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Breast Carcinoma in Young Women: No Evidence of Increasing Rates of Metastatic Breast Carcinoma in a Single Tertiary Center Review

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Abstract

Purpose—Breast carcinoma in young women aged less than 40 years attracts a disproportionate level of mainstream media coverage, and there is a gap between societal perceptions of the disease as a growing problem, and epidemiologic trends. Several population studies have suggested that the overall incidence of breast carcinoma in young women is stable, while one study suggested that the relative proportion of breast carcinoma in young women that is metastatic at diagnosis is growing. We sought to establish whether these trends were apparent at our institution.

Methods—In this study, the clinical database at a breast carcinoma tertiary center was reviewed in terms of clinicopathologic data on patient age, diagnosis, clinical and pathologic stage, hormone receptor status and HER2 overexpression status for the period 2000–2011.

Results—Over the study period, young patients represented a decreasing proportion of all breast carcinoma cases (10.8% [2000–2003] to 8.7% [2008–2011]; p <0.0001). Young patients were more likely than patients aged forty years or older to present with metastatic disease (6.1% vs 4.4%; p = 0.0004), to be triple negative (21.6% vs 13 %; p < 0.001) or to be HER2 positive (HER2+) (24.3% vs 14.8%, p <0.01). Young patients with HER2+ cancers were significantly more likely to present with metastatic disease (8.3% vs 5%; p = 0.001).

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Conclusions—This study showed no demonstrable increase in the relative proportion of breast cancer occurring in patients aged < 40 years over the twelve year period 2000–2011 and no increase in the proportion of young patients presenting with metastatic disease.

INTRODUCTION

Breast carcinoma has an unparalleled prominence in the mainstream media, typified by the success of public awareness campaigns such as the pink ribbon campaign in capturing the imagination of both the media and the general public. One striking feature of much of this media attention is the relative absence of images of the peri- and post-menopausal breast carcinoma patient from the media discussion of breast carcinoma, and the very prominent position of young women [1]. A recent Australian study [2] which analyzed media coverage of breast cancer reported that 55% of statements about age and breast cancer referred to young women aged less than 40 years, while 67% of imagery used in the report involved such young women. They also noted the disproportionate level of attention given by the media to breast carcinoma cases in young celebrities.

In light of this media coverage, it is not surprising that the general public is confused about both the relationship between age and breast carcinoma risk, and the assessment of the relative risk to their survival posed by breast cancer in comparison to other conditions such as cardiovascular disease [3]. Within the media, breast carcinoma in young women is frequently represented as a growing problem.

However, contrary to this subjective impression, epidemiologic data would suggest that the incidence of breast cancer in young women on a population level is steady and has been for several decades [4, 5]. Interestingly, Johnson et al [6] recently used Surveillance, Epidemiology and End Results 9 (SEER 9) data to investigate trends in the incidence of breast cancer by age group and tumor extent (localized, regional or metastatic) at presentation from 1976 to 2009 and demonstrated that while there was no increase in the incidence of localized and regional disease in young women, a small but statistically significant increase in the incidence of metastatic breast carcinoma (MBC) in young women was observed over the period.

The current retrospective review was undertaken in order to assess whether these epidemiologic trends were evident in our patient population. In light of the disparity between the population-based epidemiologic data of stable breast cancer incidence rates, and the subjective societal impression of increased frequency of breast carcinoma in the young, we reviewed the breast cancer clinical database at Memorial Sloan Kettering Cancer Center (MSKCC) documenting all breast carcinoma cases treated at our institution over a twelve year period in order to establish whether breast carcinoma in young women represents a increasing proportion of total breast carcinoma, and whether we could detect an increase in the rate of MBC among our young patients.

METHODS

After securing Institutional Research Board (IRB) approval, we searched the breast carcinoma clinical database to identify all patients who were treated for breast carcinoma at

MSKCC over a twelve year period (2000–2011). This patient population was then divided into two main groups based on patient age at diagnosis; patients aged less than forty years (defined as “young women” or YW), and patients forty years of age and older. Patients who attended MSKCC for a clinical consult but who did not subsequently undergo any treatment at our institution were not included.

Clinicopathologic features recorded in the database included tumor size, grade, hormonal receptor status, HER-2 status, stage, family history of breast carcinoma and patient parity. In order to make the comparison with the Johnson et al [6] paper, cases were staged according to whether the patient had localized (Tx N0 M0), regional (Tx N≥1 M0) and metastatic (Tx Nx M1) disease. For data analysis purposes, the twelve year period of this study was divided into three four year periods (2000–2003, 2004–2007 and 2008–2011). Statistical tests used included Chi square and Student t-tests.

RESULTS

Over the twelve years of this retrospective study, 26,806 patients were treated for breast carcinoma at MSKCC. YW constituted 9.6% of this total population (2,563 patients). Analysis of the trend from 2000 to 2011 demonstrates that while the absolute numbers of breast carcinoma cases in YW increased (from 735 cases in 2000–2003 to 796 cases in 2008–2001), the overall proportion of all breast carcinoma cases diagnosed at MSKCC that occurred in YW declined over the period (from 10.8% (860/7681) in 2000–2003, to 8.7% (907/10397) 2008–2011, $p < 0.0001$). This was due to a proportionally greater increase in the numbers of women aged 40 or over who were treated at MSKCC in 2008–2011. The proportion of total invasive breast carcinoma that involved YW showed a statistically significant decrease from 11.6% (735/6324) to 9.3% (796/8561); p=0.0005. While the overall proportion of total ductal carcinoma in situ (DCIS) involving YW showed a downward trend (from 7% (95/1357) to 6% (111/1818)), this was not statistically significant (Table 1).

DCIS constituted 12.4% (319/2563) of all carcinoma in young women and 18.3% (4428/24243) of all carcinoma in women aged 40 and over. This figure remained stable throughout the study period in both groups (Table 1).

8.2% (210/2563) of YW underwent genetic testing. 7.8% (200/2563) had BRCA mutation testing, of whom 20/200 (10%) of patients had a deleterious BRCA1 mutation and 10% (20/200) had a deleterious BRCA2 mutation. Four additional patients had a mutation of uncertain significance in either BRCA1 or BRCA2, and five patients had BRCA polymorphisms. Twenty four patients underwent other genetic testing. Analysis for p53 mutation demonstrated a single case with a germline mutation and one case with a somatic mutation. PIK3CA sequencing detected a mutation in six of twenty two cases tested.

Data on family history of breast carcinoma was available in 2,164 young patients; 1167 (54%) patients had a known history of breast carcinoma in at least one relation. Median patient parity was 1 (n= 2098) and 33% (688/2098) were nulliparous at the time of their diagnosis with breast carcinoma.

Table 2 demonstrates the key pathologic features of breast carcinoma in YW. Mean tumor size within this cohort was larger than in patients aged 40 and over (1.99 cm vs 1.62 cm, p <0.0001). Additionally, tumors in YW were more likely to be high grade (79.5% v 63.2%) and showed different hormone receptor and HER-2 profiles than tumors in older women. YW were also more likely to present with MBC (6.1% vs 4.4%, p=0.0004).

Analysis of the temporal trends in extent of disease at diagnosis of the YW patient cohort showed no definite evidence of an increase in MBC at diagnosis (Table 3). While there was a trend towards greater absolute numbers of YW with MBC over the time period, and the proportion of all YW with MBC rose from 5.6% (41/726) in 2003–2007 to 7.1% (56/790) in 2008–2011, this did not reach statistical significance (p=0.2). Interestingly, a statistically significant stage migration from regional to localized disease was identified over the time period, with a rise in the proportion of YW presenting with localized disease (39.8% [289/726] vs 47.6% [376/790], p=0.046) and a corresponding fall in the proportion presenting with regional disease.

Within the YW cohort subset in whom HER2 status was known (n=2125), those patients with a HER-2 positive tumor were more likely to have metastases at the time of diagnosis than those with a HER-2 negative tumor (8.3% [43/516] vs 5% [81/1609], p=0.001). There was no evidence of any relationship between ER status and the rate of MBC in YW, with 6.3% (94/1483) of patients with ER-positive carcinoma presenting with MBC versus 5.6% (39/697) of patients with ER-negative carcinoma (p=0.56). YW with triple negative breast carcinoma (TNBC) (number with hormone status documented (n) = 2110) showed a trend towards having a lower rate of MBC at diagnosis than receptor positive carcinoma (4.6% [21/455] vs 6.7% [118/1655], p=0.055). Among YW with localized or regional breast carcinoma, those with a HER-2 positive tumor were more likely to have regional disease (60% vs 51%, p=0.008) (Table 4).

DISCUSSION

This study represents a retrospective review of trends in breast carcinoma in YW from 2000–2011 in a single tertiary cancer center. In contrast to the epidemiologic population review of Johnson et al [6], there was no statistically significant evidence at this institution of a rise in the rate of MBC in YW during the period under review.

The analysis of trends in the epidemiology of breast cancer is complex. Data interpretation involving comparisons between different time periods must be conducted with due regard for multiple confounding factors such as changes in the quality of data collection over time and the dynamic nature of breast cancer risk factors such as the advent of breast screening, OCP and HRT use and societal trends in terms of mean parity and mean age of primigravidas. The wide reported variation in population breast cancer incidence between European nations, from 40 per 100,000 in Poland to 90 per100,000 in Holland illustrates the fact that any comparison between different countries are subject to these multiple biases [7]. The analysis of the rate of breast cancer in YW can be particularly subject to apparent variation over short time periods, due to the much lower number of patients in this population, and such results should be interpreted with caution [8, 9].

Epidemiologic data from the USA has consistently demonstrated no increase in the incidence of breast cancer in young women in the US population over the last few decades [4, 5, 10]. Brinton et al [5] used SEER6 data to demonstrate that while absolute patient numbers in this age group had increased between 1992 and 2004, this was predominantly due to changes in population demographics. In this study, the overall annual percentage change in incidence rate (APC) of breast cancer in YW had only slightly increased (0.62 [0.05–1.19]) and this was predominantly due to more frequent diagnoses of in-situ carcinoma. In the US, the quality of breast cancer data collected by the SEER program has been steadily improving over several decades, and each version of the registry has covered a greater proportion of the total population. SEER 18 covered 28% of the US population, the highest level yet recorded. While the increase in MBC seen in the Johnson et al [6] paper was statistically significant (from 1.53 to 2.9 per 100,000 women), the incidence of MBC in YW remains very low and it is difficult to separate the impact of the superior data collection with greater population coverage, and more accurate data recording (reflected in the fact that the proportion of unstaged cases fell over time) from a true epidemiologic increase in MBC incidence.

Furthermore, it is important to note that the SEER 18 data used by Johnson et al [6] stretches from 1976 to 2009, a period with wide variation in the availability of sensitive imaging techniques such as computerized tomography (CT) and positron emission tomography (PET). Such advances in imaging over this thirty-year period must impact to some extent on the ability to accurately stage a patient with MBC, and thus impact on incidence rates in this small patient population. The rate of increase in the APC of MBC appeared to be increasing in the latter years of the Johnson et al [6] analysis; one could speculate that this could be related to a growing readiness among clinicians to comprehensively stage any symptomatic young women (and sometimes asymptomatic young women) with breast carcinoma using multiple imaging modalities, but this has not been proven. Admittedly, the counterargument to this assertion is that no evidence of a reciprocal, statistically-significant reduction in localized or regional disease (as would be expected in the context of an overall stable population rate of breast cancer in YW) has been detected. Thus, while the absence of an increased rate of MBC in YW at our institution cannot be said to definitively undermine the findings of this SEER 18 analysis, it does suggest that a question mark still exists over the significance of this apparent trend, and further analysis of data in other tertiary cancer centers and population analyses from other countries would be informative.

It could be argued that as the absolute increase in the population incidence of MBC in YW shown in Johnson et al [6] was so small, this single-institution study was not adequately powered to detect this increase. However we contend that as MSKCC is a tertiary referral center involved in several clinical trials for patients with stage IV breast cancer, this lack of power is likely to be compensated for to some degree by a referral bias. Therefore if there was an increase in MBC in YW in the American population, it would be reflected in patterns of referral to our institution. YW represent 9.6% of all breast carcinoma treated at MSKCC which is significantly higher than the population rate of approximately 6% [6, 11], confirming that a referral bias exists at our tertiary institution. In common with prior reports [11–16], our study demonstrates that breast cancer in YW is characterized by a higher frequency of aggressive pathologic features. It is consequently not surprising that breast

cancer in YW has been associated with both increased rates of tumor recurrence and decreased patient survival. Bharat et al [17] demonstrated a relative risk of disease-related mortality of 1.53 for YW in comparison to those 40 years of age or older. Gnerlich et al [11] reported a breast cancer mortality rate of 18.3% in women aged less than 40 years, versus 12.1 % for women aged 40 and older. Fredholm et al [13] showed a relative risk of cancer-related death (RER) of 4.63 for patients aged 20–34 and 3.37 for patients aged 34–39, in comparison to older patients (aged 50–69). Interestingly, both Fredholm et al[13] and Gnerlich et al [11] demonstrated that the majority of the excess mortality risk in YW occurred in patients with Stages I and II disease at diagnosis, which may simply be related to the inherent biological aggressiveness of the tumors that occur in young women. However, it also raises the question of whether a tendency to establish early clinically-silent metastases may constitute a component of this tumor biology in this age group. It is important to note however that these studies predate the era of anti-HER2 therapy and the routine use of anti-estrogen therapy in patients aged less than 40 with ER-positive tumors and therefore, this survival data may not be relevant to the modern era. It is clear that any decreased survival in the young is likely to be related to the inherent biological aggressiveness of tumors in this age group, and this is reflected in their increased propensity to demonstrate HER2 overexpression and to be metastatic at diagnosis. The time period covered in this study is too recent to provide an adequate follow up period for a survival analysis, but this information will be reported at a later date.

Breast carcinoma in YW presents unique challenges for holistic oncologic patient care. While it has been demonstrated that these patients have a higher disease specific mortality than older patients and can benefit more from chemotherapy [18, 19], clinical decision-making can be complicated by the patient's wishes for future fertility [20–23]. In keeping with prior studies [21] and western societal trends, a high rate of nulliparity (33%) was demonstrated in our study population, and the median parity was only one. Pregnancy-associated breast carcinoma is another challenging issue in this age group and NCCN guidelines are available to guide clinicians in patient management [24]. In this study, we have not reported on the association between breast carcinoma diagnosis and recent or current pregnancy, as historically the number of pregnant breast cancer patients who undergo their care at MSKCC is low, due to the absence of obstetric care at this cancer center.

Inherited breast carcinoma is another major issue for younger women, with rates of germline BRCA mutations estimated at 6–10% in patients aged less than 35 years [25–27]. The higher rates of deleterious BRCA germline mutation seen in the small subset of cases tested in this current study (20%) is likely related to the institutional referral bias, patient demographics and the selection of patients with high risk pedigrees for testing. Thus this data cannot be directly extrapolated to the general population.

In summary, this single institution study of breast carcinoma in YW has demonstrated no evidence of an increase in either the overall incidence in this population or of an increase in MBC at presentation over the period 2000–2011. These results were consistent with most population epidemiologic data on trends in breast carcinoma but do not confirm the findings of Johnson et al [6] of increased rates of MBC at presentation in YW. In common with prior studies, we have demonstrated the aggressive pathologic features of breast cancer in YW.

While the incidence of breast cancer in YW may not be increasing, it remains an extremely important clinical challenge. YW are more likely to have triple negative or HER2 positive breast cancer and to have metastatic disease at presentation than older women and the development of new and effective treatments for these patients groups is absolutely vital.

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TABLE 1

Trends in the relative proportions of breast carcinoma diagnosed in women aged < and ≥ 40 years

	2000–2003	2004–2007	2008–2011	p value
AGE	**ALL BREAST CARCINOMA**			
<40 YRS	830 (10.8%)	826 (9.4%)	907 (8.7%)	P<0.0001
≥40 YRS	6851 (89.2%)	7920 (90.6%)	9472 (91.3%)	
TOTAL	7681	8746	10397	
	INVASIVE BREAST CARCINOMA			
<40 YRS	735 (11.6%)	713 (9.9%)	796 (9.3%)	P=0.0005
≥40 YRS	5589 (88.4%)	6461 (90.1%)	7765 (90.7%)	
TOTAL	1357	1572	1818	
	DUCTAL CARCINOMA IN SITU			
<40 YRS	95 (7%)	113 (7.2%)	111 (6.1%)	P=0.86
≥40 YRS	1262 (93%)	1459 (92.8%)	17 07 (93.9%)	
TOTAL	1357	1572	1818	
	DCIS AS A PROPORTION OF ALL BREAST CARCINOMA			
<40 YRS	95/830 (11.4%)	113/826 (13.7%)	111/907 (12.2%)	P= 0.8
≥40 YRS	1262/6851 (18.4%)	1459/7920 (18.4%)	1707/9472 (18%)	P=0.98

Table 2

Comparative analysis of the features of invasive breast carcinoma in women aged <40 and ≥40 yrs

	Women <40 yrs	Women ≥40 yrs	p value
Mean Tumor Size (cm)	1.99	1.62	<0.0001
High Grade (%)	79.5%	63.2%	<0.0001
ER+ (%)	68%	80%	<0.0001
HER2+ (%)	24.3%	14.8%	<0.0001
TNBC (%)	21.6%	13%	<0.0001
Stage IV at presentation	6.1%	4.4%	0.0004

Table 3

Patterns in extent of breast carcinoma at diagnosis in YW 2000–2011

N=2242	2000–2003	2004–2007	2008–2011	p value
METASTATIC DISEASE	41 (5.6%)	41 (5.8%)	56 (7.1%)	0.2
REGIONAL DISEASE	396 (54.5%)	327 (46.6%)	358 (45.3%)	0.046
LOCALIZED DISEASE	289 (39.8%)	334 (47.6%)	376 (47.6%)	
Case totals	726	702	790	

TABLE 4

Relationship between HER-2 status and local/regional extent of disease at diagnosis in YW

Extent of Disease	HER-2 positive	HER-2 negative	p value
Localized	40% (165)	49% (855)	
Regional	60% (247)	51% (880)	P=0.0008
TOTALS	412	1735	