Breast Cancer Res Treat (2015) 154:171–180
DOI 10.1007/s10549-015-3597-7

EPIDEMIOLOGY

Adjuvant radiotherapy for primary breast cancer in *BRCA1* and *BRCA2* mutation carriers and risk of contralateral breast cancer with special attention to patients irradiated at younger age

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Received: 2 October 2015 / Accepted: 5 October 2015 / Published online: 14 October 2015

Abstract The purpose of this study was to estimate the influence of adjuvant radiotherapy for primary breast cancer (BC) on the risk of contralateral BC (CBC) in *BRCA1* or *BRCA2 (BRCA1/2)* mutation carriers, with special attention to patients irradiated at age younger than 40 years. Additionally, tendencies in locoregional treatments and rates of contralateral risk-reducing mastectomy over time were explored. In this retrospective cohort study, 691 *BRCA1/2*-associated BC patients treated between 1980 and 2013 were followed from diagnosis until CBC or censoring event including ipsilateral BC recurrence, distant metastasis, contralateral risk-reducing mastectomy, other invasive cancer diagnosis, death, or loss to follow up. Hazard ratios (HR) for CBC associated with radiotherapy were estimated using Cox regression. Median follow-up time was 8.6 years [range 0.3–34.3 years]. No association between radiotherapy for primary BC and risk of CBC was found, neither in the total population (HR 0.82, 95 % CI 0.45–1.49) nor in the subgroup of patients younger than 40 years at primary diagnosis (HR 1.36, 95 % CI 0.60–3.09). During follow-up, the number of patients at risk decreased substantially since a large proportion of patients were censored after contralateral risk-reducing mastectomy or BC recurrence. Over the years, increasing preference for mastectomy without radiotherapy compared to breast-conserving surgery with radiotherapy was found ranging from less than 30 % in 1995 to almost 50 % after 2010. The rate of contralateral risk-reducing mastectomy increased over the years from less than 40 % in 1995 to more than 60 % after 2010. In this cohort of *BRCA1/2*-associated BC patients, no association between radiotherapy for primary BC and risk of CBC was observed in the total group, nor in the patients irradiated before the age of 40 years. The number of patients at risk after 10 and 15 years of follow-up, however, was too small to definitively exclude harmful effects of adjuvant radiotherapy.

Keywords Radiotherapy · *BRCA* mutation · Contralateral breast cancer · Risk-reducing mastectomy · Breast-conserving surgery

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Introduction

Both normal breast tissue and breast cancer cells are sensitive to ionizing radiation. Although adjuvant radiotherapy for early breast cancer (BC) reduces the risk of local recurrence and improves BC-specific survival [1, 2], it also leads to a low-dose scatter radiation to the surrounding healthy tissue with potentially carcinogenic effects. In sporadic BC patients, adjuvant radiotherapy has been associated with an increased risk of contralateral breast cancer (CBC), although only among women younger than

45 years at primary BC diagnosis and after a latency period of at least 10–15 years [3–6].

The vulnerability of cells for ionizing radiation largely depends on the rate of cell proliferation, the total dose of radiation, the fractionation scheme, and the capability of the cells to repair DNA damage [7]. Younger patients have higher breast cell proliferation (in particular during puberty, adolescence, and pregnancy) and thus increased DNA synthesis that might render breast tissue particularly susceptible to the carcinogenic effects of radiation [8, 9]. The capacity to repair DNA damage might substantially differ between BC patients, in particular when considering patients with or without a *BRCA1* or *BRCA2* (*BRCA1/2*) mutation.

BRCA1/2-associated BC is characterized by homologous recombination deficiency, leading to inadequate repair of double-strand DNA breaks [10, 11]. Ionizing radiation can cause cell damage by induction of double-strand DNA breaks. This has led to the hypothesis that adjuvant radiotherapy administered for *BRCA1/2*-associated BC might be more effective than radiotherapy administered for sporadic BC. On the contrary, surrounding healthy breast tissue among BC patients with a *BRCA1/2* mutation might be more vulnerable to the deleterious effects of adjuvant radiotherapy, including the development of a CBC, compared to those without a *BRCA1/2* mutation.

In unaffected *BRCA1/2* mutation carriers, exposure to low cumulative doses of diagnostic radiation (including screening mammography) at young age (<30 years) has been reported to be associated with an increased risk of BC, with a clear dose–effect relationship [12] compared to no exposure to diagnostic radiation. The possible carcinogenic effect of scatter ionizing radiation after adjuvant radiotherapy on the contralateral breast in *BRCA1/2*-associated BC patients, however, is not clear. Although a number of studies addressed this question, all these studies are compromised by a short duration of follow-up and the lack of subgroup analyses regarding young BC patients. [13–15]. Knowledge about the possibly increased risk of CBC by radiotherapy might be of great importance for optimal shared decision making regarding mastectomy without radiotherapy versus breast-conserving surgery including radiotherapy at primary BC diagnosis.

We therefore studied the impact of radiotherapy on the risk of CBC among *BRCA1/2*-associated BC patients in a retrospective cohort study, with special attention to patients younger than 40 years at primary BC diagnosis. Since over the years an increasing proportion of *BRCA1/2* mutation carriers after developing BC seems to opt for bilateral mastectomy instead of unilateral mastectomy or breast-conserving treatment with radiotherapy [16], we also explored potential tendencies in locoregional treatments and the rates of contralateral risk-reducing mastectomy over the past decades.

Methods

Patient selection

From the Rotterdam Family Cancer Clinic database, we extracted all female patients with early stage BC ($n = 2{,}268$). From this population, we selected proven or obligate *BRCA1* or *BRCA2* mutation carriers, treated at the Erasmus MC Cancer Institute. Patients diagnosed from January 1st 1980, corresponding to the start of linear accelerators use for adjuvant breast radiotherapy at the Erasmus MC, to January 1st 2013 were included ($n = 790$). Time of observation ended at April 1st 2014. Patients with less than 3 months of follow-up were excluded ($n = 52$; see statistical analysis). Patients who were treated with breast/chest wall radiotherapy or systemic anticancer therapy because of another invasive malignancy, either prior or synchronous to the primary BC, were excluded ($n = 16$). Patients who had synchronous bilateral BC and received bilateral radiation therapy or mastectomy ($n = 31$) were also excluded, leaving a total of 691 patients available for the analyses.

For the eligible patients, data on primary BC and CBC characteristics (type of histology, differentiation grade, estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status, and stage) and primary BC therapy (surgery, radiotherapy, chemotherapy, and/or endocrine therapy) were retrieved. We also collected data on type of mutation (i.e., *BRCA1* or *BRCA2*), date of birth, primary and contralateral BC diagnoses, dates of and findings at contralateral risk-reducing mastectomy and salpingo-oophorectomy, and dates of disease recurrence and death or date of last follow-up if no event occurred.

Statistical analysis

The primary endpoint was the development of CBC defined as the occurrence of carcinoma in situ or invasive BC in the contralateral breast at least 3 months after primary BC diagnosis and no signs of metastatic disease. CBC diagnosis within 3 months was considered as synchronous bilateral BC and assumed to be unrelated to the delivery of radiotherapy for the first BC [3–5]. For this reason, patients with less than 3 months of follow-up were excluded.

For comparisons of patient, tumor, and treatment characteristics between subgroups, we used Pearson's χ^2 tests. Differences in age at primary BC diagnosis and follow-up time were analyzed using the Wilcoxon rank-sum test (Mann–Whitney).

In the Cox analyses, we applied left truncation of analysis time and so considered outcome data from prospective follow-up only. Hereby, we aimed to correct for potential selection bias, possibly arising due to inclusion of patients undergoing genetic testing after primary BC or CBC diagnosis [17, 18]. Censoring events were ipsilateral BC recurrence for which radiotherapy or systemic therapy was applied, distant metastasis, contralateral risk-reducing mastectomy, other (non-breast) invasive cancer for which radiotherapy or systemic therapy was applied, death, and loss to follow up.

We estimated hazard ratios (HRs) and 95 % confidence intervals (CIs) for radiotherapy (after lumpectomy vs. after mastectomy vs. none), adjuvant chemotherapy (yes vs no), adjuvant endocrine therapy (yes vs. no), salpingo-oophorectomy (treated as time-dependent variable), age at primary BC, and *BRCA* mutation type (*BRCA1* vs. *BRCA2*) using Cox regression in univariate and multivariate analyses. The cumulative 5-, 10-, and 15-year risks of CBC were calculated using Kaplan–Meier analysis including only patients who underwent DNA testing for *BRCA1/2* mutation before the diagnosis of CBC, to correct for potential selection bias.

Analyses were performed for the total group and for patients younger than 40 years at primary BC, as it has been previously reported that younger patients are more susceptible for radiation-induced BC [3–6].

The proportion of patients undergoing different locoregional treatments over time, including breast-conserving treatment and mastectomy with or without radiotherapy, was estimated with a regression line of best fit and 95 % CI based on the proportion per year. The same was performed for the proportion of patients undergoing contralateral prophylactic mastectomy over time. For statistical analysis STATA, version 13.0, was used. For computing the figures, R version 3.2.2 (released on 2015-08-14) and the package GGplot version 1.0.1. were used.

Results

A total of 691 *BRCA1/2*-associated BC patients, consisting of 517 *BRCA1* and 174 *BRCA2* mutation carriers, were eligible for data analysis (Tables 1, 2). Median time of follow-up of the entire cohort was 8.6 years with a range from 0.3 to 34.3 years. A total of 439 patients were treated with radiotherapy either after lumpectomy ($n = 349$) or after mastectomy ($n = 85$). A total of 325 patients were younger than 40 years at primary BC diagnosis (Table 2). Further details on patient, tumor, and treatment characteristics are presented in Tables 1 and 2.

Of all patients, 161 (23 %) developed CBC, of whom 87 were younger than 40 years at BC onset. The cumulative 5-, 10-, and 15-year risks of CBC for the total cohort were 8, 19, and 32 %, respectively. Among the patients younger than 40 years, the cumulative 5-, 10-, and 15-year CBC risks were 11, 32, and 40 %, respectively. Cumulative risks for age- and *BRCA*-specific subgroups suggest a higher cumulative risk for *BRCA1*-associated patients compared to *BRCA2*-associated patients (Table 3). Median time interval between primary BC and CBC was 4.8 years (range 0.5–29.0) for the entire cohort and 5.5 years (range 0.5–29.0 years) for patients diagnosed before the age of 40.

Left truncation was applied to correct for survival bias that may occur in studies with patient recruitment at a variable time after diagnosis (see statistical analysis). Consequently, a considerable number of patients did not contribute person-time to the prospective follow-up, leaving 418 patients for the main analyses. In univariate analysis, the risk of CBC was increased in patients younger than 40 years compared to those older than 40 years at primary BC (HR 2.42, 95 % CI 1.34–4.38). Furthermore, mutation carriership of *BRCA1* was associated with increased risk of CBC as compared to *BRCA2* mutation carriership (HR 2.32, 95 % CI 0.98–5.51). Both chemotherapy and endocrine therapy were significantly associated with a decreased risk of CBC (HR 0.45, 95 % CI 0.25–0.81 and HR 0.27, 95 % CI 0.08–0.86, respectively). For salpingo-oophorectomy, no association with CBC risk was found (HR 0.73, 95 % CI 0.37–1.43) (Table 4).

No deleterious effect of radiotherapy for primary BC, either after lumpectomy or after mastectomy, on CBC risk was found for the entire population (HR 0.84, 95 % CI 0.46–1.55 and HR 0.62, 95 % CI 0.17–2.23, respectively) (Table 4). Adjusting for age, adjuvant chemotherapy, adjuvant endocrine therapy, and type of *BRCA* mutation in a multivariate analysis still showed no association of radiotherapy on CBC risk (HR 0.74, 95 % CI 0.40–1.37 and HR 0.96, 95 % CI 0.23–3.97, respectively).

Subgroup analyses of patient younger than 40 years at BC onset

Also in the subgroup of patients younger than 40 years at primary BC diagnosis, no effect of radiotherapy for primary BC, either after lumpectomy or after mastectomy, on CBC risk was found in univariate analysis ($n = 211$; HR 1.41, 95 % CI 0.62–3.23 and HR 0.94, 95 % CI 0.18–4.86, respectively), and this was maintained in multivariate analysis (HR 1.53, 95 % CI 0.22–10.51 and HR 0.97, 95 % CI 0.41–2.30, respectively) (Fig. 1; Table 4). Median time interval between primary BC and CBC diagnoses was not significantly different between those treated with radiotherapy for primary BC compared to those patients not receiving radiotherapy (5.5 vs. 4.9 years, $p = 0.88$).

During follow-up, the number of patients at risk substantially decreased because a large proportion of patients

Table 1 Characteristics of the patients, radiotherapy vs. no radiotherapy

	Total ($n = 691$)* n (%)	RT after lumpectomy ($n = 349$) *n* (%)	No RT after mastectomy ($n = 252$) *n* (%)	RT after mastectomy ($n = 85$) *n* (%)	*p* value
Age at primary BC					
<30 years	55 (8.0)	29 (8.3)	19 (7.5)	7 (8.2)	0.943
30–34 years	115 (16.6)	59 (16.9)	39 (15.5)	15 (17.0)	
35–39 years	155 (22.4)	78 (22.3)	57 (22.6)	20 (23.5)	
40–44 years	129 (18.7)	64 (18.3)	49 (19.4)	16 (18.8)	
45–50 years	100 (14.5)	48 (13.8	35 (13.9)	16 (18.8)	
>50 years	137 (19.8)	71 (20.3)	53 (21.0)	11 (12.9)	
Mutation status					
BRCA1	517 (74.8)	277 (79.4)	186 (73.8)	50 (58.8)	<0.001
BRCA2	174 (25.2)	72 (20.6)	66 (26.2)	35 (41.2)	
Period of primary BC					
1980–1989	105 (15.2)	64 (18.3)	27 (10.7)	14 (16.5)	0.017
1990–1999	256 (37.1)	139 (39.8)	101 (35.3)	27 (31.8)	
2000–2013	330 (47.8)	146 (41.8)	164 (54.0)	44 (51.8)	
Tumor stage					
Tis	26 (4.0)	14 (4.1)	12 (5.2)	0	<0.001
T1	364 (56.0)	209 (61.8)	130 (56.5)	25 (30.9)	
T2	227 (34.9)	114 (33.7)	80 (34.8)	32 (39.5)	
T3	25 (3.9)	0	7 (3.0)	18 (22.2)	
T4	8 (1.2)	1 (0.3)	1 (0.4)	6 (7.4)	
Unknown	41	11	22	4	
Nodal status					
N0	424 (64.3)	241 (71.9)	169 (70.1)	13 (16.0)	<0.001
N1–3	235 (35.7)	94 (28.1)	72 (29.9)	68 (84.0)	
Unknown	32	14	11	4	
Histological grade					
Grade 1	17 (3.3)	8 (3.1)	7 (3.6)	2 (3.0)	0.988
Grade 2	106 (20.4)	54 (21.0)	37 (19.2)	14 (20.9)	
Grade 3	396 (76.3)	195 (75.9)	149 (77.2)	51 (76.1)	
Unknown	172	92	59	18	
Hormone receptor status					
Positive	227 (39.5)	108 (37.8)	80 (37.9)	39 (50.0)	0.124
Negative	348 (60.5)	178 (62.2)	131 (62.1)	39 (50.0)	
Unknown	116	63	41	7	
HER2 status					
Positive	17 (6.7)	9 (8.1)	5 (5.2)	3 (7.5)	0.646
Negative	236 (93.3)	101 (91.8)	95 (94.8)	37 (92.5)	
Unknown	438	239	152	45	
(Contralateral) risk-reducing mastectomy					
No	424 (64.5)	243 (73.0)	127 (51.8)	54 (68.4)	<0.001
Yes	233 (35.5)	90 (27.0)	118 (46.2)	25 (31.7)	
Unknown	34	16	7	6	
Salpingo-oophorectomy					
No	259 (41.2)	135 (42.5)	87 (38.2)	35 (44.3)	0.499
Yes	370 (58.8)	183 (57.5)	141 (61.8)	44 (55.7)	
Unknown	62	31	24	6	

Table 1 continued

	Total ($n = 691$)* n (%)	RT after lumpectomy ($n = 349$) n (%)	No RT after mastectomy ($n = 252$) n (%)	RT after mastectomy ($n = 85$) n (%)	p value
(Neo-) adjuvant chemotherapy					
No	319 (46.6)	176 (51.0)	109 (43.6)	30 (35.7)	0.022
Yes	365 (53.4)	169 (49.0)	141 (56.4)	54 (64.3)	
Unknown	7	4	2	1	
Adjuvant endocrine therapy					
No	555 (81.1)	300 (87.2)	203 (81.2)	48 (56.5)	<0.001
Yes	129 (18.9)	44 (12.8)	47 (18.9)	37 (43.5)	
Unknown	7	5	2	0	

RT radiotherapy; *BC* breast cancer

* Data on type of surgery (either lumpectomy or mastectomy) were missing in 5 patients who were treated with radiotherapy

were censored as they underwent a contralateral risk-reducing mastectomy, developed a BC recurrence or a second non-breast malignancy. In the group younger than 40 years at BC onset, 165 of 325 patients (51 %) were censored in the first 10 years of follow-up because of these three reasons (Fig. 2). Furthermore, since a large proportion of patients had less than 10 years of follow-up time, only 29 and 14 patients were available for the prospective analyses after 10 and 15 years of follow-up in this age group, respectively.

Treatment choices over time

Over the past decades, the proportion of patients at risk for radiation-induced CBC changed substantially as a result of an increased rate of mastectomy without radiotherapy instead of breast-conserving therapy for primary breast cancer, and an increased rate of contralateral risk-reducing mastectomy (Figs. 3, 4). For example, patients aged younger than 40 years at diagnosis more often opted for mastectomy without radiotherapy instead of breast-conserving therapy in 2010 (reaching 50 %), compared to less than 30 % in 1995. The proportion of patients receiving radiotherapy following mastectomy was relatively stable over time being around 10–15 % (Fig. 3). Since 2010, more than 60 % of patients younger than 40 years at primary diagnosis opted for contralateral risk-reducing mastectomy, after primary breast cancer treatment, which was less than 40 % in 1995 (Fig. 4).

Discussion and conclusion

The risk of CBC among BC patients with a *BRCA1/2* mutation is high, especially for younger patients. An association between adjuvant radiotherapy and the development of CBC in *BRCA1/2*-associated BC patients was not observed, neither in the entire cohort, nor in the subgroup of patients younger than 40 years at primary diagnosis. We found in this study that during follow-up the number of patients at risk for developing CBC substantially decreased due to either contralateral risk-reducing mastectomy or BC recurrence (26 and 14 %, respectively, within the first 5 years after primary BC among patients younger than 40 years). As a consequence, the number of patients at risk after 10 and 15 years of follow-up was too small to definitively exclude harmful effects of radiotherapy on the development of CBC among young *BRCA1/2* mutation carriers.

A few other studies also reported on CBC risk in *BRCA1/2*-associated BC patients treated with adjuvant radiotherapy compared to patients not treated with radiotherapy [13–15], and did not find an increased risk of CBC associated with adjuvant radiotherapy either. In the two multi-center retrospective cohort studies of breast cancer patients attending high-risk clinics [13, 14], the numbers of young *BRCA1/2* mutation carriers and follow-up periods were comparable to our study (145 out of 655 patients younger than 35 years with a median follow-up of 8 years in the study of Pierce et al. [13], and 357 out of 810 patients younger than 40 years with a median follow-up of 11 years in the study of Metcalfe et al. [14]). However, subgroup analyses among these younger patients were not reported. Bernstein performed a nested case–control study within the WECARE study (Women's Environmental Cancer and Radiation Epidemiology Study), which is a population-based study of patients with metachronous CBC [15], but again no results of subgroup analysis in younger patients were shown.

The main limitation of our study regarding the impact of radiotherapy on the CBC risk is the small number of patients at risk for CBC after 10–15 years of follow-up, as

Table 2 Characteristics of the patients with age at primary breast cancer diagnosis <40 years, radiotherapy vs. no radiotherapy

	Total ($n = 325$)* *n* (%)	RT after lumpectomy ($n = 166$) *n* (%)	No RT after mastectomy ($n = 115$) *n* (%)	RT after mastectomy ($n = 42$) *n* (%)	*p* value
Age at primary BC					
<30 years	55 (16.9)	29 (17.5)	19 (16.5)	7 (16.7)	0.996
30–34 years	115 (35.4)	59 (35.5)	39 (33.9)	15 (35.7)	
35–39 years	155 (47.7)	78 (47.0)	57 (49.6)	20 (47.6)	
Mutation status					
BRCA1	261 (80.3)	143 (86.1)	89 (77.4)	27 (64.3)	0.004
BRCA2	64 (19.7)	23 (13.9)	26 (22.6)	15 (35.7)	
Period of primary BC					
1980–1989	43 (13.2)	33 (19.9)	5 (4.4)	5 (11.9)	<0.001
1990–1999	114 (35.1)	68 (41.0)	35 (30.4)	10 (23.8)	
2000–2013	168 (51.7)	65 (39.2)	75 (65.2)	27 (64.3)	
Tumor stage					
Tis	9 (2.9)	4 (2.6)	5 (4.5)	0	<0.001
T1	179 (58.5)	95 (60.5)	70 (63.6)	14 (35.9)	
T2	103 (33.7)	57 (36.3)	31 (28.2)	15 (38.5)	
T3	8 (2.6)	0	3 (2.7)	5 (12.8)	
T4	7 (2.3)	1 (0.6)	1 (0.9)	5 (12.8)	
Unknown	19	9	5	3	
Nodal status					
N0	206 (66.0)	120 (74.5)	78 (70.3)	7 (17.9)	<0.001
N1–3	106 (34.0)	41 (25.5)	33 (29.7)	32 (82.1)	
Unknown	13	5	4	3	
Histological grade					
Grade 1	6 (2.5)	2 (1.7)	2 (2.1)	2 (6.5)	0.561
Grade 2	45 (18.4)	21 (17.7)	17 (18.1)	7 (22.6)	
Grade 3	193 (79.1)	96 (80.7)	75 (79.8)	22 (71.0)	
Unknown	81	47	21	11	
Hormone receptor status					
Positive	93 (33.1)	41 (29.5)	31 (30.7)	21 (52.5)	0.020
Negative	188 (66.9)	98 (70.5)	70 (69.3)	19 (47.5)	
Unknown	44	27	14	2	
HER2 status					
Positive	10 (7.6)	4 (7.8)	3 (5.5)	3 (12.0)	0.592
Negative	122 (92.4)	47 (92.2)	52 (94.5)	22 (88.0)	
Unknown	193	115	60	17	
(Neo-) adjuvant chemotherapy					
No	125 (38.9)	75 (45.7)	33 (28.9)	16 (39.0)	0.019
Yes	196 (61.1)	89 (54.3)	81 (71.1)	25 (61.0)	
Unknown	4	2	1	1	
Adjuvant endocrine therapy					
No	262 (81.4)	148 (90.2)	90 (78.9)	22 (52.4)	<0.001
Yes	60 (18.6)	16 (9.8)	24 (21.1)	20 (47.6)	
Unknown	3	0	1	0	
Contralateral risk-reducing mastectomy					
No	174 (55.8)	105 (66.0)	46 (41.1)	23 (56.1)	<0.001
Yes	138 (44.2)	54 (34.0)	66 (58.9)	18 (43.9)	
Unknown	13	7	3	1	

Table 2 continued

	Total ($n = 325$)* n (%)	RT after lumpectomy ($n = 166$) n (%)	No RT after mastectomy ($n = 115$) n (%)	RT after mastectomy ($n = 42$) n (%)	p value
Salpingo-oophorectomy					
No	128 (42.8)	66 (43.7)	43 (40.6)	18 (45.0)	0.825
Yes	171 (57.2)	85 (56.3)	63 (59.4)	22 (55.0)	
Unknown	26	15	9	2	

RT radiotherapy; *BC* breast cancer

* Data on type of surgery (either lumpectomy or mastectomy) were missing in 2 patients who were treated with radiotherapy

Table 3 Cumulative 5-, 10-, and 15-year risks of contralateral breast cancer

Years after diagnosis	Overall % (n at risk)	*BRCA1* mutation % (n at risk)	*BRCA2* mutation % (n at risk)	Age < 40 % (n at risk)	Age ≥ 40 % (n at risk)
5	8 (198)	9 (140)	5 (58)	11 (86)	6 (112)
10	19 (98)	21 (75)	15 (23)	32 (39)	10 (59)
15	32 (47)	35 (37)	15 (10)	40 (17)	23 (30)

Cumulative 5-, 10-, and 15-year risks of contralateral breast cancer in different subgroups of breast cancer patients (*BRCA1* mutation carriers vs. *BRCA2* mutation carriers and age at primary breast cancer <40 vs. ≥40 years). Only those patients who underwent DNA testing for *BRCA1/2* mutation before the diagnosis of contralateral breast cancer were included

studies including sporadic patients suggest that a minimal latency period of 10–15 years is needed to develop radiation-induced BC [19, 20]. It is, however, not known whether the latency period between exposure and development of a radiation-induced malignancy is similar for *BRCA1/2* mutation carriers compared to sporadic patients. Even, if the latency period in *BRCA1/2* mutation carriers is shorter, the number of patients at risk for CBC in our study group was too small to make definitive conclusions, especially since a large proportion of patients were already censored in the first 5 years. Given the number of events in patients younger than 40 years at primary BC diagnosis, our study had 80 % power to find an HR of at least 2.8 for adjuvant radiotherapy to be associated with increased risk of CBC.

In our total cohort, the 10-year cumulative risk of CBC in *BRCA1/2* mutation carriers was 19 %, while in the subgroup of patients younger than 40 years at BC onset this risk was 32 %. These risks are comparable to the risks reported in other studies [14, 21, 22]. Furthermore, the CBC risk was higher in *BRCA1* compared to *BRCA2* mutation carriers. Both the increased risk in younger patients and the increased risk in *BRCA1*- compared to *BRCA2*-associated BC patients have been described in other studies [14, 21–23]. Additionally, in our cohort adjuvant systemic therapy for primary BC, applying for both endocrine therapy and chemotherapy, was associated with a decreased risk of CBC. This effect, however, was only significant in the entire cohort and not in the subgroup of younger patients. Since the HRs were similar, this might be due to the lack of statistical power. The risk-reductive effect of adjuvant endocrine therapy on CBC risk in *BRCA1/2* mutation carriers has been reported in previous studies [14, 24, 25]. Regarding chemotherapy, three studies have investigated the association between chemotherapy and CBC [14, 23, 26], whereby only Reding et al. found a significant association with a relative risk of 0.5. Although this latter association is biologically not totally clear, further research is certainly warranted. We did not find any impact of salpingo-oophorectomy on CBC risk, which is in contrast with previous reports [27, 28], but is in line with more recent literature [29].

In our cohort, we found a growing preference over time for mastectomy without radiotherapy instead of breast-conserving therapy including radiotherapy. At the same time, the rate of contralateral risk-reducing mastectomy after primary breast cancer treatment has increased. Important reasons for the shift toward ablative breast surgery might be the improvements in and availability of (direct) breast reconstructive options, the increased awareness of the magnitude of the CBC risk and distress of screening, and the wish to avoid another treatment session for a second primary BC. Finally, the important findings of Heemskerk et al. showing that contralateral risk-reducing mastectomy improves survival, mainly in younger patients and those with favorable primary tumor characteristics [30], might lead to an even larger proportion of younger

Table 4 Univariate and multivariate hazard ratios for risk of contralateral breast cancer associated with selected factors

	Overall	Age < 40 years	
	Univariate analyses Number of patients: $n = 418$ Person years: 1105 years HR (95 % CI)	Univariate analyses Number of patients: $n = 211$ Person years: 467 years HR (95 % CI)	Multivariate analysis* Number of patients: $n = 211$ Person years: 467 years HR (95 % CI)
Age at primary breast cancer			
<40 years	2.42 (1.34–4.38)		
≥40 years	1		
Age at primary breast cancer			
Continuous	0.94 (0.90–0.97)	0.93 (0.85–1.01)	0.96 (0.88–1.06)
BRCA mutation			
BRCA1	2.32 (0.98–5.51)	3.52 (0.83–14.99)	2.33 (0.51–10.73)
BRCA2	1	1	1
Chemotherapy			
No	1	1	1
Yes	0.45 (0.25–0.81)	0.51 (0.24–1.09)	0.52 (0.24–1.14)
Endocrine therapy			
No	1	1	1
Yes	0.27 (0.08–0.86)	0.24 (0.06–1.02)	0.25 (0.05–1.23)
Salpingo-oophorectomy (time-dependent)			
No	1	1	
Yes	0.73 (0.37–1.43)	1.22 (0.53–2.81)	
Radiotherapy			
No radiotherapy after mastectomy	1	1	1
Radiotherapy after mastectomy	0.62 (0.17–2.23)	0.94 (0.18–4.86)	0.97 (0.41–2.30)
Radiotherapy after lumpectomy	0.84 (0.46–1.55)	1.41 (0.62–3.23)	1.53 (0.22–10.51)

HR Hazard ratio

* The following variables were incorporated in the multivariate model: age at primary breast cancer (continuous variable), type of *BRCA* mutation (*BRCA1* vs. *BRCA2*), adjuvant chemotherapy (yes vs. no), adjuvant endocrine therapy (yes vs. no), and radiotherapy (no radiotherapy after mastectomy vs. radiotherapy after mastectomy and vs. radiotherapy after lumpectomy)

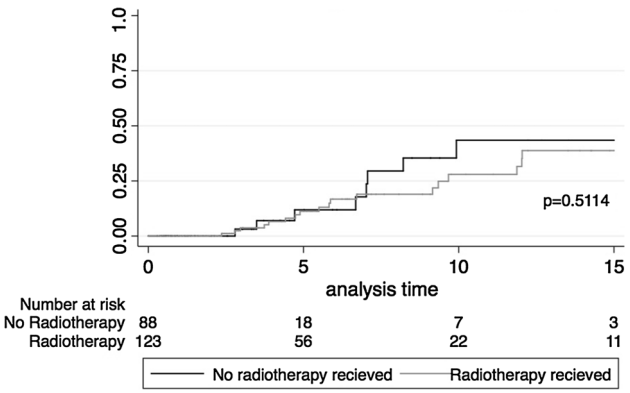

Fig. 1 Kaplan–Meier estimates of the contralateral breast cancer (CBC) risk in *BRCA1/2* mutation carriers, younger than 40 years of age at primary BC diagnosis. For this analysis, left truncation of analysis time at the DNA test date was applied, to correct for survival bias. Patients treated with radiotherapy (either after lumpectomy or after mastectomy) were compared to those not treated with radiotherapy at primary BC diagnosis

patients opting for mastectomy without radiotherapy and contralateral risk-reducing mastectomy after primary breast cancer diagnosis in the nearby future.

These trends in locoregional treatments eventually decreased the proportion of patients at risk for radiation-induced CBC over the past few decades. Nevertheless, the question whether adjuvant radiotherapy has deleterious effect on CBC risk still remains clinically important for a significant number of patients, who want to conserve their (ipsilateral and) contralateral breast. Moreover, in the nearby future a larger proportion of patients potentially might opt for breast-conserving treatment and abstain from contralateral risk-reducing mastectomy, due to an increased use of endocrine therapy as chemoprevention, improved diagnostic imaging techniques for screening, and improved effectiveness of adjuvant systemic therapy (for example, in combination with PARP inhibitors) [31–33].

In the current study, we could not find an association between radiotherapy for primary BC and risk of CBC in

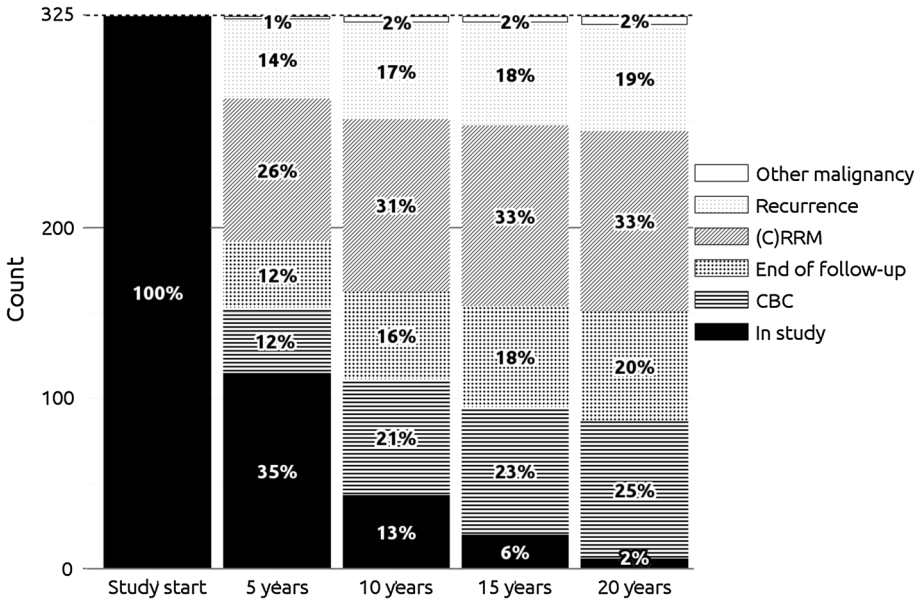

Fig. 2 Cumulative frequency of contralateral breast cancer (CBC) or reasons for censoring event at study start and after 5, 10, 15, and 20 years of follow-up in all included patients who were younger than 40 years of age at primary breast cancer diagnosis. Recurrence includes both ipsilateral recurrence, a second ipsilateral primary tumor, and metastatic disease. (C)RRM = (contralateral) risk-reducing mastectomy. End of FU (follow-up) comprises patients who did not reach the primary endpoint or other censoring event at data cut-off or were lost to follow up

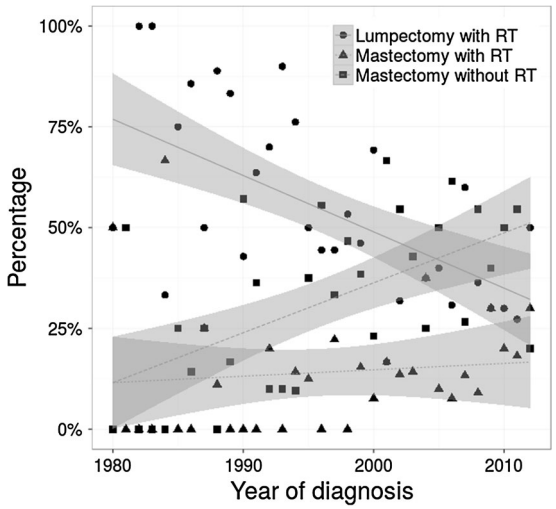

Fig. 3 Distribution of the choice of local therapy at primary breast cancer diagnosis by year of diagnosis among patients younger than 40 years of age with a *BRCA1* or *BRCA2* mutation. Regression line of best fit and estimate of 95 % confidence interval (*gray*). *RT* Radiotherapy

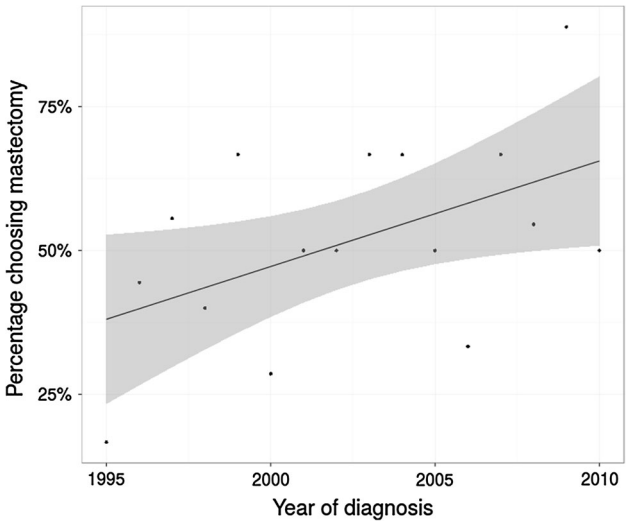

Fig. 4 Proportion of patients with a *BRCA1* or *BRCA2* mutation and breast cancer diagnosis below the age of 40 opting for contralateral (or bilateral) risk-reducing mastectomy (either at primary breast cancer treatment or within the years after primary breast cancer) by year of breast cancer diagnosis. Regression line of best fit and estimate of 95 % confidence interval (*gray*)

(young) *BRCA1/2* mutation carriers compared to sporadic patients; however, the number of patients at risk after 10 and 15 years of follow-up was too small to definitively exclude harmful effects of adjuvant radiotherapy. An increase in the percentage of young patients with *BRCA1/2*-associated breast cancer choosing for conserving their (ipsilateral and) contralateral breast is not unlikely. Therefore, future research in larger study populations with minimal follow-up of 10 years is needed to achieve a better understanding of the true effect of radiotherapy on the CBC risk in *BRCA1/2*-associated BC patients. This will only be possible by combining study populations through collaborative efforts on a national or even international level.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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