Supplementary Materials

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

Authors: Iris Kramer[1,2], Michael Schaapveld[2], Hester S.A. Oldenburg[3], Gabe S. Sonke[4], Danielle McCool[2], Flora E. van Leeuwen[2], Koen K. Van de Vijver[5], Nicola S. Russell[6], Sabine C. Linn[4,7], Sabine Siesling[8,9], C. Willemien Menke- van der Houven van Oordt[10], Marjanka K. Schmidt[1,2]

Affiliations: [1] Division of Molecular Pathology, the Netherlands Cancer Institute, Amsterdam, the Netherlands [2] Division of Psychosocial Research and Epidemiology, the Netherlands Cancer Institute, Amsterdam, the Netherlands [3] Department of Surgical Oncology, the Netherlands Cancer Institute, Amsterdam, the Netherlands [4] Department of Medical Oncology, the Netherlands Cancer Institute, Amsterdam, the Netherlands [5] Department of Pathology, the Netherlands Cancer Institute, Amsterdam, the Netherlands [6] Department of Radiation Oncology, the Netherlands Cancer Institute, Amsterdam, the Netherlands [7] Department of Pathology, University Medical Centre Utrecht, Utrecht, the Netherlands [8] Department of Research, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands [9] Department of Health Technology and Service Research, Technical Medical Center, University of Twente, Enschede, the Netherlands [10] Department of Medical Oncology, VU University Medical Center, Amsterdam, the Netherlands

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)

***** Patients diagnosed between 2003-2004 were excluded, since recommendation for HER2 testing and the use of trastuzumab was implemented from 2005 onwards. No. = number, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR+ = hormone receptor positive, HR− = hormone receptor negative

† 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 contralateral breast cancer for all patients and for patient subgroups

Characteristics	No.	Cumulative Incidence contralateral breast cancer*			
		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

* Accounting for death and distant metastases as competing risk. ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, CT = chemotherapy, ET = endocrine therapy, TRA = trastuzumab, No. = number of patients, CI = confidence interval
† 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 contralateral breast cancer risk related to adjuvant therapy, stage, age, and receptor status at first breast cancer 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	-	-	-

* Additionally adjusted for year of first breast cancer diagnosis. CI = confidence interval, CT = chemotherapy, ET = endocrine therapy, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, Ref = reference group

†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 contralateral breast cancer risk related to (neo)adjuvant systemic therapy for the first breast cancer (as described in Table 2) based on: selection of years of diagnosis of the first breast cancer, 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 breast cancer 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 breast cancer 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

* Adjusted for age and stage at first breast cancer diagnosis. CBC = contralateral breast cancer, CT = chemotherapy, ET = endocrine therapy, TRA = trastuzumab, No. = number of patients, HR = hazard ratio, CI = confidence interval, Ref. = reference group

† 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 breast cancer and contralateral breast cancer, synchronous or metachronous, stratified for endocrine therapy*

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

* CBC = contralateral breast cancer, ER = estrogen receptor, No. = number

Supplementary Table 6. Multivariable Cox regression analysis for ER-negative first breast cancer patients assessing the association between various (neo)adjuvant chemotherapy regimens and ER-negative contralateral breast cancer 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

* Adjusted for year of diagnosis, endocrine therapy, trastuzumab, age and stage at first breast cancer diagnosis. CBC = contralateral breast cancer, CT = chemotherapy, No. = number, HR = hazard ratio, CI = confidence interval, Ref. = reference group

† 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

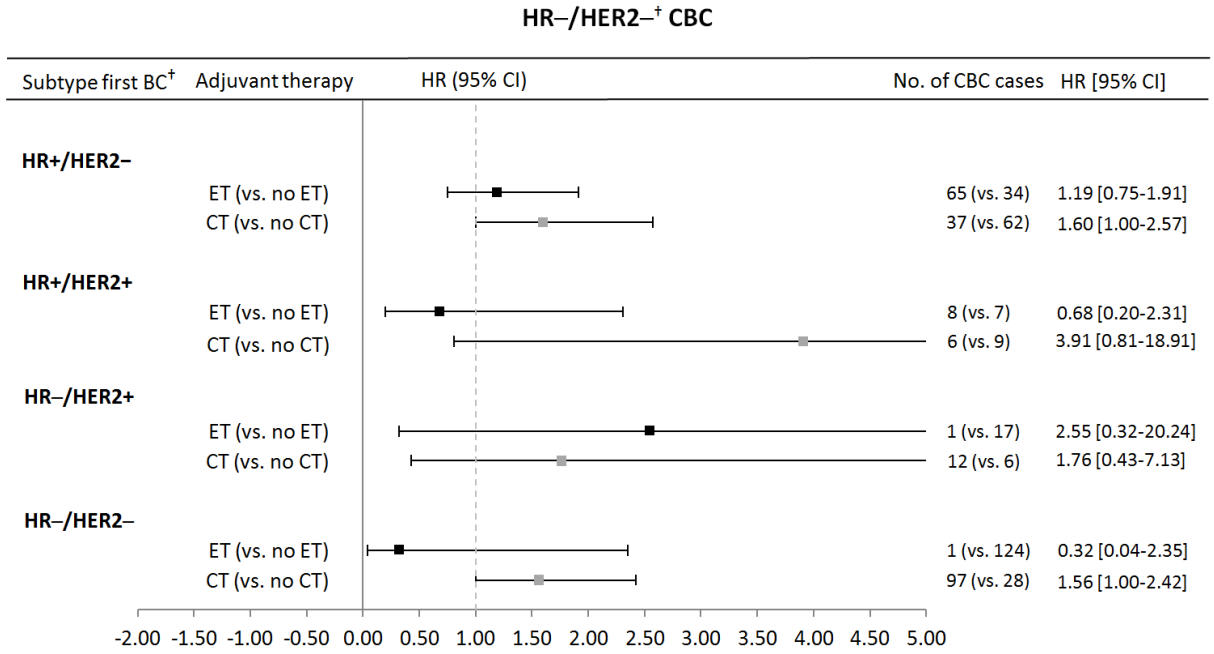
Supplementary Table 7. HER2 status of first breast cancer and contralateral breast cancer, synchronous or metachronous, stratified for trastuzumab therapy*

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

* Patients diagnosed between 2003-2004 were excluded, since recommendation for HER2 testing and the use of trastuzumab was implemented from 2005 onwards. CBC = contralateral breast cancer, HER2 = human epidermal growth factor receptor 2, No. = number

Supplementary Figure

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 breast cancer (BC) with triple negative (HR−/HER2−) contralateral breast risk*



*Adjusted for trastuzumab therapy, age, and stage at first breast cancer diagnosis. CBC = contralateral breast cancer, CT = chemotherapy, ET = endocrine therapy, HR = hazard ratio, CI = confidence interval

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