Estimates of Young Breast Cancer Survivors at Risk for Infertility in the U.S.

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Key Words. Breast neoplasms • Infertility • Fertility preservation • Survivors • Reproductive behavior • Pregnancy

ABSTRACT

Background. Standard treatments for breast cancer can impair fertility. It is unknown how many U.S. survivors are at risk for infertility. We estimated the population at risk for infertility secondary to treatment among reproductive-aged breast cancer survivors.

Methods. We combined data from three sources: the National Program of Cancer Registries (NPCR) and Surveillance, Epidemiology, and End Results cancer registry data on incident breast cancers diagnosed in women aged 15–44 years between 2004 and 2006; treatment data from NPCR's 2004 Breast and Prostate Cancer Data Quality and Patterns of Care (PoC) study; and data on women's intentions to have children from the 2006–2010 National Survey of Family Growth (NSFG).

Results. In the cancer registry data, an average of 20,308 women with breast cancer aged <45 years were diagnosed

annually. Based on estimates from PoC data, almost all of these survivors (97%, 19,416 women) were hormone receptor positive or received chemotherapy and would be at risk for infertility. These women need information about the impact of treatments on fertility. Estimates based on NSFG data suggest approximately half of these survivors (9,569 women) might want children and could benefit from fertility counseling and fertility preservation.

Conclusion. Nearly all young breast cancer survivors in the U.S. are at risk for infertility. Physicians should discuss the potential impact of treatment on fertility. A smaller but sizeable number of at-risk survivors may be interested in having children. Given the magnitude of potential infertility and its quality-of-life implications, these survivors should have access to and potential coverage for fertility services. *The Oncologist* 2014;19:814–822

Implications for Practice: Nearly all young breast cancer survivors are at risk for infertility. Physicians need to discuss infertility effects with these patients prior to treatment. Half of at-risk survivors may wish to have children in the future and may need access to fertility preservation services. Further physician education is needed about the magnitude of infertility and its importance among young breast cancer survivors. Moreover, we need to strengthen the infrastructure so that patients can access fertility preservation services.

INTRODUCTION

Treatment for breast cancer can affect fertility. Chemotherapy is directly toxic by destroying the ovarian follicles that make up a woman's reserve of ova [1–4]. Endocrine treatments have indirect effects [2–6]. First, pregnancy is contraindicated while on endocrine therapy because of the risk of teratogenicity [2–4], including a high frequency of severe congenital abnormalities [6]. Consequently, a woman would have an increased risk of age-related infertility, particularly if she remains on endocrine therapy for 5 years or longer [2–4]. Second, endocrine therapy can impair ovulatory and endometrial function, resulting in fertility disorders in some women, including an increased risk of temporary amenorrhea [4].

Chemotherapy can induce temporary or permanent amenorrhea, but even if a woman regains regular menstrual cycles, early menopause could result because she has lost a fraction of her ovarian reserve [3]. Chemotherapy's effects are variable and depend on ovarian reserve, chemotherapy type and dose, and patient age. Age at diagnosis is an important predictor of infertility, with 5% of those diagnosed at age 30, 32% diagnosed at age 35, and 80% diagnosed at age 40 remaining infertile after resumption of menses [7]. Alkylating agents (e.g., cyclophosphamide) are unlikely to cause permanent amenorrhea in women younger than age 30 but are particularly harmful in high doses and in older women [2, 4, 8].

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Less than 20% of survivors younger than 40 years of age on four cycles of doxorubicin plus cyclophosphamide (AC) had ovarian failure, whereas 20%–80% of those older than age 40 experienced ovarian failure [9]. There are limited data on how newer chemotherapy regimens affect infertility. Those on AC followed by docetaxel (T) had the highest rate of amenorrhea 12 months after treatment (70%), followed by concurrent docetaxel plus AC (58%), and doxorubicin plus docetaxel (38%) [10]. However, another study found no statistically significant association between amenorrhea and use of trastuzumab or dose-dense regimens (every 2 weeks) [11].

Approximately 11% of all breast cancer cases occur in women < 45 [12]. Five-year survival for women has increased from 75.2% for those diagnosed between 1975 and 1977 to 88.2% for those diagnosed between 2001 and 2008 [13], leading to an increase in the number of survivors. More than 50% of young survivors will live 20 years or longer following diagnosis [14], and their unique survivorship concerns, including risk of infertility, need to be addressed. Fertility preservation gives survivors the possibility of becoming pregnant after treatment. Established procedures include embryo and oocyte cryopreservation [4, 15]. Most survivors have limited knowledge that treatment can cause infertility [16], and patients report great distress about the prospect of infertility [17]. Estimates of infertility discussions between patients and physicians ranged from 34% to 72% [18–23], and 45%–47% of physicians offered a referral for fertility preservation [22, 24]. Approximately 4%–10% of survivors underwent fertility preservation [3, 21].

The American Society of Clinical Oncology and the American Society for Reproductive Medicine [8, 25] recommend that for reproductive-aged cancer patients, the possibility of infertility and options for fertility preservation should be discussed prior to therapy initiation. We will refer to this discussion as “fertility education” (disclosure from a physician that cancer treatment can affect fertility). Some women may choose to undergo fertility counseling (receiving detailed and comprehensive information from a fertility specialist on options) or fertility preservation. Infertility discussions should occur as early as possible after diagnosis so that women have sufficient time to explore options and undergo preservation [26].

It is unknown how many U.S. breast cancer survivors are at risk for infertility. This study estimates the number of breast cancer survivors at risk of infertility for whom education is necessary. Second, we estimate the number of at-risk survivors who might desire pregnancy, as determined by a general population sample, thus mimicking their precancer intentions, for whom more detailed fertility counseling and fertility preservation might be warranted.

METHODS

This project was reviewed by the institutional review boards of the Centers for Disease Control and Prevention (CDC) and ICF International and was determined to be exempt from review.

Data Sources

We combined several data sources. Breast cancer incidence data (2004–2006) came from the CDC’s National Program of Cancer Registries (NPCR) and the National Cancer Institute’s

(NCI’s) Surveillance, Epidemiology, and End Results (SEER) program [27]. Together, these data supply information for 100% of the U.S. population for these diagnosis years [27]. Patient demographics and tumor characteristics are systematically collected and reported to the CDC and NCI according to standards [28].

We assessed infertility risk among cancer survivors by estimating receipt of chemotherapy and hormone receptor status. Data on hormone receptor status (as a proxy for receipt of hormone therapy) and chemotherapy were provided by NPCR’s Breast and Prostate Cancer Data Quality and Patterns of Care (PoC) study [29]. The PoC study included a random stratified sample of all women aged ≥20 years diagnosed with microscopically confirmed breast cancer in 2004 from the population-based cancer registries of seven states. Medical records were reviewed for demographic, tumor, and treatment information [29]. Data from all states were combined, and all analyses were weighted for the sampling frame and adjusted for age and registry. We modeled hormone receptor status instead of hormone therapy because National Comprehensive Cancer Network guidelines recommend hormone therapy for all women with receptor-positive tumors [30]. Because conversations regarding fertility occur prior to treatment initiation, hormone receptor status better reflects who needs to have discussions about the impact of treatment on fertility.

For survivors at risk of infertility, we estimated who was interested in future fertility using population-based survey data from the 2006–2010 National Survey of Family Growth (NSFG), a national in-person survey of men and women aged 15–44 years [31]. We choose the NSFG because it is the nation’s comprehensive data source on reproductive health among young people, and there are no national (or subnational) population-based studies of cancer survivors with similar data. Furthermore, the NSFG may more accurately reflect a newly diagnosed patient’s intentions and thus who needs education, compared with surveys of survivors that were potentially fielded months or years after diagnosis, because it provides data on women’s intentions in the absence of cancer.

Study Population

The NPCR and SEER data set was restricted to breast cancers diagnosed between 2004 and 2006 among women aged 15–44 years. This selection of years allows for similar time frames from all three data sources.

Exclusions were applied. Women with in situ cancer were excluded because chemotherapy is not recommended for this stage of cancer. Taking hormone therapy for in situ cancer is not associated with a survival benefit. Consequently, women wishing to get pregnant could choose to forgo hormone therapy and not delay pregnancy [32, 33]. Conversely, women with metastatic breast cancer were excluded because their treatment regimens are less standard and more difficult to estimate. Women for whom cancer stage was missing were also excluded. Phyllodes tumors and Paget disease were also excluded because these are not treated with chemotherapy. We excluded autopsy-only and death certificate-only cases and those with nonpathologically confirmed tumors. Women with a previous cancer were excluded because fertility should be addressed at the first diagnosis. The same inclusion and exclusion criteria were applied to the PoC data.

Variable Definitions

The following tumor-characteristic variables were included in analyses of the NPCR and SEER data set: tumor grade (grade I or well differentiated, grade II or moderately differentiated, grade III or poorly differentiated, undifferentiated/anaplastic), SEER summary stage (local, defined as confined to the breast tissue, or regional, defined as extension to chest wall, inflammatory carcinoma, or regional lymph node involvement), and histology (ductal, lobular, mixed). From the PoC study, hormone receptor status (coded as estrogen receptor positive [ER+] or progesterone receptor positive [PR+], negative for both) and receipt of chemotherapy (yes or no) were included. The NSFG provided data on whether women intended to have a child in the future (response to the question, "Looking to the future, do you intend to have a/nother baby at some time," response options were "yes," "no," or "not sure"). We grouped respondents who answered "not sure" and "yes."

The following variables were included from all three data sources: age (in 5-year age groups), race (white, black, or other), and ethnicity (Hispanic or non-Hispanic).

Statistical Analysis

The PoC data set was used to estimate the likelihood that a woman's tumor was either ER+ or PR+ and the likelihood of chemotherapy receipt. The variables included in our prediction models were those indicated by previous literature [34, 35] and available in the NPCR and SEER cancer data set. Multivariable logistic regression models with the independent variables and sampling and weighting variables were developed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, <http://www.sas.com>). In the receptor-positivity model, independent variables included age at diagnosis; race; ethnicity; and tumor grade, stage, and histological type. In the chemotherapy-receipt model, we included the same independent variables as the receptor-positivity model plus hormone receptor status.

The NSFG data set was used to estimate the probability of desiring at least one more child from multivariable adjusted logistic regression models based on age, race, and ethnicity.

We applied the results of the prediction models from PoC and NSFG data to the NPCR and SEER cancer data set, as outlined in Figure 1. Using the multivariable logistic regression models, we calculated the probability of the outcome of interest (first of having an ER+/PR+ tumor, then of chemotherapy receipt) for each woman. Women with the same values for all of the variables in the model would have the same probability, and their results were grouped. The NPCR and SEER cancer data set was also grouped by values for the individual variables, and the probability from the PoC study was multiplied by the number of women in the NPCR and SEER cancer data set to arrive at the number of cancer survivors who might be at risk for infertility. In a similar fashion, for the group of women with ER+/PR+ tumors or who received chemotherapy, the probability of intending to have children based on the NSFG data was multiplied by the stratum-specific number of cancer survivors to estimate the number of at-risk survivors who may be interested in having children. The numbers for all groups were then added to get the total. To provide a range of appropriate estimates, we ran all analyses using the lower and

upper 95% confidence intervals (CIs) of the stratum-specific probabilities from the models and have reported those.

RESULTS

Prior to exclusions, 87,216 young women were diagnosed with breast cancer between 2004 and 2006, an average of 29,072 per year. We excluded 27,101 women, as described above, leaving 60,115 (20,038 per year) for analysis. Most of the patients (Table 1) were aged 40–44 years (57.9%), were white (78.6%), and had local stage (54.4%) and poorly differentiated disease (47.4%). In the PoC data, 68.3% of cases were ER+ or PR+ and 77.6% received chemotherapy (Table 1). Of those who received chemotherapy, 77% received AC or AC plus docetaxel (21.2% and 55.9%, respectively).

The strongest predictor of ER+ or PR+ was grade (Table 2); well-differentiated tumors were 33.6 times (95% CI: 5.1–219.5) more likely to be ER+ or PR+ than were poorly differentiated tumors. Other predictors included age, race, ethnicity, stage, and histology. The strongest predictors of receipt of chemotherapy (Table 2) were stage and grade, along with age, race, ethnicity, and histology. Women with regional-stage cancers were approximately nine times more likely to receive chemotherapy than those with local-stage tumors (95% CI: 5.1–15.5). The strongest predictor of wanting a child was age.

Figure 2 summarizes the combined results. The annual number of women diagnosed with cancer was 20,038. Based on PoC data, we estimated that of those 20,038 women, 14,265 were ER+ or PR+ and 16,040 received chemotherapy (data not shown). We estimate that 19,416 women (97%) would be at risk of infertility because they had ER+ or PR+ tumors or received chemotherapy, with a range of possible estimates from 18,150 to 19,854; these women would require education about their infertility risk. Of the women requiring fertility education, an estimated 9,569 (49%) might desire children, based on the application of our probabilities from analyses of the NSFG data, ranging from 8,064 to 10,804. This latter group of women would require fertility counseling and may be interested in pursuing fertility preservation. When age stratifying, the majority of survivors who might want a child (5,459) were between 40 and 44 years of age (Fig. 2).

DISCUSSION

This study is the first to determine that almost all young women diagnosed with early stage breast cancer will receive therapy that puts them at risk for infertility. These individuals should be educated about the risks before treatment [8, 25]. Nearly half of at-risk women may desire children in the future and might require additional fertility counseling or fertility preservation. These services require access to fertility specialists and must be explored before treatment begins.

Many survivors report not receiving needed fertility education, counseling, or preservation [2, 3, 16, 18–24, 36]. Barriers to receiving optimal care include lack of physician knowledge about fertility preservation and where and to whom to refer patients, lack of time for discussion, and concern about a perceived delay of cancer treatment [21–23, 37]. Financial constraints are a formidable barrier [22]. As one group noted, embryo cryopreservation could cost upward of \$15,000, with an additional \$5,000 for each transfer attempt

Figure 1. Analytic method using prediction of hormone receptor status as an example.

Abbreviations: NPCR, National Program for Cancer Registries; NSFG, National Survey of Family Growth; PoC, Breast and Prostate Cancer Data Quality and Patterns of Care; SEER, Surveillance, Epidemiology, and End Results.

[38], and insurance typically does not cover the cost [38]. Discussions about future fertility are emotionally difficult for both patients and providers. Nevertheless, front-line providers have a critical role in discussing potential risk of infertility in the context of treatment decision making and determining the patient's interest in having children. Our results quantify which reproductive-aged breast cancer survivors might be at risk for infertility and which survivors who are at-risk for infertility may be interested in having children. These estimates can inform initiatives to decrease barriers to receiving recommended care. Because cost is a large barrier to uptake of fertility preservation, a recent American Medical Association policy

supports the coverage by all insurance companies of fertility preservation techniques for cancer patients requiring treatment that may result in infertility [39]. Our estimates indicate that a sizeable number of breast cancer survivors would be interested in having children after diagnosis. Because all of these breast cancer survivors may not ultimately undergo fertility preservation [3, 21], the number needing coverage for fertility preservation services may be smaller, despite the need for almost all survivors to receive education. Fertility education, counseling, and preservation involve important access, social, legal, ethical, and resource issues that are beyond the scope of the current paper but that warrant further

Table 1. Demographic and tumor characteristics

Variable	NPCR and SEER, n (%)	PoC, n (%)	NSFG, n (%)
Age group (years)			
15–19	24 (0.0)	0	2,284 (17.0)
20–24	307 (0.5)	3 (0.4)	2,098 (16.8)
25–29	2,011 (3.4)	38 (2.9)	2,366 (17.1)
30–34	6,782 (11.3)	128 (10.2)	2,047 (14.9)
35–39	16,181 (26.9)	316 (26.3)	1,798 (17.1)
40–44	34,810 (57.9)	651 (60.3)	1,686 (17.2)
Race			
White	47,260 (78.6)	640 (76.1)	8,082 (73.2)
Black	8,812 (14.7)	394 (19.2)	2,722 (15.5)
Other	3,634 (6.0)	102 (4.6)	1,475 (11.2)
Missing	409 (0.7)	0	0
Ethnicity			
Non-Hispanic	53,527 (89.0)	965 (88.9)	9,556 (83.0)
Hispanic	6,588 (11.0)	171 (11.1)	2,723 (17.0)
Stage			—
Local	32,719 (54.4)	589 (52.5)	
Regional	27,396 (45.6)	547 (47.5)	
Grade			—
I (well differentiated)	6,676 (11.1)	105 (10.4)	
II (moderately differentiated)	20,184 (33.6)	385 (33.7)	
III (poorly differentiated)	28,513 (47.4)	583 (50.9)	
Undifferentiated/anaplastic	937 (1.6)	18 (1.5)	
Unknown	3,805 (6.3)	45 (3.5)	
Histologic type			—
Ductal	47,281 (78.6)	892 (79.4)	
Lobular	2,506 (4.2)	28 (2.5)	
Mixed	3,804 (6.3)	65 (5.8)	
Other	6,524 (10.8)	151 (12.3)	
Hormone receptor	—		—
ER+/PR+		745 (68.3)	
ER and PR negative		334 (27.2)	
Missing		57 (4.5)	
Chemotherapy	—		—
Received		879 (77.6)	
Not received		237 (20.2)	
Missing		20 (2.3)	

Women studied were in the NPCR and SEER cancer database, 2004–2006; the Centers for Disease Control and Prevention's PoC study, 2004; and the NSFG, 2006–2010. Data are shown as number (weighted percentage). Numbers are actual counts, but percentages are weighted based on the study's sampling strategies.

Abbreviations: —, variable was not available in the data set; ER+, estrogen receptor positive; NPCR, National Program for Cancer Registries; NSFG, National Survey of Family Growth; PoC, Breast and Prostate Cancer Data Quality and Patterns of Care; PR+, progesterone receptor positive; SEER, Surveillance, Epidemiology, and End Results.

exploration, given the great importance of fertility concerns for young patients and their families when facing a diagnosis of early breast cancer. In particular, a detailed and thorough cost-effectiveness analysis would be beneficial for insurance companies. Access to fertility specialists is also geographically constrained. Educational materials, better coordination of care, and development of systemwide guidelines on who should discuss fertility preservation [22], along with the dissemination of decision aids [40], could increase fertility-

related services. More than half of the survivors in this sample were 40–44 years of age at diagnosis, and fertility may already be compromised in this group, regardless of their cancer diagnosis. This group of women may be unlikely to undergo fertility preservation but should still be educated about the risks of infertility and be able to make informed decisions about their options and choices.

Birth rates are generally lower at older ages; birth rates for women aged 30–34 years and 40–44 years were 96.5 births per

Table 2. Associations between demographic and tumor characteristics with estrogen or progesterone receptor positivity and receipt of chemotherapy^a and intention to have children^b

Outcome variable	PoC study				NSFG survey (women only)	
	ER+/PR+ status		Receipt of chemotherapy		Intention to have children	
	n (%) ^c	OR (95% CI) ^d	n (%) ^c	OR (95% CI) ^d	n (%) ^c	OR (95% CI) ^d
Age group (years)						
15–19	0	—	0	—	2,027 (89.9)	Reference
20–24 ^e	—	—	—	—	1,661 (80.5)	0.47 (0.37–0.59)
25–29	27 (86.7)	1.7 (0.58–5.0)	32 (86.4)	2.4 (0.50–11.6)	1,447 (64.1)	0.20 (0.13–0.31)
30–34	80 (70.2)	0.97 (0.56–1.7)	109 (89.0)	1.9 (0.71–5.0)	828 (40.7)	0.08 (0.05–0.11)
35–39	201 (67.3)	0.76 (0.48–1.2)	245 (83.6)	1.6 (0.94–2.7)	409 (19.9)	0.03 (0.02–0.04)
40–44	437 (73.2)	Reference	474 (77.9)	Reference	127 (6.0)	0.007 (0.005–0.011)
Race						
White	443 (73.4)	Reference	488 (81.1)	Reference	4,213 (49.3)	Reference
Black	229 (61.7)	0.85 (0.56–1.3)	303 (82.8)	0.60 (0.36–0.99)	1,396 (50.3)	0.87 (0.84–0.91)
Other	73 (80.2)	1.0 (0.48–2.3)	69 (68.1)	0.53 (0.26–1.1)	890 (55.5)	1.5 (1.1–1.9)
Ethnicity						
Non-Hispanic	632 (71.4)	Reference	725 (80.9)	Reference	5,048 (50.1)	Reference
Hispanic	113 (72.3)	0.80 (0.43–1.5)	135 (80.2)	0.65 (0.29–1.5)	1,451 (50.5)	1.2 (1.07–1.4)
Stage					—	—
Local	377 (72.1)	Reference	361 (67.2)	Reference		
Regional	368 (70.9)	1.2 (0.85–1.8)	499 (95.2)	8.9 (5.1–15.5)		
Grade					—	—
I (well differentiated)	94 (97.2)	33.6 (5.1–219.5)	46 (46.7)	0.15 (0.07–0.32)		
II (moderately differentiated)	333 (91.7)	10.1 (6.2–16.5)	281 (77.9)	0.43 (0.26–0.72)		
III (poorly differentiated)	277 (51.5)	Reference	492 (90.1)	Reference		
Undifferentiated/anaplastic	12 (83.9)	5.3 (1.5–18.5)	14 (85.1)	0.74 (0.14–3.9)		
Unknown	29 (86.1)	6.2 (2.4–16.1)	27 (67.5)	0.45 (0.17–1.2)		
Histologic type					—	—
Ductal	571 (69.5)	Reference	686 (81.8)	Reference		
Lobular	26 (96.2)	4.5 (0.66–30.9)	22 (83.4)	2.5 (0.60–10.3)		
Mixed	58 (88.8)	2.0 (0.56–7.2)	52 (87.2)	3.0 (0.98–8.9)		
Other	90 (71.3)	0.84 (0.49–1.4)	100 (70.4)	0.70 (0.36–1.4)		
Hormone receptor	—	—			—	—
ER+/PR+			560 (76.9)	0.61 (0.34–1.1)		
ER and PR negative			300 (90.8)	Reference		

^aData are from breast cancer patients in the Centers for Disease Control and Prevention's PoC study, 2004.^bData are from the NSFG, 2006–2010, which is a nationally representative survey of participants aged 15–44 years.^cPercentages are weighted but unadjusted.^dModels are adjusted for state of residence and sampling clusters and weights in addition to the variables included in the tables.^eFor the PoC study, ages 20–29 were combined in the models due to sparse data in one of the categories.

Abbreviations: —, variable was not available in the data set; CI, confidence interval; ER+, estrogen receptor positive; NSFG, National Survey of Family Growth; OR, odds ratio; PoC, Breast and Prostate Cancer Data Quality and Patterns of Care; PR+, progesterone receptor positive.

1,000 women and 10.3 births per 1,000 women in 2011, respectively [41]. However, considering that fertility is nearly impossible past 45 years of age and given that even delay related only to hormone treatment can also result in the loss of opportunity to conceive in these remaining reproductive years, this age group deserves special scrutiny for fertility preservation education. Although there may be safety concerns with fertility preservation, recent preliminary studies present a reassuring safety profile [26, 42]. Any discussion of fertility preservation in cancer patients needs to include a balanced discussion of risks and benefits. The best available

evidence suggests that pregnancy after breast cancer does not increase a woman's risk of developing a recurrence or dying [43–45]; however, there are no prospective studies, and there are methodological concerns related to some of the studies, including the possibility of a "healthy mother effect." Success rates of fertility preservation are, with recent techniques, clinically satisfying [8]; embryo and oocyte cryopreservation are now considered established techniques [15]. There are even newer ovarian-stimulation techniques that do not raise physiological hormone levels and that may be as effective as traditional methods and could be used in patients with

Figure 2. Annual estimates of the number of young women diagnosed with breast cancer (from the National Program for Cancer Registries and Surveillance, Epidemiology, and End Results cancer database), the numbers with estrogen receptor-positive or progesterone receptor-positive tumors or who received chemotherapy (from the Centers for Disease Control and Prevention's Breast and Prostate Cancer Data Quality and Patterns of Care study) and who may intend to have children (from the National Survey of Family Growth).

hormone-sensitive tumors [8, 42]. Some patients may not be good candidates for fertility preservation (e.g., those with advanced stage and/or very aggressive tumors requiring neoadjuvant treatment). Treatment delays can be a concern with fertility preservation; however, fertility preservation does not always require a clinically meaningful delay, particularly in early-stage cancers and with timely referral to specialists [26].

This study has limitations. Although two of the three data sets were national, PoC data represent a combination of seven states, and nationwide treatment data had to be imputed from the experience in those states. Consequently, it is possible that

despite the geographic diversity of the states represented, additional geographic differences in receipt of hormone therapy or chemotherapy could be present. However, PoC has a large sample size and is population based, a rarity in the adjuvant therapy literature [29]. We focused on predictors that were reliably captured in all data sets, so additional predictors such as socioeconomic status were not considered. Survivors who do not receive chemotherapy or endocrine therapy may face the prospect of age-related infertility because they may be encouraged to wait a few years to become pregnant. This was not considered in our analysis. Fertility may also be of concern

for those >44 years of age, but that was not measured in this study. Taking tamoxifen for 10 years may provide greater reduction in breast cancer mortality, compared with stopping at 5 years [46]; this could ultimately increase the number of women facing infertility after diagnosis. Thus, our findings may not completely estimate the number of women at risk. There are minimal data on the safety of interrupting tamoxifen use to attempt pregnancy, and there is no proven indicator of remaining ovarian reserve while on tamoxifen. Nevertheless, a physician's ability to counsel patients on optimal strategies to achieve a healthy pregnancy and retain the majority of tamoxifen's benefits is limited. We used a general population survey of women to determine childbirth intentions, rather than estimates from breast cancer survivors. It is unknown whether cancer changes survivors' interest in having children [3]. Published estimates from breast cancer survivors indicate between 35% and 56% [2, 3, 18, 36, 47] desired children at diagnosis, comparable to the 49% in our sample. In a recent prospective cohort study, survivors' intentions did change (from 37% at diagnosis to 26% at the time of the survey) [47]. All breast cancer survivors who desire children should have the option to explore services regardless of whether they ultimately change their minds due to their cancer diagnosis; therefore, the NSFG provides more accurate data on which survivors might be in need of referral to fertility specialists. We also could not factor the specific effect of parity (i.e., number of children) into the estimates. Our conclusions are based on chemotherapy regimens common in the mid-2000s, and newer regimens may have less risk of acute amenorrhea. However, long-term data on risk of permanent amenorrhea or early menopause from new regimens are not available, and they still have some risk of infertility; patients would still need fertility education. In addition, given the wide variation in infertility risk, one cannot accurately predict who will become infertile. Among the strengths of this population-based study, it is the first to provide a national estimate of the impact of infertility on breast cancer survivors of reproductive age.

REFERENCES

- Soleimani R, Heytens E, Darzynkiewicz Z et al. Mechanisms of chemotherapy-induced human ovarian aging: Double strand DNA breaks and microvascular compromise. *Aging (Albany, NY)* 2011;3:782–793.
- Ruddy KJ, Partridge AH. The unique reproductive concerns of young women with breast cancer. *Adv Exp Med Biol* 2012;732:77–87.
- Partridge AH, Gelber S, Peppercorn J et al. Fertility and menopausal outcomes in young breast cancer survivors. *Clin Breast Cancer* 2008;8:65–69.
- Hulvat MC, Jeruss JS. Fertility preservation options for young women with breast cancer. *Curr Opin Obstet Gynecol* 2011;23:174–182.
- Rodriguez-Wallberg KA, Oktay K. Fertility preservation in women with breast cancer. *Clin Obstet Gynecol* 2010;53:753–762.
- Braems G, Denys H, De Wever O et al. Use of tamoxifen before and during pregnancy. *The Oncologist* 2011;16:1547–1551.
- Letourneau JM, Ebbel EE, Katz PP et al. Acute ovarian failure underestimates age-specific reproductive impairment for young women undergoing chemotherapy for cancer. *Cancer* 2012;118:1933–1939.
- Loren AW, Mangu PB, Beck LN et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013;31:2500–2510.
- Oktay K, Sönmez M. Chemotherapy and amenorrhea: Risks and treatment options. *Curr Opin Obstet Gynecol* 2008;20:408–415.
- Ganz PA, Land SR, Geyer CE Jr et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. *J Clin Oncol* 2011;29:1110–1116.
- Abusief ME, Missmer SA, Ginsburg ES et al. The effects of paclitaxel, dose density, and trastuzumab on treatment-related amenorrhea in premenopausal women with breast cancer. *Cancer* 2010;116:791–798.
- United States Cancer Statistics (USCS). 1999–2009 incidence and mortality data. Available at http://www.cdc.gov/cancer/npcr/uscs/download_data.htm. Accessed December 1, 2013.
- Surveillance, Epidemiology, and End Results program [SEER*Stat database: Incidence, SEER 9 registration research data, November 2011 submission, vintage 2009 populations (1973–2009)]. Available at <http://seer.cancer.gov/>. Accessed December 1, 2013.
- Previous version: SEER cancer statistics review, 1975–2009 (vintage 2009 populations). Available at http://seer.cancer.gov/csr/1975_2009_pops09/. Updated August 20, 2012. Accessed December 1, 2013.
- Practice Committees of American Society for Reproductive Medicine; Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: A guideline. *Fertil Steril* 2013;99:37–43.
- Jukkala AM, Azuero A, McNeese P et al. Self-assessed knowledge of treatment and fertility preservation in young women with breast cancer. *Fertil Steril* 2010;94:2396–2398.
- Howard-Anderson J, Ganz PA, Bower JE et al. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: A systematic review. *J Natl Cancer Inst* 2012;104:386–405.

CONCLUSION

These novel data indicate the importance of and the need for fertility education among almost all young breast cancer survivors. Access to fertility counseling and preservation services is needed for the sizeable number of survivors who may desire children after treatment, given the quality-of-life implications of chemotherapy-induced ovarian failure and infertility.

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DISCLOSURES

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18. Partridge AH, Gelber S, Peppercorn J et al. Web-based survey of fertility issues in young women with breast cancer. *J Clin Oncol* 2004;22:4174–4183.
19. Duffy CM, Allen SM, Clark MA. Discussions regarding reproductive health for young women with breast cancer undergoing chemotherapy. *J Clin Oncol* 2005;23:766–773.
20. Thewes B, Meiser B, Taylor A et al. Fertility- and menopause-related information needs of younger women with a diagnosis of early breast cancer. *J Clin Oncol* 2005;23:5155–5165.
21. Letourneau JM, Smith JF, Ebbel EE et al. Racial, socioeconomic, and demographic disparities in access to fertility preservation in young women diagnosed with cancer. *Cancer* 2012;118:4579–4588.
22. Quinn GP, Vadaparampil ST, Gwede CK et al. Discussion of fertility preservation with newly diagnosed patients: Oncologists' views. *J Cancer Surviv* 2007;1:146–155.
23. Niemasi EE, Letourneau J, Dohan D et al. Patient perceptions of reproductive health counseling at the time of cancer diagnosis: A qualitative study of female California cancer survivors. *J Cancer Surviv* 2012;6:324–332.
24. Quinn GP, Vadaparampil ST, Lee JH et al. Physician referral for fertility preservation in oncology patients: A national study of practice behaviors. *J Clin Oncol* 2009;27:5952–5957.
25. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer patients. *Fertil Steril* 2005;83:1622–1628.
26. Lee S, Ozkavukcu S, Heytens E et al. Value of early referral to fertility preservation in young women with breast cancer. *J Clin Oncol* 2010;28:4683–4686.
27. United States Cancer Statistics (USCS) [1999–2007 incidence and mortality data]. Available at http://www.cdc.gov/cancer/npcr/uscs/download_data.htm.
28. Havener L, Hulstrom D. Standards for cancer registries, volume II: Data standards and data dictionary. 10th ed., version 11.1. Springfield, IL: North American Association of Central Cancer Registries, 2006.
29. Wu XC, Lund MJ, Kimmick GG et al. Influence of race, insurance, socioeconomic status, and hospital type on receipt of guideline-concordant adjuvant systemic therapy for locoregional breast cancers. *J Clin Oncol* 2012;30:142–150.
30. NCCN clinical practice guidelines in oncology (NCCN Guidelines). Breast cancer. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.
31. National Survey of Family Growth. 2006–2010 NSFG: Public use data files, codebooks, and documentation [user's guide]. Available at http://www.Cdc.Gov/nchs/nsfg/nsfg_2006_2010_puf.Htm. 2011.
32. Burstein HJ, Polyak K, Wong JS et al. Ductal carcinoma in situ of the breast. *N Engl J Med* 2004;350:1430–1441.
33. Partridge AH, Elmore JG, Saslow D et al. Challenges in ductal carcinoma in situ risk communication and decision-making: Report from an American Cancer Society and National Cancer Institute workshop. *CA Cancer J Clin* 2012;62:203–210.
34. Setiawan VW, Monroe KR, Wilkens LR et al. Breast cancer risk factors defined by estrogen and progesterone receptor status: The multiethnic cohort study. *Am J Epidemiol* 2009;169:1251–1259.
35. Grann VR, Troxel AB, Zojwalla NJ et al. Hormone receptor status and survival in a population-based cohort of patients with breast carcinoma. *Cancer* 2005;103:2241–2251.
36. Letourneau JM, Ebbel EE, Katz PP et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. *Cancer* 2012;118:1710–1717.
37. Lee S, Heytens E, Moy F et al. Determinants of access to fertility preservation in women with breast cancer. *Fertil Steril* 2011;95:1932–1936.
38. Quinn GP, Vadaparampil ST, McGowan Lowrey K et al. State laws and regulations addressing third-party reimbursement for infertility treatment: Implications for cancer survivors. *Fertil Steril* 2011;95:72–78.
39. AMA adopts new policies on first day of voting at annual meeting [press release]. Available at <http://www.ama-assn.org/ama/pub/news/news/2013/2013-06-17-new-ama-policies-annual-meeting.page>. Updated June 17, 2013. Accessed December 1, 2013.
40. Peate M, Meiser B, Cheah BC et al. Making hard choices easier: A prospective, multicentre study to assess the efficacy of a fertility-related decision aid in young women with early-stage breast cancer. *Br J Cancer* 2012;106:1053–1061.
41. Martin JA, Hamilton BE, Ventura SJ et al. Births: Final data for 2011. *Nat Vital Stat Rep* 2013;62. Available at http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_01.pdf. Accessed December 1, 2013.
42. Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: A prospective controlled study. *J Clin Oncol* 2008;26:2630–2635.
43. Rippy EE, Karat IF, Kissin MW. Pregnancy after breast cancer: The importance of active counselling and planning. *Breast* 2009;18:345–350.
44. Azim HA Jr, Kroman N, Paesmans M et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: A multicenter retrospective study. *J Clin Oncol* 2013;31:73–79.
45. Kranick JA, Schaefer C, Rowell S et al. Is pregnancy after breast cancer safe? *Breast J* 2010;16:404–411.
46. Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805–816.
47. Ruddy KJ, Gelber SI, Tamimi RM et al. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. *J Clin Oncol* 2014;32:1151–1156.

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EDITOR'S NOTE: For further reading on the topic of infertility in young breast cancer survivors, see "Breast Cancer, BRCA Mutations, and Attitudes Regarding Pregnancy and Preimplantation Genetic Diagnosis," by Ashley H. Woodson et al., on pages 797–804 of this issue.