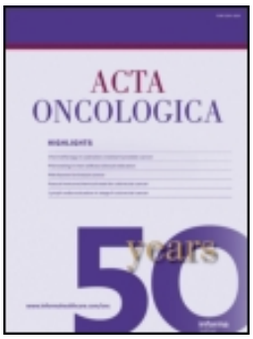

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ORIGINAL ARTICLE

Radiation dose and relapse are predictors for development of second malignant solid tumors after cancer in childhood and adolescence: A population-based case-control study in the five Nordic countries

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Abstract

The aim of the study was to assess the risk with radiation therapy and chemotherapy of the first cancer in childhood and adolescence for the development of a second malignant solid tumor (SMST). Also, the role of relapse of the primary tumor was studied. It is a nested case-control study within a Nordic cohort of patients less than 20 years of age at first diagnosis 1960 – 1987. SMSTs were diagnosed in 1960–1991. There were 196 cases and 567 controls. The risk was increased only for radiotherapy given more than five years before the development of the SMST. A significantly increased relative risk of 1.8 was found already at doses below 1 Gy. The risk increased rapidly up to a maximum of 18.3 for doses above 30 Gy. Chemotherapy alone did not increase the risk to develop an SMST. However, in combination with radiotherapy, chemotherapy showed a significant potentiating effect. Relapse was found to be an independent risk factor for development of an SMST, with a higher relative risk for females than for males.

An increasing number of children and adolescents with cancer are expected to become long-term survivors. Development of a second malignant neoplasm (SMN) is one of the most serious events in those patients. Most of the papers addressing this issue are based on selected hospital populations and deal either with SMN after a specific first malignant neoplasm (FMN), most often after acute lymphoblastic leukemia [1] or Hodgkin lymphoma [2,3] or with specific types of SMN, such as thyroid cancer [4] or melanoma [5]. Still other papers describe specific combinations of FMN and SMN, such as brain tumors after acute lymphoblastic leukemia [6] or acute myelogenous leukemia after renal tumors [7].

Several studies have addressed the role of radiotherapy and chemotherapy in the development of SMN [8,9] as well as the importance of genetic factors [10]. Recent study from France and Great Britain [11] found that the high risk of breast cancer after childhood Hodgkin lymphoma probably was not only due to a higher radiation dose to the breasts,

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but also to a specific susceptibility. These studies being based on hospital series might be subject to less variation in exposures to radiation therapy and chemotherapy (due to uniformity of treatment policies), making it difficult to assess the risk for SMN as a consequence of exposure [12]. Population-based studies are better in this respect, since, due to heterogeneity of treatment policies, they normally have larger variation in exposures. However, most of them have either difficulties in following up the childhood cancer patients into adulthood or do not have details regarding exposure to radiotherapy and chemotherapy [13–17].

In a Nordic population-based study of patients with cancer in childhood or adolescence diagnosed during the period 1943 – 1987, a 3.6 times higher risk for developing a new cancer compared with that in the general population was found [18]. A nested case-control study based on the Nordic childhood cancer cohort showed that radiotherapy was the most important risk factor for later development of SMN [19]. In that study, the amount of radiation was estimated entirely on the basis of figures obtained from the medical records. In the present study, the same cohort was studied with more precise estimates of the radiation dose as well as with the type and dose of chemotherapy.

The aim of the present study was to estimate the relative risk of a second malignant solid tumor in relation to different levels of absorbed dose of radiation, to evaluate in detail the effect of chemotherapy and the effect of combination of radiotherapy and chemotherapy. Also the role of relapse as a risk factor in the development of an SMST was assessed.

Patients and methods

Data sources

Patients included in this study were identified in the population-based cancer registries in each of the five Nordic countries. Nationwide cancer registration started in Denmark in 1943, in Finland 1953, in Norway 1953, in Iceland 1955, and in Sweden 1958. All five cancer registries have fairly complete coverage of incident cancers. The methods of data collection and coding used in each registry have been described in detail previously [18].

Study population

A cohort of childhood cancer patients was formed of individuals diagnosed before the age of 20 years with a malignant neoplasm notified to one of the five Nordic national cancer registries during the years 1960 through 1987, as described previously [19]. There were 25 120 individuals (13 947 males, 11 173 females) that were followed-up through December 1991 for the occurrence of a second malignant neoplasm (SMN), date of death or date of emigration, whichever occurred first.

First malignant neoplasms (FMN) were grouped according to the Birch and Marsden classification scheme for childhood cancer [20], while the SMNs were classified according to the International Classification of Diseases for Oncology, ICD-O [21]. There was no time limit between the occurrence of FMN and SMN. Only the second (and not any subsequent) diagnosis was taken into account in the analyses.

A nested case-control study was performed [22]. For each case, controls were randomly sampled within the cohort among patients with SMN-free follow-up at least as long as that of the case and matched according to gender, age, and calendar year of diagnosis (± 3 years), aiming at three controls for each case. The controls were not matched on the type of FMN or country of origin in order to avoid overmatching. In this study, only second malignant solid tumors (SMST) were analyzed, thus excluding leukemia and lymphomas.

In the final analysis, 196 cases with SMST (104 males and 92 females) were included. Three controls were available for 178 cases, two controls for 15 cases and one control for three cases, totaling 567 controls (296 males and 271 females).

Medical record extraction

Medical records of all cases and controls were scrutinized and data were abstracted using specially designed registration forms. The items included date of FMN, occurrence and date of relapses of FMN, dates and modalities of primary treatment and treatment of relapses. At this stage the data collection was performed without knowing if the individual was a case or a control. The diagnoses of FMN and SMST were verified and coded for site and morphological type.

Chemotherapy

Chemotherapeutic agents were grouped into five categories according to their mechanism of action: electrophilic agents (comprising classical and non-classical alkylating agents), spindle inhibitors (vinca-alkaloids), inhibitors of nucleotide synthesis (antimetabolites), topoisomerase II inhibitors (including antibiotics and podophyllotoxins), and other drugs [23]. Total cumulative dose of every drug was calculated in mg per m^2 body surface for the primary and relapse treatment, given before the occurrence

of an SMST. For further analyses, the doses were converted to moles per m^2 of body surface and the number of mol/m^2 were summarized within each drug category, as described elsewhere [23].

Radiation dosimetry

Radiotherapeutic charts, dose plans and photographs were scrutinized concerning target volume, treatment technique, radiation quality and type of apparatus, target dose, number of fractions and days, and the size of the patient. In the oldest treatments, where the radiation dose in the charts was expressed in R, conversion was made to absorbed dose in Gy in water. If the radiation therapy was given with orthovoltage beams, correction was also made for the higher biologic effect of this radiation quality compared to high voltage X- and gamma rays [24]. Dose calculation was performed with a software package, Dos_EG, which was developed for retrospective studies at the Institut Gustave Roussy [25,26].

In the first step of this software, a "virtual" individual phantom is designed for each patient based on the patient's gender, height, anatomical dimensions of the trunk and inclination of the head. The phantom simulates water and lung heterogeneity, but no bony structures. Upper extremities are not included in the phantom. For about 40% of the patients height or weight was missing and for those patients growth charts for Swedish children from 1970 were used.

The second part of the program deals with dose calculation based on entered patient treatment data. The calculation of absorbed dose is based on an algorithm that includes the primary beam, and takes account of scatter in- and outside of the treatment beams and of leakage and scattered radiation around different treatment machines (derived from measurements around 28 different treatment machines in eight radiotherapy centers). Wedges and blocks can be simulated and correction for air in the lungs of the phantom is made. The absorbed dose is determined at 151 points in the body for each course of radiation therapy for each child. All dose values are valid for water. The absorbed dose received at the site of SMST for the case was compared with the dose at the corresponding site in the controls.

For 12 patients with SMST, the absorbed dose distribution could not be calculated. For seven of these patients, the Dos_EG could not be used; one patient was treated with the "Gamma-knife", four patients had application therapy, and two patients were treated for malignancies located in the arms. Treatment charts could not be found in five cases. Among the controls, radiotherapy treatment could not be evaluated for 32 patients; two were treated with the "Gamma-knife", seven had application therapy, two were treated to the arms, and in 21 cases the radiation treatment charts were missing.

Statistical analysis

Relative risks (RR) of various exposures and interaction between exposures were estimated by means of conditional logistic regression. A case was considered to be exposed to a treatment if the treatment was administered before the occurrence of the SMST, and the controls – within a corresponding follow-up period. Standard models with multiplicative effects of categorized radiation doses and other factors (CHT and relapse) were fitted. Moreover, the relative risk of RT was modeled as a factor $(1+\beta \star \text{dose})$, i.e. with constant excess relative risk per Gy, β. By analyzing subgroups of case-control sets, effect modification of the variables age at primary diagnosis and type of SMST was assessed. Nested models were compared by means of likelihood-ratio tests and all analyses were performed with the Stata [27] and Epicure [28] statistical programs.

All confidence intervals (CI) and tests are two-sided.

Results

Patients and exposures

Table I shows the distribution of second malignant solid tumors by primary IARC group in the cases. As can be seen, lymphomas (23.0%, mainly Hodgkin lymphoma), central nervous system tumors (20.9%), and carcinomas (13.3%) prevailed as FMN, whereas brain and other nervous system tumors (24.5%) and breast cancer (12.2%) prevailed as SMST. In respect to the largest groups of FMN, the most frequent SMST in patients with leukemia were brain tumors; in patients with Hodgkin lymphoma they were female breast cancers, tumors of the digestive tract and thyroid cancer; in patients with CNS tumors they were other brain and nervous system tumors; and in patients with retinoblastoma-bone tumors. Among the controls, the most frequent diagnoses were central nervous system tumors (23.8%), carcinomas (17.5%) and lymphomas (15.3%). For the cases, the mean age at diagnosis of FMN was 11.7 years and that at diagnosis of SMST 24.7 years. For the control patients, the mean age at diagnosis was 11.6 years. The mean interval between the first and the second diagnoses for all cases was 13.0 years. The interval was shortest for tumors of male genitalia as SMST (8.1 years) and brain tumors (8.8 years) and longest for breast

Table I. Second malignant solid tumors (ICD-O classification) by primary IARC group (according to Birch and Marsden) in the cases.

		Second malignant solid tumors								
IARC group	First malignant diagnosis	*Digest*	*Bone*	*Conn*	*Skin*	*Breast*	*CNS*	*Thyr*	*Other*	Total
I	Leukemia	*0*	*0*	*0*	*0*	*1*	*6*	*2*	*3*	12
II	Lymphomas	*9*	*2*	*1*	*4*	*13*	*4*	*7*	*5*	45
III	CNS neoplasms	*4*	*0*	*4*	*1*	*1*	*26*	*0*	*5*	41
IV	Sympathetic nerv. system	*0*	*1*	*0*	*1*	*0*	*1*	*0*	*1*	4
V	Retinoblastoma	*2*	*7*	*2*	*3*	*0*	*1*	*0*	*1*	16
VI	Renal tumors	*3*	*1*	*1*	*0*	*0*	*1*	*1*	*0*	7
VII	Hepatic tumors	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	0
VIII	Bone tumors	*0*	*1*	*2*	*0*	*4*	*1*	*1*	*1*	10
IX	Soft tissue sarcomas	*0*	*2*	*3*	*1*	*0*	*4*	*0*	*1*	11
X	Germ-cell neoplasms	*1*	*0*	*2*	*3*	*1*	*1*	*1*	*14*	23
XI	Carcinomas	*3*	*0*	*2*	*6*	*4*	*2*	*2*	*7*	26
XII	Other malign. neoplasms	*0*	*0*	*0*	*0*	*0*	*1*	*0*	*0*	1
Total		*22*	*14*	*17*	*19*	*24*	*48*	*14*	*38*	196

Digest (ICD < =159) – Tumors in digestive tract, incl. oral cavity and pharynx.
Bone (ICD = 170) – Tumors in bones.
Conn (ICD = 171) – Tumors in connective tissues.
Skin (ICD = 173) – Tumors in skin.
Breast (ICD = 175) – Tumors in breast.
CNS (ICD = 191–192) – Brain tumors and other nervous system tumors.
Thyr (ICD = 193) – Thyroid carcinoma.
Other – Other malignant neoplasms.

tumors (17.2 years) and tumors in the digestive tract (18.0 years).

The extent of exposure to radiotherapy was different in the cases compared to the controls. Approximately 69% of the cases were exposed to radiotherapy, the corresponding figure for the controls being 48% (Table II).

Cytostatic drugs were used in approximately 39% of the cases and 30% of the controls (Table II). The exposure to different categories of chemotherapy in cases and controls is shown in Table III.

Effect of radiation dose

The risk of SMST was not increased for radiation given within five years before the development of the SMST (data not shown); therefore only radiation given more than five years before the SMST is used as exposure. The distribution of the radiation dose in the SMST volume for the cases and the corresponding volume for the controls is shown in Table IV. The cases were exposed to higher doses than the controls. Table IV also exhibits relative risks for different doses at the site of the SMST with reference to patients with zero dose. Already doses below 1 Gy significantly increased the risk of developing an SMST and the risk increased with increasing dose.

Models with the relative risk as a linear function of dose were also fitted; see Table V. For each Gy in the SMST volume the relative risk increased with 0.32 (95% CI 0.16 – 0.63), and the effect was hardly changed when adjusting for other exposures or effect of IARC group for the primary cancer (cf. models B – E, Table V). A potential risk factor for an SMST is the number of fractions used when administering the radiotherapy. No effect was found, though; i.e. in combination with radiation dose at the SMST site, number of fractions was not an independent risk factor (data not shown).

Because the controls were not matched according to primary diagnosis we had the possibility to analyze the significance of FMN on the SMST risk. Only retinoblastoma as FMN had effect on this risk when exposure to radiation and chemotherapy was taken into account (RR = 4.0, 95% CI 1.7 – 9.4, non-retinoblastoma as reference).

Table II. Radiation therapy (RT) and chemotherapy (CHT) in cases and in controls.

Exposure	Percentage of cases (n = 196)	Percentage of controls (n = 567)	Percentage of total material (n = 763)
RT −, CHT −	27.5	40.7	37.4
RT +, CHT −	33.7	29.5	30.5
RT −, CHT +	3.1	11.5	9.3
RT +, CHT +	35.7	18.3	22.8

Table III. Exposure to different categories of chemotherapy in cases and controls.

	Cases (n = 196)		Controls (n = 567)	
Type of patients (number)	Percentage treated	Median and largest dose*	Percentage treated	Median and largest dose*
Category of chemotherapy				
Electrophilic agents	29.1	19.4; 256.4	18.5	24.5; 434.4
Spindle inhibitors	29.1	0.03; 0.97	22.4	0.03; 0.57
Inhibitors of nucleoside synthesis	11.2	137.5; 571.7	11.3	219.8; 934.2
Inhibitors of topoisomerase II	16.8	0.3; 4.2	13.8	0.2; 7.2

* Median and largest dose in moles per square meter body surface, in those treated (dose >0).

Effect of chemotherapy and interaction between chemotherapy and radiotherapy

Chemotherapy (irrespective of the interval between exposure and the occurrence of SMST) without radiotherapy did not increase the risk of developing an SMST (Table IV). This was true for all the categories of chemotherapeutic agents and also when the doses (under and above the median value for each category) were taken into account and used in trend analyses (data not shown).

Radiotherapy without chemotherapy yielded the relative risk 2.3 (95% CI 1.4 – 3.7) and this risk increased to 4.3 (95% CI 2.6 – 7.0) when both radiotherapy and chemotherapy were used, either simultaneously or sequentially (Table IV). Also when using a linear excess relative risk model for RT dose, a significant interaction between CT and RT was found (Table V, models C – E).

In the analysis of interaction between chemotherapy and radiotherapy, only individuals, who were exposed to radiotherapy (at any site, not only in the SMST volume) more than five years before occurrence of SMST, and in whom the radiation dose was known, were taken into account. Of totally 407 individuals (cf. 53.3% of 763 in Table II) who got radiation therapy (at any time) this condition was fulfilled by 297.

Effect of uncertainty in dose estimations

A total of 35 SMST were classified to have an RT-dose in the interval 5 – 30 Gy, and 29 of them were in a penumbra region, where most probably the dose estimates are quite uncertain. Out of these, ten were breast cancers after treatment of Hodgkin lymphoma and three were testicular tumors. After excluding breast cancers and/or testicular tumors from the analysis only marginal changes in relative risk estimates were observed and the shape of the dose-response curve remained unchanged (data not shown).

Effect of relapse of the first primary cancer

Among cases, 28.6% experienced at least one relapse, while the corresponding figure was 12.7% among controls (Table IV). Thus, occurrence of the relapse significantly increased the risk of developing SMST (RR = 2.7, 95% CI = 1.8 – 4.1). The effect of

Table IV. Percentage of cases and controls and relative risk (with 95% confidence interval) to develop SMST of all types by different treatments and relapse.

Exposure	Percentage of cases (n = 196)	Percentage of controls (n = 567)	RR	95% CI
RT 0 Gy*	38.8	62.6	1.0	Ref. group
RT >0 – 1 Gy*	16.3	19.8	1.8	1.1 – 3.1
RT >1 – 5 Gy*	8.7	4.4	3.7	1.8 – 7.5
RT >5 – 30 Gy*	17.9	6.0	7.1	3.7 – 13.5
RT >30 Gy*	12.2	1.6	18.3	7.3 – 45.8
RT unknown dose	6.1	5.6	1.5	0.7 – 3.3
*No CHT & no RT***	35.2	49.6	1.0	Ref. group
*CHT without RT***	9.2	17.3	0.5	0.3 – 1.1
*RT** without CHT*	26.0	20.6	2.3	1.4 – 3.7
*CHT and RT***	29.6	12.5	4.3	2.6 – 7.0
No relapse	71.4	87.3	1.0	Ref. group
Relapse	28.6	12.7	2.7	1.8 – 4.1
*Relapse adjusted for CHT&RT***			2.4	1.5 – 3.7

* Radiotherapy with latency 5 years at site of SMST.
** Radiotherapy with latency 5 years at any site.

Table V. Additive excess relative risks (95% CI) and deviances for models including dose of radiation (Gy, latency 5 years) at the site of the SMST as a continuous exposure, CHT (without latency), interaction between CHT and RT and relapse before SMST.

Exposure	Model A	Model B	Model C	Model D	Model E*
Radiation	0.32	0.32	0.27	0.28	0.35
(per Gy)	(0.16,0.63)	(0.16, 0.63)	(0.12, 0.55)	(0.13, 0.59)	(0.14, 0.81)
CHT	–	−0.12	−0.49	−0.53	−0.36
(yes vs. no)		(−0.48, 0.44)	(−0.75, −0.03)	(−0.79, −0.07)	(−0.72, 0.40)
CHT and RT	–	–	1.31	1.10	1.85
(yes vs. no)			(0.34, 2.86)	(0.11, 2.72)	(0.23, 5.35)
Relapse before SMST	–	–	–	0.93	1.21
(yes vs. no)				(0.16, 2.28)	(0.21, 3.10)
Deviance (530.64 for no model)	461.98[a)]	461.73	453.97[b)]	447.61[c)]	431.63[d)]

* Model adjusted with multiplicative effects of 12 IARC groups for first cancer.
[a)] Model A compared with no model, $p < 0.001$ (1 df).
[b)] Model C vs. model A, $p = 0.018$ (2 df).
[c)] Model D vs. model C, $p = 0.011$ (1 df).
[d)] Model E vs. model D, $p = 0.14$ (11 df).

the relapse persisted after adjustment for radiotherapy and chemotherapy (RR = 2.4, 95% CI = 1.5–3.7), as shown in Table IV. When gender was taken into account as an effect modifier a significant difference in effect between men and women was found ($p = 0.039$): relapse was only associated with a slightly increased (and statistically insignificant) risk in males (RR = 1.3, 95% CI 0.7–2.5), while relapse in females carried a significantly increased risk of SMST (RR = 3.4, 95% CI 1.7–6.8).

As seen from Table V, the effect of relapse persisted when using a linear excess relative risk model for RT dose (Model D), and when adjusting for primary cancer diagnosis (Model E).

The role of age

The data was split in four groups according to age at first malignancy of the cases (Table VI). Since the controls were matched on this variable, the age limits hold approximately also for the controls. The youngest and the oldest age groups followed most closely the pattern seen in the whole material, but generally no striking differences could be seen between the age groups.

Relative risk of SMST for different exposures in some groups of SMST

The same models as for all types of SMST (Table IV) were used to assess the risk of developing certain specific types of SMST. Generally, due to the limited number of patients in respective SMST group, these analyses are uncertain. For the development of SMST in the digestive tract the risk increased with radiation dose, being statistically significant for the highest one, and the combination of radiotherapy and chemotherapy significantly increased the risk (Table VII). Exposure to radiation above 1 Gy significantly increased the risk of SMST in bone (Table VII). The same was true only for the highest dose of radiation in connective tissue tumors (Table VII). For skin tumors no significant risk factor could be found (Table VII). For the development of SMST in breast, radiation, combination of radiotherapy and chemotherapy as well as occurrence of relapse was of significance (Table VIII). Doses above 5 Gy were significant for development of SMST in central nervous system (Table VIII). Finally, in the development of thyroid tumors, radiotherapy increased the risk, but the confidence limits were extremely large and relapse was a significant risk factor, but not after adjustment for chemotherapy and radiotherapy (Table VIII). Models with the excess relative risk as a linear function of dose were also fitted for the various types of SMST; see Tables VII and VIII. The effect of radiation was consistent, and statistically significant (since lower confidence limit was greater than or equal to zero), for all types. The largest effect was found for thyroid cancer as SMST (excess RR = 1.70 per Gy) and the smallest for tumors in the central nervous system (excess RR = 0.14 per Gy).

Discussion

The carcinogenic effect of ionizing radiation is well established, but the relationship between absorbed dose and the later occurrence of a radiation induced neoplasm is difficult to evaluate and quantify. In our previous report, based on an analysis of a case-control study nested in the Nordic childhood cancer cohort [19], we found that the relative risk of developing an SMN within an irradiated volume was 4.3 (95% CI 3.0–6.2) compared to a non-irradiated volume. The risk was highest in children diagnosed below five years of age and increased with

Table VI. Relative risk (with 95% confidence interval) to develop SMST of all types by different treatments and relapse in the four age groups.

Exposure/Age group	0–4 years (47 cases, 138 contr) **RR** (95% CI)	5–9 years (18 cases, 54 contr) **RR** (95% CI)	10–14 years (40 cases, 117 contr) **RR** (95% CI)	15–19 years (91 cases, 258 contr) **RR** (95% CI)
RT* 0 Gy	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)
RT* >0–1 Gy	**1.1** (0.4–3.6)	**4.8** (0.8–28.7)	**0.9** (0.3–2.6)	**2.6** (1.1–6.1)
RT* >1–5 Gy	**7.9** (1.7–36.6)	**8.9** (1.0–77.5)	**1.2** (0.2–7.2)	**3.3** (1.1–9.9)
RT* >5–30 Gy	**9.2** (1.8–46.4)	**3.6** (0.4–36.5)	**4.6** (1.1–18.9)	**9.7** (3.8–24.7)
RT* >30 Gy	**19.1** (3.4–108.9)	**4.5** (0.2–82.1)	**8.5** (0.8–90.7)	**30.5** (7.4–126.6)
RT unknown dose	**2. 9** (0.8–11.0)	–	**1.1** (0.4–3.7)	**1.4** (0.3–6.9)
No CHT & no RT**	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)
CHT without RT**	**0.4** (0.1–1.4)	**0.9** (0.1–7.8)	**1.3** (0.4–4.4)	**0.3** (0.1–1.2)
RT** without CHT	**2.6** (0.9–7.1)	**6.4** (1.0–40.2)	**0.8** (0.3–2.4)	**3.1** (1.4–6.5)
CHT and RT**	**2.3** (0.9–5.7)	**4.9** (0.9–26.9)	**3.3** (1.1–9.6)	**7.8** (3.4–17.8)
No relapse	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)
Relapse	**6.1** (2.3–16.1)	**2.3** (0.7–7.5)	**1.6** (0.7–3.5)	**2.8** (1.5–5.1)
Relapse adjusted for CHT&RT**	**5.1** (1.9–14.1)	**3.3** (0.8–13.7)	**1.2** (0.5–2.9)	**2.1** (1.0–4.6)

* Radiotherapy with latency 5 years at site of SMST.
** Radiotherapy with latency 5 years at any site.

follow-up time. Chemotherapy was found to play a potentiating role.

In the present study we found a significant increase in risk of developing an SMST already at doses below 1 Gy (RR = 1.8, 95% CI 1.1 – 3.1). The cancerogenic effect of low doses of radiation was observed previously after treatment of benign conditions in childhood [29–31].

An important unanswered question is the shape of the dose response curve for malignant transformation for the whole continuous dose span from low doses to the doses in the therapeutic range.

In the low dose region UNSCEAR's calculations [32] are based on a linear model for solid tumors. For the high dose region (> 4 Gy) studies are rare. Travis et al. [33] and van Leeuwen et al. [34] have studied the induction of mammary cancers after treatment of Hodgkin lymphoma. Both reports show a linear increase of relative risk for radiation doses from 4 Gy to at least 40 Gy. Dose effect for lung cancer induction after radiation treatment of Hodgkin lymphoma studied by Gilbert et al. [35] also showed a linear dose response for a dose between 5 Gy and more than 40 Gy. Evidence of turn down at

Table VII. Relative risk (with 95% confidence interval) to develop some types of SMST by different treatments and relapse.

Exposure/Type of SMST	Digestive tract (22 cases, 60 contr) **RR** (95% CI)	Bone (14 cases, 42 contr) **RR** (95% CI)	Connective tissue (17 cases, 47 contr) **RR** (95% CI)	Skin (19 cases, 54 contr) **RR** (95% CI)
RT* 0 Gy	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)
RT* >0–1 Gy	**3.7** (0.8–17.2)	**1.7** (0.2–12.9)	**1.0** (0.1–13.2)	**1.1** (0.2–6.3)
RT* >1–5 Gy	**7.2** (0.8–64.0)	**24.5** (1.2–497.6)	**9.9** (0.6–169.7)	–
RT* >5–30 Gy	**6.5** (0.7–60.2)	**38.4** (1.4–1066.2)	**5.8** (0.1–471.5)	–
RT* >30 Gy	**17.6** (2.1–148.4)	**34.7** (1.3–957.3)	**29.6** (1.8–490.8)	–
RT unknown dose	**8.5** (1.0–70.2)	**15.8** (0.6–389.4)	**3.0** (0.2–48.0)	**0.8** (0.1–5.0)
No CHT & no RT**	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)
CHT without RT**	**0.6** (0.1–3.8)	**0.8** (0.1–8.8)	–	–
RT** without CHT	**1.3** (0.3–6.1)	**3.0** (0.6–15.6)	**2.8** (0.5–16.3)	**0.5** (0.1–3.1)
CHT and RT**	**8.6** (1.5–49.3)	**2.2** (0.5–9.9)	**4.7** (0.7–31.7)	**3.7** (0.8–16.8)
No relapse	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)
Relapse	**2.4** (0.7–8.2)	**2.7** (0.8–9.2)	**1.8** (0.4–8.3)	**4.4** (0.8–24.9)
Relapse adjusted for CHT&RT**	**0.7** (0.1–3.9)	**2.9** (0.8–11.0)	**1.5** (0.3–8.5)	**2.4** (0.3–18.1)
Additive excess relative risk per Gy at the SMST site	**0.1** (0.0–0.8)	**3.1** (0.1–53.0)	**0.8** (0.0–21.4)	**0.2** (0.0–1.7)

* Radiotherapy with latency 5 years at site of SMST.
** Radiotherapy with latency 5 years at any site.

Table VIII. Relative risk (with 95% confidence interval) to develop some types of SMST by different treatments and relapse.

Exposure/Type of SMST	Breast (24 cases, 71 contr) **RR** (95% CI)	Central nervous system (48 cases, 143 contr) **RR** (95% CI)	Thyroid (14 cases, 41 contr) **RR** (95% CI)
RT* 0 Gy	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)
RT* >0–1 Gy	**10.6** (1.7–65.6)	**0.7** (0.2–2.7)	**3.4** (0.3–40.9)
RT* >1–5 Gy	**2.7** (0.3–21.2)	**1.5** (0.3–8.4)	**40.6** (1.3–1226.2)
RT* >5–30 Gy	**74.7** (6.4–869.4)	**3.4** (1.1–10.2)	**51.0** (2.0 -1329.5)
RT* >30 Gy	–	**10.0** (1.9–52.8)	**21.3** (0.3–1568.0)
RT unknown dose	-	**0.7** (0.1–3.2)	**11.8** (0.4–373.7)
No CHT & no RT**	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)
CHT without RT**	-	**0.4** (0.1–1.3)	**0.6** (0.0–7.0)
RT** without CHT	**8.0** (1.6–40.2)	**2.3** (0.9–6.1)	**1.7** (0.3–11.9)
CHT and RT**	**27.5** (4.1–185.9)	**1.6** (0.6–4.6)	–
No relapse	**1.0** (Ref. group)	**1.0** (Ref. group)	**1.0** (Ref. group)
Relapse	**9.0** (2.5–33.0)	**1.9** (0.8–4.6)	**4.9** (1.5–16.4)
Relapse adjusted for CHT&RT**	**18.6** (1.5–234.8)	**2.3** (0.9–5.9)	**3.6** (0.7–19.3)
Additive excess relative risk per Gy at the SMST site	**0.7** (0.2–2.9)	**0.1** (0.0–0.5)	**1.7** (0.1–22.1)

* Radiotherapy with latency 5 years at site of SMST.
** Radiotherapy with latency 5 years at any site.

higher doses due to cell killing could not be observed in these three studies. In the present study the relative risk increased with dose, without inclining, for doses up to and over 30 Gy, in line with the above three studies. With the new intensity modulated radiotherapy (IMRT) technique the dose outside the treated volume can be up to a factor of ten higher than with conventional radiotherapy [36] and the integral dose will be elevated accordingly. A doubling of the cumulative risk for developing SMN has been postulated [37] and the importance of reducing the radiation dose outside the treated volume has been stressed. These facts must be taken into account when planning radiotherapy for children, especially when a combination with chemotherapy will be used.

The dose calculation process with Dos_EG has some limitations. There are uncertainties in the algorithm itself [25], but the largest uncertainties are due to the fact that the organ with SMST is represented by one point only. If this point is located near the borders of the treated volume (penumbra region) with rapid dose change, the estimated dose to that point may not be representative for the dose to the organ with SMST. In the study by Dorr et al. [38] on breast cancer risk after mantle treatment for Hodgkin lymphoma, a dose reconstruction was made from dose-volume histograms showing a variation in dose to the breast from 4 Gy to 40 Gy depending on the position of the dose point. In order to minimize the influence of such uncertainty the analyses behind Table IV were also carried out omitting breast cancer as SMST, but this did only marginally change the relationship between dose and risk in the present study. In some situations, special protective measures were applied during treatment. A typical example is the shielding of the testicle(s) when irradiating the pelvic region. If the testis is the site of the SMST, the dose will be overestimated since no correction can be made in Dos_EG of the dose in a single, specific point.

The patients with SMST in this study constitute a very heterogeneous group from radiobiologic and dosimetric points of view. They include children that were between newborn and twenty years of age at first diagnosis and treatment. Consequently, the radiation sensitivity of organs can differ. It is well known that young children have an elevated risk of thyroid tumors [4], while the risk of breast cancer is increased with puberty [39]. To cope with this we have split the data in four subgroups determined by age at primary diagnosis and seven groups by type of SMST. The general pattern, with increasing relative risk for higher doses, was seen in all age and SMST groups.

Robison [40] considered that the major obstacle encountered in evaluating the multifactorial nature of SMN risk is the lack of access to a sufficiently large and heterogenous population. The heterogeneity of our material regarding the diagnoses and treatments and not matching the controls for the FMN improved the evaluation of the effects of radiotherapy. Some studies [3,41] either failed to identify radiotherapy as a significant risk factor for the development of SMN or were not able to analyze its role because of the homogeneity of the material or the treatment given in a single institution. The population-based German case-control

study [15] did not show a significant effect of radiotherapy, possibly because of the more uniform treatment and the matching on primary diagnosis, rendering too few informative discordant sets of case-controls. In a recent population-based study in Britain [17], the highest risk of SMN was found among those exposed to both radiotherapy and chemotherapy, but treatment details were not available. Our study did not show any significant effect of chemotherapy alone, most probably because of the very low percentage of cases treated with chemotherapy without radiotherapy.

One interesting finding in our study was the importance of relapse as an independent risk factor for development of SMST. A similar observation was made previously regarding SMN after treatment of Hodgkin lymphoma by some investigators [2,42,43], but not by all [3]. Usually, the finding was interpreted as a consequence of increased therapy in relapsed cases. Van Leeuwen et al. [44] showed that the patients who received salvage chemotherapy had significantly greater risk of solid cancers other than breast cancer than did patients whose treatment was restricted to initial radiotherapy or initial combined-modality treatment. In a recent study, Bhatia et al. [1] also found that relapse was a significant risk factor in the development of SMN after acute lymphoblastic leukemia. However, since detailed information regarding actual doses of therapeutic exposures given to patients for relapses was not available, the relapse was thought to serve as a surrogate marker for extended therapy given.

In Bhatia's study [1] female sex was also found to be an independent risk factor for SMN. Gender differences in the risk of SMN after Hodgkin lymphoma were observed by Tarbell et al. [45] as well as by Wolden et al. [2] but in the latter paper the high occurrence of breast cancer in females fully accounted for the difference.

In our study, relapse remained a highly significant risk factor for SMST in multivariate analyses taking into account the dose of radiotherapy and chemotherapy. There was a significant interaction between gender and relapse in the risk of SMST; the effect of relapse was large and significant in females but not so in males. In order to avoid the influence of breast cancer, as well as thyroid cancer, which also correlated with female sex and with relapse, we performed analyses excluding those two cancers as SMST in our study. Despite this manoeuvre the significance of the relapse persisted. The same was also true when Hodgkin lymphoma was excluded as the FMN.

Conclusions

Our study including many patients treated with radiotherapy alone and with combination of radiotherapy and not so intensive chemotherapy was well suited for the evaluation of the role of radiation and radiation dose in the development of SMST but less suited for the evaluation of the role of chemotherapy. This was especially true for the newer drugs and the more intensive treatment regiments. Nevertheless, the increased risk already at low radiation doses and synergistic effect of radiotherapy and chemotherapy indicates that an alternative to avoid development of SMST would be to minimize the use of radiotherapy, provided that the treatment results are not compromised. This has already been successfully accomplished to some extent in the modern treatment protocols for the youngest children and for some tumors in the earliest stages (e.g. the omission of radiotherapy to the central nervous system in acute leukemia, and in Wilms' tumor stage I), but has failed in some situations e.g. early Hodgkin lymphoma in complete remission after chemotherapy [46]. It is of utmost importance that such modifications of existing treatment protocols always are carried out within the framework of controlled clinical trials, and that second malignancies as well as other serious adverse events are surveyed. In cases where radiotherapy constitutes an essential component of an effective treatment schedule, the irradiation of healthy tissue must be minimized by the use of available imaging techniques for more precise definition of the target volume, and by improved treatment techniques.

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