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Clinical Investigation

Breast Cancer Risk After Radiation Therapy for Hodgkin Lymphoma: Influence of Gonadal Hormone Exposure

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Summary

It is unknown whether gonadal hormone exposure affects the risk of radiation-associated breast cancer in female survivors of Hodgkin lymphoma. We performed a nested case-control study to assess the separate and joint effects of radiation dose to the breast and hormone exposure on breast cancer risk. Risk increased linearly with radiation dose, decreased with shorter duration of ovarian function, and did not appear to be influenced by hormone use among women with treatment-induced early menopause.

Background: Young women treated with chest radiation therapy (RT) for Hodgkin lymphoma (HL) experience a strongly increased risk of breast cancer (BC). It is unknown whether endogenous and exogenous gonadal hormones affect RT-associated BC risk.

Methods: We conducted a nested case-control study among female 5-year HL survivors treated before age 41. Hormone exposure and HL treatment data were collected through medical records and questionnaires for 174 BC case patients and 466 control patients. Radiation dose to breast tumor location was estimated based on RT charts, simulation films, and mammography reports.

Results: We observed a linear radiation dose-response curve with an adjusted excess odds ratio (EOR) of 6.1%/Gy (95% confidence interval [CI]: 2.1%-15.4%). Women with menopause <30 years (caused by high-dose procarbazine or pelvic RT) had a lower BC risk (OR, 0.13; 95% CI, 0.03-0.51) than did women with menopause ≥50 years. BC risk increased by 6.4% per additional year of post-RT intact ovarian function ($P<.001$). Among women with early menopause (<45 years), hormone replacement therapy (HRT) use for ≥2 years did not increase BC risk (OR, 0.86; 95% CI, 0.32-2.32), whereas this risk was nonsignificantly increased among women without early menopause (OR, 3.69; 95% CI, 0.97-14.0; P for interaction: .06). Stratification by duration of post-RT intact ovarian function or HRT use did not statistically significantly modify the radiation dose-response curve.

Conclusions: BC risk in female HL survivors increases linearly with radiation dose. HRT does not appear to increase BC risk for HL survivors with therapy-induced early menopause. There are no indications that endogenous and exogenous gonadal hormones affect the radiation dose-response relationship.

Background

Women who received radiation therapy (RT) to the chest for Hodgkin lymphoma (HL) have a substantially increased risk of breast cancer (BC) up to 40 years after treatment, with an overall cumulative incidence of 20% to 35% (1-11). Risk increases with younger age at HL diagnosis and larger irradiation fields (2, 3, 6). Moreover, 2 previous studies have observed a linear dose-response curve with an excess odds ratio (EOR) per Gy of 27% in childhood cancer survivors (12) and 5% to 15% after adult HL (13).

Furthermore, BC risk after chest RT appears to be reduced after high doses of alkylating chemotherapy (CT) or pelvic RT (2, 3, 6, 13, 14). This observation has been attributed to therapy-induced premature menopause. We previously found that women with an intact ovarian function of <10 years after RT had a 50% lower BC risk than did women with a post-RT ovarian function of 10 to 19 years (6). Some data suggest that alkylating CT and/or pelvic RT, might modify the radiation dose-dependent BC risk (12, 13), but the potential effect modification by duration of post-RT intact ovarian function has not yet been examined. Because premature menopause is associated with menopausal symptoms, osteoporosis at older age, and possibly cardiovascular disease (15, 16), HL survivors with therapy-induced premature menopause may often opt for hormone replacement therapy (HRT). However, among recent HRT users in the general population, BC risk increases by 2.3% per year of HRT use (17). This raises the important question whether HRT use could counteract the protective effect of early menopause in young irradiated HL survivors. Up to now, the effects of long-term HRT use after early menopause on RT-associated BC risk have not been investigated. We therefore conducted a case-control study among young female HL survivors to examine the separate and joint effects of radiation dose to the breast, reproductive factors, and hormone use on BC risk.

Methods

Study population

We performed a nationwide case-control study nested within a cohort of 3905 HL survivors treated in the Netherlands between 1965 and 2000. Patient selection and study procedures have been described previously (3, 14). Forty-eight case patients and 175 control patients were included in an earlier case-control study (14). Eligible women were treated before age 41 years in 9 hospitals and survived ≥5 years after HL treatment. Case patients with primary BC ≥5 years after HL were identified by reviewing medical records, through questionnaires sent to general practitioners, and by record linkage with the Netherlands Cancer Registry since 1989. Another invasive cancer before BC diagnosis was allowed if treated with surgery only. Only pathologically confirmed primary BCs (invasive or ductal carcinoma in situ [DCIS]) were included. We aimed to individually match each case patient with at least 4 control patients based on age

at HL treatment (±3 years) and date of HL treatment (±5 years). Moreover, we matched on region/hospital of HL treatment (n=5) for practical reasons related to data collection. Dependent on the availability of matching control patients, the matching ratio ranged between 1 and 7 control patients. The control patients had to survive without BC at least as long as the interval between HL and BC for the case. If patients were diagnosed with DCIS and an invasive tumor, we matched on the invasive tumor.

Data collection

Detailed data on HL treatment, reproductive factors (ie, ages at menarche and menopause, parity), oral contraceptive (OC) and HRT use (ie, duration, brand, indication), body mass index (BMI), and family history of cancer were abstracted from medical records. Radiation charts and simulation films were obtained. For BC patients, detailed clinical, radiological, and pathologic information was collected. Moreover, a questionnaire on reproductive and lifestyle factors, OC and HRT use, and family history of cancer was sent to all case patients and control patients still alive at study enrollment between 1996 and 2015 (n=512, 80% of included patients). The response rate was 89.8% for case patients and 80.8% for control patients (n=426). The study was approved by the Institutional Review Board of the Netherlands Cancer Institute.

Dosimetry

We adapted a previously used dosimetry method (for detailed information see Appendix A; available online at www.redjournal.org) (14). In brief, we established a library of all radiation field setups used in our study population (n=46). The 3-dimensional dose distribution was then simulated using the Isogray (Dosisoft, Cachan, France) planning system for all field setups on a voxel-based anthropomorphic phantom based on an RT planning computed tomography scan obtained from a 21-year-old woman. Based on available radiation charts, medical records, and surgery and imaging reports (simulation films, mammography), we determined the location of the breast tumor. Subsequently, we estimated the point dose in the center of the tumor and the same location for matched control patients. Furthermore, we determined a margin to reflect uncertainty in tumor location for each patient and calculated the difference between the lowest and highest possible dose. For patients diagnosed with two tumors on the same date, we estimated the dose to the largest tumor.

Statistical analysis

Conditional logistic regression analyses were performed to calculate odds ratios (ORs) for BC risk according to HL treatment, radiation dose, reproductive factors, OC use for contraception, and HRT use. Confounding and effect modification were assessed where appropriate using multivariable regression analyses. The following variables were tested for confounding: procarbazine dose, pelvic RT, radiation dose to the breast, age at menarche, parity, age at first birth, duration of post-RT intact ovarian function, OC and HRT use, BMI, and family history of BC. Confounders were selected during a forward stepwise selection based on a 10% change in risk estimate. Post-RT duration of intact ovarian function was defined as the number of premenopausal years between RT (or menarche, whichever came last) and BC diagnosis (for case patients) or cutoff date (for control patients). For brevity, we will refer to this as duration of ovarian function. HRT use was defined as any use of registered HRT, use of OCs prescribed for menopausal symptoms, or postmenopausal use of OCs, because in these patients OCs were often used as HRT. Methods to resolve incidentally encountered inconsistencies between medical record and questionnaire data regarding women's menopausal age or hormone use are described in Appendix B (available online at www.redjournal.org). There were 6 case patients and 11 control patients with an unknown menopausal status because of hysterectomy. Menopausal age was missing and imputed for 21 case patients and 81 control patients. Imputation was based on HL treatment; women treated with nongonadotoxic treatment (ie, no pelvic RT and no alkylating CT) were assigned the age of 51, and women treated with pelvic RT were assigned the age at HL treatment. For women treated with alkylating CT, we predicted menopausal age based on procarbazine dose using a Cox regression model with Weibull distribution.

The radiation dose-response relationship was estimated by modeling the BC rate as $\mathrm{Km}(1+\beta \mathrm{d})$, where Km is a constant specific to each matched set, and β is the excess odds ratio (EOR) of BC per Gy increase in radiation dose d to a patient's specific breast tumor location. Nonlinearity was evaluated by including an exponential term: $\mathrm{Km}[1 + \beta d \cdot \exp(\gamma \mathrm{d})]$ and testing for an upward ($\gamma>0$) or downward curvature ($\gamma<0$). Effect modifications were assessed by using interaction terms and goodness of fit by likelihood ratio tests. The joint effect of radiation dose and duration of ovarian function was evaluated by comparing the goodness of fit of models with a multiplicative or additive joint effect with models including an interaction term. Approximate cumulative incidence of BC was predicted stratified by radiation field (no chest RT, mediastinal RT ± neck RT and (in)complete mantle field) and prescribed dose (≤35 Gy and >35 Gy). The (in)complete mantle field was also stratified by duration of ovarian function (<10, 10-19, and ≥20 years). Cumulative incidences, with death as competing risk, were estimated based on the ORs for BC estimated in our case-control study and the cumulative BC incidence within the entire cohort from which the case patients and control patients were derived. We thereby assumed that the distribution of radiation field/dose and duration of ovarian function for all individuals in the cohort were equal to those for the control patients.

Significance tests were 2-sided, and $P<.05$ was considered statistically significant. Analyses were performed

Table 1 Patient characteristics

Characteristic	Case patients (n = 174)*		Control patients (n = 466)*	
	n	%	n	%
Age at HL diagnosis, y (median, IQR)†	23.4	19.6-28.8	23.5	19.7-29.5
<20	51	29.3	129	27.7
20-24	50	28.7	136	29.2
25-29	39	22.4	96	20.6
30-34	21	12.1	70	15.0
35-41	13	7.5	35	7.5
Year of HL diagnosis				
1960-1969	26	14.9	53	11.4
1970-1979	60	34.5	165	35.4
1980-1989	64	36.8	185	39.7
1990-2000	24	13.8	63	13.5
HL treatment				
RT only	88	50.6	174	37.3
RT + CT	85	48.8	268	57.5
CT only	1	0.6	24	5.2
Radiation fields‡				
No RT	1	0.6	24	5.2
Supra RT ± infra RT, no pelvic RT	167	96.0	390	83.7
Supra RT ± infra RT, pelvic RT	6	3.5	41	8.8
Infra RT only, no pelvic RT	0	0.0	7	1.5
Infra RT only, pelvic RT	0	0.0	4	0.9
Time between HL and BC diagnosis, y (median, IQR)	21.9	16.9-26.8		
5-9	6	3.5	NA	
10-19	71	40.8	NA	
20-29	75	43.1	NA	
30-41	22	12.6	NA	
Age at BC diagnosis, y (median, IQR)§	46.1	39.9-52.4		
<30	4	2.3	NA	
30-39	40	23.0	NA	
40-49	75	43.1	NA	
50-59	42	24.1	NA	
≥60	13	7.4	NA	
Laterality of breast tumor				
Right	78	44.8	NA	
Left	86	49.4	NA	
Bilateral (<3 months)	10	5.8	NA	
Menopausal status at cutoff date‖				
Premenopausal	91	52.3	227	48.7
Perimenopausal	9	5.2	8	1.7
Postmenopausal, at age (y)	74	42.5	231	49.6
18-29	4	5.4	47	20.4
30-39	18	24.3	80	34.6
40-49	33	44.6	78	33.8
≥50	19	25.7	26	11.3
Duration of post-RT intact ovarian function, y¶				
<10	29	16.7	137	29.4
10-19	76	43.7	216	46.4
≥20	69	39.7	113	24.3
BMI at cutoff date#				
<20	16	9.2	37	7.9
20-24	71	40.8	171	36.7
25-29	33	19.0	80	17.2
≥30	8	4.6	22	4.7
Missing	46	26.4	156	33.5
Family history of BC**				
Yes	53	30.5	91	19.5
No	103	59.2	294	63.1
Missing	18	10.3	81	17.4

Abbreviations: BC = breast cancer; BMI = body mass index (kg/m^2); CT = chemotherapy; HL = Hodgkin lymphoma; IQR = interquartile range; RT = radiation therapy.

* 1 case patient was matched with 7 control patients, 5 case patients with 5 control patients, 13 case patients with 4 control patients, 99 case patients with 3 control patients, and 29 case patients with 2 control patients; 27 case patients could be matched with only 1 control patient. There were 59 case patients that were also included as controls for case patients with a shorter interval between HL and BC diagnosis. Eighteen case patients had a diagnosis of ductal carcinoma in situ (DCIS) only.

† Age at HL ranged between 11 and 41 years, with a median age of 18 years in the lowest category.

‡ Pelvic RT encompassed RT to the whole abdomen or iliacal nodes on both sides, or RT with inverted Y field in women with no (successful) oophoropexy. For 1 control patient with a missing RT field, RT field was imputed based on year and hospital of HL treatment.

§ Age at BC diagnosis ranged between 27 and 74 years, with a median age of 63 years in the highest category.

‖ For case patients, the cutoff date was date of BC diagnosis. For control patients, we determined the cutoff date by adding the interval between HL and BC diagnosis of the corresponding case patient to the date of HL diagnosis. There were 6 case patients and 11 control patients with an unknown menopausal status because of hysterectomy.

¶ Duration of post-RT intact ovarian function was defined as the number of premenopausal years between RT (or menarche, whichever came last) and BC diagnosis (for case patients) or cutoff date (for control patients).

BMI ranged between 17 and 43, with a median of 32 in the highest category.

** Family history was coded yes when a sister, mother, or grandmother had a diagnosis of BC.

using STATA (version 13.0; STATA, College Station, TX) and Epicure (version 1.8; Hiro Soft International Inc, Seattle, WA).

Results

Patient characteristics

In total, 193 BC case patients were identified. For 15 case patients, no control patients could be found, and for 4 case

patients, no medical record data were available, leaving 174 case patients and 466 matched control patients for analyses. The median age at HL diagnosis was 23.5 years. BC was diagnosed after a median interval of 21.9 years, at a median age of 46.1 years (Table 1). Twenty-six patients received diagnoses of a second breast tumor, of which 10 were synchronous (<3 months).

HL treatment

Ninety-nine percent of case patients received chest RT compared with 90% of control patients. Women treated with chest RT and alkylating CT had a 5.51-fold (95% CI, 1.22-24.8) higher BC risk than did women treated without chest RT, but a lower risk than did women who received chest RT and no (alkylating) CT (OR, 0.68; 95% CI, 0.46-1.00). Treatment with a high dose of procarbazine (>4.2 g/m^2), and/or pelvic RT, was associated with a significantly reduced risk (OR, 0.54; 95% CI, 0.34-0.86) (Table 2).

The median radiation dose to the breast tumor location was 31.7 Gy (interquartile range [IQR], 8.0-38.2) for case patients and 15.9 Gy (IQR, 3.1-34.9) for control patients. A linear dose-response curve fitted our data well with no evidence for an upward curvature ($P = .80$). The crude EOR was 7.9%/Gy (95% CI, 3.1%-19.8%). Adjustment for duration of post-RT ovarian function yielded an EOR of 6.1%/Gy (95% CI, 2.1%-15.4%). Adjustment for parity, age at first birth, and BMI did not affect the EOR. Figure 1

Table 2 Risk of breast cancer according to Hodgkin lymphoma treatment

Treatment	Case patients		Control patients		Crude analysis		Adjusted analysis*	
	n	%	n	%	OR	95% CI	OR	95% CI
Chest RT + alkylating CT†								
No chest RT ± alkylating CT	2	1.2	44	9.4	1.00	Reference	1.00	Reference
Chest RT ± nonalkylating CT	104	59.8	194	41.6	12.6	2.96-53.6	8.26	1.83-37.2
Chest RT + alkylating CT	68	39.1	225	48.3	7.38	1.72-31.6	5.51	1.22-24.8
Pelvic RT								
No	168	96.6	421	90.3	1.00	Reference	1.00	Reference
Yes	6	3.5	45	9.7	0.30	0.12-0.73	0.33	0.13-0.84
Procarbazine dose‡								
RT only	88	50.6	174	37.3	1.00	Reference	1.00	Reference
CT without procarbazine	24	13.8	59	12.7	0.82	0.47-1.43	0.99	0.56-1.76
Procarbazine ≤4.2 g/m^2	23	13.2	68	14.6	0.77	0.43-1.35	0.95	0.53-1.70
Procarbazine >4.2 g/m^2	37	21.3	156	33.5	0.48	0.31-0.76	0.62	0.38-1.00
Missing	2	1.2	9	1.9	0.35	0.07-1.66	0.31	0.06-1.68
Pelvic RT and procarbazine dose								
RT only, no pelvic RT	86	49.4	166	35.6	1.00	Reference	1.00	Reference
CT includes ≤4.2 g/m^2 procarbazine ± RT, no pelvic RT	47	27.0	114	24.5	0.88	0.56-1.38	1.09	0.68-1.75
CT includes >4.2 g/m^2 procarbazine or pelvic RT	40	23.0	179	38.4	0.44	0.28-0.68	0.54	0.34-0.86
Missing	1	0.6	7	1.5	0.26	0.03-2.20	0.27	0.03-2.45
Radiation dose to breast tumor location in Gy (median)§								
0.0-2.9 (1.2)	18	10.3	112	24.0	1.00	Reference	1.00	Reference
3.0-7.9 (4.9)	25	14.4	86	18.5	1.67	0.81-3.40	1.33	0.64-2.77
8.0-27.9 (17.5)	36	20.7	87	18.7	2.65	1.34-5.26	2.21	1.09-4.46
28.0-35.9 (33.9)	33	19.0	85	18.2	2.76	1.39-5.48	2.38	1.17-4.83
36.0-61.2 (39.4)	62	35.6	96	20.6	5.83	2.97-11.5	4.70	2.36-9.38

Abbreviations: CI = confidence interval; CT = chemotherapy; OR = odds ratio; RT = radiation therapy.

* Adjusted for radiation dose to breast tumor location (<6, 6-35, ≥36 Gy). Pelvic RT was additionally adjusted for alkylating CT (yes, no, missing). Radiation dose to breast tumor location was adjusted for duration of post-RT intact ovarian function (continuous).

† Chest RT was defined as mantle field RT, or RT to the mediastinum, lungs, or axilla. Alkylating CT consists of combinations of cytostatic agents with at least 1 alkylating agent (ie, procarbazine, cyclophosphamide, ifosfamide, lomustine, melphalan, dacarbazine, cisplatin, mechlorethamine, chlorambucil, and carmustine).

‡ 4.2 g/m^2 procarbazine is equal to 6 cycles of a hybrid regimen of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) plus doxorubicin, bleomycin, and vinblastine (ABV) or 6 cycles of a regimen of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), or 3 cycles of MOPP or MOPP plus doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD).

§ There were 14 patients with missing data on prescribed radiation dose needed to calculate the radiation dose to the specific tumor location. Prescribed radiation dose was imputed based on RT field type and year of HL diagnosis. For 5 out of the 14 patients we also had to impute RT field type based on year and hospital of HL treatment. The categories for radiation dose were based on the distribution of radiation dose among the control patients. A low radiation dose was defined as <3 Gy. Subsequently, control patients were divided into quartiles.

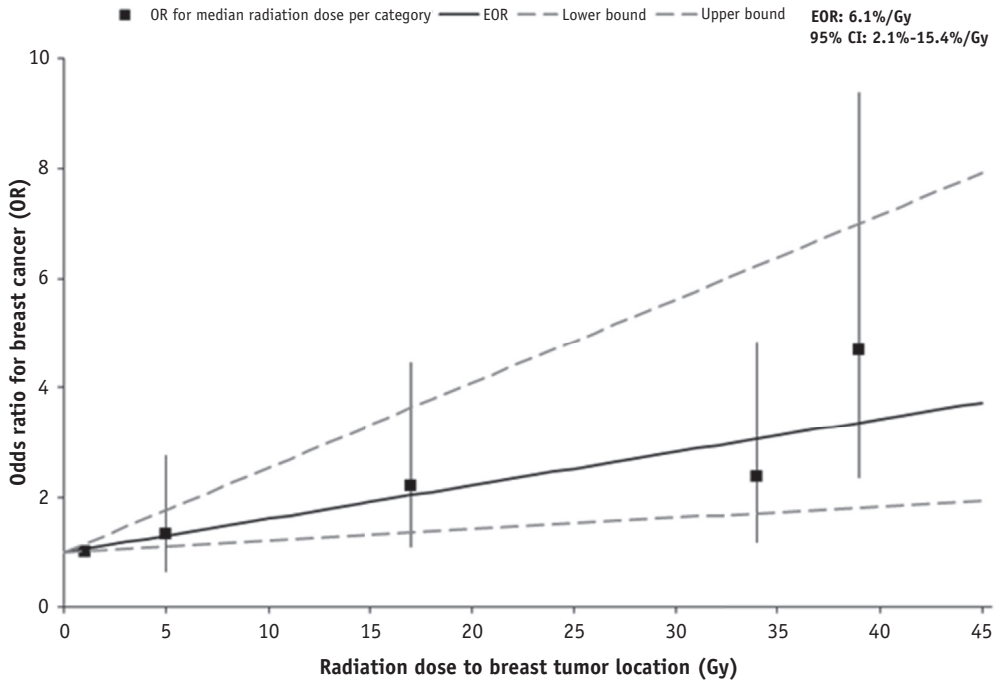

Fig. 1. Dose-response curve for radiation dose to breast tumor location and breast cancer risk, adjusted for duration of post-RT intact ovarian function (continuous).

shows the linear dose-response curve together with the ORs for BC risk for the median of quintiles of radiation dose to the breast tumor location. Women who received ≥36 Gy had a 4.70-fold (95% CI, 2.36-9.38) higher BC risk than did women who received <3 Gy. In a sensitivity analysis including only patients with an uncertainty margin of <5 Gy (n=312), the unconditional adjusted EOR/Gy was 8.0% compared with 4.6% in all patients.

Reproductive factors

Twenty-two case patients (12.6%) and 127 control patients (27.3%) experienced premature menopause (<40 years), which was associated with a significantly decreased risk of BC (OR, 0.43; 95% CI 0.25-0.75). Risk significantly decreased with younger age at menopause, with ORs of 0.13 (95% CI, 0.03-0.51) and 0.61 (95% CI, 0.27-1.36) for menopausal ages of <30 and 40 to 49 years, respectively, compared with menopausal age ≥50 years (Table 3). Furthermore, BC risk increased by 6.4% per additional year of ovarian function, adjusted for radiation dose (P<.001). Compared to women with an ovarian function of <10 years, women with an ovarian function of 10 to 19 and ≥20 years had 1.75-fold (P=.07) and 3.49-fold (P=.001) increased BC risks, respectively. We did not find an association between BC risk and menstruation disorders after HL (ie, infrequent menstruations or temporary cessation of ≥3 months) nor with a pregnancy around HL diagnosis, nor menarche close to start of HL treatment (Table E1; available online at www.redjournal.org).

HRT and OC use

Thirty-five case patients (20.1%) and 129 control patients (27.7%) used HRT after HL, with median durations of 3.5 (IQR, 0.9-7.7 years) and 7.0 (IQR, 2.0-12.4 years), respectively. Use of HRT and duration of use were not associated with BC risk, adjusted for radiation dose and duration of ovarian function (Table 3). Estrogen-only users had a nonsignificantly lower BC risk than did women who used HRT with estrogens and progestins (OR, 0.46; 95% CI, 0.13-1.71). Among women with an early menopause (<45 years), 57.7% had used HRT compared with 13.4% among women without early menopause. We found no evidence for increased BC risk after HRT use for ≥2 years compared with no use for early menopausal women (OR, 0.86; 95% CI, 0.32-2.32). However, among women without an early menopause ≥2 years, HRT use was associated with a nonsignificantly increased BC risk (OR, 3.69; 95% CI, 0.97-14.0, P for interaction, .06) (Table 4). Women who used OCs for contraception for ≥15 years had a significantly higher BC risk than did never-users, which remained after adjustment for duration of ovarian function (OR, 2.55; 95% CI, 1.07-6.09) (Table 3).

Modifying effects of HL treatment and endogenous and exogenous hormones

We found no evidence for significant modification of the effect of radiation dose on BC risk by age at and time since HL treatment, pelvic RT, procarbazine dose, or OC and HRT use (Table E2; available online at www.redjournal.org).

Table 3 Risk of breast cancer by menopausal age, duration of post-RT intact ovarian function, and hormone use

Factor	Case patients		Control patients		Crude analysis		Adjusted analysis*	
	n	%	n	%	OR	95% CI	OR	95% CI
Premature menopause								
Menopause ≥40 y/premenopausal ≥40 y	110	63.2	224	48.1	1.00	Reference	1.00	Reference
Menopause <40 y	22	12.6	127	27.3	0.37	0.21-0.63	0.43	0.25-0.75
Pre/perimenopausal <40 y	42	24.1	115	24.7	0.94	0.38-2.37	1.03	0.40-2.64
Age at menopause, y								
≥ 50	21	12.1	27	5.8	1.00	Reference	1.00	Reference
40-49	31	17.8	77	16.5	0.57	0.26-1.24	0.61	0.27-1.36
30-39	18	10.3	80	17.2	0.39	0.17-0.91	0.48	0.20-1.15
18-29	4	2.3	47	10.1	0.09	0.02-0.37	0.13	0.03-0.51
Pre/perimenopausal at cutoff date	100	57.5	235	50.4	0.74	0.32-1.69	0.85	0.36-2.01
Duration of post-RT intact ovarian function, y								
<5	15	8.6	87	18.7	1.00	Reference	1.00	Reference
5-9	14	8.1	50	10.7	1.56	0.66-3.72	1.53	0.63-3.72
10-14	25	14.4	87	18.7	1.54	0.68-3.50	1.45	0.62-3.37
15-19	51	29.3	129	27.7	3.19	1.44-7.09	2.69	1.20-6.05
20-24	42	24.1	72	15.5	5.69	2.35-13.8	4.42	1.80-10.9
≥25	27	15.5	41	8.8	4.83	1.69-13.8	3.82	1.27-11.5
Duration per year (continuous)							1.064	1.029-1.100
Duration before age 45, per year (continuous)							1.075	1.025-1.128
Duration after age 45, per year (continuous)							1.030	0.928-1.145
HRT use†								
No	121	69.5	273	58.6	1.00	Reference	1.00	Reference
Yes	35	20.1	129	27.7	0.55	0.35-0.86	0.82	0.48-1.39
Missing	18	10.3	64	13.7	0.51	0.28-0.92	0.63	0.34-1.19
Recency of HRT use								
Never user	121	69.5	273	58.6	1.00	Reference	1.00	Reference
Current user	8	4.6	51	10.9	0.36	0.16-0.80	0.61	0.26-1.44
Past user	23	13.2	65	14.0	0.69	0.40-1.20	0.99	0.52-1.87
Missing	22	12.6	77	16.5	0.51	0.30-0.90	0.64	0.36-1.16
Duration of HRT use, y								
No HRT use	121	69.5	273	58.6	1.00	Reference	1.00	Reference
<5	19	10.9	49	10.5	0.75	0.41-1.36	0.93	0.49-1.77
5-9	6	3.5	27	5.8	0.51	0.20-1.27	0.91	0.34-2.46
≥10	7	4.0	37	7.9	0.40	0.17-0.93	0.84	0.30-2.32
Missing	21	12.1	80	17.2	0.48	0.27-0.84	0.58	0.32-1.06
Timing of HRT use								
Postmenopausal only	17	9.8	81	17.4	1.00	Reference	1.00	Reference
Perimenopausal only	6	3.5	7	1.5	4.32	1.25-14.9	2.81	0.73-10.7
Premenopausal only	5	2.9	14	3.0	2.14	0.64-7.15	1.25	0.34-4.63
Combinations‡	7	4.0	23	4.9	1.66	0.61-4.49	1.15	0.39-3.40
No HRT use	121	69.5	273	58.6	2.52	1.39-4.57	1.51	0.71-3.22
Missing	18	10.3	68	14.6	1.18	0.56-2.47	0.88	0.38-2.03
Type of HRT								
HRT with estrogens and progestins	10	5.8	32	6.9	1.00	Reference	1.00	Reference
HRT with estrogens only	5	2.9	19	4.1	0.52	0.15-1.85	0.46	0.13-1.71
HRT with progestins only	8	4.6	14	3.0	1.83	0.57-5.86	1.33	0.38-4.64
HRT with combinations of estrogens and/or progestins§	3	1.7	21	4.5	0.42	0.10-1.74	0.40	0.09-1.84
OC	5	2.9	15	3.2	1.02	0.29-3.62	1.08	0.28-4.13
HRT and OC	3	1.7	19	4.1	0.45	0.11-1.86	0.62	0.14-2.68
No HRT use	121	69.5	273	58.6	1.45	0.68-3.07	0.95	0.41-2.35
Missing	19	10.9	73	15.7	0.65	0.27-1.59	0.53	0.20-1.41
OC use for contraception								
No	13	7.5	48	10.3	1.00	Reference	1.00	Reference
Yes	148	85.1	359	77.0	1.56	0.78-3.10	1.44	0.70-2.95
Missing	13	7.5	59	12.7	0.82	0.34-2.02	0.83	0.33-2.13

(*continued on next page*)

Table 3 (*continued*)

Factor	Case patients		Control patients		Crude analysis		Adjusted analysis*	
	n	%	n	%	OR	95% CI	OR	95% CI
Recency of OC use for contraception								
Never user	13	7.5	48	10.3	1.00	Reference	1.00	Reference
Current user	20	11.5	54	11.6	1.60	0.67-3.84	1.32	0.53-3.31
Past user	113	64.9	244	52.4	1.66	0.83-3.30	1.57	0.77-3.24
Missing	28	16.1	120	25.8	0.85	0.38-1.89	0.77	0.33-1.76
Duration of OC use for contraception, y								
No OC use	13	7.5	48	10.3	1.00	Reference	1.00	Reference
<5	34	19.5	105	22.5	1.29	0.60-2.76	1.26	0.57-2.79
5-9	35	20.1	91	19.5	1.38	0.64-2.95	1.26	0.57-2.78
10-14	30	17.2	70	15.0	1.82	0.80-4.12	1.67	0.71-3.92
≥15	32	18.4	42	9.0	3.00	1.31-6.87	2.55	1.07-6.09
Missing	30	17.2	110	23.6	1.01	0.45-2.25	1.02	0.44-2.35

Abbreviations: CI = confidence interval; HRT = hormone replacement therapy; OC = oral contraceptives; OR = odds ratio; RT = radiation therapy.

* Adjusted for radiation dose to breast tumor location (<6, 6-35, ≥36 Gy). Variables related to HRT and OC use were also adjusted for duration of post-RT intact ovarian function (continuous). Durations of post-RT intact ovarian function before and after age 45 were also adjusted for each other.

† HRT use is defined as any use of registered HRT (premenopausal or postmenopausal), use of OC prescribed for menopausal symptoms, or any postmenopausal use of OC.

‡ Use of premenopausal and perimenopausal HRT or perimenopausal and postmenopausal HRT.

§ Consecutive use of HRT with estrogens only and progestins only, or use of HRT with estrogens only followed by use of HRT with estrogens and progestins.

Moreover, there was no significant difference in EOR/Gy among women with a duration of ovarian function of <10, 10 to 19, and ≥20 years ($P = .40$). The data were consistent with both an additive and a multiplicative joint effect between radiation dose and ovarian function. For women who received ≥36 Gy to the breast tumor location and had ≥20 years of ovarian function, the OR was 23.9 (95% CI, 6.85-83.6), which was higher than the sum of the separate risks (ORs of 5.23 [95% CI, 1.44-19.0], and 7.49 [95% CI, 2.33-24.1], respectively) (Table E3; available online at www.redjournal.org).

We used our entire cohort to predict the 35-year cumulative BC incidence according to radiation field, prescribed dose, and duration of ovarian function. The predicted 35-year cumulative incidence was highest (27.6%) for women with high-dose mantle field RT (≥35 Gy) and long duration of ovarian function (≥20 years). Women with lower-dose (in)complete mantle field RT (≤35 Gy) and long duration of ovarian function had a lower cumulative incidence (22.4%), followed by women with high-dose (in)complete mantle field RT and medium and short durations of ovarian function (10-19 and <10 years) (19.6% and 13.8%, respectively). Thirty-five-year cumulative incidences for women with high-dose and lower-dose mediastinal RT were 13.5% and 11.2%, respectively, and only 2.1% for women without chest RT, not taking into account the duration of ovarian function (Fig. 2) (Table E4; available online at www.redjournal.org).

Discussion

In the largest study to date of BC among young women irradiated for HL, we confirm a linear radiation dose-response relationship, with an adjusted EOR/Gy of 6.1%. A premature menopause strongly decreased BC risk, and risk increased by 6.4% per additional year of post-RT intact ovarian function. To our knowledge, we are the first to examine the effects of HRT on RT-associated BC. We expected that HRT might counteract the reduced BC risk associated with treatment-induced early menopause, but our data do not support this hypothesis. We also postulated that low levels of endogenous and exogenous hormone exposure after RT would decrease the carcinogenic effect of breast RT, resulting in a lower EOR/Gy. However, gonadotoxic treatment, duration of ovarian function, and HRT use did not modify the dose-response relationship.

The observed EOR/Gy of 6.1% is in line with 2 other similar studies among women with fractionated high-dose RT (EOR/Gy 5%-27%) (12, 13). However, from studies among atomic bomb survivors, it is known that the EORs/Gy are considerably higher after exposure to low radiation doses (<2 Gy) (18, 19). Possible explanations for this include the effect of fractionation on cell killing, and the lower baseline cancer risks in Japan (18).

Remarkably, we found no evidence that HRT use for ≥2 years increases BC risk for early menopausal women. It therefore seems that HRT does not counteract the strong protective effect of early menopause, whereas HRT use in women with menopause after age 45 was associated with a nonsignificantly increased BC risk (P for interaction was borderline significant). Possibly, the timing of first HRT use in relation to age or to time since menopause is important (20-22), but this needs further research. Interestingly, the effect of duration of ovarian function on BC risk was stronger in our young RT-exposed population (6.4% risk increase per year) than observed in the general population,

Table 4 Risk of breast cancer by use of hormone replacement therapy and oral contraceptives, stratified by early menopause (before and after age 45)

Factor	Women with early menopause*				Women without early menopause*			
	No. of case patients	No. of control patients	OR†	95% CI	No. of case patients	No. of control patients	OR†	95% CI
	36	172			67	120		
HRT use								
No	10	38	1.00	Reference	48	87	1.00	Reference
Yes	17	103	0.74	0.29-1.88	14	11	2.68	1.04-6.90
Missing	9	31	1.03	0.35-3.07	5	22	0.50	0.17-1.47
P for interaction‡	.06							
Recency of HRT use								
Never user	10	38	1.00	Reference	48	87	1.00	Reference
Current user	6	43	0.72	0.22-2.36	1	3	0.73	0.07-8.02
Past user	9	51	0.73	0.25-2.13	11	5	5.14	1.49-17.7
Missing	11	40	0.98	0.35-2.76	7	25	0.58	0.22-1.53
Duration of HRT use, y								
No HRT use	10	38	1.00	Reference	48	87	1.00	Reference
<2	3	18	0.57	0.13-2.56	5	1	7.35	0.77-69.7
≥2	13	75	0.86	0.32-2.32	7	5	3.69	0.97-14.0
Missing	10	41	0.87	0.30-2.48	7	27	0.55	0.21-1.43
Timing of HRT use								
No HRT use	10	38	1.00	Reference	48	87	1.00	Reference
Pre/perimenopausal only	1	4	0.99	0.09-10.8	7	3	4.73	1.08-20.7
Postmenopausal only	12	76	0.70	0.25-1.92	5	5	2.75	0.63-12.1
Combinations§	4	20	0.85	0.22-3.31	2	3	0.86	0.12-6.24
Missing	9	34	0.99	0.33-2.93	5	22	0.51	0.17-1.52
Duration of OC use for contraception, y								
No OC use	4	23	1.00	Reference	4	13	1.00	Reference
<5	8	46	1.17	0.29-4.68	15	24	1.57	0.41-6.09
≥5	15	62	1.42	0.38-5.25	42	48	2.47	0.69-8.80
Missing	9	41	1.65	0.41-6.64	6	35	0.54	0.12-2.36

Abbreviations: CI = confidence interval; HRT = hormone replacement therapy; OC = oral contraceptives; OR = odds ratio; RT = radiation therapy.

* Early menopause was defined as menopause before the age of 45 years. Women without early menopause were women who reached menopause at 45 years or later or who were premenopausal at age 45 or later.

† Analyzed unconditionally and adjusted for the matching factors (age at HL treatment [continuous] and year of HL treatment [1960-1969, 1970-1979, 1980-1989, 1990-2000]), duration of post-RT intact ovarian function (continuous), and radiation dose to breast tumor location (<6, 6-35, ≥36 Gy).

‡ In the unadjusted model (only including HRT use and early menopause) *P* for interaction was .02, whereas the interaction regression coefficient was unchanged.

§ Use of premenopausal and perimenopausal HRT or perimenopausal and postmenopausal HRT.

where a risk increase of 2.8% for each year older at menopause was found (17). This may be due to the history of chest irradiation of our study population but also to young age, inasmuch as we observed that the increase of BC risk was higher per additional year of ovarian function before the age of 45 years than after the age of 45 years (7.5% vs 3.0%, respectively) (Table 3).

Of note, HRT preparations used in our study somewhat differed from those in the general population. Some women used HRT with progestins only to treat menstrual disorders after alkylating CT, or OCs as HRT because of their young age at menopause. It is unlikely that this has influenced our conclusions. Although literature suggests that mainly the progestin component of HRT increases BC risk (23-25), a systematic review reported no increased risk after progestin-only OC use (26). Moreover, although synthetic hormone levels in OCs are higher than in HRT (27), we found no increased BC risk for women using OCs as HRT.

An unexpected finding was that duration of OC use for contraception was associated with BC risk, whereas current OC use was not. This is inconsistent with findings in the general population, where recency of OC use seems to be the most important risk factor (28). No differential effects of OC use before and after HL treatment were observed (data not shown). Possibly, our adjustment for duration of ovarian function in OC users was not sufficient, inasmuch as the prevalence of premature menopause was 31.5% in women with no or <5 years of OC use, and 6.8% in women with ≥15 years of OC use. More research is needed to examine the effect of OCs in HL survivors.

Our study investigated for the first time the effects of both endogenous and exogenous hormones on the radiation dose-response relationship. Three previous studies reported

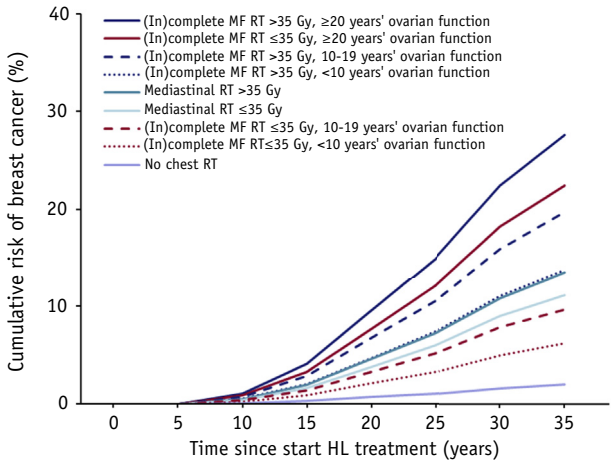

Fig. 2. Cumulative incidence of breast cancer among female Hodgkin lymphoma (HL) survivors according to radiation field, prescribed dose, and duration of post-RT intact ovarian function. *Abbreviations:* MF = mantle field; RT = radiation therapy. The median duration of post-RT intact ovarian function in women without chest RT was 8.7 years. The median duration of post-RT intact ovarian function for women with low-dose and high-dose mediastinal RT was 16.1 years and 12.8 years, respectively.

a lower EOR/Gy for women treated with pelvic RT and/or alkylating CT, (12-14). Based on much larger numbers, we do not observe significant modification of the radiation dose-response slope by gonadotoxic treatment or by endogenous and exogenous hormones. Whereas our power to detect possible effect modification is still limited, it is important to present these exploratory results to compare with results from other studies. International collaboration and pooled analyses are needed to reach sufficient power for effect modification analyses.

The 35-year cumulative incidence for subgroups according to radiation field/dose and duration of ovarian function illustrates that in the long run more than one-quarter (27.6%) of all women treated with high-dose mantle field RT ($\geq$35 Gy) and $\geq$20 years' ovarian function are affected by BC. Both a shorter duration of ovarian function and smaller radiation doses and fields reduce this risk considerably. For women who did not receive chest RT and had a short duration of ovarian function, the 35-year cumulative incidence was 2.1%, which is quite similar to the BC risk in the general population at the age of 65 years (29).

When interpreting our results, some strengths and limitations should be considered. First, detailed and nearly complete data on HL treatment and radiation dose to the breast tumor location were available from retrospective radiation dosimetry. However, inevitable uncertainties remain regarding the position of the blocks during RT (individual shielding) and exact breast tumor location (slice), leading to uncertainty in point dose. Given that sensitivity analyses showed a higher adjusted EOR in women with <5 Gy uncertainty in dose, the true radiation dose-response relationship may be even stronger.

Detailed data on hormone use were collected through medical records and questionnaires (response rate of 80%) and were available for the large majority of women (87%). However, we were not always able to retrieve data on hormone use for the entire follow-up period, which may have led to an underestimation of the total duration. Because control patients were slightly more likely to have missing data, we may have overestimated the ORs for OC and HRT use. A limitation of our study was that the number of case patients with long-term HRT use was relatively small, resulting in insufficient power for subgroup analyses regarding duration and type of HRT.

Importantly, most patients in our study were treated with classic RT fields using parallel-opposed fields. Nowadays, patients are treated with less gonadotoxic CT (30) and with RT using lower doses, smaller volumes, and modern techniques (31). The effect of these treatment changes on BC risk is yet unknown and deserves further study.

In conclusion, we observed a strong linear radiation dose-response relationship for BC, which was not significantly modified by exposure to endogenous or exogenous hormones. Among women with a short duration of ovarian function who did not receive chest RT, long-term BC risk did not appear to be increased compared with the general population. Current guidelines prescribe BC screening after any type of chest RT (32, 33), independently of duration of ovarian function, but this might be reconsidered when our results are confirmed by others. Furthermore, HRT use did not appear to increase BC risk in female HL survivors with an early menopause. It may therefore be safe for these women to use HRT to alleviate menopausal symptoms and prevent osteoporosis, but our findings need to be confirmed in future studies.

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