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Original Paper

Soft Tissue Sarcoma after Treatment for Breast Cancer—A Swedish Population-based Study

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The aim was to quantify the risk of post-treatment sarcoma in breast cancer patients. All 122 991 women with a breast cancer from 1958 to 1992 in the Swedish Cancer Register were followed up for soft tissue sarcomas and 116 were found, giving a standardised incidence ratio of 1.9 (95% CI 1.5–2.2). The absolute risk was 1.3 per 10^4 person-years. The sarcomas were located in the breast region or on the ipsilateral arm in 63% (67/106). There were 40 angiosarcomas and 76 sarcomas of other types. In a case–control study, angiosarcoma correlated significantly with lymphoedema of the arm, odds ratio (OR) 9.5 (95% CI 3.2–28.0), but no correlation with radiotherapy was observed. For other types of sarcoma there was a correlation with the integral dose. The dose–response relationship indicated that the risk increased linearly with the integral dose to 150–200 J and stabilised at higher energies. The OR was 2.4 (95% CI 1.4–4.2) for an energy of 50 J, approximately corresponding to the radiation of the breast after breast-conserving surgery. Thus, only oedema of the arm correlated with angiosarcoma, but for other types of sarcoma the integral dose of radiotherapy was a predictor of the risk.

Key words: soft tissue sarcoma, breast cancer, radiotherapy, long-term effects
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INTRODUCTION

THERE ARE numerous reports on sarcomas developing in radiation fields after breast cancer treatment [1–8]. Some population-based register studies have also emphasised that the risk of soft tissue sarcoma is increased in breast cancer patients [9, 10]. In a previous population-based study on all women with breast cancer in the West of Sweden Health Care Region from 1960 to 1980 and followed up to 1988, we reported that there seems to be a dose–response relationship between the integral dose and the subsequent risk of developing a soft tissue sarcoma [11]. However, the confidence limits for the risk estimations were wide and the small size of that study did not permit any analyses of different types of sarcomas. Soft tissue sarcomas represent a heterogeneous histopathological group with possibly different aetiologies. Although angiosarcomas may develop in irradiated volumes without chronic lymphoedema, they are mainly considered to correlate with oedema of the extremities [12, 13], which in itself may be induced or aggravated by postoperative radiotherapy whilst other types of soft tissue sarcomas could be directly induced by ionising radiation. Genetic links exist between the risk of developing a soft tissue sarcoma and breast cancer in some families, e.g. in the Li–Fraumeni syndrome [14].

In order to elucidate the role of ionising radiation and lymphoedema in the carcinogenesis of soft tissue sarcoma, we extended our study to include all soft tissue sarcomas in breast cancer patients in the whole of Sweden during the years 1958–1992. Furthermore, the aim was to study whether the integral dose, i.e. a combination of 'dose' and irradiated volume, could be used as a predictor of a subsequent sarcoma. If so, the integral dose might also be useful as a predictor of radiation-induced carcinomas.

MATERIALS AND METHODS

This study was based on data from the Swedish Cancer Register (SCR). The SCR was established in 1958. All new cancers in Sweden must be reported to the register by the clinicians and pathologists, separately. The under notification

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of new cancers has been estimated to be low, less than 5% of diagnosed cancer cases [15].

During the period 1958–1992, 123 716 women with primary breast cancer as their first malignancy were reported to the SCR. This population of women with breast cancer has been followed up in the SCR until death or to the end of 1992. Of these women, 673 lacked follow-up data and in another 42 women there were inconsistent data and these individuals were excluded. Ten women were reported with a sarcoma on the same date as the breast cancer. As these cases do not contribute any information about the relationship between the treatment of breast cancer and sarcoma, they were also omitted from the study, leaving 122 991 women with a follow-up of 908 580 person years (PY). The mean age at breast cancer diagnosis was 62.7 years (median 63 years).

The study was confined to soft tissue sarcomas in the following sites according to the International Classification of Diseases, ICD-7 [16]: 197 (connective tissue), 170 (breast), and 191 (skin) if the histopathological type was consistent with a soft tissue sarcoma, i.e. all the types that were allowed within the site 197 [17]. Thus, most of the soft tissue sarcomas in internal organs were excluded. During 1958 to 1992 4,217 cases of soft tissue sarcoma with this definition in females were reported to the SCR. Of this number, 116 cases (3% of the total number of sarcomas) were found in 114 individuals belonging to the breast cancer population. The sarcoma cases were divided into three groups according to the pathology code in the SCR [17], i.e. angiosarcoma (WHO/CAN C24 codes 505, 506, 546), fibrosarcoma or malignant fibrous histiocytoma (705, 706, 715, 716) and other types. The angiosarcomas, Kaposi's sarcoma excluded (C24 505), in this population comprised 20% of all angiosarcomas ($n = 200$) in females in the SCR whereas the corresponding percentage of the total numbers in the SCR was 2% of both the fibrosarcomas ($n = 1{,}486$) and the other types of sarcoma ($n = 2{,}531$).

Seven cases were discovered within one year of breast cancer diagnosis, and 107 cases were discovered 13–371 months after the reported breast cancer. For each of the 107 cases that were detected one year or more after breast cancer diagnosis, three controls were selected according to the following rules: the breast cancer of the controls was diagnosed within ± 1 year of the cases and the age of the women at breast cancer diagnosis was the same within ± 2 years. The control patients were required to have survived with no other reports of cancer to the register for the same period of time as the time between the initial breast cancer diagnosis and the diagnosis of soft tissue sarcoma in the case. The cases and controls were to live in the same county at the time of breast cancer diagnosis.

For each case and control, clinical records were collected. The aim was to collect information about the histopathology of the sarcomas from the pathologists' reports, as well as detailed information about the location of the sarcomas in relation to the treated breast. A sarcoma was considered to be located within the treatment region if its primary site was within the volumes covered by 'standard' radiation fields on the ipsilateral chest wall, in the ipsilateral breast if the treatment was less than total mastectomy, in the ipsilateral supraclavicular fossa, or on the ipsilateral arm. Further, information was sought on whether radiotherapy was part of the primary breast cancer treatment or not. Treatment charts were needed to estimate the integral dose (see below). The presence or absence of radiotherapy to other locations was also looked for. Information about the presence of arm oedema was obtained from the clinical follow-up records, and for the cases it had to be recorded before the detection of a sarcoma.

Since this was a population-based study, clinical records were obtained from hospitals all over Sweden. Surgical treatment was performed in all kinds of hospitals. Until the mid-1970s radiotherapy was often given in diagnostic X-ray departments in local hospitals. Thereafter, all radiotherapy became centralised to radiotherapy departments in regional and in some county hospitals.

The collection resulted in sufficient information about the histopathology in all cases and about the site of the sarcoma in 106 of 107 cases (99%). Information about whether radiotherapy was given or not was obtained in 291 of the 321 controls (91%) and in 105 of the 107 cases (98%). Radiotherapy charts gave information about the radiation portals and treatment data, which allowed estimation of the integral dose for 96 (90%) of the cases and for 268 (83%) of the controls. Clinical follow-up information about the presence or absence of lymphoedema was available in 103 (96%) of the cases and in 282 (88%) of the controls, but could only be coded as a binary variable since there was seldom any objective measurement concerning the gravity of the oedema.

Statistical methods

The standardised incidence ratio (SIR) for soft tissue sarcoma has been calculated as the ratio between observed and expected number. The expected numbers were calculated on the basis of sex, year and age-specific incidence rates of soft tissue sarcoma in Sweden obtained from the SCR. The confidence intervals were estimated assuming a Poisson distribution of the cases. Differences between different groups were tested with ANOVA tests, Fisher's exact test or the Student's *t*-test, when appropriate. Trends were tested using a Wilcoxon-type test for trend [18]. The relationship between energy imparted, presence of oedema of the ipsilateral arm, radiotherapy to sites other than the breast and the occurrence of soft tissue sarcoma was calculated by means of the conditional logistic regression model for matched sets [19]. These analyses were performed with all types of sarcomas, the angiosarcomas, or all other types (fibrosarcoma and other types) as dependent variables. Oedema of the ipsilateral arm and radiotherapy outside the index breast cancer region were binary variables, and the energy imparted of the radiotherapy as part of the breast cancer treatment was a continuous variable in units of 100 J. The energy imparted was also grouped into four categories, one category consisting of those who had received no radiotherapy and the other three categories being constructed so that each contained one-third of the treated patients (0, >0–<120, 120–<200, ≥ 200 J). The significance of the addition of parameters to a model was tested taking minus twice the difference of the log likelihoods, which under the assumption of no effects has an approximately chi-squared distribution with the degrees of freedom equal to the difference in parameters between the models. All the statistical tests and models were performed using the STATA Statistical software [20].

Determination of energy imparted

In order to compare the impact of radiotherapy given by different treatment protocols, the total absorbed energy was

estimated. The total energy absorbed from the beam by the patient is called the energy imparted (integral dose) and was defined for photon beams by Mayneord in 1942 [21]. The energy imparted is the product of the mass of the patient and the dose absorbed. An approximate method for single photon beams has also been given by Mayneord [21] for the determination of the energy imparted. The expression for estimation of the energy imparted, E, per photon beam is:

$$E = 1.44 \times Do \times A \times R_{50}\left(1 - e^{-0.693 \times d/R_{50}}\right) \times (1 + 2.88 \times R_{50}/\mathrm{SSD})$$

where

Do = the dose at the depth of dose maximum along the beam axis
A = the size of the beam in cm^2 at SSD
R_{50} = the depth of the 50% dose along the beam axis
d = the thickness of the patient along the beam axis
SSD = the source-to-skin distance

For electron beams, the energy imparted per beam is estimated by the expression:

$$E = A \times R_{50} \times Do$$

The total energy imparted from the different beams is found by adding the contribution from the different beams. The energy imparted is basically a product of mass (kg) and dose (Gy) and its unit is then simply joules.

For each field and patient, the SSD, the area of the beam, the given dose and the depth of 50% dose have been taken into account in the calculation of the energy imparted. The thickness of the patients along the beam axis has been estimated based on the direction of the beam and by using the same transversal body-contours for both cases and controls. The contours were derived from the averages of the contours obtained from two women whose weight and length were 61 kg and 166 cm, and 78 kg and 170 cm, respectively.

RESULTS

The register study

In 122 991 women diagnosed with breast cancer followed for 908 580 person-years, 116 soft tissue sarcoma appeared in 114 individuals, whereas 62.6 were expected. The SIR was thus 1.9 with a 95% confidence interval (95% CI) of 1.5–2.2. The absolute risk of soft tissue sarcoma in the population diagnosed with breast cancer was 1.3/10^4 PY, compared with the expected risk of 0.7 per 10^4 PY. The risk in different time intervals since treatment is shown in Table 1. The point estimates of SIRs were above one in all intervals after the first year and were significantly increased after 5 years. The observed and the expected numbers were for angiosarcoma 40 and 6.9 (SIR 5.8, 95% CI 4.2–7.9), for fibrosarcoma 35 and 22.2 (SIR 1.6, 95% CI 1.1–2.2) and for other types 41 and 33.6 (SIR 1.2, 95% CI 0.9–1.7). The highest excess was found for the angiosarcomas, and this was significantly raised after 5 years. The SIR of angiosarcoma reached its highest value, 12.1, (95% CI 3.3–31.0) in the interval 20–35 years. Fibrosarcomas were also significantly increased during the periods 5–9 and 10–19 years after the breast cancer treatment.

The case–control study

Cases. The case–control study concerned 107 individuals with a sarcoma detected 1 year or more after breast cancer diagnosis. After scrutiny of the clinical records of the cases, discrepancies of the histopathological classification from that reported to the Swedish Cancer register were found in only 3 cases (2.8%). One case classified in the register as a fibrosarcoma (706) was described as an angiosarcoma in the pathological report, there was 1 case in the register reported as an angiosarcoma (506) in which the pathologist's report stated a fibrosarcoma and a Kaposi's sarcoma according to the pathologist's report had been classified as an unspecified sarcoma (796). These three cases were reclassified for the further analysis. Kaposi sarcomas were grouped together with angiosarcomas for the analyses and there were four such cases. 2 persons had two sarcomas according to the SCR. In both cases, however, the clinical records showed that the second report to the SCR concerned metastatic spread of the first one.

Some characteristics of the sarcoma patients are given in Table 2. The mean age at breast cancer diagnosis was 58.7 years (range 30–86 years), and the age at diagnosis of the sarcoma was 68.4 years (range 31–91 years). The women who developed different types of sarcomas differed both in age at breast cancer diagnosis ($P = 0.02$) and in age at the time of diagnosis of the sarcoma ($P = 0.004$); patients who later developed any sarcomas other than angiosarcomas were younger both at the time of breast cancer diagnosis (mean age 56.5 years) and at the time of diagnosis of the sarcoma (mean 65.4 years) compared with angiosarcomas. The mean time between the two diagnoses (10.1 years, range 1.1–30.9 years) did not differ significantly between the groups ($P = 0.12$) (Table 2).

The mean age at breast cancer diagnosis of women who later developed an angiosarcoma was similar to that of the

Table 1. *Numbers and standardised incidence ratios (SIR) of soft tissue sarcoma (STS) in the Swedish breast cancer population by type according to the histopathology code in the SCR and period of follow-up since breast cancer diagnosis.* 116 *soft tissue sarcomas were reported in* 114 *women*

		Angiosarcoma		Fibrosarcoma		Other types		All STS	
Period years	Person years	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)
0	113 615	1	1.3 (0.02–7.0)	3	1.3 (0.3–3.7)	3	0.7 (0.2–2.3)	7	1.0 (0.4–2.1)
1–4	325 001	3	1.3 (0.3–3.7)	7	1.0 (0.4–2.0)	17	1.5 (0.9–2.4)	27	1.3 (0.9–1.9)
5–9	227 888	14	7.6 (4.2–12.8)	11	2.0 (1.0–3.6)	6	0.7 (0.3–1.5)	31	2.0 (1.3–2.8)
10–19	192 121	18	11.8 (7.0–18.5)	12	2.3 (1.2–3.9)	11	1.4 (0.7–2.6)	41	2.8 (2.0–3.8)
20–35	49 955	4	12.1 (3.3–31.0)	2	1.1 (0.1–3.9)	4	1.4 (0.5–4.6)	10	2.3 (1.1–4.2)
0–35	908 580	40	5.8 (4.2–7.9)	35	1.6 (1.1–2.2)	41	1.2 (0.9–1.7)	116	1.9 (1.5–2.2)

Table 2. Some characteristics of the soft tissue sarcomas, and the initial treatment of breast cancer

Type	No.	Close to breast	Mean age at breast cancer years (range)	Mean age at sarcoma years (range)	Time between breast cancer and sarcoma years (range)	Radiotherapy given	Dose of RT if given J (No.*)	Oedema of arm
Angiosarcoma	38	32/38 (84%)	62.8 (42–81)	73.8 (49–91)	11.4 (1.1–24.8)	34/37 (92%)	167 (29)	26/35 (74%)
Fibrosarcoma	31	20/31 (65%)	54.7 (30–86)	64.6 (36–88)	10.2 (1.6–25.3)	27/30 (90%)	210 (26)	9/30 (30%)
Other	38	15/37 (41%)	57.9 (30–81)	66.1 (31–83)	8.8 (1.3–30.9)	33/38 (87%)	189 (30)	11/38 (29%)
All	107	67/106 (63%)	58.7 (30–86)	68.4 (31–91)	10.1 (1.1–30.9)	94/105 (90%)	188 (85)	46/103 (45%)

The sarcomas were classified into three groups according to the pathologists' reports. No.*, Number of individuals with information.

background breast cancer population, 62.8 and 62.7 years, respectively, whereas the mean age of women who later developed a fibrosarcoma or other types of sarcoma was significantly lower (56.5 years, $P = 0.0002$).

The site of the sarcoma was close to the treated breast or on the ipsilateral arm in 67 (63%) of the 106 cases. In one case with a metastasising sarcoma, the primary location was impossible to identify from the clinical records. There was a significant difference concerning the proximity of the sarcoma to the breast cancer region between the three sarcoma types ($P = 0.007$). Angiosarcomas were more often located close to the treatment region (84%, 30 in a swollen arm and two in conserved breasts) than fibrosarcomas (65%) and other types (41%) (Table 2). One angiosarcoma was located in the swollen contralateral arm. This patient had been treated for a contralateral breast cancer 15 years after the index cancer and the angiosarcoma appeared 9 years after the treatment of the second cancer. Two of the four Kaposi's sarcomas were located on the arm of the treated side, one in a lympoedemateous leg and one had multiple locations. Of 33 sarcomas of other types than angiosarcomas that were located outside the 'standard' treatment volume, 13 were intra-abdominal, 13 were in a leg, four on an arm, two in the head or upper neck and one on the contralateral thoracic wall. Three of the patients with intra-abdominal sarcomas had been castrated radiologically. The patient with a sarcoma in the upper neck had been treated with radiation for a glomus tumour close to this site 30 years before the breast cancer and before the start of the Swedish Cancer Register.

In 94 of the cases radiotherapy had been given as part of the breast cancer treatment and in 11 cases radiotherapy had not been given. For two patients information was lacking. For 85 of 94 patients given radiotherapy treatment, charts were available, which allowed estimation of the energy imparted, which was mean 188 J. No significant difference was seen concerning the frequency of radiotherapy ($P = 0.82$) or the energy imparted ($P = 0.39$) between the three types of sarcomas. Radiotherapy other than as local treatment for the breast cancer had been given in 22 cases (7 angiosarcomas, 6 fibrosarcomas, 9 other types).

Arm oedema was recorded in 46 cases (45%). For four of the cases (three with angiosarcoma and one fibrosarcoma) information was lacking. There was a highly significant difference between the three types of sarcomas ($P = 0.0001$), oedema being more commonly recorded in patients who developed angiosarcomas (74%) than in those with fibrosarcoma (30%) or other types (29%) (Table 2).

A logistic regression within the cohort of the 107 sarcoma cases showed that oedema of the arm, age at breast cancer diagnosis and time between breast cancer and sarcoma diagnosis were positively and the energy imparted was negatively related to the odds for a case to be an angiosarcoma in a model when all factors were considered together.

Controls. Three controls were selected per case. Due to difficulties retrieving all relevant clinical records, information was lacking on whether radiotherapy was given or not in 30 controls (9%) and about oedema of the arm in 39 (12%) of 321 controls. Treatment charts were lacking in a further 23 patients of 216 known to have been treated with radiotherapy (11%). Some details of the control patients are given in Table 3.

Radiotherapy had been given in 216 (74%) of 291 patients. During the period 1958–1969, 94% of patients were treated with radiotherapy, during 1970–1979 58% and after 1979 55% of the patients had received this treatment. The decreasing trend was highly significant ($P < 0.0001$). However, the energy imparted, in those who were treated increased significantly from 159 J before 1970 to 167 J during the 1970s and 300 J thereafter ($P = 0.01$).

In Sweden there are six healthcare regions. There was no significant difference in frequency of radiotherapy between the regions ($P = 0.58$), but the energy imparted differed significantly between the regions, irrespective of whether the test was performed in all patients or only in those who had been treated with radiotherapy ($P < 0.0004$). The mean energy imparted varied over the six regions from 142 J (West of Sweden) to 235 J (Uppsala-Örebro region) in those who were treated with radiotherapy.

Information was obtained from the clinical records about radiotherapy given outside the local treatment of breast cancer

Table 3. Some characteristics of the control patients by period of treatment

Period	No.	Mean age at breast cancer diagnosis, years (range)	Radiotherapy given (%)	Mean energy imparted if radiotherapy given, J (No.)	Oedema of arm (%)
1958–1969	152	57.9 (31–80)	125/133 (94)	159 (104)	36/126 (29)
1970–1979	127	59.4 (29–86)	70/120 (58)	167 (69)	16/119 (13)
1980–1992	42	59.7 (30–78)	21/38 (55)	300 (20)	9/37 (24)
Total	321	58.8 (29–86)	216/291 (74)	177 (193)	61/282 (22)

No., Number of individuals with information.

Table 4. *Comparison between cases and controls*

	Cases $n = 107$*	Controls $n = 321$*	Difference
Complete clinical information	96/107 (90%)	265/321 (83%)	$P = 0.09$
Age at breast cancer diagnosis, years (range)	58.7 (30–86)	58.8 (29–86)	–
Radiotherapy given	94/105 (90%)	216/291 (74%)	$P = 0.001$
Energy imparted if radiotherapy given, J	188 ($n = 85$)	177 ($n = 193$)	$P = 0.39$
Radiotherapy to other sites	22/102 (22%)	39/284 (14%)	0.06
Oedema of arm	46/103 (45%)	61/282 (22%)	$P < 0.001$

*$n = 107$ for cases and 321 for controls unless otherwise stated.

in 39 of the controls. Oedema of the ipsilateral arm was recorded in 61 of 282 clinical records (22%). There was no significant trend over the three treatment periods ($P = 0.11$, Table 3).

Radiotherapy had been given to 58 of 61 patients with lymphoedema recorded (95%) and in 150 of 220 without oedema (68%). This difference was highly significant ($P = 0.002$). The energy imparted was 171 J in those with oedema, and 116 J if no edema was recorded, a significant difference ($P = 0.002$). However, most of this difference was due to whether radiotherapy was given or not, and there was no significant difference in energy imparted in those who had been treated with radiotherapy (181 J and 175 J, respectively, $P = 0.77$).

Comparison between cases and controls. A comparison between cases and controls is shown in Table 4. Complete information concerning radiotherapy and the presence or absence of oedema was obtained for 90% of the cases and 83% of the controls, a difference which was not significant ($P = 0.09$). However, all clinical information was lacking for only 2% of the cases but for 9% of the controls ($P = 0.01$).

Radiotherapy as part of the initial breast cancer treatment was given significantly more often to the cases than the controls ($P = 0.001$), but in those treated with radiotherapy, there was no significant difference in the energy imparted ($P = 0.39$). Some patients had been treated with radiotherapy in other locations or at other times, but the difference between the two groups in this respect only approached significance ($P = 0.06$). Oedema of the ipsilateral arm was more common in cases than in controls ($P < 0.001$).

A conditional logistic regression analysis of the odds ratio (OR) of sarcoma showed that oedema of the arm ($P = 0.003$) and energy imparted ($P = 0.0009$) were significant predictors, but not radiotherapy given outside the breast cancer treatment ($P = 0.13$) (Table 5, model 1.1–1.4). Further, replacing the categorical variable for energy imparted with a numerical one indicated that there was a significant departure from a linear dose–response relationship ($P = 0.03$). The addition of a quadratic energy imparted term to the linear one significantly improved the fit (Table 5, model 1.6, $P = 0.02$).

Table 6 gives the coefficients of the significant variables. Overall the coefficient of oedema was 0.9, which corresponds to an OR of 2.4 (95% CI 1.4–4.3) for a patient with oedema of the arm in comparison with a patient without oedema. The coefficient of energy imparted was 2.1 if a numerical variable was introduced into the model and 1.8 if it was a continuous variable. For the quadratic term, the coefficient had a negative sign (-0.5 and -0.4, respectively), indicating that the

Table 5. *Predictors of soft tissue sarcoma*

		Difference			
Group of sarcoma Model	Deviance	Comparison with model	Deviance	dF	*P*
1. All soft tissue sarcoma					
1.1. Oedema + energy imparted* + other radiotherapy	199.98	–	–	–	–
1.2. Model 1.1—other radiotherapy	202.19	1.1	2.30	1	0.13
1.3. Model 1.1—oedema	208.72	1.1	8.83	1	0.003
1.4. Model 1.1—energy imparted*	216.31	1.1	16.43	3	0.0009
1.5. Model 1.4 + (energy imparted†)	206.63	1.1	6.75	2	0.03
1.6. Model 1.5 + (energy imparted†)	201.17	1.5	5.46	1	0.02
2. Angiosarcoma					
2.1. Oedema + energy imparted* + other radiotherapy	58.68	–	–	–	–
2.2. Model 2.1—other radiotherapy	58.68	2.1	0.00	1	0.98
2.3. Model 2.1—oedema	73.65	2.1	14.98	1	0.0001
2.4. Model 2.1—energy imparted*	59.47	2.1	0.80	3	0.85
3. Other soft tissue sarcoma					
3.1. Oedema + energy imparted* + other radiotherapy	133.55	–	–	–	–
3.2. Model 3.1—other radiotherapy	136.49	3.1	2.95	1	0.09
3.3. Model 3.1—oedema	134.43	3.1	0.88	1	0.35
3.4. Model 3.1—energy imparted*	150.46	3.1	16.91	3	0.0007
3.5. Model 3.4 + (energy imparted†)	138.74	3.1	5.19	2	0.07
3.6. Model 3.5 + (energy imparted†)	134.80	3.5	3.94	1	0.047

Results of conditional logistic regression of odds of sarcomas and comparisons with a model containing all the investigated parameters. *Energy imparted as a set of categorical parameters with four levels. †[Energy imparted] as a numerical parameter to estimate the linear effect of energy imparted.

Table 6. Estimates of the coefficients of the independent variables in the models of odds ratio (OR) of soft tissue sarcoma: $OR = e^{\beta_1 \text{oedema} + \beta_2(\text{energy imparted}^*) + \beta_3(\text{energy imparted}^*)^2}$

Type of sarcoma	Oedema (n) β_1 (95% CI)	Energy imparted β_2 (95% CI)	(Energy imparted)^2 β_3 (95% CI)
All soft tissue sarcoma			
Energy imparted (n)	0.9 (0.3–1.4)	2.1 (0.7–3.5)	− 0.5 (− 0.9– − 0.1)
Energy imparted (c)	0.9 (0.3–1.5)	1.8 (0.8–2.7)	− 0.4 (− 0.6– − 0.1)
Angiosarcoma	2.2 (1.2–3.3)	–	–
Other sarcoma			
Energy imparted (n)	–	2.4 (0.8–4.0)	− 0.5 (− 1.0– − 0.1)
Energy imparted (c)	–	1.9 (0.8–3.0)	− 0.4 (− 0.6– − 0.1)

*Energy imparted was a numerical variable with four levels (n) or a continuous variable (c).

increase in OR by increasing energy imparted decreases at higher energies. This corresponds to an OR of 4.0 (95% CI 1.5–11.1) at 100 J and of 7.9 (95% CI 0.9–70.6) at 200 J. Figure 1 illustrates the observed OR in the actual data by energy imparted and model predicted OR, estimated over the strata that gave information on oedema and doses. The OR increases with energy imparted up to 150–200 J and is stable or possibly decreases thereafter. The predicted OR-values were adjusted according to oedema.

The analysis of angiosarcoma alone showed only oedema of the arm to be a significant predictor ($P = 0.0001$, Table 5). Energy imparted ($P = 0.85$) and other radiotherapy ($P = 0.98$) did not improve the fit of the model which contained information on oedema of the arm. The coefficient for oedema was 2.2 (Table 6), which corresponds to OR 9.5 (95% CI 3.2–28.0). Restricting the analysis to angiosarcomas within the treatment region or on the ipsilateral arm gave OR 12.0 (95% CI 3.51–41.0).

For other types of sarcoma than angiosarcoma only energy imparted fitted the model ($P = 0.0007$, Table 5; model 3.1–3.4). The addition of a quadratic energy term improved the fit over that of only a linear numeric variable (Table 5; model 3.6, $P = 0.047$). Both energy imparted as a continuous and as a numerical variable with four dose levels fitted the linear-quadratic model (Table 6). For energy imparted as a numerical variable, the coefficient for the linear term was 2.4 and for the quadratic term − 0.5 (Table 6). If the numerical variable of energy imparted (n) was replaced with a continuous energy variable, the coefficients were 1.9 and − 0.4, respectively. These coefficients correspond to an OR of 4.8 (95% CI 1.6–14.9) at 100 J in comparison with 0 J. At 50 J, which approximately corresponds to the energy imparted of tangential radiation after breast-conserving surgery OR is 2.4 (95% CI 1.4–4.2) and at 150 J, a common energy imparted in postoperative radiotherapy to the chest wall and regional lymph nodes, the OR was 8.0 (95% CI 1.4–46.1). If the analysis was restricted to the strata containing non-angiomatous sarcomas located within the treatment area, the coefficient for the linear term was 6.2, (95% CI 2.1–10.4), and for the quadratic term − 1.3, (95% CI − 2.3– − 0.4).

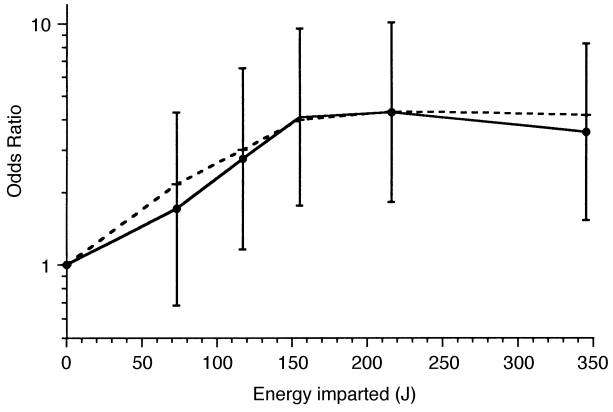

Figure 1. Observed odds ratio (—) in different energy imparted categories, with 95% confidence intervals and model-fitted odds ratio (– – –) determined for the same data. The reference category was not treated with radiotherapy (energy imparted 0 J).

DISCUSSION

In the total cohort of 122 991 women with a primary diagnosis of breast cancer from 1958 to 1992 in Sweden, 116 soft tissue sarcomas later developed in 114 individuals. The SIR was 1.9, which was similar to the SIR estimate in our previously published study from the West of Sweden Health Care Region based on 19 cases of soft tissue sarcoma after breast cancer, in which the SIR was 2.2 [11]. Among 107 cases with a sarcoma more than one year after the breast cancer diagnosis, 67 (63%) arose in the vicinity of the treated breast, which suggests a relation to the treatment. This result was also in agreement with our previous study from the West of Sweden [11], in which 72% of sarcomas were located in the treated breast region.

We used energy imparted (integral dose) to quantify the total amount of ionisations. The estimation in Mayneords formula is however, only an approximate one, and is defined for orthovoltage radiotherapy. Furthermore, the actual sizes of the treated women were not known and a standardised contour was created as the mean of two actual patients.

If there was a linearily increased risk with increasing dose, the energy imparted should be an ideal measurement in order to allow a comparison between the risks between different treated volumes, doses and energies. The risk of other soft tissue sarcomas than angiosarcoma showed a significant correlation with energy imparted in our study. The dose–response relationship between energy imparted and the odds ratio of sarcoma was non-linear; the risk increased with increasing energy up to 150–200 J (Figure 1) and stabilised or even diminished at higher energies. This is compatible with cell-sterilisation at high-doses which is observed in many other studies on radiation-induced cancer [22]. To encompass a non-linear dose–response relationship in the energy imparted, different weights for volumes with different 'doses' would have to be defined. This is an area for future research.

Our previous study [11] showed that there was a correlation between the energy imparted and the later occurrence of

a soft tissue sarcoma. The size of the present study allowed separate analyses of angiosarcomas and of other types of soft tissue sarcomas with regards to energy imparted and oedema of the arm. As already referred to, there was a correlation between the energy imparted and sarcoma of other types than angiosarcoma. For such sarcomas, there was, however, no correlation with oedema. The OR of radiation-induced sarcoma might be much higher than that we found in our study since an analysis restricted only to the cases that occurred in close vicinity of the standard treatment area of the breast cancer, increased the OR considerably. Furthermore, in a few such sarcomas that occurred outside the treatment area of the breast, radiation therapy had been given in the vicinity of the later sarcoma for other reasons than for local control of the breast cancer.

Angiosarcomas had the highest SIR, approximately 12, 10 years or more after the breast cancer treatment. In fact, the angiosarcomas, excluding the Kaposi's type, of this breast cancer cohort constituted one-fifth of all angiosarcomas in women in Sweden during the same period. It may be difficult to interpret the SIR values for the angiosarcomas since the effect of the high proportion of all cases in this group could lead to an underestimation of the relative risk of angiosarcoma in the breast cancer population.

In our study, we only found a correlation between the presence of arm oedema of the ipsilateral arm and the appearance of an angiosarcoma, with OR = 9.5, but not with energy imparted when both factors were analysed together, although the presence of oedema correlated with radiotherapy. In this retrospective study, oedema could only be evaluated as a binary variable, without any quantification of its extent or duration. To avoid a bias of recording oedema because of the known connection between oedema and angiosarcoma, oedema was only recorded in the cases if it had been mentioned in the clinical records before the diagnosis of a soft tissue sarcoma.

The correlation between chronic lymphoedema and angiosarcoma constitutes the Stewart–Treves syndrome [12]. As long ago as 1948, Stewart and Treves published a paper, 'Lymphangiosarcoma in Postmastectomy Lymphedema—a report of six cases of Elephantiasis Chirurgica'. The correlation with oedema seemed obvious but a population-based quantification of the risk or assessment of the possible direct role of radiation dose was never done at that time. There are, however, several case reports of angiosarcoma arising within irradiated volumes without a visible lymphoedema [23]. In our study, the integral dose of radiotherapy was not significantly correlated to angiosarcoma when the effect of oedema was accounted for, but there were two cases of angiosarcomas in the breast after breast-conserving treatment.

A genetic connection between sarcoma and breast cancer could influence the results in this study. The Li–Fraumeni syndrome [14] with a mutation in the germ-line *p53* is a familial syndrome with many different kinds of cancers usually seen at young ages including both sarcomas and breast cancer. However, there was only one woman with breast cancer before 30 years of age and four diagnosed with breast cancer before 40 years of age among the cases. One of them could well be a case of the Li–Fraumeni syndrome since she had multiple tumours, cancer of the right breast at the age of 32 years, a soft tissue sarcoma at the age of 33 years, cancer of the left breast at the age of 35 years followed by a bone sarcoma at the age of 41 years. In cases like this there probably exists a genetic association between the breast cancer and the sarcoma. However, there are also reports of germline *p53* mutations in families with later onset of breast cancer [24]. The mean age at breast cancer diagnosis among the cases other than angiosarcomas was significantly lower than that of a general breast cancer population (56.5 versus 62.7). Although genetic associations between the diseases are probably not a major cause of the excess of sarcomas in the breast cancer population, in some cases such an association cannot be ruled out. Whether a genetic link also infers an increased radiosensitivity is not known.

The strength of a register-based study is that it gives the possibility of unbiased sampling of the cases from the total population. The Swedish Cancer Register has a high quality and is validated concerning the completeness of primary cancer registrations [15]. Concerning the quality of the recording of pathological subgroups in the register, one has to be careful. A comparison with the pathologists' reports revealed only a few discrepancies from the recorded diagnoses but we judged it prudent to limit the analyses to the wide groups of angiosarcomas and sarcomas of other types, although there are subgroups within each category that may have different aetiologies.

The results of this study confirm the relationship between breast cancer treatment and development of soft tissue sarcoma. Angiosarcoma correlates with oedema, with the angiosarcomas in the breast cancer population comprising approximately 20% of all angiosarcomas. The other types of sarcoma correlate with energy imparted and the dose–response relationship seems to show a complex pattern with a quadratic term, which, at higher-doses, may reduce the risk. Although soft tissue sarcomas are rare in the population of breast cancer patients, the long-term effects of radiotherapy after breast cancer treatment become increasingly important. Increasing numbers of women are being treated with breast-conserving surgery combined with radiotherapy as a result of a change of opinion as to what constitutes the best treatment and of the increasing use of mammography. This will lead to an increasing population of women with a very long life expectancy who have been exposed to radiotherapy.

Energy imparted seems to provide an opportunity to evaluate different radiotherapy regimens as predictors of secondary malignancies in the breast cancer population. Its value for other secondary malignancies should also be studied with the aim of gaining a better knowledge of this type of late side-effect, which has to be weighed against tumour control benefits of the treatment.

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