

## Web-Based Survey of Fertility Issues in Young Women With Breast Cancer

Ann H. Partridge, Shari Gelber, Jeffrey Peppercorn, Ebonie Sampson, Katherine Knudsen, Marc Laufer, Randi Rosenberg, Michele Przypyszny, Alison Rein, and Eric P. Winer

From the Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; and Young Survival Coalition, New York, NY.

Submitted January 23, 2004; accepted August 4, 2004.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Ann H. Partridge, MD, MPH, Dana-Farber Cancer Institute, 44 Binney St, D1210, Boston, MA 02115; e-mail: ahpartridge@partners.org.

© 2004 by American Society of Clinical Oncology

0732-183X/04/2220-4174/\$20.00

DOI: 10.1200/JCO.2004.01.159

### A B S T R A C T

#### Purpose

Young women with breast cancer often seek advice about whether treatment will affect their fertility. We sought to gain a better understanding of women's attitudes about fertility and how these concerns affect decision making.

#### Patients and Methods

We developed a survey about fertility issues for young women with a history of early-stage breast cancer. The survey was e-mailed to all registered Young Survival Coalition survivor members (N = 1,702). E-mail reminders were used.

#### Results

Six hundred fifty-seven eligible respondents completed the survey. Mean age at breast cancer diagnosis was 32.9 years; mean current age was 35.8 years. Ninety percent of women were white; 62% were married; 76% were college graduates. Stages at diagnosis were as follows: 0, 10%; I, 27%; II, 47%; III, 13%. Sixty-two percent of women were within 2 years of diagnosis. Fifty-seven percent recalled substantial concern at diagnosis about becoming infertile with treatment. In multivariate logistic regression, greater concern about infertility was associated with wish for children/more children (odds ratio [OR], 1.20;  $P < .0001$ ), number of prior pregnancies (OR, 0.78;  $P = .01$ ), and prior difficulty conceiving (OR, 1.86;  $P = .08$ ). Twenty-nine percent of women reported that infertility concerns influenced treatment decisions. Seventy-two percent of women reported discussing fertility concerns with their doctors; 51% felt their concerns were addressed adequately. Women seemed to overestimate their risk of becoming postmenopausal with treatment.

#### Conclusion

Fertility after treatment is a major concern for young women with breast cancer. There is a need to communicate with and educate young patients regarding fertility issues at diagnosis and a need for future research directed at preserving fertility for young breast cancer survivors.

*J Clin Oncol* 22:4174-4183. © 2004 by American Society of Clinical Oncology

### INTRODUCTION

More than 11,500 women in their 20s and 30s are diagnosed with breast cancer each year in the United States.<sup>1</sup> An additional 2,200 women in this age group are diagnosed with noninvasive disease. For these young women, and some older women, the impact of their breast cancer diagnosis and treatment on fertility may be of great concern. Adjuvant chemotherapy for breast

cancer may render a premenopausal woman amenorrheic, either temporarily or permanently. Even those women who continue to have regular menstrual cycles after chemotherapy may be less fertile than women who have not received chemotherapy, or they may go through menopause earlier than they might have otherwise.<sup>2-4</sup> Although standard endocrine therapies such as tamoxifen do not generally cause permanent infertility, they entail years of treatment during which time

a pregnancy is contraindicated. There is also increased interest in ovarian suppression or ablation as a treatment for breast cancer<sup>5</sup>; several ongoing trials are assessing whether ovarian suppression may add to our current treatments. Thus fertility concerns may complicate the treatment decision-making process for young women with breast cancer.

Premenopausal women with breast cancer often seek advice about whether they will become infertile after treatment, and for those who wish to bear children, whether a subsequent pregnancy will alter their risk of disease recurrence. Because breast cancer is responsive to various endocrine changes, there has been concern that continued menstrual cycling and/or pregnancy after breast cancer may worsen prognosis.<sup>6-15</sup> Although the data regarding pregnancy after breast cancer are reassuring, the available studies are imperfect and concerns about a negative impact for some patients remain. There is no question, however, that many young women are interested in preserving their fertility and hope to have children after a diagnosis of breast cancer.

There is little information available about women's attitudes regarding fertility surrounding the diagnosis and treatment of breast cancer. The prevalence and degree of concern over these issues is unknown, and the clinical, sociodemographic, and psychologic factors that influence these concerns are unclear. The extent to which attitudes about fertility affect treatment decisions for young women is similarly unknown. There is evidence that younger women may experience greater psychosocial distress and more difficulty with adjustment to the diagnosis and treatment of breast cancer.<sup>16-21</sup> One aspect of this may be related to anxiety about future infertility or premature menopause.

We collaborated with the Young Survival Coalition (YSC)<sup>22</sup> ([www.youngsurvival.org](http://www.youngsurvival.org)) in an effort to better understand fertility concerns. The YSC, an international nonprofit network of breast cancer survivors and supporters specifically dedicated to the unique issues facing young women with breast cancer, serves as an advocacy group seeking to educate and raise awareness about breast cancer in young women. We surveyed YSC survivor members to understand their concerns and attitudes regarding fertility.

The objectives of this study were as follows: to determine the proportion of premenopausal women age  $\leq 40$  years at diagnosis of early-stage breast cancer who were concerned about the possibility of becoming infertile after treatment, to determine the percentage of women for whom fertility concerns impacted on treatment decision making, and to compare women who desired to preserve their fertility with those who did not with regard to fear of recurrence and relevant sociodemographic, clinical, and psychologic variables.

## PATIENTS AND METHODS

We developed and piloted a one-time survey about fertility issues for young women with a history of early-stage breast cancer. Pilot testing was performed in the Dana-Farber Breast Cancer Program. We also used two previously validated questionnaires for women to recall their psychologic state before and at diagnosis: the Lasry Fear of Recurrence Scale<sup>23</sup> and the Hospitalized Anxiety and Depression Scale (HADS).<sup>24,25</sup> A link to the revised survey was e-mailed to all registered YSC survivor members with a history of breast cancer ( $N =$  approximately 1,702 at the time of the survey, including some individuals without a history of breast cancer). Eligible members (women who were premenopausal and age 40 years or younger at diagnosis of breast cancer) were encouraged to complete the survey. E-mail reminders to nonresponders were used to maximize response rates. Preliminary findings<sup>26</sup> were sent to survey respondents via e-mail as well as posted on the YSC Web site at study completion. The study received local institutional review board approval, and informed consent was obtained via the Internet from each respondent before responding to the survey.

Logistic regression was used for univariate analyses to compare women who reported greater levels of concern about fertility with those who did not. We used multiple variable logistic regression modeling to predict more concern about fertility and whether fertility concerns impacted a woman's treatment decisions. We used the Spearman rank correlation coefficient to assess the relationship between concern about fertility and concern about menopause.

## RESULTS

A total of 1,702 members were invited to participate in the survey (Fig 1). Not all of these members were eligible for the survey because some had not had breast cancer or were older than 41 years of age at diagnosis. Eight hundred sixty women gave electronic informed consent and began the survey; however, 203 women were excluded from these analyses for the following reasons: screened out due to ineligibility (no history of breast cancer;  $n = 8$ ), completed only a small portion of the survey ( $n = 120$ ), hysterectomy and/or bilateral oophorectomy at diagnosis ( $n = 11$ ), pregnancy at diagnosis ( $n = 32$ ), age greater than 40 years ( $n = 15$ ), stage IV disease ( $n = 19$ ; two women fell into two exclusion categories). Therefore, 657 women were eligible for analysis. Of note, two women who did not respond to the question regarding the primary outcome were excluded from those analyses.

### Responder Characteristics

Responder characteristics are listed in Table 1. The mean age at breast cancer diagnosis was 32.9 years, and mean age when responding to the survey was 35.8 years. The vast majority of respondents was white (90%) and most were at least college graduates (76%). At diagnosis, 62% were married, 8% were living as married, 7% were divorced or separated, and 23% were never married. Sixty-five

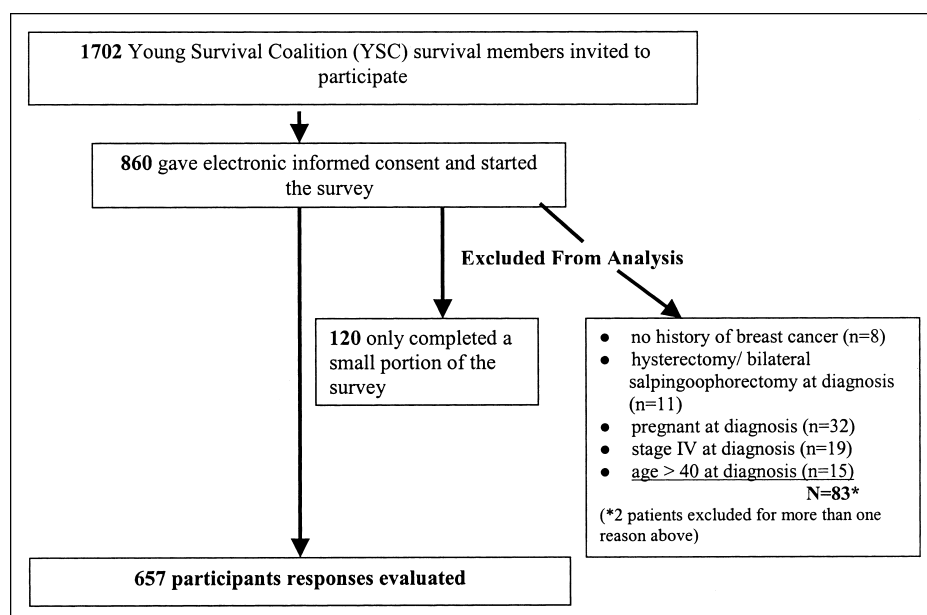


Fig 1. Flow chart of responders.

percent of women were working full-time at the time of diagnosis. Most respondents (60%) reported that after paying bills, they could afford special things, and 11% of women reported difficulty paying bills or having to cut back in order to pay bills.

When responding to the survey, the majority (62%) of women were 2 years from diagnosis. The distribution of stage of breast cancer at diagnosis was as follows: stage 0, 10%; I, 27%; II, 47%; III, 13%; unsure, 3%. Forty percent of women underwent breast-conserving surgery for their breast cancer. Few women (7%) reported any comorbidities at the time of their diagnosis. Forty-one percent had a first-degree relative with a history of breast or ovarian cancer, and 70% of women had a family history of any cancer in a first-degree relative.

### Fertility History at Diagnosis

Most women (92%) reported regular monthly periods at the time of diagnosis (Table 2). Fifty-nine percent of women had been pregnant at least once before diagnosis, and approximately half of respondents (48%) had had at least one live birth before diagnosis. Fifty percent had tried to become pregnant before diagnosis, and relatively few reported a prior spontaneous or therapeutic abortion or stillbirth. A small number of women reported having had a prior tubal ligation or single oophorectomy. At diagnosis, 13% had had difficulty conceiving in the past, 11% had undergone prior evaluation for infertility, and 8% had undergone prior treatment for infertility. The majority of women (56%) indicated that at the time of diagnosis they wanted to have a child or more children in the future.

### Psychologic State

Women were asked to reflect on their psychologic state in the weeks before diagnosis in an effort to evaluate baseline levels of anxiety and depression (Table 2). Twenty-two percent of women recalled severe anxiety before diagnosis by scoring greater than 10 on the HADS anxiety subscale. Only 4% of women recalled severe depression symptoms as assessed by a score of  $\geq 10$  on the HADS depression subscale. When women were asked to reflect on their feelings at diagnosis, 56% of women reported that they had substantial fear of breast cancer recurrence, as indicated by a score greater than 10 on the Lasry Fear of Recurrence Scale.

### Concern About Fertility

Women were asked how concerned they were about the possibility of becoming infertile (unable to become pregnant) after treatment for their breast cancer. Seventy-three percent of respondents reported at least some degree of concern: 16% were a little concerned; 18% were somewhat concerned; 39% were very concerned. When women's responses were dichotomized as more concerned (somewhat concerned, very concerned) or less concerned (a little concerned or not at all concerned), 57% of women were categorized as more concerned about the possibility of becoming infertile with treatment. On univariate analyses, more concern about infertility was associated with the following variables: young age at diagnosis, greater education, unmarried, working full time, having breast-conserving surgery, having a first-degree relative with cancer, regular menstrual periods, fewer prior pregnancies and live births, no history of having tried to become pregnant or prior miscarriages, no prior tubal ligation, history of prior

**Table 1.** Responder Characteristics of All Women, Women Who Were Concerned About Infertility, and Women Who Were Not Concerned

	All Women (N = 657)		Feelings About Infertility at Diagnosis (n = 655)*			
	No. of Patients	%	Concerned About Infertility		Not Concerned About Infertility	
			No. of Patients	%†	No. of Patients	%†
Total No. of patients			374	57	281	43
Age at diagnosis,‡ years						
≤ 30	154	23	118	77	36	23
31-35	283	43	171	61	110	39
> 35	220	33	85	39	135	61
Race						
African-American	13	2	9	69	4	31
White	590	90	336	57	252	43
Other	48	7	23	48	25	52
Missing	6	1	6	100	0	
Education‡						
Less than college graduate	150	23	62	41	88	59
College graduate	324	49	194	60	129	40
Postcollege graduate	180	27	117	65	63	35
Missing	3	0.5	1	50	1	50
Marital‡						
Married	406	62	195	48	210	52
Living as married	52	8	30	58	22	42
Divorced/separated/widowed	45	7	29	64	16	36
Never married	150	23	118	79	31	21
Missing	4	1	2	50	2	50
Employment‡						
Full	429	65	270	63	157	37
Less than full time	226	34	103	46	123	54
Missing	2	0.3	1	50	1	50
Finances						
Special things	394	60	225	57	167	43
No special things	187	28	107	57	80	43
Pay bills	44	7	25	57	19	43
Difficulty paying bills	25	4	13	52	12	48
Missing	7	1	4	57	3	43
Time since diagnosis						
0-6 months	65	10	35	54	30	46
6-12 months	122	19	70	57	52	43
1-2 years	214	33	120	56	94	44
3-5 years	158	24	99	63	58	37
6-10 years	54	8	28	52	26	48
> 10 years	25	4	13	52	12	48
Missing	19	3	9	50	9	50
Stage						
0 (noninvasive)	64	10	31	48	33	52
I	175	27	104	60	70	40
II	312	47	184	59	127	41
III	86	13	45	52	41	48
Missing	20	3	10	50	10	50
Breast-conserving surgery§						
Yes	261	40	161	62	99	38
No	360	55	190	53	169	47
Missing	36	5	23	64	13	36
Comorbid condition						
Yes	47	7	27	57	20	43
No	602	92	340	57	260	43
Missing	8	1	7	88	1	12
Any first-degree relative with cancer§						
Yes	459	70	275	60	182	40
No	197	30	98	50	99	50
Missing	1	0.2	1	100	0	
Any first-degree relative with breast or ovarian cancer						
Yes	267	41	151	57	115	43
No	389	59	222	57	166	43
Missing	1	0.2	1	100	0	

\*Two women did not answer the fertility question.

†Percentage of the women in each subgroup who answered the fertility question.

‡P < .0001.

§P < .05.

**Table 2.** Fertility and Psychologic History at Diagnosis of All Women, Women Who Were Concerned About Infertility, and Women Who Were Not Concerned

	All Women (N = 657)		Feelings About Infertility at Diagnosis (n = 655)*			
			Concerned About Infertility		Not Concerned About Infertility	
	No. of Patients	%	No. of Patients	%†	No. of Patients	%†
Total No. of patients			374	57	281	43
Menstrual frequency at diagnosis‡						
Once a month	603	92	341	57	261	43
Twice a month or more	6	0.9	1	20	4	80
Once every 2 months	13	2	9	69	4	31
Once every 2-6 months	7	1	5	71	2	29
Less than once every 6 months	20	3	16	80	4	20
Missing	8	1	2	25	6	75
Prior pregnancy§						
None	275	42	208	76	65	24
1	129	20	92	71	37	29
2+	253	39	74	29	179	71
Live births prior§						
None	343	52	261	77	80	23
1	116	18	73	63	43	37
2+	198	30	40	20	158	80
Tried to become pregnant prior to diagnosis§						
Yes	328	50	150	46	177	54
No	328	50	223	68	104	32
Missing	1	0.2	1	100	0	
Miscarriages prior						
None	566	86	338	60	226	40
1	67	10	28	42	39	58
2+	24	4	8	33	16	67
Abortions prior						
None	547	83	313	57	232	43
1	78	12	48	62	30	38
2+	32	5	13	41	19	59
Stillbirths prior						
None	653	99	372	57	279	43
1	3	0.5	2	67	1	33
2+	1	0.2	0	0	1	100
Prior tubal ligation§						
Yes	36	5	1	3	35	97
No	621	95	373	60	246	40
Prior single oophorectomy						
Yes	8	1	5	63	3	37
No	649	99	369	57	278	43
Difficulty becoming pregnant prior diagnosis§						
Yes	87	13	41	48	45	52
No	275	42	115	42	160	58
Not applicable	292	44	215	74	76	26
Missing	3	0.5	3	100	0	
Prior infertility evaluation						
Yes	71	11	34	49	36	51
No	581	88	338	58	242	42
Missing	5	0.8	2	40	3	60
Prior infertility treatment‡						
Yes	53	8	22	42	30	58
No	604	92	352	58	251	42
Wish to have more children§						
Yes	371	56	311	84	58	16
No	159	24	5	3	154	97
Unsure	126	19	57	45	69	55
Missing	1	0.2	1	100	0	

(continued on following page)

**Table 2.** Fertility and Psychologic History at Diagnosis of All Women, Women Who Were Concerned About Infertility, and Women Who Were Not Concerned (continued)

	All Women (N = 657)		Feelings About Infertility at Diagnosis (n = 655)*			
			Concerned About Infertility		Not Concerned About Infertility	
	No. of Patients	%	No. of Patients	%†	No. of Patients	%‡
HADS-anxiety subscale score > 10						
Yes	146	22	76	52	70	48
No	495	75	286	58	207	42
Missing	16	2	12	75	4	25
HADS-depression subscale score > 10						
Yes	29	4	14	48	15	52
No	599	91	345	58	252	42
Missing	29	4	15	52	14	48
Fear of recurrence > 10‡						
Yes	370	56	198	54	171	46
No	264	40	158	60	105	40
Missing	23	4	18	78	5	22

Abbreviation: Hospital Anxiety and Depression Scale.

\*Two women did not answer fertility question.

†Percentage of women in each subgroup who answered the fertility question.

‡ $P < .05$ .

§ $P < .0001$ .

|| $P < .001$ .

difficulty conceiving, no prior infertility treatment, desire to have more children, and less fear of recurrence at diagnosis (Tables 1 and 2).

In multivariate analysis, more concern about fertility at diagnosis was associated with wish to have more children (odds ratio [OR], 120;  $P < .0001$ ), prior number of pregnancies (OR, 0.78;  $P = .01$ ), and a history of prior difficulty conceiving (OR, 1.86;  $P = .08$  for yes, and OR, 3.15;  $P = .0001$  for not applicable, indicating that a woman had not tried to conceive previously) when forcing age at diagnosis and stage into the model. Nonsignificant variables included age at diagnosis, race, education, employment status, financial situation, comorbidity, anxiety or depression as measured on the HADS before diagnosis, family history of cancer, stage, perceived risk of recurrence, type of surgery, radiation therapy, prior treatment for infertility and prior difficulty conceiving, abortions, miscarriages, stillbirths, and prior tubal ligation.

### Fertility Concerns and Treatment Decisions

Twenty-nine percent of women indicated that concern about fertility impacted on their treatment decisions (Table 3). Fertility concern impacting on treatment decisions was associated with the desire for children/more children (OR, 32.04;  $P < .0001$ ), prior difficulty conceiving (OR, 2.28;  $P = .01$  for yes, and OR, 2.56;  $P < .0001$  for not applicable), and recalling severe depressive symptoms before diagnosis as measured by the HADS (OR, 3.05;  $P = .03$ ).

Women were asked the minimal decrease in absolute risk of recurrence that they would have been willing to accept from chemotherapy, given that adjuvant chemother-

apy might reduce the chances of a future pregnancy and result in other side effects (Table 3). Women who reported greater concern about fertility required greater risk reduction from chemotherapy than women who were less concerned about fertility ( $P < .05$ ). Women were also asked about the maximum risk of infertility that they would have accepted from a course of chemotherapy. Women who were more concerned about fertility were much less likely to accept a higher risk of infertility from adjuvant chemotherapy ( $P < .0001$ ), although 57% of women who reported great concern were willing to accept a risk of infertility of  $\geq 50\%$ .

Concern about menopause was significantly correlated with concern about infertility (Spearman rank correlation coefficient = 0.57;  $P < .0001$ ). However, a substantial minority (36%) of women who reported less concern about infertility were concerned about going through menopause with treatment. For 11% of these women, menopausal concerns impacted on their treatment decisions (Table 3).

Women were also asked to what extent they questioned the decisions they made about their breast cancer treatment at the time of the survey. Forty-five percent of all respondents questioned their treatment decisions, although most questioned their decisions only a little (Table 3). Those who were more concerned were not more likely to question their decision ( $P = .28$ ). However, 33% of the women who were more concerned about fertility reported that such questioning was related to fertility issues, at least to some degree, compared with 8% of the women who were less concerned about fertility at diagnosis.

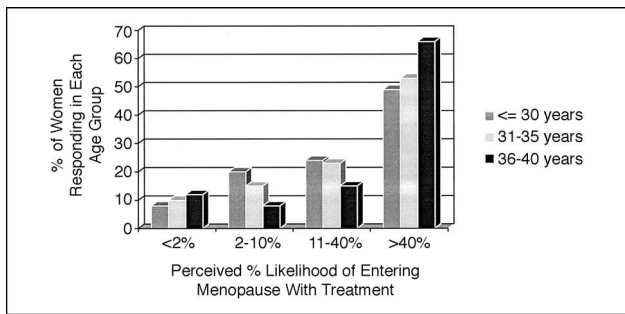
**Table 3.** Fertility and Menopausal Issues of All Women, Women Who Were Concerned About Infertility, and Women Who Were Not Concerned

	All Women (N = 657)		Feelings About Infertility at Diagnosis (n = 655)*			
			Concerned About Infertility		Not Concerned About Infertility	
	No. of Patients	%	No of Patients	%†	No. of Patients	%†
Total No. of patients			374	57	281	57
Infertility concerns impacted decision‡						
Yes	193	29	188	98	4	2
No	461	70	186	40	274	60
Missing	3	0.5	0		3	100
Minimal benefit (absolute risk reduction) required to accept chemotherapy§						
1-5%	200	30	96	48	104	52
5-9%	89	14	58	65	31	35
10-19%	95	14	54	57	40	43
20-29%	64	10	42	66	22	34
30-39%	23	4	14	61	9	39
40-49%	12	2	4	33	8	67
50%+	105	16	67	64	37	36
Missing	69	11	39	57	30	43
Maximal risk of infertility willing to assume with chemotherapy‡						
0-20%	42	6	34	81	8	19
21-30%	58	9	41	71	17	29
31-40%	32	5	28	88	4	12
41-50%	36	5	28	78	8	22
50%+	430	65	215	50	213	50
Missing	59	9	28	47	31	53
Concerned re menopause‡						
Yes	404	61	302	75	101	25
No	250	38	70	28	179	72
Missing	3	0.5	2	67	1	33
Menopausal concern impacted decision‡						
Yes	197	30	164	84	32	16
No	457	70	210	46	246	54
Missing	3	0.5	0		3	100
Question decision						
None	354	54	190	54	164	46
A little	200	30	131	66	69	34
Somewhat	73	11	42	58	30	42
A lot	23	4	8	36	14	64
Missing	7	1	3	43	4	57
If question decision, is it related to infertility issues‡						
Not at all	244	37	96	40	146	60
A little	60	9	44	73	16	27
Somewhat	42	6	38	90	4	10
Very	43	7	41	95	2	5
Missing	268	41	155	58	113	42
Discussed fertility issues with physician‡						
Yes	474	72	343	73	129	27
No	175	27	27	15	148	85
Missing	8	1	4	50	4	50
Discussed fertility issues with specialist‡						
Yes	114	17	102	90	11	10
No	533	81	268	50	264	50
Missing	10	2	4	40	6	60
Fertility concerns adequately addressed§						
Yes	337	51	176	53	159	47
No	171	26	122	71	49	29
Unsure	128	19	72	56	56	44
Missing	21	3	4	19	17	81
Knew adjuvant chemotherapy affected fertility§						
Yes	562	86	333	59	227	41
No	57	9	23	40	34	60
Unsure	28	4	13	46	15	54
Missing	10	2	5	50	5	50

\*Two women did not answer fertility question.

†Percentage of women in each subgroup who answered the fertility question.

‡ $P < .0001$ .§ $P < .05$ .



**Fig 2.** Perceived percentage likelihood of menopause with therapy among young women with breast cancer.

### Attention to Fertility Issues and Risk Perceptions

Seventy-two percent of women reported that they had discussed fertility concerns with a doctor, and 17% discussed the issues with a fertility specialist (Table 3). Half of the women felt their concerns about fertility were addressed adequately, but a substantial minority of women (26%) reported that their concerns had not been adequately addressed at the time of diagnosis. The majority of respondents (86%) reported knowing at diagnosis that adjuvant chemotherapy might affect fertility. Women who were diagnosed more recently were more likely to know that chemotherapy may impact on fertility than women diagnosed several years ago ( $P = .0028$ ).

Women were asked to estimate how likely they had thought breast cancer treatment would make them go through menopause when they were making treatment decisions (Fig 2). Seventy-six percent of all respondents indicated that their chance of becoming postmenopausal with treatment was greater than 10%, and 56% felt their risk was greater than 40%. Nearly 50% of women age 30 years or younger at diagnosis reported that they perceived a greater than 40% chance of entering menopause with therapy. Risk perceptions varied significantly with age, with younger women estimating lower risk of treatment-related menopause ( $P = .0031$ ).

Of women who reported that they did not want a future biologic child or were unsure ( $n = 309$ ), 36% ( $n = 111$ ) thought a future pregnancy would increase the risk of breast cancer recurrence, 48% ( $n = 148$ ) did not think it would, and 16% ( $n = 50$ ) were unsure. Of the women who felt a future pregnancy would increase their risk ( $n = 111$ ), 20% ( $n = 22$ ) reported greater concern about infertility at diagnosis compared with 80% ( $n = 89$ ) who were less concerned.

## DISCUSSION

The risk of infertility and menopause after treatment is a major issue for many young women with breast cancer.

Previous research reveals that infertile women in the general population often report feelings of loss of control, depression, and low self-esteem, and women are generally more adversely affected psychologically by infertility than men.<sup>27,28</sup> There is only limited information available about fertility concerns in women who have been diagnosed with breast cancer. Concerns about fertility may contribute to the greater psychosocial distress that younger women experience with the diagnosis and treatment of breast cancer.<sup>16-20</sup> The potential for infertility may impact on a woman's self-esteem and self-concept as a sexual person.<sup>20</sup> Small qualitative studies have revealed that loss of choice about having children is a key concern both common and unique to young women with breast cancer,<sup>29</sup> and that the possibility of becoming pregnant subsequent to breast cancer is a powerful stimulus for young women to get well.<sup>30</sup> There is also evidence that the informational needs and concerns of women with breast cancer about fertility issues may change over time, with increasing concern and need for information further from diagnosis.<sup>31</sup>

The present study confirms the clinical experience that suggests that desire for children is an important factor in predicting greater concern about fertility and whether fertility issues will impact on treatment decisions. Some physicians may use the age of the patient and the stage of disease to prompt the discussion about fertility issues, assuming that younger women and women with lower-risk disease are more likely to be worried about treatment-related amenorrhea and the possibility of future infertility. However, our findings indicate that concerns about fertility are present for the majority of young premenopausal women, regardless of their age and extent of disease.

Many younger women are also concerned about entering menopause with treatment, independent of their fertility. Problems related to premature ovarian failure include menopausal symptoms such as hot flashes, genitourinary problems, psychologic and psychosexual difficulties, and accelerated bone mineral density loss.<sup>21,32-38</sup> Premature menopause may also contribute to increased cardiovascular morbidity, although data to support this in women with breast cancer are lacking. For many of these symptoms or complications, there are nonhormonal interventions available.<sup>39</sup>

Our findings suggest that a substantial proportion of women overestimate their risk of becoming postmenopausal with breast cancer therapy. This misperception is particularly worrisome in light of the fact that nearly one third of respondents indicated that fertility concerns impacted on their treatment decisions. Although therapy-related menopause is a consequence of adjuvant chemotherapy, the risk of premature menopause is related to patient age, the specific chemotherapeutic agents used, and the total dose administered.<sup>40,41</sup> In women younger than 30 years, premature ovarian failure with standard regimens is quite uncommon, although available studies are

generally limited by the small number of women evaluated in this particular age group. With standard anthracycline-based adjuvant chemotherapy including four cycles of doxorubicin and cyclophosphamide, at least two studies have found a 0% incidence in this age group, with risks of premature ovarian failure that increase to the 10% to 15% range when considering women younger than 40 years of age.<sup>42-45</sup> Rates in younger women after six cycles of cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide, epirubicin, and fluorouracil are somewhat higher; up to 20% of women 30 years of age and younger and up to 40% of women 40 years of age and younger will experience premature menopause.<sup>40,42-45</sup> The impact of treatment duration and dose density, as well as newer drugs (eg, the taxanes), remains uncertain.<sup>46</sup> Our study also reveals that some women may have been concerned about the impact of a subsequent pregnancy on breast cancer prognosis. Given available data, clinicians can try to correct inaccurate risk perceptions and educate young women about what is known and not known about risks of infertility and the potential impact of a future pregnancy on breast cancer prognosis.

The present study suggests that there may be a need for improved communication about fertility between young women with breast cancer and their health care providers. Clinicians can share information on risk of infertility and premature menopause and discuss currently available options to preserve fertility, acknowledging the limitations of the data. Young women should be made aware of the conflicting evidence that chemotherapy-related amenorrhea may have a beneficial effect on breast cancer prognosis, of the benefits of ovarian suppression in those who do not receive chemotherapy,<sup>47-51</sup> and of the availability of clinical trials currently being conducted to answer many of the issues that remain unclear. Finally, the lack of definitive data about the effects of a subsequent pregnancy on breast cancer prognosis remains problematic for many women.<sup>7,9,10,12,52-55</sup>

Our study is the largest research effort published to date addressing fertility concerns among young women with breast cancer. The sample size allowed us to evaluate a range of factors associated with fertility concern and allowed us to better understand the feelings of substantial numbers of women in all young age groups. However, this study has a number of limitations. Selection, nonresponder,

and recall bias should be considered in evaluating the results. In particular, the women surveyed in this study were highly educated and motivated, and the feelings of members of a Web-based advocacy group may not reflect fully the sentiments or understanding of these issues among all young women with breast cancer. For example, women who join such a group are likely more educated and may be more concerned about infertility. Women in this group may also be more likely than the average young patient to have their concerns addressed, and yet a substantial proportion of women in this group did not feel fertility concerns had been addressed adequately. Many variables were evaluated, and the *P* values presented in the tables have not been adjusted for multiple comparisons. Thus findings of borderline statistical significance should be interpreted with caution. Finally, this was a cross-sectional retrospective survey of breast cancer survivors, and it is possible that perceptions of concern at diagnosis may change over time. Furthermore, use of psychometric measures such as the HADS and Lasry Fear of Recurrence Scale retrospectively may be limited by memory recall and distortions based on subsequent events.<sup>56</sup>

In conclusion, fertility remains a major issue for many young breast cancer survivors, and efforts should be made to elicit and adequately address fertility concerns at the time of diagnosis and treatment planning. Ongoing and future studies will help delineate the potential trade-offs between therapy-related menopause, future fertility, and breast cancer prognosis. In the meantime, increased attention to fertility issues at diagnosis and in follow-up may improve patient-provider communication and the quality of care received by young women with breast cancer. Clinicians and researchers should consider interventions, both psychosocial and medical, to diminish the impact of infertility on young breast cancer survivors.

## Acknowledgment

We thank the members of the YSC for making this work possible.

## Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

## REFERENCES

1. American Cancer Society: Breast Cancer Facts and Figures 2003-2004. Atlanta, GA, American Cancer Society, 2003
2. Bath LE, Wallace WH, Shaw MP, et al: Depletion of ovarian reserve in young women after treatment for cancer in childhood: Detection by anti-Müllerian hormone, inhibin B and ovarian ultrasound. *Hum Reprod* 18:2368-2374, 2003
3. Byrne J, Fears TR, Gail MH, et al: Early menopause in long-term survivors of cancer during adolescence. *Am J Obstet Gynecol* 166:788-793, 1992
4. Bath LE, Wallace WH, Critchley HO: Late effects of the treatment of childhood cancer on the female reproductive system and the potential for fertility preservation. *BJOG* 109:107-114, 2002
5. Baum M, O'Shaughnessy JA: Management of premenopausal women with early-stage breast cancer: Is there a role for ovarian suppression? *Clin Breast Cancer* 3:260-267, 2002
6. Petrek JA: Pregnancy safety after breast cancer. *Cancer* 74:528-531, 1994
7. Surbone A, Petrek JA: Childbearing issues in breast carcinoma survivors. *Cancer* 79:1271-1278, 1997
8. Gemignani ML, Petrek JA: Pregnancy after breast cancer. *Cancer Control* 6:272-276, 1999
9. Velentgas P, Daling JR, Malone KE, et al: Pregnancy after breast carcinoma: Outcomes and influence on mortality. *Cancer* 85:2424-2432, 1999
10. Dow KH, Harris JR, Roy C: Pregnancy after breast-conserving surgery and radiation therapy for breast cancer. *J Natl Cancer Inst Monogr* 16:131-137, 1994

11. Higgins S, Haffty BG: Pregnancy and lactation after breast-conserving therapy for early stage breast cancer. *Cancer* 73:2175-2180, 1994
12. Gelber S, Coates AS, Goldhirsch A, et al: Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer. *J Clin Oncol* 19:1671-1675, 2001
13. Upponi SS, Ahmad F, Whitaker IS, et al: Pregnancy after breast cancer. *Eur J Cancer* 39:736-741, 2003
14. Mueller BA, Simon MS, Deapen D, et al: Childbearing and survival after breast carcinoma in young women. *Cancer* 98:1131-1140, 2003
15. Blakely LJ, Buzdar AU, Lozada JA, et al: Effects of pregnancy after treatment for breast carcinoma on survival and risk of recurrence. *Cancer* 100:465-469, 2004
16. Wenzel LB, Fairclough DL, Brady MJ, et al: Age-related differences in the quality of life of breast carcinoma patients after treatment. *Cancer* 86:1768-1774, 1999
17. Mor V, Malin M, Allen S: Age differences in the psychosocial problems encountered by breast cancer patients. *J Natl Cancer Inst Monogr* 191-197, 1994
18. Mor V, Allen S, Malin M: The psychosocial impact of cancer on older versus younger patients and their families. *Cancer* 74:2118-2127, 1994
19. Compas BE, Stoll MF, Thomsen AH, et al: Adjustment to breast cancer: Age-related differences in coping and emotional distress. *Breast Cancer Res Treat* 54:195-203, 1999
20. Schover LR: Sexuality and body image in younger women with breast cancer. *J Natl Cancer Inst Monogr* 177-182, 1994
21. Ganz PA, Greendale GA, Petersen L, et al: Breast cancer in younger women: Reproductive and late health effects of treatment. *J Clin Oncol* 21:4184-4193, 2003
22. Rosenberg R, Levy-Schwartz R: Breast cancer in women younger than 40 years. *Int J Fertil Womens Med* 48:200-205, 2003
23. Lasry JC, Margolese RG: Fear of recurrence, breast-conserving surgery, and the trade-off hypothesis. *Cancer* 69:2111-2115, 1992
24. Hermann C: International experiences with the hospital anxiety and depression scale: A review of validation data and clinical results. *J Psychosom Res* 42:17-41, 1997
25. Spinhoven P, Ormel J, Sloekers PP, et al: A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med* 27:363-370, 1997
26. Partridge A, Gelber S, Knudsen K, et al: A Web-based survey of fertility issues in young women with breast cancer. *Breast Cancer Res Treat* 82:S15-16, 2003 (suppl 1, abstr 31)
27. Litt MD, Tennen H, Affleck G, et al: Coping and cognitive factors in adaptation to in vitro fertilization failure. *J Behav Med* 15:171-187, 1992
28. Wright J, Duchesne C, Sabourin S, et al: Psychosocial distress and infertility: Men and women respond differently. *Fertil Steril* 55:100-108, 1991
29. Dunn J, Steginga SK: Young women's experience of breast cancer: Defining young and identifying concerns. *Psychooncology* 9:137-146, 2000
30. Dow KH: Having children after breast cancer. *Cancer Pract* 2:407-413, 1994
31. Thewes B, Meiser B, Rickard J, et al: The fertility- and menopause-related information needs of younger women with a diagnosis of breast cancer: A qualitative study. *Psychooncology* 12:500-511, 2003
32. Ganz PA, Coscarelli A, Fred C, et al: Breast cancer survivors: Psychosocial concerns and quality of life. *Breast Cancer Res Treat* 38:183-199, 1996
33. Ganz PA, Rowland JH, Desmond K, et al: Life after breast cancer: Understanding women's health-related quality of life and sexual functioning. *J Clin Oncol* 16:501-514, 1998
34. Meyerowitz BE, Desmond KA, Rowland JH, et al: Sexuality following breast cancer. *J Sex Marital Ther* 25:237-250, 1999
35. Kreuser ED, Felsenberg D, Behles C, et al: Long-term gonadal dysfunction and its impact on bone mineralization in patients following COPP/ABVD chemotherapy for Hodgkin's disease. *Ann Oncol* 3:105-110, 1992 (suppl 4)
36. Bruning PF, Pit MJ, de Jong-Bakker M, et al: Bone mineral density after adjuvant chemotherapy for premenopausal breast cancer. *Br J Cancer* 61:308-310, 1990
37. Park KH, Song CH: Bone mineral density in premenopausal anovulatory women. *J Obstet Gynaecol* 21:89-97, 1995
38. Howell SJ, Berger G, Adams JE, et al: Bone mineral density in women with cytotoxic-induced ovarian failure. *Clin Endocrinol (Oxf)* 49:397-402, 1998
39. Burstein HJ, Winer EP: Primary care for survivors of breast cancer. *N Engl J Med* 343:1086-1094, 2000
40. Burstein HJ, Winer EP: Reproductive issues, in Harris JR (ed): *Diseases of the Breast* (ed 2). Philadelphia, PA, Lippincott Williams & Wilkins, 2000, pp 1051-1059
41. Minton SE, Munster PN: Chemotherapy-induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer. *Cancer Control* 9:466-472, 2002
42. Hortobagyi GN, Buzdar AU, Marcus CE, et al: Immediate and long-term toxicity of adjuvant chemotherapy regimens containing doxorubicin in trials at M.D. Anderson Hospital and Tumor Institute. *NCI Monogr* 1:105-109, 1986
43. Valagussa P, De Candis D, Antonelli G, et al: VIII. Women's health perception and breast cancer: Issues of fertility, hormone substitution, and cancer prevention. *Recent Results Cancer Res* 140:277-283, 1996
44. Weber B, Luporsi E: Ovarian toxicity of breast cancer chemotherapy. *Eur J Cancer* 34:S42, 1998 (suppl 5)
45. Goodwin PJ, Ennis M, Pritchard KI, et al: Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol* 17:2365-2370, 1999
46. Partridge AH, Burstein HJ, Winer EP: Side effects of chemotherapy and combined chemohormonal therapy in women with early-stage breast cancer. *J Natl Cancer Inst Monogr* 135-142, 2001
47. Pagani O, O'Neill A, Castiglione M, et al: Prognostic impact of amenorrhoea after adjuvant chemotherapy in premenopausal breast cancer patients with axillary node involvement: Results of the International Breast Cancer Study Group (IBCSG) Trial VI. *Eur J Cancer* 34:632-640, 1998
48. Davidson NE: Ovarian ablation as adjuvant therapy for breast cancer. *J Natl Cancer Inst Monogr*:67-71, 2001
49. Early Breast Cancer Trialists' Collaborative Group: Ovarian ablation in early breast cancer: Overview of the randomised trials. *Lancet* 348:1189-1196, 1996
50. Goldhirsch A, Gelber RD, Castiglione M: The magnitude of endocrine effects of adjuvant chemotherapy for premenopausal breast cancer patients: The International Breast Cancer Study Group. *Ann Oncol* 1:183-188, 1990
51. Davidson N, O'Neill A, Vukov A, et al: Effect of chemohormonal therapy in premenopausal node (+) receptor (+) breast cancer: An Eastern Cooperative Oncology Group Phase III Intergroup Trial (E5188, INT-0101). *Proc Am Soc Clin Oncol* 18:67a, 1999 (abstr 249)
52. Danforth DN Jr: How subsequent pregnancy affects outcome in women with a prior breast cancer. *Oncology (Huntingt)* 5:23-30, 1991
53. Kroman N, Jensen MB, Melbye M, et al: Should women be advised against pregnancy after breast-cancer treatment? *Lancet* 350:319-322, 1997
54. Sankila R, Heinavaara S, Hakulinen T: Survival of breast cancer patients after subsequent term pregnancy: "Healthy mother effect". *Am J Obstet Gynecol* 170:818-823, 1994
55. von Schoultz E, Johansson H, Wilking N, et al: Influence of prior and subsequent pregnancy on breast cancer prognosis. *J Clin Oncol* 13:430-434, 1995
56. Fowler FJ: *Survey Research Methods* (ed 3). Thousand Oaks, CA, Sage Publications, 2002