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Article

Radiotherapy-Related Dose and Irradiated Volume Effects on Breast Cancer Risk Among Hodgkin Lymphoma Survivors

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Abstract

Background: Breast cancer (BC) risk is increased among Hodgkin lymphoma (HL) survivors treated with chest radiotherapy. Case-control studies showed a linear radiation dose-response relationship for estimated dose to the breast tumor location. However, these relative risks cannot be used for absolute risk prediction of BC anywhere in the breasts. Furthermore, the independent and joint effects of radiation dose and irradiated volumes are unclear. Therefore, we examined the effects of mean breast dose and various dose-volume parameters on BC risk in HL patients. **Methods:** We conducted a nested case-control study of BC among 5-year HL survivors (173 case patients, 464 matched control patients). Dose-volume histograms were obtained from reconstructed voxel-based 3-dimensional dose distributions. Summary parameters of dose-volume histograms were studied next to mean and median breast dose, Gini index, and the new dose metric mean absolute difference of dose, using categorical and linear excess odds ratio (EOR) models. Interactions between dose-volume parameters and mean dose were also examined. **Results:** Statistically significant linear dose-response relationships were observed for mean breast dose (EOR per Gy = 0.19, 95% confidence interval [CI] = 0.05 to 1.06) and median dose (EOR/Gy = 0.06, 95% CI = 0.02 to 0.19), with no statistically significant curvature. All metrics except Gini and mean absolute difference were positively correlated with each other. These metrics all showed similar patterns of dose-response that were no longer statistically significant when adjusting for mean dose. No statistically significant modification of the effect of mean dose was observed. **Conclusion:** Mean breast dose predicts subsequent BC risk in long-term HL survivors.

ARTICLE

Strong evidence exists for a causal relationship between chest radiotherapy (RT) and subsequent breast cancer (BC) among female cancer survivors, including Hodgkin lymphoma (HL) (1,2). Cohort studies among long-term cancer survivors show increasing risk of RT-related BC with younger age at RT, RT fields covering larger breast volumes, and higher prescribed radiation doses (1-6). Several case-control studies (7-11) demonstrated a linear increase of relative risk (RR) for BC with radiation dose to the affected site in the breast.

Cohort studies on BC risk after chest RT are typically too large to capture heterogeneity of radiation dose distributions in the breast, especially the steep gradients typically seen near shielding blocks (1,4). Case-control studies have used dose to the breast tumor location (and equivalent location in matched control patients). However, the estimated RR of BC cannot be used for prediction of absolute risk anywhere in the breasts (ie, breast cancer risk experienced by the patient). Yet, this risk is required to inform clinical practice, particularly to assess risks and benefits of novel RT techniques for new patients, including proton therapy (12,13), and to implement surveillance guidelines among cancer survivors treated with chest RT (14,15).

Despite the need to understand the role of radiation dose-volume parameters in late effects risk, data are sparse. Specifically, estimated mean breast dose derived from doses to

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multiple locations in the breast has not been studied as a determinant of subsequent BC risk. Moreover, no standard approach exists in the literature for evaluating radiation dose-volume data and BC risk (16-21), whereas standard treatment planning systems provide 3-dimensional (3D) dose distributions for organs contoured on the planning computed tomography examination.

Therefore, we examined how the distribution of dose across the breasts of female HL survivors, summarized by mean delivered breast dose and dose-volume parameters, determines BC risk. As radiation-associated BC has a long induction period, we used the Dutch multicenter HL cohort (ie, women treated for HL during 1965-2000 who were followed for several decades) (2).

Methods

Study Population

We used data from our previous case-control study (10) nested within a cohort of Dutch female 5-year survivors of HL treated in 1965-2000 (2). Case patients, ie, patients with pathologically confirmed invasive primary BC or ductal carcinoma in situ without another cancer before HL except those treated with surgery only, were identified by medical records, general practitioner questionnaires, and the Netherlands Cancer Registry. Control patients were individually matched to case patients on hospital of HL treatment, age at treatment (range 11-41 years, within 3 years), and date of treatment (within 5 years). The original study included 174 case patients and 466 control patients, previously analyzed for BC risk according to radiation dose to the breast tumor location among case patients and corresponding locations among matched control patients (10). We excluded 1 case patient and 2 control patients because of treatments for which accurate reconstruction of doses to all locations in the breast was not possible. The analysis dataset consisted of 173 case patients and 464 matched control patients. The study was approved by the institutional review board of the Netherlands Cancer Institute.

Radiation Exposure

Each patient's treatment was assigned to 1 of 43 commonly occurring radiation field setups (Supplementary Figure 1, available online) or a combination. Field setups were applied to a 3D computed tomography phantom scan of the breasts of an HL patient aged 21 years and of average build. Breast tissue was mapped to a grid of approximately 300 000, 2 x 2 x 2 mm^3 voxels. The proportion of prescribed dose to each voxel was estimated for each field setup (22) using the Isogray treatment planning system (Dosisoft, Cachan, France). Individual distributions of absorbed dose were estimated by multiplying the field setup dosimetry with the patient's prescribed dose(s) and summing over all fields the patient received.

Using voxel-specific dose estimates, we calculated mean absorbed dose and dose-volume histograms (DVHs) for both breasts combined. The following metrics were derived from the DVH: D20, D50, D80 (Dx = minimum dose received by x% of breast volume with the highest dose; D50 = median dose), V5, V20, V30, and V35 (Vy = % of breast volume receiving at least y Gy) (23).

In addition, the Gini index (24), a relative measure of dose distribution heterogeneity, was determined for each patient as $G = \sum_i \sum_j |d_i - d_j| / 2n^2 D_{mean}$, where $d_1, \ldots, d_n$ are the patient's voxel doses and D_{mean} is the average of all voxel doses. It equals 0 for perfectly homogeneous distributions across both breasts and approaches 1 for distributions with all dose concentrated in a single voxel. The Gini index for an unexposed patient was defined as 0.

Finally, as a measure of absolute dose heterogeneity, we evaluated the mean absolute difference (MAD) between all pairs of voxels as $MAD = \sum_i \sum_j |d_i - d_j| / n^2$, which equals the Gini index multiplied by twice the mean dose. Quantiles of all metrics were obtained based on their distribution among second primary BC case patients.

Post-RT Intact Ovarian Function

Studies have shown that treatments inducing premature menopause in most women (eg, ovarian radiation exposure or chemotherapy with high-dose alkylating agents) strongly reduce radiation-associated BC risk (7-11). Therefore, we included the duration of post–RT intact ovarian function, defined as the number of premenopausal years between RT (or menarche, whichever came last) and the cutoff date, in our modeling (10). The cutoff date was the date of BC (case patients) or the date obtained by adding the duration between HL and BC for the matched case patient to the control patient's HL diagnosis date (control patients).

Statistical Analysis

Distributions of covariates were compared between case patients and control patients and tested using χ^2 tests. We calculated odds ratios (ORs) of BC for categories of mean and median dose, DVH metrics, the Gini index, and MAD, adjusted for duration of post-RT intact ovarian function, with and without adjustment for mean dose, using conditional logistic regression. We used quartiles of mean and median dose and tertiles of other metrics for parsimonious interaction modeling. To model the effect of continuous metrics D, eg, $D = D_{mean}$ or $D = V20$, we used the linear excess odds ratio (EOR) model

$$OR = \exp(\alpha\ T)(1 + \beta\ D), \qquad \text{(M1)}$$

with β the linear EOR per unit of D and T the duration of post-RT intact ovarian function with log-odds ratio α. The likelihood ratio test for β was interpreted as a test of trend. Extending the EOR model (M1), we evaluated curvature of the dose-response relationship for mean or median dose D, that is, $OR = \exp(\alpha\ T)(1 + \beta\ D\ \exp(\gamma\ D))$, with exponential curvature term γ. We found no evidence against linearity and used linear models subsequently. Models were repeated including adjustment for mean dose D_{mean}, $OR = \exp(\alpha\ T)(1 + \beta\ D + \theta\ D_{mean})$. Smaller deviance indicated better goodness of fit of models.

We also estimated effects of mean dose within tertiles of other metrics using the model $OR = \exp(\alpha\ T)[1 + (\beta_1 D_1 + \beta_2 D_2 + \beta_3 D_3)\ D_{mean}]$, where D_i is equal to 1 if D is in tertile i and 0 otherwise, with β_i the linear EOR/Gy mean dose for tertile i, respectively. Trend of the EOR/Gy mean dose across tertiles of other metrics was evaluated based on a likelihood ratio test of δ in the model $OR = \exp(\alpha\ T)[1 + \beta\ D_{mean}\ \exp(\delta\ D)]$ with continuous metric D. We similarly assessed effect modification by duration of intact ovarian function.

Cumulative incidence of breast cancer was estimated by mean breast dose and duration of intact ovarian function based on model (M1).

Analyses were done using Epicure version 2.00.02 (25), and R version 4.1.1 (26). Tests were 2-sided, and P values less than .05 were considered statistically significant.

Results

Most patients were diagnosed with HL in 1970-1989 at ages 11-24 years (Table 1). Most patients received RT, particularly supradiaphragmatic RT with average prescribed doses exceeding 30 Gy (Supplementary Figure 2, available online). Case patients were diagnosed with BC in 1981-2014, the majority of whom at ages 40-49 years, typically 10-29 years after HL treatment (median 22 years, range 6-42 years), and roughly half were screen-detected (2). Case patients and control patients differed statistically significantly by HL treatment and radiation fields. Chemotherapy and pelvic RT were more common among control patients. Case patients had a statistically significantly longer duration of post-RT intact ovarian function with higher menopausal age than control patients (10).

Average mean breast dose was 22.1 Gy for case patients and 18.4 Gy for control patients. Median dose and all DVH metrics, except the Gini index, were higher for case patients vs control patients (Supplementary Table 1, available online). Proportions of breast volume receiving at least 20 Gy (V20) and 30 Gy (V30) were usually 25%-75%, and the proportion of breast volume receiving 35 Gy (V35) or more was less than 50% (Supplementary Figure 3, available online). Minimum dose received by the 20% of breast volume with highest dose (D20) was around 40 Gy. Median dose (D50) ranged from 0 to 40 Gy, and minimum dose received by the 80% of breast volume with highest dose (D80) was generally less than 10 Gy. MAD was less than 20 Gy, and the Gini index was 0.25-0.60 for most patients.

Pairwise correlations between dose metrics generally exceeded 0.8, except for MAD, with correlations generally from 0.4 to 0.8 (Supplementary Figure 4, available online). The Gini index was moderately negatively correlated with all metrics.

Subsequent BC risk was statistically significantly associated with mean and median dose (D50), adjusting for years of intact ovarian function (Figure 1 and Table 2). Odd ratios reached 3.23 for mean doses of more than 28.6 Gy (95% confidence interval [CI] = 1.81 to 5.76) relative to doses no more than 18.8 Gy and 2.57 for median doses of more than 37.2 Gy (95% CI = 1.26 to 5.23) relative to doses no more than 11.8 Gy, with statistically significant trends (both $P < .001$). The EOR/Gy for mean dose was 0.19 (95% CI = 0.05 to 1.06) and 0.06 (95% CI = 0.02 to 0.19) for median dose. Data were consistent with a linear dose-response relationship for both metrics, with some downward curvature for median dose ($P = .06$). BC risk increased statistically significantly by approximately 5% per year of intact ovarian function (not shown), as previously observed for these patients (10).

Statistically significant, positive associations with BC risk were observed for other DVH metrics and MAD (Table 3). The highest EOR was observed for D80, the minimum dose received by the 80% of breast volume with highest dose (EOR = 0.41, 95% CI = 0.13 to 1.43). EORs for the Vy metrics were similar to each other (eg, 0.06, 95% CI = 0.01 to 0.23) for V20, the percentage of breast volume receiving at least 20 Gy. The EORs for the MAD and the Gini index were 0.37 per Gy (95% CI = 0.06 to 4.93) and -0.08 (95% CI = -0.10 to 0.01) per 0.1 units, respectively. Although not nested, models for V35 (deviance = 395.9) and D80 (deviance = 396.5) fit better than the Gini index (deviance = 412.2) and MAD (deviance = 403.2). When adjusted for mean breast dose, however, none of the reported dose metrics were statistically significantly associated with BC risk.

The EOR/Gy for mean dose was not statistically significantly modified by any dose metric (Table 4). The EOR/Gy was generally highest in the middle dose metric tertile except for D20 and MAD, which showed increasing EOR/Gy, and Gini index, which showed decreasing EOR/Gy. No statistically significant trends were observed. The EOR/Gy for mean dose was also not statistically significantly modified by duration of intact ovarian function, although a short duration of ovarian function reduced EORs (Table 2).

Cumulative incidence of breast cancer by age 50 years for a patient treated at age 20 years was, for example, 24% for 40 Gy mean breast dose and 15 years post-RT intact ovarian function vs 3% for 5 Gy and no post-RT ovarian function (Figure 2).

Discussion

This is the first study to evaluate the effects of mean and median breast radiation dose and dose-volume parameters on BC risk among HL survivors. We observed a statistically significant dose-response relationship for mean and median breast dose, which can be used to predict BC risk. Dose-volume metrics were not associated with BC risk after adjusting for mean dose and did not modify the effect of mean dose on BC risk.

We aimed to understand whether risk of cancer induction depends only on mean organ dose or also on the dose distribution within the organ, particularly the spatial distribution in the highest dose region. This phenomenon has been observed for non-neoplastic side effects of RT (eg, structural damage to the spinal cord or the salivary glands) (27,28). Another motivation is the evolution of RT technology from a simple field-based setup to target volume-based techniques. Using multiple intensity-modulated RT treatment fields or rotation methods (volumetric modulated arc therapy), the highest (prescribed) dose concentration is delivered selectively to the target tissue, sparing surrounding tissues from high doses. However, larger volumes of normal tissue are exposed to a low-dose "bath" compared with older field-based setups. Moreover, proton therapy, a treatment option for many cancer types including HL (29,30), is expected to reduce normal tissue damage and subsequent tumor risk by sparing of tissues distal to the target volume (31). Unfortunately, empirical data on long-term follow-up of patients treated with contemporary RT techniques will not be available for several decades. To bridge this divide and inform guidelines on how to treat current patients (17), we obtained retrospective dose distribution data suited to calculate dose-volume metrics and evaluated their impact on risk.

Current HL treatment encompasses modern chemotherapy and RT to smaller volumes and with substantially lower doses than treatments studied here (32). Patients with such exposures and decades of follow-up for second cancers do not exist—today's patients and doctors have to extrapolate results obtained from patients treated in the past. The use of empirical data on late effects of cancer treatment to assess risks associated with modern treatment is an active research field. Understanding dose-volume-response relationships, as illustrated in this report, may offer new insights.

Although case patients and control patients differed by HL radiation field and chemotherapy, no adjustment for those variables was performed because they are represented by dose-volume parameters and duration of intact ovarian function in

Table 1. Characteristics of the study population of female 5-year survivors of HL diagnosed during 1963-1998 in the Netherlands[a]

Characteristic	Subsequent breast cancer case patients (n = 173) No. (%)	Matched control patients (n = 464) No. (%)	$P_{heterogeneity}$[b]	P_{trend}[c]
Age at HL, y			.89	.59
11-19	51 (29.5)	128 (27.6)		
20-24	49 (28.3)	135 (29.1)		
25-29	39 (22.5)	96 (20.7)		
30-34	21 (12.1)	70 (15.1)		
35-41	13 (7.5)	35 (7.5)		
Year of HL diagnosis			.67	.48
1963-1969	25 (14.5)	51 (11.0)		
1970-1979	60 (34.7)	165 (35.6)		
1980-1989	64 (37.0)	185 (39.9)		
1990-1998	24 (13.9)	63 (13.6)		
HL treatment			.001	—
CT only	1 (0.6)	24 (5.2)		
RT only	88 (50.9)	173 (37.3)		
RT plus CT	84 (48.6)	267 (57.5)		
Radiation fields[d]			.001[e]	—
No RT	1 (0.6)	24 (5.2)		
Supra with or without infra, no pelvic	167 (96.5)	389 (83.8)		
Supra with or without infra, pelvic	5 (2.9)	40 (8.6)		
Infra, no pelvic	0 (0)	7 (1.5)		
Infra, pelvic	0 (0)	4 (0.9)		
Duration of post-RT intact ovarian function, y			<.001	<.001
<1	5 (2.9)	39 (8.4)		
1-9	24 (13.9)	98 (21.1)		
10-19	76 (43.9)	216 (46.6)		
20-33	68 (39.3)	111 (23.9)		
Family history of BC[f]			.02	—
No	103 (59.5)	293 (63.1)		
Yes	52 (30.1)	90 (19.4)		
Missing	18 (10.4)	81 (17.5)		
BMI[g], kg/m^2			.94	.62
17-20	16 (9.2)	37 (8.0)		
20-24	71 (41.0)	171 (36.9)		
25-30	33 (19.1)	80 (17.2)		
30-43	7 (4.0)	22 (4.7)		
Missing	46 (26.6)	154 (33.2)		
Menopausal status[g]			<.001	—
Pre- or perimenopausal	100 (57.8)	234 (50.4)		
Menopausal at age 50 years or older	19 (11.0)	25 (5.4)		
Menopausal at age 40-49 years	32 (18.5)	78 (16.8)		
Menopausal at age 30-39 years	18 (10.4)	80 (17.2)		
Menopausal at younger age than 30 years	4 (2.3)	47 (10.1)		
Year of BC diagnosis				
1981-1989	10 (5.8)	—		
1990-1999	52 (30.1)	—		
2000-2009	93 (53.8)	—		
2010-2014	18 (10.4)	—		
Years between HL and BC diagnoses				
6-9	6 (3.5)	—		
10-19	71 (41.0)	—		
20-29	75 (43.4)	—		
30-42	21 (12.1)	—		
Median	22	—		
Age at breast cancer, y				
27-29	4 (2.3)	—		
30-39	40 (23.1)	—		
40-49	75 (43.4)	—		

(continued)

Table 1. (continued)

Characteristic	Subsequent breast cancer case patients (n = 173) No. (%)	Matched control patients (n = 464) No. (%)	$P_{heterogeneity}$[b]	P_{trend}[c]
50-59	41 (23.7)	—		
60-74	13 (7.5)	—		
Breast cancer laterality				
Left	85 (49.1)	—		
Right	78 (45.1)	—		
Bilateral[h]	10 (5.8)	—		

[a]Missing categories were removed before testing. BC = breast cancer; BMI = body mass index; CT = chemotherapy; HL = Hodgkin lymphoma; RT = radiotherapy.
[b]P-value of χ^2 test.
[c]P-value of χ^2 test for trend.
[d]Pelvic RT is defined as irradiation to the whole abdomen or iliacal nodes on both sides or irradiation to an inverted Y field for women without oophoropexy. RT field was imputed for 1 control patient based on year and hospital of HL treatment.
[e]Simulated P-values were obtained for variables with at least 1 category with an expected count smaller than 5.
[f]Family history included first-degree family history and grandmothers.
[g]At cutoff date, which is the date of BC diagnosis for case patients and the date obtained by adding the time duration between HL and BC of the matched case patient to the HL diagnosis date for control patients.
[h]Within 3 months.

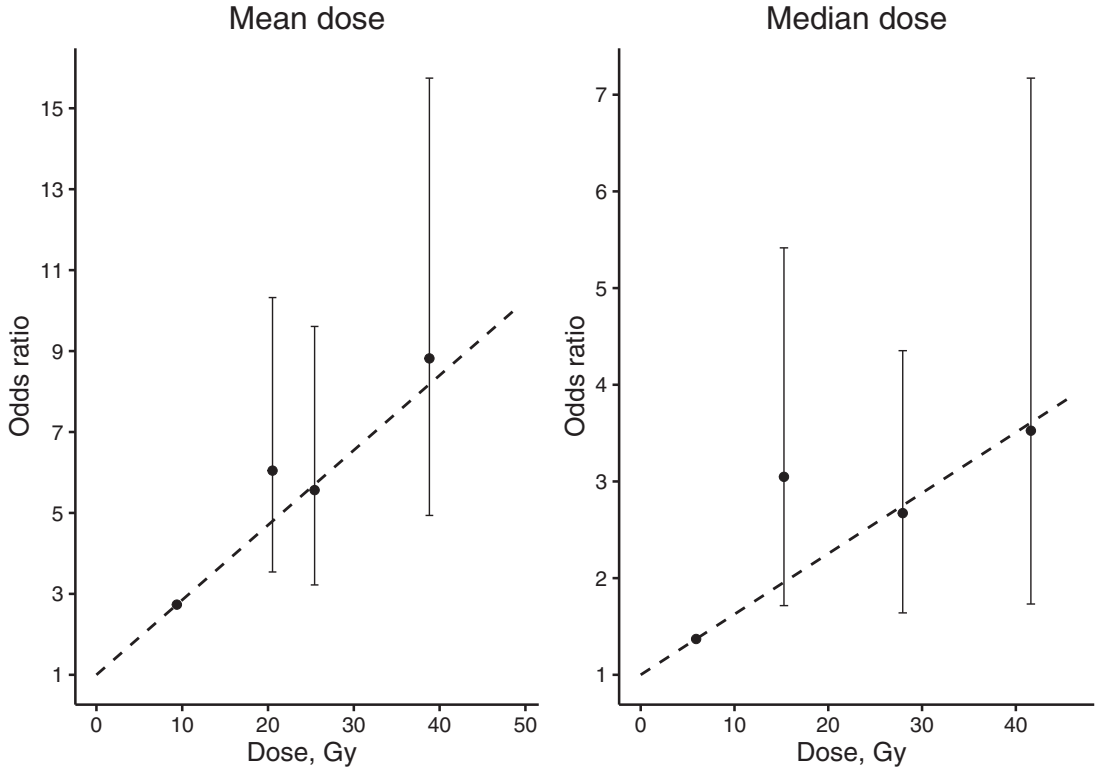

Figure 1. Dose-response for mean and median breast dose. Categorical odds ratios are given for quartiles of dose, displayed at category midpoints. The categorical risks from Table 2 were multiplied with the relative risk in the midpoint of the referent category based on the dose-response for continuous dose such that they represent risks relative to 0 Gy, to allow for comparisons between continuous and categorical results. The **dashed lines** display the dose-response relationships for continuous dose. All analyses were adjusted for duration of post-radiotherapy intact ovarian function.

our analysis. Adjusted dose-related risks were slightly decreased but generally similar.

Mean and median breast dose are used as alternatives to summarize patient exposure. The EOR/Gy was substantially smaller for median than for mean dose. Although strongly correlated, median dose was generally lower than mean dose for patients with mean doses below 24 Gy and higher for larger mean doses (not shown). Given the linear dose-response for mean dose, an attenuated EOR/Gy for median dose is expected. We prefer mean dose because mean but not median dose is sensitive to local changes of dose, and radiation carcinogenesis is predominantly a local phenomenon (eg, a woman with 10 and 30 Gy to 2 halves of her breast volume has a median and mean dose of 20 Gy; if dose to a part of the higher dose half increases, mean dose and cancer risk change, but not median dose).

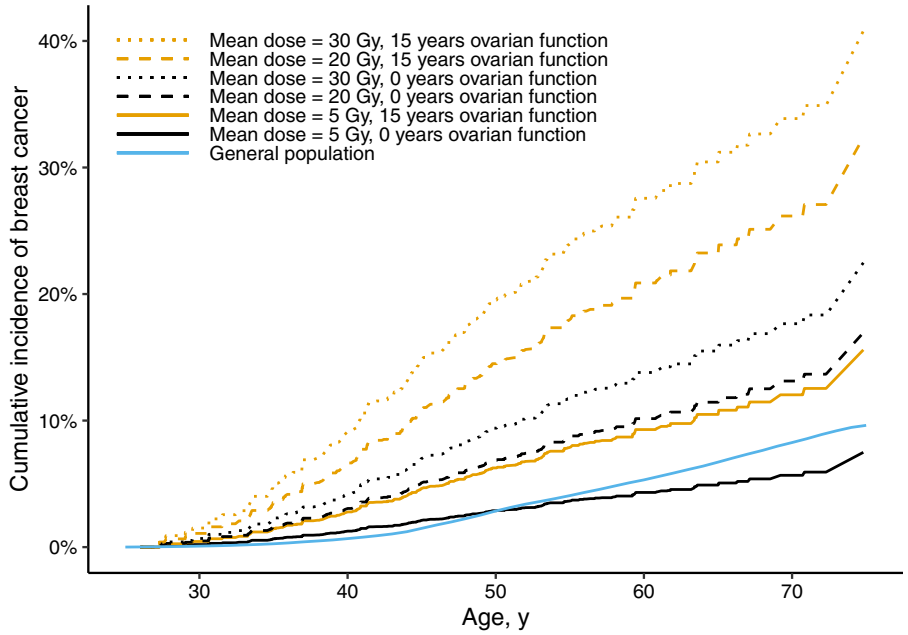

Figure 2. Cumulative incidence of breast cancer for a 5-year survivor of Hodgkin lymphoma treated at age 20 years, according to mean breast dose and duration of intact ovarian function. Case-control data were combined with information from the Hodgkin lymphoma survivors cohort (37), and cumulative incidence estimates were based on model (M1). Death and other cancers (except those treated with surgery only) were treated as competing events.

Table 2. Risk of second primary breast cancer among Hodgkin lymphoma survivors by mean and median dose to the breasts

Dose metric	Subsequent breast cancer case patients No. (%)	Matched control patients No. (%)	OR[a] (95% CI)	EOR/Gy (95% CI)	P_{trend}[b]
Mean dose, Gy					
0-18.8	44 (25.4)	208 (44.8)	1 (Referent)		
18.8-22.3	44 (25.4)	88 (19.0)	2.21 (1.30 to 3.78)		
22.3-28.6	39 (22.5)	91 (19.6)	2.04 (1.18 to 3.51)		
28.6-49.1	46 (26.6)	77 (16.6)	3.23 (1.81 to 5.76)		
Overall[c]				0.19 (0.05 to 1.06)	<.001
By years of intact ovarian function					
0-16	—	—	—	0.17 (0.04 to 1.22)	
16-21	—	—	—	0.39 (0.07 to 3.30)	
21-33	—	—	—	0.59 (0.09 to 5.64)	.56
Median dose, Gy					
0-11.8	51 (29.5)	215 (46.3)	1 (Referent)		
11.8-18.7	36 (20.8)	68 (14.7)	2.22 (1.25 to 3.95)		
18.7-37.2	64 (37.0)	141 (30.4)	1.95 (1.20 to 3.18)		
37.2-46.1	22 (12.7)	40 (8.6)	2.57 (1.26 to 5.23)		
Overall[c]				0.06 (0.02 to 0.19)	<.001
By years of intact ovarian function					
0-16	—	—	—	0.05 (0.01 to 0.18)	
16-21	—	—	—	0.08 (0.02 to 0.35)	
21-33	—	—	—	0.09 (0.00 to 0.63)	.18

[a]Adjusted for years of intact ovarian function. CI = confidence interval; EOR = excess odds ratio; OR = odds ratio.
[b]For overall dose-response, likelihood ratio test of parameter β in linear EOR model $OR = \exp(\alpha\ T)(1 + \beta\ D)$; for dose-response by categories of years of intact ovarian function, likelihood ratio test of parameter γ in the model $OR = \exp(\alpha\ T)(1 + \beta\ D \exp(\gamma\ T))$.
[c]Based on linear EOR model, tests of curvature parameter γ in the curvature model $OR = \exp(\alpha\ T)(1 + \beta\ D \exp(\gamma\ D))$ yielded $P = .74$ for mean dose and $P = .06$ for median dose.

Our analytical approach can directly compare BC risk between exposure via a homogeneous distribution of relatively low doses (a little to a lot) and high doses concentrated in a small part of the breasts (a lot to a little), keeping mean dose fixed. A previous study among lung cancer patients has used RT technique as a surrogate for dose distribution (rapid arc vs 4-field intensity-modulated RT, respectively), but no differences in clinical outcome or short-term side effects were observed (33). Schneider et al. (20) addressed effects of irradiated volume to compare treatment plans with respect to their associated risk of radiation-

Table 3. Breast cancer risk among Hodgkin lymphoma survivors by dose metrics

Dose metric	OR (95% CI) Tertile of dose metric 1st	2nd	3rd	EOR/unit[a] (95% CI)	P_{trend}[b]	Deviance[c]
Not accounting for mean dose						
Mean dose	1 (Referent)	2.11 (1.29 to 3.43)	2.15 (1.31 to 3.52)	0.19 (0.05 to 1.06)	<.001	398.26
D20	1 (Referent)	2.03 (1.31 to 3.15)	2.49 (1.26 to 4.95)	0.08 (0.02 to 0.27)	<.001	401.35
D50[d]	1 (Referent)	2.28 (1.38 to 3.76)	2.04 (1.25 to 3.33)	0.06 (0.02 to 0.19)	<.001	402.50
D80	1 (Referent)	2.34 (1.42 to 3.83)	2.05 (1.24 to 3.37)	0.41 (0.13 to 1.43)	<.001	396.51
V5	1 (Referent)	2.13 (1.31 to 3.46)	2.16 (1.30 to 3.60)	0.05 (0.01 to 0.30)	<.001	399.20
V20	1 (Referent)	2.27 (1.39 to 3.73)	2.06 (1.25 to 3.39)	0.06 (0.01 to 0.23)	<.001	400.69
V30	1 (Referent)	2.08 (1.30 to 3.33)	2.14 (1.31 to 3.50)	0.06 (0.02 to 0.21)	<.001	398.15
V35	1 (Referent)	2.41 (1.48 to 3.92)	2.16 (1.33 to 3.52)	0.07 (0.02 to 0.22)	<.001	395.94
Gini index	1 (Referent)	0.79 (0.48 to 1.28)	0.53 (0.30 to 0.91)	−0.08 (−0.10 to 0.01)[e]	.06	412.24
MAD	1 (Referent)	1.44 (0.92 to 2.26)	1.97 (1.20 to 3.24)	0.37 (0.06 to 4.93)	<.001	403.17
Accounting for mean dose[f]						
D20	1 (Referent)	1.38 (0.84 to 2.27)	1.52 (0.72 to 3.18)	−0.01 (−0.30 to 0.17)	.85	398.23
D50[d]	1 (Referent)	1.45 (0.83 to 2.55)	1.09 (0.61 to 1.95)	−0.01 (−0.54 to 0.18)	.91	398.25
D80	1 (Referent)	1.48 (0.84 to 2.60)	1.10 (0.60 to 2.00)	0.37 (−0.23 to 1.42)	.17	396.38
V5	1 (Referent)	1.31 (0.75 to 2.31)	1.10 (0.59 to 2.05)	−0.008 (NA to 0.22)	.90	398.24
V20	1 (Referent)	1.44 (0.83 to 2.51)	1.09 (0.60 to 1.97)	−0.33 (NA to 0.02)	.07	394.89
V30	1 (Referent)	1.35 (0.79 to 2.30)	1.15 (0.64 to 2.07)	0.04 (NA to 0.21)	.66	398.07
V35	1 (Referent)	1.68 (0.98 to 2.88)	1.23 (0.69 to 2.21)	0.08 (−0.04 to 0.22)	.12	395.83
Gini index	1 (Referent)	0.79 (0.48 to 1.31)	0.83 (0.47 to 1.49)	0.17 (−0.09 to 5.94)[e]	.42	397.60
MAD	1 (Referent)	0.99 (0.60 to 1.61)	1.44 (0.84 to 2.46)	−0.01 (−0.28 to 1.08)	.94	398.25

[a]Parameter β in linear EOR model $OR = \exp(\alpha\ T)(1 + \beta\ D)$. CI = confidence interval; Dy = minimum dose received by the y% of breast volume with highest dose; EOR = excess odds ratio; MAD = mean absolute difference; NA = not available; Vx = % of breast volume receiving ≥ x Gy.
[b]Likelihood ratio test of parameter β in linear EOR model.
[c]Deviance for linear EOR model.
[d]D50 is the same as median dose.
[e]EOR per 0.1 increase in Gini.
[f]Adjusted for mean dose using a linear EOR model [ie, $OR = \exp(\alpha\ T)(1 + \beta\ D + \theta\ D_{mean})$].

Table 4. Modification of the effect of mean dose on breast cancer risk by tertiles of dose metrics

Dose metric	EOR/Gy[a] mean dose Tertile of dose metric 1st	2nd	3rd	P_{trend}[b]
D20	0.11 (0.01 to 0.67)	0.16 (0.04 to 0.82)	0.18 (0.04 to 0.94)	.49
D50[c]	0.20 (0.02 to 1.74)	0.21 (0.05 to 1.44)	0.18 (0.04 to 1.27)	.98
D80	0.13 (0.01 to 0.87)	0.21 (0.05 to 1.14)	0.15 (0.03 to 0.80)	.31
V5	0.14 (0.01 to 0.96)	0.19 (0.05 to 1.10)	0.15 (0.04 to 0.87)	.65
V20	0.13 (0.01 to 0.90)	0.21 (0.05 to 1.16)	0.15 (0.03 to 0.83)	.92
V30	0.13 (0.01 to 0.89)	0.19 (0.05 to 1.07)	0.16 (0.04 to 0.85)	.73
V35	0.11 (0.01 to 0.71)	0.21 (0.06 to 1.09)	0.14 (0.03 to 0.74)	.48
Gini index	0.20 (0.05 to 1.12)	0.14 (0.03 to 0.87)	0.14 (0.01 to 1.01)	.95
MAD	0.16 (0.03 to 1.00)	0.16 (0.04 to 0.88)	0.25 (0.07 to 1.35)	.69

[a]Adjusted for years of intact ovarian function. EOR = excess odds ratio; Dy = minimum dose received by the y% of breast volume with highest dose; MAD = mean absolute difference; Vx = % of breast volume receiving ≥ x Gy.
[b]P-value for trend in EOR/Gy across dose metric tertiles, based on likelihood ratio test of interaction between dose-volume histogram metric and mean dose.
[c]D50 is the same as median dose.

induced cancer at any site. To our knowledge, only 1 larger epidemiologic study (34) has evaluated the role of DVH metrics on subsequent esophageal cancer risk. No clear association was observed, and DVH metrics did not modify the effects of mean and median dose, consistent with our findings for BC. Our analytical approach, applied to patients treated with a larger variety of dose distributions, may further elucidate dose-volume effects.

Although DVH metrics are established in RT, the Gini index, applied for the first time in this context, is commonly used to summarize the concentration of financial resources in the world (24). The new dosimetric index MAD is a derived measure. Although no clear patterns were observed, these metrics quantify the spatial dose concentration in the organ. Future late effects studies in varying exposure scenarios may show the utility of these novel metrics for epidemiologic studies and risk projection.

In this report, we did not use the dose to subsequent BC location, although this was done in previous studies including our

own (8,10,11). In our previous analysis of the same data (10), the EOR/Gy (adjusted for duration of post-RT intact ovarian function) was 0.06 (95% CI = 0.02 to 0.15) based on tumor location dose compared with 0.19 (95% CI = 0.05 to 1.06) for mean breast dose in this study. Similarly, Travis et al. (8) found an EOR/Gy of 0.05 (95% CI = 0.004 to 0.34) for HL survivors who received alkylating agents or ovarian radiation doses of at least 5 Gy and an EOR/Gy of 0.15 (95% CI = 0.04 to 0.73) for women who did not. Among childhood cancer survivors, a larger overall EOR/Gy of 0.39 (95% CI = 0.25 to 0.65) was found, with a statistically significant modification by ovarian RT dose (11). In the same population, Schonfeld et al. (35) compared BC risks for tumor location dose and 2 crude dose metrics based on maximum prescribed dose to the chest, with or without correction for blocking using field-specific assumptions. Risks were statistically significantly elevated for all 3 metrics, although the absolute values differed by twofold. Despite general consistency, it is unclear whether and to what extent risks estimated with tumor location dose and mean breast dose differ.

Our study is the first evaluation of dose and DVH metrics as determinants of BC among HL survivors. Several limitations might have contributed to the failure of DVH metrics to substantially improve the models, including uncertainty in reconstruction of historic 3D dose distributions, although systematic errors are unlikely (22). Some field types were very common, and many were variations of similar (mantle) fields (Supplementary Figures 1 and 2, available online), that is, most dose-volume metrics were highly correlated. Although our dosimetry was more individualized than most previous efforts, we may have missed subtle patterns because of dose uncertainty and lack of statistical power for interaction analyses. The proportion of screen-detected breast cancers increased during case patient ascertainment (2). However, it is unlikely that control patients (matched to case patients by center and calendar year) were screened differently. Finally, small-sample bias in the EORs was observed in a recent simulation study (36), although most bias was observed for sample sizes below 100 case patients and for EORs larger than observed in our study. Despite these limitations, we showed the utility and potential of DVH metrics.

In conclusion, we showed that BC risk increased linearly with increasing mean and median breast dose and demonstrated the utilization of radiation dose distributions for BC risk analysis. The value of dose distribution parameters remains to be established. Mean breast dose is an easily calculated metric that can be used to predict BC risk, either to optimize RT plans in new HL patients or to tailor BC screening in HL survivors.

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Moskowitz CS, Chou JF, Wolden SL, et al. Breast cancer after chest radiation therapy for childhood cancer. *J Clin Oncol*. 2014;32(21):2217-2223.
2. Schaapveld M, Aleman BMP, Van Eggermond AM, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. *N Engl J Med* . 2015; 373(26):2499-2511.
3. Guibout C, Adjadj E, Rubino C, et al. Malignant breast tumors after radiotherapy for a first cancer during childhood. *J Clin Oncol*. 2005;23(1):197-204.
4. De Bruin ML, Sparidans J, van't Veer MB, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. *J Clin Oncol*. 2009;27(26):4239-4246.
5. Ehrhardt MJ, Howell CR, Hale K, et al. Subsequent breast cancer in female childhood cancer survivors in the St Jude Lifetime Cohort Study (SJLIFE). *J Clin Oncol*. 2019;37(19):1647-1656.
6. Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. *Breast Cancer Res*. 2005;7(1):21-32.
7. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst*. 2003;95(13):971-980.
8. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA*. 2003; 290(4):465-475.
9. Inskip PD, Robison LL, Stovall M, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. *J Clin Oncol*. 2009;27(24):3901-3907.
10. Krul IM, Opstal-van Winden AWJ, Aleman BMP, et al. Breast cancer risk after radiation therapy for Hodgkin lymphoma: influence of gonadal hormone exposure. *Int J Radiat Oncol Biol Phys*. 2017;99(4):843-853.
11. Veiga LH, Curtis RE, Morton LM, et al. Association of breast cancer risk after childhood cancer with radiation dose to the breast and anthracycline use: a report from the childhood cancer survivor study. *JAMA Pediatr*. 2019;173(12):1171-1179.
12. Ntentas G, Dedeckova K, Andrlik M, et al. Clinical intensity modulated proton therapy for Hodgkin lymphoma: which patients benefit the most? *Pract Radiat Oncol*. 2019;9(3):179-187.
13. Holmes JA, Chera BS, Brenner DJ, et al. Estimating the excess lifetime risk of radiation induced secondary malignancy (SMN) in pediatric patients treated with craniospinal irradiation (CSI): conventional radiation therapy versus helical intensity modulated radiation therapy. *Pract Radiat Oncol*. 2017;7(1): 35-41.
14. Mulder RL, Hudson MM, Bhatia S, et al. Updated breast cancer surveillance recommendations for female survivors of childhood, adolescent, and young adult cancer from the International Guideline Harmonization Group. *J Clin Oncol*. 2020;38(35):4194-4207.
15. Dekker N, van 't Veer MB, Aleman BM, et al. BETER na hodgkinlymfoom; nazorg op maat voor langetermijneffecten van de behandeling [The BETER survivorship care initiative for Hodgkin lymphoma; tailored survivorship care for late effects of treatment]. *Ned Tijdschr Geneeskd*. 2015;159:A9269.
16. de Vathaire F, El-Fayech C, Ben Ayed FF, et al. Radiation dose to the pancreas and risk of diabetes mellitus in childhood cancer survivors: a retrospective cohort study. *Lancet Oncol*. 2012;13(10):1002-1010.
17. Ronckers CM. SP-0024: Questions in radiotherapy and answers from late effects population studies: proposed approaches to bridge the gap. *Radiother Oncol*. 2013;106:S8-S9.
18. Venkatramani R, Kamath S, Wong K, et al. Correlation of clinical and dosimetric factors with adverse pulmonary outcomes in children after lung irradiation. *Int J Radiat Oncol Biol Phys*. 2013;86(5):942-948.
19. De A, Kamath S, Wong K, et al. Correlation of pulmonary function abnormalities with dose volume histograms in children treated with lung irradiation. *Pediatr Pulmonol*. 2015;50(6):596-603.
20. Schneider U, Zwahlen D, Ross D, et al. Estimation of radiation-induced cancer from three-dimensional dose distributions: concept of organ equivalent dose. *Int J Radiat Oncol Biol Phys*. 2005;61(5):1510-1515.

21. Jackson A, Marks LB, Bentzen SM, et al. The lessons of QUANTEC: recommendations for reporting and gathering data on dose-volume dependencies of treatment outcome. *Int J Radiat Oncol Biol Phys*. 2010;76(3 suppl): S155-60.
22. Russell NS, Krul IM, van Eggermond AM, et al. Retrospective methods to estimate radiation dose at the site of breast cancer development after Hodgkin lymphoma radiotherapy. *Clin Transl Radiat Oncol*. 2017;7: 20-27.
23. Mallick S, Rath GK, Benson R. *Practical Radiation Oncology* 1st ed. Singapore: Springer; 2020.
24. Lambert P, *The Distribution and Redistribution of Income* 3rd ed. Manchester University Press; 2002.
25. Risk Sciences International. *Epicure* v2.00.02. Ottawa, Canada: Risk Sciences International; 2016.
26. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2021.
27. Konings AW, Cotteleer F, Faber H, et al. Volume effects and region-dependent radiosensitivity of the parotid gland. *Int J Radiat Oncol Biol Phys*. 2005;62(4):1090-1095.
28. Ma L, Wang L, Lee Y, et al. Correlation between small-volume spinal cord doses for spine stereotactic body radiotherapy (SBRT). *J Radiosurg SBRT*. 2018; 5(3):229-236.
29. Widder J, van der Schaaf A, Lambin P, et al. The quest for evidence for proton therapy: model-based approach and precision medicine. *Int J Radiat Oncol Biol Phys*. 2016;95(1):30-36.
30. Dabaja BS, Hoppe BS, Plastaras JP, et al. Proton therapy for adults with mediastinal lymphomas: the International Lymphoma Radiation Oncology Group guidelines. *Blood*. 2018;132(16):1635-1646.
31. Barker C, Lowe M, Radhakrishna G. An introduction to proton beam therapy. *Br J Hosp Med (Lond)*. 2019;80(10):574-578.
32. Specht L, Yahalom J, Illidge T, et al.; for the ILROG. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the International Lymphoma Radiation Oncology Group (ILROG). *Int J Radiat Oncol Biol Phys* . 2014;89(4):854-862.
33. Schröder C, Engenhart-Cabillic R, Vorwerk H, et al. A lot to a little or a little to a lot-which dose-volume relationship ensures the best clinical outcome in the high dose radiation therapy of thoracic tumors? A prospective approach. *J Thorac Dis*. 2016;8(8):2053-2060.
34. Journy N, Schonfeld SJ, Hauptmann M, et al. Dose-volume effects of breast cancer radiation therapy on the risk of second oesophageal cancer. *Radiother Oncol*. 2020;151:33-39.
35. Schonfeld SJ, Howell RM, Smith SA, et al. Comparison of radiation dose reconstruction methods to investigate late adverse effects of radiotherapy for childhood cancer: a report from the Childhood Cancer Survivor Study. *Radiat Res*. 2020;193(2):95-106.
36. Roberti S, van Leeuwen FE, Hauptmann M, et al. Bias correction for estimates from linear excess relative risk models in small case-control studies. *Stat Med*. 2021;40(26):5831-5852.
37. Langholz B, Borgan O. Estimation of absolute risk from nested case-control data. *Biometrics*. 1997;53(2):767-774.