Incidence of metachronous contralateral breast cancer in the Canton of Zurich: a population-based study of the cancer registry

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DOI: https://doi.org/10.1007/s00432-015-2031-1

Incidence of metachronous contralateral breast cancer in the Canton of Zurich - a population-based study of the Cancer Registry

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Abstract

Purpose: To examine the incidence and characteristics of metachronous contralateral breast cancer (CBC) among women in the Canton of Zurich, Switzerland.

Methods: For 1980-2006, patients with unilateral invasive breast cancer (UBC) were analysed for metachronous CBC. Poisson regression was used to estimate incidence rates of metachronous CBC according to age, year of diagnosis, follow-up period since first breast cancer and morphology.

Results: Of 16,323 patients with UBC, 700 (4.3%) developed a second malignant tumour of the opposite breast. Median age at first breast cancer was lower in the CBC group than in the full cohort. Median interval time between first and second breast cancer was 5.5 (interquartile range, 2.6-10.1) years. Incidence rate at age 20-29 was 1,006 (95% confidence interval, CI, (452-2238) cases per 100,000 person-years and decreased to 299 (199-450) at 80-84. Age-adjusted incidence rates according to period of diagnosis decreased from 618 (530-721) for 1980-1984 to 329 (217-500) cases per 100,000 person-years for 2005-2006. Incidence rate ratio of CBC for lobular carcinoma was 1.28 (95% CI 0.99 - 1.67) adjusted by age group and period of diagnosis compared to ductal carcinoma.

Conclusions: In our study, incidence rates for CBC are comparable with findings from the literature. A reduction in the incidence of metachronous CBC, thought to be due to adjuvant therapies, is seen in our data. In our cohort, younger age and lobular carcinoma was associated with increased risk for CBC.

Keywords Metachronous contralateral breast cancer, lobular carcinoma, incidence rates, year of diagnosis, follow-up period

Introduction

In Switzerland, about 5250 women develop a new malignant tumour of the breast every year. Five years after diagnosis 80% of these women are still alive (Bouchardy et al. 2011b). Breast cancer is the most frequent malignancy in the age group 30 years and older and accounts for 33% of new cancer cases in the female population (Krebsregister der Kantone Zürich und Zug 2014). 19% of all women who die of cancer die of a malignancy of the breast (Bouchardy et al. 2011b). Thus, breast cancer deaths are responsible for the largest number of female cancer deaths in Switzerland, but, on the whole, the survival is favourable (Bouchardy et al. 2011b). In the Canton of Zurich breast cancer incidence increased up to around 2003 and then dropped slightly in the following years (Ceschi et al. 2009).

A study of the Swiss National Institute for Cancer Epidemiology and Registration (NICER) showed an increasing prevalence of long term cancer survivors, which was also clearly evident in breast cancer (Lorez et al. 2013). This development is due to a better prognosis as a result of earlier detection and adjuvant therapies. As a consequence regular follow-up of these patients to detect recurrence and metachronous CBC is becoming increasingly important.

A new malignant tumour of the opposite breast is the most frequent second malignancy of breast cancer patients (Curtis et al. 2006). The risk of a new occurrence of breast cancer is significantly increased compared to the general risk of developing breast cancer (Bernstein et al. 2003; Kollias et al. 1999; Lizarraga et al. 2013; Rubino et al. 2010; Sandberg et al. 2012a). The annual risk of developing a second invasive tumour of the opposite breast has been reported to be between 0.3-0.8% (Kollias et al. 1999; Lizarraga et al. 2013; Narod 2014; Nichols et al. 2011). This means a woman with breast cancer has approximately a doubled risk of developing a second primary tumour of the breast compared to the risk of breast cancer in the general female population (Sandberg et al. 2012a).

A reduction in the global incidence of CBC over the last couple of decades is thought to be due to adjuvant chemotherapeutic therapies. Tamoxifen, an antagonist of oestrogen

receptors in breast tissue, is used in the endocrine treatment of hormone-sensitive breast cancer. It has been regularly prescribed to breast cancer patients since the 1980s (Jordan 2003). Its benefit has been shown in many - also recent - studies (Bouchardy et al. 2011a; Chen et al. 1999; Cuzick and Baum 1985; Narod 2014; Sandberg et al. 2012a; Yerushalmi et al. 2009), which has finally led to a wide clinical acceptance (Jordan 2003). Tamoxifen was approved in Switzerland in 1976.

Switzerland is one of the European countries with the highest incidence rates of breast cancer (Bouchardy et al. 2011b). The number of women with a diagnosis of breast cancer living in Switzerland is continually rising. With an increasing survival, the demand for good treatment and care for cancer patients is growing. The aim of our study is to examine the incidence of CBC and the histology of the index cancer in the Canton of Zurich between 1980 and 2011, particularly as breast cancer represents a major health care issue in Switzerland.

Materials and Methods

The epidemiological Cancer Registry Zurich and Zug is the largest cancer registry in Switzerland. The cancer registry in the Canton of Zurich was one of the first cancer registries to be founded in Switzerland in a close collaboration of the Institute of Pathology of the University Hospital Zurich and the Institute of Social and Preventive Medicine of the University of Zurich. The Cancer Registry Zurich exists since 1980. In the study period, the population of the Canton of Zurich increased to well over a million (BFS Statistical office 2010).

Inclusion criteria. In our present study, we included all female patients with UBC recorded in the population-based Cancer Registry Zurich and Zug from the beginning of the aggregation of data in 1980 up until the year 2006, therefore allowing for a minimum follow-up period of five years for every notified cancer case for detecting patients who developed metachronous CBC up until 2011. Of 19,271 breast cancer patients identified in our database, we excluded all patients with other malignancies prior to the first incidence of

breast cancer, in situ breast cancer, morphologies breast sarcoma and lymphoma and unclassified malignant breast tumours (n=615). Patients with malignant tumours before CBC were censored at date of other malignancy. As in some other studies older patients - older than 84 years of age in our case - were not included because of the insufficient follow-up of older patients (Font-Gonzalez et al. 2013; Kollias et al. 1999; Nichols et al. 2011). Patients younger than 20 were also excluded because of the small number of cases (n=1175). We also excluded patients with a follow-up of less than three months to distinguish between synchronous and metachronous cancer, an interval time often used by other groups (n=878) (Alkner et al. 2011; Sandberg et al. 2012a; Sandberg et al. 2012b; Schmid et al. 2011). Patients with a follow-up of less than 90 days had usually died within three months of initial diagnosis. Further, we excluded 280 patients with non-valid data, predominantly due to a lack of information on the laterality of tumours.

Statistical analyses. The person-time at risk for calculation of incidence of CBC started three months after initial primary breast cancer until occurrence of CBC or the endpoints of exclusion criteria, i.e., second non-breast cancer, death or end of study period (December 31, 2011). Because of insufficient follow-up in most cases person-years were simulated with Swiss breast cancer survival data provided by NICER. A constant hazard rate of 0.0575 y^{-1} for survival after UBC was assumed for the whole period from 1980-2011 to compute random survival time. Univariate and multivariate Poisson regression was performed to estimate incidence rates and incidence rate ratios of metachronous CBC adjusting for age at diagnosis and year of diagnosis of UBC, morphology of UBC and follow-up period. To consider overdispersion we used quasi-Poisson regression. Results were presented as number of cases per 100,000 person-years and 95 % confidence intervals (95% CI) were obtained. Statistical analyses were performed in R (version 2.13.1, The R Foundation for Statistical Computing, Vienna, Austria).

Results

In the study period from 1980 to 2006, of 19,271 female breast cancer patients living in the Canton of Zurich at the time of diagnosis 16,323 women with unilateral invasive breast cancer met the eligibility requirements. Of this cohort of UBC 700 (4.3%) developed a second malignancy of the opposite breast (table 1). Highest incidence rates of CBC were noted in patients with diagnosis of first breast cancer at a younger age (table 2). Median age at first breast cancer was 55 (interquartile range [IQR] 46-64) in the CBC group compared to 60 (IQR 50-70) years in the full cohort. The median interval time to CBC was 5.5 (IQR 2.6-10.1) years. The median estimated follow-up time was 7.8 (IQR 4.2-12.8) years (table 1). Crude incidence rates of CBC decreased by period of diagnosis and by age at index cancer (table 2). Incidence rates remained stable throughout the follow-up period (table 2), but CIs became wider with follow-up period. There was no relevant difference between crude and age-adjusted incidence rates by period of diagnosis (figure 1). The estimated annual incidence rates varied between 463 per 100,000 person-years (95% CI 410-522) for the follow-up period 0-3 years and 513 (95% CI 407-646) for the follow-up period 12-15 years (figure 2). There was no relevant difference between crude and age-adjusted incidence rates (data not shown).

Lobular carcinoma had higher crude and age-adjusted incidence rates than ductal carcinoma but the confidence intervals overlapped. Age-adjusted rates did not differ materially (data not shown). Incidence rate ratio of CBC from univariate Poisson regression for lobular morphology compared to patients with ductal morphology had no significant effect (1.15, 95% CI 0.83 - 1.59), whereas adjusted by age group and period of diagnosis incidence rate ratio was 1.28 (95% CI 0.99 - 1.67) (table 3).

Sensitivity analysis. To study how the lag time between breast cancer at index and CBC affected incidence rate ratios, multivariate Poisson regression was performed for lag times of 3, 6 and 12 months. Incidence rates and incidence rate ratios did not change or showed only slight alterations whereas the power decreased due to lost cases which fell into the lag time (results not shown).

Discussion

Declining incidence rates of CBC over the last couple of decades have been reported in many countries. Numerous studies support this finding (Bernstein et al. 2003; Bouchardy et al. 2011a; Hartman et al. 2007; Lizarraga et al. 2013; Nichols et al. 2011; Sandberg et al. 2012a; Vichapat et al. 2011b). As the Cancer Registry has been collecting population-based data over a long period of time we were able to show a distinct decrease in CBC incidence since around 1985 in the Canton of Zurich.

Adjuvant therapies are said to be responsible for the reduction in the incidence of metachronous CBC. Tamoxifen reduces the risk of CBC by approximately 40% (Bertelsen et al. 2008; Rutqvist et al. 1991). About 70% of all breast cancers are oestrogen receptor positive. So far, the use of tamoxifen/aromatase inhibitor had been recommended for 5 years. But several recent studies demonstrated a benefit of prolonged use of tamoxifen, preventing recurrence and CBC and also improving survival. On this account new guidelines have been issued by the American Society of Clinical Oncology (ASCO) (Burstein et al. 2014). Trials initiated by the International Breast Cancer Study Group (IBCSG) exhibited a favourable result of aromatase inhibitor and ovarian suppression for premenopausal women with receptor positive breast cancer, a group which had so far been given tamoxifen (Pagani et al. 2014). Correspondingly, a survey with data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database in the U.S. showed that women with hormone receptor negative tumours had a substantially higher risk of developing CBC than woman with receptor positive breast cancer (Kurian et al. 2009). The focus of most studies concerning outcome is on regional or distant recurrence, but the incidence of CBC is also always reduced as an effect of adjuvant therapies.

In our study population, younger age at incidence of the initial breast cancer was a risk factor for CBC as also found in various other studies (Bernstein et al. 2003; Chen et al. 1999; Hartman et al. 2007; Kollias et al. 1999; Kurian et al. 2009; Lizarraga et al. 2013; Narod 2014; Nichols et al. 2011; Rubino et al. 2010; Sandberg et al. 2012b; Schaapveld et

al. 2008; Verkooijen et al. 2007; Vichapat et al. 2011a). In the Canton of Vaud, the age incidence pattern of CBC was examined as it was not comparable to the pattern of incidence for most cancers or breast cancer. A peak was reached at age 30-39 and the incidence gradually declined afterwards up to 70 years of age, reaching levels similar to primary breast cancers in that age group (Levi et al. 2001). In a publication of the Geneva Cancer Registry, young age was associated with an increased risk for CBC in women with ER-negative tumours, but the study found family history in these patients an even stronger predictor for contralateral disease (Bouchardy et al. 2011a). A deficiency of our study is missing information on hormone status of breast cancer and, thus, we cannot replicate the finding of the Geneva Cancer Registry. Furthermore, a slight increase in the incidence of breast cancer in younger Swiss women has recently been reported (Bodmer et al. 2015). Young women might still have an increasing risk of developing a malignant tumour of the breast compared to a declining incidence in general and are probably more likely to develop CBC. A recently published paper with data from the Danish Cancer Registry examined the influence of the longer follow-up of younger patients on the incidence of CBC and also still found a decreasing incidence of CBC with age when limiting the follow-up time (Rasmussen et al. 2014).

Lobular cancer is frequently seen as a risk factor for CBC (Arpino et al. 2004; Bernstein et al. 2003; Chen et al. 1999; Kollias et al. 1999; Lizarraga et al. 2013; Narod 2014; Schaapveld et al. 2008; Soran et al. 2014), but not all studies show this result (Lizarraga et al. 2013; Narod 2014; Rubino et al. 2010; Verkooijen et al. 2007; Vichapat et al. 2011b). Invasive lobular carcinoma represents about 10-15% of breast cancers. It tends to occur at a somewhat older age than invasive ductal/no special type carcinoma. The Geneva Cancer Registry reported a higher risk of synchronous bilateral breast cancers in patients with lobular histology, but not of metachronous tumours (Verkooijen et al. 2007). In other studies lobular carcinoma corresponded to a higher rate of CBC (Arpino et al. 2004; Bernstein et al. 2003; Chen et al. 1999; Kollias et al. 1999; Lizarraga et al. 2013; Narod 2014; Schaapveld et al. 2008; Soran et al. 2014). Our data supports this finding. The

adjusted incidence rates showed a higher risk for CBC after lobular compared to ductal carcinoma (table 3). A study of the risk of invasive cancer after lobular carcinoma in situ found an equal risk of malignancies in both breasts and a higher incidence of invasive lobular carcinoma than would be expected (Chuba et al. 2005). A recent analysis of genetic predisposition to in situ and invasive lobular carcinoma of the breast found a novel lobular-specific breast cancer gene locus (Sawyer et al. 2014). All this might support the assumption of invasive lobular carcinoma as a general risk factor for CBC.

The incidence rate of CBC was in the range of 300-1,000 per 100,000 person-years. This is consistent with other studies(Kollias et al. 1999; Rubino et al. 2010). The risk of second breast cancer remained higher during the whole follow-up period compared to the general risk of breast cancer in the female population. The risk of a first primary tumour of the breast in the canton of Zurich in 2002-2006 was 110.8 per 100,000 person-years and therefore the risk of CBC about three times higher than the risk of a woman to develop breast cancer in the same period.

Our data showed constant incidence rates of CBC during the follow-up after primary breast cancer. The Danish study referred to above exhibited an increasing incidence in younger patients with a peak 2-4 years after diagnosis, but when adjusted for age and calendar period, incidence rates where more or less constant over time (Rasmussen et al. 2014). We are not able to investigate the influence of age on the time to incidence of CBC, as our number of cases is too small for examining incidence rates for certain age groups with regard to follow-up. Further studies about the influence of the follow-up period on the incidence of CBC are necessary.

To separate synchronous from metachronous contralateral breast cancer cases we used an interval time between the first and the second breast cancer of three months. Contralateral tumours occurring within three months were classified as synchronous. The WHO Classification of Tumours of the Breast adopts this definition, which is used frequently in studies (Alkner et al. 2011; Hartman et al. 2007; Sandberg et al. 2012b; Schmid et al. 2011), but also mentions the benefit of a longer time interval for epidemiological

assessments. Many studies favour a longer cut-off time to distinguish bilateral breast cancers (Bernstein et al. 2003; Londero et al. 2014; Nichols et al. 2011; Rubino et al. 2010; Schaapveld et al. 2008; Verkooijen et al. 2007; Vichapat et al. 2011a; Vichapat et al. 2012; Vichapat et al. 2011b; Yerushalmi et al. 2009). As there is no consensus concerning these definitions, we conducted further analyses with different cut-off times. Our comparison of cut-off times of three, six and twelve months did not show any significant differences, and we therefore concentrated on the one time interval of three months for our final calculations.

A shortcoming of our study is the lack of information on tumour stage. Information on distant spread at diagnosis would allow for better comparison with other studies, as stage IV index tumours are generally excluded. Whether CBC should be looked at as distant spread or new primary is still open to debate (Rubino et al. 2010; Vichapat et al. 2012; Yerushalmi et al. 2009). Complete data on tumour characteristics and therapies is not available for our present study. In comparison, in 2007 the Registry of the Canton of Zurich participated in an extensive survey on the patterns of care in breast cancer patients in Switzerland. The Cancer Registry of the Canton of Zurich collected information on roughly 500 breast cancer patients diagnosed from 2003-2005. 4% of the cases in the Canton of Zurich were diagnosed at stage IV. Oestrogen receptor expression was found in 79% of the patients in the Canton of Zurich, and in 97% of patients with hormone-responsive disease, endocrine therapy had been prescribed (Ess et al. 2010). Therefore, it can be stated that at the beginning of the year 2000 female breast cancer patients in the Canton of Zurich with hormone-sensitive tumours were basically all receiving chemoprophylaxis.

The high quality of the Registry's cancer data concerning incidence and morphology of cancer cases of all the inhabitants of the Canton of Zurich and the completeness of registration are a good basis for future endeavours in epidemiological studies (Krebsregister der Kantone Zürich und Zug 2014).

Conclusions

Declining incidence rates of CBC since 1985 in the Canton of Zurich confirm trends observed in other studies. The risk of CBC and recurrence after UBC still calls for a continuing follow-up after breast cancer, despite this positive development.

Compliance with Ethical Standards

Funding: Julia Prater was funded by Cancer League Zurich.

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

Research involving human patients and/or animals & Informed consent: Cancer cases in the Canton of Zurich are registered with presumed consent and registration based on a decision by the Zurich Government Council from 1980 and the general registry approval by the Federal Commission of Experts for professional secrecy in medical research from 1995. All data were used anonymously in this analysis and no approval from the ethical committee of the canton of Zurich was necessary.

Table1: Characteristics of breast cancer cohort, Canton of Zurich 1980-2006.

	Cohort	CBC	
		BC1	BC2
N	16,323	700	700
Age (years)			
mean (SD)	60 (13)	56 (13)	63 (13)
median (IQR)	60 (50-70)	55 (46-64)	63 (53-73)
Follow up time (years)			
mean (SD)	9.2 (6.6)		
median (IQR)	7.8 (4.2-12.8)		
Interval time to CBC (years)			
mean (SD)		6.9 (5.7)	
median (IQR)		5.5 (2.6-10.1)	

CBC, contralateral breast cancer; BC1, index case (first breast cancer); BC2, second primary breast cancer; SD, standard deviation; IQR, interquartile range

Table 2: Incidence rates of CBC (cases per 100,000 person-years), Canton of Zurich 1980-2006.

	Total N	Cases N	Percentage	Person years	Incidence	95% CI
All	16323	700	4.3%	150289	466	(433-502)
Diagnosis period						
1980 - 1984	2498	162	6.5%	26197	618	(530-721)
1985 - 1989	2729	169	6.2%	29737	568	(489-661)
1990 - 1994	2809	129	4.6%	29865	432	(363-513)
1995 - 1999	3293	127	3.9%	30378	418	(351-497)
2000 - 2004	3720	91	2.4%	27430	332	(270-407)
2005 - 2009	1274	22	1.7%	6682	329	(217-500)
Age						
20 - 29	79	6	7.6%	597	1006	(452-2238)
30 - 39	870	52	6.0%	8359	622	(474-816)
40 - 49	3010	193	6.4%	31526	612	(532-705)
50 - 59	3908	186	4.8%	38442	484	(419-559)
60 - 69	4018	152	3.8%	37160	409	(349-480)
70 - 79	3258	88	2.7%	26506	332	(269-409)
80 - 84	1180	23	1.9%	7699	299	(199-450)
Histology						
ductal	11380	474	4.2%	104542	453	(414-496)
lobular	1683	77	4.6%	14796	520	(416-651)
others	3260	149	4.6%	30950	481	(410-565)
Follow-up period						
0 - 3	16323	266	1.6%	57481	463	(410-522)
4 - 7	12430	191	1.5%	41137	464	(403-535)
8 - 11	7920	121	1.5%	24408	496	(415-592)
12 - 15	4568	72	1.6%	14042	513	(407-646)
16 - 19	2594	23	0.9%	7562	304	(202-458)
20 - 23	1339	20	1.5%	3797	527	(340-817)
24 - 27	584	5	0.9%	1522	329	(137-789)
28 - 31	208	2	1.0%	341	587	(147-2346)

Table 3: Incidence rate ratio computed from a univariate and a multivariate Poisson regression, Canton of Zurich 1980-2006

	Univariate			Multivariate		
	Rate ratio	95% CI	P-value	Rate ratio	95% CI	P-value
Diagnosis period						
1980 - 1984	1.00	(reference)		1.00	(reference)	
1985 - 1989	0.92	(0.70 - 1.21)	0.55	0.86	(0.68 - 1.11)	0.25
1990 - 1994	0.70	(0.52 - 0.94)	0.02	0.66	(0.51 - 0.86)	0.003
1995 - 1999	0.68	(0.50 - 0.91)	0.01	0.63	(0.49 - 0.83)	0.001
2000 - 2004	0.54	(0.39 - 0.75)	0.000	0.50	(0.38 - 0.67)	0.00001
2005 - 2009	0.53	(0.30 - 0.95)	0.03	0.51	(0.31 - 0.82)	0.01
Age						
20 - 29	2.46	(0.93 - 6.53)	0.07	2.58	(1.07 - 6.20)	0.04
30 - 39	1.52	(1.04 - 2.22)	0.03	1.45	(1.03 - 2.04)	0.03
40 - 49	1.50	(1.16 - 1.93)	0.002	1.45	(1.16 - 1.83)	0.002
40 - 49	1.50	(1.16 - 1.93)	0.002	1.45	(1.16 - 1.83)	0.002
50 - 59	1.18	(0.92 - 1.53)	0.20	1.17	(0.93 - 1.48)	0.18
60 - 69	1.00	(reference)		1.00	(reference)	
70 - 79	0.81	(0.59 - 1.11)	0.20	0.79	(0.59 - 1.04)	0.10
80 - 89	0.73	(0.43 - 1.23)	0.24	0.71	(0.45 - 1.15)	0.17
Histology						
ductal	1.00	(reference)		1.00	(reference)	
lobular	1.15	(0.83 - 1.59)	0.41	1.28	(0.99 - 1.67)	0.06
others	1.06	(0.83 - 1.36)	0.64	0.92	(0.74 - 1.14)	0.45

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