Breast Cancer in Women Aged 25 Years and Younger

Constantine Dimitrakakis, MD, PhD, Alexandra Tsigginou, MD, PhD, Flora Zagouri, MD, PhD, Spyros Marinopoulos, MD, PhD, Theodoros N. Sergentanis, MD, PhD, Antonis Keramopoulos, MD, PhD, Paraskevi Liakou, MD, PhD, George C. Zografos, MD, PhD, Christos A. Papadimitriou, MD, PhD, Meletios-Athanassios Dimopoulos, MD, PhD, and Aris Antsaklis, MD, PhD

OBJECTIVE: To evaluate breast cancer characteristics in women aged 25 years and younger.

METHODS: This was a retrospective, nested, within-cases matched study. The study design was based on a two-phase protocol. In the first phase, stage, grade, histologic subtype, estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status were compared between 28 patients (aged 25 years and younger) and 685 older premenopausal women (aged older than 25 years) with breast cancer. The second phase aimed to determine whether young patients exhibited worse prognosis when compared with older premenopausal women.

RESULTS: Young patients presented at a more advanced stage (P=.012) and exhibited a higher grade (P=.018). No significant differences were noted regarding histologic subtype, estrogen receptor, and progesterone receptor status. Genetic testing for *BRCA1* and *BRCA2* mutations was performed in 12 of 28 young patients and mutations were found in 25% of them. Moreover, young women presented poorer overall survival (hazard ratio [HR] 4.30, 95% confidence interval [CI] 1.09–17.03) than their older counterparts, matched by histologic subtype, stage, and grade; a similar pattern was noted regarding relapse-free survival (HR 8.28, 95% CI 2.24–30.60).

CONCLUSION: Breast cancer diagnosis in women aged 25 years and younger is uncommon; however, these patients present at a more advanced stage, with a higher grade, and exhibit poorer survival.

(Obstet Gynecol 2013;121:1235–40)
DOI: 10.1097/AOG.0b013e318291ef9a

LEVEL OF EVIDENCE: II

Breast cancer represents the second most common cause of female cancer-related mortality, with an anticipated rate of death 24.3 per 100,000 women in Europe.[1] These figures remain rather high despite the continuously decreasing incidence and mortality rates. According to the Surveillance, Epidemiology, and End Results database, the reported median age for breast cancer diagnosis is 61 years, with 0% of diagnosed cases in women younger than age 20 years, 1.8% of diagnosed cases in women between ages 20 and 34 years, 3.4% of diagnosed cases in women between ages 35 and 54 years, and 65.8% of diagnosed cases in women older than age 55 years.[2] Therefore, breast cancer diagnosis in women aged 25 years and younger is extremely uncommon.

Young women, in the first decade after adolescence, may confront breast problems that are mostly connected to steroid hormonal imbalance or developmental neoplasms such as fibroadenomas that are abundantly benign and, in many cases, self-confined. However, malignancies that appear during adolescence are mostly nonepithelial, and epithelial cancers in females become predominant after the age of 25 years.[3] Breast cancer in the early 20s is extremely uncommon; thus, when a young woman presents with a breast mass, there is reduced awareness about breast cancer diagnosis.[4]

Although breast cancer is a well-studied tumor involving advanced experience in diagnosis, treatment, and management, young patients may face different

From the Departments of Obstetrics and Gynecology and Clinical Therapeutics, Alexandra Hospital, Medical School, University of Athens, and the 1st Propaedeutic Surgical Department, Hippocrateio Hospital, Medical School, University of Athens, Athens, Greece.

Corresponding author: Flora Zagouri, MD, PhD, Department of Clinical Therapeutics, Alexandra Hospital, University of Athens, Vas Sofias Ave and Lourou Str, Athens 11521, Greece; e-mail: florazagouri@yahoo.co.uk.

Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/13

challenges. Despite limited data, there is evidence of a more aggressive nature of the disease in young patients.[4,5] However, treatment in the aforementioned subpopulation mostly follows the guidelines for the older patients, without evaluating complications regarding premature menopause choice, fertility and childbearing, body image, and long-term side effects of therapy.

Breast cancer diagnosis in young women, although uncommon, is a reality. Because the experience is limited, proper management appears challenging. This is a retrospective, nested, within-cases matched study that aimed to evaluate breast cancer characteristics in women aged 25 years and younger.

MATERIALS AND METHODS

The study population comprises all invasive breast cancer cases diagnosed and treated in the 1st Department of Obstetrics and Gynecology, Alexandra Hospital, and in the 1st Propaedeutic Surgical Department, Hippocrateio Hospital, University of Athens, Athens, Greece, from 1991 to 2012. The term "young" that has been adopted throughout the article refers to patients aged 25 years and younger. We used the age of 25 years as the cut-off point because, according to cancer registry data, the shift from a predominance of non-epithelial cancers to a predominance of epithelial cancers in women occurs at this age.[3] Moreover, until age 25 years, it is the first decade after adolescence. Early onset of breast cancer occurring among adolescents and young adults is more likely related to genetic predisposition and exposure to risk factors early in life as compared with cancers among the elderly.[3]

The study design is based on a two-phase protocol. The first phase aimed to elucidate whether breast cancer in young patients exhibits special features when compared with cancer cases among older premenopausal women. To this end, stage, grade, histologic subtype, estrogen receptor status, progesterone receptor (PR) status, and human epidermal growth factor receptor 2 status were compared between 28 young patients and 685 older premenopausal women treated for breast cancer (premenopausal defined at diagnosis). Pearson χ^2 tests were appropriately performed to assess the differences between the two groups.

The second phase aimed to determine whether young patients exhibited worse prognosis when compared with older premenopausal cases. To overcome the potential confounding role of stage, grade, or other features, a nested 1:1 matched study was designed within our study population. Specifically, 23 young patients were included in the nested study because 4 of 28 were lost during follow-up, within several weeks after diagnosis, and one patient with metaplastic leiomyosarcoma had to be excluded post hoc to obtain a clearer picture of epithelial breast cancer. Moreover, no pure ductal carcinoma in situ cases were identified in the study population; hence, cases of ductal carcinoma in situ were excluded from the control group. Consequently, 23 premenopausal women with breast cancer aged older than 25 years matched for histologic subtype, stage, grade, type of surgery, radiotherapy, and chemotherapy were randomly selected from the total pool of 685 older patients to minimize the effect of the aforementioned known confounders. Multivariate Cox regression analysis was performed to assess whether breast cancer–specific survival in young patients differs from that in older premenopausal women. Censoring date was June 30, 2012; 52.2% of the total study sample (24/46 women) were followed-up for more than 5 years. Separate analyses were performed regarding overall (breast cancer–specific) and relapse-free survival, adjusting for stage, estrogen receptor status, grade, and year of diagnosis. In addition, Kaplan-Meier survival curves were estimated for the graphic presentation of the results.

Statistical analysis was performed using STATA 11.1 statistical software. The study was approved by the Institutional Review Board of Alexandra Hospital, Medical School, University of Athens, Athens, Greece, and Hippocrateio Hospital, Medical School, University of Athens, Athens, Greece.

RESULTS

Twenty-eight young patients with a breast cancer diagnosis were identified in our database. The mean age of these young patients was 24.3 years (standard deviation [SD] 0.9, range 22–25). The mean age of the 685 older premenopausal women was 44.1 years (SD 6.2, range 26–55). Descriptive characteristics of the study population in the first phase of the study are presented in Table 1. Young women presented at a more advanced stage (χ^2 with 1 degree of freedom for trend=6.37, P=.012); indeed, 35.7% of young women had stage III and 10.7% had stage IV, whereas the respective frequencies for older premenopausal women were 22.8% and 2.8%. This pattern also was reflected in the differences regarding tumor size (P=.030) and nodal status (P=.009), as expected. Young women exhibited higher grade (χ^2 with 1 degree of freedom for trend=5.57; P=.018), with 75.0% of them having grade 3 whereas only 51.8% of older premenopausal women had grade 3. However, no significant differences were noted regarding histologic subtype (P=.676, Fisher exact test), estrogen receptor status (χ^2 with 1 degree of freedom=1.33;

Table 1. Baseline Characteristics From the First Phase of the Study

Categorical Variable	Premenopausal Cases (Age Older Than 25 y)	Young Cases (Age 25 y and Younger)	*P*
Stage			.012*
I	224 (32.7)	6 (21.4)	
II	286 (41.7)	9 (32.1)	
III	156 (22.8)	10 (35.7)	
IV	19 (2.8)	3 (10.7)	
Tumor size			.030†
T1	345 (50.4)	8 (28.6)	
T2	210 (30.7)	14 (50.0)	
T3	104 (15.2)	3 (10.7)	
T4	21 (3.1)	3 (10.7)	
Tx	5 (0.7)	0 (0.0)	
Nodal status			.009†
N0	368 (53.7)	11 (39.3)	
N1	164 (23.9)	4 (14.3)	
N2	53 (7.7)	4 (14.3)	
N3	89 (13.0)	6 (21.4)	
Nx	11 (1.6)	3 (10.7)	
Grade			.018*
1	79 (11.5)	1 (3.6)	
2	251 (36.7)	6 (21.4)	
3	355 (51.8)	21 (75.0)	
Histologic subtype			.676†
Invasive ductal	564 (82.3)	22 (78.6)	
Invasive lobular	79 (11.5)	4 (14.3)	
Other	42 (6.1)	2 (7.1)	
Estrogen receptor status			.249‡
Negative	268 (39.1)	14 (50.0)	
Positive	417 (60.9)	14 (50.0)	
Progesterone receptor status			.216‡
Negative	310 (45.3)	16 (57.1)	
Positive	375 (54.7)	12 (42.9)	
Human epithelial growth receptor 2 status			.785†
Negative	585 (85.4)	25 (89.3)	
Positive	100 (14.6)	3 (10.7)	
Surgery			.605‡
Modified radical mastectomy	213 (31.1)	10 (35.7)	
Lumpectomy and lymph node dissection	472 (68.9)	18 (64.3)	
Radiation therapy			.331†
Yes	621 (90.7)	24 (85.7)	
No	64 (9.3)	4 (14.3)	
Chemotherapy			.207†
Anthracyclin-based	101 (14.7)	2 (7.1)	
Taxane-based	38 (5.6)	1 (3.6)	
Anthracyclin-based and taxane-based	433 (63.2)	24 (85.7)	
Other	52 (7.6)	1 (3.6)	
No	61 (8.9)	0 (0.0)	

Data are n (%) unless otherwise specified.
* χ^2 test for trend.
† Fisher exact test.
‡ Pearson χ^2 test.

P=.249), PR status (χ^2 with 1 degree of freedom=1.53; *P*=.216), and human epidermal growth factor receptor 2 status (*P*=.785, Fisher exact test).

Family history of breast or ovarian cancer was present in 4 of 28 young patients (14.3%) and in 132 of 685 premenopausal patients (19.3%); the difference was not statistically significant (*P*=.630, Fisher exact test). Genetic testing for *BRCA1* and *BRCA2* mutations was performed in 12 of 28 young patients, and mutations were found three of them (25%), whereas *BRCA1* and *BRCA2* mutations were found in 31 premenopausal patients.

The results of the second phase of the study (nested, within-cases matched study) are presented in Table 2. Among the 28 young patients, four were lost to follow-up some weeks after diagnosis. As a result, the analysis was based on 23 patients (19 with invasive ductal carcinomas, three with invasive lobular carcinomas, and one with medullary carcinoma).

Figure 1 presents the Kaplan-Meier overall survival curves for young and older premenopausal women with breast cancer (log-rank χ^2 with 1 degree of freedom=3.88; *P*=.048). Relapse was distant in all 13 young patients whose disease relapsed during the follow-up period; the matched older premenopausal women presented with distant recurrence in six and with distant as well as local recurrence in one.

During the multivariate analysis adjusted for stage, estrogen receptor status, grade, and year of diagnosis, young women presented poorer overall survival (hazard ratio 4.30, 95% confidence interval 1.09–17.03) than their matched older counterparts; a similar pattern was noted regarding relapse-free survival (hazard ratio 8.28, 95% confidence 2.24–30.60).

Table 2. Multivariate Cox Regression Analysis for Overall and Relapse-Free Survival From the 1:1 Matched-Case Phase of the Study

Variable	Category or Increment	HR (95% CI)	*P*
Analysis of overall survival			
Younger age (y)	Older than 25 compared with 25 or younger	4.30 (1.09–17.03)	.038
Stage	1-level increase	3.98 (1.64–9.65)	.002
Estrogen receptor status	Positive compared with negative	0.69 (0.21–2.28)	.543
Grade	1-level increase	0.89 (0.21–3.84)	.878
Year of diagnosis	1-year increase	1.00 (0.88–1.12)	.948
Analysis of relapse-free survival			
Younger age (y)	Older than 25 compared with 25 or younger	8.28 (2.24–30.60)	.002
Stage	1-level increase	5.28 (2.29–12.16)	<.001
Estrogen receptor status	Positive compared with negative	1.19 (0.41–3.42)	.747
Grade	1-level increase	1.25 (0.34–4.64)	.738
Year of diagnosis	1-year increase	0.98 (0.89–1.07)	.593

HR, hazard ratio; CI, confidence interval.

DISCUSSION

This is a retrospective, nested, within-cases matched study showing that young women with breast cancer present at a more advanced stage, with higher grade, and exhibit poorer overall survival. This observation is in accordance with accumulating data in the literature in premenopausal patients.[6,7] More specifically, younger age during breast cancer occurrence has been considered as an independent adverse prognostic factor in premenopausal women.[8] Furthermore, according to our data, it seems that breast cancer in young women is associated with unfavorable characteristics, eg, higher grade. So, is the aggressive natural history[5] of the disease a reality? Is the common belief true? Our finding is in accordance with the observation that breast cancer in premenopausal women is correlated with tumors of higher grade, higher proliferation indexes, and poorer hormonal receptor status.[9–11] However, it should be mentioned that no differences were observed between the young patients and the premenopausal study population regarding histologic subtype, estrogen receptor, and human epidermal growth factor receptor 2 status.

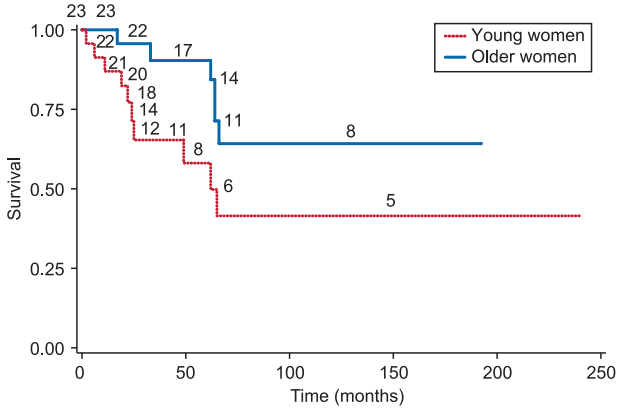

Fig. 1. Kaplan-Meier overall survival curves for young women and matched older premenopausal women. Numbers of patients at risk at the beginning of each interval also are shown for each subgroup.

Dimitrakakis. Young Patients and Breast Cancer. Obstet Gynecol 2013.

Another finding of our matched case-case study is the more advanced stage at breast cancer presentation in young patients. This was expected, given the reduced awareness among young women and clinicians. Moreover, breast tissue of young women tends to be more nodular and indistinct in clinical examination, with alterations during the different phases of the menstrual cycle. Fibrocystic changes represent the most common case, and physicians tend to reassure this age group for the benign nature of breast conditions.[6] There is no established screening for breast cancer in this age group; clinical and imaging examination is often insufficient and diagnosis is mainly established after the malignancy becomes clinically apparent and in some cases advanced.[4] Additionally, mammography is demonstrating reduced sensitivity among young women, and the majority of the cases are self-detected.[12]

In our database, the rate of breast cancer diagnosis at the age of 25 years or younger among premenopausal women is nearly equal to 4%. However, this increased percentage could be explained by the fact that these two hospitals are referral centers for breast cancer, and the results cannot be extrapolated to the general population. In parallel, there is lack of data and registries regarding primary breast malignancy in women aged 25 years and younger; thus, accurate incidence rate cannot be calculated. The risk rate in the general population is unknown, and genetic risk as the

only established factor fails to explain the majority of cases reported.[6]

Worthy of note, in this project, almost half of the young patients had a genetic analysis. Mutations of *BRCA1* and *BRCA2* were found in 3 of the 12 young women examined, representing a rate of 25%. Mutations in *BRCA1* and *BRCA2* are expected to be responsible for 5% of all breast cancer cases,[13,14] with a more profound representation in younger patients.[15] In accordance with these findings, inherited predisposition appears to have a concrete role in the presentation of breast cancer in our study population. However, this ratio was not adequately high to provide a solid explanation of disease occurrence in this population; therefore, other genetic factors may be responsible and need to be further investigated in the future. Other risk factors like hormonal factors, oral contraceptive use or other treatments, nulliparity, alcohol consumption, and age at menopause cannot be applied in this age group.[16,17]

Despite its originality, this study has certain limitations that should be declared and discussed. A meaningful limitation pertains to the relatively small sample size that may have limited the statistical power. Nevertheless, the fact that statistically significant associations emerged in this study and were robust enough to persist at the multivariate analysis may well point to their replication in future larger studies with substantial power. Moreover, year of diagnosis and estrogen receptor status were not treated as matching factors, but were taken into consideration as adjustment factors; however, according to the *Cochrane Handbook* guidelines for the assessment of risk of bias in published studies, matching or adjusting for a potential confounder may be considered adequate alternative strategies for control of confounding.[18]

Further limitations of our study may pertain to the model-building procedure. Potentially meaningful variables, such as PR status, human epidermal growth factor receptor 2 status, and histologic subtype were not entered in the multivariate models. Specifically, because of the small sample size, only three cases were human epidermal growth factor receptor 2–positive, whereas only four cases of invasive lobular carcinomas were recorded; the robustness of results based on such small numbers would be heavily compromised at the multivariate analysis. Moreover, PR status was not included in the models because of collinearity with estrogen receptor status ($P<.001$, derived from χ^2 test for the totality of the sample); as a result, estrogen receptor status also may well be interpreted as a proxy marker for PR status in our sample.

Moreover, there are not sufficient data regarding proper management of young patients; recommended treatment guidelines and techniques need to be validated for preventing relapse in this population. Furthermore, there is not enough experience regarding the proper surgical breast-conserving and oncoplastic management, chemotherapy regimens, and follow-up. More importantly, young survivors expect to recover and have full rehabilitation in most aspects of their lives; hence, the extended survival has to be translated to years with quality of life gained after diagnosis. Hence, specially adapted treatment is required for this age group, but because these cases are rare it is difficult to know how the standard treatment should be changed.

In conclusion, breast cancer diagnosis is uncommon in women aged 25 years and younger; however, this diagnosis, often in advanced stages, adds complexity to cancer treatment recommendations. Taking into consideration our results from a well-designed retrospective, nested, within-cases matched study, it seems that breast cancer diagnosis in women aged 25 years and younger is correlated with worse prognosis, advanced stage, and more aggressive tumors. Larger collaborative prospective studies are warranted to further substantiate our findings and to elucidate methods for early detection and treatment of an aggressive disease in this population. Absence of screening, extremely high life expectancy, reproductive and hormonal factors, and quality of life have to be taken into consideration. For the moment, increased awareness is extremely important.

REFERENCES

1. Aebi S, Davidson T, Gruber G, Cardoso F. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011;22:vi12–24.
2. Cancer Facts & Figures 2011 [database on the Internet]. American Cancer Society; 2011. Available at: www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-029771.pdf. Retrieved October 4, 2012.
3. Wu X, Groves FD, McLaughlin CC, Jemal A, Martin J, Chen VW. Cancer incidence patterns among adolescents and young adults in the United States. Cancer Causes Control 2005; 16:309–20.
4. Simmons PS, Jayasinghe YL, Wold LE, Melton LJ 3rd. Breast carcinoma in young women. Obstet Gynecol 2011;118:529–36.
5. Azim HA Jr, Michiels S, Bedard PL, Singhal SK, Criscitiello C, Ignatiadis M, et al. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clin Cancer Res 2012;18:1341–51.
6. Mintzer D, Glassburn J, Mason BA, Sataloff D. Breast cancer in the very young patient: a multidisciplinary case presentation. Oncologist 2002;7:547–54.
7. Beadle BM, Woodward WA, Tucker SL, Outlaw ED, Allen PK, Oh JL, et al. Ten-year recurrence rates in young women with breast cancer by locoregional treatment approach. Int J Radiat Oncol Biol Phys 2009;73:734–44.

8. Kim IK, Park S, Hwang H, Lee JS, Ko SM, Kim SI, et al. Clinical Significance of Age at the Time of Diagnosis among Young Breast Cancer Patients. J Breast Cancer 2011;14:314–21.
9. Weigel MT, Dowsett M. Current and emerging biomarkers in breast cancer: prognosis and prediction. Endocr Relat Cancer 2010;17:R245–62.
10. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312:146–51.
11. Allred DC, Harvey JM, Berardo M, Clark GM. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Mod Pathol 1998;11:155–68.
12. Yankaskas BC, Haneuse S, Kapp JM, Kerlikowske K, Geller B, Buist DS. Performance of first mammography examination in women younger than 40 years. J Natl Cancer Inst 2010;102: 692–701.
13. Foulkes WD. Inherited susceptibility to common cancers. N Engl J Med 2008;359:2143–53.
14. Begg CB, Haile RW, Borg A, Malone KE, Concannon P, Thomas DC, et al. Variation of breast cancer risk among BRCA1/2 carriers. JAMA 2008;299:194–201.
15. Narod SA. BRCA mutations in the management of breast cancer: the state of the art. Nat Rev Clin Oncol 2010;7:702–7.
16. Santen RJ, Boyd NF, Chlebowski RT, Cummings S, Cuzick J, Dowsett M, et al. Critical assessment of new risk factors for breast cancer: considerations for development of an improved risk prediction model. Endocr Relat Cancer 2007;14:169–87.
17. Zografos GC, Panou M, Panou N. Common risk factors of breast and ovarian cancer: recent view. Int J Gynecol Cancer 2004;14:721–40.
18. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0, 2011. The Cochrane Collaboration. Available at: www.cochrane-handbook.org. Retrieved October 4, 2012.