Double trouble: exploring risk factors to better predict contralateral breast cancer

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CHAPTER 3

The influence of adjuvant systemic regimens on contralateral breast cancer risk and receptor subtype

J Natl Cancer Inst. 2019 Jul 1;111(7):709-718

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Abstract

Background

An increasing number of breast cancer (BC) survivors are at risk of developing contralateral breast cancer (CBC). We aimed to investigate the influence of various adjuvant systemic regimens on, subtype-specific, risk of CBC.

Methods

This population-based cohort study included female patients diagnosed with first invasive BC between 2003-2010; follow-up was complete until 2016. Clinico-pathological data were obtained from the Netherlands Cancer Registry and additional data on receptor status through linkage with PALGA: the Dutch Pathology Registry. Cumulative incidences (death and distant metastases as competing risk) and hazard ratios (HRs) were estimated for all invasive metachronous CBC and CBC subtypes.

Results

Of 83,144 BC patients, 2,816 developed a CBC; the 10-year cumulative incidence was 3.8% (95% confidence interval [CI]=3.7-4.0%). Overall, adjuvant chemotherapy (HR=0.70, 95%CI=0.62-0.80), endocrine therapy (HR=0.46, 95%CI=0.41-0.52), and trastuzumab with chemotherapy (HR=0.57, 95%CI=0.45-0.73) were strongly associated with a reduced CBC risk. Specifically, taxane-containing chemotherapy (HR=0.48, 95%CI=0.36-0.62) and aromatase inhibitors (HR=0.32, 95% CI=0.23-0.44) were associated with a large CBC risk reduction. More detailed analyses showed that endocrine therapy statistically significantly decreased the risk of estrogen receptor (ER)-positive CBC (HR=0.41, 95%CI=0.36-0.47), but not ER-negative CBC (HR=1.32, 95%CI=0.90-1.93), compared with no endocrine therapy. Patients receiving chemotherapy for ER-negative first BC had a higher risk of ER-negative CBC from 5 years of follow-up (HR=2.84, 95%CI=1.62-4.99), compared with patients not receiving chemotherapy for ER-negative first BC.

Conclusion

Endocrine therapy, chemotherapy, as well as trastuzumab with chemotherapy reduce CBC risk. However, each adjuvant therapy regimen had a different impact on the CBC subtype distribution. Taxane-containing chemotherapy and aromatase inhibitors were associated with the largest CBC risk reduction.

Introduction

Breast cancer (BC) survival has increased considerably, largely as a result of increasing use of (neo)adjuvant therapies[1]. As a consequence, a greater number of women are at risk of developing a second primary tumor in the contralateral breast. Studies have shown that the 10-year risk of contralateral breast cancer (CBC) is 4-7%[2-5].

There is increasing evidence that patients who received adjuvant endocrine therapy or chemotherapy for their first BC have a lower risk of developing CBC. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that 5-year tamoxifen use was associated with a 38% reduction in CBC risk after 10 years of follow-up[6], and adjuvant chemotherapy with a 20% decrease[7].

CBC patients may have a worse prognosis compared with patients with unilateral BC[2,4,8,9]. An explanation for this worse prognosis, besides having been diagnosed with yet another cancer, may be found in the impact of adjuvant systemic therapy on CBC tumor biology[9], or misclassification of metastatic disease as a CBC[8].

Little is known about the influence of adjuvant systemic therapy on the (hormone) receptor subtype of CBC. Some studies showed a higher proportion of estrogen receptor (ER)-negative CBC among patients who received endocrine therapy for their first BC compared with those who did not[10-14]. The studies that evaluated the effects of adjuvant therapy on subtype-specific CBC risk, however, were based on small numbers. Since adjuvant trastuzumab was introduced for early-stage BC in 2005, the impact on CBC risk has not yet been described.

We therefore aimed to investigate the influence of different regimens of adjuvant endocrine therapy, chemotherapy, and trastuzumab on CBC risk overall and by (hormone) receptor subtype within a large population-based cohort of women diagnosed with invasive BC.

Methods

Study population

The cohort included 83,144 female patients diagnosed with invasive BC, who underwent surgery, in 2003-2010 (Figure 1). Patients were selected from the population-based Netherlands Cancer Registry (NCR), which contains data on all newly diagnosed cancer patients nationwide. Follow-up for all patients started 3 months after first BC diagnosis; therefore, patients who had developed distant metastases or CBC or died within 3 months after diagnosis were excluded.

Patient and tumor characteristics

The NCR provided clinico-pathological data; follow-up on second cancers and vital status

was complete until February 1, 2016, but information of recurrences was complete only for patients diagnosed in 2003-2006 and for 56% in 2007-2008. Pathological information on tumor size, lymph node status, and metastasis collected was coded into tumor stage according to the TNM Classification of Malignant Tumors [15]; if pathological information was missing, clinical stage was used.

Since 2003, the NCR registers receptor status, as determined by immunohistochemistry (IHC). Tumors were defined ER-positive or progesterone receptor (PR)-positive when at least 10% of tumor cells stained positive. In the Netherlands, recommendations for HER2/neu-receptor (HER2) testing and use of adjuvant trastuzumab were implemented from 2005[16]. A tumor was considered HER2-positive if IHC was 3+ (strong and complete membranous expression in >10% of tumor cells) or if IHC was 2+ when additional confirmation with in situ hybridization was available, but considered unknown if in situ hybridization confirmation was missing. To overcome incompleteness in data on receptor status, all CBC patients were linked to the nationwide network and registry of histo- and cytopathology (PALGA)[17] to retrieve where possible information on ER, PR, and HER2 status for both the first BC and CBC.

Data were handled in accordance with privacy regulations for medical research[18]. The review boards of the NCR and PALGA approved the proposal. All data were anonymous to the researchers involved.

Statistical analysis

The primary outcome was the development of metachronous CBC, defined as an invasive BC in the contralateral breast at least 3 months after the first BC diagnosis. Time at risk ended at the date of CBC, distant metastases, death, or end of follow-up, whichever came first. The cumulative incidence of CBC was estimated with distant metastases and death as competing risks.

Multivariable Cox Proportional Hazards (CPH) analysis with time since first BC diagnosis as time-scale was used to examine the effect of adjuvant systemic therapy (chemotherapy, endocrine therapy, trastuzumab, or combined) on CBC risk (hazard ratios [HRs]). Subdistribution HRs were calculated accounting for death and distant metastases as competing risks. We examined the association between specific types of chemotherapy (taxane-containing/anthracycline-containing) and endocrine therapy (tamoxifen/aromatase inhibitors) and CBC risk. All models included all systemic therapies and were adjusted for age and stage (III vs I-II) at first BC diagnosis, factors that were previously shown to be important predictors of CBC in the Dutch population[2], though in our dataset only stage changed the log HR of systemic therapy by greater than 15%. Radiotherapy, ER-status, HER2-status, and year of diagnosis did not change the log HR by more than 15%, and were only included for sensitivity analyses. Using the nlcheck function in STATA, there was no evidence for nonlinearity of age in the multivariable model[19]; therefore, age was continuous in all models, except for Supplementary Tables 1-3 to illustrate the differences between age categories. Because the NCR did not register menopausal status, we used age younger than 50 years and at least 50 years as a proxy for pre- and post-menopausal status[20]. Potential effect modification of menopause was assessed with a specification link test for single-equation models[21,22]. The proportional hazard assumption was assessed using Schoenfeld residuals[23]. We performed sensitivity analyses based on selection of years with complete recurrence information, additional censoring on local/regional recurrence, and a stricter definition of metachronous CBC (≥1 year after first BC).

The effect of adjuvant therapy on subtype-specific CBC was estimated using cumulative incidence curves, additionally accounting for other CBC subtypes as competing risks; for example, to determine risk of ER-positive CBC, the following events were treated as competing risks: ER-negative CBC, ER-unknown CBC, distant metastases, and death. The HER2-specific analysis included only patients diagnosed since 2005. Because there was interaction between treatment and subtype ($P_{interaction}$<.001), we used joint multivariable CPH analyses[24] to determine the association of adjuvant therapies with CBC ER status in separate models for each of the first BC subtypes. We defined subtype as hormone receptor (HR)+/HER2− (ie, ER+ and/or PR+ and HER2−), HR+/HER2+ (ie, ER+ and/or PR+ and HER2+), HR−/HER2+ (ie, ER−/PR−/HER2+), and HR−/HER2− (ie, ER−/PR−/HER2-). Each model included ER-specific CBC (ER-positive/ER-negative/ER-unknown), distant metastases, and death as possible outcome. These subtype-specific models were adjusted for trastuzumab, age, and stage.

All P-values are two sided with the statistical significance level set at less than .05. Tests for heterogeneity between subtypes or follow-up period were performed using the Wald test. Analyses were performed using STATA, version 13.1 (StataCorp).

Results

The cohort included for analyses comprised 83,144 patients diagnosed with invasive first BC with a median follow-up of 7.7 years (range 0.3-13.1) (Figure 1). Median time to develop a CBC (N=2,816) after a first BC was 4.6 years (range 0.3-12.7). Characteristics of the cohort are presented in Table 1. The distributions of adjuvant systemic therapies according to patient and tumor characteristics are presented in Supplementary Table 1.

The 5- and 10-year cumulative incidences of CBC were 1.9% (95% confidence interval [CI]=1.8-2.0%) and 3.8% (95%CI=3.7-4.0%), respectively (Supplementary Table 2). CBC cumulative incidence increased at a rate of 0.4% per year.

In a multivariable CPH model (Table 2), treatment with adjuvant chemotherapy (HR=0.70, 95%CI=0.62-0.80), endocrine therapy (HR=0.46, 95%CI=0.41-0.52), endocrine and chemotherapy (HR=0.35, 95%CI=0.31-0.39), and chemotherapy combined with trastuzumab (HR=0.57, 95%CI=0.45-0.73) were strongly associated with a reduced CBC

risk compared with patients who did not receive systemic therapy. Patients receiving trastuzumab combined with endocrine therapy and chemotherapy were the least prone to develop CBC (HR=0.24, 95%CI=0.17-0.33; P<.05 compared with any other treatment group; Table 2). Adjustment for radiotherapy, year of diagnosis, ER and HER2 status, or taking distant metastases and death as competing risks into account did not substantially alter these results (Supplementary Table 3), neither did additional censoring on local and regional recurrence or a stricter definition of CBC (Supplementary Table 4). Radiotherapy was not associated with CBC risk (HR=0.94, 95%CI=0.86-1.02; Supplementary Table 3). Therapy-specific analysis showed that taxane-containing chemotherapy was strongly associated with a CBC risk reduction (HR=0.48, 95%CI=0.36-0.62; Table 2) compared with patients who did not receive chemotherapy, but not anthracycline-containing chemotherapy (HR=0.91, 95%CI=0.77-1.06). Treatment with aromatase inhibitors (HR=0.32, 95%CI=0.23-0.44) was associated with a stronger CBC risk reduction compared to tamoxifen (HR=0.48, 95%CI=0.44-0.53) ($P_{heterogeneity}$=.01). There was no evidence for effect modification between menopausal status and any adjuvant therapy on CBC risk.

Table 1. Patient, tumor, and treatment characteristics of all patients diagnosed with first BC between 2003-2010 and subsequent CBC

Characteristics	First BC No. (%)*	CBC No. (%)*
Total	83,144 (100.0)	2,816 (100.0)
Age at diagnosis, y		
<35	1,826 (2.2)	22 (0.8)
35-44	9,693 (11.7)	153 (5.4)
45-54	22,154 (26.7)	523 (18.6)
55-64	21,778 (26.2)	801 (28.4)
65-74	17,222 (20.7)	771 (27.4)
75-84	8,242 (9.9)	444 (15.8)
≥85	2,229 (2.7)	102 (3.6)
Median age at diagnosis, y (range)	58.5 (19.4-101.3)	63.9 (24.8-97.0)
Tumor stage		
I	39,676 (47.7)	1,736 (63.3)
II	32,158 (38.7)	703 (25.6)
III	11,310 (13.6)	237 (8.6)
IV	†	68 (2.5)
Unknown	†	72
Histological grade		
Grade 1	17,393 (22.8)	706 (28.9)
Grade 2	34,153 (44.8)	1,091 (44.6)
Grade 3‡	24,632 (32.3)	647 (26.5)
Unknown	6,966	372
Morphology		
Ductal	64,044 (77.0)	2,051 (72.8)
Lobular	9,233 (11.1)	380 (13.5)
Mixed ductal/lobular	3,013 (3.6)	112 (4.0)
Other	6,854 (8.2)	273 (9.7)
ER status		
Positive	64,886 (81.7)	2,200 (81.7)
Negative	14,579 (18.3)	492 (18.3)
Unknown	3,679	124
PR status		
Positive	50,674 (66.1)	1,618 (61.6)
Negative	26,004 (33.9)	1,010 (38.4)
Unknown	6,466	188
HER2 status§		
Positive	11,061 (17.3)	335 (12.6)
Negative	52,956 (82.7)	2,314 (87.4)
Unknown	19,127	167
Subtype‖		
HR+/HER2−	45,441 (71.8)	1,935 (74.9)
HR+/HER2+	6,957 (11.0)	189 (7.3)
HR−/HER2+	3,618 (5.7)	117 (4.5)
HR−/HER2−	7,304 (11.5)	344 (13.3)
Unknown	19,824	231
(Neo)adjuvant therapy for first BC		
No (neo)adjuvant therapy¶	31,290 (37.6)	-
CT	8,889 (10.7)	-
ET	17,359 (20.9)	-
CT + ET	19,923 (24.0)	-
CT + TRA	2,728 (3.3)	-
CT + ET + TRA	2,955 (3.6)	-
(Neo)adjuvant CT		
No CT	48,717 (58.6)	-
Taxane-containing CT#	4,427 (5.3)	-
Anthracycline-containing CT**	6,802 (8.2)	-
Taxane- + anthracycline-containing CT	3,590 (4.3)	-
CT, other or type unknown††	19.608 (23.6)	-
(Neo)adjuvant ET		
No ET	42,861 (51.6)	-
Tamoxifen‡‡	33,862 (40.7)	-
Aromatase inhibitors	2,393 (2.9)	-
Tamoxifen‡‡ + aromatase inhibitors	4,028 (4.8)	-

Abbreviations: BC = breast cancer; CBC = contralateral breast cancer; CT = chemotherapy; ER = estrogen receptor; ET = endocrine therapy; HER2 = human epidermal growth factor receptor2; HR+ = hormone receptor positive; HR− = hormone receptor negative; NCR = Netherlands Cancer Registry; PR = progesterone receptor; TRA = trastuzumab

* Percentages may not total 100 because of rounding

† Excluded

‡ Including 12 first BCs and 1 CBC that were defined as 'undifferentiated' in the NCR

§ HER2 status distribution of first BCs from 2005-2010: positive N=10.388 (17.0%), negative N=50.652 (83.0%), unknown N=2.313

‖ HR+ = ER+ and/or PR+; HR− = ER− and PR−

¶ No chemotherapy, endocrine therapy or trastuzumab (with or without radiotherapy)

The chemotherapeutic combination contains taxanes, but no anthracyclines

** The chemotherapeutic combination contains anthracyclines, but no taxanes

†† All other chemotherapeutic drugs and combinations (e.g. CMF) or type unknown

‡‡ The NCR specifically codes aromatase inhibitors; Tamoxifen is coded as endocrine therapy

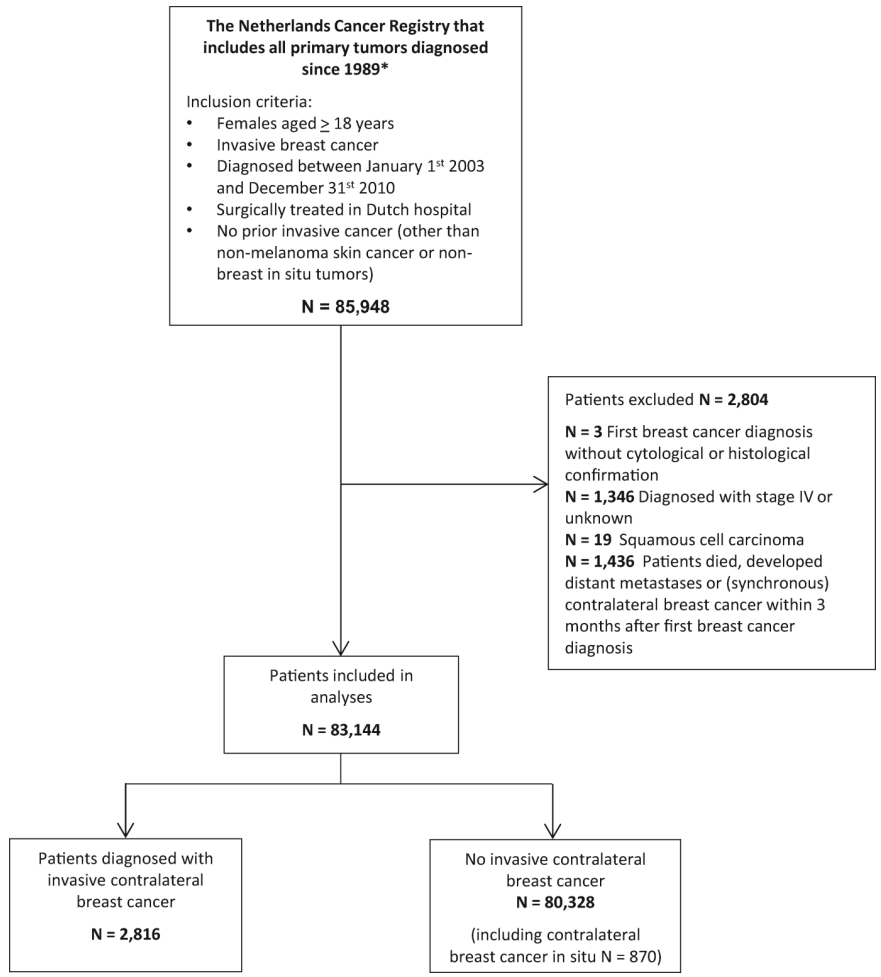

Figure 1. Overview of the selection of breast cancer patients
*After notification by the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) and the national hospital discharge database, trained NCR personnel collected data directly from patients' files

Because the proportional hazard assumption was violated for chemotherapy, endocrine therapy, and trastuzumab, the multivariable CPH analyses were also performed stratified for follow-up duration up to and including 5 years and longer than 5 years (Table 2)[25], following higher recurrence risk reductions for the period up to and including 5 years shown by the EBCTCG[6,26]. In our study, CBC risk was statistically significantly stronger reduced in the first 5 years of follow-up among patients who had received chemotherapy and endocrine therapy combined ($P_{heterogeneity}$<.001) or chemotherapy and trastuzumab combined ($P_{heterogeneity}$=.04) than in the period longer than 5 years of follow-up. However, overall, systemic therapy remained statistically significantly associated with a reduced CBC risk after 5 years of follow-up.

Patients diagnosed with stage III first BC showed a statistically significantly higher risk of CBC (HR=1.48, 95%CI=1.30-1.69) compared with patients with stage I-II BC, but not if distant metastases and death were considered as competing risks (Supplementary Table 1). CBC risk did not differ by age at first BC, apart from a lower CBC risk for patients aged 45-54 years (HR=0.88, 95%CI=0.80-0.98) and 85 years and older (HR=0.55; 95%CI=0.37-0.81) compared with patients aged 55-64 years.

A greater proportion of CBCs among patients treated with endocrine therapy was ER-negative (23.2%) compared with that among patients without endocrine therapy for ER-positive first BC (6.9%; Supplementary Table 5). The proportion of ER-negativity between the first BC and CBC of all patients did not differ (both 18.3%; Table 1). Among patients with ER-positive first BC (Figure 2A), the difference for ER-positive CBC was 3.4% after 10-years of follow-up between patients who received endocrine therapy (1.8%, 95%CI=1.6-2.0) and those who did not (5.2%, 95%CI=4.9-5.5). Multivariable joint CPH analyses (Table 3) classifying the first BCs in four BC subtypes showed that among patients diagnosed with HR+/HER2− first BC, endocrine therapy statistically significantly decreased the risk of ER-positive CBC (HR=0.41, 95%CI=0.36-0.47), but not ER-negative CBC (HR=1.32, 95%CI=0.90-1.93) ($P_{heterogeneity}$=<.001).

We observed a 10-year cumulative incidence of ER-negative CBC of 1.9% (95%CI=1.6-2.2) for patients who received chemotherapy for ER-negative first BC and 1.2% (95%CI=0.9-1.6) for patients who did not (Figure 2B). Multivariable joint CPH analyses showed that patients diagnosed with HR−/HER2− (triple negative) first BC had a higher risk of triple-negative CBC when they received adjuvant chemotherapy (HR=1.56, 95%CI=1.00-2.42), compared to patients who did not (Supplementary Figure 1). In subsequent analyses within ER-negative tumors (insufficient data for triple negatives), we found no association between chemotherapy received for ER-negative first BC and risk of an ER-negative CBC in the first 5 years of follow-up (HR=1.28, 95%CI=0.84-1.95). However, risk of ER-negative CBC was increased for patients treated with chemotherapy after more than 5 years of follow-up (HR=2.84, 95%CI=1.62-4.99) compared with patients who did not receive chemotherapy for ER-negative first BC. Therapy-specific analyses (Supplementary Table 6) showed a statistically non-significant increased risk of ER-negative CBC for anthracycline-containing chemotherapy (HR=1.32, 95%CI=0.86-2.04), which was the strongest after 5 years of follow-up (HR=1.88, 95%CI=0.91-3.86), but a statistically significant decreased risk for taxane-containing chemotherapy (HR=0.36, 0.17-0.75). The combination of taxane- and anthracycline-containing chemotherapy was associated with a statistically nonsignificant decreased risk of ER-negative CBC (HR=0.59, 95%CI=0.28-1.22; Supplementary Table 6). The proportion of HER2-positive CBC was 33.7% for patients treated with trastuzumab for HER2-positive first BC (Supplementary Table 7) with a 5-year cumulative incidence of 0.4% (95%CI=0.3-0.7; Figure 2C), and this was 12.0% for patients who did not receive trastuzumab, with a 5-year cumulative incidence of 0.2% (95%CI=0.1-0.4; Figure 2C).

Table 2. Multivariable Cox regression analyses of CBC risk related to the (neo)adjuvant systemic therapy for the first BC

(Neo)adjuvant systemic therapy	Total follow-up				≤5 years follow-up					>5 years follow-up					$P_{heterogeneity}$ †
	No. of patients	HR	95% CI	P*	No. of patients	No. of CBC	HR	95% CI	P*	No. of patients	No. of CBC	HR	95% CI	P*	
Model 1: (Neo)adjuvant therapy combined‡															
No (neo)adjuvant therapy§	31,290	1.00	Ref.		4,644	913	1.00	Ref.		26,646	700	1.00	Ref.		
CT	8,889	0.70	0.62-0.80	<.001	2,208	172	0.66	0.56-0.78	<.001	6,681	146	0.79	0.65-0.95	.01	.16
ET	17,359	0.46	0.41-0.52	<.001	3,678	218	0.42	0.36-0.49	<.001	13,681	149	0.50	0.42-0.60	<.001	.13
CT + ET	19,923	0.35	0.31-0.39	<.001	2,287	177	0.26	0.22-0.30	<.001	17,636	227	0.50	0.42-0.59	<.001	<.001
CT + TRA	2,728	0.57	0.45-0.73	<.001	477	43	0.47	0.35-0.64	<.001	2,251	33	0.77	0.54-1.10	.16	.04
CT + ET + TRA	2,955	0.24‖	0.17-0.33	<.001	261	21	0.20	0.13-0.31	<.001	2,694	17	0.31	0.19-0.51	<.001	.19
Model 2: Therapy-specific subgroups¶															
(Neo)adjuvant CT															
No CT	48,717	1.00	Ref.		8,341	1,132	1.00	Ref.		40,376	849	1.00	Ref.		
Taxane-containing CT#	4,427	0.48	0.36-0.62	<.001	620	36	0.42	0.30-0.58	<.001	3,807	24	0.64	0.42-0.97	.04	.13
Anthracycline-containing CT**	6,802	0.91	0.77-1.06	.23	1,127	100	0.85	0.68-1.07	.16	5,675	140	0.98	0.79-1.22	.86	.38
Taxane+anthracycline-containing CT	3,590	0.69	0.52-0.91	.009	475	44	0.71	0.50-0.99	.05	3,115	27	0.66	0.42-1.06	.08	.83
CT, other or type unknown††	19,608	0.70	0.62-0.78	<.001	2,992	232	0.61	0.52-0.71	<.001	16,616	232	0.84	0.71-1.00	.05	.01
(Neo)adjuvant ET															
No ET	42,861	1.00	Ref.		7,319	1,127	1.00	Ref.		35,542	879	1.00	Ref.		
Tamoxifen‡‡	33,862	0.48	0.44-0.53	<.001	5,458	352	0.41	0.37-0.47	<.001	28,404	312	0.57	0.49-0.65	<.001	.001
Aromatase inhibitors	2,393	0.32	0.23-0.44	<.001	407	20	0.31	0.20-0.48	<.001	1,986	18	0.33	0.20-0.53	<.001	.86
Tamoxifen‡‡ + aromatase inhibitors	4,028	0.45	0.36-0.56	<.001	371	45	0.40	0.29-0.55	<.001	3,657	63	0.50	0.38-0.67	<.001	.28

Abbreviations: BC = breast cancer; CBC = contralateral breast cancer; CI = confidence interval; CT = chemotherapy; ET = endocrine therapy; HR = hazard ratio; Ref. = reference group; TRA trastuzumab

* Two-sided Wald test P-value

† Heterogeneity of HRs between ≤5 and >5 years follow-up duration

‡ Adjusted for age and stage at first breast cancer diagnosis

§ No chemotherapy, endocrine therapy or trastuzumab (with or without radiotherapy)

‖ We compared the CT+ET+TRA group versus the other treatment groups by changing the reference (vs. CT, P<.001) (vs. ET, P<.001) (vs. CT+ET, P=.03) (vs. CT+TRA, P<.001)

¶ Adjusted for trastuzumab therapy, age, and stage at first breast cancer diagnosis

The chemotherapeutic combination contains taxanes, but no anthracyclines

** The chemotherapeutic combination contains anthracyclines, but no taxanes

†† All other chemotherapeutic drugs and combinations (e.g. CMF) or type unknown

‡‡ The registry specifically codes aromatase inhibitors; Tamoxifen is coded as hormonal treatment

Table 3. Joint multivariable Cox regression analyses for each of the first tumor subtypes assessing the association of (neo)adjuvant systemic treatment of the first BC with subtype-specific CBC risk*

Subtype first BC	No. of patients	ER-positive CBC				ER-negative CBC				$P_{heterogeneity}$ ‡
		No. of CBC cases	HR	95% CI	P†	No. of CBC cases	HR	95% CI	P†	
Model 1: HR+/HER2−§										
ET										
No ET	18,125	860	1.00	Ref.		54	1.00	Ref.		
ET	27,316	397	0.41	0.36-0.47	<.001	107	1.32	0.90-1.93	.15	<.001
CT										
No CT	28,973	1,048	1.00	Ref.		100	1.00	Ref.		
CT	16,468	209	0.56	0.46-0.67	<.001	61	1.15	0.78-1.70	.48	<.001
Model 2: HR+/HER2+§										
ET										
No ET	2,282	83	1.00	Ref.		8	1.00	Ref.		
ET	4,675	46	0.43	0.28-0.66	<.001	22	1.22	0.50-2.98	.66	.04
CT										
No CT	3,186	96	1.00	Ref.		13	1.00	Ref.		
CT	3,771	33	0.61	0.29-1.27	.19	17	2.33	0.71-6.62	.16	.05
Model 3: HR−/HER2+§										
ET										
No ET	3,538	77	1.00	Ref.		36	1.00	Ref.		
ET	80	0	$7.15 \cdot 10^{-10}$	$1.67 \cdot 10^{-10}$-$3.06 \cdot 10^{9}$	<.001	2	2.19	0.51-9.36	.29	-
CT										
No CT	1,041	19	1.00	Ref.		9	1.00	Ref.		
CT	2,557	58	1.22	0.57-2.64	.61	29	4.01	1.64-9.81	.002	.05
Model 4: HR−/HER2−§										
ET										
No ET	7,126	124	1.00	Ref.		134	1.00	Ref.		
ET	178	4	1.22	0.45-3.32	.69	1	0.30	0.04-2.13	.23	.21
CT										
No CT	2,255	42	1.00	Ref.		32	1.00	Ref.		
CT	5,049	86	0.60	0.38-0.93	.02	103	1.17	0.77-1.78	.47	.02

Abbreviations: BC = breast cancer; CBC = contralateral breast cancer; CI = confidence interval; CT = chemotherapy; ER = estrogen receptor; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; HR+ = hormone receptor positive; HR− = hormone receptor negative; PR = progesterone receptor; Ref. = reference group

* Adjusted for trastuzumab therapy, age and stage at first breast cancer diagnosis

† Two-sided Wald test P-value

‡ Heterogeneity of HRs between ER-positive and ER-negative CBC

§ R+ = ER+ and/or PR+; HR− = ER− and PR−

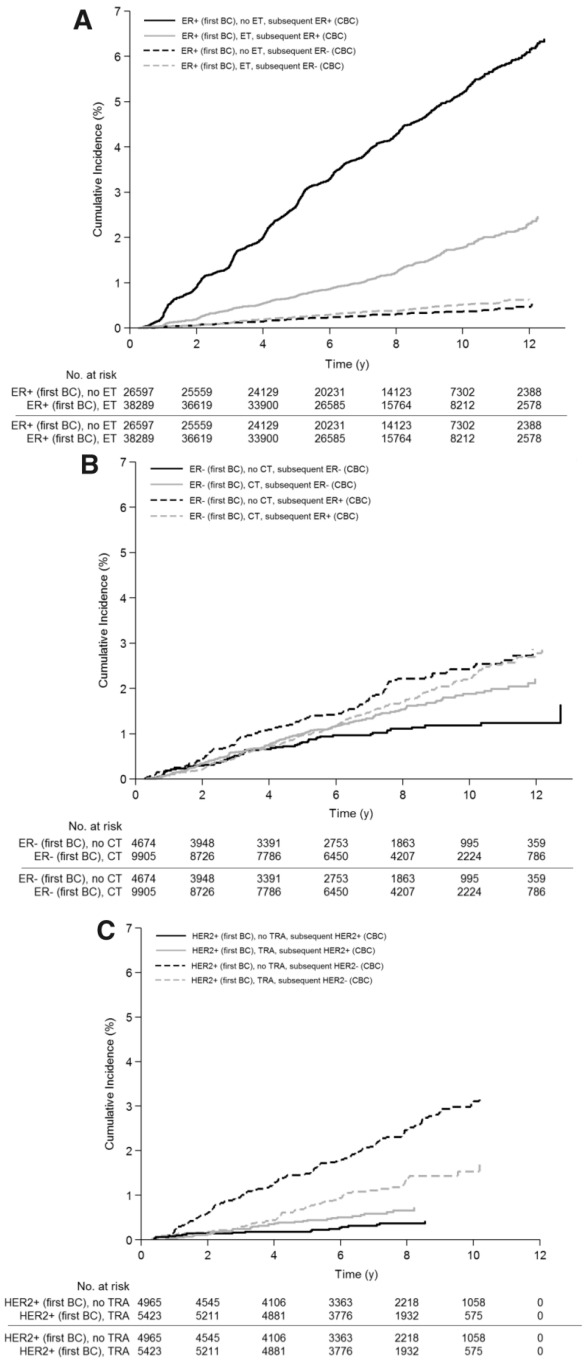

Figure 2. Cumulative incidence of contralateral breast cancer (CBC) by estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status

Panel A) Cumulative incidence curves showing the risk of ER-positive or ER-negative CBC after ER-positive first breast cancer (BC), stratified for adjuvant endocrine therapy; **Panel B)** Cumulative incidence curves showing the risk of ER-positive or ER-negative CBC after ER-negative first BC, stratified for adjuvant chemotherapy; **Panel C)** Cumulative incidence curves showing the risk of HER2-positive or HER2-negative CBC after HER2-positive first BC, stratified for adjuvant trastuzumab therapy. For these analyses, patients diagnosed with invasive BC between 2003-2004 were excluded because trastuzumab was not yet widely prescribed in those years. Each panel in the figure consist of two cumulative incidence curves combined (duplicated risk table). In all panels, analyses were performed accounting for death, distant metastases, and CBC-subtype as competing risks (e.g. for the analysis of ER-positive CBC, the following events were treated as competing risks: ER-negative CBC, ER-unknown CBC, distant metastases, and death). Abbreviations: CT = chemotherapy; ET = endocrine therapy

Discussion

In this population-based cohort study comprising 83,144 BC patients, we observed a 10-year cumulative incidence of metachronous CBC of 3.8%. Overall, receipt of adjuvant chemotherapy, endocrine therapy, and/or trastuzumab with chemotherapy was strongly associated with a reduced CBC risk. More detailed analyses showed that endocrine therapy was only associated with a reduced risk of ER-positive CBC and did not protect against the development of ER-negative CBC. Patients receiving chemotherapy for ER-negative first BC had a higher risk of ER-negative CBC after 5 years of follow-up compared with patients who did not receive chemotherapy for ER-negative first BC.

The 10-year cumulative incidence of CBC in our study was relatively low compared with earlier studies[3,4,27], but consistent with other, more contemporary studies[2,5,28,29]. In our study, adjuvant endocrine therapy, chemotherapy, and trastuzumab combined with chemotherapy were associated with overall 54%, 30%, and 43% risk reductions of CBC, respectively. The risk reductions associated with endocrine therapy and chemotherapy in our study are slightly higher than the reductions seen in meta-analyses of the EBCTCG[6,7,26]. Radiotherapy was not associated with an increased CBC risk, which is consistent with other studies with a mean follow-up time less than 15 years[2,29-31].

We observed a strongly reduced CBC risk among patients treated with taxane-containing chemotherapy. The increase in use of taxane-containing chemotherapy coincided with a declining trend in CBC incidence over the years (Supplementary Table 2). Unfortunately, we have no biological explanation for the different effect of taxanes vs anthracyclines. However, our finding is consistent with a randomized adjuvant trial showing an improvement in disease-free survival for docetaxel and cyclophosphamide compared with doxorubicin and cyclophosphamide[32]. The WECARE case-control study[33] found a lesser, statistically nonsignificant CBC risk reduction among patients treated with taxane-containing or with anthracycline-containing chemotherapy of approximately 0.80, but patients were diagnosed in an earlier period (1986-2008) and the study had smaller numbers.

Little is known about the influence of chemotherapy on subtype distribution of CBC. In our study, adjuvant chemotherapy provided for ER-negative first BC was associated with a decreased risk of ER-positive CBC, which might partly be explained by chemotherapy-

induced amenorrhea[34,35]. However, we found an increased risk of ER-negative CBC for patients receiving chemotherapy after 5 years of follow-up. This might possibly be a chance finding. Another possibility is that the ER-negative CBCs that developed after 5 years were chemotherapy-induced tumors. Although effects were not statistically significant because of small numbers, our therapy-specific analyses showed that this increased risk was only seen in the anthracycline-containing chemotherapy group, which is consistent with earlier reports discussing that anthracyclines might increase the risk of development of BC[36,37]. Possibly the risk is only seen for ER-negative CBC because the ER-positive CBCs were prevented due to endocrine therapy irrespectively. The protective effect of taxane-containing chemotherapy seemed attenuated when given in combination with anthracyclines, which might indicate that the increased effect of anthracyclines may be counteracted by taxanes. Thus, anthracycline-containing chemotherapy might induce ER-negative CBC, but further research will be needed to establish the definite role of anthracyclines in second BC development.

We found a larger reduction in CBC risk among patients who received aromatase inhibitors compared to tamoxifen. This finding is consistent with a meta-analysis of randomized trials, which observed that the carryover benefit for CBC was larger for patients randomized to aromatase inhibitors versus tamoxifen[38]. Although endocrine therapy was associated with an overall statistically significantly decreased CBC risk, we and others[33,39,40] showed that it was particularly effective in reducing risk of ER-positive CBC, whereas the risk of ER-negative CBC did not decrease. This is consistent with endocrine therapy selectively inhibiting growth of ER-expressing tumor cells, thus reducing the incidence of ER-positive BCs only[6,41].

It was not possible to investigate the individual effect of trastuzumab on CBC risk, since all patients received trastuzumab combined with chemotherapy. Besides, we were not able to perform multivariable CPH analyses to assess the effect of trastuzumab on HER2-specific CBC because of small numbers of CBCs within this subgroup. Our cumulative incidence curve suggests a slightly higher risk of HER2-positive CBC for patients treated with, compared with patients not treated with trastuzumab. We expected a reduction of HER2-positive CBC after trastuzumab as a consequence of elimination of HER2-overexpressing clones[42].

We observed an increased CBC risk for patients diagnosed with a stage III first BC in the cause-specific CPH model, and there was no association when taking death and distant metastases into account as competing risks. This suggests that part of CBCs were in fact metastases even though these were considered to be by definition a second primary BC. One study, assessing the relationship between first BC and CBC using exome sequencing, has shown that 12% of CBCs represents metastatic spread from the first BC[43]. We attempted to minimize the contribution of metastases to the contralateral breast beforehand by starting follow-up 3 months after first BC diagnosis, only including patients without distant metastasis at initial diagnosis, and censoring for distant metastases during follow-up. Sensitivity analyses showed that additional censoring on local and regional recurrence or a stricter definition of CBC did not alter the results (Supplementary Table 4).

In our study patients younger than 35 years did not have a higher CBC risk compared to older patients, which is in contrast to findings in a previous cohort study using NCR data, including BC patients diagnosed between 1989 and 2002[2]. A potential explanation for these discrepant observations might be the increasing use of adjuvant systemic therapy in the last two decades[2,44]. In our study, 96% of all patients younger than 35 years at first BC diagnosis received adjuvant systemic therapy, whereas this was 59% in the period 1990-2000[45].

This study harbors some limitations. Since this study was observational, patients who received adjuvant systemic therapy differed with respect to some patient and tumor characteristics to patients who did not receive adjuvant therapy (Supplementary Table 1). In the years of diagnosis included, patients with favorable tumor characteristics could avoid systemic therapy following Dutch guidelines[46]. Importantly, in the analyses we adjusted for all these characteristics, but the possibility of some unmeasured residual confounding might still exist. Follow-up on recurrences was not completely recorded by the NCR. This could influence our results, because censoring on distant metastases was not possible for patients outside this period. However, sensitivity analyses showed similar results when including only patients diagnosed between 2003 and 2006 in the analyses (Supplementary Table 4). We lacked data on contralateral prophylactic mastectomy, which could have resulted in an underestimation of the CBC risk. However, our previous cohort study showed that the uptake of contralateral prophylactic mastectomy among BC patients (younger than 50 years) is only approximately 4% in the Netherlands[47]. Therefore, it is unlikely that this missing information affected our main conclusions. Finally, we had no data available on *BRCA1/2* mutation carriership. However, we do not expect that this significantly affected our results, because the proportion of carriers is limited in the general population[47]. We also lacked data on other germline mutations in genes such as *CHEK2* or *PALB2*, or on breast cancer associated single nucleotide polymorphisms. However, because there is no indication that these mutation carriers are treated differently with adjuvant systemic therapy compared to non-carriers[48-50] or that there is interaction with adjuvant systemic therapy[49,51], we do not expect that the absence of these data significantly influenced our results.

The main strengths of this study were the use of a large population-based cohort including all BC patients diagnosed between 2003-2010 in the Netherlands, the comprehensive tumor and therapy information, and active follow-up on CBC occurrence, allowing reliable estimations of CBC risks.

In conclusion, our large population-based study showed a 10-year cumulative CBC incidence of 3.8%. Adjuvant systemic therapy strongly reduced CBC risk in a subtype-dependent manner. According to this study, there is no clear indication to change current

guidelines on adjuvant systemic therapy. Further research disentangling true primary CBCs from metastases may be useful in further personalization of CBC prevention and treatment choices.

Article information

Funding

This work was supported by the Alpe d'HuZes/Dutch Cancer Society (KWF Kankerbestrijding) (2013-6253 ALPE). The sponsor had no 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.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank the registration team of the Netherlands Comprehensive Cancer Organization (IKNL) for the collection of data for the Netherlands Cancer Registry (NCR) as well as IKNL staff for scientific advice. We acknowledge the PALGA foundation for providing us the linkage with the NCR data. We thank all patients whose data we used for this study and the clinicians who treated these patients

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Supplementary Tables

Supplementary Table 1. Distribution of adjuvant chemotherapy, endocrine therapy, and trastuzumab, according to patient and tumor characteristics

Characteristics	Chemotherapy No. (%)		Endocrine therapy No. (%)		Trastuzumab (with chemotherapy)* No. (%)	
	No	Yes	No	Yes	No	Yes
Total	48,717 (58.6)	34,427 (41.4)	42,861 (51.6)	40,283 (48.4)	57,749 (91.2)	5,604 (8.8)
Age at diagnosis, y						
<35	105 (5.8)	1,721 (94.2)	942 (51.6)	884 (48.4)	1,036 (76.8)	313 (23.2)
35-44	2,158 (22.3)	7,535 (77.7)	4,384 (45.2)	5,309 (54.8)	5,972 (82.4)	1,273 (17.6)
45-54	8,387 (37.9)	13,767 (62.1)	10,789 (48.7)	11,365 (51.3)	14,842 (87.7)	2,081 (12.3)
55-64	12,747 (58.5)	9,031 (41.5)	12,066 (55.4)	9,712 (44.6)	15,315 (91.2)	1,473 (8.8)
65-74	14,984 (87.0)	2,238 (13.0)	9,986 (58.0)	7,236 (42.0)	12,894 (96.9)	419 (3.2)
75-84	8,115 (98.5)	127 (1.5)	3,732 (45.3)	4,510 (54.7)	6,044 (99.3)	40 (0.7)
≥85	2,221 (99.6)	8 (0.4)	962 (43.2)	1,267 (56.8)	1,646 (99.7)	5 (0.3)
Tumor stage						
I-II	45,895 (63.9)	25,939 (36.1)	39,533 (55.0)	32,301 (45.0)	50,839 (92.4)	4,163 (7.6)
III	2,822 (25.0)	8,488 (75.0)	3,328 (29.4)	7,982 (70.6)	6,910 (82.7)	1,441 (17.3)
Histological grade						
Grade 1	14,647 (84.2)	2,746 (15.8)	12,261 (70.5)	5,132 (29.5)	13,529 (99.1)	118 (0.9)
Grade 2	22,415 (65.6)	11,738 (34.4)	15,093 (44.2)	19,060 (55.8)	24,734 (94.6)	1,411 (5.4)
Grade 3†	8,554 (34.7)	16,078 (65.3)	12,117 (49.2)	12,515 (50.8)	15,160 (82.6)	3,199 (17.4)
Unknown	3,101 (44.5)	3,865 (55.5)	3,390 (48.7)	3,576 (51.3)	4,326 (83.2)	876 (16.8)
Morphology						
Ductal	36,644 (57.2)	27,400 (42.8)	33,739 (52.7)	30,305 (47.3)	44,168 (90.0)	4,932 (10.0)
Lobular	5,902 (63.9)	3,331 (36.1)	3,468 (37.6)	5,765 (62.4)	6,893 (98.0)	143 (2.0)
Mixed ductal/lobular	1,776 (58.9)	1,237 (41.1)	1,186 (39.4)	1,827 (60.4)	2,127 (95.1)	110 (4.9)
Other	4,395 (64.1)	2,459 (35.9)	4,468 (65.2)	2,386 (34.8)	4,561 (91.6)	419 (8.4)
ER status						
Positive	41,463 (63.9)	23,423 (36.1)	26,597 (41.0)	38,289 (59.0)	48,110 (93.7)	3,221 (6.3)
Negative	4,674 (32.1)	9,905 (67.9)	13,724 (94.1)	855 (5.9)	8,848 (79.2)	2,323 (20.8)
Unknown	2,580 (70.1)	1,099 (29.9)	2,540 (69.0)	1,139 (31.0)	791 (92.9)	60 (7.1)
HER2 status						
Positive	4,637 (41.9)	6,424 (58.1)	6,274 (56.7)	4,787 (43.2)	4,965 (47.8)	5,423 (52.2)
Negative	31,333 (59.2)	21,623 (40.8)	25,420 (48.0)	27,536 (52.0)	50,556 (99.8)	96 (0.2)
Unknown	12,747 (66.6)	6,380 (3z3.4)	11,167 (58.4)	7,960 (41.6)	2,228 (96.3)	85 (3.7)
Subtype‡						
HR+/HER2−	28,973 (63.8)	16,468 (36.2)	18,125 (39.9)	27,316 (60.1)	43,508 (99.8)	66 (0.2)
HR+/HER2+	3,186 (45.8)	3,771 (54.2)	2,282 (32.8)	4,675 (67.2)	3,353 (51.1)	3,214 (48.9)
HR−/HER2+	1,041 (28.8)	2,577 (71.2)	3,538 (97.8)	80 (2.2)	1,191 (35.5)	2,163 (64.5)
HR−/HER2−	2,255 (30.9)	5,049 (69.1)	7,126 (97.6)	178 (2.4)	6,869 (99.6)	28 (0.4)
Unknown	13,262 (66.9)	6,562 (33.1)	11,790 (59.5)	8,034 (40.5)	2,828 (95.5)	133 (4.5)

Abbreviations: ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor positive; HR− = hormone receptor negative

***** Patients diagnosed between 2003-2004 were excluded, since recommendation for HER2 testing and the use of trastuzumab was implemented from 2005 onwards

† Including 12 first breast cancers that were defined as 'undifferentiated' in the Netherlands Cancer Registry

‡ HR+ = ER+ and/or PR+; HR− = ER− and PR−

Supplementary Table 2. Cumulative incidences of CBC for all patients and for patient subgroups

Characteristics	No.	Cumulative Incidence CBC*			
		5-year		10-year	
		%	95% CI	%	95% CI
All patients	83,144	1.9	1.8- 2.0	3.8	3.7- 4.0
Year of first BC diagnosis					
2003	9,853	2.2	1.9- 2.5	4.4	4.0 – 4.8
2004	9,938	2.0	1.7 – 2.3	3.8	3.4 – 4.1
2005	9,945	1.9	1.6 – 2.1	3.8	3.4 – 4.2
2006	10,294	2.0	1.8- 2.3	†	
2007	10,643	1.9	1.6- 2.1	†	
2008	10,706	1.9	1.6- 2.2	†	
2009	10,836	1.6	1.4- 1.9	†	
2010	10,929	1.5	1.3- 1.7	†	
Age, y					
<35	1,826	1.9	1.4- 2.6	3.9	2.9- 5.1
35-44	9,693	1.6	1.4- 1.9	3.6	3.2- 4.0
45-54	22,154	1.6	1.5- 1.8	3.7	3.4- 4.0
55-64	21,778	2.0	1.8- 2.2	4.4	4.0- 4.7
65-74	17,222	2.2	2.0- 2.4	4.1	3.8- 4.5
75-84	8,242	2.0	1.7- 2.3	3.1	2.7- 3.5
≥85	2,229	0.9	0.6- 1.4	1.4	0.9- 2.1
Stage					
I-II	71,834	1.9	1.8- 2.0	4.0	3.8- 4.1
III	11,310	1.6	1.4- 1.8	3.0	2.6- 3.3
Histological grade					
Grade 1	17,393	2.3	2.1- 2.6	4.8	4.4- 5.1
Grade 2	34,153	1.9	1.8- 2.1	4.0	3.7- 4.2
Grade 3‡	24,632	1.5	1.3- 1.6	3.0	2.8- 3.3
Morphology					
Ductal	64,044	1.8	1.7- 1.9	3.7	3.5- 3.9
Lobular	9,233	2.0	1.8- 2.3	4.1	3.7- 4.6
Mixed ductal/lobular	3,013	2.5	2.0- 3.1	5.1	4.2- 6.1
Other	6,854	2.2	1.8- 2.5	3.8	3.4- 4.4
ER status					
Positive	64,886	1.8	1.7- 1.9	3.8	3.6- 4.0
Negative	14,579	2.2	2.0- 2.4	4.2	3.8- 4.6
HER2 status§					
Positive	10,388	1.5	1.3- 1.7	3.1	2.7- 3.6
Negative	50,652	1.9	1.8- 2.0	3.9	3.7- 4.1
Subtype‖					
HR+/HER2–	45,441	2.0	1.8- 2.1	4.1	3.9- 4.4
HR+/HER2+	6,957	1.5	1.2- 1.8	2.9	2.4- 3.4
HR–/HER2+	3,618	2.0	1.6- 2.5	4.3	3.5- 5.2
HR–/HER2–	7,304	2.5	2.2- 2.9	4.8	4.2- 5.5
(Neo)adjuvant therapy¶					
No (neo)adjuvant therapy	31,290	2.9	2.7- 3.1	5.5	5.3- 5.8
CT	8,889	1.9	1.7- 2.2	4.0	3.6- 4.5
ET	17,359	1.3	1.1- 1.4	2.4	2.2- 2.7
CT + ET	19,923	0.9	0.8- 1.0	2.4	2.2- 2.7
CT + TRA	2,728	1.6	1.2- 2.1	3.5	2.7- 4.4
CT + ET + TRA	2,955	0.7	0.5- 1.1	1.8	1.2- 2.7
Radiotherapy					
No radiotherapy	27,265	1.9	1.7- 2.0	3.6	3.3- 3.8
radiotherapy	55,879	1.9	1.7- 2.0	3.9	3.7- 4.1

Abbreviations: BC = breast cancer; CI = confidence interval; CT = chemotherapy; ER = estrogen receptor; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TRA = trastuzumab

* Accounting for death and distant metastases as competing risk

† Not sufficient follow-up time to report the 10-year cumulative incidence

‡ Including 12 first breast cancers that were defined as 'undifferentiated' in the Netherlands Cancer Registry

§ Patients diagnosed between 2003-2004 were excluded, since recommendation for HER2 testing and the use of trastuzumab was implemented from 2005 onwards

‖ HR+ = ER+ and/or PR+; HR– = ER– and PR–

¶ No chemotherapy, endocrine therapy, and trastuzumab (with or without radiotherapy)

Supplementary Table 3. Multivariable Cox regression analyses (cause-specific hazard ratios and subdistribution hazard ratios), in all patients and those with complete co-variate information, of CBC risk related to adjuvant therapy, stage, age, and receptor status at first BC diagnosis*

Characteristics	Cause-specific hazard ratio (HR)						Subdistribution hazard ratio (SHR)†					
	All patients N = 83,144			Complete case analysis N = 63,251			All patients N = 83,144			Complete case analysis N = 63,251		
	HR	95% CI	P‡	HR	95% CI	P‡	SHR	95% CI	P‡	SHR	95% CI	P‡
(Neo)adjuvant therapy												
No (neo)adjuvant therapy§	1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.	
CT	0.65	0.56- 0.77	<.001	0.68	0.56- 0.82	<.001	0.63	0.55- 0.73	<.001	0.66	0.56- 0.78	<.001
ET	0.45	0.40- 0.51	<.001	0.46	0.40- 0.52	<.001	0.45	0.40- 0.50	<.001	0.45	0.39- 0.52	<.001
CT + ET	0.33	0.29- 0.37	<.001	0.27	0.23- 0.31	<.001	0.34	0.30- 0.38	<.001	0.28	0.24- 0.32	<.001
CT + TRA	0.62	0.47- 0.82	.001	0.64	0.48- 0.86	.003	0.68	0.52- 0.89	.005	0.72	0.54- 0.95	.02
CT + ET + TRA	0.27	0.19- 0.39	<.001	0.27	0.19- 0.39	<.001	0.29	0.21- 0.42	<.001	0.29	0.20- 0.42	<.001
Radiotherapy												
No radiotherapy	1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.	
Radiotherapy	0.94	0.86- 1.02	.12	0.96	0.87- 1.06	.41	0.98	0.90 – 1.07	.64	1.00	0.90- 1.10	.95
Stage												
I-II	1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.	
III	1.48	1.30- 1.69	<.001	1.47	1.27- 1.72	<.001	1.10	0.97- 1.26	.14	1.10	0.95- 1.28	.21
Age												
<35	1.08	0.82- 1.42	.55	1.17	0.86- 1.59	.32	1.10	0.84- 1.44	.48	1.21	0.90- 1.63	.22
35-44	0.98	0.85- 1.12	.72	1.03	0.88- 1.21	.72	0.99	0.87- 1.13	.89	1.04	0.89- 1.22	.63
45-54	0.88	0.80- 0.98	.02	0.85	0.75- 0.96	.007	0.90	0.82 – 1.00	.05	0.86	0.76 – 0.97	.02
55-64	1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.	
65-74	0.93	0.84- 1.03	.18	1.00	0.88- 1.13	.98	0.89	0.80 – 0.99	.03	0.96	0.85- 1.09	.54
75-84	0.89	0.76- 1.04	.14	0.93	0.77- 1.11	.40	0.69	0.59 – 0.80	<.001	0.75	0.63 – 0.90	.002
≥85	0.55	0.37- 0.81	.002	0.50	0.32- 0.80	.004	0.31	0.21- 0.45	<.001	0.31	0.20- 0.50	<.001
ER status												
Negative	1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.	
Positive	0.96	0.85- 1.09	.55	0.93	0.80- 1.08	.34	1.08	0.96- 1.21	.21	1.04	0.63- 1.19	.52
Unknown	0.58	0.46- 0.73	<.001	-	-	-	0.63	0.50- 0.80	<.001	-	-	-
HER2 status												
Negative	1.00	Ref.		1.00	Ref.		1.00	Ref.		1.00	Ref.	
Positive	0.86	0.74- 1.00	.05	0.82	0.70- 0.96	.02	0.84	0.72 – 0.97	.02	0.79	0.68 – 0.92	.003
Unknown	0.36	0.31- 0.41	<.001	-	-	-	0.38	0.32- 0.45	<.001	-	-	-

Abbreviations: BC = breast cancer; CBC = contralateral breast cancer; CI = confidence interval; CT = chemotherapy; ER = estrogen receptor; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; Ref = reference group; TRA = trastuzumab

* Additionally adjusted for year of first breast cancer diagnosis

†Accounting for death and distant metastases as competing risk

‡ Two-sided Wald test P-value

§ No chemotherapy, endocrine therapy or trastuzumab (with or without radiotherapy)

Supplementary Table 4. Sensitivity analyses of CBC risk related to (neo)adjuvant systemic therapy for the first BC (as described in Table 2) based on: selection of years of diagnosis of the first BC, differences of censoring events, and definition of metachronous CBC*

(Neo)adjuvant systemic therapy	Total follow-up				<5 years follow up			≥5 years follow up			$P_{heterogeneity}$‡
	No.	HR	95% CI	P†	HR	95% CI	P†	HR	95% CI	P†	
First BC diagnosed 2003-2010											
No censoring											
No (neo)adjuvant therapy§	31,290	1.00	Ref.		1.00	Ref.		1.00	Ref.		
CT	8,889	0.70	0.62- 0.80	<.001	0.66	0.56- 0.78	<.001	0.79	0.65- 0.95	.02	.17
ET	17,359	0.46	0.41- 0.52	<.001	0.42	0.36- 0.48	<.001	0.51	0.43- 0.61	<.001	.08
CT + ET	19,923	0.35	0.31- 0.40	<.001	0.27	0.23- 0.32	<.001	0.50	0.42- 0.59	<.001	<.001
CT + TRA	2,728	0.56	0.45- 0.73	<.001	0.46	0.35- 0.63	<.001	0.79	0.55- 1.12	.19	.02
CT + ET + TRA	2,955	0.24	0.17- 0.33	<.001	0.20	0.13- 0.31	<.001	0.31	0.19- 0.51	<.001	.19
Censoring: distant metastases											
No (neo)adjuvant therapy§	31,290	1.00	Ref.		1.00	Ref.		1.00	Ref.		
CT	8,889	0.70	0.62- 0.80	<.001	0.66	0.56- 0.78	<.001	0.79	0.65- 0.95	.01	.16
ET	17,359	0.46	0.41- 0.52	<.001	0.42	0.36- 0.49	<.001	0.50	0.42- 0.60	<.001	.13
CT + ET	19,923	0.35	0.31- 0.39	<.001	0.26	0.22- 0.30	<.001	0.50	0.42- 0.59	<.001	<.001
CT + TRA	2,728	0.57	0.45- 0.73	<.001	0.47	0.35- 0.64	<.001	0.77	0.54- 1.10	.16	.04
CT + ET + TRA	2,955	0.24	0.17- 0.33	<.001	0.20	0.13- 0.31	<.001	0.31	0.19- 0.51	<.001	.19
Censoring: distant metastases, local and regional recurrence											
No (neo)adjuvant therapy§	31,290	1.00	Ref.		1.00	Ref.		1.00	Ref.		
CT	8,889	0.70	0.62- 0.80	<.001	0.57	0.48- 0.68	<.001	0.79	0.65- 0.96	.02	.12
ET	17,359	0.47	0.42- 0.53	<.001	0.47	0.40- 0.54	<.001	0.52	0.43- 0.62	<.001	.38
CT + ET	19,923	0.35	0.31- 0.40	<.001	0.22	0.19- 0.27	<.001	0.50	0.42- 0.60	<.001	<.001
CT + TRA	2,728	0.52	0.41- 0.67	<.001	0.37	0.26- 0.51	<.001	0.74	0.52- 1.07	.11	.01
CT + ET + TRA	2,955	0.23	0.17- 0.33	<.001	0.16	0.10- 0.26	<.001	0.32	0.20- 0.52	<.001	.05
Censoring: distant metastases, local and regional recurrence. Only stage I-III CBC included, and follow-up <1 year excluded‖											
No (neo)adjuvant therapy§	30,045	1.00	Ref.		1.00	Ref.		1.00	Ref.		
CT	8,742	0.75	0.65- 0.86	<.001	0.61	0.51- 0.73	<.001	0.81	0.67- 0.98	.03	.03
ET	17,280	0.48	0.43- 0.55	<.001	0.49	0.41- 0.57	<.001	0.52	0.43- 0.62	<.001	.61
CT + ET	19,884	0.36	0.32- 0.41	<.001	0.22	0.18- 0.27	<.001	0.49	0.41- 0.59	<.001	<.001
CT + TRA	2,715	0.55	0.42- 0.71	<.001	0.36	0.25- 0.52	<.001	0.76	0.53- 1.10	.15	.005
CT + ET + TRA	2,948	0.20	0.14- 0.29	<.001	0.13	0.08- 0.23	<.001	0.27	0.16- 0.46	<.001	.07
First BC diagnosed 2003-2006											
No censoring											
No (neo)adjuvant therapy§	16.810	1.00	Ref.		1.00	Ref.		1.00	Ref.		
CT	4.633	0.79	0.68- 0.93	.003	0.77	0.62- 0.96	.02	0.83	0.67- 1.03	.10	.61
ET	7.862	0.46	0.39- 0.53	<.001	0.39	0.31- 0.49	<.001	0.51	0.41- 0.64	<.001	.08
CT + ET	9.074	0.42	0.36- 0.49	<.001	0.29	0.23- 0.37	<.001	0.56	0.46- 0.68	<.001	<.001
CT + TRA	750	0.75	0.53- 1.06	.11	0.71	0.44- 1.15	.16	0.80	0.48- 1.34	.40	.73
CT + ET + TRA	901	0.32	0.20- 0.50	<.001	0.28	0.14- 0.54	<.001	0.37	0.20- 0.68	.001	.52
Censoring: distant metastases											
No (neo)adjuvant therapy§	16.810	1.00	Ref.		1.00	Ref.		1.00	Ref.		
CT	4.633	0.79	0.68- 0.93	.004	0.76	0.61- 0.95	.02	0.83	0.56- 0.78	.09	.61
ET	7.862	0.45	0.39- 0.53	<.001	0.39	0.31- 0.49	<.001	0.50	0.36- 0.49	<.001	.12
CT + ET	9.074	0.41	0.35- 0.48	<.001	0.28	0.22- 0.36	<.001	0.55	0.22- 0.30	<.001	<.001
CT + TRA	750	0.78	0.55- 1.11	.17	0.75	0.47- 1.22	.25	0.81	0.35- 0.64	.43	.83
CT + ET + TRA	901	0.33	0.21- 0.51	<.001	0.28	0.15- 0.55	<.001	0.38	0.13- 0.31	.002	.53
Censoring: distant metastases, local and regional recurrence											
No (neo)adjuvant therapy§	16.810	1.00	Ref.		1.00	Ref.		1.00	Ref.		
CT	4.633	0.79	0.67- 0.92	.004	0.61	0.48- 0.77	<.001	0.85	0.68- 1.05	.14	.45
ET	7.862	0.48	0.41- 0.56	<.001	0.47	0.37- 0.59	<.001	0.54	0.43- 0.67	<.001	.40
CT + ET	9.074	0.43	0.37- 0.50	<.001	0.23	0.18- 0.30	<.001	0.56	0.46- 0.69	<.001	<.001
CT + TRA	750	0.69	0.48- 1.00	.05	0.53	0.32- 0.90	.02	0.76	0.45- 1.27	.29	.35
CT + ET + TRA	901	0.31	0.19- 0.50	<.001	0.19	0.09- 0.40	<.001	0.39	0.21- 0.71	.002	.15
Censoring: distant metastases, local and regional recurrence. Only stage I-III CBC included, and follow-up <1 year excluded‖											
No (neo)adjuvant therapy§	16.647	1.00	Ref.		1.00	Ref.		1.00	Ref.		
CT	4.514	0.83	0.70- 0.98	.03	0.65	0.51- 0.83	.001	0.87	0.70- 1.09	.22	.08
ET	7.818	0.50	0.42- 0.58	<.001	0.49	0.38- 0.62	<.001	0.54	0.44- 0.68	<.001	.50
CT + ET	9.054	0.43	0.37- 0.51	<.001	0.23	0.18- 0.30	<.001	0.56	0.46- 0.69	<.001	<.001
CT + TRA	743	0.66	0.44- 0.98	.04	0.45	0.25- 0.83	.01	0.78	0.46- 1.31	.35	.18
CT + ET + TRA	897	0.22	0.13- 0.40	<.001	0.12	0.05- 0.33	<.001	0.29	0.14- 0.59	.001	.17

Abbreviations: CBC = contralateral breast cancer; CI = confidence interval; CT = chemotherapy; ET = endocrine therapy; HR = hazard ratio; Ref. = reference group; TRA = trastuzumab

* Adjusted for age and stage at first breast cancer diagnosis

† Two-sided Wald test P-value

‡ Heterogeneity of HRs between <5 and ≥5 years follow-up duration

§ No chemotherapy, endocrine therapy and trastuzumab (with or without radiotherapy)

‖ CBC only included tumor stage I-III (excluding those with metastases present <3 months after CBC diagnosis). Follow-up started 1 year after first BC diagnosis (regarding CBC developed <1 year after the first BC as synchronous BC), and ended at the date of: CBC, distant metastasis, local recurrence, regional recurrence, and death (whichever came first)

Supplementary Table 5. ER status of first BC and CBC, synchronous or metachronous, stratified for endocrine therapy

ER status of first BC and endocrine therapy	No. of patients	ER-positive CBC No. of patients (%)	ER-negative CBC No. of patients (%)
Synchronous CBC (<3 months after first breast cancer)			
ER-positive first BC	1,071	994 (92.8)	77 (7.2)
ER-negative first BC	132	80 (60.6)	52 (39.4)
Metachronous CBC (≥3 months after first breast cancer)			
ER-positive first BC			
No endocrine therapy	1,368	1,273 (93.1)	95 (6.9)
Endocrine therapy	737	566 (76.8)	171 (23.2)
ER-negative first BC			
No endocrine therapy	494	278 (56.3)	216 (43.7)
Endocrine therapy	27	19 (70.4)	8 (26.6)

Abbreviations: BC = breast cancer; CBC = contralateral breast cancer; ER = estrogen receptor

Supplementary Table 6. Multivariable Cox regression analysis for ER-negative first BC patients assessing the association between various (neo)adjuvant chemotherapy regimens and ER-negative CBC risk (n = 217)*

(Neo)adjuvant CT	Total follow-up				≤5 years follow-up				>5 years follow-up			
	No. of patients	No. of CBC	HR (95% CI)	P†	No. of patients	No. of CBC	HR 95% CI	P†	No. of patients	No. of CBC	HR 95% CI	P†
No CT	4,674	54	1.00 (Ref)		1,481	38	1.00 (Ref)		3,193	16	1.00 (Ref)	
Taxane-containing CT‡	1,182	9	0.36 (0.17-0.75)	.007	297	5	0.26 (0.09-0.72)	.009	885	4	0.61 (0.19-1.98)	.41
Anthracycline-containing CT§	1,718	56	1.32 (0.86-2.04)	.21	466	31	1.17 (0.66-2.06)	.59	1,252	25	1.88 (0.91-3.86)	.09
Taxane + anthracycline-containing CT	1,149	11	0.59 (0.28-1.22)	.16	248	9	0.67 (0.29-1.55)	.35	901	2	0.48 (0.10-2.41)	.38
CT, other or type unknown ‖	5,856	87	0.68(0.46-1.00)	.05	1,358	54	0.65 (0.40-1.06)	.08	4,498	33	0.83 (0.43-1.59)	.57

Abbreviations: BC = breast cancer; CBC = contralateral breast cancer; CI = confidence interval; CT = chemotherapy; HR = hazard ratio; Ref. = reference group

* Adjusted for year of diagnosis, endocrine therapy, trastuzumab, age and stage at first breast cancer diagnosis

† Two-sided Wald test P-value

‡ The chemotherapeutic combination contains taxanes, but no anthracyclines

§ The chemotherapeutic combination contains anthracyclines, but no taxanes

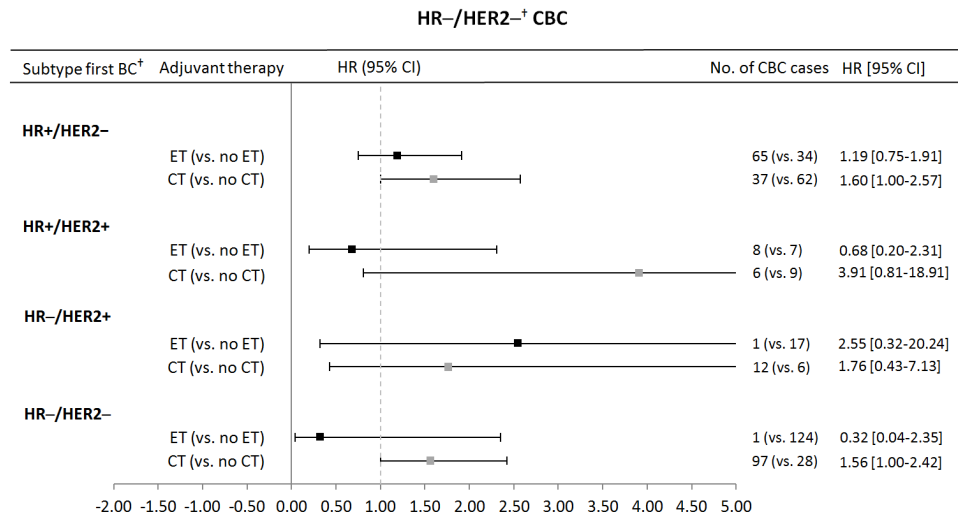
‖ All other chemotherapeutic drugs and combinations (e.g. CMF) or type unknown

Supplementary Table 7. HER2 status of first BC and CBC, synchronous or metachronous, stratified for trastuzumab therapy*

HER2 status of first BC and trastuzumab	No. of patients	HER2-positive CBC	HER-negative CBC
		No. of patients (%)	No. of patients (%)
Synchronous CBC (<3 months after first BC)			
HER2-positive first BC	117	36 (30.8)	81 (69.2)
HER2-negative first BC	875	70 (8.0)	805 (92.0)
Metachronous CBC (≥3 months after first BC)			
HER2-positive first BC			
No trastuzumab	150	18 (12.0)	132 (88.0)
Trastuzumab	101	34 (33.7)	67 (66.3)
HER2-negative first BC			
No trastuzumab	1,490	149 (10.0)	1,341 (90.0)

Abbreviations: BC = breast cancer; CBC = contralateral breast cancer; HER2 = human epidermal growth factor receptor 2

* Patients diagnosed between 2003-2004 were excluded, since recommendation for HER2 testing and the use of trastuzumab was implemented from 2005 onwards



Supplementary Figure 1. Joint multivariable Cox regression analyses for each of the first tumor subtypes assessing the association of (neo)adjuvant systemic therapy of the first BC with triple negative (HR–/HER2–) CBC risk

Adjusted for trastuzumab therapy, age, and stage at first breast cancer diagnosis. Abbreviations: BC = breast cancer; CBC = contralateral breast cancer; CI = confidence interval; CT = chemotherapy; ET = endocrine therapy; HR = hazard ratio; PR = progesterone receptor. † HR+ = ER+ and/or PR+; HR– = ER– and PR–