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Breast Cancer Diagnosis in Women ≤ 40 versus 50 to 60 Years: Increasing Size and Stage Disparity Compared With Older Women Over Time

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Background: Women ≤ 40 years account for 5% of new breast cancer diagnoses. Although there is increased awareness of genetic and other breast cancer risk factors, it is not clear whether this has resulted in earlier diagnosis in young women.

Methods: A database review identified 8892 women treated for breast cancer from 1980 to 2002. We compared 925 women aged ≤ 40 years with 2362 women aged 50 to 60 years. The mean and median tumor size and lymph node status were determined for each group.

Results: There were significant differences in tumor size and lymph node status in younger versus older women. From 1980 to the mid 1990s, tumor size and nodal status did not differ. Since the mid 1990s, tumor size has decreased more rapidly for women aged 50 to 60 years than for those ≤ 40 years. In 1998 to 2002, the mean tumor size reached a plateau of 1.8 cm in women 50 to 60 years, compared with a plateau of 2.4 cm in women ≤ 40 years ($P < .001$). The median tumor size in 1998 to 2002 was 1.4 cm in women 50 to 60 years compared with 1.9 cm in women ≤ 40 years ($P < .001$). Lymph node status was also significantly different during 1998 to 2002: 23.9% positive in women 50 to 60 years versus 35.2% in women ≤ 40 years ($P < .001$).

Conclusions: Since the 1980s, women aged 50 to 60 years have enjoyed a greater decrease in tumor size and percentage with positive nodes. These data could be the result of ineffective screening of younger women or of more aggressive tumor biology. Further study is required to determine whether more effective identification and screening of young, high-risk women can result in earlier detection.

Key Words: Early-onset breast cancer—Diagnosis—Young women—Screening—High risk.

One in eight American women will develop breast cancer over a lifetime, thus making breast cancer the most common malignancy diagnosed in women and the second leading cause of death from cancer.[1,2] Given these risks, breast cancer screening programs have been designed with the goal of detecting breast cancers at as small a size and as early a stage as possible. Screening mammography programs have generally been shown to reduce breast cancer mortality in women older than 50 years,[3–5] although not all studies have shown a benefit.[6,7] The benefit of screening mammography for women aged 40 to 49 years has been more controversial,[3,4,8–15] but at the present time, the American Cancer Society and

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National Institutes of Health recommend annual mammographic screening after age 40.[16]

The diagnosis and treatment of breast cancer in women <40 years continue to be particularly challenging. Women aged ≤ 40 years comprise approximately 5% of all new breast cancer diagnoses, or approximately 11,000 cases per year.[17] Diagnosis of breast cancer may be more difficult in women <40 years,[18–21] and in recent years there has been controversy about the need for breast cancer screening in this age group.[10] From 1976 to 1993, it was recommended that a baseline mammogram be obtained at some time between the ages of 35 and 40 years.[10,22] In recent years, however, the recommendation for mammography before age 40 has been discontinued, and only clinical breast examinations as part of routine medical care are recommended.[10,16] For higher-risk young women, it has been suggested that each woman decide with her physician whether or not to undergo routine mammographic screening.

The potential for delays in diagnosis of breast cancer in young women is a source of concern for both women and their physicians and has been a major area for malpractice litigation. More than 30% of breast cancer lawsuits filed between 1995 and 2002 were initiated by women younger than 39 years, and most were based on "failure to make a timely diagnosis."[23]

Identification of risk gene mutations and availability of genetic testing have provided means to identify young women at increased risk for breast cancer. Other high-risk groups have been identified, including women with breast biopsies showing atypical hyperplasia or lobular carcinoma-in-situ and women with a history of mantle irradiation for Hodgkin's disease. It is not clear whether the current ability to assess risk has translated into earlier detection of breast cancer in younger women.

To address these issues, we reviewed trends in breast tumor size and nodal status at diagnosis in our institution since 1980 in two age groups: women aged 50 to 60 years, for whom annual screening mammography and clinical breast examination were consistently recommended and practiced at our institution during the study period,[24] and women aged ≤ 40 years, for whom screening recommendations have varied over time.

MATERIALS AND METHODS

A retrospective institutional review board–approved database review identified 8892 women treated for breast cancer at the Massachusetts General Hospital from 1980 to 2002. We compared 925 women ≤ 40 years at diagnosis with 2362 women aged 50 to 60 years at diagnosis. Mean and median tumor sizes and lymph node status at diagnosis were determined for each year in women ≤ 40 years and were compared with the results for women aged 50 to 60 years. For statistical analysis, tumor sizes were pooled over 5-year periods from 1983 to 2002. Statistical analysis was performed with Microsoft Excel and Winstat (Microsoft Corp, Redmond, WA). Mean tumor sizes between subgroups of patients were compared by using Student's *t*-test for independent samples. Graphical representation of tumor size distribution was achieved by examining median tumor sizes for each subgroup, and the statistical validity of comparisons between the distributions of these subgroups was assessed by the Mann-Whitney nonparametric test. Comparison of lymph node positivity between subgroups was achieved through χ^2 analysis.

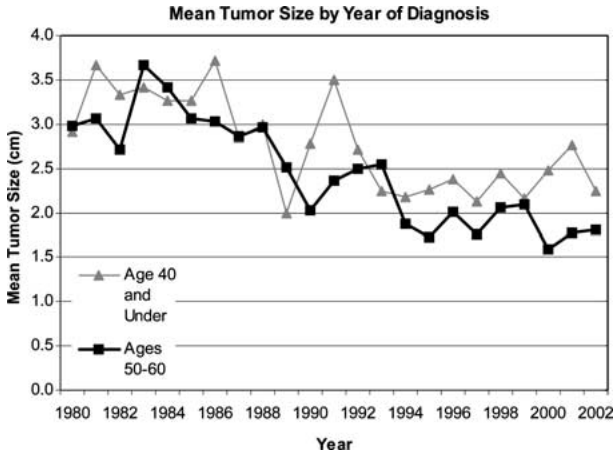

FIG. 1. Mean tumor size by year of diagnosis.

RESULTS

Tumor size and nodal status at diagnosis during each year from 1980 to 2002 were determined for 925 women aged ≤ 40 years and for 2362 women aged 50 to 60 years. Women aged ≤ 40 years comprised 10% of new breast cancer diagnoses at our institution during this time period. Mean and median tumor sizes were calculated for each age group for each year of the study (Figs. 1 and 2) and combined for 5-year intervals for statistical analysis (Tables 1 and 2; Figs. 3 and 4).

The mean and median size of breast cancers at diagnosis decreased over time for both the younger

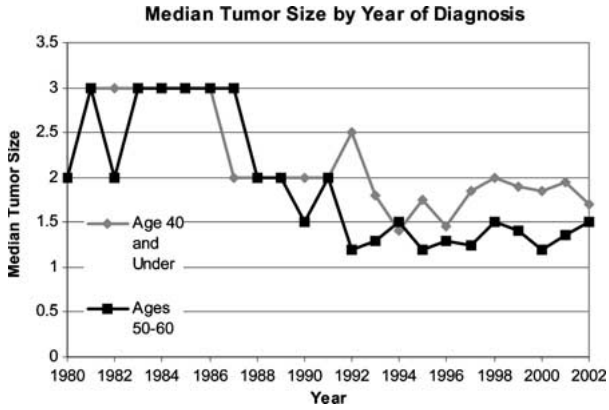

FIG. 2. Median tumor size by year of diagnosis.

TABLE 1. *Mean tumor sizes (cm)*

Period	≤ 40 y	50–60 y	*P* value (independent t-test)
1983–1987	3.31	3.18	.64
1988–1992	2.79	2.5	.365
1993–1997	2.22	1.93	.117
1998–2002	2.43	1.84	.000052

TABLE 2. *Median tumor sizes (cm)*

Period	≤ 40 y	50–60 y	*P* value (Mann-Whitney test)
1983–1987	3	3	.35
1988–1992	2	2	.58
1993–1997	1.7	1.3	.000064
1998–2002	1.9	1.4	.000000024

and older age groups studied. Tumor sizes decreased through the 1980s and seemed to reach a plateau in the mid 1990s. The overall decrease in tumor size over time was greater for women aged 50 to 60 years than for women ≤ 40 years. In 1980, the mean size of tumors for women aged ≤ 40 years was 2.9 cm, and in women aged 50 to 60 years, it was 3.0 cm (Fig. 1). The median tumor size in 1980 was 2.0 cm for both younger and older women. There was no statistical difference between the mean or median tumor sizes in the younger and older groups between 1983 and 1992. Overall, tumor sizes at diagnosis were not significantly different for women ≤ 40 years compared with women aged 50 to 60 years from 1980 through the early 1990s.

By the mid 1990s, tumor sizes decreased more rapidly for women aged 50 to 60 years than for women aged ≤ 40 years. During the most recent 5-year period studied, 1998 to 2002, mean and median tumor sizes were significantly larger at diagnosis for

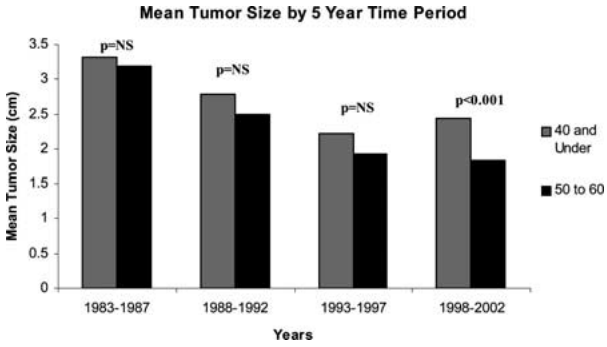

FIG. 3. Mean tumor size by 5-year time period. NS, not significant.

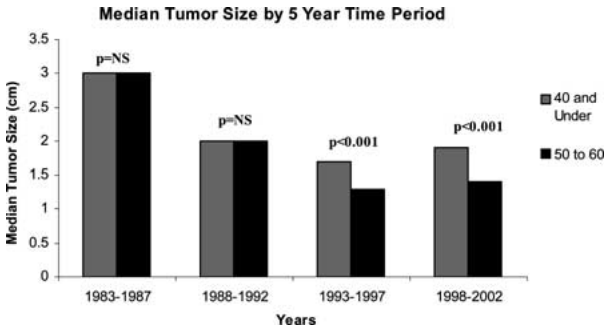

FIG. 4. Median tumor size by 5-year time period. NS, not significant.

women ≤ 40 years than for women aged 50 to 60 years (mean: 2.43 vs. 1.84 cm, respectively, $P < .001$; median: 1.9 vs. 1.4 cm, respectively, $P < .001$; Figs. 3 and 4).

The percentage of women with pathologically positive nodes at diagnosis was determined for each 5-year interval for each age group (Table 3; Fig. 5). From 1980 until the late 1990s, the percentage of women with positive nodes at diagnosis was not significantly different in women ≤ 40 years compared with women aged 50 to 60 years. From 1983 to 1987, the percentage of women ≤ 40 years with positive nodes was 41.3% and was 40.4% for women 50 to 60 years (not significant; Table 3; Fig. 5). However, by 1998 to 2002, the rate of positive nodes had declined to a greater extent in older women than in younger women, to 23.9% of women aged 50 to 60 years versus 35.2% of women ≤ 40 years old ($P < .001$).

DISCUSSION

The goal of breast cancer screening programs is detection of breast cancers at as small a size as possible, before metastasis has occurred. Detection of

TABLE 3. *Lymph node positivity*

Period	≤ 40 y	50–60 y	*P* value (χ^2 test)
1983–1987	41.3%	40.4%	.860245
1988–1992	27.3%	26.8%	.929774
1993–1997	31.9%	26.1%	.111663
1998–2002	35.2%	23.9%	.0000921

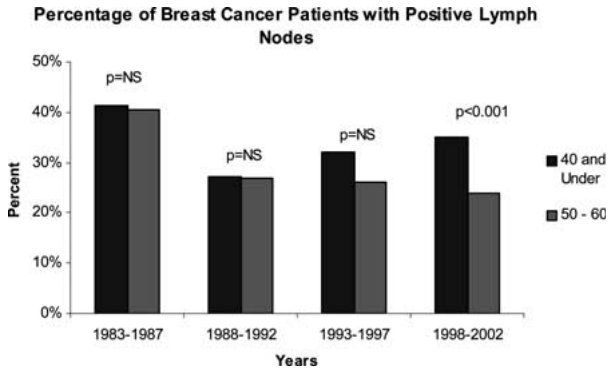

FIG. 5. Percentage of breast cancer patients with positive lymph nodes. NS, not significant.

smaller tumors may improve survival, reduce the need for chemotherapy and/or radiotherapy, and allow smaller, more cosmetic surgical procedures. The ability to achieve early detection of breast cancer will depend on a variety of factors, including the screening regimen used and the biology of breast cancer in the population being screened. Our data suggest that significant progress has been made toward the goal of early detection in women aged 50 to 60 years. There has been much less progress toward achieving early detection of breast cancer for women aged ≤ 40 years, with tumors remaining larger and with a higher frequency of positive nodes than in older women.

Detection of breast cancers while they are still small is important for reducing mortality. Michaelson et al.[25] showed that the survival of patients with an invasive breast cancer was a direct function of tumor size, regardless of the method of tumor detection. Tumors detected by screening mammography have been found to have a better survival compared with clinically detected tumors.[3,26] The Two-County trial found that for each size category, screen-detected tumors had a better survival compared with clinically detected tumors at 16 years of follow-up.[3]

In the Two-County trial, the effects of tumor size, lymph node status, and malignancy grade on survival were found to be the same irrespective of patient age.[3] These data reaffirm the value of detection of breast cancers at as small a size as possible in women of all ages.

Our data show that the size of breast cancers at diagnosis and the percentage of women with positive axillary lymph nodes were the same for women aged ≤ 40 years as for women aged 50 to 60 years from 1980 through the mid 1990s. Tumor sizes decreased for both younger and older age groups over time, likely as a result of increased screening for breast cancer and increased breast cancer awareness among patients and physicians. During this period of time, a baseline mammogram was recommended for women at some time between the ages of 35 and 40 years, and annual mammography was recommended for women aged ≥ 50 years.[10,22]

Decreases in tumor size and the percentage with positive nodes over time were greater for women aged 50 to 60 years than for women aged ≤ 40 years. This downstaging of tumor size and nodal status for older women would be expected to contribute to the improvement in overall breast cancer survival seen in recent years.[3,18,27] For younger women, however, tumor size at diagnosis did not decrease after the mid 1990s and, in fact, increased somewhat to plateau at a significantly larger tumor size than seen in women aged 50 to 60 years. Rates of positive lymph nodes also remained higher for younger women, whereas rates declined for older women. This change in tumor size and nodal status for younger women corresponds to the issuing of the 1993 screening guidelines, which dropped the recommendation for a baseline mammogram between ages 35 and 40.

Several studies have suggested that mammogram and magnetic resonance imaging (MRI) screening are able to detect breast cancers in young, high-risk women. We previously reported that 73% of breast cancers diagnosed in women ≤ 40 years were visualized on mammograms performed before biopsy.[28] Recent data suggest that MRI screening may be especially effective in identifying cancers in young, high-risk women, including BRCA1 and BRCA2 mutation carriers, with a sensitivity of MRI for detecting breast cancers of 77% to 100%.[29–33] MRI screening was not often used during the time period covered by our study. Its effect on tumor size and stage at diagnosis in young women will need to be addressed in future studies.

Although the timing of the increase in tumor size and the larger tumor size plateau for younger women suggest that the reduction in mammographic screening may be at fault, other possibilities must also be considered. There may be a higher frequency of more rapidly growing tumors in women aged ≤ 40 years, with a greater likelihood that the tumor will have grown larger and spread to the axillary lymph nodes

before diagnosis.[34,35] Younger women do have a higher incidence of poorly differentiated, estrogen receptor–negative, aneuploid, and high S-phase tumors than do older women.[18] Dense or nodular breast tissue, common in younger women, may make detection of small breast cancers less likely than in older women. However, our data showing no difference in tumor size or nodal status for the first decade or more of the study period argue that a priori differences in tumor biology in older and younger women are unlikely to account for all of the observed differences in tumor size and nodal status.

The plateaus in tumor size currently seen for both older and younger women suggest that continuing current breast-screening practices for both age groups is unlikely to result in additional improvements in early detection. For younger women, identification and aggressive screening of high-risk women may help reduce tumor size and rates of nodal metastases. Support for such an approach comes from sensitivity rates of $>70\%$ for mammography[28,33,36] and 77% to 100% for MRI in identifying breast cancers in women ≤ 40 years.[29–33] Genetic testing for BRCA gene mutations was not commonly performed until the latest years of our study period, and additional studies will be required to see whether increased use of genetic testing will result in improved screening and earlier detection in young mutation carriers.

For older women, continued progress toward early detection may be made by increasing use of mammography beyond current levels. Only a minority of women undergo annual mammography as recommended in screening guidelines. Our group reviewed data from 72,417 women who received screening mammograms at our institution from 1985 to 2002. Overall, only 6% of women used 10 screening mammograms, and the median number of mammograms received was only 5. Among women who received a diagnosis of invasive breast cancer, women who had prompt annual mammograms had a lower risk of death (11.97%) than women who received five mammograms in 10 years (16.01%) or once every 5 years (25.26%).[37] These data suggest that even modest increases in use of screening mammography may result in earlier detection of breast cancer and improved survival.

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