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OXFORD

JNCI: Journal of the National Cancer Institute, 2023, **115(11),** 1318–1328

https://doi.org/10.1093/jnci/djad116
Advance Access Publication Date: June 27, 2023
Article

Contralateral breast cancer risk in patients with breast cancer and a germline-*BRCA1/2* pathogenic variant undergoing radiation

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Received: November 23, 2022. **Revised:** March 06, 2023. **Accepted:** May 27, 2023

Abstract

Background: Radiation-induced secondary breast cancer (BC) may be a concern after radiation therapy (RT) for primary breast cancer (PBC), especially in young patients with germline (g)*BRCA*–associated BC who already have high contralateral BC (CBC) risk and potentially increased genetic susceptibility to radiation. We sought to investigate whether adjuvant RT for PBC increases the risk of CBC in patients with g*BRCA1/2*-associated BC.

Methods: The g*BRCA1/2* pathogenic variant carriers diagnosed with PBC were selected from the prospective International *BRCA1/2* Carrier Cohort Study. We used multivariable Cox proportional hazards models to investigate the association between RT (yes vs no) and CBC risk. We further stratified for *BRCA* status and age at PBC diagnosis (<40 and >40 years). Statistical significance tests were 2-sided.

Results: Of 3602 eligible patients, 2297 (64%) received adjuvant RT. Median follow-up was 9.6 years. The RT group had more patients with stage III PBC than the non-RT group (15% vs 3%, $P < .001$), received chemotherapy more often (81% vs 70%, $P < .001$), and received endocrine therapy more often (50% vs 35%, $P < .001$). The RT group had an increased CBC risk compared with the non-RT group (adjusted hazard ratio [HR] = 1.44; 95% confidence interval [CI] = 1.12 to 1.86). Statistical significance was observed in g*BRCA2* (HR = 1.77; 95% CI = 1.13 to 2.77) but not in g*BRCA1* pathogenic variant carriers (HR = 1.29; 95% CI = 0.93 to 1.77; P = .39 for interaction). In the combined *gBRCA1/2* group, patients irradiated when they were younger than or older than 40 years of age at PBC diagnosis showed similar risks (HR = 1.38; 95% CI = 0.93 to 2.04 and HR = 1.56; 95% CI = 1.11 to 2.19, respectively).

Conclusions: RT regimens minimizing contralateral breast dose should be considered in g*BRCA1/2* pathogenic variant carriers.

Breast cancer (BC) is the most common type of cancer diagnosed in women worldwide, affecting about 1 in 7 women in industrialized countries at some point during their lifetime (1,2). Radiation therapy (RT) is an important part of treatment, especially in the context of breast-conserving therapy for invasive primary BC (PBC) and treatment of ductal carcinoma in situ. Meta-analyses of randomized clinical trials have demonstrated a clear survival benefit from RT in treating BC in the general population, after both radical mastectomy and breast-conserving surgery (3,4). The prognosis for patients with BC used to depend mostly on successful (local) treatment of the PBC. As treatments and consequently survival continue to improve, however, long-term effects of therapy are becoming more important. Some of the main long-term concerns of RT are the adverse effects on the heart and the risk of secondary cancer of the lung or contralateral breast (3).

RT uses ionizing radiation to achieve antitumor effects. Ionizing radiation induces varying types and degrees of DNA damage, but the double-strand DNA breaks (DSBs), especially when clustered with other types of damage, are the most consequential in both carcinogenesis and cell death (5). These DSBs are primarily repaired by homologous recombination, a process in which the BRCA1 and BRCA2 proteins play an essential role (6). When homologous recombination, which is typically error free (6,7), is impaired, error-prone methods of DNA repair are used, instead (8). This switch increases the likelihood of variations and ultimately the development of cancer (9-11). Breast RT can lead to incidental radiation dose exposure of the contralateral breast (because of the proximity of the breast RT field/treatment volume, a concept illustrated in Figure 1) (12). This exposure may be sufficient to increase the risk of contralateral BC (CBC) in patients with BC (13).

Several BC susceptibility genes have been identified that explain approximately 25% of the familial aggregation of BC (14,15). The most prominent of these are the genes encoding the aforementioned BRCA1 and BRCA2 proteins. In addition, women carrying a pathogenic germline (g) variant in the *BRCA1/2* genes are often younger at the time of diagnosis than women with non-hereditary BC, especially g*BRCA1* pathogenic variant carriers (16). Breast tissue of young premenopausal women has greater density and is more actively proliferating than that of older women. In addition, breast tissue is less differentiated in nulliparous women (17,18). These factors potentially increase vulnerability to DNA-damaging agents, providing additional reasons for why this particular group could be at greater risk of CBC after RT. Moreover, the already-high baseline CBC risk in g*BRCA1/2* pathogenic variant carriers further stresses the importance of identifying risk-increasing factors such as breast irradiation. Then, the risks and benefits can be weighted in clinical decision-making, and preventive measures (eg, intensive screening, prophylactic surgery, lifestyle intervention, RT techniques further minimizing mean heart or lung dose, and contralateral breast dose) can be taken.

Current evidence from observational studies is inconclusive, however, and large studies with sufficient follow-up are lacking (19). To obtain more robust evidence, we here use a large population from an international collaboration. The primary research question we aimed to answer was whether CBC risk in g*BRCA1/2* pathogenic variant carriers increases after RT compared with no RT. The goal was first to investigate whether an effect of RT on CBC risk in *gBRCA1/2* pathogenic variant carriers even exists. If an effect were to be found, future studies may investigate whether this effect is stronger for carriers than for noncarriers, which will not be evaluated here. We further investigated whether having a young age at PBC diagnosis was associated with an increased effect of RT on CBC risk. Because *BRCA1* and *BRCA2* pathogenic germline variants have distinct functional effects, we also evaluated the effects of RT separately within these groups (20-22).

Methods

Study population

For this study, we used data from the prospective International *BRCA1/2* Carrier Cohort Study (IBCCS). The IBCCS is described by Goldgar et al. (23). In summary, proven *gBRCA1* and g*BRCA2* pathogenic variant carriers from 13 European countries, Australia, and Canada were eligible for inclusion, either with a history of any cancer or unaffected at the time of recruitment. Other requirements were being at least 18 years of age and provision of informed consent for participation in a longitudinal study. Eligible participants either entered the cohort through a hereditary cancer clinic or through previous participation in a hereditary cancer study. Upon study entry, an IBCCS-standardized questionnaire was filled out and repeated during follow-up at

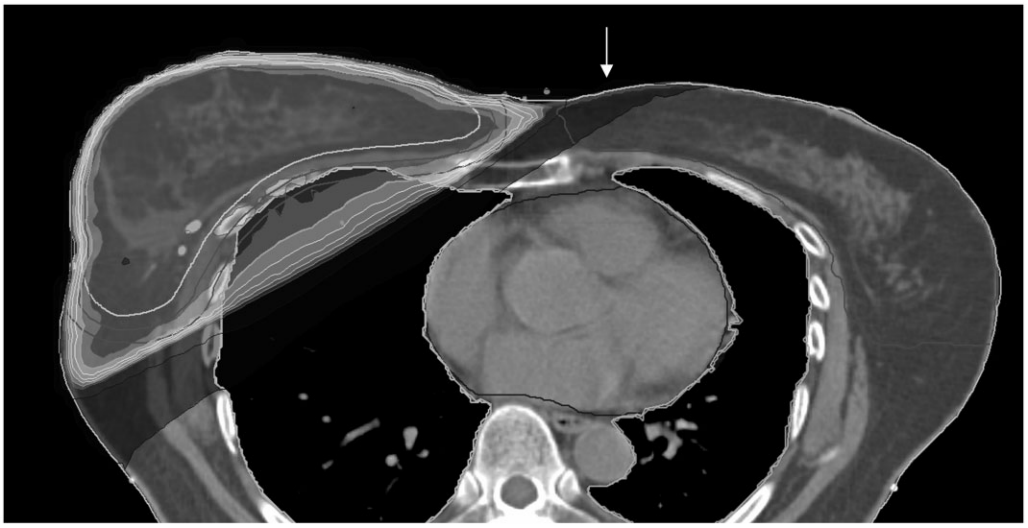


Figure 1. Example of 3D-CRT planning, showing 1% to 5% of the total prescribed dosage (darkest shaded area, **white arrow**) on the contralateral breast as a result of the breast anatomy or tumor localization (more likely if medial). 3D-CRT = 3-dimensional–conformal radiation therapy.

regular intervals, depending on country. Data on any cancer incidence, tumor characteristics, and treatments were collected through the respective national/regional cancer registries or pathology reports. To ensure sufficient power per individual study, we included only studies with at least 10 incident CBCs.

The IBCCS includes data from Hereditary Breast and Ovarian cancer research Netherlands (HEBON) (24). For this particular study, we had a more recently updated version (ie, more complete follow-up and larger sample size) of the data available from the HEBON database.

Medical Ethics Committee approval was obtained for all participating centers. Written informed consent was obtained from each individual participant, or, for deceased individuals, from a close relative or proxy.

We included patients with a proven deleterious *gBRCA1* or *gBRCA2* pathogenic variant. Further requirements for current study inclusion were a diagnosis of either in situ or invasive stage I through III PBC, diagnosed between 1990 and 2018, without diagnosis of another cancer before PBC diagnosis. Latest follow-up was available until 2019. The flow diagram in Figure 2 provides a complete overview of the inclusion and exclusion process.

Data collection

We retrieved dates of BC diagnosis, DNA test results, and birth and death as well as information about *gBRCA* pathogenic variant; tumor type (ie, in situ or invasive), size, and grade; lymph node status; presence of distant metastasis; estrogen receptor status; progesterone receptor status; and HER2 status. Further, we collected data on type of surgery, chemotherapy, RT, endocrine therapy (ET), HER2-targeted therapy, risk-reducing salpingo-oophorectomy, and risk-reducing mastectomy (either bilateral or contralateral). All tumor characteristics were histologically determined.

Statistical analysis

The endpoint of our study was the occurrence of a metachronous CBC, which was defined as a secondary invasive or noninvasive tumor in the contralateral breast diagnosed at least 3 months after PBC diagnosis. We considered a CBC within 3 months to be synchronous. Patients were therefore considered to be at risk for CBC starting from 3 months after PBC diagnosis.

To avoid cancer-induced testing bias—a serious pitfall in studies using cohorts of *gBRCA* pathogenic variant carriers—we applied left-truncation in the analyses and started the observation period either at the date of DNA test result or of PBC, whichever came latter (25). As a result, anyone with a CBC or censoring event before this moment would be left-censored and therefore excluded from analysis.

We compared baseline characteristics between RT and non-RT groups. Differences in relative frequencies between these groups were tested for using the χ^2 test; differences in continuous variables were tested for using the Kruskal-Wallis test.

We first fitted a Cox proportional hazards model (complete-case analysis) for RT compared with no RT to assess the overall effect of RT for the PBC-on-CBC risk. We allowed for the baseline hazard to vary by country to account for variability/heterogeneity between them. We considered age, adjuvant ET, chemotherapy, risk-reducing salpingo-oophorectomy, and stage as potential confounders, based on current knowledge. In addition, we stratified the analysis for patients younger and older than 40 years of age at PBC diagnosis. Further, we evaluated the effects separately for *gBRCA1* and *gBRCA2* pathogenic variant carriers. Ipsilateral second BC, any invasive cancer (except nonmelanoma skin cancer and cervical intraepithelial neoplasia), bilateral or contralateral risk-reducing mastectomy, and death were considered censoring events. Patients were also censored when they reached date of last follow-up without an event. The models were tested for interaction among covariables (age, chemotherapy, ET, *gBRCA* pathogenic variant) and the main variable of interest (RT). We tested for satisfaction of the proportional hazard assumption, both graphically and statistically. Considering the high prevalence of contralateral prophylactic mastectomy (CPM) as a competing risk, cumulative incidence curves were estimated using a competing risks model, where death and CPM were considered competing risks. Multivariable subdistribution hazards models based on this competing risks model were computed to address the effect of confounders on CBC risk after RT.

All statistical tests and reported *P* values are 2-sided. $P < .05$ was considered significant. All analyses were performed using

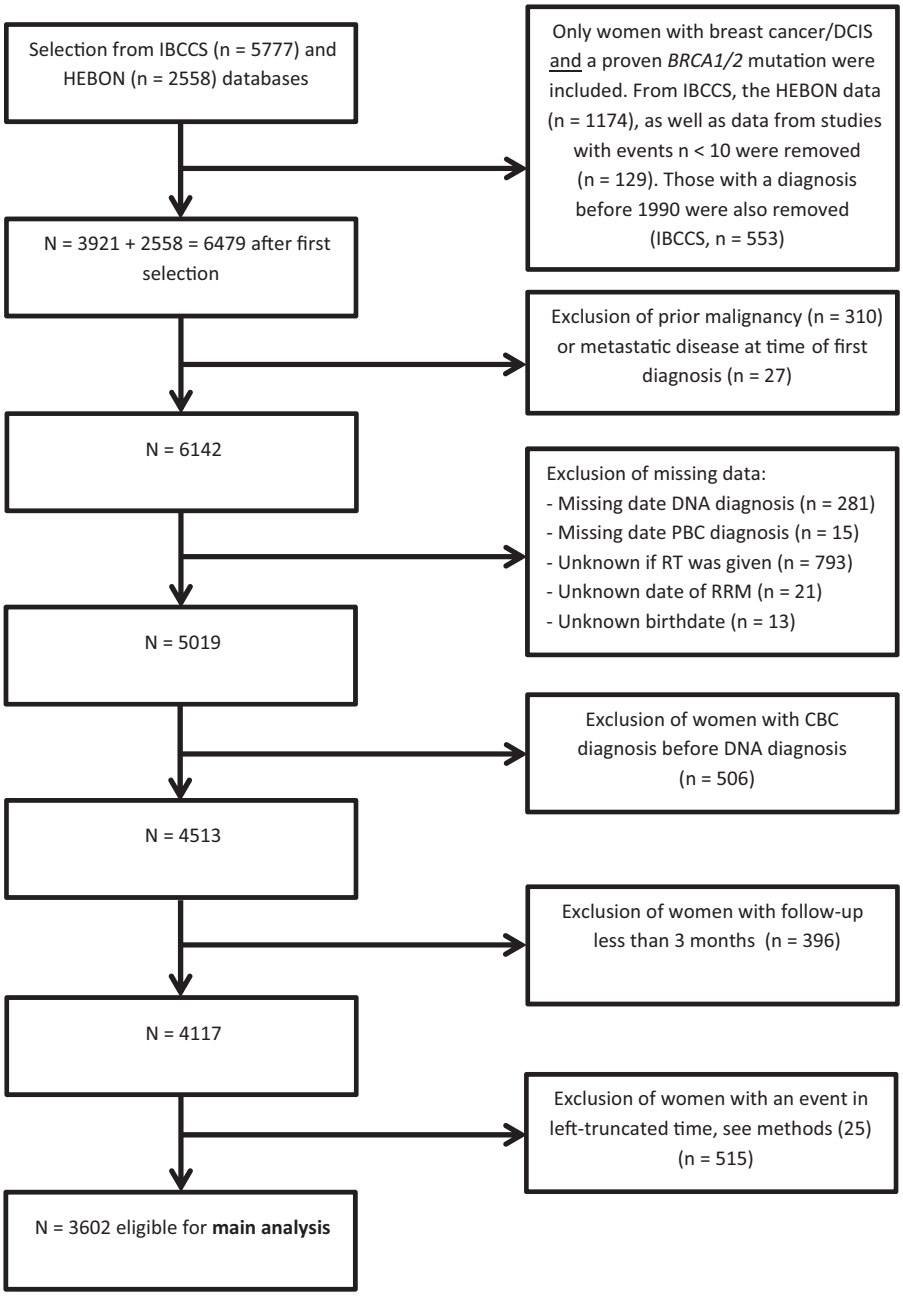


Figure 2. Flow diagram of patient inclusion. CBC = contralateral breast cancer; DCIS = ductal carcinoma in situ; HEBON = Hereditary Breast and Ovarian cancer research Netherlands; IBCCS = International *BRCA1/2* Carrier Cohort Study; PBC = primary breast cancer; RRM = risk-reducing mastectomy; RT, radiation therapy.

STATA, versions 16 and 17, software (StataCorp, College Station TX).

Results

Study population and characteristics

We selected 3602 eligible patients with PBC, of whom 2297 (64%) received RT. Median follow-up was 9.6 years. Additional patient, tumor, and treatment characteristics for the different groups are displayed in Table 1. Overall, patient characteristics were similar (eg, median age at diagnosis, type of g*BRCA* pathogenic variant). The most notable difference was stage, with 15% of patients in the RT group diagnosed with stage III PBC compared with 3% in the non-RT group ($P < .001$). Furthermore, patients in the RT group received more often chemotherapy than patients in the non-RT group (81% vs 70%, $P < .001$) and more often ET (50% vs 35%, $P < .001$). Similar treatment patterns were observed for g*BRCA1* and g*BRCA2* pathogenic variant carriers separately (Table 1) and for patients younger than and older than 40 years of age at PBC diagnosis (Supplementary Table 1, available online).

Contralateral breast cancer

CBC occurred in 252 patients in the RT group (with n = 180 being invasive) and in 98 patients in the non-RT group (n = 70 invasive). Risk-reducing mastectomy was the main censoring event (with n = 784 in the RT group and n = 564 in the non-RT group). Death was a censoring event in 235 patients in the RT group and in 95 patients in the non-RT group.

Table 1. Comparison of patient and tumor characteristics of patients, grouped by treatment with RT and gBRCA pathogenic variant status

N = 3602	RT n = 2297 (64%)	No RT n = 1305 (37%)	gBRCA1[a]		gBRCA2[a]		P
			RT n = 1340	No RT n = 801	RT n = 954	No RT n = 503	
Follow-up time, median (range), y	10.0 (0.3-27.6)	9.0 (0.3-26.6)	10.2 (0.3-27.6)	8.8 (0.3-26.6)	9.5 (0.3-25.6)	9.2 (0.3-25.4)	<.001[b] <.001[c] .55[d]
Age at PBC diagnosis, median (range), y	42.0 (18.0-85.2)	41.4 (19.5-86.7)	40 (19.4-81.1)	40 (21.5-84.6)	45.1 (18.0-85.2)	44.0 (19.5-86.7)	.21[b] .63[c] .046[d]
Year of PBC diagnosis, median (range)	2004 (1990-2017)	2005 (1990-2018)	2004 (1990-2017)	2005 (1990-2018)	2004 (1990-2016)	2005 (1990-2018)	<.001[b] <.001[c] .01[d]
5-y category, No. (%)							<.001[b]
1990-1994	219 (9)	87 (7)	145 (11)	59 (7)	74 (8)	28 (5)	<.001[c]
1995-1999	413 (18)	207 (16)	259 (19)	138 (17)	153 (16)	69 (14)	.02[d]
2000-2004	573 (25)	311 (24)	320 (24)	183 (23)	253 (27)	128 (25)	
2005-2009	666 (29)	364 (28)	388 (29)	205 (26)	276 (29)	159 (32)	
2010-2014	389 (17)	291 (22)	205 (15)	191 (24)	184 (19)	99 (20)	
2015-2020	37 (2)	45 (3)	23 (2)	25 (3)	14 (1)	20 (4)	
Timing of gBRCA DNA diagnosis, No. (%)							<.001[b]
After PBC diagnosis	2102 (92)	970 (74)	1230 (92)	576 (72)	869 (91)	393 (78)	<.001[c]
Before PBC diagnosis	195 (8)	335 (26)	110 (8)	225 (28)	85 (9)	110 (22)	<.001[d]
Stage, No. (%)							<.001[b]
0 (DCIS)	37 (3)	71 (8)	9 (1)	26 (5)	28 (5)	45 (14)	<.001[c]
1	558 (40)	410 (46)	366 (43)	282 (50)	192 (35)	128 (40)	<.001[d]
2	593 (42)	378 (43)	384 (45)	244 (43)	208 (38)	134 (42)	
3	216 (15)	23 (3)	91 (11)	9 (2)	125 (22)	14 (4)	
Unknown	893	423	490	240	401	182	
Tumor grade, No. (%)							.001[b]
1	38 (3)	15 (2)	13 (1)	6 (1)	25 (5)	9 (3)	.21[c]
2	326 (22)	235 (30)	131 (15)	89 (18)	194 (35)	146 (48)	.001[d]
3	1077 (75)	539 (68)	749 (84)	392 (80)	328 (60)	147 (49)	
Unknown	856	516	447	314	407	201	
ER status, No. (%)							.001[b]
ER positive	698 (48)	362 (41)	232 (27)	132 (23)	465 (80)	230 (75)	.10[c]
ER negative	751 (52)	523 (59)	638 (73)	445 (77)	113 (20)	77 (25)	.06[d]
Unknown	848	420	470	224	376	196	
PR status, No. (%)							<.001[b]
PR positive	494 (38)	250 (31)	158 (20)	98 (18)	336 (66)	152 (58)	.24[c]
PR negative	792 (62)	565 (69)	622 (80)	457 (82)	170 (34)	107 (42)	.04[d]
Unknown	1011	490	560	246	448	244	
HER2 status, No. (%)							.21[b]
HER2 positive	73 (8)	51 (10)	37 (6)	24 (7)	36 (10)	27 (13)	.59[c]
HER2 negative	881 (92)	484 (90)	544 (94)	305 (93)	337 (90)	179 (87)	.20[d]
Unknown	1343	770	759	472	581	297	
Chemotherapy, No. (%)							<.001[c]
Yes	1829 (81)	904 (70)	1126 (85)	602 (76)	700 (75)	301 (61)	<.001[c]
No	425 (19)	384 (30)	194 (15)	189 (24)	231 (25)	195 (39)	<.001[d]
Unknown	43	17	20	10	23	7	
ET, No. (%)							<.001[b]
Yes	1083 (50)	446 (35)	435 (35)	171 (22)	646 (70)	274 (56)	<.001[c]
No	1097 (50)	825 (65)	816 (65)	607 (78)	280 (30)	218 (44)	<.001[d]
Unknown	117	34	89	23	28	11	
Type of surgery, No. (%)							<.001[b]
No surgery	12 (1)	12 (1)	9 (1)	3 (0.4)	3 (0.3)	9 (2)	<.001[c]
Lumpectomy	1414 (65)	231 (19)[e]	890 (70)	153 (21)	522 (58)	78 (16)	<.001[d]
Mastectomy	753 (34)	956 (80)	375 (29)	567 (78)	377 (42)	389 (82)	
Unknown	118	106	66	78	52	27	
RRM, No. (%)							<.001[b]
RRM	911 (40)	611 (47)	541 (40)	399 (50)	369 (39)	212 (42)	<.001[c]
No RRM	1382 (60)	688 (53)	796 (60)	400 (50)	584 (61)	287 (58)	.16[d]
Unknown	4	6	3	2	1	4	
Timing of RRSO, No. (%)							<.001[b]
No RRSO	574 (25)	338 (26)	349 (26)	193 (24)	224 (24)	144 (29)	<.001[c]
Before PBC	81 (4)	110 (9)	45 (3)	87 (11)	36 (4)	23 (5)	.11[d]

(continued)

Table 1. (continued)

N = 3602	RT n = 2297 (64%)	No RT n = 1305 (37%)	gBRCA1[a]		gBRCA2[a]		P
			RT n = 1340	No RT n = 801	RT n = 954	No RT n = 503	
After PBC	1634 (71)	842 (65)	942 (71)	511 (64)	690 (72)	331 (66)	
At the same time	2 (0.1)	5 (0.4)	0 (0)	4 (0.5)	2 (0.2)	1 (0.2)	
Unknown RRSO	6	10	4	6	2	4	

[a] Four patients simultaneously had a *gBRCA1* and *gBRCA2* pathogenic variant; because they are not included in these columns, totals do not sum to 3602. DCIS, ductal carcinoma in situ; ER = estrogen receptor; ET, endocrine therapy; gBRCA = germline-*BRCA*; PBC = primary breast cancer; PR = progesterone receptor; RRM = risk-reducing mastectomy; RRSO = risk-reducing salpingo-oophorectomy; RT = radiation therapy.
[b] Comparison of RT with no RT group, overall.
[c] Comparison of RT with no RT group, in *gBRCA1* carriers only.
[d] Comparison of RT with no RT group, in *gBRCA2* carriers only.
[e] In part, these women were initially treated with a lumpectomy, postponing RT while waiting on DNA test results to undergo risk-reducing surgery.

Table 2. Cox proportional hazards model for combined invasive and noninvasive CBC risk after RT, overall and stratified by *gBRCA* status

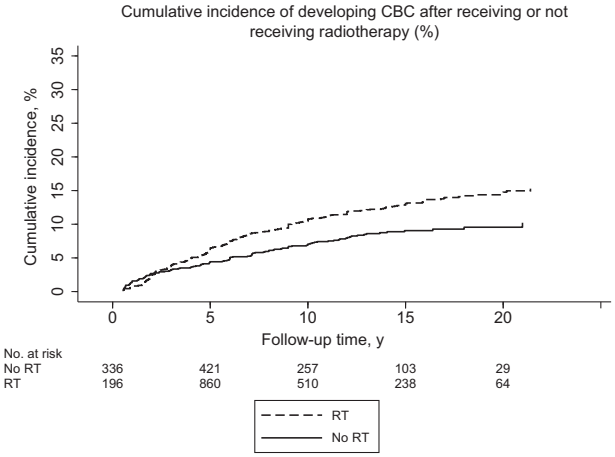
	RT		No RT
Overall model			
No.	2297		1305
No. of events	252		98
PYO	9997		5266
Incidence rate per 1000 person-years (95% CI)	25.2 (22.3 to 28.5)		18.6 (15.3 to 22.7)
		HR (95% CI)	
Univariable analysis			
RT (yes vs no)		1.35 (1.06 to 1.72)	
Multivariable analysis[a]			
RT (yes vs no)		1.44 (1.12 to 1.86)	
Age (per year increase)		0.98 (0.97 to 0.99)	
Chemotherapy (yes vs no)[b]		0.35 (0.22 to 0.54)	
ET (yes vs no)		0.78 (0.61 to 1.00)	
BRCA1 pathogenic variant carriers			
No.	1340		801
No. of events	171		69
PYO	5927		2994
Incidence rate per 1000 person-years (95% CI)	28.9 (24.8 to 33.5)		23.0 (18.2 to 29.2)
		HR (95% CI)	
Univariable analysis			
RT (yes vs no)		1.25 (0.92 to 1.69)	
Multivariable analysis			
RT (yes vs no)		1.29 (0.93 to 1.77)	
Age (per year increase)		0.98 (0.96 to 0.99)	
Chemotherapy (yes vs no)[b]		0.34 (0.19 to 0.61)	
ET (yes vs no)		0.99 (0.72 to 1.36)	
BRCA2 pathogenic variant carriers			
No.	954		503
No. of events	81		29
PYO	4058		2269
Incidence rate per 1000 person-years (95% CI)	20.0 (16.1 to 24.8)		12.8 (8.9 to 18.4)
		HR (95% CI)	
Univariable analysis			
RT (yes vs no)		1.60 (1.04 to 2.47)	
Multivariable analysis			
RT (yes vs no)		1.77 (1.13 to 2.77)	
Age (per year increase)		0.98 (0.96 to 1.00)	
Chemotherapy (yes vs no)[b]		0.33 (0.16 to 0.69)	
ET (yes vs no)		0.79 (0.50 to 1.23)	

[a] Stage and risk-reducing salpingo-oophorectomy (as a time-varying variable) were not included as covariables because their inclusion did not have a meaningful effect on the hazard ratio for R, nor did they result in a statistically significant likelihood-ratio test for the model ($P = .98$ and $P = .76$, respectively). For all models, we allowed the baseline hazard to vary by country. Multivariable models adjusted for age at PBC diagnosis, chemotherapy and endocrine therapy. CBC = contralateral breast cancer; CI = confidence interval; ET = endocrine therapy; gBRCA = germline-*BRCA*; HR = hazard ratio; PBC = primary breast cancer; PYO = person-years of observation; RT = radiation therapy.
[b] The effect of chemotherapy is not constant over time; hazard ratio increases with time and reaches 1.00 between 11 and 13 years after PBC diagnosis.

Associations between RT and CBC risk

Risk of invasive and in situ CBC increased for patients receiving RT compared with patients without RT (adjusted hazard ratio [HR] = 1.44; 95% confidence interval [CI] = 1.12 to 1.86; Table 2, Figure 3). The risk associated with RT compared with no RT was proportional over time, and in both groups CBC risk appears to peak around 5 to 6 years after PBC diagnosis (data not shown). In *gBRCA2* pathogenic variant carriers, an increased risk of CBC was observed (HR = 1.77; 95% CI = 1.13 to 2.77). For *gBRCA1* pathogenic variant carriers, we found a similar trend (HR = 1.29; 95% CI = 0.93 to 1.77; $P = .39$ for interaction).

In patients younger than 40 years of age at PBC diagnosis, the hazard ratio for CBC was 1.38 (95% CI = 0.93 to 2.04) for RT compared with no RT. For patients 40 years of age and older, the



	Cumulative CBC risk, % (95% CI)		
Treatment	5-year	10-year	15-year
Radiotherapy	6.1 (4.9 to 7.5)	10.4 (9.0 to 12.0)	12.9 (11.2 to 14.6)
No radiotherapy	4.4 (3.2 to 5.8)	6.9 (5.4 to 8.6)	9.1 (7.3 to 11.0)

Figure 3. Fine and Gray competing risks model–derived CBC cumulative incidence curves, by RT. Cumulative incidences at 5-year intervals for both groups displayed in the table below the graph. CBC = contralateral breast cancer; CI = confidence interval; RT = radiation therapy.

hazard ratio was 1.56 (95% CI = 1.11 to 2.19; Supplementary Table 2, available online).

The effects of RT associated with invasive CBC solely (HR = 1.51; 95% CI = 1.12 to 2.04) were in line with those of the main analysis and for the gBRCA1 and gBRCA2 pathogenic variant carriers stratified analyses (HR = 1.41; 95% CI = 0.97 to 2.03 for gBRCA1 and HR = 1.72; 95% CI = 0.99 to 2.98 for gBRCA2; P = .72 for interaction; Supplementary Table 3, available online).

No statistically significant interactions of chemotherapy, ET, gBRCA pathogenic variant status, or age at PBC diagnosis with the main variable of interest were observed.

Fine and Gray competing risks models are shown in Supplementary Table 4 (available online). Considering CPM and death as competing risks, we found an adjusted subdistribution hazard ratio for RT on CBC risk of 1.76 (95% CI = 1.38 to 2.24). For gBRCA1 pathogenic variant carriers, the subdistribution hazard ratio for RT was 1.64 (95% CI = 1.23 to 2.20), while for gBRCA2 pathogenic variant carriers, it was 1.94 (95% CI = 1.26 to 3.00).

Discussion

Our results show an association with moderately increased CBC risk for gBRCA1/2 pathogenic variant carriers receiving RT after PBC diagnosis, especially for gBRCA2 pathogenic variant carriers. We observed comparable hazard ratios in the combined gBRCA1/2 carrier analyses for patients both younger than and older than 40 years of age at PBC diagnosis, although results were statistically significant only for the latter group.

In contrast to our results, Reiner et al. observed no evidence of a direct effect of RT on CBC risk in gBRCA1/2 pathogenic variant carriers in their recent nested case-control study (26). Moreover, several other studies did not demonstrate an increased risk of CBC after RT for PBC in gBRCA1/2 pathogenic variant carriers (19,27-29). For some of these studies, failure to demonstrate an increased risk may be explained by relatively small effects in combination with an insufficient sample size or follow-up.

In contrast, results from a large randomized controlled trial–based meta-analysis did show a small but consistent effect in the general BC population (3). In addition, other studies in patients with sporadic BC have linked exposure to RT for PBC to increased risks of CBC, as well. The effect was small (ie, relative-risks of 1.10-1.20) (30), unless a strong family history was present (18). Stovall et al. (13) found larger effects of RT on CBC risk in unselected patients younger than 40 years of age with PBC, mostly for contralateral breast doses exceeding 1 Gy (mean dose) based on phantom dosimetry, which included a statistically significant dose-effect relationship. There may have been a higher predominance of gBRCA1/2 pathogenic variants in their case population (patients with CBC), however, than the control population (patients without CBC), especially in young age groups.

Asaithamby et al. found that lower doses (ie, 5 mGy to 1 Gy), unlike high (therapeutic) dose exposure, do not induce a sufficient number of DSBs to cause cell death or apoptosis because cells have the capacity to repair them efficiently (31). A small number of DSBs; single-strand DNA breaks; and other, smaller DNA lesions are still induced nonetheless. Following faulty repair of these DSBs (eg, because of impaired BRCA function), mutations can still accumulate, increasing the likelihood of cancer. Indeed, low-dose (<1 Gy) radiation exposure from diagnostic procedures has been associated with increased PBC incidence in gBRCA pathogenic variant carriers (32).

Remarkably, in the overall analysis we observed similar trends of increased risks of CBC after RT in patients both older and younger than 40 years of age at PBC diagnosis compared with those who did not receive RT. The effect of young age as a risk factor for CBC after RT has previously been reported (risk ratios of 1.5-2.5), usually in patients 35, 40, or 45 years of age as a cutoff between younger and older patients (13,18,19,32). We chose the age of 40 to maintain consistency with previous studies and to keep a large enough population for subgroup analysis. In our study, we observed that especially in carriers younger than 40 years of age at PBC diagnosis, more chemotherapy was administered. Chemotherapy decreases CBC risk and thus (at least partially) negates the potential side effects of RT in this group (even though we saw no evidence for interaction in our analyses) (33,34). This phenomenon can also be observed when further stratifying the analysis for chemotherapy in patients younger than 40 years of age (HR = 1.13; 95% CI = 0.72 to 1.77 with chemotherapy vs HR = 2.63; 95% CI = 1.18 to 5.85 without chemotherapy; data not shown).

In a separate analysis, the effect size for gBRCA2 pathogenic variant carriers was larger than for gBRCA1 pathogenic variant carriers and statistically significant only in the first group. To our knowledge, this finding was not described earlier. The effect may in part be explained by the fact we have included both invasive and noninvasive CBCs in our analysis, the latter group being more frequent within gBRCA2 pathogenic variant carriers. Indeed, when we considered only invasive CBC as an outcome, RT compared with no RT was no longer statistically significantly associated with an increased risk of CBC in gBRCA2 pathogenic variant carriers (Supplementary Table 3, available online). Because RT can induce new cancer growth, however, and because ductal carcinoma in situ is considered a precursor of an invasive tumor, it may be important to consider noninvasive CBCs as an outcome, as well, even if the direct potential clinical impact is not as large as being diagnosed with invasive cancer.

The main strengths of our study are the large population size, combining several international datasets of gBRCA1/2 pathogenic variant carriers diagnosed with BC, as well as separating radiation exposure by gBRCA pathogenic variant status and age at PBC diagnosis. Although from a biological standpoint it seems

plausible that gBRCA pathogenic variant carriers are at increased risk of developing CBC after RT for PBC, the evidence from observational clinical studies is currently inconclusive (19). One reason for this could be that CBC risk as a result of RT exposure is not linear but may increase with time (19,30). This effect may also in part be mediated by transient protection from other treatments, such as chemotherapy and ET. In addition, Drooger et al. (19) noted that rates of CPM increased over time. The resulting decrease in numbers of patients at risk for 10- and 15-year follow-up analyses impeded their ability to discern a statistically significant effect. In the current analyses, we used a much larger study sample, which obviated above-described limitations concerning follow-up and made our results much more robust, in our opinion.

A limitation of this study was the lack of detailed information about the exact RT dose and modality (ie, photons or electrons) given, treatment volumes (ie, breast or chest wall with or without internal mammary chain), and contralateral breast dose. Having this information could result in a better estimation of the association between RT and CBC risk. In addition, further evidence for a dose-effect relationship would be the finding that CBCs are more frequent on the medial (most highly exposed) side after RT, in accordance with the results of Hooning et al. (13) and Stovall et al. (18).

Further, we noted a higher uptake of CPM in the non-RT than in the RT group. This finding resulted in earlier censoring for the non-RT group. The Cox model handles differences in censoring well if the assumption of proportional hazards holds. The only exception would be if censoring on prophylactic mastectomy would be informative—that is, when those who more often opt for prophylactic mastectomy are at higher risk of CBC (eg, because of strong family history). Given that the proportion of women tested before PBC (likely the result of positive family history) was higher in the non-RT group, this is probably the case. For the context of our study, this would mean that those not receiving RT have a higher baseline risk of CBC, which would decrease the difference in risk between both groups, independent from RT effects. As a result, we may have underestimated the true effect. Another way to deal with a situation where competing risks are prominent, such as CPM in our population, is to perform a competing risks analysis. For the sake of completeness, we have added the results of such an analysis in the supplementary material (Supplementary Table 4, available online). The results were fairly similar to the cause-specific models, providing some reassurance that the influence of bias was most likely limited. It should be noted, however, that competing risks analysis comes with its own limitations. Most notably, the competing event influences the subdistribution hazard ratio for the event under investigation and is generally considered to be more suitable for prediction rather than questions of etiology (35,36). In addition, some have questioned the validity of the model when dealing with left-truncation or nonproportional hazards (37,38). Considering that we aimed to investigate the effect of RT on CBC risk, an etiological question, we considered the cause-specific Cox proportional hazards model to be more suitable for our main analysis.

Finally, we observed an association with increased risk of CBC among gBRCA1/2 pathogenic variant carriers who received RT compared with those who did not receive RT. Interestingly, the risk was comparable for different age groups, and gBRCA2 pathogenic variant carriers showed the highest risk. More evidence is required to conduct a proper risk-benefit analysis of tailoring RT around the contralateral breast (ie, dosage, techniques) while maintaining oncological safety. Future studies could investigate the relationship between RT and CBC risk by looking into dose-response and localization effects (which may require individual radiation treatment plans), both potentially providing more evidence for a causal effect. In addition, we may study other RT techniques (eg, proton beam RT, contralateral breast–sparing techniques) and factors that could affect radiation sensitivity of the contralateral breast (eg, reproductive factors, such as parity and lactation duration) as well as compare gBRCA1/2 pathogenic variant carriers to noncarriers. Knowledge of the risks associated with RT can help guide decision-making for gBRCA1/2 pathogenic variant carriers together with their physician regarding their post-treatment choices concerning surveillance and prophylactic surgery. Confirmation of these results in other studies is required, however, before they can be applied to clinical decision-making.

Data availability

A request for data can be made by non-commercial parties by requesting a concept form via y.tan@nki.nl. The concept will be evaluated by the IBCCS steering committee for scientific content and potential overlap with ongoing studies. The institute of the data recipient will need to sign the standard IBCCS Data Transfer Agreement. Only pseudonymized data will be transferred.

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Epidemiological Study of Familial Breast Cancer (EMBRACE): Steve Ellis (data manager on the EMBRACE study 2010-2014).

German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC): Rita K. Schmutzler, recipient of grants (no 110837 and 01GY1901).

GENEPSO: Catherine Noguès; Lilian Laborde; Emmanuel Breysse; Dominique Stoppa-Lyonnet, PhD, MD; Marion Gauthier-Villars, MD; Bruno Buecher, MD; Olivier Caron, MD; Emmanuelle Fourme-Mouret, MD; Jean-Pierre Fricker, MD; Christine Lasset, MD; Valérie Bonadona, PhD, MD; Pascaline Berthet, MD; Laurence Faivre, MD; Elisabeth Luporsi, PhD, MD; Véronique Mari, MD; Laurence Gladieff, MD; Paul Gesta, MD; Hagay Sobol, PhD, MD; François Eisinger, MD; Michel Longy, PhD, MD; Catherine Dugast†, MD; Chrystelle Colas, MD; Isabelle Coupier, MD; Pascal Pujol, MD; Carole Corsini, MD; Alain Lortholary, MD; Philippe Vennin†, MD; Claude Adenis, MD; Tan Dat Nguyen, MD; Capucine Delnatte, MD; Julie Tinat, MD; Isabelle Tennevet, MD; Jean-Marc Limacher, MD; Christine Maugard, PhD; Yves-Jean Bignon, MD; Liliane Demange†, MD; Clotilde Penet, MD; Hélène Dreyfus, MD; Odile Cohen-Haguenauer, MD; Laurence Venat-Bouvet, MD; Dominique Leroux, MD; Hélène Zattara-Cannoni, MD; Sandra Fert-Ferrer, MD; and Odile Bera, MD. †Deceased.

Medical University of Vienna: Daniela Muhr.

Funding

No specific external funding for this study was acquired.

The individual participating centers and studies of the IBCCS are supported by a number of research grants, all listed in the acknowledgements under their respective acknowledgements.

Conflicts of interest

All authors have completed and submitted the Form for Disclosure of Potential Conflicts of interest.

D. Gareth Evans reports potential conflict of interest from AstraZeneca and AmGen; Karin Kast from Roche Pharma AG; Jacques Simard reports holding *BRCA1* and *BRCA2* patents. The other authors report no conflicts of interest.

Acknowledgements

The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON) consists of the following collaborating centers in the Netherlands: Netherlands Cancer Institute (coordinating center), Amsterdam; Erasmus Medical Center, Rotterdam; Leiden University Medical Center; Radboud University Medical Center Nijmegen; University Medical Center Utrecht; Amsterdam Universiy Medical Center, University of Amsterdam; Amsterdam University Medical Center, Vrije Universiteit Amsterdam; Maastricht University Medical Center; University of Groningen; The Netherlands Comprehensive Cancer Organisation (IKNL); the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA). HEBON thanks the study participants and the registration teams of IKNL and PALGA for part of the data collection. The HEBON study is supported by Dutch Cancer Society grants NKI1998-1854, NKI2004-3088, NKI2007-3756, and NKI 12535; the Netherlands Organisation of Scientific Research grant NWO 91109024; Pink Ribbon grants 110005 and 2014-187.WO76; BBMRI grant NWO 184.021.007/CP46; the Transcan grant JTC 2012 Cancer 12-054.

INHERIT would like to thank the staff for the sample management and skillful assistance.

INHERIT was supported by the Canadian Institutes of Health Research for the CIHR Team in Familial Risks of Breast Cancer program—grant No. CRN-87521—and the Ministry of Economic Development, Innovation and Export Trade—grant No. PSR-SIIRI-701. Jacques Simard is a chairholder of the Canada Research Chair in Oncogenetics.

We acknowledge the Epidemiological Study of Familial Breast Cancer (EMBRACE) Centres; the Coordinating Centre: University of Cambridge and the Collaborating Centres; Guy's and St Thomas' NHS Foundation Trust, London; Central Manchester University Hospitals NHS Foundation Trust, Manchester: Chapel Allerton Hospital, Leeds; the Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton; Birmingham Women's Hospital Healthcare NHS Trust, Birmingham; South Glasgow University Hospitals, Glasgow; Addenbrooke's Hospital, Cambridge; St Georges, London Royal Devon & Exeter Hospital, Exeter; Southampton University Hospitals NHS Trust, Southampton; Sheffield Children's Hospital, Sheffield; Newcastle Upon Tyne Hospitals NHS Trust, Newcastle; Great Ormond Street Hospital for Children NHS Trust, London; Churchill Hospital, Oxford; Western General Hospital, Edinburgh; St Michael's Hospital, Bristol; Belfast City Hospital, Belfast; Nottingham University Hospitals NHS Trust, Nottingham; University Hospital of Wales, Cardiff; Alder Hey Hospital, Liverpool; Kennedy Galton Centre, Harrow; Trinity College

Dublin and St James's Hospital, Dublin; University Hospitals of Leicester NHS Trust, Leicester; NHS Grampian & University of Aberdeen, Aberdeen; Glan Clwyd Hospital, Rhyl; and Singleton Hospital, Swansea.

EMBRACE is supported by the Cancer Research UK grants C1287/A23382, C1287/A26886 and PRCPJT-Nov21\100004). D. Gareth Evans is supported by an NIHR grant to the Biomedical Research Centre, Manchester (IS-BRC-1215-20007). Antonis C. Antoniou is funded by Cancer Research UK grants PPRPGM-Nov20\100002 and C12292/A20861. M. Tischkowitz was supported by the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014).

We thank all study participants for contributing to the registry of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC), which is supported by the German Cancer Aid (grant No. 110837) and the Federal Ministry of Education and Research (grant No. 01GY1901).

We acknowledge the GENEPSO Centers: the Coordinating Center (Institut Paoli-Calmettes, Marseille, France), which contributed by centralizing, managing the data, and organizing *BRCA1* and *BRCA2* mutation carriers' follow-up, and the collaborating centers, which contributed to the mutation carriers recruitment and follow-up: Institut Curie, Paris; Institut Gustave Roussy, Villejuif; Hôpital René Huguenin/Institut Curie, Saint Cloud; Centre Paul Strauss, Strasbourg; Centre Léon Bérard, Lyon; Centre François Baclesse, Caen; Hôpital d'Enfants CHU and Centre Georges François Leclerc, Dijon; CHR Metz-Thionville, Hôpital de Mercy, Metz, France; Centre Antoine Lacassagne, Nice; Institut Claudius Regaud, Toulouse; Réseau Oncogénétique Poitou Charente, Niort; Institut Bergonié, Bordeaux; Centre Eugène Marquis, Rennes; GH Pitié Salpétrière, Paris; CHU Arnaud de Villeneuve, Montpellier; Centres Paul Papin, and Catherine de Sienne, Angers, Nantes; Centre Oscar Lambret, Lille; Institut Jean Godinot, Reims; Centre René Gauducheau, Nantes; Centre Henri Becquerel, Rouen; Hôpital Civil, Strasbourg; Centre Jean Perrin, Clermont-Ferrand; Polyclinique Courlancy, Reims; Clinique Sainte Catherine, Avignon; Hôpital Saint-Louis, Paris; CHRU Dupuytren, Limoges; Couple-Enfant-CHU de Grenoble; Hôpital de la Timone, Marseille; Hôtel Dieu—Centre Hospitalier, Chambery; and CHU Fort de France, Fort de France.

The national French cohort, GENEPSO, had been supported by a grant from the Fondation de France, the Ligue Nationale Contre le Cancer, by a grant from INCa as part of the European program ERA-NET on Translational Cancer Research (TRANSCAN-JTC2012, No. 2014-008) and is being supported by Institut National du Cancer-DGOS, grant PRT-K22-076 and by the "Programmes labellisés (PGA) 2022" of the Fondation ARC (N°ARCPGA2022010004414_4863).

We would like to thank the participating patients and their families for their contribution to the International Hereditary Cancer Cohort. The IHCC was supported by grants PBZ_KBN_122/P05/2004 and ERA-NET TRANSAN JTC 2012 Cancer 12-054 (ERA-NET-TRANSCAN/07/2014).

Czech Republic, MMCI, Brno—for the data collection and management. The patients and their families for participating.

The Masaryk Memorial Cancer Institute study is supported by MH CZ-DRO (Masaryk Memorial Cancer Institute 00209805).

We wish to thank the Hungarian Breast and Ovarian Cancer Study Group members; the Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary; and the clinicians and patients for their contributions to this study.

The Hungarian Breast and Ovarian Cancer Study group at the Hungarian National Institute of Oncology was supported by Hungarian research grant NKFIH-OTKA K-112228 to Dr Olah.

We thank the research and clinical staff at the Medical University of Vienna, who contributed to the follow up of members of the families, and the study participants and their family members for their participation in the study.

We would like to thank the study participants and their families in the Odense University Hospital cohort for their participation.

We thank the study participants and their families in the MSC cohort for their participation.

Hospital Clinico San Carlos: This work was supported by grant RD06/0020/0021 from ISCIII, Spanish Ministry of Science and Innovation.

This work was partially supported by Spanish Association Against Cancer grant AECC08, RTICC 06/0020/1060, FISPI08/1120, Mutua Madrileña Foundation grant SAF2010-20493 and the Spanish Ministry of Economy and Competitiveness grant SAF2014-57680-R.

The funding organizations did not play a role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

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