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EPIDEMIOLOGY

Presentation and characteristics of breast cancer in young women under age 40

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Abstract

Purpose Although uncommon, breast cancer is the leading cause of cancer death in young women. There are limited studies on the presentation and characteristics of breast cancer in women under age 40.

Methods This is a retrospective study investigating patient demographics, clinical presentations, imaging findings, and cancer characteristics of a cohort of 145 women under age 40 with breast cancer.

Results Our cohort had more aggressive cancer subtypes than reported in older women; 33.1% triple negative, 80% high Ki-67, and 21.3% with stage 3+ disease. Most were referred from primary care or obstetrician/gynecologist, though 5.5% initially presented from the emergency department and another 2.1% were incidental findings. 16.6% of patients presented while pregnant or breastfeeding. Most patients presented with breast related symptoms. Of the 9.1% of patients diagnosed through our high-risk screening program, 84.6% of the cancers were identified on mammography or simultaneously with mammography and MRI. Most breast cancers presented with typically worrisome imaging (82.6%), though several cancers presented with findings that were typically benign.

Conclusions We recommend prompt breast imaging for young women presenting with breast-related symptoms or an incidental breast finding, as younger patients have more aggressive cancer subtypes and are of a higher grade at presentation compared to older women. We also recommend vigilance when distinguishing suspicious symptoms from pregnancy-related breast changes to minimize delays in diagnosis. Additionally, it is important to identify patients who qualify for high risk screening, since cancers in screening patients were found at a lower grade than those presenting with symptoms.

Keywords Breast cancer · Young women · Pregnancy · High risk screening · Detection/diagnosis

Introduction

While breast cancer risk increases with age, it surprisingly continues to be one of the most diagnosed cancers and a leading cause of cancer death in young adult women in many countries [1]. The American Cancer Society estimates that there were approximately 11,870 new invasive breast cancer cases and 1180 new ductal carcinoma in situ (DCIS) cases in women under age 40 in 2019 [2]. Furthermore, the US Surveillance, Epidemiology and End Results (SEER) database found a breast cancer incidence of 64.4 cases per 100,000 women in the 35–39-year-old age group [3].

Under current United States guidelines, population-wide breast cancer screening is not the standard of care for average risk women under age 40 [4]. Therefore, imaging young women for breast cancer requires a high index of suspicion. Unfortunately, women in this age group often have more aggressive cancers [5] with worse outcomes and survival rates [6] compared to women in older age groups.

There are individualized screening procedures for higher-than-average risk women under age 40. Patients can be at an increased risk for breast cancer for multiple reasons, including genetic predispositions (e.g. *PT53, CHEK2,* breast cancer gene *[BRCA] 1, BRCA2* pathogenic variants), prior mantle/chest wall radiation, and extensive family history of breast cancer. Many statistical models have been created to estimate a woman's lifetime risk of developing breast cancer. The American College of Radiology (ACR) recommends

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evaluating each woman's breast cancer risk by age 30 to identify those that may benefit from earlier screening. They also give specific recommendations for breast cancer screening, including the age to initiate screening for both average-risk and high-risk women and the screening modality to use (i.e. mammography and/or MRI and/or ultrasound) [4].

Work-up of patients with breast-related symptoms is necessary regardless of age. Younger patients typically have increased breast tissue density, which decreases the sensitivity and specificity of mammography. Additionally, consideration should be given to the risks of radiation exposure to radiosensitive breast tissue in younger patients, as they have a longer time to develop radiation-induced cancers given their longer life expectancy. Thus, the ACR appropriateness criteria rates breast ultrasound to be usually appropriate for the initial evaluation of women younger than 30 presenting with a palpable breast mass, and mammography or ultrasound usually appropriate in women 30–39 years old with a palpable breast mass [7].

There have been limited studies focused on the presentation of breast cancer in women under age 40, regardless of risk. Some studies focused on younger patients have looked at patient demographics and cancer characteristics in developing countries such as Jordan [8] or Mexico [9], while others have explored general breast cancer histologic subtypes in several European countries [1]. Several papers have addressed characteristics, prognosis, management and outcomes specifically in young women with breast cancer [6, 10]. This current study investigates the clinical presentations, breast imaging findings, patient demographics, and unique cancer characteristics of young women diagnosed with breast cancer at our academic institution located in the United States. We present the characteristics of a large cohort of women under 40 years old with breast cancer to better inform clinical practice.

Methods

This study was approved by the hospital's institutional review board with a waiver for informed consent.

We conducted a retrospective cohort study of all women diagnosed with breast cancer before age 40 at our tertiary care center between July 1, 2013 and November 1, 2019.

Patient sociodemographic information including age, race, ethnicity, employment status, and marital status was obtained from the Epic electronic medical record (EMR) system (Epic Systems Corporation, Verona, Wisconsin). Additional breast related medical history was manually extracted from the EMR including whether or not the patient was breastfeeding or pregnant at the time of diagnosis, family history of breast cancer (and specifically premenopausal breast cancer), known genetic mutation resulting in predisposition for breast cancer, reason for presentation (i.e. screening versus breast related symptom), and presenting symptom when applicable. Breastfeeding status was defined as breastfeeding within 1 month of breast cancer diagnosis.

The patients' mammographic, ultrasound, and/or MRI findings were included in the data extraction. The Breast Imaging Reporting and Data System (BI-RADS) assessments and breast density were also recorded.

Cancer characteristics were also manually extracted from the EMR, including invasive versus in situ disease, invasive cancer subtype, Ki-67 grade, and cancer stage. Hormone receptor status, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2) were recorded when applicable. All patients had histopathology reviewed at our institution.

The time between initial presentation and diagnosis was defined as the number of days from the date of the patient's first symptom to the date that the first breast cancer histopathology specimen was obtained, as defined in prior literature [11]. The date when the first symptom was noticed was obtained from the documented patient history either in a clinical note or the diagnostic breast imaging report. Exact dates were used when available, with the first day of the documented month of first symptom used if no specific date was given.

All breast imaging studies were interpreted by a dedicated breast radiologist with 1–34 years of experience in breast imaging.

Descriptive statistics were used to present the baseline characteristics of young women with breast cancer at our institution. The Chi-square test was used to compare cancer characteristics (invasive disease versus DCIS, hormone receptor status, and stage of cancer) based on patients' race, whether the cancer was diagnosed on screening versus diagnostic examination, and whether the patients were pregnant or breastfeeding at the time of diagnosis. A p-value <0.05 was considered statistically significant. All analyses were done using the computing program R [12].

Results

150 women were originally identified for the study, of which 5 were diagnosed with recurrent breast cancer and excluded from this analysis. Therefore, the study population consisted of a total of 145 women who were diagnosed with breast cancer at our institution during the study period.

Patient presentation

Baseline sociodemographic characteristics of these 145 women are shown in Table 1.

Table 1 Demographics of women under age 40 with breast cancer (n = 145)

Patient demographics	Number (%) or Mean (SD)
Age	34.6 (4.0)
Race[a]	
White	72 (49.7%)
Black	42 (29.0%)
Neither black nor white[b]	31 (21.4%)
Ethnicity[c]	
Hispanic	10 (7.1%)
Not Hispanic	130 (92.9%)
Marital status	
Married	81 (55.9%)
Single	52 (35.9%)
Divorced, separated, or widowed	12 (8.3%)
Employment status	
Full time	93 (64.1%)
Not full time	52 (35.9%)
Family history of breast cancer[d]	76 (55.6%)
Premenopausal family history of breast cancer[e]	35 (26.5%)
Known genetic predisposition	48 (33.3%)
Pregnant	10 (6.9%)
Breastfeeding	14 (9.7%)

SD = standard deviation

[a]3 patients did not have a documented race

[b]This group includes American Indian or Alaska Native (1), Asian (13), and "Other" (17)

[c]5 patients did not have a documented ethnicity

[d]8 patients did not have a documented family history of breast cancer

[e]13 patients did not have a documented premenopausal family history of breast cancer

Most of the women in this cohort (128/145 = 88.3%) presented with one or more breast-related symptoms. 105 (84.0%) patients had a palpable finding, 11 (8.8%) had a change in breast shape, 7 (5.6%) had nipple discharge, and 6 (4.8%) had pain without a corresponding palpable finding. Note that one patient had both a palpable finding and nipple discharge.

Patients presented to the breast department for further workup from several different providers. Most (83%) patients were referred from a primary care physician or obstetrician/gynecologist. However, 8 (5.5%) patients initially presented to the Emergency Department (ED). Six of these cases was thought to represent a breast malignancy based on physical exam and radiologic studies performed in the ED. One woman presented with symptoms and findings consistent with a breast abscess. Another presented with chest pain and dyspnea who was believed to have a pulmonary embolism, with computed tomography angiography (CTA) incidentally showing enlarged axillary lymph nodes and a breast mass. This patient's imaging is shown in Fig. 1. Two other patients were found to have incidental breast masses on chest computed tomography (CT) imaging performed at outpatient centers for non-breast related complaints.

The time between initial presentation and diagnosis was 53 days (IQR 13–135 days) for all the women presenting with breast related symptoms.

Our institution's high-risk breast cancer screening procedures identified 13 (9.0%) of the breast cancers in the cohort, including one case that was identified on a whole-body MRI for cancer screening in a patient with Li Fraumeni syndrome. Nine (69.2%) were initially found on mammographic screening and 2 (15.4%) on MRI screening. The final 2 (15.4%) patients had findings seen simultaneously on mammographic and MRI screening. An example case of a screen detected cancer on mammography and MRI is shown in Fig. 2.

Imaging Findings of breast cancers

Imaging characteristics are included in Table 2. Most (127/145 = 87.6%) of the breast cancers were described as masses on ultrasound or MRI. Initial imaging was available for 109 of these cases, and while 90 (82.6%) had irregular shape, 12 (11.0%) cases were round or oval shaped with circumscribed margins. An example of a patient with an oval mass with circumscribed margins that turned out to be cancerous is shown in Fig. 3. All patients were given a BI-RADS 4 or 5 assessment when first presenting to breast imaging for the finding which was ultimately found to represent a breast cancer.

Cancer characteristics

Imaging and cancer characteristics are listed in Table 2. Of the 145 patients in our cohort, 127 (87.6%) patients had invasive breast cancer and 18 (12.4%) had ductal carcinoma in situ (DCIS). Most patients with invasive cancer had a ductal subtype (117/127 = 92.1%). Of the invasive cancers, 77 (60.6%) were ER/PR positive, 27 (21.3%) were HER2/neu positive, 42 (33.1%) were triple negative, and 72 (80%) had a high (>20%) Ki-67. At the time of diagnosis, 38 patients were stage 1 (32.5%), 54 stage 2 (46.2%), 15 stage 3 (12.8%), and 10 stage 4 (8.5%).

Screen detected versus symptomatic cancers

As shown in Table 3, screen detected cancers were significantly more likely to be DCIS (6/14 = 42.9% in high risk screening patients, versus 11/125 = 8.8% in symptomatic patients, p = 0.002). There was no significant difference in the hormone receptor status or stage of the invasive cancers in screening versus symptomatic patients, although there

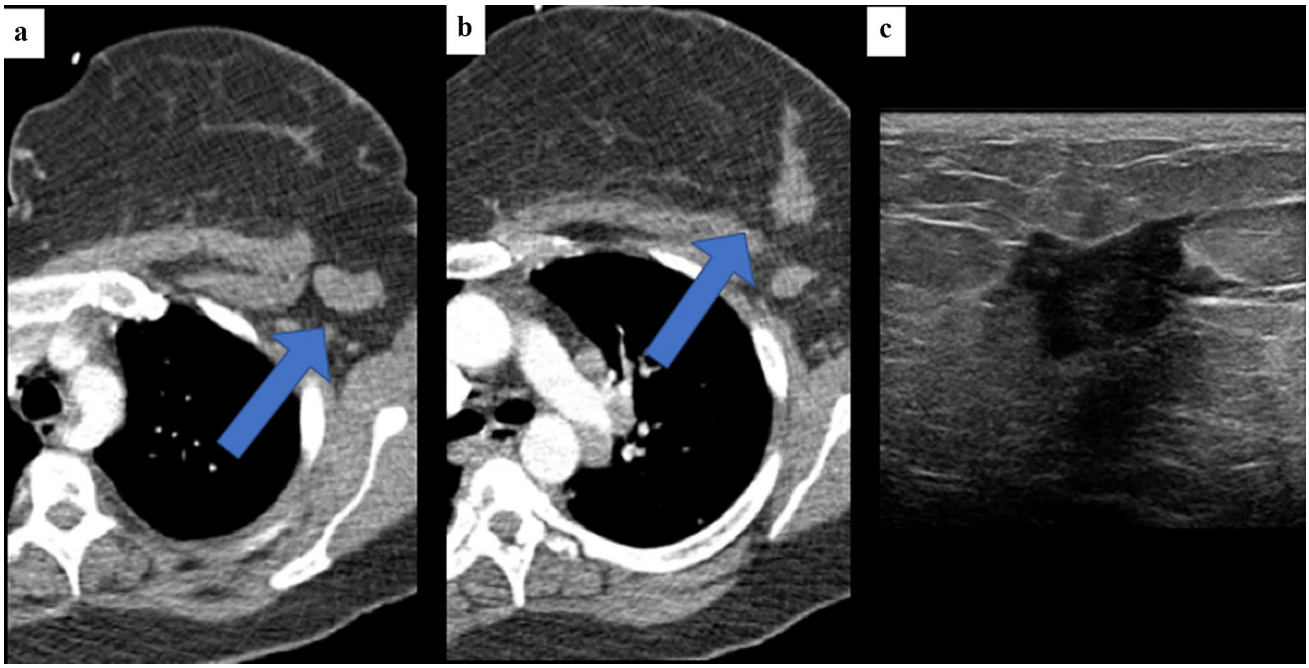

Fig. 1 39 year-old female without history of cancer presents to the emergency department with a 2 month history of bronchitis and sharp burning chest pain not improved with antibiotics. Initial differential was pulmonary embolism vs infection. (**a**) Chest computed tomography angiography shows multiple enlarged axillary lymph nodes and (**b**) asymmetric irregular mass-like tissue in the left breast. (**c**) Breast ultrasound shows a spiculated mass with posterior acoustic shadowing. Surgical pathology revealed infiltrating poorly differentiated ductal adenocarcinoma

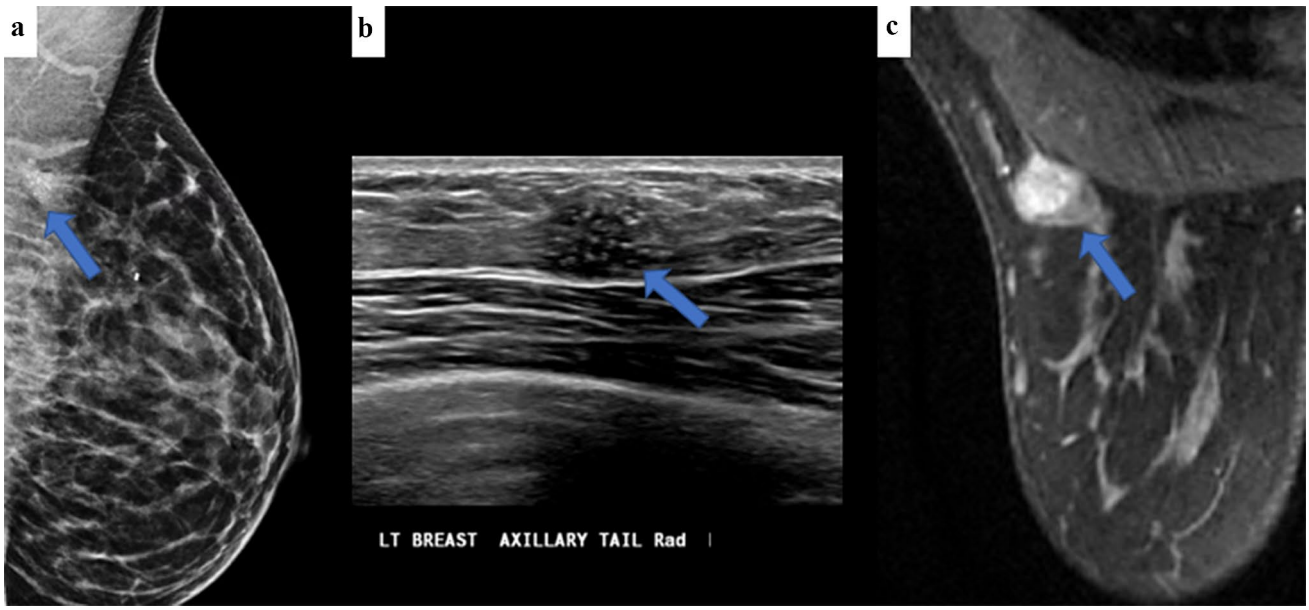

Fig. 2 35 year-old female with breast cancer gene (*BRCA) 2* pathogenic variant and a paternal family history of *BRCA 1* and *2* pathogenic variants presents for screening mammogram and magnetic resonance imaging. She had a prior benign left breast biopsy. (**a**) Mammogram shows coarse heterogeneous and pleomorphic calcifications seen in the left upper outer quadrant posterior depth. (**b**) Breast ultrasound shows a mass with calcifications in the left axillary tail and (**c**) breast magnetic resonance imaging demonstrates an irregular enhancing mass in the left axillary tail region. Pathology revealed infiltrating ductal adenocarcinoma

Table 2 Imaging and cancer characteristics of women under age 40 with breast cancer (n = 145)

Imaging/cancer characteristics	Number (%)
Predominant suspicious imaging finding	
Mass	127 (87.6%)
Calcifications[a]	32 (22.1%)
Non mass enhancement	2 (1.4%)
Size of mass (mean [standard deviation])	2.7 cm (1.8 cm)
Modality of initial biopsy[b]	
Ultrasound	126 (88.1%)
Stereotactic	14 (9.8%)
MRI	3 (2.1%)
BI-RADS classification at presentation	
4 or 5	145 (100%)
Type	
Ductal carcinoma in situ	18 (12.4%)
Invasive	127 (87.6%)
Invasive subtype	
Ductal	117 (92.1%)
Mammary	4 (3.1%)
Lobular	4 (3.1%)
Mucinous	2 (1.6%)
Receptor status of invasive cancers	
Both estrogen and progesterone receptor positive	77 (60.6%)
HER2neu	27 (21.3%)
Triple negative receptor status of invasive cancers	42 (33.1%)
Ki-67 for invasive cancers[c]	
Low (<= 20%)	18 (20.0%)
High (>20%)	72 (80.0%)
Stage of invasive cancers[d]	
1	38 (32.5%)
2	54 (46.2%)
3	15 (12.8%)
4	10 (8.5%)

[a]14 patients had suspicious calcifications only. 18 patients had both a suspicious mass and suspicious calcifications

[b]One patient had ultrasound and stereotactic biopsy on the same day. One patient had excision of calcifications due to the posterior location not amenable to biopsy. Modality of initial biopsy was not available for one patient

[c]Documented for 90 patients

[d]Documented in 117 patients

was a trend toward patients in the symptomatic group being stage 3 or 4 (0% in high risk screening patients, versus 21.3% in symptomatic patients, p = 0.25).

Pregnant and breastfeeding patients

Pregnant patients had a shorter median time to diagnosis compared to nonpregnant patients (24 days IQR 5.5–49.3 days, versus 56 days IQR 18–143 days, p = 0.05). There was no significant difference in the amount of time between symptoms and diagnosis for breastfeeding patients compared to non-breastfeeding patients (81 days IQR 24–122 versus 48.5 days IQR 15.5–137.5 days, p = 0.41).

All of the 24 (100%) pregnant or breastfeeding patients in our cohort were found to have invasive breast cancer, compared to 103 (85.1%) cases of invasive and 18 (14.9%) cases of DCIS in nonpregnant and not breastfeeding patients (p-value 0.04). While there was no difference in receptor status of the invasive cancers, the pregnant patients were statistically more likely to be diagnosed at stage 3 or 4 (9 women, 37.5%) compared to nonpregnant or breastfeeding patients (16 women, 17.2%).

Effect of race on time to presentation and cancer characteristics

As shown in Table 4, the time to presentation was similar among white patients, black patients, and patients of other races (p = 0.74). We also did not find significant differences between the percentages of women diagnosed with invasive cancer versus DCIS (p = 0.43), triple negative cancers (p = 0.23), or higher stage cancers (p = 0.81) when stratified by race.

Discussion

We present results from a large cohort of women under age 40 with new diagnoses of breast cancer, describing their demographics, presentation warranting breast imaging, imaging features, and cancer characteristics.

Our cohort had more aggressive cancer subtypes than reported in older women; 33.1% triple negative, 80% high Ki-67, and 21.3% with stage 3+ disease. This is in keeping with findings from multiple prior studies [5, 13] showing that younger women's breast malignancies were of a higher grade and more likely to be aggressive. Prior studies evaluating women in the SEER database have also shown higher mortality in younger patients with breast cancer, which was even more prominent in stage 1 or 2 disease, when compared to older patients [13]. Additionally, the data from the US and multiple European countries show the greatest rise in the incidence of breast cancer in younger women (highest in women 20–29 years old in the US, 15–34 years old in Europe) [1, 14].

While most patients were referred from a primary care physician or obstetrician/gynecologist, 5.5% initially presented from the ED and another 2.1% were found incidentally on another imaging modality (i.e. chest CT). Some patients who presented to the ED had findings suggestive of breast cancer, while others were thought to have a breast abscess or a pulmonary cause for symptoms. Our findings

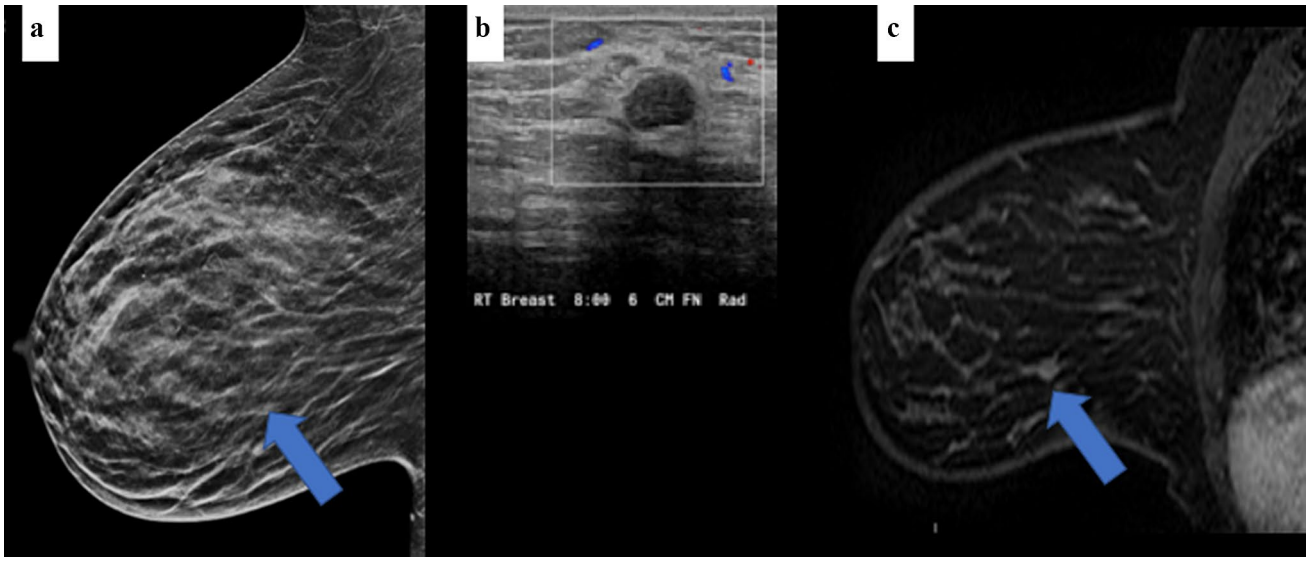

Fig. 3 34 year-old female with a palpable right breast mass. (**a**) Right mediolateral oblique mammogram showing an oval mass with partly obscured margins. (**b**) Breast ultrasound demonstrates a circumscribed oval mass. Ultrasound biopsy was performed yielding ductal carcinoma in situ. (**c**) Breast magnetic resonance imaging shows multicentric ductal carcinoma in situ including an enhancing mass in the right breast correlating to the mass seen on mammogram and ultrasound

emphasize that breast malignancy should be considered not only when young women present to the emergency department with breast-related symptoms, but when there is difficult-to-localize chest symptoms as well. This is in keeping with prior studies performed in patients of all ages which showed that while breast abscesses and mastitis are the most common breast related diagnoses in the ED, 0.5–5% of ED breast ultrasounds resulted in a diagnosis of malignancy [15, 16]. An additional 3 patients had breast masses and/or suspicious lymph nodes incidentally found on a chest CT performed for non-breast related complaints, further emphasizing that all incidental breast findings should be promptly followed-up with breast imaging. In fact, one prior study showed that 35% of incidental breast abnormalities first identified on chest CT turned out to be malignant [17].

Prior studies including women of all ages have shown that black race is associated with a delay in diagnosis of breast cancers [18] and with presentation at a later stage [19]. In our cohort of young women, we did not find a significant difference in the time to presentation, percentages of invasive cancer versus DCIS, triple negative cancers, or higher stage cancers when stratified by race. This suggests that racial disparities can vary by age group, although larger studies are needed to confirm our findings.

Most breast cancers presented as masses that were described as having an irregular shape on imaging (82.6%), as would typically be expected for breast malignancies. However, several cancers presented with unusual morphologies. For example, 12 masses that turned out to be malignant were round or oval in shape with circumscribed margins, which is a common appearance for a fibroadenoma. An oval circumscribed mass can be assessed as a BI-RADS 3 [20] only after a careful history and exam is performed to assess for other risk factors to ensure a biopsy is not warranted. For example, there is evidence that all masses, even those with typically benign features such as circumscribed margins should be biopsied in patients with a *BRCA1 or 2* gene mutation. This highlights the overlap that can exist in the imaging features of fibroadenomas and breast malignancies, which underscores the importance of carefully considering the clinical history and recommending short-interval follow-up imaging for oval masses with an imaging appearance suggestive of a fibroadenoma. These women were recommended for biopsy due to a reported change in size, strong genetic/family history of breast cancer, associated pain, or strong patient preference.

Of the patients in our study cohort, 16.6% of patients presented while pregnant or breastfeeding, emphasizing the importance of distinguishing suspicious symptoms from expected pregnancy-related breast changes of increased size and density during this period. Interestingly, the median time between first symptom and diagnosis in pregnant patients was only 24 days, which is significantly less than the median of 53 days within the whole cohort. Perhaps more frequent access to healthcare providers during routine obstetric visits helped to decrease the time interval from when the patient perceives a reason to discuss a concerning symptom and the time the patient consults with a healthcare provider [11]. Some studies [21] have shown a delay in diagnosis in pregnancy associated breast cancer (defined as breast cancer

Table 3 Demographics and cancer characteristics of women under age 40 with breast cancer (n = 145) who were diagnosed by high risk screening compared to breast related symptoms and for patients not pregnant or breastfeeding compared to women pregnant or breastfeeding

	Screening N = 14 Number (%)	Breast related symptom N = 125 Number (%)	P-value
Type			
Ductal carcinoma in situ	6 (42.9%)	11 (8.8%)	0.002[a]
Invasive	8 (57.1%)	114 (91.2%)	
Receptor status of invasive cancers			
Estrogen and progesterone receptor positive	7 (87.5%)	62 (54.4%)	0.14[a]
HER2neu	1 (12.5%)	25 (21.9%)	1.00 [a]
Triple negative receptor status of invasive cancers	1 (12.5%)	40 (35.1%)	0.48
Stage of invasive cancers[b]			
1	4 (66.7%)	34 (31.5%)	0.25
2	2 (33.3%)	51 (47.2%)	
3 or 4	0 (0%)	23 (21.3%)	
	Not pregnant or breastfeeding N = 121 Number (%)	Pregnant or breastfeeding N = 24 Number (%)	P-value
Type			
Ductal carcinoma in situ	18 (14.9%)	0 (0%)	0.04[a]
Invasive	103 (85.1%)	24 (100%)	
Receptor status of invasive cancers			
Estrogen and progesterone receptor positive	63 (61.2%)	9 (37.5%)	0.06[c]
HER2neu	22 (21.4%)	5 (20.8%)	1.00[c]
Triple negative receptor status of invasive cancers	30 (29.1%)	12 (50.0%)	0.08[c]
Stage of invasive cancers[d]			
1	36 (38.7%)	2 (8.3%)	0.008[c]
2	41 (44.1%)	13 (54.2%)	
3 or 4	16 (17.2%)	9 (37.5%)	

[a]Fisher Test

[b]No stage documented for 8 patients

[c]Chi-squared test

[d]No stage documented for 10 patients

diagnosed during pregnancy or within one year of delivery). Our data suggests that there may actually be three different groups of women, with the pregnant patients experiencing less delay than the breastfeeding or the non-pregnant patients.

While most patients were diagnosed after presenting with a breast related symptom, 9.1% were diagnosed through our high-risk screening program. Most (84.6%) breast cancers in this group were identified on mammography or simultaneously with mammography and MRI. Two (15.4%) patients were screened with MRI only, and thus their cancer was identified on MRI. Screened asymptomatic patients in our cohort of young breast cancer patients were significantly more likely to have DCIS compared to symptomatic patients, consistent with multiple prior studies involving older populations [22, 23]. When looking at the screen-detected invasive cancers, there was no significant difference in the hormone receptor status or stage of cancer, although there was a trend toward patients in the symptomatic group being of a higher stage at time of detection, as would be expected.

This study has several limitations. We present results from a single tertiary care institution which limits the generalizability of our findings. This was a retrospective cohort project, and patient histories were obtained from either clinical notes or imaging reports, with a range of available details. While this is a large cohort compared to other studies focused on this population of young breast cancer patients, the size is still relatively small (especially when performing subgroup analysis), thus limiting the power to detect differences between the small subgroups.

Table 4 Cancer characteristics of women under age 40 with breast cancer by race

	White N = 72 (49.7%)	Black N = 42 (29.0%)	Neither black nor white[a] N = 31 (21.4%)	P-value
Days from symptom to diagnosis				
Median (interquartile range)	63 (18–117)	36 (17–143)	50 (13–221)	0.74[b]
Type				
Ductal carcinoma in situ	10 (13.9%)	3 (7.1%)	5 (16.1%)	0.43[c]
Invasive	62 (86.1%)	39 (92.6%)	26 (83.4%)	
Triple negative receptor status of invasive cancers	22 (35.5%)	15 (38.5%)	5 (19.2%)	0.23 [d]
Stage of invasive cancers[d]				
1	19 (32.8%)	14 (37.8%)	5 (22.7%)	0.81[c]
2	27 (46.6%)	16 (43.2%)	11 (50.0%)	
3 or 4	12 (20.7%)	7 (18.9%)	6 (27.3%)	

[a]This group includes American Indian or Alaska Native (1), Asian (13), and "Other" (17)

[b]Kruskal-Wallis Test

[c]Fisher Test

[d]Documented in 117 patients

[e]Chi-squared test

In conclusion, we report our institution's experience with women under age 40 diagnosed with breast cancer. Based on our results, we recommend emphasizing prompt breast imaging for young women presenting with either breast-related symptoms or an incidental breast finding, as younger patients have more aggressive cancer subtypes and are of a higher grade at presentation compared to older women. We also recommend vigilance when distinguishing suspicious symptoms from expected pregnancy-related breast changes in pregnant and breastfeeding patients to minimize delays in diagnosis. Women under 40 years old are not routinely recommended for screening unless they are considered high risk based on validated risk models. It is important to note that women in our cohort who presented with findings from high risk screening tend to have a lower cancer stage compared to those who presented with a breast-related symptom, suggesting that their cancer was caught earlier than if they were not screened. This emphasizes the importance of identifying patients who qualify for high risk screening. Understanding the demographics, presentations, and cancer characteristics allows us to better target the diagnosis and treatment of breast cancer in this population.

Author contributions Emily Ambinder and Xueying Hu designed the study. Xueying Hu and Armina Azizi performed chart review. Emily Ambinder and Xueying Hu analyzed the data and wrote the manuscript with input from all authors. All authors revised the manuscript critically for important intellectual content, read, and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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