Is Age Still the Deciding Factor? Commentary on “The Effect of Age on Delay in Diagnosis and Stage of Breast Cancer” by Partridge et al.

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Young breast cancer patients face multiple different challenges when diagnosed and when undergoing treatment for breast cancer than do postmenopausal patients. Very young breast cancer patients, especially those aged <35 years, have been described in multiple reports to have a worse prognosis [1–3]. Additionally, because women are not routinely recommended to consider initiating screening mammography until their 40s or 50s, a younger woman is more likely to develop a cancer at an advanced stage and to be diagnosed because of the onset of symptoms. There remains concern that a delay in diagnosis of breast cancer in a younger woman is one of the contributing factors to these worse outcomes in young breast cancer patients.

It was estimated by the American Cancer Society that ~5% of cases of breast cancer will be diagnosed each year in women aged <40 years [4]. Several case series have demonstrated worse outcomes in younger breast cancer patients. Nixon et al. [1] reported on 107 patients aged <35 years with either stage I or stage II breast cancer and compared them with their older counterparts. The younger patients were found to have a statistically significant greater recurrence risk and risk for developing distant metastatic disease. Kroman et al. [3] reported that younger women who had node-negative cancers or tumors <2 cm were significantly more likely to die from their cancer if they did not receive systemic adjuvant therapy. However, this effect was mitigated if they received cytotoxic therapy. Race may also play a factor in the diagnosis of breast cancer in young women. Black women have a twofold higher chance of being diagnosed at <35 years of age than white females. In addition, black women have higher presenting stages and higher

mortality rates from breast cancer in the U.S. than white women [5, 6].

When looking at the underlying biology of younger women with breast cancer, the majority of reports show a higher rate of hormone receptor–negative tumors [1–3] than in postmenopausal breast cancer patients. When evaluating very low-risk disease, such as node-negative tumors that are ≤1 cm, age was identified as an independent risk factor for the recurrence-free survival interval. This was more significant in women with human epidermal growth factor receptor (HER)-2⁺ and hormone receptor–positive tumors and was not demonstrated to be significant in patients with triple-negative tumors [7]. Additionally, Anders et al. [8] used microarray data from 784 women with early-stage breast cancers, again demonstrating lower percentages of hormone receptor positivity and higher grade tumors. There were 367 gene sets found to significantly differentiate the tumors arising in younger women from those in older women. Examples of gene sets that were differentiated by age included those encoding epidermal growth factor receptor and mammalian target of rapamycin as well as *BRCA1*, among many others [8]. This information was particularly intriguing and hypothesis generating regarding combination therapy that could take advantage of such pathways in younger breast cancer patients. Therefore, the question remains, is it truly the age of the patient herself that is the underlying cause of this described worse prognosis or is age just a surrogate marker for more aggressive tumor subtypes that occur more frequently in younger patients?

Another confounding factor in this debate is the question surrounding a delay in diagnosis. There have been conflicting reports on whether or not a delay in diagnosis and a delay from

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the time of first symptom to the time of treatment initiation influence breast cancer prognosis. One large systematic review demonstrated that delays of 3–6 months from the time of diagnosis to the time of initiation of treatment were associated with a statistically significant lower 5-year survival rate [9]. However, it was noted that, in the included studies that did account for stage, a delay was not associated with a worse overall survival outcome. Younger patients who had not previously been designated to be high risk and had not undergone earlier screening would be expected to present with more advanced stages of disease than postmenopausal women whose cancer was diagnosed on screening mammography. In the most recent screening mammography recommendations by the U.S. Prevention Services Task Force, mammogram recommendations were changed to start after age 49, to increase the interval between screenings, and to individualize the decision for women in their 40s [10]. This change was a result of the lack of available randomized data showing a lower mortality rate with screening in this age group, although recently Hellquist et al. [11] used data collected from the Swedish mammography screening program to evaluate their experience with screening women aged 40–49 years and showed a relative risk for mortality for those who underwent screening of 0.71, which was statistically significant, and estimated that 1,252 women needed to be screened to save one life. There currently are no recommendations for screening mammography in women aged <40 years unless they have been identified to be at high risk for developing breast cancer, such as women with a hereditary predisposition to develop breast cancer, such as patients with *BRCA1* or *BRCA2* mutations. Therefore, as routine strategies for screening are currently evaluating women aged >40 years, except in special populations, younger women who develop breast cancer are more likely to present with clinical symptoms.

In the current retrospective study by Partridge et al. [12], the authors use the National Comprehensive Cancer Center Network database to evaluate 21,818 women with breast cancer, stages I–IV, of whom 2,445 were aged ≤40 years. The purpose of the study was to evaluate if age alone was considered an independent risk factor for a delay from the time of the first symptom to the time that the woman sought treatment and was initially diagnosed with breast cancer. This study therefore asks a slightly different question: does age factor into actually seeking evaluation and undergoing diagnostic procedures? Additionally, the authors evaluated other socioeconomic factors such as race, education, employment status, and type of initial sign or symptom. When evaluating age as a factor in delay to breast cancer diagnosis, age

≤40 years old was initially found to be associated with a >60-day delay in diagnosis—odds ratio (OR), 1.52; 95% confidence interval (CI), 1.39–1.67; $p < .0001$. However, when the multivariate model was adjusted for the initial sign or symptom, there was no longer a statistically significant difference. Also in multivariate modeling, those women who had an initial sign or symptom had a significantly greater association with a >60-day delay in diagnosis (OR, 3.31; 95% CI, 3.08–3.56). Women with screening-detected tumors were more likely to be diagnosed with an earlier stage of breast cancer (64% of women diagnosed using screening were diagnosed with stage I tumors, compared with 28% of women who presented with an initial sign or symptom).

This was a very well-conducted study using a very detailed database that spans several cancer centers throughout the U.S. The study has the expected limitations of a retrospective database study, including recall bias and the lack of information regarding previous screenings and whether or not patients had been identified as having a high risk for developing breast cancer. Also, women who were included had been referred to or sought treatment at a large comprehensive cancer center and may not reflect presentation patterns elsewhere. It would be interesting to note if there is any difference in time to delay not by age but by tumor biology. If a tumor has a more aggressive growth pattern, such as triple receptor-negative or HER-2⁺ tumor, will that influence more substantially the time to diagnosis? For this analysis, the authors did not include tumor receptor information in their modeling. Given the understanding of these inherent limitations, the study does provide insight as to whether or not age is a barrier to seeking treatment and being diagnosed with breast cancer.

The failure of age to be consistently associated with a delay in diagnosis of breast cancer in this study when controlling for stage of disease leads back to the original concern: is it age or is it biology? If a delay does not appear to be the significant factor for young breast cancer patients and thus not likely to be the underlying cause of worse outcomes, the underlying biology of the disease that commonly presents in younger women should continue to be the main target. It will also be important to identify those women diagnosed at a young age with less biologically aggressive tumors who should be spared systemic therapy. In order to improve our therapies as well as to improve patient outcomes, we need to continue to develop strategies for identifying women at higher risk for developing breast cancer, for improving knowledge on the importance of family history, for improving genetic risk assessment, for identifying known and yet to be identified hereditary cancer syndromes, and, finally, for personalizing screening, prevention, and treatment strategies.

REFERENCES

1. Nixon AJ, Neuberger D, Hayes DF et al. Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. *J Clin Oncol* 1994;12:888–894.
2. Xiong Q, Valero V, Kau V et al. Female patients with breast carcinoma age 30 years and younger have a poor prognosis: the M.D. Anderson Cancer Center experience. *Cancer* 2001;92:2523–2528.
3. Kroman N, Jensen MB, Wohlfahrt J et al. Factors influencing the effect of age on prognosis in breast cancer: Population based study. *BMJ* 2000;320:474–478.
4. American Cancer Society. Breast Cancer Facts and Figures 2011–2012. Available at <http://www.cancer.org/acs/groups/content/@epidemiologyandprevention/documents/2012/acs-epidemiologyandprevention-breastcancer-facts-and-figures-2011-2012.pdf>, accessed March 23, 2012.
5. Newman LA, Mason J, Cote D et al. African-American ethnicity, socioeconomic status, and breast cancer survival: A meta-analysis of 14 studies involving over 10,000 African-American and 40,000 white American patients with carcinoma of the breast. *Cancer* 2002;94:2844–2854.
6. De Jesus MA, Fujita M, Kim KS et al. Retrospective analysis of breast cancer among young African-American females. *Breast Cancer Res Treat* 2003;78:81–87.
7. Theriault RL, Litton JK, Mittendorf EA et al. Age and survival estimates in patients who have node-negative T1ab breast cancer by breast cancer subtype. *Clin Breast Cancer* 2011;11:325–331.
8. 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.

9. Richards MA, Smith P, Ramirez AJ et al. The influence on survival of delay in the presentation and treatment of symptomatic breast cancer. *Br J Cancer* 1999;79:858–864.

10. U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;151:716–726.

11. Hellquist BN, Duffy SW, Abdsaleh S et al. Effectiveness of population-based service screening with

mammography for women ages 40 to 49 years: Evaluation of the Swedish Mammography Screening in Young Women (SCRY) cohort. *Cancer* 2011;117:714–722.

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

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