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Breast Cancer in Chinese Women Younger than Age 40: Are They Different from Their Older Counterparts?

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Abstract

Background Breast cancer in young women is uncommon, but when it does occur it has been reported to have aggressive biological characteristics. The incidence of breast cancer peaks at age 40 in Hong Kong Chinese women, earlier than in Caucasians. This study is the first to report the tumor characteristics and management of breast cancer in Chinese women younger than age 40 and a comparison with their older counterparts.

Materials and methods Demographic and clinicopathologic findings of 1,485 Chinese women with breast cancer seen during the period September 2003 to November 2006 were prospectively recorded, and comparisons were made between those who were under the age of 40 and those 40 years of age and older. These results were then compared with a reference population obtained from the Surveillance, Epidemiology and End Results (SEER) database between 2003 and 2004.

Results 17.6% of the women were younger than 40 years old, and age distribution was significantly different from women in the SEER database. The mean age at menarche was lower in women under age 40 ($p < 0.0005$), and age at first live birth was also higher ($p = 0.017$). The rate of first detection by screening mammography was significantly higher among women who were 40 of age and older ($p = 0.002$). Breast conservation surgery was more commonly performed in the younger age group of Chinese women, particularly when tumor size was less than 2 cm ($p = 0.001$). A significantly higher proportion of women under age 40 had breast reconstruction ($p < 0.001$). The majority of women presented with stage 0-II disease, but in the Chinese groups the younger patients presented at a later stage ($p = 0.04$). Younger women had higher pathological grade and poorly differentiated tumors ($p = 0.02$), more nodal involvement ($p = 0.024$), and lymphovascular permeation involvement ($p < 0.001$). The majority of tumors were ER and PR positive in both groups, but younger women had a higher proportion of cerbB2-positive tumors.

Conclusion Chinese women present with breast cancer at an earlier age. Younger women present with more advanced disease and more aggressive tumor characteristics. More ethnic-specific screening protocols and treatment decisions may benefit this group of patients.

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Introduction

The risk of developing breast cancer at a young age is uncommon. Breast cancer in women under 40 years of age has been reported in the West to account for 2%–4% of all breast cancer cases [1], and only 6.5% of all breast cancers are detected in women under the age of 40 [2]. There is

accumulating evidence that breast cancer in younger women is biologically more aggressive than that in their older counterparts [3, 4], and age itself is an independent prognostic factor for premenopausal breast cancer [5]. Various investigators have reported the association of young age with poorer overall survival or cause-specific survival [6–11], and age as a significant independent prognostic factor for relapse [12]. Most published studies are based on Caucasian populations.

The incidence of breast cancer is rising in Asia. It is now the most common female cancer in Hong Kong, with an age-adjusted incidence of 47.5 per 100,000 women [13]. Unlike the Caucasian population, where breast cancer peaks between the ages of 45 and 55 [11], breast cancer in Hong Kong Chinese women peaks at the age of 40 [13], much earlier than in the Caucasian population. With the rise in incidence and young age at presentation, management of young breast cancer patients bears important socioeconomic implications.

Materials and methods

Clinical records and pathological reports of Chinese female patients with operable breast cancer who received primary treatment and were discussed at the Multidisciplinary Breast Conference at Hong Kong Sanatorium and Hospital, a private hospital with a dedicated Breast Care Center, between September 2003 and November 2006 were prospectively recorded. Data collection including patient demographic data; clinical management such as mode of presentation, diagnosis, surgical treatment, and adjuvant therapy given; prognostic markers, such as tumor size, tumor type, tumor grade, lymph node status, estrogen (ER) and progesterone receptors (PR) status, cerbB2 status, and presence of lymphovascular permeation, were recorded. Tumor staging was carried out according to the American Joint Committee on Cancer criteria (AJCC) [14]. Histological tumor grading was performed using the Bloom and Richardson classification system [15].

A total of 1,485 patients recruited during this period, 20 of whom were excluded from the study because their age was unavailable, were divided into two age groups: <40 years old and ≥40 years old at the time of surgical treatment. The cut-off age of 40 years old was chosen because of the peak incidence in this age group among Chinese breast cancer patients in Hong Kong. A total of 1,465 women were eligible for the study: 258 (17.6%) in the younger age group and 1,207 (82.4%) in the older age group.

Surgical treatment details, including breast conservation surgery (BCS), modified radical mastectomy (MRM), performance of sentinel lymph node biopsy, or simple mastectomy with or without breast reconstruction, were recorded. No details of the chemotherapy regime or dosage of radiotherapy were available, although all adjuvant therapy given was administered according to international guidelines. Endocrine treatment was administered if the tumor was hormone receptor positive.

Comparison of the age distribution, stage, tumor size, grade of tumor, and type of treatment were made with a reference population obtained from the SEER database from the year 2003 to 2004. Statistical tests were performed with SPSS 14.0 for Windows statistical software (SPSS Inc., Chicago, IL). Pearson's chi-squared test, Fisher's exact chi-squared test, and the independent sample *t*-test were used to assess differences in pathological and clinical features between the two groups of patients.

Results

Clinical findings and imaging

Of the women in this series, 258 (17.6%) were younger than 40 years of age with a median age of 36 (range: 24–39 years), and 1,207 (82.4%) women 40 years of age and older. The median age of the older age group was 49 years (range: 40–91 years). There was a significant difference in the age distribution between Hong Kong Chinese (HK Chinese) and Chinese and Caucasian women residing in the United States. Notably, in the HK Chinese group the increased trend of breast cancer after menopause was not observed, as compared to the American populations (Fig. 1). There were no significant differences in the presence of family history of breast cancer (11% versus 12%) in the two HK Chinese groups. The mean age at menarche (12.6 versus 13.1; $p = 0.0005$) and mean age at first life birth (28.5 versus 27.4; $p = 0.017$) were significantly different. The majority of women in both groups presented with self-detected symptoms of which the most common finding was the presence of a breast lump (83.7% versus 76.6%). The proportion of abnormality detected by screening mammography alone was significantly higher in the older age group (4.7%, versus 10.6%; $p = 0.02$). The most common mammography finding in the younger women was microcalcifications (12.0% versus 10.9%; $p = 0.587$), whereas for the older age group, opacity was the most common finding (11.6% versus 17.3%; $p = 0.026$). There were no significant differences in the sensitivity of mammography, ultrasound, and magnetic resonance imaging (MRI) tests between the two groups, although sensitivity was much increased when the tumor was palpable (Table 1). Image-detected tumors presented at a significantly earlier stage compared with those found by breast self-examination or clinical breast examination in both groups ($p = 0.05$).

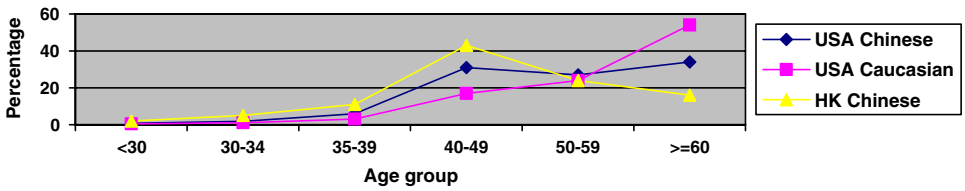

Fig. 1 Age distribution

Table 1 Sensitivity of mammogram and ultrasound by palpability of tumor, Hong Kong Chinese (HK Chinese)

Sensitivity (%)	Age groups	Palpable (%)	Nonpalpable (%)	Total (%)	*p* Value
Mammogram	<40	76 (164/216)	56 (15/27)	74 (179/243)	<0.035*
	≥40	74 (683/925)	69 (122/176)	73 (805/1101)	<0.228
Ultrasound	<40	90 (195/216)	48 (13/27)	86 (208/243)	<0.001*
	≥40	91 (841/925)	57 (100/176)	85.5 (841/1101)	<0.001*

* Significant

Surgery and adjuvant therapy

Overall, women in Hong Kong who were younger were significantly more likely to receive BCS (40.4% versus 28.5%; $p = 0.007$), and the older age group was more likely to have mastectomy performed as a definitive treatment ($p = 0.001$). Of those who opted for mastectomy, the younger women were nearly twice as likely as the older women ($p = 0.001$) to agree to breast reconstruction, and this difference was highly significant ($p < 0.001$) (Fig. 2).

The differences in breast conservation rate were mainly in the group where tumor size was between 1.01 cm and 2 cm (<0.0005). For women who had mastectomy and reconstruction, the differences were significant only in tumor size less than 4 cm. For both groups of women, as the tumor size increased, the likelihood of receiving mastectomy as a surgical treatment increased. In addition, the mode of detection significantly influenced the surgical decision for BCS in both age groups where patients who had radiology screen-detected tumors were more likely to have BCS (59% versus 20.1%; $p = 0.09$). The BCS rate was similar for both the USA Chinese and USA Caucasian groups for both age groups, whereas in Hong Kong Chinese there was a much lower rate of BCS in the older age group. The same proportion of women in both age groups

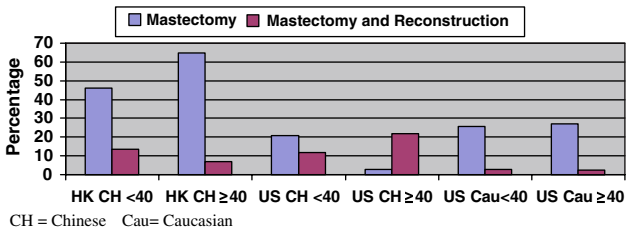

Fig. 2 Mastectomy rate among Hong Kong Chinese (HK Chinese), U.S. Chinese, and U.S. Caucasian women

received axillary surgery and sentinel lymph node biopsy, which is similar to that of women in USA.

Both the younger and the older patients who underwent BCS were given radiotherapy (88.5% versus 90.1%; $p = 0.612$). The younger women, however, were more likely to have received chemotherapy after BCS (54.0% versus 40.2%; $p = 0.08$). For those who had mastectomy, women under 40 years of age were more likely to receive radiotherapy (43.5% versus 35.2%; $p = 0.138$) and chemotherapy (54.1% versus 48.1%; $p = 0.304$), although the difference was not significant. For patients who were ER positive, hormonal treatments were received in a similar manner in the younger and the older groups (48.7% versus 51.4%; $p = 0.501$).

Pathology

When the histological types of cancer were compared, there were similar proportions of noninvasive malignancies in the two groups. All the in-situ cancers in the younger age group were ductal carcinoma in-situ (DCIS), whereas, in the older age groups, 94.9% were DCIS and a smaller proportion were lobular carcinoma in-situ (LCIS) or mixed DCIS and LCIS. The proportions of invasive ductal carcinomas, being the most common form of disease in both groups, were also similar (83% versus 84%). Invasive lobular cancers were rare in our cohort but were significantly more common in the older age group (1% versus 5%; $p = 0.017$). Other types of invasive cancers included papillary, mucinous, medullary, tubular, invasive tubulolobular, and mucoid cancers. There were only 4 (1.9%) cases of invasive phylloides carcinomas, all of which occurred in the younger age group. The median tumor size in the older age group was 18 mm, which was slightly smaller than the 20 mm of the younger group, but the younger women were significantly more likely to have a

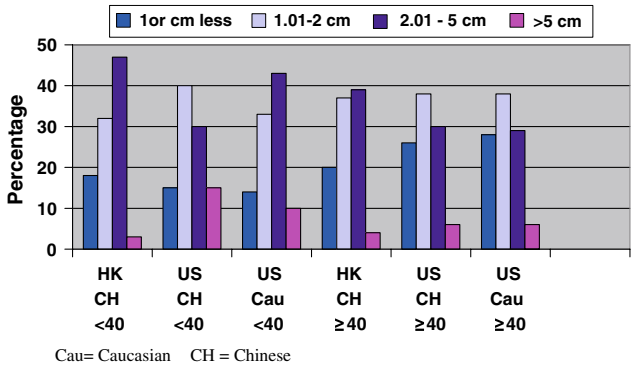

Fig. 3 Tumor size differences by age group

larger tumor (50% versus 43%). This finding was similar among patients in the USA, although there was a significantly higher proportion of USA women in the younger age group–particularly among the Chinese women—who presented with tumors larger than 5 cm (Fig. 3). Younger HK Chinese women also presented with higher grade tumors according to the Bloom and Richardson grading scheme ($p = 0.023$) (Table 2). This is similar to the findings in both USA groups, although significantly more HK Chinese women presented with higher grade tumors. Further analysis of the HK Chinese group found that, in tumors of the same size, it was more likely for women in the younger age group to have higher grade tumors, although this difference was significant only in the 1.01–2 cm tumor size group ($p = 0.015$). Lymphovascular permeation was significantly more common in the younger group of patients (39.9% versus 29.2; $p < 0.001$), as was nodal involvement (40.7% versus 32.8%; $p = 0.024$).

Although the most common presenting stages were stages I and II in both groups, women under the age of 40 were more likely to present at stage II, whereas women who were 40 years of age and above were more likely to present at an earlier stage. This pattern is very similar to that seen in USA Chinese women. However, for USA Caucasian women there is no difference in presentation stage between the two age groups.

The status of ER and PR receptors and cerbB2 positivity was not statistically different, although women younger than 40 have a slightly higher proportion of cerbB2 positive tumors (28% versus 22%). There were no significant correlations in either group of women between negative prognostic indices and tumor grade, lymph node involvement, cerbB2 positivity, lymphovascular permeation, or presence of family history.

The maximum follow-up time was 38 month, and the overall median follow-up time was 21 months. During this period there was a total of six recurrences, 2 in the younger age group and 4 in the older age group, resulting in a recurrence rate of 0.8% (2/258) and 0.3% (4/1207), respectively. There were no deaths during this period of follow-up. The mean time of recurrence was 11.2 months, and recurrences occurred both locally and distally.

Discussion

Breast cancer is the most frequent cancer in Hong Kong Chinese females. The Hong Kong Chinese population is compromised mainly of Southern Chinese. Hong Kong is a cosmopolitan city and its Chinese population has been significantly influenced by the Western culture and lifestyle, unlike citizens residing in mainland China. The age-adjusted incidence of breast cancer has increased from 32.3 to 47.5 per 100,000 women over the past 20 years [13, 16]. Although this incidence is only one-third that of women in USA and half that in Europe, the rise in the incidence of breast cancer and the younger age of presentation is becoming an important health concern in Hong Kong. The incidence of breast cancer in women under the age of 40 was recorded in the analysis of the SEER data in the USA to be 8% [17]. In comparison, statistics from the Hong Kong Cancer Registry showed a correspondingly higher incidence of breast cancer in women younger than 40 years of age: 15.4%, 16.8%, and 12.1% for the periods of 1983–1989, 1990–1999, and 2000–2004 respectively [13]. Although this finding may be partially due to the age structure of the population in Hong Kong, age-adjusted incidence still found that a higher proportion of young women who present with breast cancer in this locality. There is also documentation that, although the Asian population has a lower incidence of

Table 2 Bloom and Richardson grading by age groups

Tumor grade	<40 ($n = 207$)			≥40 ($n = 956$)		
	HK Chinese (%)	p Value compared to USA Chinese (85)	p Value compared to USA Caucasian (3,652)	HK Chinese (%)	p Value compared to USA Chinese (948)	p Value compare to USA Caucasian (68,881)
I	10 (21)	0.953 (9%)	0.385 (17%)	17 (161)	0.094 (7%)	0.002* (23%)
II	34 (70)	0.045 (44%)	0.445 (46%)	38 (363)	0.099 (32%)	0.957 (42%)
III	56 (116)	<0.0005* (47%)	0.009* (37%)	45 (432)	0.353 (61%)	<0.0005* (35%)

* Significant difference on proportion

breast cancer, they have an earlier age at maximal risk and less increase after menopause [18]. The full reason for the peak of onset of breast cancer at the age of 40 is still unclear. This may be attributed in part to a more Westernized lifestyle, reflected by a significant difference in the mean age at first live birth and mean age of menarche in our cohort. Further studies on the predisposition and gene-environmental interaction in this age group [19, 20] may increase this understanding.

Most HK Chinese women in our study had symptoms such as a palpable breast mass. This is to be expected, as routine mammography screening programs commonly available in Western societies have not be replicated in Hong Kong, and most women are either screened voluntarily or seek medical advice when an abnormality is found. Only one quarter of the women screened in Hong Kong are 40 years of age and younger [21]. As women in this age group are even less likely to participate in a voluntary screening program, they are more likely to present with a self-discovered abnormality.

Cancer in the older age group is more likely to be screen detected. The age of presentation in the HK Chinese population is younger, and age distribution is significantly different from that of USA Caucasians, with no increase in breast cancer after menopause, comparable to what has been suggested in the literature for all Asian women. Most women of the younger age group are less likely screen detected, and the absence of routine screening in the younger age group may possibly contribute to the later stage of presentation. The mode of detection in our series of patients significantly influenced both the stage of presentation and the surgical outcome in the two age groups, where screening by radiological methods resulted in earlier staging and an increased rate of BCS. The biological difference of women in our locality may warrant an earlier screening protocol. The cost-benefit of such a program would require further study.

The sensitivity of imaging using mammography and ultrasonography in diagnosing malignancy in HK Chinese women was similar in both age groups, although ultrasonography appeared to be the superior technique This mammograpic sensitivity of 77%–78% is in keeping with some of the published studies in the literature [1]. In our cohort, the mammographic sensitivity is not statistically different between the two groups, contradicting previously published studies where mammographic sensitivity was lower in young women, who are more likely to have dense breasts [22, 23]. It is believed that Asian women generally have denser breast tissue which can obscure cancers on mammography [24, 25]. The insignificant differences between the two groups is likely due to the higher breast density overall, even after menopause [21], although details on breast density were not available for analysis in this study. Previous studies have shown that by combining mammography and ultrasonography, the sensitivity of detection is increased, especially in young women [26–28]. In Hong Kong ultrasonography is more sparingly used, because of greater breast density. Our study found that only 2.7% of the lesions were seen on mammography and not ultrasonography in the younger women; this result is similar to that of the older age group, where 3.2% of the lesions were seen on mammography alone ($p = 0.844$), whereas 13.6% of the lesions were seen on ultrasonography but not mammography in women younger than 40 compared to 15.5% in women older than 40 years of age ($p = 0.503$). This is different from the published literature, where ultrasonography is found to be more reliable than mammography but less reliable in women age 40 and older compared with those younger than 40 [22]. This highlights the importance of the use of ultrasonography in our locality.

Despite the better sensitivity of ultrasonography compared with mammography, the value of mammography should be emphasized as it is the only satisfactory investigation for demonstrating small clusters of microcalcifications, the most common disease presentation in our cohort. Microcalcifications may be unsuspected on clinical examination and also difficult to find on ultrasonography [22].

In our series, 5% and 4.6% of breast cancers were not detected by either mammography or ultrasonography in the two groups, and 4.6% and 2.8% of these missed lesions were detected by MRI Breast in the two groups; the rest were diagnosed by clinical examination. Previous studies have suggested that MRI is more sensitive than mammography in detecting breast lesions in young women and women with dense breasts [29, 30]. Magnetic resonance imaging is generally not indicated in older women who have fatty breasts, although this modality of imaging may be of added value in suitable Chinese women who have dense breasts.

Women younger than 40 years of age were significantly more likely to have BCS, and those who had mastectomy, either by choice or because of failed BCS, were more likely to opt for breast reconstruction. The overall BCS rate compared to the literature describing Caucasian patients and that found in the Seer database is lower in our cohort, on a par with findings of several studies conducted in the United States which demonstrated that BCS was less commonly performed among Asians [31, 32]. A previous study suggested that patients who had BCS had significantly better body image scores compared to mastectomy patients [33], and similar patterns are seen in women who received breast reconstruction after mastectomy [34]. The significance in choice of surgery in the two age groups may be due in part to the women's choice and the feasibility of BCS, but it may also be due to an age biased

recommendation by the physician, as younger women are more likely to be offered BCS or mastectomy with reconstruction, a result of perceived concern about the psychological impact on body image after definitive breast surgery [35, 36]. This difference is significant when the tumor size is less than 2 cm, likely because of the smaller breast size of Chinese women [21], where tumors larger than 2 cm may warrant mastectomy and reconstruction if good cosmetic results are to be achieved. Breast conserving surgery can result in unacceptable deformity in small sized breasts.

Adjuvant chemotherapy has been shown to benefit younger patients more than older patients [37]. The Early Breast Cancer Trialists' Collaborative Group showed that women under 40 years of age had a 37% reduction in recurrence rates and a 27% reduction in death rates when adjuvant chemotherapy was given [38]. Although not significant, women in the younger group of women in our study were more likely to receive chemotherapy after both BCS or mastectomy. Radiation uptake rates, however, were similar in both age groups after BCS. Although radiation is the standard of care after BCS [39, 40], the uptake rate may be affected by socioeconomic status, and also by predetermined patient misconceptions regarding radiation [41].

Although not a significant factor in recurrence, it is more likely for young women to have radiation after mastectomy; this highlights the perceived positive value of adjuvant radiation treatment among young women, who are more likely to have more aggressive tumor characteristics [41, 42], in providing optimal local and systemic control [43].

Various studies have proposed that the underlying tumor pathology contributes to the poorer prognosis seen in young patients with breast cancer [44, 45]. Specifically, younger women have been found to have a higher likelihood of having histologic higher grade and more poorly differentiated tumors [22, 41, 46] , lymphovascular permeation involvement, estrogen receptor negativity [41, 47], more cerbB2 receptor positivity [48], later stage at presentation of larger tumors with more extensive lymph node involvement [12, 42, 49], more proliferative tumors, and genetic alterations [50]. Investigators have also suggested that younger women tend to have a higher recurrence rate [9, 42], poorer recurrence free survival (RFS), and overall survival [51, 52].

In our present series of HK Chinese patients, the majority of the women presented with stage 0-II disease. Women less than 40 years old, however, tended to present at a later stage and also had larger tumor sizes. Both younger HK Chinese women and those in the USA were found to have this characteristic. Caucasian USA women in the older age group had a higher chance of presenting with smaller sized tumors. This may reflect the possibility of a partial delay of diagnosis due to reduced knowledge and clinical suspicion in this young group of women, in particular Chinese women. It may also be that young women have biologically more aggressive tumors. When the histological tumor types were compared, there were similar proportions of noninvasive carcinomas in the two age groups. The most common invasive cancers in both groups was invasive ductal carcinoma, known to be the most common type of invasive breast malignancy [22]. Invasive lobular carcinomas were rare in our cohort but more common in the older age group, a finding similar to that published in the literature [49, 53]. Phyllodes tumors, as expected, were predominantly present in the younger age group. Our series also found that the younger women had considerably more poorly differentiated and higher pathological grade tumors, particularly in the smaller sized tumors. This was so in both the HK and USA cohorts (although HK women had significantly higher grade tumors overall), a finding that supports the aggressive nature of the tumors in the younger age group. Similar to previously published reports, there was more nodal involvement in our younger group of women, and the difference was significant. Lymph node involvement is a known independent prognostic factor for relapse [12]. In both HK and USA Chinese women, the younger age group presented at a later stage. This difference was not seen in the USA Caucasian group, possibly because of the greater availability of breast screening and also cultural differences in disease perception. The younger women in our cohort also had a significantly higher lymphovascular permeation involvement. However, the higher proportion of estrogen receptor negativity seen in Caucasian data was not found in the present study. The proportion of estrogen receptor negativity and positivity is similar to that found in a previous study in Asians [49], suggesting that there may be differences in the molecular basis of breast tumors in different ethnicities, which may result in different biological tumor behavior. CerbB2 positivity was not significantly different between the two groups, although its proportion was higher in the younger age group.

Because of limitations imposed by the short follow-up time of this study, no deaths occurred, and therefore further analyses on RFS and overall survival between the two groups of women were not performed.

This is the first study comparing the tumor characteristics and management of breast cancer in Chinese women younger than 40 years of age and their older counterparts, with subsequent comparison to the Chinese and Caucasian population of the SEER database. Our study found that there are more young women who present with breast cancer in Chinese population. In addition, young Chinese women tend to present with more advanced disease and have more aggressive tumor characteristics, suggesting the likelihood of a worse prognosis. Management of this group of women may include an ethnic-specific screening

protocol and will depend on these tumor characteristics. The impact on body image and choice of surgery may be a more sensitive issue in this young group of Chinese women who have proportionally smaller breast size.

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