-term impact of the 70-gene signature on breast cancer outcome. Breast Cancer Res Treat 2014;143:587–592.

34. Prat A, Bianchini G, Thomas M et al. Research-based PAM50 subtype predictor identifies higher responses and improved survival

outcomes in HER2-positive breast cancer in the NOAH study. Clin Cancer Res 2014;20:511–521.

35. Dunbier AK, Anderson H, Ghazoui Z et al. Association between breast cancer subtypes and response to neoadjuvant anastrozole. Steroids 2011;76:736–740.

36. Esserman LJ, Berry DA, Cheang MC et al. Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: Results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). Breast Cancer Res Treat 2012;132:1049–1062.

37. Martín M, Prat A, Rodríguez-Lescure A et al. PAM50 proliferation score as a predictor of weekly paclitaxel benefit in breast cancer. Breast Cancer Res Treat 2013;138:457–466.

38. Jones EL, Leak A, Muss HB. Adjuvant therapy of breast cancer in women 70 years of age and older: Tough decisions, high stakes. Oncology (Williston Park) 2012;26:793–801.

39. Yourman LCLS, Lee SJ, Schonberg MA et al. Prognostic indices for older adults: A systematic review. JAMA 2012;307:182–192.

40. Lewis JHKM, Kilgore ML, Goldman DP et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003;21:1383–1389.

For Further Reading:

Hyman Muss, Javier Cortes, Linda T. Vahdat et al. Eribulin Monotherapy in Patients Aged 70 Years and Older With Metastatic Breast Cancer. ***The Oncologist*** 2014;19:318–327.

Implications for Practice:

Although metastatic breast cancer (MBC) affects women of all ages, the use of sequential single-agent chemotherapy treatment in patients with hormone-refractory MBC can be particularly challenging in the elderly because of patient comorbidities and functional deficits. There is a major unmet need to find new, effective therapies with favorable safety profiles for older patients. This exploratory analysis of pooled data from selected older patients with pretreated MBC in phase II and III clinical trials showed similar efficacy and tolerability for eribulin among patients who were 70 years of age or older when compared with younger patient subgroups. These data indicate that eribulin may be an effective option for selected older patients with MBC.