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Increased incidence of stroke in women with breast cancer

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Abstract

Meta-analyses have shown an excess of vascular deaths in women with breast cancer given radiotherapy (RT). In women with breast cancer, RT to the supraclavicular lymph nodes gives a substantial radiation dose to the proximal carotid artery. RT is known to increase the risk of carotid stenosis and ischaemic stroke in head and neck cancer. A study base of 25,171 women with breast cancer was defined. A linkage between the study base and the Hospital Discharge Register yielded 1766 women who were diagnosed with a stroke after a breast cancer. The observed number of strokes was compared with the expected number in the background population. The Relative Risk (RR) of stroke in the study group with breast cancer was 1.12 (95% Confidence Interval (CI) = 1.07–1.17). The increased risk was confined to the subtype cerebral infarction, RR = 1.12 (95% CI = 1.05–1.19). A statistically significant increase in the risk of stroke was seen among women with a history of breast cancer. Whether this risk is associated with the breast cancer disease *per se* or related to any treatment requires further study.

Keywords: Breast cancer; Stroke; Cerebral infarction; Cerebrovascular

1. Introduction

Randomised clinical trials [1–3] and meta-analyses by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [4] have shown a benefit of postoperative adjuvant radiotherapy in breast cancer in terms of reducing local recurrences and in the risk of dying from breast cancer. By contrast, there is an excess of vascular deaths in women given radiotherapy [4]. An increase of cardiac deaths [5] was seen in some of the early radiotherapy trials. Left-sided breast cancers [6–8] were associated with a higher mortality due to myocardial infarction compared with right-sided ones, indicating a radiation-induced injury to the coronary arteries.

In adjuvant breast cancer, radiotherapy to the supraclavicular lymph nodes, the proximal part of the carotid artery, is included in the irradiation portals. Studies in patients with head and neck cancer have shown an increased risk of carotid stenosis and ischaemic stroke post-radiotherapy [9–11]. Whether postoperative irradiation in breast cancer increases the risk of cerebrovascular disease has, to our knowledge, never been studied. The aim of this study was to elucidate the possible association between breast cancer and stroke in a large study group of breast cancer patients with long-term follow-up.

2. Patients and methods

Our study is confined to the Uppsala-Örebro healthcare region, which includes seven counties with both urban and rural areas in the central part of Sweden. The population in the year 2000 in this region was 1.9 million. We used the Swedish Cancer Register and the nationwide Hospital Discharge Register as data sources.

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The study was approved by the ethics committee of Uppsala University.

2.1. The cancer register

Since 1958, all physicians and pathologists in Sweden are required to submit reports on all new cases of malignant disease detected on clinical and histopathological grounds to the Swedish Cancer Register [12]. Diagnoses are based on morphological findings in 98% of cases [12]. The proportion of under-reporting is estimated to be only approximately 2% [13]. Causes of death are included in The Swedish Cancer Register.

2.2. The hospital discharge register

The Hospital Discharge Register has filed data on hospital admissions. Among the seven counties in the Uppsala-Örebro health-care region, there are differences concerning the register coverage during the study period of 1970–2000 [12]. Three counties have full coverage from 1970 to 2000, three counties started reporting to the register in 1974–1976 and one county started reporting in 1984. Thus, from 1984, there is full coverage of the register in all seven counties [12].

2.3. Identification of women with breast cancer

The time period of our study was from 1970 to 2000. We identified women diagnosed with breast cancer from the date of the start of the Hospital Discharge Register in each of the seven counties. Thus, recruitment to the study group started at different times between 1970 and 1984 in different counties, resulting in an incomplete coverage of the Hospital Discharge Register. We estimate that this incompleteness reduces the amount of person-years by 14% compared with a hypothetical register of full coverage. Twenty six thousand and one sixty eight such women in the Uppsala-Örebro health-care region were identified from the Cancer Register. Of these, 129 women were diagnosed with breast cancer at the date of death, and were excluded.

2.4. Definition of the study group

We linked women with breast cancer to the Hospital Discharge Register by the woman's unique national registration number. Eight sixty eight women had a stroke before being diagnosed with breast cancer during the study period of 1970–2000 and were excluded. After these exclusions, our study included 25,171 women with breast cancer. In this study group, we defined in our linkage analysis women who after breast cancer had a main diagnosis of stroke recorded during the study period of 1970–2000. Only the first event of stroke was registered and 1766 women were noted.

2.5. Definition of stroke

Our definition of stroke was broad and based on the International Classification of Disease (ICD) codes (Table 1). Our definition is similar to the one used by Lawlor and co-workers [14], with the exception that "ill-defined stroke-diagnoses" (arteriosclerotic dementia, psychosis associated with cerebral atherosclerosis and hemiplegia) were excluded. The ICD-codes were grouped into the following subtypes of stroke: cerebral infarction, cerebral haemorrhage and ill-defined cerebrovascular lesions.

2.6. Follow-up

The date of entry into the study was defined as the date of the breast cancer report to the Cancer Register. For stroke, the date of admission to hospital for patients who subsequently were discharged with a main diagnosis of stroke was defined as the date of the diagnosis of stroke. The follow-up period in our study group was defined as the interval between diagnosis of breast cancer and stroke, death or the end of the study (31st December, 2000), whichever was the earliest.

2.7. Statistical methods

The observed number of women in our study group with breast cancer who suffered a stroke was compared with the expected numbers of cerebrovascular events in the background population. Comparisons are expressed as a quotient between the observed and expected number of cases to produce a Relative Risk (RR) (i.e. a standardised incidence ratio) [12,15]. The expected number of strokes was calculated by combining the person-time at risk in the study group with breast cancer with the number of strokes recorded in the Hospital Discharge Register per person-time unit, stratifying on five-year age groups and calendar year of observation. RR of stroke for different subsets, such as calendar year of diagnosis of breast cancer, age at diagnosis of breast cancer, follow-up period and subtypes of stroke, were calculated. The 95% Confidence Intervals (CI) for the RRs were established by assuming that the observed cases have a Poisson distribution using Byar's normal approximation [15]. All the statistical analyses were carried out using the SAS (version 8.2) (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients' characteristics

In the study group, the mean age at diagnosis of breast cancer was 63.6 years (standard deviation (SD) 13.9 years). Fifty-one percent of the breast cancers were

Table 1
International Classification of Disease (ICD) codes and definition of subtypes of stroke

ICD 8	(1970–1986)	ICD 9	(1987–1996)	ICD 10	(1997–2000)
Cerebral infarction					
432	Occlusion of precerebral arteries	433	Occlusion and stenosis of pre-cerebral arteries	G45	Transient cerebral ischaemic attacks and related syndromes
433	Cerebral thrombosis	434	Occlusion of cerebral arteries	G46	Vascular syndromes of brain in cerebrovascular diseases
434	Cerebral embolism	435	Transient cerebral ischaemia	I63	Cerebral infarction
435	Transient cerebral ischaemia				
437	Generalised ischaemic cerebrovascular disease				
Cerebral haemorrhage					
430	Subarachnoid haemorrhage	430	Subarachnoid haemorrhage	I60	Subarachnoid haemorrhage
431	Cerebral haemorrhage	431	Intracerebral haemorrhage	I61	Intracerebral haemorrhage
		432	Other and unspecified intracranial haemorrhage	I62	Other nontraumatic intracranial haemorrhage
Ill-defined cerebrovascular lesion					
344	Other cerebral paralysis	344	Other paralytic syndromes	I64	Stroke, not specified as haemorrhage or infarction
436	Acute, but ill-defined cerebrovascular disease	436	Acute, but ill-defined cerebrovascular disease	I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral Infarction
438	Other and ill-defined cerebrovascular disease	437	Other and ill-defined cerebrovascular disease	I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
		438	Late effects of cerebrovascular disease	I67	Other cerebrovascular diseases
				I69	Sequelae of cerebrovascular disease

left-sided and 47% right-sided, while 2% were of unknown side. The median follow-up period was 5.4 years (25th-percentile 2.3 years; 75th-percentile 10.4 years). Among women who had a stroke, the mean age at diagnosis of breast cancer was 71.4 years (SD 10.0 years) and the mean age at diagnosis of stroke was 78.5 years (SD 8.7 years). The median follow-up period was 5.7 years (25th-percentile 2.3 years; 75th-percentile 10.2 years).

3.2. Risk of stroke

The results are summarised in Table 2. The observed number of strokes was 1766 in our study group of 25,171 women with breast cancer. The expected number was 1576 and RR was 1.12 (95% CI = 1.07–1.17). The increased risk was confined to cerebral infarction, while there were no increases in risk for cerebral haemorrhage or ill-defined cerebrovascular lesions. As expected, most cerebrovascular events occurred in women aged 70 years and older at the breast cancer diagnosis. In women aged 55–69 years and 70 years and older, the risk of stroke was statistically significantly increased by 11% and 14%, respectively, while there was no statistically significantly increased risk of stroke in women below 55 years of age at breast cancer diagnosis.

We analysed further the incidence of stroke in relation to the length of follow-up. There was a 22% increase in the risk of stroke in the first year after the breast cancer diagnosis. This increase was confined exclusively to the women who were 70 years or older (RR = 1.26; 95% CI = 1.08–1.46; data not shown). Between 1 and 5 years after the breast cancer diagnosis, there was no statistically significant increase in the incidence. However, with longer follow-up, an increase in the risk of stroke of 17% was seen after 5–10 years of follow-up and 14% after >10 years of follow-up after the breast cancer diagnosis.

We also divided the women in our study into two subgroups according to the time of breast cancer diagnosis (1970–1985 and 1986–2000) to explore if differences in treatment policies for breast cancer may have influenced risk. In both subgroups, the RR was statistically significantly increased, being 1.22 in the period of 1970–85 and 1.08 in the period of 1986–2000. A trend towards a higher risk in the earlier time period versus the later one was seen, but the difference was non-statistically significant.

3.3. Causes of death

Causes of death are included in the Cancer Register (Table 3). When the follow-up ended on 31st of December, 2000, 51% (12,840/25,171) of the women in our study had died. In the whole study group, breast cancer contributed to 50% (6447/12,840) of the deaths and stroke to 7% (863/12,840).

Among women with a stroke, 74% (1303/1766) had died when follow-up ended. Cardiovascular disorders

Table 2
Relative Risk (RR) of stroke

	Stroke		Cerebral Infarction		Ill-defined cerebrovascular lesion		Cerebral haemorrhage	
	RR (95%CI)	Cases/Exp.	RR (95%CI)	Cases/Exp.	RR (95%CI)	Cases/Exp.	RR (95%CI)	Cases/Exp.
Study group with breast cancer	1.12 (1.07–1.17)	1766/1576	1.12 (1.05–1.19)	977/874	1.06 (0.98–1.15)	606/571	1.05 (0.90–1.21)	183/175
Age at breast cancer diagnosis (years)								
<55	1.01 (0.83–1.21)	114/113	1.07 (0.84–1.35)	72/67	1.00 (0.61–1.55)	20/20	0.81 (0.51–1.23)	22/27
55–69	1.11 (1.02–1.21)	566/509	1.13 (1.01–1.25)	350/311	1.04 (0.88–1.22)	149/143	1.01 (0.78–1.28)	67/67
>69	1.14 (1.07–1.21)	1086/954	1.12 (1.03–1.22)	555/496	1.07 (0.97–1.18)	437/408	1.16 (0.94–1.42)	94/81
Follow-up after breast cancer diagnosis (years)								
<1	1.22 (1.06–1.39)	216/177	1.18 (0.97–1.44)	104/88	1.22 (0.97–1.51)	85/70	1.32 (0.87–1.92)	27/20
1–<5	1.04 (0.96–1.13)	577/555	1.05 (0.93–1.17)	299/286	1.05 (0.92–1.20)	227/216	0.82 (0.61–1.07)	51/63
f 5–<10	1.17 (1.07–1.27)	515/441	1.13 (1.00–1.27)	277/245	1.05 (0.90–1.22)	170/162	1.42 (1.10–1.80)	68/48
>10	1.14 (1.04–1.25)	458/402	1.16 (1.04–1.31)	297/255	1.01 (0.84–1.20)	124/123	0.84 (0.59–1.16)	37/44
Breast cancer diagnosis and stroke								
1970–1985 *	1.22 (1.10–1.34)	388/319	1.18 (0.99–1.39)	138/117	1.17 (1.01–1.34)	204/175	1.36 (0.99–1.81)	46/34
1986–2000	1.08 (1.01–1.17)	742/684	1.07 (0.98–1.17)	479/447	1.09 (0.94–1.25)	185/170	0.97 (0.76–1.20)	78/81

95% Confidence Interval (95% CI). Number of cases. Expected number of cases (Exp.) by age at diagnosis of breast cancer and time of follow-up after breast cancer. The expected number of cases in the various subgroups does not sum to the expected number of cases of stroke due to censoring effects.

* Follow-up ended on 12-31-1985.

Table 3
Causes of death

Causes of death	Study group with breast cancer (n = 25,171)		Women with stroke (n = 1766)	
	Cases	(Per cent)	Cases	(Per cent)
Breast cancer	6447	(50.2)	165	(12.7)
Cardiovascular diagnosis	3684	(28.7)	884	(67.8)
- Myocardial infarction	892	(6.9)	84	(6.4)
- Cerebrovascular diseases	863	(6.7)	505	(38.8)
- Other cardiovascular diagnosis	1929	(15.0)	295	(22.6)
Other malignancies except breast cancer	1102	(8.6)	71	(5.4)
Respiratory diseases	501	(3.9)	57	(4.4)
Other causes	1106	(8.6)	126	(9.7)
Total	12,840	(100)	1303	(100)

contributed to 68% (884/1303) of these deaths, including 39% (505/1303) lethal strokes, while breast cancer contributed to only 13% (165/1303) of these deaths.

4. Discussion

The main finding in this study was a statistically significant increase in the incidence of stroke in women who had breast cancer during the period of 1970–2000. To our knowledge, this is the first study to describe an association between breast cancer and stroke. The increased risk of stroke was confined to women 55 years and older at breast cancer diagnosis and to the subtype cerebral infarction.

4.1. Methodological considerations

The strength of this study is the large study size of women with breast cancer and the large number of strokes observed. The study is population-based and the registers have good coverage and are of a high quality [12]. The 14% loss of person-years during the early part of the study influences both the observed number cases of stroke in the study group of women breast cancer and the expected cases of stroke in the background population in a similar manner and the quotient between them (the RR) is therefore not influenced.

We do not have any information about strokes that occurred before 1970 and some patients who had a stroke before 1970 and then breast cancer during 1970–2000 may therefore have been included. In the later study-period (1990–2000), we have more than 20 years observation time regarding the occurence of stroke before the breast cancer diagnosis. On the basis of the incidence of stroke before breast cancer, approximately 225 of 25,171 women in our study may have had a stroke before 1970. Thus, less than 1% of the study group is expected to have been erroneously included in the early years. By contrast, there may be an underestimation of the RR due to an overestimate of the expected number of cases in the denominator of the RR. The reason for this is that in the background population we registered each event of stroke during the study period of 1970–2000 with no exceptions being made for consecutive strokes.

A drawback of the study is that the risk factor profile of individual patients, including data on cancer therapy (such as radiotherapy) and cardiovascular risk factors

are not included in the registers we used. Thus, we cannot elucidate the pathogenesis behind the association between breast cancer and stroke. However, one may speculate about possible mechanisms.

4.2. Endocrine therapy

Tamoxifen has been linked to both hypercoagulability [16] and favourable changes in the lipid profile [17]. Tamoxifen has also been linked to a lower rate of thickened carotid intima-media in menopausal women with breast cancer [18] and increased intima-media thickness is considered an early marker of atherosclerosis [19]. However, in a recent meta-analysis of vascular and neoplastic events associated with tamoxifen [20], an increased risk of stroke was seen among patients treated with tamoxifen; RR = 1.49 (95% CI = 1.16–1.90). The stroke-analysis was composed of data from both prevention trials and treatment trials and included nine randomised controlled trials. The combined result corresponded to the non-significant increase of stroke in the largest study included, the Breast Cancer Prevention Trial P-1 Study [21], and the first results of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [22].

In Sweden, tamoxifen was registered for adjuvant treatment in 1983. We observed an increased risk of stroke during the whole study period from 1970 to 2000. In fact, this increase was more pronounced from 1970 to 1985. We therefore, do not believe that the use of tamoxifen is the main cause of the increased risk of stroke among breast cancer patients in our study, but it may be a contributing factor in the later time periods of our study.

4.3. Chemotherapy

Wall and colleagues [23] compared the incidence of arterial thrombosis (and stroke) in patients with breast cancer entered on two Cancer and Leukaemia Group B (CALGB)-protocols [24,25] with the incidence in the general population and concluded that the incidence of both peripheral arterial thrombosis and stroke among the women receiving chemotherapy was much higher than expected.

In Sweden, most breast cancer patients in the 1970s and 1980s did not receive adjuvant chemotherapy. Chemotherapy seems to increase the incidence of stroke during the time the courses are administered. We noted an increased risk of stroke during the first year after breast cancer diagnosis, RR = 1.22 (95% CI = 1.06–1.39), but this increase was exclusively confined to women 70 years and older, where chemotherapy is seldom used, even today. Thus, chemotherapy is probably not a major contributor of risk in our study group.

4.4. Radiotherapy

We are not aware of any published data from randomised studies of radiotherapy in breast cancer on the incidence of stroke. Several radiotherapy trials have indicated an increased risk of myocardial infarction, especially after treatment of left-sided tumours [5,6,8]. There is often a long interval between the exposure to radiation and vascular complications, as shown in the early breast cancer radiotherapy trials [5,6] and the atomic bomb survivor-studies [26]. In patients treated with radiotherapy for head and neck malignancies, ultrasonography studies have shown an increased risk of carotid stenoses [9], and in the same patient category, two studies have shown an increased incidence of ischaemic stroke [10,11].

Some lymph node-positive breast cancer patients receive radiotherapy to the lymph nodes in the supraclavicular region. In these cases, the proximal carotid artery is included in the irradiation portals. Radiotherapy has been used as a routine treatment method in early breast cancer throughout the whole time period encompassed by our study. Thus, it is conceivable that radiotherapy could be one of the factors responsible for the increased incidence of stroke. There is a long latency period between breast cancer treatment and the increase in radiation-induced heart disease [5,6]. In this respect, our epidemiological data on stroke differs from those concerning the risk for radiation-related myocardial infarction. Our study base shows a very early risk peak at year 0–1, which has no correspondence to the data currently published on myocardial infarction, where no early peak has been demonstrated. Thus, further studies are needed to identify the factor(s) responsible for this increased risk of stroke that we have demonstrated in our present study.

4.5. Predisposition to thrombosis

Thromboembolic complications are known to occur in patients with overt malignancy and venous thrombosis appears in patients with, at worst, only microscopic residual cancer [27]. Hence, the malignancy *per se* could be responsible for some of these vascular events.

4.6. Confounding factors

It is possible that confounding factors are responsible for an increased risk of both breast cancer and stroke. There is a link between breast cancer and the metabolic syndrome [28,29], and obesity is a risk factor for both of them. Experimental evidence suggests that hyperinsulinaemia can increase the promotion of mammary carcinogenesis and the mechanism is likely to involve increased bioactivity of insulin-like growth factor 1 (IGF-1) [29].

Hypertension is an established risk factor of stroke [30] and the prevalence of hypertension seems to be slightly elevated in women with breast cancer, compared with other tumour sites [31]. In an Italian network of case-control studies in women with breast cancer, the Odds Ratio for treated hypertension was 1.2 (95% CI = 1.1–1.4) [32]. In a prospective study of women attending a breast cancer screening project in the Netherlands, there was a non-significant increase of 14% (Hazard Ratio 1.14; 95% CI = 0.93–1.40) in the breast cancer risk among women with hypertension [33]. There was no statistically significant correlation between breast cancer and antihypertensive drugs [33].

Thus, if there is a link between hypertension and breast cancer, it is likely to be weak.

5. Conclusions

We found an association between breast cancer and the risk of stroke, the mechanisms of which cannot be further elucidated in the present study. Analytical studies with data from individual patients are needed to study the aetiology of the increased incidence of stroke in women treated for breast cancer.

Conflict of interest statement

None of the authors have conflicts of interest regarding the content of this paper.

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