Acta Oncologica 29 (1990) Fasc. 5

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TUMORS AFTER RADIOTHERAPY FOR SKIN HEMANGIOMA IN CHILDHOOD

A case–control study

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Abstract

A case–control study was conducted to investigate the possible association between absorbed dose and cancer risk in a cohort of 14 647 individuals (33% males and 67% females) less than 18 months old and irradiated for skin hemangioma between 1920 and 1959. The cases consisted of 56 breast cancers (in 55 patients), 14 thyroid cancers, 16 brain tumors and 8 tumors of bone and soft tissues. Four controls were matched to each case. They were matched for sex, age at treatment, treatment modality and treatment year. Absorbed doses were categorized in three exposure groups, <0.1 Gy, 0.1–0.4 Gy, and ≥ 0.5 Gy, and odds ratios (OR) were estimated with the lowest exposure group as reference. A statistically significant positive dose–response relationship was found for thyroid cancer (OR: 1.0; 4.8; 4.3) and for tumors of bone and soft tissues (OR: 1.0; 1.6; 19.5). For breast cancer and brain tumors no significant dose–response relationship could be found. The median absorbed dose in the tumor sites among the cases of thyroid cancer, tumors of bone and soft tissues, breast cancer and brain tumors was 0.2 Gy, 0.3 Gy, 0.03 Gy and 0.04 Gy respectively. The dose was probably too low to detect any dose–response relationship for breast cancer and brain tumors.

Key words: Hemangioma, children, radiotherapy, cancer, case–control study.

The present knowledge of radiation-induced cancer after irradiation in childhood is based on studies of children who have survived nuclear warfare or have been irradiated for pediatric tumors or benign conditions. Increased risks have been found for several tumor types, e.g. leukemia (1), thyroid cancer (2, 3), breast cancer (4–6) brain tumors (7, 8) and tumors of bone and soft tissues (9, 10). A dose–response relationship has been observed, but the shape of the dose–response curve is still uncertain.

Observation of the atomic bomb survivors in Hiroshima and Nagasaki has supplied the most important information for estimation of cancer risks after exposure to rather low doses of ionizing radiation (11). According to a recent revision of the dosimetry the cancer risks based on shielded kerma in the exposed populations appear to be somewhat higher than previously estimated. However, in terms of organ doses, relatively small differences were found except for breast and ovaries (5, 12).

In a large Swedish cohort study of infants, children and adolescents irradiated with radium-226 or orthovoltage x-rays for skin hemangioma between 1920 and 1959, an increased relative risk (RR) for cancer of 1.2 [95% confidence interval (CI) 1.04–1.40] was found for the period 1958–1982 (13). Increased risks were observed for breast cancer (RR: 1.7; 95% CI 1.26–2.13) and soft tissue tumors (RR: 2.7; 95% CI 1.18–5.38). The risk of thyroid cancer was also increased (RR: 1.8) although not statistically significant. The tumors appeared within previously irradiated areas in the majority of the patients with brain tumors, thyroid carcinomas and bone sarcomas suggesting a dose–response relationship.

The purpose of the present case–control study was to investigate possible dose–response relationships for brain tumors, malignant tumors of the breast, thyroid, bone and soft tissues in the cohort of patients irradiated for skin hemangioma.

Material and Methods

A population of 18 460 patients was admitted to Radiumhemmet for skin hemangioma between 1920 and 1959 (13). The cases and the controls of the present study were derived from the 14 647 patients (33% males and

Accepted for publication 15 November 1989.

67% females) who were irradiated with radium-226, x-rays or phosphorus-32 and were younger than 18 months (median age 6 months) at the time of the first treatment. This age group was chosen to facilitate dose calculations. The population was identified through hospital files and registration books. Local parishes and population registers were used for the tracing of patients.

Cancers in the cohort were searched by three different methods and primarily through a record-linkage with the nationwide Swedish Cancer Register (SCR) covering the period 1958–1984 (13). About 96% of all cancers are reported to the SCR by physicians and pathologists or cytologists independently (14). The cohort was also matched with the Swedish Cause of Death Register covering the period 1952–1986. For cancers and leukemias occurring before 1952 the source of information was hospital records from Radiumhemmet and reports from local parishes on causes of death (15).

In the present study only patients with tumors of the brain and malignant tumors of the breast, thyroid, bone and soft tissues were included. The majority of the patients were reported to the SCR (90 cases). Additional cases were found in the Swedish Cause of Death Register (1 patient with a brain tumor and 1 patient with a soft tissue tumor). Two patients died of brain tumors before 1952, when the computorized register started. In total 92 patients with cancer (1 patient had bilateral breast cancers and 1 patient had both breast cancer and thyroid cancer) was included in the study, viz. 56 breast cancers, 16 brain tumors, 14 thyroid cancers, 3 bone sarcomas, and 5 other tumors originating from bone or soft tissues.

Four controls to each case were randomly chosen from the total population of irradiated subjects. They were matched for sex, time of treatment, treatment modality and age at treatment. The controls had to be alive and living in Sweden at least as long as the time from treatment to cancer diagnosis for the corresponding case. Complete information about mortality and emigrations was not available before matching which led to the exclusion of 16 controls. One control was excluded due to incomplete information on treatment.

The year and age at treatment and the treatment modalities, which were the matched variables, were similar in cases and controls. The treatments were somewhat more often localized to the trunk and extremities among the cases and to the head and neck among the controls (Table 1). The mean number of controls per case was 3.8. The period from first treatment to cancer diagnosis ranged from 1 to 60 years (mean 35 years, median 34 years; Table 2).

The slides of the pathological specimens had been reviewed earlier (15). Of the breast carcinomas approximately 89% were of the ductal type, the rest being of the lobular type or Paget's disease of the nipple. Eight of the brain tumors were classified as gliomas, 4 were meningeomas. The histopathology of the remaining 4 were craniopharyngeoma, endothelioma, medulloblastoma, and papilloma of the plexus. All thyroid carcinomas were of the papillary type and two occurred in men. Two of the bone tumors were osteosarcomas and one was a chondrosarcoma. The 5 soft tissue sarcomas had all different histopathology: angiosarcoma, rhabdomyosarcoma, hemangioendothelioma, liposarcoma, and malignant fibrohistiocytoma.

Table 1

Characteristics of cases and controls

Characteristics	Percentage	
	Cases	Controls
	(n = 94)	(n = 359)
Age at first treatment (months)		
<6	49	47
6–11	33	36
12–17	18	17
Year of first treatment		
1920–39	50	49
1940–59	50	51
No. of treatments		
1–2	71	75
3–27	29	25
No. of treated sites per person		
1–2	96	96
3–27	4	4
	(n = 203)	(n = 745)
Type of treatments		
radium-226	96	97
x-rays	2	3
phosphorus-32	2	0
Treatment sites		
head-neck	49	59
trunk	35	29
extremities	16	12

Table 2

Time from treatment to diagnosis

Years after treatment	Total %	Breast	No. of tumors		
			Brain	Thyroid	Bone and soft tissue
0–9	4	–	4	–	–
10–19	6	–	1	2	3
20–29	15	3	2	7	2
30–39	36	22	5	5	2
40–49	26	21	3	–	–
50–59	13	10	1	–	1
Total	100	56	16	14	8

Dosimetry

The most commonly used treatment modality during the study period was radium-226 applications (flat ones, needles or tubes) on the skin (16). The desired absorbed

dose was usually 6–9 Gy calculated as the so-called 'average' dose in the first 10 mm of tissue (17). During the period 1945–1959 contact x-ray therapy ($\leq$60 kVp, HVL < 1.0 mm Al) was also used and the skin dose was usually 5–10 Gy. Orthovoltage x-rays (100–175 kVp, HVL 0.1–1.0 mm Cu) were less frequently used. One patient received treatment with phosphorus-32 additional to radium-226 and x-rays. The dose contribution by the phosphorus-32 to other tissues than the hemangioma was negligible.

Dosimetry was performed with thermoluminescence dosimeters (TDL) on a phantom representing a 6-month-old child. The phantom was made of a tissue-equivalent material and cork was the substitute for lung tissue (18). The design of the phantom was based on measurements of the Swedish child population (19). All dimensions of the phantom were adjusted according to the age at treatment. Measurements on the phantom were used for the 5–8-month age group. Corrections based on data from Karlberg et al. (19) were made for 4 additional age groups 0–1 month, 2–4 months, 9–13 months, and 14–18 months.

The absorbed dose in the cancer site was estimated for the cases and in the same site for the corresponding controls.

The location of the hemangiomas, as well as of the observed malignant tumors of the breast, thyroid, bone and soft tissues were coded according to a division of the body surface into 28 areas (Figure). The coding of brain tumor sites was made according to a division of the brain into 6 compartments. All treatments were assumed to have been centered in the midpoint of each treatment area. The distance between the midpoint and the tumor site was calculated for each case. For each control the same distance was used in the calculations as for the corresponding case. When the hemangioma was located in the same area as the tumor (n = 12), a more precise distance from the hemangioma to the subsequent tumor site was calculated according to photographs, drawings and other information available in the hospital records. In cases of bone and soft tissue tumors the doses at a depth of 5 mm below the skin surface were calculated.

When the distance from the radium source to the subsequent tumor site exceeded 10 cm, the absorbed dose was calculated with regard to distance, absorption and scattering. For distances up to 10 cm from the source, the absorbed dose was calculated with a computerized brachytherapy planning program (Siemens, Sidos-Brachy).

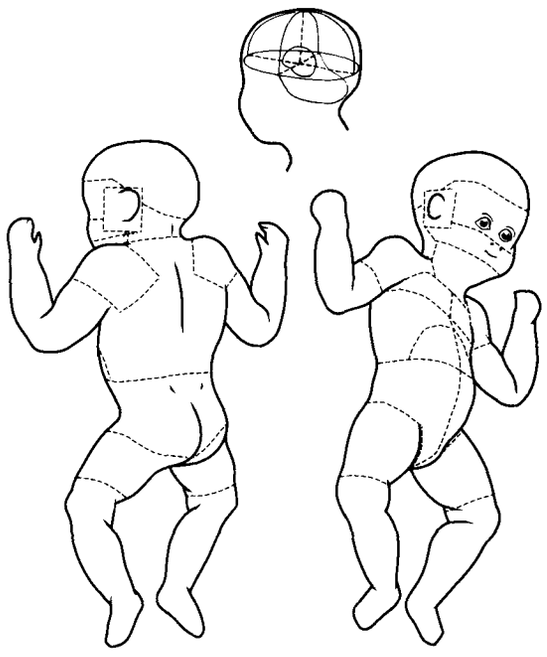

Figure. Phantom representing a 6-month-old child. Body surface divided into 28 areas and skull into 6 compartments.

Statistics

The absorbed doses to different tumor sites and the corresponding sites for controls were grouped into three categories ($<$0.1 Gy, 0.1–0.4 Gy, $\geq$0.5 Gy). Odds ratios (OR) with 95% exact confidence intervals (CI) were calculated between the dose categories, using the lowest dose level as the reference (20). Tests for linear trend with correction for continuity were performed using the method described by Mantel (21). Matched and unmatched analyses yielded essentially the same results and only the results of the unmatched analyses are presented.

Results

The mean absorbed dose in the tumor site for the cases of thyroid cancer was 0.8 Gy as compared to 0.3 Gy for the controls. For bone and soft tissue tumors the mean dose was 3 Gy and for the controls 0.07 Gy. One patient with a bone sarcoma and one with a soft tissue tumor received doses of 12 Gy and 11 Gy respectively. In the remaining cases of the bone and soft tissue tumors all doses were 0.5 Gy or less. The differences between mean absorbed doses in breast cancer cases and controls, as well as for brain tumor cases and controls, were small (Table 3).

For thyroid cancer the OR was increased (4.8 and 4.3 respectively) for the two dose levels 0.1–0.4 Gy and $\geq$0.5 Gy. The χ^2 for linear trend was 4.14 ($p < 0.05$; Table 4).

For tumors of bone and soft tissues a statistically significant increased OR was observed for the group $\geq$0.5 Gy; χ^2 for linear trend = 5.27 ($p < 0.05$; Table 4).

The overall OR for breast cancer did not increase with the absorbed dose (Table 4). However, an increased risk of breast cancer was observed in the two highest dose groups (OR: 1.99 and 1.57 respectively) treated before 1940 but the increase was not statistically significant. For patients

Table 3

Mean, median, and range of absorbed doses (Gy) for cases and controls

Tumor site	Cases			Controls		
	Mean	Median	Range	Mean	Median	Range
Thyroid	0.8	0.2	0.01–4	0.3	0.05	0.01–4
Bone and soft tissue	3	0.3	0.01–12	0.07	0.03	0.01–0.5
Breast	0.2	0.03	0.01–3	0.2	0.03	0.01–8
Brain	0.1	0.04	0.01–1	0.1	0.03	0.01–1

treated in 1940–1959 the ORs were 1.0, 0.46 and 0.36 (n.s.) respectively in the three dose groups. No increased risks were found in a separate analysis of breast cancer cases diagnosed before 50 years of age (n = 44).

For brain tumors no increased OR were observed. Four of the patients with brain tumor had a latency interval of less than 10 years. The result did not alter significantly when these patients were excluded from the analyses (Table 4).

Discussion

In this case–control study, performed within a large cohort of infants irradiated for skin hemangioma, a positive dose–response relationship was found for thyroid cancer and for tumors of bone and soft tissues using the lowest exposed group of patients as reference. Increased OR for thyroid cancer was detected already after an absorbed dose of 0.1–0.4 Gy. An increased risk has previously been observed at similar dose levels (2, 3). The cases of bone and soft tissue tumors were few and were therefore analyzed together, and the result suggests a dose–response relationship. Increased risk of bone sarcomas has previously been observed after radiotherapy for childhood cancer at an absorbed dose above 10 Gy (9). In children treated for retinoblastoma at doses of at least 60 Gy secondary soft tissue tumors have also been observed (22). In the present study an increased risk was detected for the group which had received an absorbed dose of ≥ 0.5 Gy, and the median absorbed dose among the cases was 0.3 Gy. The results suggest a higher risk than previously estimated for these tumors.

Neither in the previous cohort study (13), nor in the present case–control study could an increased risk of brain tumors be found. A possible explanation could be that the absorbed dose in the brain was too low to detect any increased risk. The median absorbed dose for the cases was 0.04 Gy and only 4% of the cases and controls received an absorbed dose exceeding 0.5 Gy. An increased risk of brain tumors after irradiation of the scalp has in other studies been detected at an absorbed dose of 0.70–1.75 Gy (7, 8). It is possible that the matching criteria in this study, excluding non-irradiated patients, may have diluted results suggesting a dose–response relationship or may have masked the actual occurrence of such relationships.

In a study of patients irradiated for skin hemangioma, in Gothenburg, Sweden, a dose-dependent increased risk of tumors of the breast, brain and thyroid was suggested. The average absorbed doses were estimated to be 0.17 Gy, 0.09 Gy, and 0.13 Gy respectively (S. Lindberg, personal communication).

A dose-response has been found for breast cancer in several irradiated cohorts. The risk seems to be greater after irradiation during the first decades of life. Among survivors after the atomic bombs in Hiroshima and Nagasaki an increased breast cancer risk has been found at an absorbed dose in the breast exceeding 0.05 Gy (5). Among

Table 4

OR in relation to absorbed dose with 95% test based CI and χ^2 tests for linear trends. For estimation of OR the group with doses < 0.1 Gy is used as reference

Tumor site	Dose Gy	Cases	Controls	OR	95% CI	χ^2 for linear trend
Thyroid	<0.1	5	38	(1.0)	–	
	0.1–0.4	5	8	4.8	0.8–25.7	
	≥0.5	4	7	4.3	0.7–25.7	4.14, $p < 0.05$
Bone and soft tissue	<0.1	4	26	(1.0)	–	
	0.1–0.4	1	4	1.6	0.0–23.5	
	≥0.5	3	1	19.5	1.1–1060.6	5.27, $p < 0.05$
Breast	<0.1	40	150	(1.0)	–	
	0.1–0.4	11	45	0.9	0.4–2.0	
	≥0.5	5	19	1.0	0.3–3.0	0.04, n.s.
Brain	<0.1	10	41	(1.0)	–	
	0.1–0.4	5	15	1.4	0.3–5.3	
	≥0.5	1	5	0.8	0.0–8.6	0.00, n.s.

patients irradiated for supposed thymic enlargements an increased breast cancer risk has also been observed (4).

In the present study an increased risk of breast cancer was observed among patients treated before 1940, receiving an absorbed dose in the breast tissue of at least 0.1 Gy. No increased risk could be detected among the patients with shorter follow-up. The median absorbed dose in the breast tissue among the cases and controls was only 0.03 Gy. However, among those treated before 1940 the median absorbed dose was 0.01 compared to 0.08 among those treated during the later period. The increase of OR for breast cancer among patients treated before 1940 was not statistically significant and no causal relationship between radiotherapy for skin hemangioma and breast cancer could be established in this study, in spite of the relatively large number of cases.

In a recent study of children irradiated for tinea capitis, the results suggested an increased risk of cancer of the breast already at an absorbed dose of only 0.016 Gy (6). This is remarkable and raises concern as to the reliability of the dosimetry. In our study, no increased risk of breast cancer was found but the CIs, of course, do not preclude such a risk having existed (Table 4). In the previous retrospective cohort study, the breast cancer risk was increased (RR: 1.6) among patients treated with radium-226 or orthovoltage x-rays and paricularly among those treated between 1920 and 1939 (RR: 1.8), which can have been an effect of the longer follow-up (13).

A dose-dependent breast hypoplasia was found among 191 girls irradiated for hemangioma in the breast region (22). These patients were included in previous studies on cancer incidence and mortality (13, 15). Only one patient with breast cancer was reported to the Swedish Cancer Registry in 1958–1982 and none was reported dead from cancer of the breast.

Sixteen of the breast cancer patients included in the cohort study were excluded in the present case–control study (13). Fourteen patients were excluded from the study since they were older than 18 months at the time of first treatment. All but one of these patients had received a dose exceeding 0.09 Gy in the breast tissue. Two were excluded because the review of the pathological slides had shown benign breast tumors.

In studies of radiation carcinogenesis in exposed children, the position of the x-ray beams or other radiation sources and shielding of other tissues make reconstruction of the dosimetry uncertain (24–27). In the present large cohort of patients irradiated in infancy at one institution and for the same benign condition, all relevant treatment data were well documented. The hospital records, photographs and drawings of the hemangiomas and radiation sources enabled dosimetry of the treatments with good accuracy. However, the majority of the patients have not yet reached an age when malignant tumors are a common disease, and therefore continuing follow-up may further elucidate the cancer risks and the dose–response relationships in this cohort.

ACKNOWLEDGEMENTS

We thank Dr Claes Silfverswärd, Department of Tumor Pathology, Karolinska Hospital, for reviewing histopathological slides. We also thank Elisabeth Bjurstedt and Anita Sandström for excellent assistance in various aspects of this study. This study was supported by the National Institute of Radiation Protection, Stockholm (project No. P208-84/85/88) and the Swedish Cancer Society (project No. 2314/B88/02PB).

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