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Age of menopause among women who remain premenopausal following treatment for early breast cancer: Long-term results from International Breast Cancer Study Group Trials V and VI

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ABSTRACT

Background: The likelihood of premature menopause has not been thoroughly explored in women who remain premenopausal after adjuvant chemotherapy for breast cancer.
Methods: We used data from the International Breast Cancer Study Group (IBCSG) Trials V and VI. Trial V enrolled 1407 eligible premenopausal women randomised to no systemic therapy (No CT) or 1 cycle of perioperative CMF-based chemotherapy (PeCT) if node negative, and 6 cycles of CMF-based chemotherapy postoperatively (CMF × 6) or 1 cycle perioperative CMF-based chemotherapy plus CMF × 6 postoperatively (CMF × 7) if node positive. From Trial VI (a 2 × 2 factorial designed study of 3 versus 6 initial cycles of CMF and a reintroduction of three additional courses of CMF), we included 375 women randomised to receive only six initial cycles of CMF (CMF × 6).
Findings: We excluded women who reported no menses during 12–24 months after randomisation ($N = 934$), hysterectomy ($N = 16$) or bilateral oophorectomy ($N = 8$), or missing menses data ($N = 57$), creating a cohort of 767 women; 540 women had been randomised to PeCT or no CT, 227 randomised to CMF × 6 or 7. A Cox proportional hazards model revealed that CMF × 6 or 7 (HR = 2.03, $p < 0.0001$) and temporary amenorrhea (HR = 1.96, $p < 0.0001$) were associated with premature menopause.
Interpretation: Women who remain premenopausal after 6 or 7 cycles of CMF-based chemotherapy have a higher likelihood of going through menopause at an earlier age than women who received little or no chemotherapy. Temporary cessation of menses appears to be a marker for earlier onset of menopause. These findings may assist women and clinicians when making treatment and reproductive decisions after a diagnosis of breast cancer.

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1. Introduction

Chemotherapy-related amenorrhea (CRA) is a common consequence of adjuvant chemotherapy in premenopausal women with breast cancer.[1–3] Risk of CRA is related to patient age and treatment regimen, and CRA may be temporary or permanent, resulting in menopause. Many younger premenopausal women with breast cancer either menstruate through cytotoxic treatment or resume menstrual cycling after treatment, whereas older premenopausal women are more likely to develop permanent amenorrhea. However, women who continue to menstruate following chemotherapy may ultimately experience menopause earlier than they would have had they not received chemotherapy.

While many young women will remain premenopausal after breast cancer, the duration of premenopausal status and their associated fertility may be shortened by premature menopause.[4] Among survivors of paediatric malignancies, three studies have found a significantly increased risk of premature menopause among childhood cancer survivors who initially remained premenopausal after treatment compared to age-matched controls.[5–7] There are reports of adult breast cancer survivors who continue menstrual cycling after chemotherapy, entering menopause seemingly prematurely, in their late 30s and early 40s.[3,8] However, sample size or follow-up has been limited.

To date, the likelihood and timing of delayed, but nevertheless premature, menopause following chemotherapy has not been thoroughly explored in any adult cancer survivor population. Many young women with breast cancer are interested in their risk of infertility and early menopause following treatment.[9] Information regarding the likelihood of premature menopause for premenopausal cancer survivors would facilitate family planning for some survivors. In addition, premature menopause may increase a woman's risk of a variety of future adverse health effects including menopausal symptoms, sexual dysfunction and osteoporosis.[10]

We sought to evaluate the age of menopause among women who initially remained premenopausal after treatment for early breast cancer using long-term follow-up data from IBCSG Trials V and VI, two randomised clinical studies. We evaluated the age of menopause among women randomised to receive little or no chemotherapy compared to women who received 6 or 7 cycles of chemotherapy.

2. Patients and methods

2.1. Study cohort

We used data from International Breast Cancer Study Group (IBCSG) Trials V and VI, including long-term follow-up menses information.[11–13] Trial V randomised 1407 eligible pre- or perimenopausal women from 1981 to 1985. 692 women with node-negative disease were randomised to receive either no systemic chemotherapy (no CT) or one perioperative cycle of CMF (cyclophosphamide 100 mg/m^2 orally, days 1–14; methotrexate 40 mg/m^2 intravenously, days 1 and 8; 5-Fluorouracil 600 mg/m^2 intravenously, days 1 and 8) (PeCT). 715 women with node-positive disease were randomised to receive either CMF repeatedly every 28 days × 6 postoperatively (CMF × 6), or 1 cycle of CMF perioperatively + CMF × 6 (CMF × 7). Patients who received perioperative CMF in Trial V (in either the node-positive or the node-negative group) received leucovorin 15 mg intravenously on day 2 and 15 mg orally on day 9 of the 28-day perioperative cycle. During the CMF × 6 in Trial V, 7.5 mg of prednisone was orally administered daily throughout the course of chemotherapy. As of September 2004 the median follow-up was 19 years. Trial VI recruited 1475 eligible premenopausal patients during 1986 to 1993 and randomised them in a 2 × 2 factorial design evaluating both 3 versus 6 initial cycles of CMF and an additional three delayed cycles of CMF. Patients who were randomised to receive only six initial cycles of CMF were included in this analysis. Neither daily oral prednisone nor leucovorin was part of the treatment regimen for Trial VI. As of September 2004 the median follow-up was 13 years.

The study cohort included only those women who had at least one report of menses during 12–24 months after enrolment (patients missing this information were excluded), and had no history of hysterectomy or bilateral oophorectomy. Therefore, this analysis does not represent a randomised comparison.

2.2. Data collection

IBCSG collected follow-up menses information for women on Trials V and VI every 3 months during the first two years of study, every 6 months during 3–5 years and every year thereafter for the life of the patient. The menses data were recorded as normal and regular during that follow-up time period, irregular and/or scanty, no period or pregnant. For this analysis, women with normal and regular, or irregular and/or scanty menses were considered to have continued menses. Age at menopause was defined as first date of follow-up when a patient had no reported menses for the prior 12 months and had not been pregnant or had a hysterectomy or bilateral oophorectomy during that time period.

2.3. Statistical analyses

The Kaplan–Meier method was used to estimate age at menopause censoring at recurrence of breast cancer, new primary, or death. Competing risk estimates were used to assess the cumulative incidences of permanent menopause and recurrence of breast cancer according to chemotherapy assigned and age group at diagnosis.[14] Cox proportional hazards modelling, also censoring at recurrence of breast cancer, new primary or death, was used to evaluate factors associated with age at onset of menopause. Candidate explanatory variables included age at diagnosis, chemotherapy assignment (CMF × 6 or 7 versus PeCT or no CT), temporary amenorrhea, two-way interaction terms for these three variables and oestrogen receptor status. Estimates of onset of menopause by age at diagnosis were derived from univariate logistic regression models of women who were alive and disease free at 5 and 10 years following diagnosis. For all analyses, patients entered the at-risk set at their enrolment age.

3. Results

3.1. *Description of the study cohort*

Of the 1782 women enrolled on Trials V and VI who were considered for this analysis, we excluded women who reported no menses during 12–24 months after randomisation ($N = 934$), history of hysterectomy ($N = 16$) or bilateral oophorectomy ($N = 8$), or were missing 12–24 month menses data ($N = 57$), creating a cohort of 767 women (see Fig. 1 for Flow Chart of Patients Included in Study Cohort). Women were in the following age groups at diagnosis: <30 years ($N = 26$), 30–34 years ($N = 89$), 35–39 years ($N = 186$), 40–44 years ($N = 237$) and 45 and over ($N = 229$). We divided the patients who met our inclusion criteria into two groups based on the chemotherapy treatment: women who received PeCT or no CT and women who received CMF × 6 or 7. We grouped women who received 1 cycle of CMF with women who received no chemotherapy based on an a priori hypothesis that women who received PeCT and remained premenopausal were unlikely to undergo menopause at substantially different age than if they had received no chemotherapy. Fig. 2 depicts the age of menopause in women who received PeCT or no CT by age at treatment, and demonstrates the similarities between the two groups.

Table 1 presents the patient and disease characteristics. Five hundred and forty women had received PeCT or no CT and 227 had received CMF × 6 or 7. The median age of the PeCT or no CT group at diagnosis was 42 (range = 22–57) and of the CMF × 6 or 7 group was 39 (range = 25–54). The women who received CMF × 6 or 7 were more likely to have oestrogen receptor-positive disease compared to women in the PeCT or no CT group (58% versus 44%). The women who received more chemotherapy also had larger tumours (55% with greater than 2 cm tumours). All women who received CMF × 6 or 7 had node-positive disease, compared with 23% of women in the PeCT or no CT group. The incidence of temporary amenorrhea (defined as any reported missed period during the first 12 months following enrolment, with resumption of menses during 12–24 months) was 63% among women in the CMF × 6 or 7 group and 36% in the PeCT or no CT group. The median age of menopause for women who received PeCT or no CT was 50 years (range 34–59) and for women who received CMF × 6 or 7 it was 45 years (range 34–55).

Using the Kaplan–Meier method, age at menopause was calculated for four groups based on age at diagnosis (under 40 years or 40 and older) and treatment received (PeCT or no

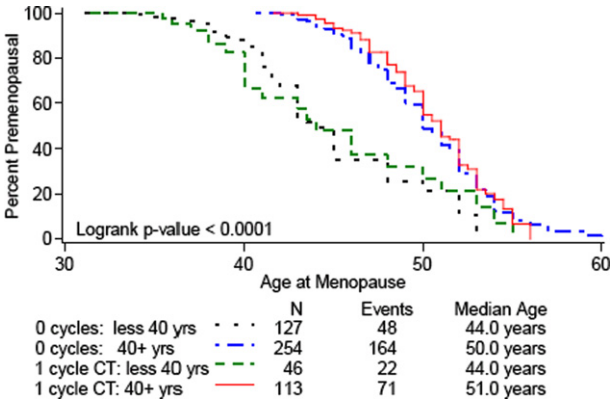

Fig. 2 – Percentage of women remaining premenopausal who received PeCT or no CT by age of treatment.

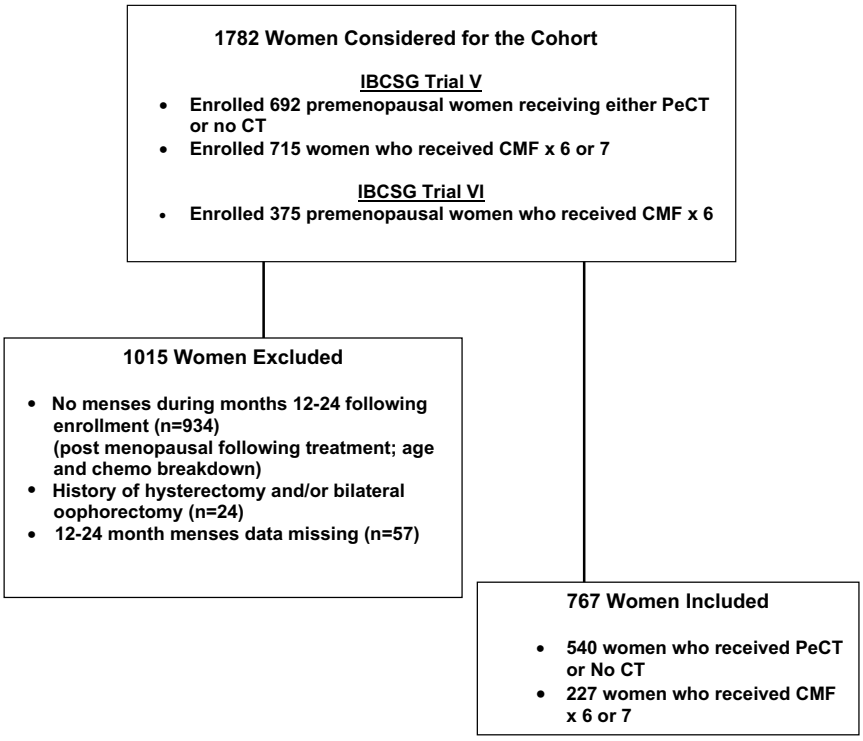

Fig. 1 – Consort flow chart.

Table 1 – Patient and disease characteristics

	No. CT or PeCT, N (%)	CMF × 6 or 7, N (%)	Total, N (%)
Total patients	540 (70)	227 (30)	767
Study			
Trial V	540 (100)	132 (58)	672
Trial VI	0	95 (42)	95
Age at enrolment			
Median, range	42, 22–57	39, 25–54	41, 22–57
Oestrogen receptor status			
ER+	239 (44)	132 (58)	371
ER-	206 (38)	73 (32)	279
ER-unk	95 (18)	22 (10)	117
Tumour size			
⩽2	265 (49)	96 (42)	361
>2	234 (43)	124(55)	358
Missing	41 (8)	7 (3)	48
Nodal status			
N–	417 (77)	0	417
N+	123 (23)	227 (100)	350
Temporary amenorrhea			
Yes	193 (36)	142 (63)	335
No	347 (64)	85 (37)	432

CT, or CMF × 6 or 7) (see Fig. 3: percentage of women remaining premenopausal by age at treatment and treatment group). For women in the PeCT or no CT group, the median age of menopause for women under 40 was 44 years, and for women 40 or older, 50.5 years. Among women assigned to CMF × 6 or 7, the median age of menopause for women diagnosed under 40 was 41 years and for women 40 or older at diagnosis it was 47.5 years. Receiving 6 or 7 cycles of chemotherapy was related to earlier onset of menopause in both age groups. Women who were diagnosed under age 40 years who remained in the analysis entered menopause at earlier ages than women in the older cohorts, regardless of treatment group. Similar trends were seen for women with oestrogen receptor-positive disease compared to women with oestrogen receptor-negative disease, however, numbers within these subgroups were small.

The percentage of women in menopause at 5 years and 10 years from diagnosis among eligible women in the different

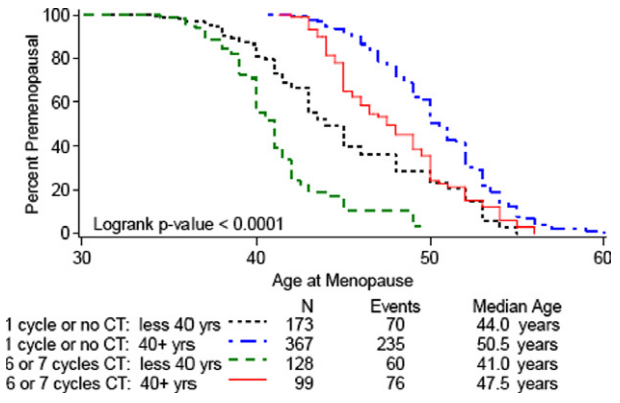

Fig. 3 – Percentage of women remaining premenopausal by age at treatment and treatment group.

treatment groups (women who remained premenopausal 24 months after diagnosis and were alive and disease free in follow-up) was evaluated using logistic regression. Table 3 presents the percentage of women in each age group who were in menopause at 5 and 10 years from diagnosis by age at diagnosis. Women who were randomised to receive CMF × 6 or 7 had a higher likelihood of being in menopause at 5 and 10 years than women who had received PeCT or no CT. For example, 91% of women diagnosed at age 35 years and assigned to CMF × 6 or 7 had entered menopause by age 45, compared with 72% of women in the same age group who were assigned to receive PeCT or no CT. Risk of premature menopause also varied with age at diagnosis. For example, 84% of women who were assigned CMF × 6 or 7 at age 30 were in menopause by age 40, while 65% of women receiving the same treatment at age 35 were in menopause by age 40.

A Cox proportional hazards analysis of age at menopause revealed statistically significant interactions for both age at diagnosis by treatment assigned (p-value = 0.004) and age at diagnosis by temporary amenorrhea (p-value = 0.0009). The interaction between treatment assigned and temporary amenorrhea was not statistically significant. Thus among patients who had menses two years post diagnosis, women treated at younger age were more likely to enter menopause prematurely than women treated at older age. This influence of age was greater for the women who had been assigned to CMF × 6 or 7 or had temporary amenorrhea.

We identified two competing risks that differed by age for the influence on premature menopause. Women 40 years of age and older were more likely to have become post-menopausal during or immediately following treatment, while the younger premenopausal women had a higher risk of relapse (see Table 2 and Fig. 3).

Table 2 displays the differences by age at diagnosis and number of chemotherapy cycles assigned, including the women who did not remain premenopausal by two years post diagnosis, and thus did not make it into our cohort. The last three rows of this table present the women who developed recurrent breast cancer prior to becoming postmenopausal, were still menstruating, or had become postmenopausal. Fig. 4 displays four competing risk curves which illustrate the differing risks for: (1) entering menopause during or immediately following treatment, and (2) recurrence of breast cancer, according to age and treatment regimen. Women in the study cohort who were 40 years and older at diagnosis were more likely to become post-menopausal at ages closer to population norms, indicating very robust ovarian function among older women who received CMF × 6 or 7 cycles. Further, younger women in our cohort who remained premenopausal for longer durations developed recurrent breast cancer at a higher rate than younger women who did not remain premenopausal.

4. Discussion

Approximately 25% of cases of breast cancer occur in premenopausal women. Breast cancer treatments have long been known to affect menopausal and fertility status.[8,15] Adjuvant chemotherapy for breast cancer may render a premenopausal woman amenorrheic, either temporarily or

Table 2 – Numbers of patients in original samples from Trials V and VI with disease and menses events by age, treatment assignment and experience of temporary amenorrhea

	Under 40 years (N = 392)				40 years and older (N = 1390)			
	PeCT or No CT		CMF × 6 or7		PeCT or No CT		CMF × 6 or 7	
	Temp amen	No temp amen	Temp amen	No temp amen	Temp amen	No temp amen	Temp amen	No temp amen
Total patients considered from Trials V and VI	65	142	115	70	498	227	637	28
Excluded patients with hysterectomy, oophorectomy, or missing menses info.	−6	−3	−5	−5	−20	−19	−15	−8
Excluded patients not premenopausal at 2 year follow-up	−25	−0	−47	−0	−319	−0	−543	−0
Included in cohort	34	139	63	65	159	208	79	20
Outcomes of cohort patients								
Recurrent breast cancer before menopause	14	54	17	26	45	32	18	4
Still menstruating	6	29	10	15	15	40	1	0
Became menopausal	14	56	36	24	99	136	60	16

Table 3 – Women in menopause by 5 and 10 years (%)[a]

Age at diagnosis	By 5 years (%)		By 10 years (%)	
	PeCT or no CT	CMF × 6 or 7	PeCT or no CT	CMF × 6 or 7
25	9	16	29	75
30	20	37	51	84
35	37	65	72	91
40	58	86	86	95
45	77	95	94	97

a Obtained from logistic regression model

permanently. The risk of chemotherapy-related amenorrhea is related to patient age, the specific chemotherapeutic agents used, and the total dose administered.[1,16] Chemotherapy-related amenorrhea may be reversible, in that some women will resume menstrual function months or occasionally years after treatment. The vast majority of women who remain amenorrheic one year following treatment will not regain ovarian function. However, many young women do continue to menstruate after breast cancer chemotherapy.[9,17] For these women, there is the possibility of entering menopause earlier than they would have in the absence of chemotherapy.

The mean age of natural menopause in western countries has remained approximately 51 years during the last several decades. While studies are inconsistent, age at natural menopause may be related to certain environmental and reproductive factors including smoking, socioeconomic status and parity.[18–23]

Among cancer survivors, no prior long-term studies have focused on the effect of chemotherapy on age at menopause among adult women who did not become post-menopausal immediately following treatment. In a paediatric oncology population, Byrne and colleagues evaluated self-reported menopausal status of 1067 women who were treated for cancer before age 20, were still menstruating at age 21 and were at least 5-year survivors, and compared them to 1599 control women.[5] Cancer survivors, who had been diagnosed between ages 13 and 19, had a risk of menopause from age 21 to 25 that was four times greater than that of controls. The risk relative to controls declined as women were further out from their treatment. Women who were treated with either radiotherapy alone (relative risk 3.7) or alkylating agents alone (relative risk 9.2) had significantly increased relative risks of menopause during the early 20s compared to other survivors. During ages 21–25 the risk of menopause increased 27-fold for women treated with both radiation below the diaphragm and alkylating agent chemotherapy. By age 31, 42% of survivors had reached menopause compared with 5% for controls. Sklar and colleagues found similar risks among 2819 childhood cancer survivors compared to 1065 female siblings.[7]

Considering adult cancer survivors, Valagussa and colleagues reported on long-term fertility and menopausal outcomes of 205 patients who were premenopausal at diagnosis of breast cancer. They described two patients who entered menopause 9 years after chemotherapy at age 39 years.[8] More recently, Petrek and colleagues have reported on menstrual bleeding after breast cancer from a cohort study of 595 women who were premenopausal at diagnosis.[3] They describe a high

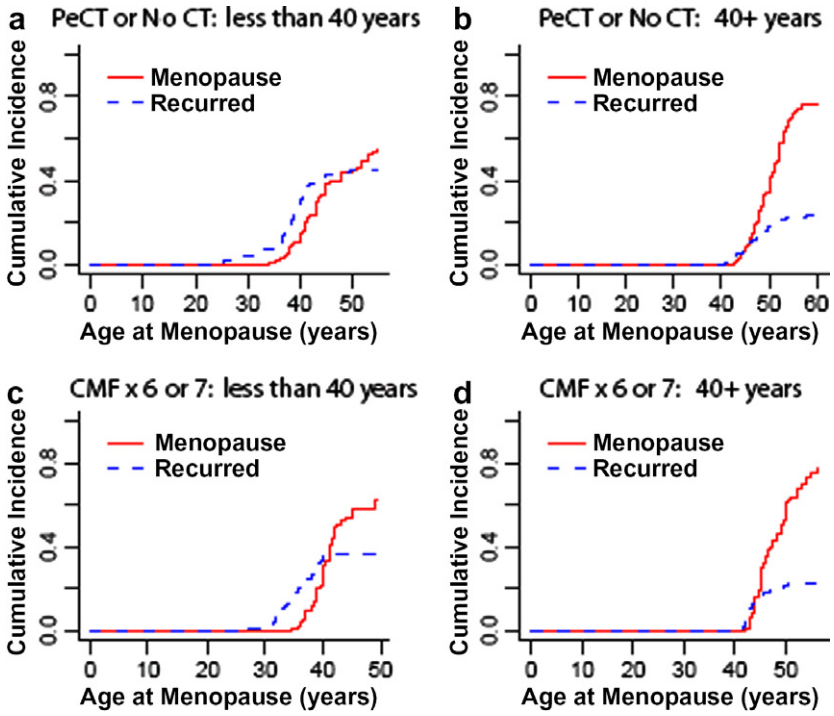

Fig. 4 – Competing risks analysis: curves include all women in subsets evaluated in Trials V and VI excluding women who did not have follow-up menstrual information or had undergone prior hysterectomy or bilateral oophorectomy.

incidence of temporary amenorrhea (approximately 40%) during chemotherapy, followed by recovery of menses for many survivors, particularly women under 40. Over the subsequent 5 years of available follow-up, monthly bleeding slowly declined in their cohort, though this seemed to be limited to women who were at least 35 at diagnosis. They also found that the incidence of CRA was related to receipt of chemotherapy, with women receiving any chemotherapy being more likely to experience amenorrhea in follow-up. Petrek and colleagues also evaluated bleeding patterns in relatively short term follow-up by type of chemotherapy received and found that women who received anthracycline-based chemotherapy were more likely to experience acute amenorrhea, but were more likely to experience recovery of menses than women receiving CMF chemotherapy.[3]

Our findings of earlier onset of menopause among women who received 6 or 7 cycles of CMF-based chemotherapy (CMF × 6 or 7) compared to women who received no chemotherapy or only 1 cycle of CMF-based chemotherapy (PeCT or no CT) are consistent with the work in the paediatric oncology population evaluating premature menopause in childhood cancer survivors who remain premenopausal immediately after treatment. Our study provides evidence that age at treatment for adult females plays a substantial role in the ultimate timing of menopause. It appears that the closer one is to natural menopause, the less impact chemotherapy has on lowering the age of menopause if a woman does not stop having menstrual cycles during or immediately following the course of chemotherapy. It is possible that this may be due in part to chemotherapy causing more damage to younger more "active" ovaries that may not become apparent for several years. Alternatively, older women who do not become immediately menopausal with chemotherapy may have greater ovarian reserve or less ovarian sensitivity to chemotherapy than the average woman. Further, there are different competing risks for younger and older patients. In particular, as demonstrated in our analysis, younger women are less likely to experience temporary amenorrhea and more likely to develop recurrent disease than older women. This may be related to the evidence that the development of amenorrhea during chemotherapy, even if only temporary, improves prognosis in women with hormone receptor-positive breast cancer.[24–26]

Our finding of early menopause even in very young women who received little or no chemotherapy is worthy of note. There are at least two hypotheses for this observation: (1) As noted above, there are competing risks and potential selection bias in our analysis. Very young women who remained premenopausal for longer durations after breast cancer may have been more likely to experience a recurrence of breast cancer and thus would have been initially excluded or censored early in our analysis; and (2) young women who develop breast cancer may be different from older premenopausal women with breast cancer and different from women in the general population with regard to their age at menopause for biologic reasons.

The use of long-term follow-up menses information from large randomised trials of premenopausal women with breast cancer allowed us to evaluate this important issue among a large group of breast cancer survivors who received standardised treatment. The findings are limited by use of data that, despite the prospective collection, were not designed to answer our research question. In addition, we utilised patient self-report of menstrual functioning that may have inaccuracies. Further, because women received an older chemotherapy

regimen, and did not receive tamoxifen in these studies, it is unclear if these results would reflect the experience of younger women today. Additionally, whenever studying issues related to cancer survivorship, the issue of competing risks and resulting bias must be considered. The majority of women who were treated on IBCSG Trials V and VI were not included in the primary analysis featured in this report for reasons including lack of menses after treatment, lack of follow-up menses data or the development of recurrent disease. We intentionally excluded these women in order to focus on the cohort of women for whom this important survivorship issue would be most relevant. It is also important to note that menstrual cycling is an imperfect surrogate for ovarian functioning. Chemotherapy-related amenorrhea may be temporary, and some women may remain fertile despite lack of menstrual cycles. Menstrual cycling may resume after a long duration of amenorrhea. Further, for older women in particular, cessation of menses may be the final symptom of ovarian failure, and infertility may have ensued years before.[27]

Nevertheless, these findings may have important implications for young women facing a breast cancer diagnosis and survivorship. A substantial proportion of young women are concerned about their fertility and menopausal status following breast cancer treatment, and for some women, such concerns may impact treatment decisions.[9] These findings may have implications for family planning among breast cancer survivors, who might not want to delay trying to become pregnant if they could project how much the duration of their fertility may have been compromised by having received adjuvant chemotherapy. Further, premature menopause, or ovarian failure, may have additional important physical and psychosocial consequences including the development of menopausal symptoms such as hot flushes, genitourinary problems, both psychological and psychosexual difficulties, and accelerated bone mineral density loss.[28–35] Screening and prevention of such problems among premenopausal cancer survivors may improve health outcomes. Future prospective studies evaluating the risk and timing of premature menopause following more modern adjuvant breast cancer chemotherapy regimens are warranted. Further, the relationship between ongoing menses and actual fertility needs further evaluation among young women with breast cancer.

Conflict of interest statement

There are no conflicts of interest for any of the authors with regard to the subject matter of this manuscript.

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REFERENCES

1. Minton SE, Munster PN. Chemotherapy-induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer. *Cancer Control* 2002;**9**(6):466–72.
2. Burstein HJ, Winer EP. Primary care for survivors of breast cancer. *N Engl J Med* 2000;**343**(15):1086–94.
3. Petrek JA, Naughton MJ, Case LD, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. *J Clin Oncol* 2006;**24**(7):1045–51.
4. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients. *J Clin Oncol* 2006;**24**:2917–31.
5. Byrne J, Fears TR, Gail MH, et al. Early menopause in long-term survivors of cancer during adolescence. *Am J Obstet Gynecol* 1992;**166**(3):788–93.
6. Chiarelli AM, Marrett LD, Darlington G. Early menopause and infertility in females after treatment for childhood cancer diagnosed in 1964–1988 in Ontario Canada. *Am J Epidemiol* 1999;**150**(3):245–54.
7. Sklar CA, Mertens AC, Mitby P, et al. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. *J Natl Cancer Inst* 2006;**98**(13):890–6.
8. Valagussa P, De Candis D, Antonelli G, Bonadonna VIII G. Women's health perception and breast cancer: issues of fertility, hormone substitution, and cancer prevention. *Recent Results Cancer Res* 1996;**140**:277–83.
9. 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**(20):4174–83.
10. Molina JR, Barton DL, Loprinzi CL. Chemotherapy-induced ovarian failure: manifestations and management. *Drug Saf* 2005;**28**(5):401–16.
11. Prolonged disease-free survival after one course of perioperative adjuvant chemotherapy for node-negative breast cancer.The Ludwig Breast Cancer Study Group. *N Engl J Med* 1989;**320**(8):491–6.
12. Combination adjuvant chemotherapy for node-positive breast cancer. Inadequacy of a single perioperative cycle. The Ludwig Breast Cancer Study Group. *N Engl J Med* 1988;**319**(11):677–83.
13. Duration and reintroduction of adjuvant chemotherapy for node-positive premenopausal breast cancer patients. International Breast Cancer Study Group. *J Clin Oncol* 1996;**14**(6):1885–94.
14. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;**16**:1141–54.
15. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol* 1999;**17**(8):2365–70.
16. Burstein HJ, Winer EP. Reproductive issues. In: Harris JR, editor. *Diseases of the breast*. 2nd ed. Philadelphia: Lippincott; 2000. p. 1051–9.
17. Hortobagyi GN, Buzdar AU, Marcus CE, Smith TL. Immediate and long-term toxicity of adjuvant chemotherapy regimens containing doxorubicin in trials at M.D. Anderson Hospital and Tumor Institute. *NCI Monogr* 1986;**1**:105–9.

18. Willett W, Stampfer MJ, Bain C, et al. Cigarette smoking, relative weight, and menopause. *Am J Epidemiol* 1983;**117**(6):651–8.
19. Stanford JL, Hartge P, Brinton LA, Hoover RN, Brookmeyer R. Factors influencing the age at natural menopause. *J Chronic Dis* 1987;**40**(11):995–1002.
20. Brambilla DJ, McKinlay SM. A prospective study of factors affecting age at menopause. *J Clin Epidemiol* 1989;**42**(11):1031–9.
21. Luoto R, Kaprio J, Uutela A. Age at natural menopause and sociodemographic status in Finland. *Am J Epidemiol* 1994;**139**(1):64–76.
22. Gold EB, Bromberger J, Crawford S, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *Am J Epidemiol* 2001;**153**(9):865–74.
23. Lawlor DA, Ebrahim S, Smith GD. The association of socio-economic position across the life course and age at menopause: the British Women's Heart and Health Study. *Bjog* 2003;**110**(12):1078–87.
24. 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* 1998;**34**(5):632–40.
25. 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* 1990;**1**(3):183–8.
26. Davidson NE. Ovarian ablation as adjuvant therapy for breast cancer. *J Natl Cancer Inst Monogr* 2001(30):67–71.
27. Oktay K, Oktem O, Reh A, Vahdat L. Measuring the impact of chemotherapy on fertility in women with breast cancer. *J Clin Oncol* 2006;**24**(24):4044–6.
28. Ganz PA, Coscarelli A, Fred C, Kahn B, Polinsky ML, Petersen L. Breast cancer survivors: psychosocial concerns and quality of life. *Breast Cancer Res Treat* 1996;**38**(2):183–99.
29. Ganz PA, Rowland JH, Desmond K, Meyerowitz BE, Wyatt GE. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. *J Clin Oncol* 1998;**16**(2):501–14.
30. Meyerowitz BE, Desmond KA, Rowland JH, Wyatt GE, Ganz PA. Sexuality following breast cancer. *J Sex Marital Ther* 1999;**25**(3):237–50.
31. 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* 1992;**3**(Suppl. 4):105–10.
32. Bruning PF, Pit MJ, de Jong-Bakker M, van den Ende A, Hart A, van Enk A. Bone mineral density after adjuvant chemotherapy for premenopausal breast cancer. *Br J Cancer* 1990;**61**(2):308–10.
33. Park KH, Song CH. Bone mineral density in premenopausal anovulatory women. *J Obstet Gynaecol* 1995;**21**(1):89–97.
34. Howell SJ, Berger G, Adams JE, Shalet SM. Bone mineral density in women with cytotoxic-induced ovarian failure. *Clin Endocrinol (Oxf)* 1998;**49**(3):397–402.
35. Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast cancer in younger women: reproductive and late health effects of treatment. *J Clin Oncol* 2003;**21**(22):4184–93.