FERTILITY PRESERVATION



Disparities in fertility preservation among patients diagnosed with female breast cancer

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Abstract

Purpose To investigate the association of specific patient factors with disparities in fertility preservation counseling and utilization of fertility preservation among patients ≤ 40 years old diagnosed with female breast cancer.

Methods A retrospective chart review was conducted investigating patients diagnosed with breast cancer between January 2012 and December 2020 in a multi-site health system. Rates of fertility counseling and utilization of preservation services were compared based on age, race/ethnicity, parity, insurance type, and treatment site.

Results Of the 6,783 patients diagnosed with female breast cancer, 306 (4.5%) were \leq 40 years old at the time of diagnosis. There was no significant difference between Black or African American and White patients in rates of fertility counseling (12.1% vs 17.4%; p=0.285) or pursuit of fertility preservation (3.3% vs 4.2%; p=0.508), nor was a difference observed when compared by insurance type. However, younger patients (<30 years of age), patients with 1 or no children, and patients treated in the more affluent county were more likely to undergo counseling and pursue fertility preservation than their matched counterparts.

Conclusion Age, parity, and location of breast cancer care may impact rates of fertility counseling and preservation among reproductive age women diagnosed with breast cancer. Thus, further attention to age discrimination, a patient's desire for future fertility, need for standardization in fertility preservation counseling, and perhaps implementation of comprehensive fertility coverage mandates across all states could help to improve gaps in fertility counseling and fertility preservation.

Keywords Breast cancer · Fertility counseling · Fertility preservation · Disparities

Introduction

Female breast cancer diagnosed in patients under age 40 years old accounted for 4% of all new breast cancer cases in 2022 in the United States [1]. It is well known that breast cancer diagnosed at a young age is more aggressive, higher grade, and hormone receptor negative. Therefore, individuals under the age of 40 who are diagnosed with female breast cancer are more likely to require treatment that may be gonadotoxic or necessarily delay their pursuit of childbearing.

Fertility preservation counseling is an invaluable aspect of care for patients with breast cancer. In 2018, the American

Monique Swain mswain1@hfhs.org Society of Clinical Oncology published guidelines to provide oncologists and other medical providers with recommendations regarding fertility preservation in people diagnosed with cancer. The guidelines clearly state that health care providers should refer patients who are interested in fertility preservation, and even those who are ambivalent about it, to reproductive specialists. Additionally, they recommend that fertility preservation should be discussed in a timely manner, before any treatments start [2].

Although American Society of Clinical Oncology has created clear guidelines to standardize fertility preservation for patients diagnosed with cancer, the guidelines are not always implemented equally among patients. Racial disparities and socioeconomic barriers to fertility preservation among patients diagnosed with cancer have been documented. Black or African American women are more likely than White women to be diagnosed with triple negative breast cancer, which is more aggressive than hormone receptor positive breast cancer and is diagnosed at younger

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ages [3]. However, White women are 2 times more likely to receive fertility preservation counseling [4]. Gonadal toxic agents such as cyclophosphamide are routinely used to treat triple negative breast cancer, thus putting Black or African American women at an increased risk for infertility.

The most established method of fertility preservation, embryo cryopreservation, costs approximately \$12,000 per cycle and is not routinely covered by health insurance [5]. It has been documented that women with cancer were less likely to utilize fertility preservation procedures if they were of lower socioeconomic position [6]. The state of Michigan does not have a state mandate requiring insurers to offer coverage for infertility treatments or assisted reproductive technologies. Also, employers in Michigan are not required to recognize the need for providing coverage for infertility to their employees. In 2020, the median household income in the state of Michigan was \$59,234. Moreover, the median household income in the city of Detroit, where 77.1% of the population is Black or African American, was \$34,762, which is less than the national household median income of \$48,297 for Black or African American families [7, 8]. Thus, many young Black or African American women with breast cancer may be unlikely to afford the high costs of fertility preservation. Evidence from past studies have shown higher utilization of in vitro fertilization procedures in states where there are comprehensive insurance mandates [9, 10]. However, state insurance mandates for fertility coverage alone were not shown to improve utilization among non-Hispanic Blacks and Hispanic/Latinx [11].

Many other factors aside from race and socioeconomic status have been shown to impact fertility preservation utilization. In a publication by Meernik et al. investigating disparities in pursuit of fertility preservation in women aged 15–39 with cancer, older age (35–39), living in a non-urban environment, and parity demonstrated lower usage of fertility preservation [6]. Villarreal Garza et al. described the initial results of a program designed to help young women with breast cancer in Latin America. They found that younger age, private insurance, higher level of education, and having less children were associated with higher rates of fertility preservation [12]. Lambertini et al. suggested that barriers to fertility preservation are linked to a lack of health care provider engagement, limited public coverage, and inequitable distribution of cancer centers and specialists [13].

The objective of this retrospective study was to investigate whether specific patient factors were associated with disparities in fertility preservation counseling and utilization of fertility preservation among patients ≤ 40 years old who were diagnosed with female breast cancer within a hospital system that spans 3 of the largest counties in southeast Michigan. Understanding disparities in access to fertility preservation is needed for developing solutions to close the gap in fertility preservation care for individuals who wish to have children after breast cancer treatment.

Methods

This was a retrospective study that assessed medical records within an established hospital system registry of 6,783 patients who were diagnosed with breast cancer between January 2012 and December 2020. The study was deemed exempt after review by the International Review Board committee at Henry Ford Hospital. The inclusion criteria included the following: all patients diagnosed with female breast cancer age 40 years old or younger and treated at our local hospital system across Wayne, Oakland, and Macomb counties. Demographics included race/ ethnicity, age, parity, stage of cancer diagnosis, hormone receptor status, insurance type (private vs public), marital status, primary or preferred language, home county as defined by the address reported in their medical record, education level, and treatment site (Wayne, Oakland, and Macomb counties). Differences in fertility counseling and utilization of fertilization preservation rates were assessed across race/ethnicity, insurance type, treatment site, parity, and age (30 years or younger vs 31-40 years old) using Fisher's exact tests. R Statistical Software (v4.2.1) was used for all statistical analysis. P value ≤ 0.05 was considered statistically significant.

Treatment sites were included for comparison due to their differences in racial and socioeconomic composition. The three treatment hospitals were in Wayne, Oakland, and Macomb counties. Wayne county is home to Detroit, the most populous city in Michigan. Detroit comprises 620,736 people [7]. According to the United Statues Census Bureau as of July 1 2022, the median household income in Detroit is \$34,762 and the poverty rate is 31.8% compared to Wayne county's overall rate of 19.6% [7]. The race/ethnic background of Wayne county includes 54.7% White alone, 38.4% Black or African American alone, 0.5% American Indian or Alaska Native, 3.7% Asian alone, 2.9% Two or more races, and 6.6% Hispanic or Latinx [14]. Oakland County has a median household income of \$86, 275 and a poverty rate of 7.8%. Oakland county's population is comprised of 74.6% White alone, 13.9% Black or African American alone, 0.3% American Indian or Alaska Native, 8.6% Asian alone, 2.4% Two or more races, and 4.8% Hispanic or Latinx [14]. Macomb County has a median household income of \$67,828 and a poverty rate of 11.6%. Macomb County's population is comprised of 78.2% White alone 13.7% Black or African American, 0.3% American Indian or Alaska Native, 5% Asian alone, 2.8% Two or more races, and 3%—Hispanic or Latinx [14].

Results

Of the 6,784 patients who were diagnosed with female breast cancer within our hospital system during the study period, 306 (4.5%) were diagnosed with female breast cancer at age 40 or younger. The racial/ethnic distribution in this study included 166 (54.2%) White patients, 91 (29.4%) Black or African American, 21 (6.9%) other or declined to answer, 16 (52%) Asian, 7 (2.3%) Hispanic/Latinx, 4 (1.3%) Two or more races and 1 (0.3%) Native Hawaiian/Pacific (Table 1). A total of 212 (69.3%) patients were diagnosed with breast cancer at Stage 0-II and 55 (18%) were diagnosed at Stage III-IV. There were 224 (73.2%) patients who were diagnosed with hormone receptor positive breast cancer and 46 (15.0%) were diagnosed with triple negative breast cancer. There were 236 (77.1%) patients who had private insurance and 66 (21.6%) with public insurance. Almost half of the patients diagnosed with breast cancer were treated in Wayne County (n = 143; 46.7%), 115 (37.6%) were treated in Oakland County, and 48 (15.7%) were treated in Macomb County (Table 1).

Table 1 Demographic and clinical information of patients diagnosed with female breast cancer (n = 306)

Variable	Patients $(n=306)$		
	n (%)		
Race / Ethnicity			
White	166 (54.2)		
Black or African American	91 (29.7)		
Other/Unknown	21 (6.9)		
Asian	16 (5.2)		
Hispanic/Latinx	7 (2.3)		
Two or more races	4 (1.3)		
Native Hawaiian/Pacific Islander	1 (0.3)		
Stage of diagnosis			
0-II	212 (69.3)		
III-IV	55 (18.0)		
Other/Unknown	39 (12.7)		
Hormone receptor status			
Estrogen and/or progesterone positive	224 (73.2)		
Estrogen, progesterone, and HER2NEU negative	46 (15.0)		
Unknown	36 (11.8)		
Insurance type			
Private	236 (77.1)		
Public	66 (21.6)		
Other/Unknown	4 (1.3)		
Treatment site by county			
Macomb	48 (15.7)		
Oakland	115 (37.6)		
Wayne	143 (46.7)		

A total of 45/306 (14.7%) patients diagnosed with breast cancer received fertility counseling (Table 2). Fertility preservation procedures were utilized by 10/306 (3.27%) (Table 2). Of the 10 who received fertility preservation 5 underwent cryopreservation therapy and 5 received leuprolide injections (Table 2). More patients who received fertility counseling were diagnosed with Stage 0-II disease 31/45 (68.9%) than patients diagnosed with Stage III-IV disease, 5/45 (11.1%). Of the 10 patients who utilized fertility preservation 9 were Stage 0-II, 3 had triple negative breast cancer, and 5 had hormone receptor positive breast cancer. More patients who received fertility counseling were diagnosed with triple negative breast cancer, 32/45 (71.1%), than patients diagnosed with triple negative breast cancer, 7/45 (15.6%) (Table 2).

Comparison of Black or African American and White patients diagnosed with breast cancer showed no significant difference in fertility counseling (12.1% vs 17.4%; P=0.285) or fertility preservation (3.3% vs 4.2%; P=0.508) between groups. Patients 30 years and younger were significantly more likely to receive fertility counseling (26.8% vs 12.8%; P=0.034) and undergo fertility preservation (12.2% vs 1.9%; P=0.005) than patients 31–40 years old (Table 3). Patients who had 1 or no children were significantly more likely to receive fertility counseling (20.0% vs 11.3%; P=0.008) and undergo fertility preservation (8.2% vs 0.9%; P=0.001) than patients with 2 or more children (Table 3).

When characterizing the population at each treatment site, Macomb County consisted of 68.8% patients who were married and 97.9% patients who reported English as their primary language (Table 4). The racial/ethnic profile included 35/48 (72.9%) White, 7/48 (14.6%) Black or African American, 3/48 (6.3%) Asian, and 3/48 (6.3%) Other or declined not to answer (Table 4). Most patients treated

 Table 2
 Stage of diagnoses and hormone receptor status of patients

 who underwent fertility counseling and preservation
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	Fertility counseling (n=45) n (%)	Fertility preservation $(n=10^{a})$ n (%)
Stage 0-II	31 (68.9)	9 (90.0)
Stage III-IV	5 (11.1)	*
Estrogen and/or progesterone positive	32 (71.1)	5 (50.0)
Estrogen, progesterone, and HER2NEU negative	7 (15.6)	3 (30.0)

^aOf these 10 patients, 5 underwent cryopreservation therapy and 5 received leuprolide injections

^{*}There was 1 undocumented stage that underwent fertility preservation

	Race/Ethnicity			Age			Parity		
	n (% of total)			n (% of total)			n (% of total)		
	Black/AA $(n=91)$	White (<i>n</i> = 166)	P value	\leq 30 years (n=41)	31-40 years (<i>n</i> =265)	P value	$\frac{\leq 1}{(n=110)}$	2+ (<i>n</i> =115)	P value
Fertility counseling	11 (12.1)	29 (17.5)	0.285	11 (26.8)	34 (12.8)	0.030	22 (20.0)	13 (11.3)	0.008
Fertility preservation	3 (3.3)	7 (4.2)	0.508	5 (12.2)	5 (1.9)	0.005	9 (8.1)	1 (0.9)	0.001

Table 3 Association of race/ethnicity, age, and parity with fertility counseling and preservation for women diagnosed with breast cancer

AA African American

 Table 4
 Demographics of

patients at each treatment site

	Macomb $(n=48)$	Oakland $(n=115)$	Wayne $(n = 143)$	P value
	n (%)	n (%)	n (%)	
Marital status			·	
Married	33 (68.8)	80 (69.6)	64 (44.8)	< 0.001
Single	10 (20.8)	24 (20.9)	62 (43.4)	
Divorced	1 (2.1)	6 (5.2)	8 (5.6)	
Other/Unknown	4 (8.3)	5 (4.3)	9 (6.3)	
Primary language				
English	47 (97.9)	109 (94.8)	131 (91.6)	0.219
Spanish	NA	NA	4 (2.8)	
Other/Unknown	1 (2.1)	5 (4.3)	8 (5.6)	
Education level				
Some college or higher	1/2 ^b	14/15 ^c	9/14 ^d	0.114
Race/ethnicity				
White	35 (72.9)	75 (65.2)	56 (39.2)	< 0.001
Black or African American	7 (14.6)	25 (21.7)	59 (41.3)	
Asian	3 (6.2)	8 (7.0)	5 (3.5)	
Hispanic/Latinx	NA	1 (0.9)	6 (4.2)	
Other or declined to answer	3 (6.2)	5 (4.3)	13 (9.1)	
Two or more races	NA	1 (0.9)	3 (2.1)	
Native Hawaiian/Pacific Islander	NA	NA	1 (0.7)	
Home county				
Macomb	39 (81.2)	11 (9.6)	15 (10.5)	< 0.001
Oakland	4 (8.3)	52 (45.2)	16 (11.2)	
Wayne	NA	29 (25.2)	101 (70.6)	
Outside Tri-County	5 (10.4)	23 (20.0)	11 (7.7)	

^b, ^c, ^d only 2 Macomb, 15 Oakland, and 14 Wayne County patients reported education level in their electronic medical record thus percentages were not calculated

in Macomb lived in Macomb, 39/48 (81.3%) (Table 4). In Oakland County, 69.6% patients were married and 94.8% reported English as their primary language (Table 4). The racial/ethnic profile in Oakland County included 75/115 (65.2%) White, 25/115 (21.7%) Black or African American, 8/115 (7%) Asian, 1/115 (0.9%) Hispanic/Latinx, 1/115 (0.9%) Two or more races and 5/115 (5.2%) Other or declined to answer (Table 4). Less than half of the patients, 45.2%, treated in Oakland County lived there (Table 4). Other patients treated in Oakland County included 29/115 (25.2%) from Wayne County, 11/115 (9.6%) from Macomb County, and 23/115 (20%) from outside the Tri-county area (Table 4). In Wayne County, 44.8% of the patients were married and 91.6% reported English as their primary language

(Table 4). The racial/ethnic profile in Wayne County was 59/143 (41.3%) Black or African American, 56/143 (39.2%) White, 5/143 (3.5%) Asian, 6/143 (4.2%) Hispanic/Latinx 13/143 (9.1%) identified as other or declined to answer, 3/143 (2.1%) Two or more races, and 1/143 (0.7%) Native Hawaii/Pacific Islander (Table 4). When comparing trends across counties, both Macomb and Oakland had a higher percentage, 68.8% and 69.9% respectively, of patients who were married compared to Wayne County, 44.8% (P < 0.001). Wayne County had significantly more Black or African American patients, 41.3% compared to Macomb, 14.6%, and Oakland, 21.7% (P < 0.001). Patients who lived in Macomb and Wayne counties were more likely to receive treatment in the county they lived, 81.3% and 70.6%

respectively, compared to patients who lived in Oakland County, 45.2% (P < 0.001). Of note, the most centralized reproductive health and fertility clinic is less than 20 miles from each treatment site.

Patients treated for breast cancer in Oakland County (21.7%) were more likely to receive fertility counseling and undergo fertility preservation than patients who were treated in Wayne (9.8%) and Macomb Counties (12.5%; P=0.026) (Table 5). However, no significant difference was observed in fertility preservation between the 3 clinical locations (P=0.053). Although more patients with private insurance received fertility counseling (16.1% vs 9.1%; P=0.522) and underwent fertility preservation (4.2% vs 0%; P=0.183) than patients with public insurance, the differences were not significant (Table 5).

Discussion

In this retrospective study, we investigated whether specific patient characteristics were associated with the likelihood of receiving fertility counseling or fertility preservation for women 40 years old or younger who had been diagnosed with female breast cancer. The rate of diagnosis in the younger population of our cohort (4.5%) was consistent with national rates of diagnoses (4%) [1].

Patients who received fertility counseling and those who received fertility counseling were more likely to be diagnosed with Stage II disease or less. Though there are no specific studies investigating breast cancer stage and rates of fertility counseling and preservation, recent findings suggest that stage and/or grade do not impact fertility outcomes or ovarian stimulation, thus patients with higher stage or higher-grade tumors may still be considered for fertility preservation options [15, 16].

More patients who received fertility counseling and more who underwent fertility preservation were diagnosed with estrogen and/or progesterone positive breast cancer than triple negative disease. Previous literature has shown that more patients with estrogen receptor positive breast cancer undergo fertility preservation [17]. The PREFER study suggests that patients diagnosed with hormone positive breast cancer are more willing to accept fertility preserving procedures compared to those diagnosed with triple negative breast disease [18]. It has been documented that fertility is a major concern for patients diagnosed with hormone receptor positive breast cancer and may impact their treatment decisions [19]. Endocrine therapy, such as Tamoxifen, is often advised to patients with hormone positive breast cancer and suggested length of time maybe five or ten years further delaying childbearing posttreatment. Younger age has been associated with more aggressive breast cancer subtypes like triple negative disease. According to the 2018 publication by Howlader et al. approximately 65% of patients less than 50 years old are diagnosed with hormone receptor positive breast cancer compared to 15% who are diagnosed with triple negative breast cancer [20].

Patients who were 30 years old or younger were significantly more likely to receive both fertility counseling and preservation, and women with 1 or fewer children were more likely to receive fertility counseling and fertility preservation. This is consistent with previous studies which demonstrated that women diagnosed with cancer over age 35 years old could be less likely to receive fertility counseling [4, 21]. Like Goodman et al., studies in Sweden and at Memorial Sloan Kettering Cancer Center demonstrated women diagnosed with breast cancer who had undergone fertility preservation were younger and had lower parity or were nulliparous [17, 22].

Regionally, we also saw that significantly more women who were treated in the more affluent county, Oakland County, received fertility counseling relative to Macomb and Wayne counties. Voigt et al. suggest that socioeconomic status may impact whether women use fertility services [23]. Demographically, Oakland County has a higher median household income than both Macomb and Wayne counties [14]. Upon reviewing the characteristics of the patients cared for at each site, a lower percentage of patients, 45.2%, whose home county was Oakland were treated in Oakland County compared to Macomb and Wayne counties, 81.2% and 70.6%. More interesting, those from outside the Tri-county area were more likely to seek care in Oakland County, 23/39 (59%). These findings may suggest the need for standardization in fertility counseling across sites and/ or differences in provider engagement. Wayne county may have demonstrated lower rates of fertility counseling and preservation due to lower rates of marriage, higher poverty rate, and lower median household income. Though the

Table 5Association oftreatment location and insurancetype with fertility counselingand preservation for womendiagnosed with breast cancer

	Treatment Site <i>n</i> (% of total)				Insurance Type n (% of total)		
	Macomb (n=48)	Oakland $(n=115)$	Wayne $(n=143)$	P value	Private $(n=236)$	Public $(n=66)$	P value
Fertility counseling Fertility preservation	6 (12.5) 0 (0.0)	25 (21.7) 7 (6.1)	14 (9.8) 3 (2.1)	0.026 0.053	38 (16.1) 10 (4.2)	6 (9.1) 0 (0.0)	0.522 0.183

most centralized reproductive health and fertility office is within 20 miles of each site it is possible that the distance from patient's home address may be much further which may impact those with transportation issues. It remains unclear as to why patients treated at Macomb had a much lower rate of fertility counseling and preservation as type of breast cancer and stage of diagnosis did not differ from the two other counties. Thus, explicit efforts and policy are needed to ensure that all women with breast cancer are provided equal access to counseling and preservation for future fertility choices. In addition, patients treated in Oakland County were more likely to be married compared to patients in Wayne County 69.6% v 44.8% Wayne County. It's been documented that being married is associated with higher rates of fertility preservation [23, 24].

Due to the small number of patients who underwent fertility preservation in our study, we did not develop a definitive understanding of whether having private insurance might be associated with a higher rate of fertility preservation. Literature suggests that merely having private insurance may not impact fertility preservation among women diagnosed with cancer [11]. In 2002, Jain et al. demonstrated that complete insurance coverage for fertility led to a 277% utilization increase in assisted reproductive technology [9]. In 2018, as demonstrated by the Center for Disease Control and Prevention assisted reproductive technology fertilization success rates, states with comprehensive fertility coverage mandates saw 6.2 cycles per 1000 women aged 25-44 as compared to only 2.7 cycles per 1000 in states without mandated coverage [25]. Thus, mandating fertility coverage across all states may help to improve fertility preservation rates among young women diagnosed with cancer.

Interestingly, in our study race/ethnicity did not appear to influence fertility counseling or fertility preservation. This is different from previous studies that suggest non-Hispanic Blacks and Hispanic/Latinx are less likely to receive fertility counseling and undergo fertility preservation procedures [4, 6, 26]. Previous studies also indicate that there may be discrimination in fertility counseling among race and ethnicity [21, 23, 24, 26]. In China, a cross sectional study was performed to determine the awareness, knowledge, and acceptance of fertility preservation. They found that only 54% patients were aware of fertility preservation, yet 84% considered fertility counseling necessary and 83% would consider undergoing fertility preservation if a treatment would lead to infertility despite delaying cancer treatment [27]. This further emphasizes the importance of counseling our patients diagnosed with cancer on their fertility options.

We tried to further characterize our population by investigating education level and primary language however, more than 90% documented English as their primary language and only 10% reported their level of education. We can hypothesize based on well-established literature that those who report English as a second language may miss opportunities for equitable healthcare and counseling.

Important next steps will be to determine what interventions can help close the gap to fertility services among people diagnosed with female breast cancer. Our hospital system developed a multidisciplinary approach to breast cancer treatment in January 2016 aiming to standardize breast cancer care among all patients. The comprehensive multidisciplinary breast cancer program that we developed involves a team treatment approach that includes breast surgeons, clinical trial teams, fertility specialists, geneticists, pathologists, oncologists, radiologist, and radiation oncologists. Results are currently being finalized to determine whether a multidisciplinary approach to breast cancer care helps increase fertility counseling and utilization of fertility preservation services among patients diagnosed with breast cancer.

Conclusion

Age, parity, and location of treatment may impact rates of fertility counseling and preservation among reproductive age women diagnosed with breast cancer. Inquiring about a patient's desire for future fertility is the start to fertility care. Addressing inequities and inconsistencies across treatment sites, paying attention to age discrimination or bias, and implementation of comprehensive fertility coverage mandates across all states could help to improve gaps in fertility counseling and preservation.

Data Availability Data are available with the permission of Henry Ford Health. The data that support the findings of this study are available from the corresponding author [MS] upon reasonable request.

Declarations

Ethics approval This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of the Henry Ford Health System who granted a waiver of ethical approval for the project.

Consent to participate This research study was conducted retrospectively from de-identified data obtained for clinical purposes, therefore consent to participate was not required.

Competing interest The authors report no financial or non-financial interests that are directly or indirectly related to the work submitted for publication.

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