Original Article

Nonsurgical Premature Menopause and Reproductive Implications in Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

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BACKGROUND: Survivors of childhood cancer are at risk of nonsurgical premature menopause (NSPM). To the authors' knowledge, risk factors for NSPM and its impact on reproduction remain poorly defined. **METHODS:** The menopausal status of 2930 survivors diagnosed between 1970 and 1986 (median age, 6 years [range, birth-20 years]) who were aged >18 years at the time of the current study (median age, 35 years [range, 18-58 years]) was compared with 1399 siblings. NSPM was defined as the cessation of menses ≥6 months in duration occurring 5 years after diagnosis and before age 40 that was not due to pregnancy, surgery, or medications. Among survivors, multivariable logistic regression identified risk factors for NSPM. Pregnancy and live birth rates were compared between survivors with and without NSPM. **RESULTS:** A total of 110 survivors developed NSPM (median age, 32 years [range, 16-40 years]), with a prevalence at age 40 years of 9.1% (95% confidence interval [95% CI], 4.9%-17.2%); the odds ratio (OR) was 10.5 (95% CI, 4.2-26.3) compared with siblings. Independent risk factors included exposure to a procarbazine dose ≥4000 mg/m^2 (OR, 8.96 [95% CI, 5.02-16.00]), any dose of ovarian radiation (OvRT) (OvRT < 500 cGy: OR, 2.73 [95% CI, 1.33-5.61] and OvRT ≥ 500 cGy: OR, 8.02 [95% CI, 2.81-22.85]; referent RT, 0), and receipt of a stem cell transplantation (OR, 6.35; 95% CI, 1.19-33.93). Compared with survivors without NSPM, those who developed NSPM were less likely to ever be pregnant (rate ratio, 0.49; 95% CI, 0.27-0.80) or to have a live birth (rate ratio, 0.42; 95% CI, 0.19-0.79) between ages 31 and 40 years. **CONCLUSIONS:** Survivors of childhood cancer are at risk of NSPM associated with lower rates of live birth in their 30s. Those at risk should consider fertility preservation if they anticipate delaying childbearing. ***Cancer* 2018;000:000–000.** *© 2018 American Cancer Society.*

KEYWORDS: childhood cancer, late effects, premature menopause, reproductive outcomes, survivorship.

INTRODUCTION

Contemporary, combined modality therapy has resulted in 5-year survival rates of >80% among children and adolescents diagnosed with cancer.[1] It is estimated that 500,000 individuals will be survivors of childhood cancer by the year 2020.[2] With increasing numbers of children surviving into adulthood,[3] the long-term complications of exposure to chemotherapy, radiotherapy (RT), and surgery have become apparent, including the impairment of gonadal function and fertility.[4,5]

Females are born with a finite supply of follicles that naturally decline with age through atresia, apoptosis, and maturation during menstrual cycles, culminating in menopause at a median age of 52.5 years in the general population.[6,7] Cancer-directed therapies can accelerate this decline, resulting in menopause earlier than would otherwise be expected.[8-13] Previous Childhood Cancer Survivor Study (CCSS) investigations have demonstrated acute ovarian failure (menopause occurring within 5 years from diagnosis) in 6.3% of female survivors and a cumulative incidence of nonsurgical premature menopause (NSPM; menopause occurring before age 40 years but after 5 years from diagnosis that is not related to surgical intervention) in 8% of female survivors.[8,9]

Treatment-related risk factors including higher doses of alkylating agents (eg, cyclophosphamide, busulfan, procarbazine, and ifosfamide) and increasing doses of RT to the ovaries (OvRT) have been implicated in premature menopause.[8-16] One study also identified unilateral oophorectomy as a risk factor.[12] Host factors, such as attained age, also have been associated with increasing risk of diminished ovarian reserve.[17-19] The current study was undertaken to provide more

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precise estimates of the prevalence of and risk factors for NSPM in the CCSS population using an additional 7 years of longitudinal follow-up. Because to the best of our knowledge little is known regarding the implications of premature menopause on reproductive outcomes in survivors of childhood cancer, we also assessed pregnancy and live birth rates among those survivors who ultimately developed NSPM.

MATERIALS AND METHODS

Childhood Cancer Survivor Study

Detailed descriptions of the design, cohort characteristics, and baseline data collection of the CCSS have been published previously.[20-22] In brief, the CCSS is a 26-center retrospective cohort study with longitudinal follow-up of 14,364 long-term survivors of childhood cancer in North America diagnosed before the age of 21 years and between January 1, 1970, and December 31, 1986. Participants completed comprehensive baseline and follow-up questionnaires that included information regarding demographics and chronic health conditions. Treatment information was abstracted from medical records at the individual institutions at the time of study entry. These data included all treatments within the first 5 years from diagnosis for the primary cancer and, if relevant, treatment for disease recurrence and preparatory regimens for stem cell transplantation (SCT). Exposure to chemotherapy was collected either quantitatively (22 agents) or qualitatively (20 additional agents). A cyclophosphamide equivalent dose (CED) was calculated when relevent.[23] Additional information regarding cancer treatment included surgeries performed from the time of diagnosis and region-specific and organ-specific radiation dosimetry. Dosimetry methods have been described previously.[24] Specifically, the RT record for each patient was abstracted for date of RT, prescription dose(s), and specific treatment parameters of each RT field including energy, weighting, configuration, field size, blocking, and anatomic borders by the CCSS study team. Ovary doses for individual patients were determined by reconstructing their RT fields on age-specific computational phantoms and calculating the average absorbed dose separately to the right and left ovaries. The minimum ovarian doses used for the analyses were the lesser of the 2 average doses (either the right or left ovary). A cohort of 3899 siblings, randomly selected, also completed questionnaires for comparison. Institutional review board approval was obtained at the coordinating institution and at each individual participating site. Participants provided informed consent.

Premature Menopause

CCSS subjects included in the current study were aged >18 years at the time they completed either of the follow-up questionnaires, which included items providing sufficient information to define the menstrual and reproductive outcomes required for this analysis. Information related to menstrual status and reproductive outcomes was not part of the comprehensive baseline questionnaire. Figure 1 details the exclusions from the 9242 female participants in the CCSS cohort, resulting in 2930 subjects who were eligible for the current analysis. The cohort did not include survivors with a second malignancy before menopause or a primary tumor in the region of the hypothalamic-pituitary gland. Subjects self-reported age at menarche, current menstrual status, and age at last menstrual period. Individuals who were no longer menstruating were asked for the cause of menstrual cessation. Subjects also reported whether they had ever been pregnant, the age at which they were pregnant in 5-year age ranges, and the outcome of each pregnancy. Of the 2930 participants in the current analysis, 2570 reported their menstrual history on the 2000 follow-up questionnaire and 2162 reported it on the 2007 follow-up questionnaire. A total of 1802 subjects completed both questionnaires.

NSPM was defined as sustained menses cessation occurring for ≥6 months beginning 5 years after the cancer diagnosis but before age 40 years that was not due to pregnancy, surgery, or medications. The sibling control group was comprised of 1399 females aged > 18 years who had achieved spontaneous menarche.

Statistical Analysis

Because data sufficient for defining the onset of NSPM were included in the follow-up questionnaires but not the baseline questionnaire, the prevalence, rather than incidence, of NSPM was analyzed. That is, the relevant data from the follow-up questionnaires support cross-sectional, but not time-to-event, analyses. If menses had ceased, we used the reported ages at the time of the last menstrual period to determine the prevalence of NSPM among subjects with a follow-up questionnaire after that time point at 5-year age points from 20 to 40 years. Generalized estimating equation logistic models were used to estimate the associations between risk factors and prevalence while adjusting for attained age. Predicted prevalence as a function of age was estimated and plotted from these models. A multivariable model was constructed by sequentially adding and removing candidate risk factors including diagnosis, age at diagnosis, exposure to alkylating agents individually and as a group, OvRT, unilateral

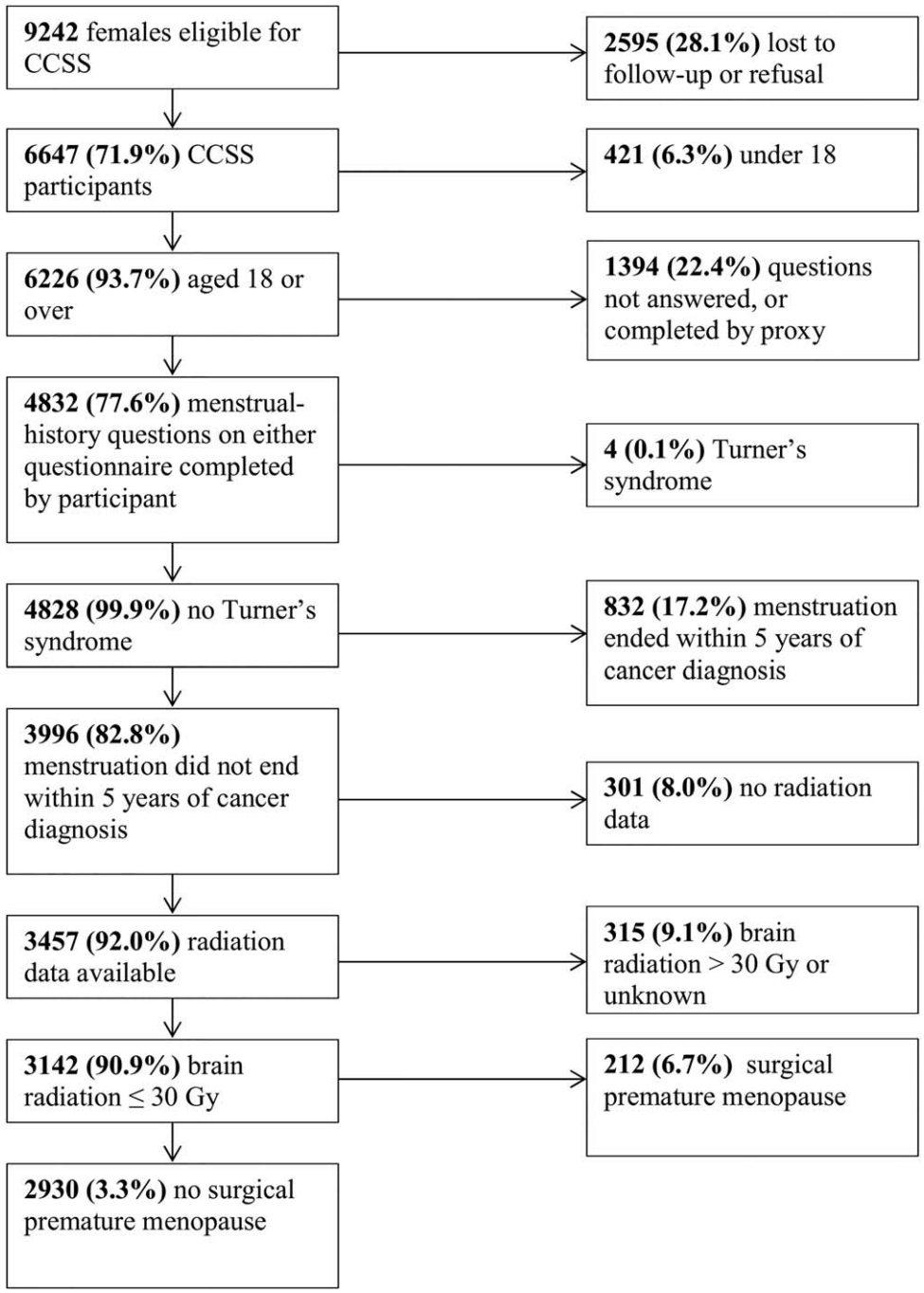

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram for the study population. CCSS indicates Childhood Cancer Survivor Study; Gy, grays.

oophorectomy, smoking status, and body mass index. The quasi-likelihood information criterion was used to determine goodness of fit; we ultimately reported the best-fitting parsimonious final model.[25]

Rates of pregnancy and live birth were modeled using Poisson models, using the number of events and the number of person-years before age of menopause or 40th birthday, and within age categories adjusted for age. Comparisons of rates between women who ultimately experienced NSPM and those who did not should be viewed as a retrospective summary of their fertility.

RESULTS

Nonsurgical Premature Menopause

Demographic and treatment characteristics of the 2930 survivors who were eligible for the current analysis are provided in Table 1. The median age at the time of the primary cancer diagnosis was 6 years (range, 0-20 years), the self-reported median age at the time of menarche was 12 years (range, 7-23 years), and the median age at the time of the current study was 35 years (range, 18-58 years). Survivors were compared with 1399 siblings with a median age at menarche of 13 years (range, 7-23 years) and a median age at the time of the current study of 38 years (range, 19-63 years). A total of 110 survivors developed NSPM at a median age of 32 years (range, 16-40 years). Of these, 46 survivors were aged < 30 years at the time of menopause, 35 were aged 31 to 35 years, and 29 survivors were aged > 35 years. The prevalence of NSPM was 9.1% among survivors at age 40 years compared with a prevalence of 0.9% among siblings (odds ratio [OR], 10.5; 95% confidence interval [95% CI], 4.2-26.3). Frequency according to diagnosis, treatment, and demographics is provided in Table 2. The frequency of NSPM by the combination of diagnosis and exposure is provided in Supporting Information Table 1.

Univariate analysis, adjusted for age point, revealed the following variables to be significant for the risk of NSPM: age > 15 years at the time of diagnosis, exposure to a dose of procarbazine $\geq$4000 mg/m^2, a CED of $\geq$6000 mg/m^2 (with procarbazine included in the CED), any RT to the ovaries, receipt of SCT, and a diagnosis of Hodgkin lymphoma. The following variables were not found to be significant: exposure to any dose of cyclophosphamide, unilateral oophorectomy, smoking status, or body mass index. When patients who had received procarbazine were removed from the analysis, the CED at any dose was no longer statistically significant (see Supporting Information Table 2).

In the final multivariable analyses, significant variables included exposure to a dose of procarbazine $\geq$4000mg/m^2 (OR, 8.96; 95% CI, 5.02-16.00 [P<.0001]), any dose of RT to the ovaries (OR, 2.73 [95% CI, 1.33-5.61; P = .0062] for an OvRT dose <500 cGy and OR, 8.02 [95% CI, 2.81-22.85; P<.0001] for an OvRT dose $\geq$500 cGy), and receipt of SCT (OR, 6.35; 95% CI, 1.19-33.93 [P = .0307]) (Table 3).

For survivors who received procarbazine at a dose of $\geq$4000 mg/m^2, the prevalence of NSPM at age 40 years was 39.7% (95% CI, 21.2%-74.5%) compared with 4.2% (95% CI, 2.8%-6.2%) among those who did not receive any procarbazine (P<.0001) (Fig. 2). RT exposure to the ovaries of >500 cGy resulted in a prevalence of NSPM at age 40 years of 24.1% (95% CI, 9.5%-49.0%) compared with a prevalence of 3.0% in those who did not receive RT to the ovaries (P<.0001) (Fig. 3).

TABLE 1. Characteristics of the Survivor Cohort

Characteristics		Total in Cohort N=2930 No. (%)
Age at diagnosis, y	Birth-9	1875 (64.0)
	10-14	571 (19.5)
	15-20	485 (16.6)
Age at study, y	21-25	302 (10.3)
	26-30	692 (23.6)
	31-35	658 (22.5)
	36-40	601 (20.5)
	>40	655 (22.4)
Diagnosis	Leukemia	1149 (39.2)
	Hodgkin lymphoma	348 (11.9)
	Kidney tumors	344 (11.7)
	Bone tumors	311 (10.6)
	Neuroblastoma	254 (8.7)
	Soft tissue sarcomas	224 (7.6)
	CNS tumors	157 (5.4)
	Non-Hodgkin lymphoma	143 (4.9)
Treatment exposure	Alkylating agent only	552 (18.8)
	Ovarian RT only	792 (27.0)
	Alkylating agent and ovarian RT	804 (27.4)
	Unilateral oophorectomy	62 (2.1)
	Stem cell transplantation	17 (0.5)
Smoking history	Yes	786 (26.8)
	No	1741 (59.4)
	Unknown	403 (13.8)
BMI, kg/m^2	>30	555 (18.9)
	25-29.9	542 (18.5)
	<24.9	1117 (38.1)
	Unknown	313 (10.7)

Abbreviations: BMI, body mass index; CNS, central nervous system; RT, radiotherapy.

Pregnancy and Live Birth

Pregnancy and live birth rates per person-years by attained age in survivors who ultimately did and did not develop NSPM are presented in Table 4. A total of 103 pregnancies and 66 live births were reported among survivors who ultimately developed NSPM. Thirteen pregnancies (12.6%) occurred within 5 years of the onset of menopause, and 51 (49.5%) occurred within 10 years of the onset of menopause. The rate ratio (RR) for pregnancy among those who developed NSPM was 0.88 (95% CI, 0.72-1.06 [P = .2]) compared with those who did not develop NSPM. The RR of ever having a live birth was 0.80 (95% CI, 0.62-1.01 [P = .07]) among those who developed NSPM compared with those without NSPM.

TABLE 2. Frequency of Nonsurgical Premature Menopause by Diagnosis, Treatment, and Demographics

		Nonsurgical Premature Menopause			
		Yes		No	
		No.	%	No.	%
Age at diagnosis, y	Birth-9	38	2.0	1837	98.0
	10-14	29	5.1	542	94.9
	15-20	43	8.9	442	91.1
Diagnosis	Leukemia	34	3.0	1115	97.0
	Hodgkin lymphoma	56	16.1	292	83.9
	Kidney tumors	7	2.0	337	98.0
	Bone tumors	2	0.6	309	99.4
	Neuroblastoma	3	1.2	251	98.8
	Soft tissue sarcomas	4	1.8	220	98.2
	CNS tumors	1	0.6	156	99.4
	Non-Hodgkin lymphoma	3	2.1	140	97.9
Treatment exposure	Any alkylating agents	78	5.7	1283	94.3
	Any procarbazine	47	23.4	154	76.6
	No procarbazine	63	2.3	2666	97.7
	Procarbazine > 0-4000 mg/m^2	4	13.8	25	86.2
	Procarbazine ≥ 4000 mg/m^2	31	24.2	97	75.8
	No OvRT	16	1.2	1290	98.8
	Minimum OvRT dose >0-500 cGy	78	5.2	1418	94.8
	Minimum OvRT dose > 500 cGy	15	13.0	100	87.0
	Alkylating agent only	12	2.2	540	97.8
	OvRT only	27	3.4	765	96.6
	Alkylating agent and OvRT	66	8.2	738	91.8
	Procarbazine and OvRT	41	23.8	131	76.2
	Unilateral oophorectomy	5	8.1	57	91.9
	Stem cell transplantation	3	17.6	14	82.4
Smoking history	Yes	29	3.7	757	96.3
	No	61	3.5	1680	96.5
	Unknown	-	-	-	-
BMI, kg/m^2	>30	21	3.8	534	96.2
	25-29.9	26	4.8	516	95.2
	<24.9	40	3.6	1077	96.4
	Unknown	-	-	-	-

Abbreviations: BMI, body mass index; cGy, centigray; CNS, central nervous system; OvRT, ovarian radiotherapy.

TABLE 3. Results of the Multivariable Model for Risk of Nonsurgical Premature Menopause

Parameter		OR	95% CI	*P*
Minimum OvRT dose	0	1.00	-	-
	>0-500 cGy	2.73	1.33-5.61	.0062
	>500 cGy	8.02	2.81-22.85	<.0001
Procarbazine dose	0 mg/m^2	1.00	-	-
	<4000 mg/m^2	3.07	0.76-12.43	.1154
	≥4000 mg/m^2	8.96	5.02-16.00	<.0001
Stem cell transplantation	No	1.00	-	-
	Yes	6.35	1.19-33.93	.0307

Abbreviations: 95% CI, 95% confidence interval; cGy, centigray; OR, odds ratio; OvRT, ovarian radiotherapy.

Although subsequent NSPM did not appear to reduce the risk for pregnancy or live birth among survivors aged 21 to 30 years, the RRs for ever being pregnant or ever having a live birth among survivors between the ages of 31 to 40 years were 0.49 (95% CI, 0.27-0.80 [$P = .009$]) and 0.42 (95% CI, 0.19-0.79 [$P = .015$]) respectively, for those who developed NSPM compared with those who did not (Table 5).

DISCUSSION

Adequately counseling female survivors about their reproductive capacity relies on the identification of risk factors for NSPM as well as estimating the window of fertility for those with such risk factors. The large size and ongoing longitudinal follow-up of aging adult survivors within the CCSS provides a unique opportunity to obtain precise estimates of NSPM after gonadotoxic exposures and to explore the impact of NSPM on pregnancy and live birth rates. We have identified that pregnancy and live birth rates before the age of 30 years are not significantly different between patients who ultimately develop NSPM and those who do not.

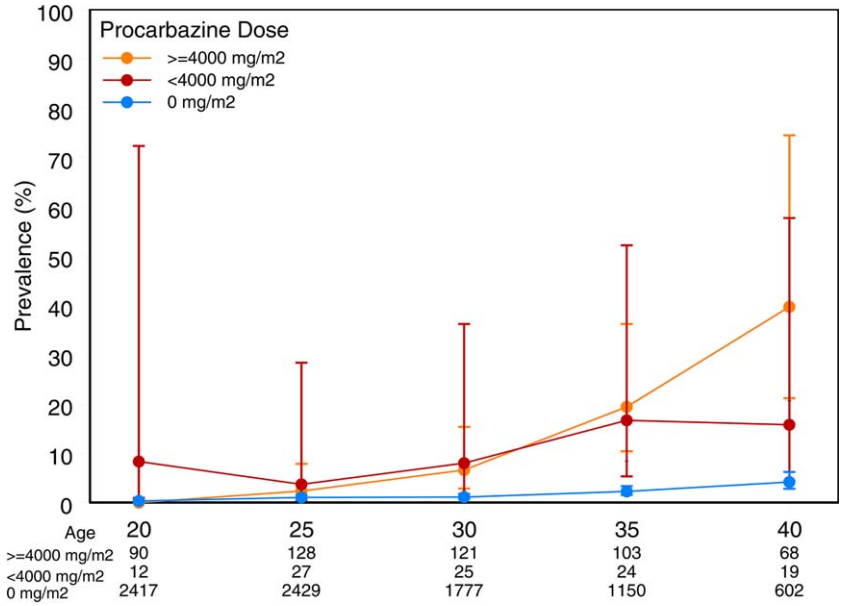

Figure 2. Prevalence and 95% confidence intervals of nonsurgical premature menopause among survivors by procarbazine dose.

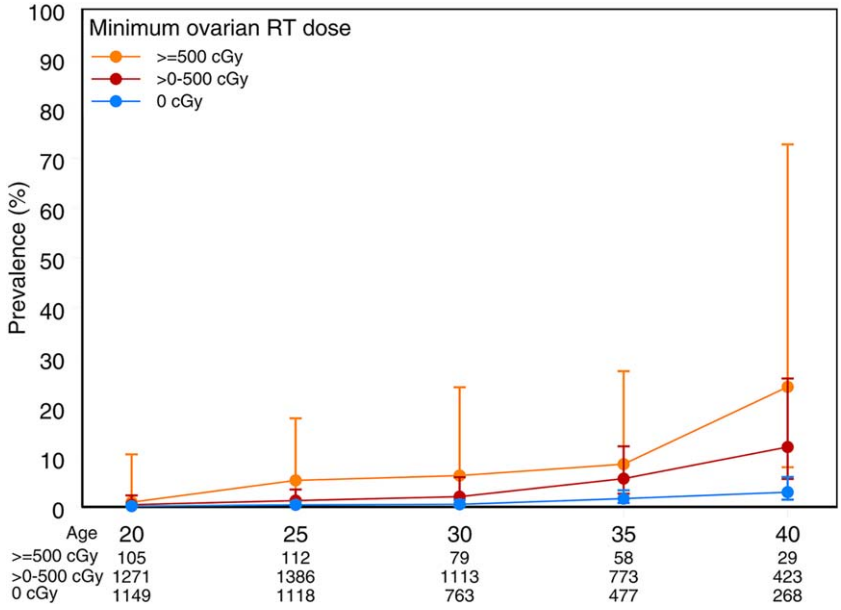

Figure 3. Prevalence and 95% confidence intervals of nonsurgical premature menopause among survivors by ovarian radiotherapy (RT) dose. cGy indicates centigray.

In the current study, we identified that 9% of female survivors developed NSPM by age 40 years in a population with a median age of 34 years, thereby providing what to our knowledge are the most stable estimates of NSPM to date, and similar to those in our previous report.[9] Furthermore, compared with siblings, the risk among these aging survivors was similar to the original estimates (RR, 10.5 vs 13.2). This suggests that the risk of NSPM among survivors is not disproportionate to that in the general population as they continue to age. Moreover, this provides clinicians with greater certainty in providing estimates of risk for NSPM as they counsel patients.

In addition to the CCSS, other large cohort studies have evaluated premature menopause in survivors of childhood cancer.[10-13] The study of the Euro2K cohort identified a cumulative incidence of NSPM of 2.1% at

TABLE 4. Pregnancy and Live Birth Rates Per Person-Years by Attained Age

	Nonsurgical Premature Menopause									
	Yes					No				
Age, Years	Person-Years	No. of Pregnancies	Pregnancy Rate per 1000 Person-Years	No. of Live Births	Live Birth Rate per 1000 Person-Years	Person-Years	No. of Pregnancies	Pregnancy Rate per 1000 Person-Years	No. of Live Births	Live Birth Rate per 1000 Person-Years
21-25	452	46	101.9	29	64.2	12,179	1172	96.2	770	63.2
26-30	364	44	120.9	29	79.7	9223	1223	132.6	899	97.5
31-35	242	10	41.4	6	24.8	5955	642	107.8	485	81.4
36-40	60	3	50.3	2	33.5	2833	194	68.5	117	41.3
21-30	816	90	110.3	58	71.1	21,402	2395	111.9	1669	78.0
31-40	301	13	43.2	8	26.6	8788	836	95.1	602	68.5
21-40	1117	103	92.2	66	59.1	30,190	3231	107.0	2271	75.2

TABLE 5. Age-Specific RRs for Pregnancies and Live Births Among Survivors With and Without Nonsurgical Premature Menopause

	Age, Years	RR	95% CI	*P*
Pregnancy	All (21-40)	0.88	0.72-1.06	.20
	21-30	1.00	0.81-1.23	.97
	31-40	0.49	0.27-0.80	.009
Live birth	All (21-40)	0.80	0.62-1.01	.07
	21-30	0.92	0.70-1.19	.55
	31-40	0.42	0.19-0.79	.015

Abbreviations: 95% CI, 95% confidence interval; RR, rate ratio.

age 40 years among 706 female survivors. This difference is likely explained, at least in part, by differences in treatment exposures because the Euro2K Cohort was weighted toward survivors of kidney tumors and neuroblastoma (50% of participants vs 21% in the CCSS), whereas the CCSS had a rate of 39% survivors of leukemia versus no leukemia survivors in the Euro 2K Study.[12] The St. Jude Lifetime Cohort Study, a cohort that is more similar in distribution to the CCSS, assessed premature menopause via self-report and clinical measurements, and reported a prevalence of 10.9% among its cohort of 921 participants.[13]

Across these studies, exposure to OvRT consistently has emerged as a risk factor implicated in the development of premature menopause in the childhood cancer population.[8-13] In the current study, we again demonstrated the adverse effect of exposure to any OvRT on the risk of NSPM, with the risk of NSPM noted to increase with increasing RT dose.

Exposure to alkylating agents also has consistently been recognized as a risk factor for diminished ovarian reserve.[26,27] However, honing in on the toxicity of specific agents, as well as the impact of dose and age at exposure (and the interplay among these factors), has proven to be more difficult. In the current study, exposure to doses of procarbazine $\geq$4000mg/m^2 was found to be an independent risk factor for NSPM. The deleterious effect of procarbazine on gonadal function has been well described. Although both procarbazine and cyclophosphamide were associated with NSPM in the Euro 2K study, the magnitude of the effect was much greater for procarbazine.[12] In cohort studies of survivors of Hodgkin lymphoma, the cumulative procarbazine dose was found to be strongly associated with the risk of premature menopause.[28]

The impact of other alkylating agents on the risk of NSPM has been more variable across different studies. The St. Jude Lifetime Cohort Study found a CED of $\geq$8000mg/m^2 to be a significant risk factor for the development of NSPM, although in a multivariable model created a combined variable of exposure to alkylating agents and OvRT (as neither, either or both) exposure to alkylating agents alone was not found to be significant.[13] It is interesting to note that in this study, a CED of $\geq$6000mg/m^2 was found to be significant in the univariate analysis but not when patients exposed to procarbazine were removed from the CED calculation, suggesting that the gonadal toxicity of procarbazine may be underestimated in this formula. Additional studies are necessary to further assess the usefulness of the CED in the setting of gonadal toxicity.

Given the reliance on total body RT and/or high-dose alkylating agents as components of conditioning regimens, patients who undergo SCT are at high risk of gonadal toxicity.[29-32] Although the numbers of patients who had undergone SCT were small in the current study,

this group of patients was identified as being independently at risk of the development of NSPM.

Age at diagnosis as a risk factor for NSPM has been observed in some but not all studies. Byrne et al., Chiarelli et al., and the Euro2K Study identified increased risk in survivors diagnosed in the postpubertal period compared with those diagnosed in the prepubertal period.[10-12] In the current analysis, age >15 years was found to be significant in a univariate analysis but was not an independent risk factor. This most likely is a result of the confounding influence of procarbazine being used primarily as treatment of patients with Hodgkin lymphoma, a disease that is more common in adolescence. Age at the time of diagnosis was not found to be a significant risk factor for premature menopause in the St. Jude Lifetime Cohort Study, which, as noted above, is demographically similar to the CCSS cohort.[13]

To the best of our knowledge, there have been limited data examining the rates of pregnancy and live births between those who ultimately develop NSPM and those who do not. We determined that for those who ultimately develop NSPM, rates of pregnancy and live birth are substantially reduced before NSPM between the ages of 31 and 40 years. However, pregnancy and live birth rates did not differ for those aged 21 to 30 years based on ultimate menopausal status, even for those in whom NSPM occurred before age 30 years. Although we do not have information regarding whether pregnancies were achieved spontaneously or with assisted reproduction, it is worth noting that nearly one-half of pregnancies in the total NSPM cohort occurred within 10 years of the onset of menopause and 12.6% occurred within 5 years, thereby suggesting that conception is possible in the perimenopausal period in this population.

A range of fertility-preserving strategies exist that can improve the chances of having a biologic child despite being exposed to gonadotoxic therapies as part of cancer-directed therapy. Two recent publications have demonstrated that, even within the setting of decreased ovarian reserve and/or clinical infertility, pregnancy and live births with or without assisted reproduction are possible.[33,34] These data reinforce the need for providers to educate survivors of childhood cancer regarding their risks of infertility and the fertility preservation options that are available to them.

In interpreting the findings of the current study, some limitations should be considered. NSPM is self-reported and therefore may be subject to both overreporting and underreporting. Cases of NSPM may be masked by women who are taking oral contraceptives or other hormone medications that result in persistent menstruation. The study cohort was treated in the 1970s and 1980s and therefore was exposed to treatment combinations and doses that may no longer be used. Data regarding RT exposure were calculated according to body region dosimetry, which does not differentiate between flank RT (ie, to one ovary) versus whole-abdomen RT (ie, involving both ovaries). Therefore, we were limited in our ability to comment on the effect of RT to the ovary when only one ovary was in the field. The current study data regarding pregnancy and live birth did not take into account an individual's desire to become pregnant, and may have led to an overestimation of impaired fertility. Furthermore, as noted above, we were not able to comment on whether pregnancies were achieved spontaneously or via assisted reproduction.

The results of the current study demonstrate that treatment with procarbazine, ovarian RT, and SCT are significant risk factors for NSPM. We also determined that the OR for pregnancy and live birth at age >30 years is decreased for those patients who ultimately develop NSPM. Clinicians should incorporate this information as they counsel female patients with childhood cancer and their families at the time of cancer diagnosis and in the years after the completion of cancer-directed treatment.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Jennifer M Levine: Conceptualization, methodology, investigation, writing, and project administration. **John A. Whitton**: Methodology, formal analysis, investigation, and writing. **Jill P. Ginsberg**: Investigation and writing. **Daniel M. Green**: Investigation and writing. **Wendy M. Leisenring**: Methodology, formal analysis, investigation, and writing. **Marilyn Stovall**: Investigation and writing. **Leslie L. Robison**: Investigation, writing, supervision, and funding. **Gregory T. Armstrong**: Investigation, writing, supervision, and funding. **Charles A. Sklar**: Conceptualization, methodology, investigation, writing, and supervision.

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