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Increased risks of third primary cancers of non-breast origin among women with bilateral breast cancer

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BACKGROUND: This study examined the risk of third cancer of non-breast origin (TNBC) among women with bilateral breast cancer (BBC; either synchronous or metachronous), focussing on the relation with breast cancer treatment.
METHODS: Risk was assessed, among 8752 Dutch women diagnosed with BBC between 1989 and 2008, using standardised incidence ratios (SIR) and Cox regression analyses to estimate the hazard ratio (HR) of TNBC for different treatment modalities.
RESULTS: Significant increased SIRs were observed for all TNBCs combined, haematological malignancies, stomach, colorectal, non-melanoma skin, lung, head and neck, endometrial, and ovarian cancer. A 10-fold increased risk was found for ovarian cancer among women younger than 50 years (SIR = 10.0, 95% confidence interval (CI) = 5.3–17.4). Radiotherapy was associated with increased risks of all TNBCs combined (HR = 1.3; 95%CI = 1.1–1.6, respectively). Endocrine therapy was associated with increased risks of all TNBCs combined (HR = 1.2; 95%CI = 1.0–1.5), haematological malignancies (HR = 2.0; 95%CI = 1.1–3.9), and head and neck cancer (HR = 3.3; 95%CI = 1.1–10.4). After chemotherapy decreased risks were found for all TNBCs combined (HR = 0.63; 95%CI = 0.5–0.87).
CONCLUSION: Increased risk of TNBC could be influenced by genetic factors (ovarian cancer) or an effect of treatment (radiotherapy and endocrine therapy). More insight in the TNBC risk should further optimise and individualise treatment and surveillance protocols in (young) women with BBC.

Breast cancer is by far the most frequent cancer in European and North American women (Parkin *et al*, 2005). Owing to earlier diagnosis and improved treatment, breast cancer survival has increased, increasing the risk of metachronous breast cancer, among the survivors (Sant *et al*, 2001). Women with a history of breast cancer have a 2–3-fold higher risk of developing a contralateral breast cancer as compared to the general female population (Soerjomataram *et al*, 2005; Levi *et al*, 2006; Mellemkjaer *et al*, 2006; Schaapveld *et al*, 2008). In a Dutch population-based study, 18% of breast cancer patients were diagnosed with a second breast cancer in the period 1989–2006 (Liu *et al*, 2011). Similar results were observed among women at high risk, who either had a unilateral breast cancer or a twin sister with breast cancer; 9–18% experienced a breast cancer event after 20 years of follow-up (Hartman *et al*, 2008). However, incidence

declined since 1980 due to the increasing use of adjuvant therapy (Hartman *et al*, 2007).

Besides an elevated risk of contralateral breast cancer, several studies revealed that women with a primary breast cancer have an increased risk of developing a subsequent non-breast cancer. Increased risks were most consistently found for tumours of the ovary, endometrium, soft tissue and for leukaemia (Rubino *et al*, 2000; Evans *et al*, 2001; Soerjomataram *et al*, 2005; Levi *et al*, 2006; Mellemkjaer *et al*, 2006; Prochazka *et al*, 2006; Kirova *et al*, 2008; Schaapveld *et al*, 2008; Cortesi *et al*, 2009; Berrington de *et al*, 2010). Excess risks of melanoma of the skin and cancer of the bone, oesophagus, kidney and lung have also been reported, though less consistently (Rubino *et al*, 2000; Evans *et al*, 2001; Soerjomataram *et al*, 2005; Mellemkjaer *et al*, 2006; Prochazka *et al*, 2006; Schaapveld *et al*, 2008; Cortesi *et al*, 2009; Berrington de *et al*, 2010). Risks of subsequent non-breast cancer appears to be associated with genetic and other risk factors that are common for both, breast cancer patients with primary breast cancer experienced an increased risk of lung cancer and soft tissue sarcomas that could be attributed to radiation. Increased risks of melanoma

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of the skin, uterine cancer and leukaemia were found to be associated with the use of chemotherapy for patients older than 50 years, whereas the increased risk of endometrial cancer was related to endocrine therapy. At the same time, chemotherapy was associated with a reduced risk of colon and lung cancer for women younger than 50 years (Schaapveld *et al*, 2008).

However, information about the risk of third cancer of non-breast origin (third non-breast cancer; TNBC) after synchronous or metachronous invasive bilateral breast cancer (BBC) is lacking. Patients with BBC may have been exposed to more carcinogenic or carcino-protective cancer treatment. Moreover, a higher risk could be expected for genetic, reproductive or lifestyle-related cancers. More insight in these risks may further optimise and individualise surveillance protocols in women with BBC. Therefore, we assessed in this study the risks of TNBC after BBC in a nationwide study based on the Netherlands Cancer Registry (NCR). In addition, we studied the associations of TNBC risk with breast cancer treatment.

MATERIALS AND METHODS

The cohort: BBC patients

Patients were selected from the population-based nationwide NCR that reached complete coverage of cancer incidence in the Netherlands since 1989 (Comprehensive Cancer Centre Netherland (IKNL), 2011). Patient registration is based on notification on a weekly basis of all newly diagnosed malignancies by the automated national pathology archive and a yearly link with the national registry of hospital discharge diagnoses. In case of multiple primaries, the definition of a new primary tumour is a primary cancer that is not an extension, a recurrence or a metastasis of a known tumour, located at another anatomic site or when arising in the same anatomic site, belonging to a different histological subgroup or to a different behaviour subgroup (*in situ vs* invasive growth). Subsequently, information on patient and tumour characteristics and primary treatment are retrieved directly from the medical records by specially trained registrars. Staging is coded according to the tumour, node and metastasis system (TNM) classification (Wittekind *et al*, 2004); topography and histology are coded according to the International Classification of Diseases for Oncology (ICD-O; Fritz *et al*, 2000). Basic treatment information was available: whether patients were surgical treated, received radiotherapy, chemotherapy or endocrine therapy. Data on vital status and migration are annually updated through linkage with the national population demographics registry of the municipal administrations (Gemeentelijke basisadministratie). Data quality is high (Schouten *et al*, 1993b), and data completeness is estimated to be at least 95% (Schouten *et al*, 1993a).

All women diagnosed with BBC, defined as invasive first breast cancer and a synchronous or metachronous invasive second contralateral primary breast cancer (without cancer before the first breast cancer or between the first and second breast cancer), between 1989 and 2008 in the Netherlands were selected ($n = 9718$). Bilateral breast cancer patients were excluded with a metastasis at time of diagnosis of the first or second breast cancer (stage IV, $n = 909$), with a sarcoma of the breast either for the first or second breast cancer (morphology code 8830–9990, $n = 17$), as well as patients who developed a third primary breast cancer after BBC ($n = 40$). In total, 8752 women with BBC were included in our study.

Statistical analysis

The patient and tumour characteristics are reported as frequencies and compared using χ^2 test. To estimate the risks of TNBC after BBC standardised incidence ratios (SIR) were calculated. The SIR is the ratio of the observed to the expected numbers of TNBC cases. Observed numbers are the TNBC cases diagnosed during

follow-up period. Patients with zero follow-up time between second breast cancer and the TNBC or the end of study period were excluded for the SIR calculation ($n = 6$). To determine the expected numbers, person years at risk by 5-year age categories and 1-year calendar period categories were multiplied with the corresponding background cancer incidence in the general Dutch female population and then summed up. Person years at risk started at the second breast cancer diagnosis and ended at the date of TNBC diagnosis, date of death or the end of the study period (e.g., 31 December 2008), whichever came first. A SIR value higher than 1 implies an increased risk, whereas values lower than 1 suggest a decreased risk. Ninety-five per cent confidence intervals (95%CI) were estimated assuming Poisson distribution of the TNBC occurrence. Standardised incidence ratios were computed for three age categories based on age at time of the second breast cancer diagnosis (< 50, $50–64$ and $65 +$ years) and for four follow-up intervals since the second breast cancer diagnosis (< 1, $1–5$, $6–10$ and > 10 years), and were plotted on a log scale. These subgroup analysis makes comparison with other studies possible and could give additional information in order to discuss and explain other outcomes. Tests for linear trend in relation to period of diagnosis were performed by incorporating a parameter in the relevant Poisson regression model with consecutive non-negative integer values corresponding to increasing or decreasing levels of the factor and comparing the deviance statistic with that of a model without the relevant parameter.

Multivariable Cox proportional hazard analysis was used to examine the effect of breast cancer treatment on the different TNBC risks. The follow-up time was defined as the time between the date of first breast cancer diagnosis and the date of TNBC diagnosis. Patients were censored at the date of death, migration or the end of the study period (e.g., 31 December 2008). Proportional hazards were tested for all entered variables using graphical (Kaplan–Meier plots) and statistical methods. The interval between first and second breast cancer (BCFI) appeared to be a non-proportional factor and therefore analyses were stratified by BCFI categories (< 1, $1–5$, $6–10$ and > 10 years) using the strata option in STATA. Factors included in the model were treatment of first breast cancer (radiotherapy (no, yes), chemotherapy (no, yes), endocrine therapy (no, yes)), age at first breast cancer (< 50, $50–64$ and $65 +$), year of first breast cancer incidence (continue variable). Second breast cancer treatment variables (radiotherapy (no, yes), chemotherapy (no, yes), endocrine therapy (no, yes)) were entered to the model as time-dependent covariates, allocating patients to no second breast cancer treatment until second breast cancer occurrence.

Statistical significance was defined as a two-sided *P*-value of less than 0.05. Statistical analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

In the Netherlands, eligible 8752 patients were diagnosed with invasive BBC between 1989 and 2008, with a median time of 2.4 years between the first and second breast cancer (Table 1). The patients accumulated 44 399 person years of follow-up since second breast cancer. Overall, 586 patients developed TNBC with a median follow-up time between the second breast cancer and TNBC of 3.9 years. Compared with patients without TNBC, patients with TNBC were significantly ($P < 0.001$) more likely to be older than 65 years at first and second breast cancer diagnosis (respectively, 40% *vs* 47% and 59% *vs* 49%), had more often a stage I second breast cancer (61% *vs* 53%), were more often surgical treated for first and second breast cancer (respectively, 98% *vs* 95% and 96% *vs* 92%) and received less often chemotherapy for first and second breast cancer (respectively, 9% *vs* 19% and 9% *vs* 19%).

Table 1 Patient and tumour characteristics of patients with bilateral breast cancer

	Total	With TNBC	Without TNBC	
	N (%)	N (%)	N (%)	Pa
Total	8752	586	8166	
Age at first breast cancer				<0.001
<50 years	2245 (26)	106 (18)	2139 (26)	
50–64 years	2993 (34)	206 (35)	2787 (34)	
65 + years	3514 (40)	274 (47)	3240 (40)	
Age at second breast cancer				<0.001
<50 years	1470 (17)	65 (11)	1405 (17)	
50–64 years	2922 (33)	175 (30)	2747 (34)	
65 + years	4360 (50)	346 (59)	4014 (49)	
Time between first and second breast cancer				0.552
Median (25–75% range)	2.4 (0.04–6.1)	2.2 (0.03–5.6)	2.4 (0.04–6.2)	
<1 year	3243 (37)	225 (38)	3018 (37)	
>1–5 years	2687 (31)	186 (32)	2501 (31)	
>5–10 years	1882 (22)	121 (21)	1761(22)	
>10 years	940 (11)	54 (9)	886 (11)	
Time between second breast cancer and TNBC				
Median (25–75% range)	NA	3.9 (1.5–7.2)	NA	
<1 year	NA	102 (17)	NA	
>1–5 years	NA	255 (44)	NA	
>5–10 years	NA	166 (28)	NA	
>10 years	NA	63 (11)	NA	
Stage of first breast cancer				0.024
I	3712 (42)	249 (43)	3463 (42)	
II	3402 (39)	253 (43)	3149 (39)	
III	682 (8)	34 (6)	648 (8)	
Unknown	956 (11)	50 (9)	906 (11)	
Stage of second breast cancer				<0.001
I	4664 (53)	359 (61)	4305 (53)	
II	2832 (32)	170 (29)	2662 (33)	
III	618 (7)	25 (4)	593 (7)	
Unknown	638 (7)	32 (5)	606 (7)	
Treatment				
Surgery				
First breast cancer	8303 (95)	573 (98)	7730 (95)	0.001
Second breast cancer	8063 (92)	565 (96)	7498 (92)	<0.001
Radiotherapy				
First breast cancer	4698 (54)	325 (55)	4373 (54)	0.371
Second breast cancer	3620 (41)	249 (42)	3371 (41)	0.565
Chemotherapy				
First breast cancer	1640 (19)	50 (9)	1590 (19)	<0.001
Second breast cancer	1628 (19)	55 (9)	1573 (19)	<0.001
Endocrine therapy				
First breast cancer	2638 (30)	171 (29)	2467 (30)	0.600
Second breast cancer	3417 (39)	209 (36)	3208 (39)	0.083

Abbreviations: NA = not applicable; TNBC = third non-breast cancer. Bold entries denote statistical significance. aP value χ^2 test indicating differences between patients with and without TNBC.

Risk of TNBC compared with the general female population

Table 2 shows the observed and expected numbers of TNBC and SIRs for TNBC by cancer site. The risk of all TNBCs combined after BBC was 1.6 (95%CI = 1.5–1.7). Elevated risks were seen for head and neck, stomach, lung, soft tissue, non-melanoma skin, ovarian, endometrial, other female genital organs and kidney cancer, and haematological malignancies.

The risk of TNBCs overall was highest among women younger than 50 years at diagnosis of second breast cancer (SIR = 2.8, 95%CI = 2.1–3.5; Figure 1). Differences between age groups were especially large for ovarian cancer, with a relative risk of 10 (95%CI = 5.3–17.4) in women younger than 50 years at second breast cancer diagnosis. Relative risks for endometrial, stomach and kidney cancer were highest for patients older than 65 years (respective SIR = 3.4; 95%CI = 2.3–4.5, SIR = 2.3; 95%CI = 1.4–3.6 and SIR = 2.9; 95%CI = 1.6–4.9). Overall, the risk of TNBCs tended

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Table 2 Observed and expected numbers and SIRs with 95% confidence intervals for third non-breast cancers after bilateral breast cancer

Site of TNBC	Observed numbers	Expected numbers	SIR	95%CI
Head and neck	18	9	**2.0**	1.2–3.2
Thyroid	3	2	1.4	0.29–4.6
Oesophagus	5	6	0.84	0.27–2.1
Stomach	25	12	**2.1**	1.4–3.2
Pancreas	15	12	1.2	0.67–2.0
Liver, intrahepatic bile ducts and biliary tract	7	5	1.5	0.60–3.2
Colorectal	91	74	1.2	0.99–1.5
Digestive organs, other	5	3	1.6	0.52–3.9
Lung	77	35	**2.2**	1.7–2.8
Soft tissue	8	2	**3.6**	1.5–7.3
Melanoma of skin	25	18	1.4	0.89–2.1
Non-melanoma skin	80	50	**1.6**	1.3–2.0
Ovarian	33	14	**2.3**	1.6–3.4
Endometrial	58	22	**2.6**	2.0–3.4
Cervix uteri	5	5	0.97	0.31–2.4
Vulva	5	4	1.1	0.36–2.8
Female genitalorgans, other[a]	6	1	**4.6**	1.7–10.4
Urinary bladder	19	15	1.3	0.78–2.0
Kidney	20	8	**2.4**	1.5–3.8
Brain	2	4	0.50	0.06–2.1
Haematological	48	33	**1.5**	1.1–1.9
All TNBCs[b]	582	363	1.6	1.5–1.7

Abbreviations: CI = confidence interval; SIR = standardised incidence ratio; TNBC = third non-breast cancer. Bold entries denote statistical significance. [a]Included, not otherwise specified and vagina. [b]Included others than the specific sites denoted: renal pelvis (2 observed cases), thymus (1 observed case), eye (3 observed cases), other or unspecified sites (4 observed cases), primary sites unknown (10 observed cases) and benign brain tumour (7 observed cases).

to slightly increase with longer follow-up time since second breast cancer diagnosis (Figure 2). Increasing SIRs over time were seen for lung and ovarian cancer and haematological malignancies. For kidney and head and neck cancer, the SIRs tended to decrease with time. No significant trends with follow-up time were found.

Risk of TNBC compared within the cohort

Table 3 shows the independent effects of cancer treatment on the risk of developing TNBC. Except for lung, ovarian and head and neck cancer, the risk of TNBC was highest in the older age patients. For lung, ovarian and head and neck cancer, a decreased risk was seen for patients older than 65 years of age (respective hazard ratio (HR) = 0.47; 95%CI = 0.23–0.95, HR = 0.13; 95%CI = 0.03–0.49 and HR = 0.07; 95%CI = 0.11–0.39). Chemotherapy for the first breast cancer was associated with a decreased risk of all TNBCs combined (HR = 0.63; 95%CI = 0.45–0.87). After radiotherapy for the second breast cancer, increased risks were found for all TNBCs combined (HR = 1.3; 95%CI = 1.1–1.6). After endocrine therapy for the second breast cancer, risks increased for all TNBCs combined (HR = 1.2; 95%CI = 1.0–1.5), haematological (HR = 2.0; 95%CI = 1.1–3.9) and head and neck cancer (HR = 3.3; 95%CI = 1.1–10.4).

DISCUSSION

This is the first population-based study reporting the risks for TNBC in patients with BBC. Results showed an elevated risk for all TNBCs combined, and a more than two-fold increased risk of head and neck, stomach, lung, soft tissue, ovarian, endometrial, other female genital organs and kidney cancer was found for women with BBC compared with women without cancer. The risk was highest for women with BBC younger than 50 years at time of their
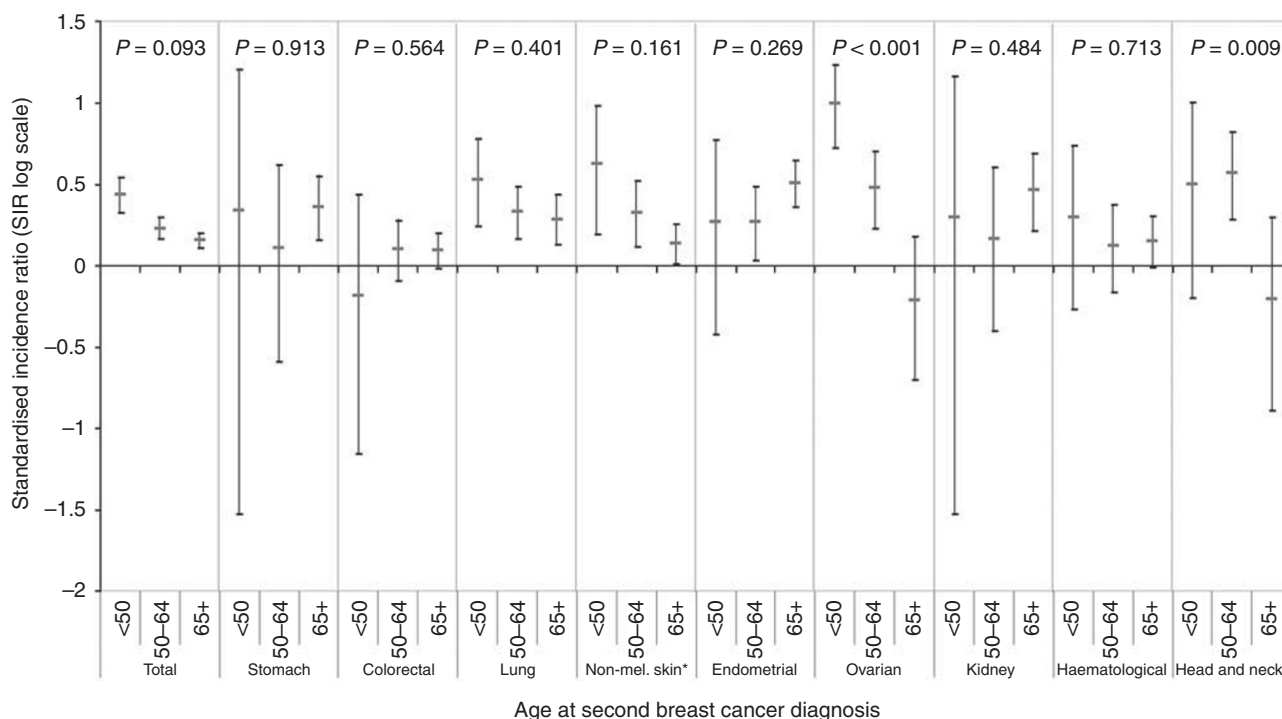

Figure 1 SIRs, 95%CI and P values for trend analyses for selected third non-breast cancers (>10 cases, increased SIR overall) according to the age at second breast cancer diagnosis. *Non-mel. skin = non-melanoma skin.
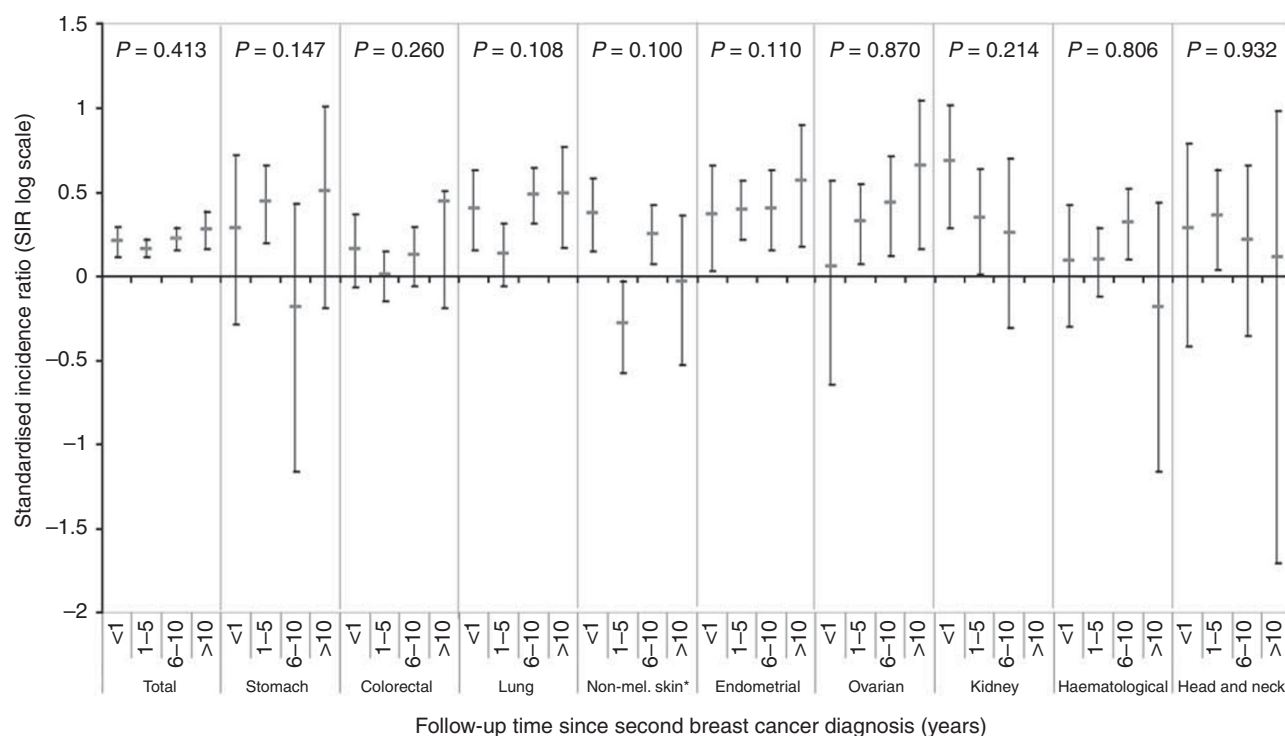
Figure 2 SIRs, 95%CI and *P* values for trend analyses for selected third non-breast cancers (>10 cases, increased SIR overall) according to follow-up time since second breast cancer diagnosis. *Non-mel. skin = non-melanoma skin.

second breast cancer. Especially marked was the 10-fold increased risk of ovarian cancer among young BBC patients. Interestingly, chemotherapy was associated with a reduced risk of all TNBCs combined.

Studies among patients with primary breast cancer reported a 23–40% increased risk of subsequent cancer (Rubino *et al*, 2000; Mellemkjaer *et al*, 2006; Cortesi *et al*, 2009). Our results showed an elevated risk of all TNBCs combined after BBC (SIR = 1.6; 95%CI = 1.5–1.7), and even higher risks (SIR = 2.8) were found in women younger than 50 years at second breast diagnosis. Other studies support higher risks for subsequent breast cancer after primary breast cancer in young women with SIRs varying from 1.3 to 5.5 (Soerjomataram *et al*, 2005; Mellemkjaer *et al*, 2006; Prochazka *et al*, 2006; Yu *et al*, 2006; Andersson *et al*, 2008). The high risk of TNBC in young women overall is influenced by the marked 10-fold increased risk of ovarian cancer among women younger than 50 years (SIR = 10). This is likely related to BRCA mutations. Women with BRCA1 or BRCA2 are prone to early age breast cancer, multiple breast cancers and have a higher risk of developing an ovarian cancer (Welcsh and King, 2001).

Radiotherapy is widely used for treatment of breast cancer. Over time modern radiation techniques reduce the exposure of normal tissue around the breast. Increased risks after radiation exposure of subsequent cancers of the oesophagus, lung, thyroid gland, soft tissue and leukaemia have been earlier reported (Rubino *et al*, 2000; Zablotska and Neugut, 2003; Roychoudhuri *et al*, 2004; Levi *et al*, 2006; Andersson *et al*, 2008; Kirova *et al*, 2008; Schaapveld *et al*, 2008; Berrington de *et al*, 2010). Our study showed excess risk of all TNBC after BBC for patients treated with radiotherapy for the second breast cancer. Although increased risk of lung cancer was expected among women with previous radiotherapy (Zablotska and Neugut, 2003; Roychoudhuri *et al*, 2004; Berrington de *et al*, 2010), we observed no significant relation between radiation and lung cancer. We found elevated risks for lung cancer after a longer follow-up period (SIR = 3.1 after 5 years of follow-up).

From literature it is known that there is at least a 5-year lag period between radiation exposure and cancer induction (PHASE 2 Committee to Assess Health Risks from Exposure to Low Levels of Ionising Radiation, 2006). Furthermore, Kaufman *et al* (2008) found no elevated risks for lung cancer among non-smoking breast cancer patients after radiotherapy. However, among ever-smokers without radiotherapy and ever-smokers treated with radiotherapy, the risk of lung cancer was significantly increased (odds ratio (OR) = 5.9 and OR = 18.9, respectively). Unfortunately, no information about smoking was available in this study, hence it remains important to study the effect of radiotherapy on lung cancer taking smoking in to account.

Owing to their radiosensitivity, even ovaries, though further located from the breast, are prone to biological changes related to radiation (Rubin and Casarett, 1968). Two large studies found a relation between radiation of the breast and higher risk of subsequent ovarian cancer (Kirova *et al*, 2008; Berrington de *et al*, 2010). Although other studies found no relation (Rubino *et al*, 2000; Andersson *et al*, 2008) or even an adverse effect for women older than 50 years treated with radiotherapy (Schaapveld *et al*, 2008), we found a non-significant increased risk of ovarian cancer after radiotherapy for the second breast cancer.

Our results showed a decreased risk after chemotherapy for the first breast cancer for all TNBCs combined, and it may have a protective effect for colorectal, lung, ovarian and head and neck cancer. In addition, younger BBC patients had a higher risk of lung, ovarian and head and neck cancer than those older than 65 years of age. Schaapveld *et al* (2008) showed a protective effect of chemotherapy only among women younger than 50 years for all second non-breast cancers combined, colon and lung cancer. The study of Andersson *et al* (2008) found in univariable analyses a protective effect of chemotherapy for bladder cancer. Rubino *et al* (2000) found no risk differences of TNBC after primary breast cancer treated with or without chemotherapy; however, information on chemotherapy was lacking in this study. An explanation

Table 3 Multivariate Cox regression analyses for the association of risk of selected third non-BC (>10 cases, increased SIR overall) with BC treatment

	All TNBCs HR (95% CI)	Stomach HR (95% CI)	Colorectal HR (95% CI)	Lung HR (95% CI)	Non-melanoma skin HR (95% CI)	Endometrial HR (95% CI)	Ovarian HR (95% CI)	Kidney HR (95% CI)	Haematological HR (95% CI)	Head and neck HR (95% CI)
No. of patients	583	25	91	77	80	58	33	20	49	18
Age at first BC diagnosis (years)										
<50	1	1	1	1	1	1	1	1	1	1
50–64	**1.3 (1.0–1.7)**	2.5 (0.45–13.5)	**3.5 (1.3–9.2)**	1.0 (0.58–1.8)	1.9 (0.82–4.2)	2.1 (0.82–5.1)	0.63 (0.29–1.4)	1.2 (0.32–4.8)	1.6 (0.66–3.9)	0.45 (0.14–1.4)
65+	**1.8 (1.4–2.3)**	**8.1 (1.5–43.8)**	**6.4 (2.4–17.1)**	**0.47 (0.23–0.95)**	**4.6 (2.0–10.6)**	**3.2 (1.2–8.3)**	**0.13 (0.03–0.49)**	1.9 (0.46–8.1)	2.2 (0.87–5.6)	**0.07 (0.11–0.39)**
Incidence year first BC	**1.1 (1.0–1.1)**	1.0 (0.91–1.1)	**1.1 (1.0–1.2)**	**1.1 (1.0–1.2)**	**1.1 (1.1–1.2)**	1.0 (0.93–1.1)	0.93 (0.84–1.0)	1.0 (0.88–1.1)	**1.1 (1.01–1.2)**	1.0 (0.91–1.2)
First BC										
Radiotherapy	1.1 (0.87–1.3)	1.8 (0.71–5.0)	0.69 (0.42–1.2)	0.93 (0.56–1.6)	1.5 (0.88–2.5)	0.69 (0.37–1.3)	1.4 (0.60–3.1)	1.6 (0.58–4.3)	1.6 (0.82–3.1)	2.9 (0.87–9.9)
Chemotherapy	**0.63 (0.45–0.87)**	0.32 (0.03–3.2)	0.40 (0.11–1.5)	0.49 (0.21–1.2)	1.4 (0.61–3.3)	1.1 (0.41–3.2)	0.24 (0.05–1.1)	0.28 (0.03–2.4)	0.82 (0.29–2.3)	0.13 (0.01–1.2)
Endocrine therapy	1.0 (0.82–1.3)	1.2 (0.43–3.5)	0.63 (0.34–1.2)	1.2 (0.66–2.3)	0.69 (0.37–1.3)	1.4 (0.70–2.7)	1.2 (0.38–3.5)	1.7 (0.60–5.0)	0.62 (0.27–1.4)	2.0 (0.54–7.3)
Second BC										
Radiotherapy	**1.3 (1.1–1.6)**	1.6 (0.63–4.2)	1.4 (0.8–2.4)	1.5 (0.89–2.5)	1.1 (0.68–1.9)	1.3 (0.69–2.4)	1.8 (0.82–4.0)	0.90 (0.33–2.5)	1.1 (0.56–2.1)	0.74 (0.26–2.1)
Chemotherapy	0.93 (0.67–1.3)	2.3 (0.38–14.0)	0.80 (0.25–2.6)	0.58 (0.25–1.4)	0.55 (0.19–1.6)	0.95 (0.31–2.9)	0.95 (0.33–2.7)	2.1 (0.48–8.8)	0.70 (0.22–2.2)	0.54 (0.10–2.8)
Endocrine therapy	**1.2 (1.0–1.5)**	0.66 (0.22–2.0)	1.5 (0.87–2.5)	1.08 (0.61–1.9)	1.6 (0.94–2.7)	1.5 (0.81–2.9)	0.57 (0.20–1.7)	2.3 (0.86–6.1)	**2.0 (1.1–3.9)**	**3.3 (1.1–10.4)**

Abbreviations: BC = breast cancer; CI = confidence interval; HR = hazard ratio; SIR = standardised incidence ratio; TNBC = third non-breast cancer. Bold entries denote statistical significance.

for the protective effect might be that TNBCs undergo a growth delay from the use of chemotherapy. Especially for colon cancer fluorouracil-containing chemotherapy could be effective.

Acute myeloid leukaemia is considered as a (anthracycline-containing) chemotherapy-induced cancer, which can present within a few years after breast cancer diagnosis (Valagussa *et al*, 1994; Diamandidou *et al*, 1996; Chaplain *et al*, 2000). We observed no association between chemotherapy and increased risks for haematological malignancies, probably because this group not only contains acute myeloid leukaemia but also (non) Hodgkin's lymphoma and other types of leukaemia. Surprisingly, we found a significant higher risk of haematological malignancies for patients treated with endocrine therapy. As far as we know, this association was not earlier reported and we could not find a clear explanation for this association.

Since 1975 tamoxifen is used for the treatment of postmeno-pausal breast cancer in patients with positive oestrogen receptor. Tamoxifen is linked to a 1.3–7.5-fold increased risk of endometrial cancer (van Leeuwen *et al*, 1994; Bergman *et al*, 2000; Polin and Ascher, 2008). Although no significant relation was found between endocrine treatment and the risk of endometrial cancer within the group of BBC patients, we found a two-fold elevated risk for endometrial cancer after BBC compared with the general female population, particularly for women older than 65 years at second breast cancer diagnosis and women treated with endocrine therapy (results not shown). However, in line with other studies, the SIR for endometrial cancer was also increased for women who received no endocrine therapy (results not shown; Schaapveld *et al*, 2008). Therefore, other shared risk factors like family history, reproductive factors (e.g., parity, hormone replacement treatment) or high body mass index probably contribute to the increased risk of endometrial cancer (Grady *et al*, 1995; Bernstein, 2002; Reeves *et al*, 2007; Reeves *et al*, 2012).

Some strengths and limitations of our study should be considered. The strengths of this study include the large population-based cohort with nearly complete follow-up data for vital status and TNBC that enables us to provide reliable estimates of TNBC risk after BBC and effects of treatment. However, information of other risk factors such as lifestyle factors, including smoking, alcohol consumption and body mass index, as well as genetic factors were not available.

Treatment information was restricted. No information was available about the specific type of radiotherapy and the doses. We found no significant differences in TNBC risks between patients treated with radiation for the first or the second breast cancer. As we included BBC patients, radiotherapy was given on different sites of the body so a cumulative effect could be expected for ovary and endometrial cancer and leukaemia, because of the equal distant to both sites and the radiosensitivity. Furthermore, information of specific endocrine therapy was not available in our database. Apart from tamoxifen, aromatase inhibitors or luteinising hormone-releasing hormone agonists have been administered. Therefore, the effect of endocrine therapy could be slightly underestimated.

Risks were estimated for the first and second breast cancer treatment. Patients with synchronous breast cancer could have received chemotherapy or endocrine therapy for both breasts; however, in fact they received only one dosage. Although the Cox regression model was corrected for BCFI and variables for second breast cancer treatment were incorporated as time-dependent covariates, outcomes need to be interpreted with caution.

CONCLUSION

Women with BBC had a 1.5 times higher risk of all TNBCs combined. Young women had a 2.8 times higher risk of all TNBCs combined and a 10-fold higher risk of ovarian cancer, compared with the general population, which is probably related to genetic factors. Chemotherapy was associated with a decreased risk of all TNBCs combined, whereas radiotherapy and endocrine therapy were associated with a increased risk. Next to the relations between treatment and the risk of TNBC and the possible role of genetics, shared environmental factors are likely to be involved for most elevated risks. Therefore, follow-up care should also be focussed on improving healthy lifestyle. This study gave more insight in the risks of TNBC and results could further optimise and individualise treatment and surveillance protocols in (young) women with BBC.

Conflict of interest

The authors declare no conflict of interest.

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