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Radiation-associated breast cancer and gonadal hormone exposure: a report from the Childhood Cancer Survivor Study

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Background: The relationship between hormone exposure and breast cancer risk in women treated with chest radiotherapy for childhood cancer is uncertain.

Methods: Participants included 1108 females from the Childhood Cancer Survivor Study who were diagnosed with childhood cancer 1970–1986, treated with chest radiotherapy, and survived to ages ⩾20 years. Hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox models adjusted for chest radiation field, delivered dose, anthracycline exposure, and age at childhood cancer estimated risk.

Results: Among 195 women diagnosed with breast cancer, 102 tumours were oestrogen-receptor positive (ER+). Breast cancer risk increased with ⩾10 years of ovarian function after chest radiotherapy *vs* <10 years (HR = 2.89, CI 1.56–5.53) and for radiotherapy given within 1 year of menarche *vs* >1 year from menarche (HR = 1.80, CI 1.19–2.72). Risk decreased with decreasing age at menopause (P_{trend} = 0.014). Risk factors did not differ for ER+ breast cancer. Survivors with an age at menopause <20 years treated with hormone therapy had a lower breast cancer risk than premenopausal survivors (HR = 0.47, CI 0.23–0.94).

Conclusions: Endogenous hormones are key contributors to breast cancer observed among childhood cancer survivors. Hormone therapy given for premature ovarian insufficiency does not fully replace the function that endogenous hormones have in breast cancer development.

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Women treated with chest radiotherapy for a pediatric malignancy have a very high risk of breast cancer. With cumulative incidence estimates ranging from 13 to 20% at age 40–45 years in all childhood cancer survivors (Bhatia *et al*, 2003; Kenney *et al*, 2004; Taylor *et al*, 2007) up to 35% by age 50 years in Hodgkin lymphoma (HL) survivors (Moskowitz *et al*, 2014), their risk compares to that observed among carriers of deleterious *BRCA* mutations (Taylor *et al*, 2007; Moskowitz *et al*, 2014).

Previous studies demonstrated that the magnitude of breast cancer risk in this population varies by treatment-related factors including chest radiation field (Koh *et al*, 2007; De Bruin *et al*, 2009; Lange *et al*, 2014; Moskowitz *et al*, 2014; Schaapveld *et al*, 2015), radiation dose to the breast tumour site (Travis *et al*, 2003; van Leeuwen *et al*, 2003; Inskip *et al*, 2009), and ovarian radiation (Travis *et al*, 2003; van Leeuwen *et al*, 2003; De Bruin *et al*, 2009; Inskip *et al*, 2009; Swerdlow *et al*, 2012; Moskowitz *et al*, 2014). Other factors that may modify risk but for which results differ across studies include ages at menarche and menopause, and parity (van Leeuwen *et al*, 2003; Hill *et al*, 2005; Inskip *et al*, 2009). Importantly, while the association of age at radiation exposure with breast cancer risk also differs across studies (Ronckers *et al*, 2005), recent work shows that among HL survivors the highest risk is observed among women treated with chest radiotherapy near puberty (Swerdlow *et al*, 2012; Cooke *et al*, 2013).

In the general population, there have been multiple studies evaluating the relationship between breast cancer and exposure to exogenous hormones. The presence and magnitude of risk has been dependent on the formulation and schedule of the specific hormones used in menopausal hormone therapy (HT). In particular, combination oestrogen and progestin therapy (E + P) is associated with an increased breast cancer risk compared with either no HT or HT with oestrogen alone (Chlebowski *et al*, 2003; Lee *et al*, 2005). Female survivors of childhood cancer exposed to either ovarian radiation or alkylating agents have an increased risk of premature ovarian insufficiency (POI). While POI is associated with a decreased breast cancer risk, HT is frequently used to prevent sequelae of oestrogen deficiency such as osteoporosis and impaired sexual function (Sklar *et al*, 2006; Panay & Kalu, 2009; van Dorp *et al*, 2016; Wijnen *et al*, 2016). It is unknown how HT affects breast cancer risk in survivors who also received chest radiotherapy. Furthermore, in the general population the association between gonadal hormonal factors and breast cancer development appears to differ by age at breast cancer diagnosis and by molecular subtype of breast cancer (Pike *et al*, 1981; Clavel-Chapelon & Gerber, 2002; Ma *et al*, 2006; Narod, 2011; Yang *et al*, 2011; Barnard *et al*, 2015; Chollet-Hinton *et al*, 2016). Published data on the influence of these factors on breast cancer risk after radiotherapy for childhood cancer are very sparse.

Using a large cohort of childhood cancer survivors with detailed treatment exposure data we evaluated the association between factors related to gonadal hormone exposure and the risk of radiation-associated breast cancer and characterised associations by age at onset of breast cancer and oestrogen receptor-status.

MATERIALS AND METHODS

Study population. The Childhood Cancer Survivor Study (CCSS) is a hospital-based retrospective cohort study with longitudinal follow-up of 5-year survivors of a cancer diagnosed prior to age 21 years at 26 participating centers in North America. Data were collected from a baseline questionnaire administered 1994–1998 and from follow-up questionnaires administered in 2000, 2003, 2005, 2007, and 2012 (available online at http://ccss.stjude.org). Next of kin were contacted for participants who died after surviving 5 years. Cohort methodology was described previously (Robison *et al*, 2002, 2009; Leisenring *et al*, 2009). The CCSS was approved by institutional review boards at participating centers. Participants provided informed consent.

We restricted this analysis to 1108 female participants diagnosed with childhood cancer 1970–1986 who received chest radiotherapy within 5 years of their childhood cancer diagnosis and survived until at least 20 years of age. Participants treated with mantle, mediastinal (including involved field), whole lung, hemithorax (one-sided anterior chest fields), abdominal (with extension above the diagram) fields or with total body irradiation (TBI) were included. A diagram showing the flow of these participants throughout the follow-up questionnaires can be found in the Supplementary Material (Supplementary Figure S1).

Childhood cancer treatment exposures. Information on treatment received within 5 years of childhood cancer diagnosis, including radiation fields and doses and chemotherapy use, was abstracted from medical records using a standardised protocol.

We defined chest radiation field as a categorical variable ordered by size of the treatment field (TBI and whole lung, mantle, other fields). Participants treated with more than one field were included in the category for the widest field received.

The delivered dose of chest radiotherapy was taken as the sum of delivered doses (as abstracted from radiation therapy records or treatment summaries) for all chest fields. The only exception were patients treated with abdominal fields including breast tissue (including the diaphragm) and a non-overlapping chest field for whom only the dose for the superior field was included.

Cumulative doses of alkylators were determined using the Cyclophosphamide Equivalent Dose (CED) method (Green *et al*, 2014).

Identification of breast cancer and hormone receptor status. Breast cancers, including invasive cancers and ductal carcinoma *in situ*, were ascertained through self- or proxy-report and the National Death Index. Pathology reports and medical records were reviewed to confirm diagnoses. Information on hormone receptor status was abstracted. Complete information was available on oestrogen receptor status for $n = 114$, progesterone receptor status for $n = 107$, and HER2 status for $n = 64$.

Endogenous hormone exposure. Across CCSS questionnaires, participants were asked about age at menarche, current menstrual status, age at last menstrual period, type of menopause (i.e., surgical or natural), pregnancy outcomes, and ages at pregnancies (< 15, 15–20, 21–25, 26–30, 31–35, 36+ years). For surgical menopause, the procedure was listed (e.g., oophorectomy). We considered participants menopausal if they had not experienced normal menses for at least 6 months and other causes such as pregnancy or hormonal contraceptives could be excluded (Sklar *et al*, 2006).

Exogenous hormone exposure. Participants were asked in all CCSS questionnaires if they had taken oestrogens or progestin in the preceding 2 years and to list the name of the oral or other hormonal contraceptive or HT. Beginning in the Follow-up 2003 questionnaire, if they responded 'yes' participants were also asked to list the age at first use of the drug.

Years of ovarian function and gonadal hormone exposure after chest radiation. We counted years of normal ovarian function starting either at menarche or initiation of chest radiotherapy, whichever occurred later, until menopause, first reported use of exogenous hormones, or last contact for women who were still menstruating at last contact. Participants were censored after reported use of hormonal contraceptives or HT if they did not previously report they were post-menopausal. Women with a

hysterectomy without a bilateral oophorectomy ($n=45$) were considered to have ovarian function until the hysterectomy and then censored at this time.

Years of gonadal hormone exposure was calculated as years of ovarian function (endogenous hormone exposure) plus years of subsequent exogenous hormone exposure. We assumed continuous exogenous hormone use from the age it was first reported until participants reported no longer taking it. If the only information on contraceptive or HT use was from questionnaires prior to 2003 we took age at which the survey was returned as age at first use.

Statistics. We used Cox proportional hazards regression to model cause-specific hazard functions with age as the time scale and modelled age at first breast cancer diagnosis. Participants were considered at risk of breast cancer beginning at age 20 years or 5 years after their primary childhood cancer diagnosis, whichever occurred later, until a late recurrence of their childhood cancer (i.e., more than 5 years after the primary diagnosis), a breast cancer diagnosis, death, or date of last contact. Participants who had a late recurrence, died, or were alive without a diagnosis of breast cancer at last contact were censored at that date. By censoring at the date of last contact, we incorporate the uncertainty that arises from participants who are lost-to-follow-up. Data were split into 1-year intervals for all analyses. Variables reflecting events occurring after age 20 years (age at first live birth, age at menopause, years of ovarian function and gonadal hormone exposure, HT) were treated as time-dependent covariates. To evaluate risk of breast cancer diagnosed before age 40 years, we included only those intervals where women were less than age 40 years at the beginning of the interval. To evaluate risk of breast cancer diagnosed at ages $\geqslant 40$ years, we included only those intervals where women were age 40 years or older at the beginning of the interval. All models were adjusted for age at childhood cancer diagnosis (using restricted cubic splines with three knots), chest radiation field and delivered dose (<20, 20–29, 30–39, 40–49, $\geqslant 50$ Gy), and exposure to anthracyclines (yes, no). All analyses involving age at first live birth were restricted to women who experienced menarche.

We assessed risk of oestrogen-receptor positive (ER+) breast cancer by modelling the hazard of a first breast cancer diagnosis being ER+. Women with breast cancer diagnoses that were not identified as ER+, including women with more than one breast cancer where an ER+ breast cancer was preceded by ER- breast cancer ($n=5$) or breast cancer with unknown receptor status ($n=7$), were censored at the date of the first breast cancer diagnosis.

To study the association between HT and breast cancer risk, we restricted the analysis to participants who never experienced menarche and, for those participants who experienced menarche, to the time after they reported menstrual periods stopped. Cox regression modelled the hazard of breast cancer after menopause as a function of combined oestrogen and progestin use, age at menopause, age at childhood cancer diagnosis, chest radiation field and delivered dose and anthracycline use. Participants entered this analysis at menopause or age 20 years, whichever occurred later, and were followed until a late recurrence, breast cancer diagnosis, death, or last contact. Participants who never experienced menarche were included from age 20 years.

RESULTS

Overall. With a median follow-up of 26 years (range 5–38 years), 195 participants were diagnosed with breast cancer, 112 prior to age 40 years and 83 at age 40 years or older. Among women diagnosed with breast cancer, median age at breast cancer diagnosis was 38 years (range 23–58 years). Median age at menarche was13 years (range 9–20 years). Among post-menopausal women, median age at menopause was 33 years (range 11–54 years); the probability of menopause by age 40 years was approximately 34%.

One hundred two women were diagnosed with ER+ breast cancer, 83 of these were also progesterone receptor-positive. Among the 93 other women, 24 had ER- breast cancer; receptor status was unknown for the remaining 69 women. Due to the small sample size, we were unable to evaluate risk of ER- breast cancer separately.

Further cohort characteristics are presented in Table 1 and Supplementary Table S1. All analyses presented below are adjusted for factors related to the treatment for the primary childhood cancer and for which previous work has suggested an association with the risk of breast cancer. Univariable analysis results for these adjustment factors are shown in Table 2.

Following ovarian-toxic therapy. Ovarian-toxic therapy, having the ovaries in a concurrent radiation field or high doses of alkylators (CED $\geqslant 14\,000\,\mathrm{mg\,m^2}$), reduced breast cancer risk (ovarian radiation: HR = 0.35, 95% CI: 0.18–0.69, $P=0.002$; CED $\geqslant 14\,000\,\mathrm{mg\,m^{-2}}$ *vs* no alkylators: HR = 0.41, 95% CI 0.21–0.79, $P=0.007$). The protective effect was particularly apparent for breast cancer diagnosed $\geqslant 40$ years of age (Figures 1 and 2, Supplementary Tables S2, S4, and S5).

Menstrual and reproductive factors. While breast cancer risk varied by age at menarche, especially for breast cancer diagnosed before age 40 years, the timing of chest radiotherapy relative to menarche was a notable risk factor. Women who began chest radiotherapy within 1 year of menarche had a significantly elevated risk of breast cancer compared to women who began chest radiotherapy further from menarche (Figure 1, Supplementary Tables S2, S4, S5, and S7). Removing 64 women who never experienced menarche and adjusting for age at menarche resulted in an attenuated but significant association (chest radiotherapy within 1 year of menarche *vs* otherwise, HR = 1.66, 95% CI 1.10–2.52, $P=0.017$). Risk of ER+ breast cancer was similar (Figure 2, Supplementary Table S5). We found no association between age at first live birth and risk of breast cancer. There was a significant trend for risk to increase with increasing age at menopause ($P_{\mathrm{trend}}=0.016$), though this effect was most pronounced before age 40 years.

Years of ovarian function and hormonal exposure. Risk was more than two-fold higher for women with 10+ years of ovarian function after chest irradiation relative to women with less than 10 years of ovarian function after chest irradiation. Both risk of breast cancer diagnosed before age 40 years (HR = 3.30, 95% CI 1.50–7.25, $P=0.003$; Figure 1, Supplementary Tables S2, S3, and S4) and risk of ER+ breast cancer (HR = 5.32, 95% CI 1.88–15.06, $P=0.002$; Figure 2, Supplementary Table S5) were significantly increased with 10+ years of ovarian function after chest irradiation. For breast cancer diagnosed at ages $\geqslant 40$ years, estimated risk was elevated but to a lesser degree (HR = 2.57, 95% CI 0.91–7.23, $P=0.074$).

Separately modelling the number of years of ovarian function prior to chest irradiation (median 1 year, range 0–12 years) and the number of years of ovarian function after chest irradiation (median 11 years, range 0–36 years) as continuous variables, there was no significant association between the risk of breast cancer and years prior to chest irradiation (HR = 0.94 per year, 95% CI 0.81–1.09, $P=0.445$) while risk was significantly increased with years of ovarian function after chest irradiation (HR = 1.04 per year, 95% CI 1.01–1.07, $P=0.003$).

Table 1. Demographic and treatment characteristics of female childhood cancer survivors treated with chest radiotherapy

			Breast Cancer							
	All participants ($n=1108$)		All ($n=195$)		Age <40 yrs ($n=112$)		Age 40+ yrs ($n=83$)		ER+ ($n=102$)	
Characteristic	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Primary cancer diagnosis										
Hodgkin lymphoma	669	60.4	160	82.1	89	79.5	71	85.5	81	79.4
Wilms tumour	125	11.3	7	3.6	6	5.4	1	1.2	5	4.9
Non-Hodgkin lymphoma	84	7.6	9	4.6	5	4.5	4	4.8	6	5.9
Neuroblastoma	61	5.5	1	0.5	1	0.9	0	0.0	1	1.0
Leukaemia	67	6.0	4	2.1	3	2.7	1	1.2	2	2.0
Bone tumour	59	5.3	11	5.6	6	5.4	5	6.0	5	4.9
Soft tissue sarcoma	43	3.9	3	1.5	2	1.8	1	1.2	2	2.0
Age at diagnosis, yrs										
0–4	164	14.8	4	2.1	4	3.6	0	0.0	2	2.0
5–9	151	13.6	7	3.4	6	5.4	1	1.2	5	5.0
10–14	327	29.5	65	33.3	41	36.6	24	28.9	38	37.6
15–20	466	42.1	119	61.0	61	54.5	58	69.9	57	55.5
Chest radiation field[a]										
Total body irradiation	66	6.0	4	2.1	3	2.7	1	1.2	2	2.0
Whole lung	112	10.1	18	9.2	12	10.7	6	7.2	9	8.9
Mantle	594	53.6	151	77.4	87	77.7	64	77.1	76	74.4
Mediastinal	217	19.6	18	9.2	7	6.3	11	13.3	11	10.8
Other chest fields	119	10.7	4	2.1	3	2.7	1	1.2	4	4.0
Delivered chest radiation dose[b]										
1–19 Gy	212	19.1	21	10.8	15	13.4	6	7.2	10	9.8
20–29 Gy	190	17.2	17	8.7	13	11.6	4	4.8	10	9.8
30–39 Gy	284	25.6	55	28.2	28	25.0	27	32.5	28	27.5
40+ Gy	418	37.7	101	51.8	56	50.0	45	54.2	53	52.0
Missing	4	0.4	1	0.5	0	0.0	1	1.2	1	1.0
Anthracyclines										
No	714	64.4	151	77.4	82	73.2	69	83.1	84	82.4
Yes	385	34.8	43	22.1	29	25.9	14	16.9	18	17.7
Missing	9	0.8	1	0.5	1	0.9	0	0.0	0	0.0
Ovaries in concurrent radiation field										
No	988	89.2	186	95.4	107	95.5	79	95.2	98	96.0
Yes	120	10.8	9	4.6	5	4.5	4	4.8	4	4.0
Cyclophosphamide equivalent dose, mg m^{-2}										
None	413	37.3	93	47.7	48	42.9	45	54.2	52	51.0
1–8499	208	18.8	33	16.9	23	20.5	10	12.1	16	15.7
8500–13 999	196	17.7	34	17.4	18	16.1	16	19.3	18	17.7
14 000+	140	12.6	11	5.6	8	7.1	3	3.6	5	4.9
Missing	151	13.6	24	12.3	15	13.4	9	10.8	11	10.8
Age at menarche, yrs										
Never	64	5.8	2	1.1	1	0.9	1	1.2	2	2.0
9–10	47	4.2	10	5.1	10	8.9	0	0.0	5	4.9
11–12	392	35.4	67	34.4	33	29.5	34	41.0	33	32.4
13–14	394	35.6	81	41.5	49	43.8	32	38.6	39	38.2
15–16	119	10.7	27	13.9	16	14.3	11	13.3	18	17.7
17+	27	2.4	3	1.5	0	0.0	3	3.6	3	2.9
Missing	65	5.9	5	2.6	3	2.7	2	2.4	2	2.0
Time of chest radiation relative to menarche[c]										
3+ yrs before menarche	274	28.3	17	9.0	14	13.0	3	3.8	10	10.3
1–3 yrs before menarche	62	6.4	8	4.3	4	3.7	4	5.0	5	5.2
±1 yr of menarche	116	12.0	34	18.1	23	21.3	11	13.8	19	19.6
1–2 yrs after menarche	78	8.0	17	9.0	15	13.9	2	2.5	11	11.3
2–3 yrs after menarche	77	7.9	24	12.8	12	11.1	12	15.0	13	13.4
3+ yrs after menarche	363	37.4	88	46.8	40	37.0	48	60.0	40	40.2
Chest radiation within ±1 yr of menarche										
No	918	82.9	156	80.0	86	76.8	70	84.3	81	79.4
Yes	116	10.5	34	17.4	23	20.5	11	13.3	19	18.6
Missing	74	6.7	5	2.6	3	2.7	2	2.4	2	2.0
Age at pregnancy with first live birth										
Nulliparous	567	51.2	78	40.0	55	49.1	23	27.7	77	75.5
Under 21 yrs	122	11.0	19	9.7	11	9.8	8	9.6	9	8.8
21–25 yrs	185	16.7	40	20.5	22	19.6	18	21.7	15	14.7
26–30 yrs	145	13.1	40	20.5	17	15.2	23	27.7	0	0.0
31+ yrs	83	7.5	17	8.7	7	6.3	10	12.1	0	0.0
Missing	6	0.5	1	0.5	0	0.0	1	1.2	1	1.0

Table 1. (Continued)

			Breast Cancer							
	All participants (*n* = 1108)		All (*n* = 195)		Age <40 yrs (*n* = 112)		Age 40+ yrs (*n* = 83)		ER+ (*n* = 102)	
Characteristic	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**
Exogenous hormone exposure										
None reported	256	23.1	66	33.9	44	39.3	22	26.5	31	30.4
Oestrogen only	36	3.3	7	3.6	2	1.8	5	6.0	5	4.9
Progestin only	39	3.5	9	4.6	5	4.5	4	4.8	6	5.9
Combination	555	50.1	77	39.5	41	36.6	36	43.4	43	42.2
Missing	222	20.0	36	18.5	20	17.9	16	19.3	17	16.7
Years of ovarian function after chest radiation										
Less than 1	122	11.0	8	4.1	4	3.6	4	4.8	4	3.9
1–9	204	29.4	18	9.2	12	10.7	6	7.2	6	5.9
10–19	245	22.1	62	31.8	44	39.3	18	21.7	36	35.3
20–29	168	15.2	42	21.5	18	16.1	24	28.9	29	28.4
30–39	43	3.9	7	3.6	0	0.0	7	8.4	5	4.9
Missing	326	29.4	58	29.7	34	30.4	24	28.9	22	21.6
Years of gonadal hormone exposure after chest radiation										
Less than 1	18	1.6	1	0.5	1	0.9	0	0.0	0	0.0
1–9	74	6.7	12	6.2	7	6.3	5	6.0	7	6.9
10–19	252	22.7	59	30.3	48	42.9	11	13.3	27	26.5
20–29	427	38.5	66	33.9	33	29.5	33	39.8	41	40.2
30–39	114	10.3	19	9.7	0	0.0	19	22.9	16	15.7
Missing	223	20.1	38	19.5	23	20.5	15	18.1	11	10.8
Age at menopause										
Still menstruating at last contact	526	47.5	99	50.8	67	59.8	32	38.6	57	55.9
Less than 20 yrs	52	4.7	11	5.6	5	4.5	6	7.2	5	4.9
20–29 yrs	40	3.6	5	2.6	4	3.6	1	1.2	2	2.0
30–39 yrs	79	7.1	15	7.7	6	5.4	9	10.8	11	10.8
40+ yrs	83	7.5	14	7.2	0	0.0	14	16.9	8	7.8
No menarche	64	5.8	2	1.0	1	0.9	1	1.2	2	2.0
Unknown due to hysterectomy	45	4.1	10	5.1	7	6.3	3	3.6	5	4.9
Missing	219	19.8	39	20.0	22	19.6	17	20.5	12	11.8
Attained age, yrs[d]										
20–29	156	16.9	18	9.2	18	16.1	0	0.0	8	7
30–39	378	41.0	94	48.2	94	83.9	0	0.0	43	42.2
40–49	337	36.6	73	37.4	0	0.0	73	88.0	44	43.1
50–59	51	5.5	10	5.1	0	0.0	10	12.1	7	6.9
Vital status at last contact										
Alive	861	77.7	136	69.7	71	63.4	65	78.3	74	72.6
Deceased	247	22.3	59	30.3	41	36.6	18	21.7	28	27.4

Abbreviation: yrs = years

[a]To account for women who had multiple chest radiation fields, we defined fields in a step-down manner. Each participant is included in only one row, which corresponds to the primary chest radiation field. Each row allows exposure to any of the fields listed under it, but not above it. For example, participants counted in the row for the whole-lung irradiation could have received mantle field irradiation or another field included in the all others category, but did not receive total body irradiation. Fields included in the all others category are mediastinal/IFRT, high abdominal fields, and one-sided chest fields.

[b]Calculated as the sum of all delivered doses to chest radiation fields. In cases where participants were treated with a field other than an abdominal field together with a non-overlapping abdominal field, the dose for the abdominal field is not included.

[c]Among women who experienced menarche and have a known age at menarche and date of chest radiotherapy.

[d]Among women alive at last contact.

Including both variables in a joint model did not substantively change these results.

The association of years of gonadal hormone exposure, including both endogenous and exogenous hormone exposure, with breast cancer was markedly weaker. Risk of breast cancer diagnosed before age 40 years was elevated with 10+ years of gonadal hormone exposure although this was not statistically significant (HR = 2.00, 95% CI 0.92–4.36, $P = 0.082$). We found no association with breast cancer diagnosed at ages ⩾40 years (HR = 1.08, 95% CI 0.43–2.72, $P = 0.873$).

Among 259 menopausal women with available information on HT, risk was elevated for women reporting E+P after adjusting for age at menopause, although the association was not statistically significant (Table 3 and Supplementary Table S6). The same was true after further adjusting for age at which use was first reported (median age = 28 years, range 10–51 years, HR = 1.72, 95% CI 0.55–5.42, $P = 0.352$) or when restricted to the 202 women with an age at menopause under 40 (HR = 1.46, 95% CI 0.35–6.16, $P = 0.607$). When compared with women who were still menstruating and had never reported E+P, women in menopause had a lower risk of breast cancer even with E+P (Table 4).

DISCUSSION

Our understanding of how hormonal factors influence breast cancer risk in childhood cancer survivors exposed to chest radiotherapy is evolving. Several findings emerge from this

Table 2. Univariable analysis of risk of breast cancer by childhood cancer treatment-related factors

	All breast cancer			Breast cancer diagnosed <40 years			Breast cancer diagnosed 40+ years		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Chest radiation field			0.001			0.002			0.342
Total body irradiation / whole lung	1.21	(0.77, 1.90)		1.08	(0.62, 1.87)		1.49	(0.68, 3.27)	
Mantle	Ref	–		Ref	–		Ref	–	
Other fields	0.46	(0.29, 0.72)		0.31	(0.16, 0.59)		0.74	(0.40, 1.38)	
Delivered chest radiation dose[a]			0.296			0.439			0.652
1–19 Gy	Ref	–		Ref	–		Ref		
20–29 Gy	0.58	(0.31, 1.11)		0.63	(0.30, 1.33)		0.47	(0.13, 1.65)	
30–39 Gy	0.68	(0.41, 1.13)		0.69	(0.36, 1.28)		0.61	(0.25, 1.50)	
40+ Gy	0.80	(0.49, 1.28)		0.88	(0.49, 1.56)		0.65	(0.28, 1.52)	
Anthracycline chemotherapy			0.090			0.674			0.008
No	Ref	–		Ref	–		Ref	–	
Yes	1.36	(0.95, 1.93)		1.10	(0.72, 1.68)		2.25	(1.24, 4.10)	
Age at diagnosis, yrs			0.070			0.106			0.559
Spline 1	1.13	(1.00, 1.27)		1.15	(1.00, 1.31)		1.00	(0.73, 1.39)	
Spline 2	0.90	(0.83, 0.97)		0.89	(0.80, 0.99)		0.97	(0.79, 1.19)	

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference; yrs = years. Estimates are from unadjusted cause-specific Cox regression models using age as the time scale. Fields included in the all others category are mediastinal/IFRT, high abdominal fields, and one-sided chest fields. *P*-values for categorical variables with *K* levels are from χ^2-tests with $K-1$ degrees of freedom testing whether each HR is significantly different from one.
[a]Tests for trend: All breast cancer $P=0.309$, Breast cancer diagnosed <40 yrs $P=0.541$, Breast cancer diagnosed ⩾40 yrs $P=0.340$.

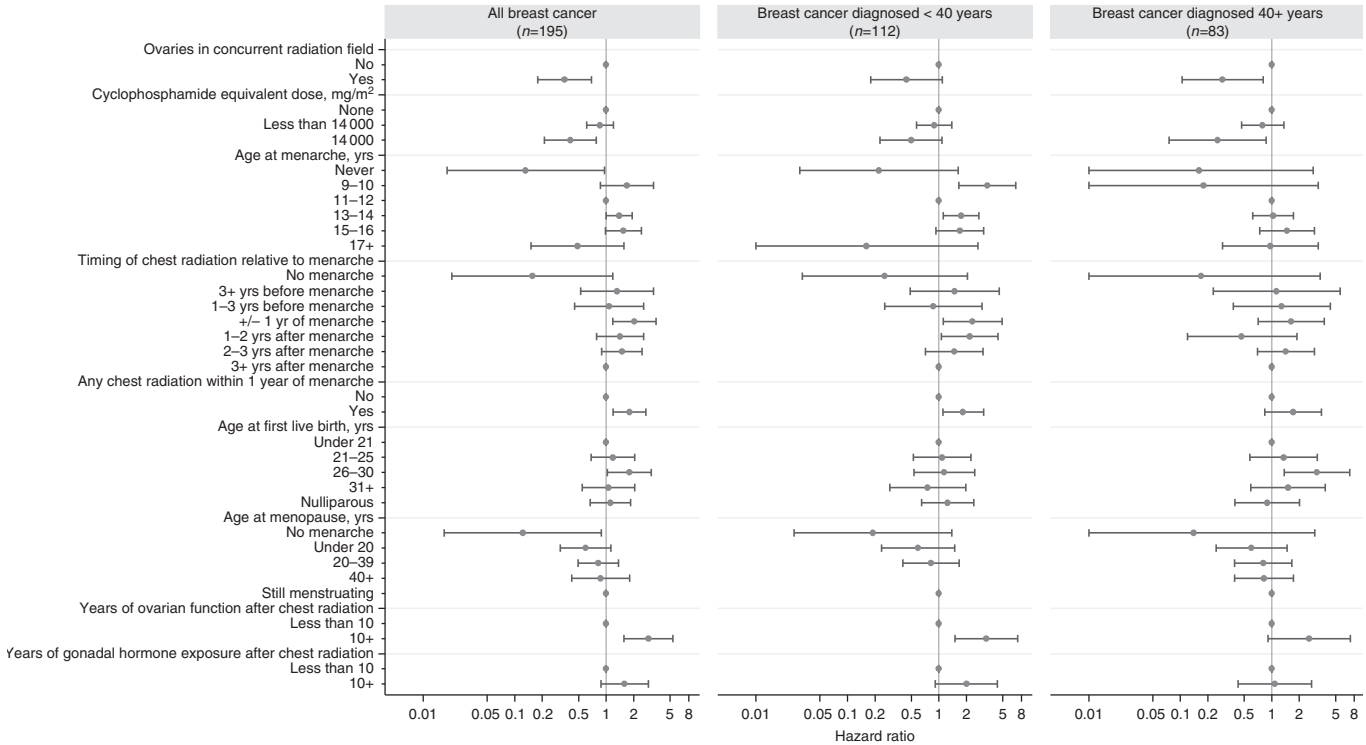

Figure 1. Risk of breast cancer overall and separately by age at breast cancer diagnosis. Estimated cause-specific hazard ratios (95% confidence intervals) for univariable associations adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis, and exposure to anthracyclines. All analyses are done using age as the time scale split into 1-year intervals. Years of ovarian function represents years of normal ovarian hormone exposure starting either at menarche or initiation of chest radiotherapy, whichever occurred last, until menopause, first reported use of exogenous hormones, or last contact for women who were still menstruating at last contact. Years of gonadal hormone exposure is estimated as years of ovarian function (endogenous hormone exposure) plus years of subsequent exogenous hormone exposure.

study. Formerly evaluated only among Hodgkin lymphoma survivors (Cooke *et al*, 2013), we corroborate that chest radiotherapy given near menarche significantly increases breast cancer risk. As previously described, treatment with ovarian-toxic therapy substantially reduces breast cancer risk (Travis *et al*, 2003; van Leeuwen *et al*, 2003; Inskip *et al*, 2009; Moskowitz *et al*, 2014). Notably, though, use of HT in postmenopausal childhood cancer survivors does not appear to impact breast cancer risk to the same degree as endogenous hormones. Our analyses suggest that HT after treatment-induced

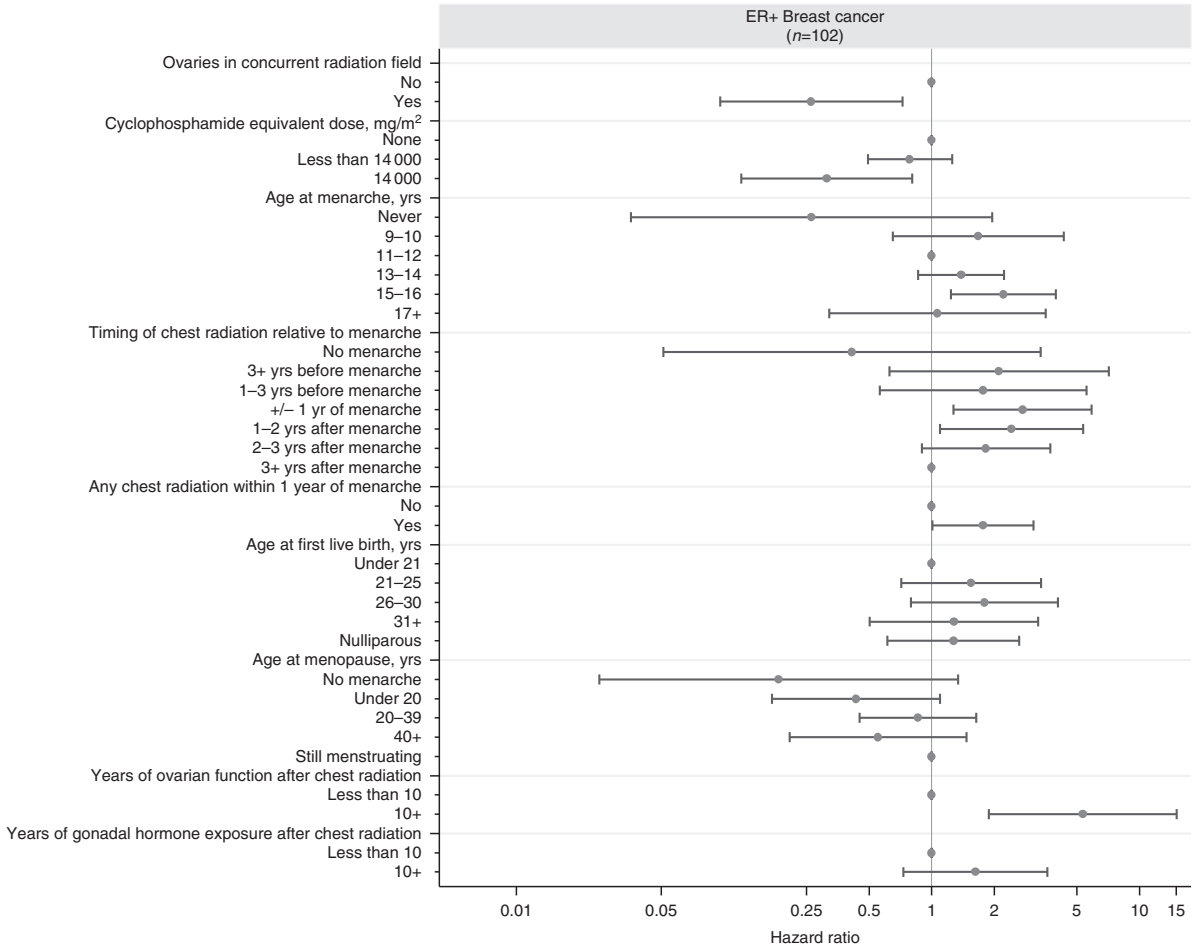

Figure 2. Risk of oestrogen receptor-positive breast cancer. Estimated cause-specific hazard ratios (95% confidence intervals) for univariable associations adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis, and exposure to anthracyclines. All analyses are done using age as the time scale split into 1-year intervals. Years of ovarian function represents years of normal ovarian hormone exposure starting either at menarche or initiation of chest radiotherapy, whichever occurred last, until menopause, first reported use of exogenous hormones, or last contact for women who were still menstruating at last contact. Years of gonadal hormone exposure is estimated as years of ovarian function (endogenous hormone exposure) plus years of subsequent exogenous hormone exposure.

Table 3. Risk of breast cancer among women ($n = 259$) who experienced menopause by oestrogen + progestin hormone therapy (E + P)

	No. of breast cancers		All breast cancer			ER+ breast cancer		
All menopausal women	**All ($n = 38$)**	**ER+ ($n = 23$)**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
E + P					0.282			0.498
No	14	9	Ref	–		Ref	–	
Yes	24	14	1.54	(0.70, 3.40)		1.44	(0.50, 4.15)	

Abbreviations: CI = confidence interval; ER = oestrogen receptor; HR = hazard ratio; Ref = reference. Analysis uses age as the time scale split into 1-year intervals and is adjusted for chest radiation field and delivered dose, age at primary childhood cancer diagnosis, exposure to anthracyclines, and age at menopause. The HR quantifies the risk of breast cancer after menopause or age 20 years, whichever comes later.

menopause may increase breast cancer risk, but does not fully reverse the protective effect of POI.

Studies have yielded inconclusive results as to whether age at childhood cancer diagnosis modifies breast cancer risk (Metayer *et al*, 2000; Travis *et al*, 2003; Hill *et al*, 2005; Inskip *et al*, 2009; Swerdlow *et al*, 2012). Cooke *et al* (2013) observed a trend for risk to increase the nearer chest radiotherapy was to menarche with risk peaking when radiotherapy was given within 6 months of menarche relative to 10 or more years after menarche (odds ratio = 5.52, 95% CI 1.97–15.46). We confirm this finding among a broader population of childhood cancer survivors. Although breast development begins 2–3 years before menarche, similar to Cooke and colleagues, we found the strongest association between breast cancer and chest radiotherapy given near menarche; the association was weaker when it was given before menarche, but this may change as the cohort matures.

A novel and clinically important finding, our data suggest that E + P menopausal HT modestly increases breast cancer risk in this population, but not to the same degree as endogenous hormones. Studies of women in natural menopause indicate that E + P increases breast cancer risk (Chlebowski *et al*, 2003). Whether these results are applicable to younger women experiencing POI where HT replaces hormones that would normally be produced has been previously unclear (Panay & Kalu, 2009). Similar to van Leeuwen *et al* (2003) and Cooke *et al* (2013) we found risk substantially increases with the number of premenopausal

Table 4. Risk of breast cancer by menopausal status and oestrogen + progestin hormone therapy (E + P)

	No. of breast cancers	HR	95% CI	*P*
Menstruating, no E + P	52	Ref	–	–
Menstruating, E + P	33	0.90	(0.57, 1.42)	0.653
Postmenopausal, no postmenopausal E + P				
Age at menopause < 20 years	2	0.30	(0.07, 1.26)	0.101
Age at menopause 20–39 years	7	0.61	(0.27, 1.37)	0.233
Age at menopause 40+ years	8	0.56	(0.23, 1.39)	0.214
Postmenopausal, postmenopausal E + P				
Age at menopause < 20 years	11	0.47	(0.23, 0.94)	0.033
Age at menopause 20–39 years	8	0.66	(0.31, 1.42)	0.287
Age at menopause 40+ years	3	0.84	(0.25, 2.85)	0.778

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference. Analysis uses age as the time scale split into 1-year intervals and is adjusted for chest radiation field and delivered dose, age at primary childhood cancer diagnosis, and exposure to anthracyclines.

years after chest radiotherapy. However, our study is the first to find this result was attenuated when considering the number of premenopausal years after chest radiotherapy together with length of time on HT after chest radiotherapy. In postmenopausal women, breast cancer risk was elevated for women reporting E + P, although this analysis, conducted in a small subset, was not statistically significant. Finally, when comparing postmenopausal women who had taken E + P to premenopausal women, premenopausal women had a higher risk of breast cancer. Collectively these analyses point to endogenous female hormones as key contributors to the elevated risk in this population.

We attempted to evaluate that it is the number of years of ovarian function after chest radiotherapy that is the salient consideration rather the total number of years (before and after chest radiotherapy) of ovarian function. While our results do support the focus on years after chest radiotherapy, it is difficult to draw definitive conclusions from this cohort where the number of years of ovarian function prior to chest radiotherapy is restricted to a narrow range and is highly correlated with the age at which radiotherapy is given and its proximity to menarche.

Studies in other populations have shown effects of gonadal hormone factors varying by tumour hormone receptor expression status (Ma *et al*, 2006; Yang *et al*, 2011) and by age at breast cancer diagnosis (Clavel-Chapelon & Gerber, 2002; Althuis *et al*, 2003; Chollet-Hinton *et al*, 2016) suggesting that early breast cancer is a clinically and biologically different disease than breast cancer diagnosed at older ages (Althuis *et al*, 2003; Chollet-Hinton *et al*, 2016). It is unknown whether these differences are applicable to radiation-associated breast cancer in childhood cancer survivors. We observed differences in the strength of associations between multiple risk factors, (ovarian radiation, high doses of alkylators, age at menarche, timing of chest radiotherapy relative to menarche, and years of ovarian function after chest radiotherapy) with breast cancer diagnosed earlier *vs* later. It may be that the mechanisms by which these factors modify breast cancer risk differ by age at breast cancer diagnosis or menopausal status. However, this is a relatively young cohort limiting our ability to test whether these are true differences. Further, due to the era in which many of the breast cancers were diagnosed, we lacked hormone receptor expression on many cancers and HER2 status on most cancers and thus were unable to evaluate risk according to luminal type.

In agreement with our previous report (Moskowitz *et al*, 2014), our data indicate that higher doses of delivered chest radiotherapy do not confer a statistically significantly higher risk of breast cancer. Lower doses of therapeutic radiation delivered to wide chest fields (e.g., whole lung irradiation) are associated with elevated breast cancer risk. These results are in contrast to the linear dose-response relationship previously observed between the absorbed dose of radiation to the breast as estimated by radiation dosimetry and breast cancer risk (Guibout *et al*, 2005; Inskip *et al*, 2009). Because delivered doses of chest radiotherapy are highly correlated with the delivered chest field (e.g., mantle field irradiation was typically used with delivered doses of 35 Gy or higher whereas whole lung irradiation and total body irradiation are used with delivered doses of 20 Gy or less), it is difficult to disentangle the effect of the delivered dose and the effect of the delivered field which may account for these discrepant findings.

Our results should be interpreted in light of several considerations. Aside from treatment-related factors, data for hormonal factors and medication use were self-reported without external validation. When participants did not reply to later questionnaires, but reported exogenous hormone use at the baseline survey, we were unable to reconstruct age at first use. In these cases, we used age at the time of the survey as age at first use, but likely miss some years. Notably, it was difficult to tease apart exogenous hormone use for contraception *vs* HT in this population. The risk we observed for premenopausal women reporting hormone use relative to premenopausal women without any hormone use may be underestimated due to instances when women were prescribed oral contraceptive pills as HT. Future work should focus on exploring and understanding possible differences in breast cancer risk associated with using oral contraceptive pills as HT as opposed to traditional HT. In some cases where women reported both oestrogen and progestin use, it was difficult to know if use occurred concurrently or sequentially. Previous work has shown that concurrent use in the U.S. has a no greater risk than sequential use possibly due to a reduction in progestin dose with concurrent use (Lee *et al*, 2005). Finally, we were unable to test for differences by age at breast cancer diagnosis due to small sample sizes.

In conclusion, chest radiotherapy substantially increases breast cancer risk, particularly when administered near menarche. Ovarian-toxic therapy significantly reduces this risk, but women treated with chest radiotherapy and ovarian-toxic therapy still have a significantly elevated risk compared with the general population (Moskowitz *et al*, 2014). Among women with POI, E + P modestly increases breast cancer risk. In spite of this increase, however, women with POI who take E + P have a lower risk of breast cancer when compared with women who continue to menstruate naturally (i.e., normal endogenous hormone function).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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