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ORIGINAL REPORT

Chemotherapy-Induced Amenorrhea in Patients With Breast Cancer With a *BRCA1* or *BRCA2* Mutation

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ABSTRACT

Purpose
To determine the likelihood of long-term amenorrhea after treatment with chemotherapy in women with breast cancer who carry a *BRCA1* or *BRCA2* mutation.

Patients and Methods
We conducted a multicenter survey of 1,954 young women with a *BRCA1* or *BRCA2* mutation who were treated for breast cancer. We included premenopausal women who were diagnosed with invasive breast cancer between 26 and 47 years of age. We determined the age of onset of amenorrhea after breast cancer for women who were and were not treated with chemotherapy, alone or with tamoxifen. We considered chemotherapy-induced amenorrhea to have occurred when the patient experienced ≥ 2 years of amenorrhea, commencing within 2 years of initiating chemotherapy, with no resumption of menses.

Results
Of the 1,426 women who received chemotherapy, 35% experienced long-term amenorrhea. Of the 528 women who did not receive chemotherapy, 5.3% developed long-term amenorrhea. The probabilities of chemotherapy-induced amenorrhea were 7.2% for women diagnosed before age 30 years, 33% for women age 31 to 44 years, and 79% for women diagnosed after age 45 years (P trend $< .001$). The probability of induced amenorrhea was higher for women who received tamoxifen than for those who did not (52% *v* 29%; $P < .001$).

Conclusion
Age at treatment and use of tamoxifen are important predictors of chemotherapy-induced amenorrhea in women who carry a *BRCA1* or *BRCA2* mutation. The risk of induced long-term amenorrhea does not seem to be greater among mutation carriers than among women who do not carry a mutation.

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INTRODUCTION

In premenopausal women with breast cancer, the benefits of treatment must be balanced by the effects of treatment on fertility and quality of life. Among the concerns of young women with breast cancer are premature menopause and infertility.[1] Long-term effects of treatment include osteoporosis, urogenital dysfunction, cardiovascular disease, and cognitive impairment.[2] Many women with a *BRCA1* or *BRCA2* mutation who are diagnosed with breast cancer will seek the expertise of a fertility specialist, who may recommend oocyte cryopreservation or embryo preservation before treatment. This is based on the expectation that a high proportion of these women will be rendered amenorrheic by chemotherapy and the hope that fertility can be preserved through intervention. It has been proposed that many *BRCA* mutation carriers who do not receive chemotherapy will experience premature menopause.[3] It is important that patients and clinicians have accurate information regarding the probabilities of induced and natural menopause and the factors that predict amenorrhea in this high-risk group.

At birth, each ovary contains approximately 300,000 oocytes. The number of residual follicles diminishes with each menstrual cycle, and the number of remaining follicles determines, in part, a woman's capability for fertility and is predictive of time to menopause. At the age of 51 years, only approximately 1,000 follicles remain.[4,5] Women treated for breast cancer are at risk of ovarian failure after chemotherapy because of depletion of follicles.

The incidence of chemotherapy-induced amenorrhea depends on the patient's age and the chemotherapy agent used.[6]

It has been proposed that women with a *BRCA1* mutation may be more sensitive to the effects of chemotherapy on ovarian follicle depletion than women without a mutation.[3] This hypothesis is based on a study of ovarian reserve of patients with breast cancer attending a fertility clinic. Little is known about the risk of induced amenorrhea in women with a *BRCA1* or *BRCA2* mutation. Our objective was to estimate the probability of chemotherapy-induced amenorrhea for premenopausal women with breast cancer and a *BRCA1* or *BRCA2* mutation. A secondary objective was to compare the age-specific probabilities of experiencing chemotherapy-induced amenorrhea in mutation carriers and noncarriers. Other members of the Hereditary Breast Cancer Clinical Study Group are listed in the Appendix (online only).

PATIENTS AND METHODS

Patients were selected from a database of 13,004 *BRCA1* and *BRCA2* mutation carriers and 2,451 noncarriers. Study patients were identified at one of 62 participating centers in seven countries. These women sought testing for *BRCA1* and *BRCA2* mutations because of a personal or family history of breast or ovarian cancer. The institutional review boards of the host institutions approved the study. All patients provided written informed consent. Mutation detection was performed using a range of techniques, but all nucleotide sequences were confirmed by direct sequencing of DNA. A woman was enrolled onto the *BRCA* carrier group when the molecular analysis established that she was a carrier of a deleterious mutation in *BRCA1* or *BRCA2*. All study patients completed a baseline questionnaire. The questionnaire requested information on family and personal histories of cancer, reproductive and medical histories, and date and cause of menopause. For women with breast cancer, information was collected on types of therapy administered, including chemotherapy (yes *v* no), hormonal therapy, and ovarian ablation. We did not have details on type of chemotherapy.

In our study, we included mutation carriers from the parent study, who were diagnosed with invasive breast cancer between 26 and 47 years of age and who were premenopausal at the time of diagnosis. The date of breast cancer was considered the date of surgery. We considered the definition of induced menopause as ≥ 2 years of amenorrhea commencing within 2 years of chemotherapy with no resumption of menses. We considered natural amenorrhea to have occurred when the onset of amenorrhea was > 2 years after breast cancer treatment. For women who did not receive chemotherapy, we considered the onset of amenorrhea within 2 years of the initiation of treatment to be the relevant comparison period (in this sense, we used the term induced amenorrhea throughout the text for comparison purposes, but given the absence of chemotherapy, we recognize that these are likely to be examples of natural menopause). As a consequence of this definition, we excluded carriers if they had experienced menopause before breast cancer diagnosis (n = 1,084), if they were age > 47 years at diagnosis (n = 255), if they had undergone an oophorectomy (bilateral or unilateral) or hysterectomy within 2 years of diagnosis (n = 213), or if the follow-up period did not extend to 2 years from the onset of amenorrhea (n = 1,202). We also excluded 102 carriers who developed ovarian cancer or a second primary breast cancer within 2 years of breast cancer diagnosis, 338 carriers for whom genetic test results were of uncertain clinical significance, and 554 carriers for whom information on key variables was missing (ie, date of last menstrual period, date of breast cancer diagnosis, or date of breast cancer treatment). In total, 1,954 *BRCA* carriers with breast cancer were eligible.

We included 167 noncarrier women with breast cancer as a comparison group. These were women who had been assessed for family history and had undergone genetic testing for *BRCA1* and *BRCA2* mutations in the Narod laboratory in Toronto between 1995 and 2012 and were found to be negative for both mutations. These women completed the same lifestyle/medical questionnaire as did the carrier women, and the exclusion criteria were identical.

Statistical Analysis

We estimated the proportion of women who experienced induced amenorrhea as the number of women who experienced amenorrhea of ≥ 2 years duration after chemotherapy with no resumption of menses, divided by the total number of women. Relevant subgroups included chemotherapy use (yes *v* no), *BRCA1* or *BRCA2* mutation, age at diagnosis (age of surgery), and use of adjuvant hormonal therapy (tamoxifen). Between-group comparisons were assessed for significance using the *t* test.

In a secondary analysis, carrier and noncarrier patients were compared for menopause by comparing of the probabilities of induced amenorrhea by age at treatment. The comparisons were tested for statistical significance using the Cochran-Mantel-Haenszel test for nonzero correlation.

RESULTS

The median age at diagnosis for carriers was 37.3 years (range, 26 to 47 years; Table 1). All patients reported experiencing menstrual cycles at the time of breast cancer diagnosis. Of the 1,954 mutation carriers, 1,506 (77%) carried a *BRCA1* mutation, 436 (22%) carried a *BRCA2* mutation, and 12 (0.6%) carried both mutations. Of the 1,954 carrier patients, 1,426 (73%) received chemotherapy. In total, 478 carrier patients received tamoxifen, of whom 410 received both tamoxifen and chemotherapy (86%).

Of the 1,426 carriers who received chemotherapy, 35.6% experienced induced amenorrhea, and of the 528 women who did not receive chemotherapy, 5.3% experienced induced amenorrhea

Table 1. Patient Characteristics by Use of Chemotherapy (*BRCA1* and *BRCA2* carriers combined)

Characteristic	No Chemotherapy (n = 528)		Chemotherapy (n = 1,426)		*P*
	No.	%	No.	%	
Year of birth					< .001
Mean	1948.4		1957.4		
Range	1910-1978		1914-1982		
Age at diagnosis, years					.37
Mean	37.1		37.4		
Range	26-47		26-47		
BRCA1					.10
Mean	36.7		37.3		
Range	26-47		26-47		
BRCA2					.35
Mean	38.4		37.9		
Range	26-47		26-47		
Mutation status					.09
BRCA1	391	25.9	1,115	74.0	
BRCA2	135	30.9	301	69.0	
Country of residence					< .001
United States	183		497		
Poland	91		382		
Canada	148		324		
Israel	22		52		
Austria	16		50		
Italy	18		31		
France	13		32		
Other	37		58		

Table 2. Probability of Induced or Natural Amenorrhea Among Women Treated With Chemotherapy by Age at Treatment (*BRCA1* and *BRCA2* combined)

Age at Treatment (years)	Induced Amenorrhea*		Natural Amenorrhea†		
	No.	%	No.	%	Total
26	0	0.0	39	100.0	39
27	2	8.0	23	92.0	25
28	2	6.9	27	93.1	29
29	5	11.1	40	88.9	45
30	4	9.3	39	90.7	43
31	3	5.1	56	94.9	59
32	3	4.3	67	95.7	70
33	13	15.1	73	84.9	86
34	15	19.5	62	80.5	77
35	12	14.1	73	85.9	85
36	16	22.2	56	77.8	72
37	15	22.1	53	77.9	68
38	26	29.2	63	70.8	89
39	35	37.6	58	62.4	93
40	40	41.2	57	58.8	97
41	36	59.0	25	41.0	61
42	45	65.2	24	34.8	69
43	44	59.5	30	40.5	74
44	42	76.4	13	23.6	55
45	56	78.9	15	21.1	71
46	42	79.3	11	20.8	53
47	52	78.8	14	21.2	66
Total	508	35.6	918	64.4	1,426

*Amenorrhea onset ≤ 2 years of breast cancer diagnosis with no resumption of menses.
†Amenorrhea onset ≥ 2 years after breast cancer diagnosis.

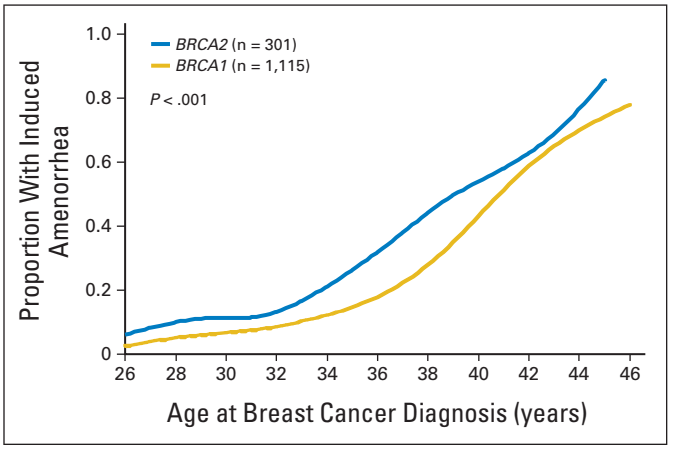

Fig 1. Proportion of patients with induced amenorrhea by age at diagnosis; *BRCA1* versus *BRCA2*; all patients received chemotherapy.

($P < .001$ for difference). The probability of induced amenorrhea increased with age at diagnosis (Table 2). Of the carrier patients who received chemotherapy, the probability of chemotherapy-induced amenorrhea was 7.2% for women diagnosed before age 30 years, 33% for women diagnosed from age 31 to 44 years, and 79% for women diagnosed at or after age 45 years (P trend $< .001$). The probability of chemotherapy-induced amenorrhea was significantly higher for *BRCA2* carriers than for *BRCA1* carriers (46.8% *v* 32.7%; $P < .001$; Table 3; Fig 1). The average age at diagnosis of *BRCA2* carriers was 1 year older than that of *BRCA1* carriers (38 *v* 37 years); after adjustment for age at diagnosis, the difference remained significant ($P < .001$). By age 38 years, 50% of *BRCA2* carriers were expected to experience amenorrhea after chemotherapy, compared with the age of 40 years expected for *BRCA1* carriers. More *BRCA2* carriers than *BRCA1* carriers received tamoxifen (41.4% *v* 16.1%); therefore, we restricted the comparison to women who did not receive tamoxifen; in this subgroup, the probability of chemotherapy-induced amenorrhea was 36.6% for *BRCA2* carriers and 27.8% for *BRCA1* carriers ($P = .04$).

We also evaluated the impact of tamoxifen use on the probability of induced amenorrhea for carrier women who did and did not receive chemotherapy (Table 4). Of 518 mutation carriers who did not receive chemotherapy, those who received tamoxifen had a 5.3% probability of induced amenorrhea, compared with 5.8% for those who did not use tamoxifen ($P = .9$; 10 carrier patients were missing tamoxifen data and were excluded). Of 1,403 *BRCA* carriers who received chemotherapy, those who received tamoxifen had a 52% probability of induced amenorrhea, compared with 29% for those who did not receive tamoxifen ($P < .001$; 33 carrier patients were missing tamoxifen data and were excluded).

We also evaluated the probability of induced menopause in 167 noncarrier patients with breast cancer who otherwise met the study criteria. Of the 167 noncarrier patients, 100 women (59%) received chemotherapy, and of these, 49 (49%) developed chemotherapy-induced amenorrhea. We compared the age-specific probabilities of induced amenorrhea among chemotherapy-treated patients for the 1,426 mutation carriers and 100 noncarriers (Fig 2). We found no significant difference between the age-specific probabilities of chemotherapy-induced amenorrhea for the two groups ($P = .18$). Furthermore, there was no significant difference when *BRCA1* carriers were compared with noncarrier controls ($P = .10$) or when *BRCA2* carriers were compared with noncarrier controls ($P = .50$). Tamoxifen had been administered to 24% of carriers and 38% of noncarriers.

Table 3. Probability of Induced Amenorrhea by Chemotherapy and Gene Mutation Status

Chemotherapy	Amenorrhea in *BRCA1* Carriers		Amenorrhea in *BRCA2* Carriers		Amenorrhea in *BRCA1* and *BRCA2* Carriers Combined	
	No.	%	No.	%	No.	%
No	22 of 391	5.6	6 of 135	4.4	28 of 526	5.3
Yes	364 of 1,115	32.7	141 of 301	46.8	505 of 1,416	35.6
Total	386 of 1,506	25.6	147 of 436	33.7	533 of 1,942	27.4

NOTE. Twelve women had both mutations and were excluded.

Table 4. Probability of Induced Amenorrhea by Chemotherapy and Tamoxifen Use

Treatments Received	Induced Amenorrhea No.	Induced Amenorrhea %	Natural Amenorrhea No.	Natural Amenorrhea %	Total
No chemotherapy; no tamoxifen	24	5.3	426	94.6	450
No chemotherapy; tamoxifen	4	5.8	64	94.1	68
Chemotherapy; no tamoxifen	288	29.0	705	71.0	993
Chemotherapy; tamoxifen	214	52.2	196	47.8	410
Total	536		1,418		1,954

NOTE. Information on tamoxifen was missing for 33 patients.

Results were similar when women who received tamoxifen were excluded (data not shown).

We also addressed the question of whether women with a *BRCA1* or *BRCA2* mutation who were treated with chemotherapy and who experienced return of menses underwent menopause earlier than women who did not receive chemotherapy. Among all women who reached age 56 years, the mean age of menopause was 45.4 years for those who received chemotherapy and resumed menses and was 49.0 years for those who did not receive chemotherapy ($P < .001$), a difference of 3.6 years. Among women who had a *BRCA1* mutation and reached age 56 years, the mean age of menopause was 45.5 years for those who received chemotherapy and 48.7 years for those who did not receive chemotherapy ($P < .001$). Among women who had a *BRCA2* mutation and reached age 56 years, the mean age of menopause was 45.2 years for those who received chemotherapy and 49.9 years for those who did not receive chemotherapy ($P = .003$).

DISCUSSION

Chemotherapy can induce transient or permanent amenorrhea. Definitions of chemotherapy-induced amenorrhea vary[7]; we defined it as ≥ 2 years of amenorrhea commencing within 2 years after chemotherapy with no resumption of menses. Patients with breast cancer for whom amenorrhea lasts > 24 months after chemotherapy are unlikely to resume menses.[7-9]

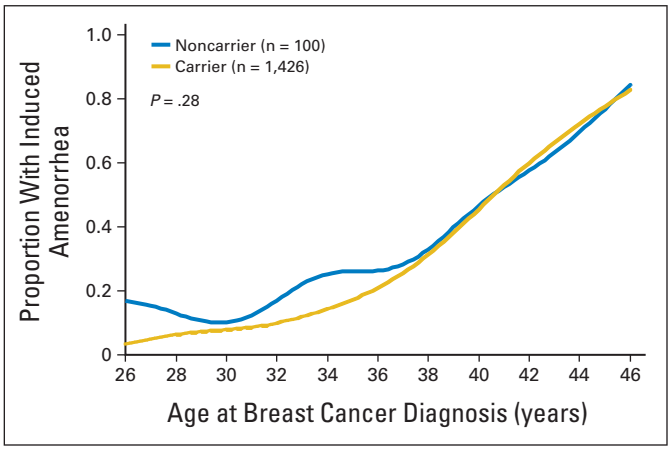

Fig 2. Proportion of patients with induced amenorrhea by age at diagnosis; mutation carriers versus noncarriers; all patients received chemotherapy.

The postmenopausal ovary is characterized by atrophy of the cortex and depletion of the follicles.[4,6,10] Chemotherapy can target the oocyte directly (germ cells) or can induce oocyte death indirectly via damage to somatic cells (granulosa cells).[9] Ovarian cytotoxicity is irreversible; women are born with a fixed number of germ cells, and these are not replenished.[9] Ovarian dysfunction after chemotherapy depends on patient age and type of chemotherapy received.[9,11,12] High-risk agents include alkylating agents; medium-risk agents include platinum, anthracycline antibiotics, and taxoids; and low-risk agents include vinca plant alkaloids, some anthracycline antibiotics such as bleomycin, and antimetabolites such as methotrexate, fluorouracil, and mercaptopurine. In our study, we did not have access to data regarding specific chemotherapy regimens.

We show here that the probability of chemotherapy-induced amenorrhea in women who carry a *BRCA1* or *BRCA2* mutation increases steadily with age at treatment; the probability of induced amenorrhea was 7% for women age ≤ 30 years, 12% for women age 31 to 35 years, and 52% for women age ≥ 36 years. It does not seem that *BRCA* mutation carriers are at particularly high risk of chemotherapy-induced menopause. The results are similar to those of previous studies that evaluated for sporadic breast cancer cases.[13-16] Forty-five percent of women with breast cancer who received CMF (cyclophosphamide, methotrexate, and fluorouracil) or a similar protocol experienced amenorrhea 1 year after treatment when age 35 to 40 years, in contrast with 28% of women age < 35 years.[18] The risk of amenorrhea resulting from a single-agent or combination regimen has been estimated to be up to 80% for patients diagnosed at age ≥ 40 years, compared with 60% if the woman is age 30 to 39 years and 20% if the patient is age < 30 years at treatment.[19,20] Rzepka-Górska et al[21] found a tendency for premature menopause in *BRCA1* mutation carriers; the mean age at menopause for *BRCA1* mutation carriers was 45.5 years, compared with 48.2 years for noncarriers. In this study, 45 of the 81 *BRCA1* carriers had breast cancer, and it is difficult to distinguish if the age of onset of menopause among *BRCA1* carriers was influenced by treatment or by *BRCA1* status per se. We also found that among women who had transient amenorrhea after chemotherapy and then resumed menses, the eventual age of amenorrhea was advanced, by 3.2 years in *BRCA1* carriers and 4.7 years in *BRCA2* carriers. A similar effect was reported by Partridge et al[22] in patients with breast cancer from the general public who did and did not receive chemotherapy.

Oktay et al[3] performed ovarian stimulation in 126 young women with breast cancer using letrozole and gonadotropins to cryopreserve embryos or oocytes. Ovarian reserve was measured by total oocyte yield and incidence of poor response (< four oocytes retrieved after ovarian stimulation). They found a higher fraction of poor responders among *BRCA1* carriers than noncarriers (four [33.3%] of 12 *v* one [3.3%] of 33; $P = .014$). The sample size of mutation carriers was small, and it is premature to make clinical recommendations based on this article. We found a statistically significantly higher proportion of women experiencing amenorrhea if they had a *BRCA2* versus *BRCA1* mutation, but for neither subgroup was the probability of amenorrhea higher than that of the noncarrier population. There is no clear biologic rationale for why a *BRCA1* germline mutation should be associated with early menopause; Oktay et al propose that because DNA

repair is deficient in patients with *BRCA* mutations, oocytes might be more prone to DNA damage.

We also evaluated the impact of tamoxifen on amenorrhea. In the absence of chemotherapy, there was no association between use of tamoxifen and onset of long-term amenorrhea, but tamoxifen augmented the toxicity of chemotherapy. Several other results support our findings.[13,22] In the NSABP (National Surgical Adjuvant Breast and Bowel Project) B-30 trial[23] 708 premenopausal patients were treated with anthracyclines and docetaxel. The rate of chemotherapy-induced amenorrhea was strongly influenced by the addition of tamoxifen (29% *v* 52%; $P = .003$). Perez-Fidalgo et al[13] reported that in younger patients, tamoxifen contributes to the delayed recovery of menses. Jung et al[24] reviewed 241 premenopausal patients with breast cancer who underwent adjuvant CMF or flourouracil, doxorubicin, and cyclophosphamide therapy and found that the addition of tamoxifen to chemotherapy increased the incidence of chemotherapy-induced amenorrhea from 48% to 64% ($P = .02$). Fornier et al[25] in a cohort of women with breast cancer age $\leq$ 40 years found the incidence of chemotherapy-induced amenorrhea to be 13% for patients treated only with chemotherapy and 17% for patients treated with chemotherapy and tamoxifen. The mechanism is unclear; however, tamoxifen increases circulating estrogen, which may induce a negative feedback of the hypothalamic-ovarian axis.[25] The opposite effect has been noted in several patients treated with an aromatase inhibitor. Aromatase inhibitors lead to an increase in the secretion of pituitary gonadotrophins, and when used as adjuvant hormonal therapy, they can sometimes induce a resumption of menses. Smith et al[26] found that of 45 women with breast cancer age 39 to 52 years who had ceased menses after chemotherapy, 12 women (27%) had a resumption of ovarian function after starting an aromatase inhibitor.

Several strategies have been used to preserve fertility in cancer survivors who receive chemotherapy, including embryo and oocyte cryopreservation.[12] Gonadotropin-releasing hormone (GnRH) has been used to suppress the ovaries during chemotherapy to protect the pool of follicles.[11] The SWOG (Southwest Oncology Group) 0230 randomized clinical trial will evaluate the rates of ovarian failure with and without GnRH in premenopausal women with hormone receptor–negative breast cancer. In the United Kingdom, OPTION (Ovarian Protection Trial in Premenopausal Breast Cancer Patients) is also assessing the impact of chemotherapy and the protective effect of GnRH on ovarian function at 12 months after breast cancer treatment.[12,29,30]

Young age at menopause has been linked to several adverse health outcomes, including osteoporosis,[31] cardiovascular disease,[32] and overall mortality.[33] Finch et al[34] reported that in the short term after surgically induced menopause, quality of life seemed to be similar before and after oophorectomy in *BRCA1* and *BRCA2* carriers; however, vasomotor symptoms and declines in sexual functioning were common. Hormone replacement therapy is not recommended after a diagnosis of breast cancer, leaving limited options for the management of menopause in this group of patients. We have recently shown that oophorectomy is associated with improved survival in *BRCA1* carriers treated for early-onset breast cancer.[35] It is important to establish whether the preservation of ovarian function in young women with breast cancer and a *BRCA* mutation has an adverse impact on disease recurrence.

In conclusion, *BRCA* mutation carriers age $>$ 35 years who receive chemotherapy for breast cancer are at high risk of developing long-term amenorrhea, but the probability of induced amenorrhea does not seem to be greater than that in the noncarrier population, and *BRCA1* or *BRCA2* status per se should not be an indication for referral to a fertility clinic. If tamoxifen is added to chemotherapy, the risk of amenorrhea is much higher. Women with breast cancer who wish to preserve fertility should be aware of the synergistic impact of chemotherapy and tamoxifen on inducing long-term amenorrhea and possibly menopause. Future studies should evaluate the impact of induced amenorrhea and ovarian preservation on survival in women with breast cancer and a *BRCA1* or *BRCA2* mutation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

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