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ARTICLE

Long-Term Risk of Skin Cancer Among Childhood Cancer Survivors: A DCOG-LATER Cohort Study

Jop C. Teepen, Judith L. Kok, Leontien C. Kremer, Wim J. E. Tissing, Marry M. van den Heuvel-Eibrink, Jacqueline J. Loonen, Dorine Bresters, Helena J. van der Pal, Birgitta Versluys, Eline van Dulmen-den Broeder, Tamar Nijsten, Michael Hauptmann, Nynke Hollema, Wil V. Dolsma, Flora E. van Leeuwen, Cécile M. Ronckers; for the DCOG-LATER Study Group

See the Notes section for the full list of authors' affiliations.
Correspondence to: Jop C. Teepen, PhD, Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25, 3584 CS, Utrecht, The Netherlands (e-mail: J.C.Teepen@prinsesmaximacentrum.nl).

Abstract

Background: Skin cancer is common after radiotherapy among childhood cancer survivors (CCSs). We studied risks and risk factors for subsequent skin cancers, with emphasis on radiation dose, exposed skin surface area, and chemotherapeutic agents.
Methods: The DCOG-LATER cohort study includes 5-year Dutch CCSs diagnosed 1963–2001. Subsequent skin cancers were identified from record linkages with the Netherlands Cancer Registry and Dutch Pathology Registry. Incidence rates were compared with general population rates. Multivariable Cox regression models were used, applying a novel method of case-control sampling enabling use of tumor location in cohort analyses. All statistical tests were two-sided.
Results: Among 5843 CCSs, 259 developed 1061 basal cell carcinomas (BCCs) (standardized incidence ratio [SIR] = 29.8, 95% confidence interval [CI] = 26.3 to 33.6; excess absolute risk per 10 000 person-years (EAR) = 24.6), 20 had melanoma (SIR = 2.3, 95% CI = 1.4 to 3.5; EAR = 1.1), and 10 had squamous cell carcinoma (SIR = 7.5, 95% CI = 3.6 to 13.8; EAR = 0.8). Cumulative incidence of BCC 40 years after childhood cancer was 19.1% (95% CI = 16.6 to 21.8%) after radiotherapy vs 0.6% expected based on general population rates. After a first BCC, 46.7% had more BCCs later. BCC risk was associated with any radiotherapy to the skin compartment of interest (hazard ratio [HR] = 14.32, 95% CI = 10.10 to 20.29) and with estimated percentage in-field skin surface area (26–75%: HR = 1.99, 95% CI = 1.24 to 3.20; 76–100%: HR = 2.16, 95% CI = 1.33 to 3.53, vs 1–25% exposed; P_{trend} among exposed = .002), but not with prescribed radiation dose and likelihood of sun-exposed skin-area. Of all chemotherapy groups examined, only vinca alkaloids increased BCC risk (HR = 1.54, 95% CI = 1.04 to 2.27).
Conclusion: CCSs have a strongly, 30-fold increased BCC risk. BCC risk appears to increase with increasing skin surface area exposed. This knowledge underscores the need for awareness by survivors and their health care providers.

Childhood cancer survivors (CCSs) face an increased risk of subsequent tumors (1–4), frequently including skin cancers (1,5–8). Specific studies on keratinocyte skin cancer (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]) are scarce (2,8,9), because most cancer registries do not routinely collect this information. Radiation exposure is an important risk factor for subsequent skin cancers, particularly BCC (5,8–15), and most subsequent skin cancers occur within the radiation field (8,9). Most studies focused on crude exposure indicators; some addressed the role of radiation dose. A landmark study among CCSs observed a statistically significant linear radiation dose response for risk of BCC (9). To our knowledge, there are no

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studies on the role of skin surface area exposed to ionizing radiation, and there is little information about chemotherapy-related risks of skin cancers.

We addressed the risks of subsequent skin cancer in our large cohort of long-term CCSs and explored the contribution of different oncological treatments, with an emphasis on prescribed radiation dose, exposed skin surface area, and the role of chemotherapy agents.

Methods

Study Population and Treatment Information

The DCOG-LATER cohort includes 6165 five-year CCSs diagnosed during 1963–2001 before age 18 years in the Netherlands. Diagnosis and treatment information, including recurrences, was collected under a standardized protocol. The study protocol was declared exempt from review of medical intervention research by institutional review boards of all participating centers. More details have been reported previously (4).

Radiotherapy Characterization

We classified skin compartment-specific radiotherapy exposure according to radiotherapy field information for external beam radiotherapy. The skin surface was divided into 17 mutually exclusive compartments (Supplementary Table 1, available online). Because some skin cancers had an unspecific location description (eg, left leg, part unspecified), these were unclassifiable initially. To ensure maximum use of the data, we added eight broad compartments (eg, abdomen/pelvis, left leg unspecified) by collapsing some of the 17 compartments (Supplementary Table 2, available online); any analyses thus included 25 compartments (Supplementary Table 3 and Supplementary Figure 1, available online). Each skin cancer was assigned to the smallest possible compartment. For every patient, we (JLK, JCT, WD) retrospectively assessed for each of 25 compartments whether it likely had been in the radiation field, based on individual treatment records (Supplementary Tables 1–3, available online). For skin compartments with any in-field radiation exposure, we assigned the prescribed dose and we estimated the proportion of the surface area of that compartment in the radiotherapy field (1–25%; 26–75%; 76–100%) (Supplementary Tables 1–2, available online). Per patient we also assigned a quality indicator for the estimation relating radiotherapy field to skin compartment to allow for sensitivity analyses.

Subsequent Skin Cancer Information

Record linkages to the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands (Dutch acronym: PALGA, 1990–2015; all skin cancers) (16) and the Netherlands Cancer Registry (1990–2015; melanoma, SCC) (17) provided outcome data information, as described previously (4,18). For each skin cancer type, we abstracted the date of the first occurring skin cancer during the at-risk period, tumor location of the first occurring skin cancer, and the total number of skin cancers. For patients who had multiple first occurring skin cancers of the same type at the same time (9 BCC patients), we randomly chose one location.

Statistical Analyses

Follow-up started 5 years after childhood cancer. Because PALGA achieved nationwide coverage during 1990, time at risk started either 5 years after childhood cancer diagnosis or on January 1, 1990, whichever occurred last. Follow-up ended on the date of first skin cancer (BCC, melanoma, or SCC; depending on the outcome of interest for analysis), date of death, date of last known vital status (emigration/loss-to-follow-up), or end of study (May 1, 2015), whichever occurred first.

We calculated ratios between observed and expected numbers (standardized incidence ratios [SIRs]) and excess number per 10 000 person-years (excess absolute risks [EARs]) for BCC, melanoma, and SCC. Population rates were provided by the Netherlands Cancer Registry (for melanoma and SCC) (17) and the Comprehensive Cancer Center South (for BCC) (17,19). Cumulative incidences of skin cancer types with at least 20 cases (BCC and melanoma) were estimated in the presence of death as a competing risk (20). Cumulative incidence of BCC was compared between subgroups of survivors with pairwise Pepe-Mori tests (21) and calculated by attained age and time since childhood cancer diagnosis.

We used Cox regression to calculate hazard ratios (HRs) with attained age as the time scale. In each risk set, consisting of one skin cancer case (there were not ties) and all other cohort members still at risk of skin cancer, the exposure to the skin compartment where the tumor occurred in the case patient was used. If the compartment was fully or partly in the treatment field, exposure was yes (otherwise zero), exposed skin surface area was the percentage surface area represented by the compartment (otherwise zero), and dose was prescribed dose to the treatment field (otherwise zero). Multivariable analyses are presented for BCC, whereas univariate results are shown for melanoma and SCC due to the small number of cases. Five separate models were fitted to evaluate potential treatment-related risk factors for BCC, all adjusted for available demographic variables sex and age (both age at diagnosis and attained age, intrinsically by using this as the time scale): 1) general treatment groups; 2-5) radiotherapy-related risks additionally adjusted for main chemotherapy groups. Model 2 evaluated radiotherapy to skin compartment of interest; model 3 evaluated radiotherapy volume and dose among radiotherapy-exposed individuals; model 4 evaluated interaction radiotherapy to skin compartment/time since diagnosis; and model 5 evaluated interaction radiotherapy to skin compartment/sun-exposed skin area. We evaluated proportionality of hazards for each variable in the multivariable Cox regression model by adding interaction terms with attained age (the time scale) and, unless explicitly stated, found no evidence of nonproportionality. Tests for trend among radiation-exposed individuals were based on the continuous variable for radiation dose and on a categorical indicator for the respective skin area groups. P values less than .05 were considered statistically significant. All statistical tests were two-sided.

Results

The analysis cohort included 5843 CCSs (Supplementary Figure 2, available online) (18). At the end of follow-up, the median time since childhood cancer diagnosis was 23.2 years (range = 5.0–52.3 years) and the median age was 30.6 years (range = 5.8–67.5 years). We identified 1061 BCCs in 259 survivors, 27 melanomas in 20 survivors, and 11 SCCs in 10 survivors (Tables 1 and 2). Among BCC patients, 46.7% developed multiple BCCs and 13.1% developed 10 or more BCCs. Among BCC cases, many

Table 1. Characteristics of the DCOG-LATER cohort of childhood cancer survivors (n = 5843) and survivors with a BCC*

Characteristic	Total cohort n = 5843 No. (%)	BCC patients n = 259 No. (%)
Childhood cancer type†		
Leukemia	1962 (33.6)	116 (44.8)
Non-Hodgkin lymphoma‡	555 (9.5)	21 (8.1)
Hodgkin lymphoma	395 (6.8)	27 (10.4)
Central nervous system	781 (13.4)	30 (11.6)
Neuroblastoma	313 (5.4)	8 (3.1)
Retinoblastoma	31 (0.5)	1 (0.4)
Renal tumors	578 (9.9)	19 (7.3)
Hepatic tumors	52 (0.9)	0 (0.0)
Bone tumors	343 (5.9)	13 (5.0)
Soft tissue tumors	426 (7.3)	11 (4.3)
Germ cell tumors	224 (3.8)	7 (2.7)
Other and unspecified§	183 (3.1)	6 (2.3)
Sex		
Male	3269 (56.0)	141 (54.4)
Female	2574 (44.1)	118 (46.6)
Age at childhood cancer diagnosis, y		
<5	2641 (45.2)	98 (37.8)
5–9	1583 (27.1)	65 (25.1)
10+	1619 (27.7)	96 (37.1)
Attained age, y		
<20	763 (13.1)	12 (4.6)
20–29	1974 (33.8)	59 (22.8)
30–39	1879 (32.1)	115 (44.4)
40+	1227 (21.0)	73 (28.2)
Time since childhood cancer diagnosis, y		
<20	2110 (36.1)	49 (18.9)
20–29	2073 (35.5)	114 (44.0)
30–39	1325 (22.7)	87 (33.6)
40+	335 (5.7)	9 (3.5)
Calendar year of childhood cancer diagnosis		
1963–1984	1791 (30.7)	192 (74.1)
1985–1994	2113 (36.2)	53 (20.5)
1995–2001	1939 (33.2)	14 (5.4)
Vital status		
Alive	5370 (91.9)	244 (94.2)
Deceased	473 (8.1)	15 (5.8)
Childhood cancer treatment‖		
Surgery only	573 (9.8)	7 (2.7)
Chemotherapy, no radiotherapy	2898 (49.6)	12 (4.6)
Radiotherapy, no chemotherapy	445 (7.6)	32 (12.4)
Radiotherapy and chemotherapy	1854 (31.7)	207 (79.9)
No treatment/treatment unknown	73 (1.3)	1 (0.4)
Radiotherapy‖		
No	3505 (60.0)	19 (7.4)
Yes	2308 (39.5)	239 (92.3)
Chemotherapy‖		
No	1050 (18.0)	39 (15.1)
Yes	4759 (81.5)	219 (84.6)
Alkylating agents‖		
No	2820 (48.3)	128 (49.4)
Yes	2987 (51.1)	130 (50.2)
Anthracyclines‖		
No	3152 (53.9)	152 (58.7)
Yes	2655 (45.4)	106 (40.9)
Epipodophyllotoxins‖		
No	4573 (78.3)	208 (80.3)
Yes	1232 (21.1)	50 (19.3)
Vinca alkaloids‖		
No	1599 (27.4)	55 (21.2)
Yes	4210 (72.1)	203 (78.4)
Platinum agents‖		
No	5035 (86.2)	250 (96.5)
Yes	770 (13.2)	8 (3.1)
Antimetabolites‖		
No	3087 (52.8)	105 (40.5)
Yes	2721 (46.6)	153 (59.1)
Hematopoietic cell transplantation‖		
No	5404 (92.5)	224 (86.5)
Allogeneic	220 (3.8)	20 (7.7)
Autologous	151 (2.6)	11 (4.3)
No. of skin cancers		
0	5566 (95.3)	—
1	148 (2.5)	138 (53.3)
2–5	78 (1.3)	70 (27.0)
6–9	17 (0.3)	17 (6.6)
10+	34 (0.6)	34 (13.1)

*Numbers do not always add up to 100% because of missing data or rounding. BCC = basal cell carcinoma; ICCC-3 = International Classification of Childhood Cancer; TBI = total body irradiation.
†Diagnostic groups included all malignancies covered by the third edition of the ICCC-3 as well as multifocal Langerhans cell histiocytosis and selected nonmalignant ependymomas and astrocytomas.
‡Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas.
§Includes all morphology codes specified in the ICCC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms as well as nonmalignant multifocal Langerhans cell histiocytosis.
‖Treatment data include primary treatment and all recurrences; radiotherapy (yes/no), chemotherapy (yes/no), and hematopoietic cell transplantation (yes/no) data were missing for 30, 34, and 68 survivors, respectively.

more had prior radiotherapy than in the cohort (92.3% vs 39.5%). Among those with 10 or more BCCs, 97.1% had prior radiotherapy and 17.7% had an Hematopoietic Cell Transplantation (HCT) with total body irradiation (TBI) treatment (data not shown).

Survivors had a 30-fold increased BCC risk compared with the general population (SIR = 29.8, 95% confidence interval [CI] = 26.3 to 33.6; EAR/10 000 person-years = 24.6) (Table 2). We also observed statistically significantly elevated, albeit less pronounced, risks of melanoma (SIR = 2.3, 95% CI = 1.4 to 3.5; EAR = 1.1) and SCC (SIR = 7.5, 95% CI = 3.6 to 13.8; EAR = 0.8). The EAR increased strongly with increasing follow-up time and attained age to 100 or more excess cases/10 000 person-years among survivors 30–39 years after diagnosis or 40–49 years of age (Table 3). Of 259 BCC-affected patients, 116 were leukemia survivors with very high risks after TBI (SIR = 174.3, 95% CI = 112.8 to 257.2; EAR = 88.2) and cranial radiotherapy (SIR = 71.8, 95% CI = 57.6 to 88.5; EAR = 83.2), but not in other leukemia survivors (SIR = 4.4, 95% CI = 0.9 to 12.7; EAR = 1.2). According to treatment, all subgroups showed excess risk of BCC, including after surgery only (SIR = 7.4, 95% CI = 3.0 to 15.3; EAR = 6.0). The largest excesses were observed among survivors who received both radiotherapy and chemotherapy (SIR = 59.3, 95% CI = 51.5 to 68.0; EAR = 60.6). Among patients who received radiotherapy, SIRs decreased with increasing age at diagnosis, whereas for the

Table 2. SIRs, EARs, and cumulative incidences of BCC, melanoma, and SCC in the DCOG-LATER cohort (n = 5843)

Skin cancer type	Person-years of follow-up	Observed number/ expected number	SIR (95% CI)	EAR	20-y cumulative incidence, % (95% CI)	30-y cumulative incidence, % (95% CI)
BCC*	101 899	259/8.7	29.8 (26.3 to 33.6)	24.6	1.0 (0.8 to 1.4)	5.1 (4.4 to 6.0)
Melanoma	103 501	20/8.9	2.3 (1.4 to 3.5)	1.1	0.1 (0.1 to 0.3)	0.4 (0.3 to 0.7)
SCC	103 644	10/1.3	7.5 (3.6 to 13.8)	0.8	0.1 (0.0 to 0.2)	0.2 (0.1 to 0.4)

*40-year cumulative incidence of BCC was 14.1 (95% CI = 12.1 to 16.3). BCC = basal cell carcinoma; CI = confidence interval; EAR = excess absolute risk per 10 000 person-years; SCC = squamous cell carcinoma; SIR = standardized incidence ratio.

Table 3. SIRs and EARs of BCC in the DCOG-LATER cohort (n = 5843) by patient and treatment characteristics*

Characteristic	Person-years of follow-up	Observed number	SIR (95% CI)	EAR
Sex				
Male	56 487	141	37.0 (31.2 to 43.7)	24.3
Female	45 412	118	24.1 (20.0 to 28.9)	24.9
Age at diagnosis, y				
<5	46 814	98	45.9 (37.3 to 56.0)	20.5
5–9	27 525	65	32.1 (24.8 to 40.9)	22.9
10–17	27 561	96	21.1 (17.1 to 25.8)	33.2
Time since childhood cancer diagnosis, y				
5–9	21 916	3	28.7 (5.9 to 84.0)	1.3
10–19	45 274	46	38.6 (28.3 to 51.5)	9.9
20–29	25 352	114	35.5 (29.3 to 42.6)	43.7
30–39	8297	87	27.2 (21.7 to 33.5)	101.0
40+	1060	9	9.1 (4.2 to 17.3)	75.6
Attained age, y				
<20	37 611	12	94.0 (48.6 to 164.2)	3.2
20–29	38 004	60	49.3 (37.6 to 63.4)	15.5
30–39	19 757	114	33.5 (27.6 to 40.2)	56.0
40–49	5656	66	23.2 (17.9 to 29.5)	111.7
50+	872	7	6.4 (2.6 to 13.1)	67.6
Childhood cancer type				
Leukemia, total	33 434	116	56.1 46.3 to 67.3)	34.1
Leukemia, no cranial radiotherapy/TBI	20 038	3	4.4 (0.9 to 12.7)	1.2
Leukemia, cranial radiotherapy, no TBI	10 434	88	71.8 (57.6 to 88.5)	83.2
Leukemia, TBI	2820	25	174.3 (112.8 to 257.2)	88.2
Lymphoma	16 997	48	29.0 (21.4 to 38.5)	27.3
Central nervous system tumor	12 254	30	31.8 (21.5 to 45.4)	23.7
Bone tumor	6099	13	11.7 (6.2 to 20.0)	19.5
Soft tissue sarcoma	7690	10	12.5 (6.2 to 22.3)	13.2
Other tumor	25 426	41	20.1 (14.4 to 27.2)	15.3
Treatment				
Surgery only	10 114	7	7.4 (3.0 to 15.3)	6.0
Chemotherapy, no radiotherapy	49 098	12	4.7 (2.4 to 8.2)	1.9
Radiotherapy, no chemotherapy	8191	32	20.0 (13.7 to 28.2)	37.1
Radiotherapy and chemotherapy	33 585	207	59.3 (51.5 to 68.0)	60.6
No treatment/treatment unknown	912	1	8.9 (0.2 to 49.4)	9.7
Radiotherapy/age at diagnosis, y				
No radiotherapy	59 666	19	5.4 (3.2 to 8.4)	2.6
Radiotherapy, age at diagnosis <5	16 026	89	72.1 (57.9 to 88.7)	54.8
Radiotherapy, age at diagnosis 5–9	12 409	60	48.0 (36.6 to 61.7)	47.3
Radiotherapy, age at diagnosis 10–17	13 417	90	34.4 (27.7 to 42.3)	65.1
Radiotherapy/time since childhood cancer diagnosis, y				
No radiotherapy	59 666	19	5.4 (3.2 to 8.4)	2.6
Radiotherapy/5–14	14 868	16	82.0 (46.9 to 133.1)	10.6
Radiotherapy/15–24	15 286	85	83.7 (66.9 to 103.5)	54.9
Radiotherapy/25+	11 698	138	35.5 (29.8 to 41.9)	114.6

*BCC = basal cell carcinoma; CI = confidence interval; E = expected; EAR = excess absolute risk per 10 000 person-years; O = observed; SIR = standardized incidence ratio; TBI = total body irradiation.

EAR no clear trend was observed (SIRs of 72.1, 48.0, and 34.4 and EARs of 54.8, 47.3, and 65.1 for age at diagnosis categories <5 years, 5–9 years, and 10–17 years, respectively).

Cumulative incidence of BCC 40 years after childhood cancer was 19.1% (95% CI = 16.6% to 21.8%) for survivors treated with any radiotherapy compared with 0.6% expected (data not shown) and 3.2% (95% CI = 1.5% to 6.0%) for all other survivors (Figure 1A). By time since childhood cancer diagnosis, cumulative incidences of BCC after 40 years were similar for those with radiotherapy at age 5 years and younger or at ages 5–17 years (18.3% vs 19.3%, $P = .25$) (Figure 1A). By attained age, the cumulative incidence of BCC at age 45 years was higher among survivors treated with radiotherapy at age 5 years and younger compared with 5–17 years (18.1% vs 13.1%, $P = .004$) (Figure 1B). The occurrence of BCC did not depend on treatment era; the cumulative incidences at a given follow-up time or attained age were similar for patients during 1985 and before, 1985–1994, or 1995–2001 (Figure 2). The cumulative incidence of melanoma was 0.8% (95% CI = 0.5% to 1.4%) 40 years after childhood cancer diagnosis and 0.8% (95% CI = 0.5% to 1.3%) by age 45 (Supplementary Figure 3, available online).

Most BCCs occurred in the head and neck area (Supplementary Table 2, available online). In multivariable regression analyses, we observed increased BCC risk for all treatment groups that included any form of radiotherapy compared with patients treated with surgery only (Table 4, model 1). Highest point estimates emerged after chemotherapy plus TBI (HR = 19.67, 95% CI = 8.51 to 45.46) and after chemotherapy plus radiotherapy exposing the head/neck area and trunk (HR = 10.23, 95% CI = 4.65 to 22.53), compared with surgery only, although with wide CIs.

In an analysis with more treatment details (Table 4, model 2), any radiotherapy to the compartment where the skin cancer occurred was associated with a 14-fold increased risk of BCC (HR = 14.32, 95% CI = 10.10 to 20.29). Moreover, BCC risk was associated with estimated percentage in-field skin surface area (26–75% exposed: HR = 1.99, 95% CI = 1.24 to 3.20; 76–100% exposed: HR = 2.16, 95% CI = 1.33 to 3.53 vs 1–25% exposed (reference group); P_{trend} among exposed = .002) (Table 4, model 3). Risks were not materially altered when excluding survivors who received TBI (data not shown). In a sensitivity analysis where we excluded patients with a low-quality indicator for the estimation relating radiotherapy field to skin compartment (Supplementary Tables 1 and 2, available online), the HRs for 26–75% and 76–100% exposure were 2.35 (95% CI = 1.25 to 4.43) and 4.07 (95% CI = 2.00 to 8.30), respectively, vs 1–25% (data not shown). BCC risk varied by exposure age, being highest for those treated prior to age 5 years (HR = 0.62, 95% CI = 0.43 to 0.90 for age 5–9 years and HR = 0.53, 95% CI = 0.37 to 0.77 for age 10–17 years vs earlier, respectively) (Table 4, model 3). Although BCC risk for 10- Gray (Gy) increments in prescribed dose was slightly increased, the risk estimate was not statistically significant (HR/10 Gy = 1.06, 95% CI = 0.95 to 1.20) with (Table 4, model 3) or without adjustment for percentage in-field skin surface area (HR/10 Gy = 1.03, 95% CI = 0.92 to 1.15; data not shown). Although BCC risk increased with longer time since diagnosis, there was a statistically significant modification by time since diagnosis of the effect of radiotherapy to the relevant skin compartment on an additive scale, but not on a multiplicative scale ($P_{interactions}$: multiplicative scale = .34; additive scale = .004). We found no statistically significant modification of radiotherapy by sun-exposed region (head/neck/forearm) ($P_{interactions}$: multiplicative scale = additive scale = .68) (Table 4, models 4 and 5). Among main chemotherapy groups, no statistically significant associations with BCC risk were observed, except for vinca alkaloids (HR = 1.54, 95% CI = 1.04 to 2.27) (Table 4, model 2).

In univariate models, we found no statistically significant associations between a history of radiotherapy to the compartment where the skin cancer occurred and the incidence of melanoma (HR = 2.14, 95% CI = 0.70 to 6.49) or SCC (HR = 2.59, 95% CI = 0.64 to 10.41) (Supplementary Table 3, available online). Melanoma incidence was also not related to any other demographic or treatment factor. In univariate analysis, allogeneic HCT (HR = 15.65, 95% CI = 2.95 to 83.02) and TBI (HR = 12.02, 95% CI = 2.39 to 0.35) were statistically significantly associated with SCC risk. Although anthracyclines appeared associated with SCC risk (HR = 6.45, 95% CI = 1.25 to 33.44), this result was attenuated and no longer statistically significant after adjustment for allogeneic HCT (HR = 4.65; 95% CI = 0.81 to 26.83) owing to a strong correlation between anthracyclines and allogeneic HCT (not shown).

Discussion

Using radiation exposure to the location where the tumor occurred in a novel way, we observed strikingly high risks for BCC after radiotherapy directed to the skin compartment where the tumor later developed. BCC risk appeared to increase with increasing skin surface area exposed. Another new finding regarding BCC includes the observation that as many as one-half of the patients who developed a subsequent BCC after childhood cancer later had more BCCs during the study period. Other BCC risk factors include cranial radiotherapy, TBI, and possibly a young age at radiotherapy and vinca alkaloids.

Risk estimates for radiotherapy (to the compartment where the skin cancer occurred) in our study were larger than in other studies among medically exposed populations, based on crude radiotherapy indicators (typically any vs none) (10,13,14,22,23). A nested case-control study from the North American Childhood Cancer Survivors Study found that the proximity of the BCC to the radiation field was associated with increased BCC risk, with an almost 15-fold increased risk for BCC to occur in the previous radiation field (9). We found that a larger percentage of exposed skin surface area of the compartment where the skin cancer occurred additionally increased BCC risk, which remained when we excluded patients who had TBI (large volume, large fraction dose). To our knowledge, this is the first study to evaluate the role of radiation-exposed skin surface area for BCC. We did not find a clear radiation dose-response relation in contrast to several other studies (9,13–15). This might be related to the use of prescribed radiation dose in our study, a modest indicator of the truly absorbed radiation dose at the BCC site (24). We used prescribed RT dose because of the opportunity for joint analysis of dose and exposed skin surface area, which allows for potential translation to clinical practice based on information from patients' medical files.

The SIR of BCC was fairly stable during follow-up, leading to highly elevated EARs when CCSs reached ages where background risks of BCC become higher. BCC risk was increased even after 40 years since childhood cancer diagnosis. Overall, CCSs diagnosed at ages 5 years and younger had, compared with those diagnosed at older ages, a higher relative risk (SIR) but a lower absolute risk (EAR); the attained age and, therefore, the background risk of BCC is lower among CCSs originally diagnosed before 5 years. In a multivariable risk model, CCSs diagnosed before 5 years were at statistically significantly increased risk compared with those diagnosed at an older age. These findings align well with those for atomic bomb survivors and tinea

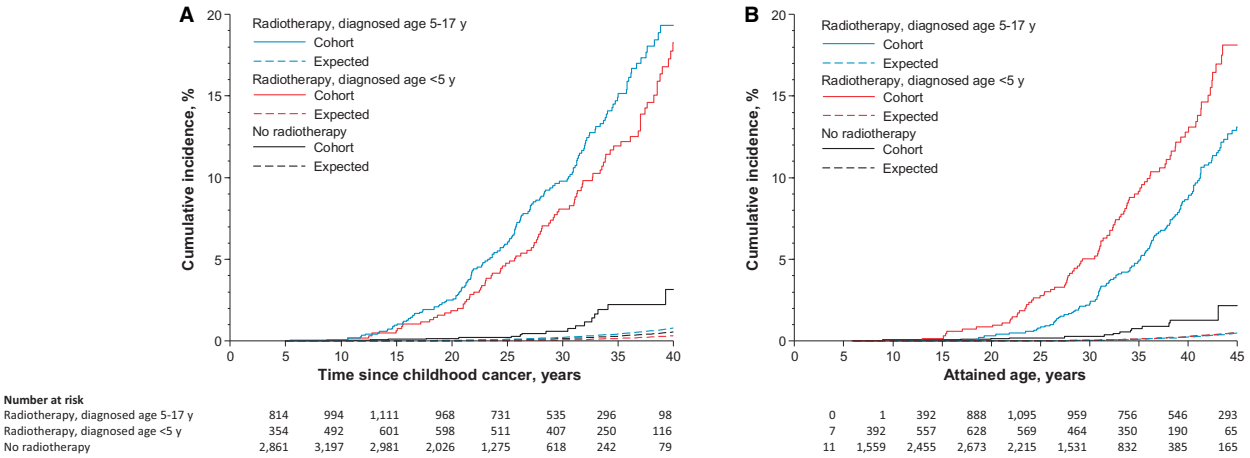

Figure 1. Cumulative incidence of basal cell carcinoma in 5-year childhood cancer survivors of the DCOG-LATER cohort and the expected cumulative incidence from the general population, separately for those who had received radiotherapy (age at diagnosis before 5 years and 5–17 years) and those who had not received radiotherapy. **A)** Cumulative incidence with time since childhood cancer diagnosis as the time scale. **B)** Cumulative incidence with attained age as the time scale. Cumulative incidences were estimated in the presence of death as a competing risk and compared between subgroups of survivors with pairwise Pepe-Mori tests. Pepe-Mori test *P* values for comparison of cumulative incidences at 40 years since childhood cancer for each category are as follows: <.001 for no radiotherapy vs radiotherapy, diagnosed before age 5 years; <.001 for no radiotherapy vs radiotherapy, diagnosed age 5–17 years; and .25 for radiotherapy, diagnosed age before 5 years vs radiotherapy, diagnosed age 5–17 years. Pepe-Mori test *P* values for comparison of cumulative incidences at attained age 45 years for each category are as follows: <.001 for no radiotherapy vs radiotherapy, diagnosed before age 5 years; <.001 for no radiotherapy vs radiotherapy, diagnosed age 5–17 years; and .004 for radiotherapy, diagnosed before age 5 y vs radiotherapy, diagnosed age 5–17 years. All statistical tests were two-sided.

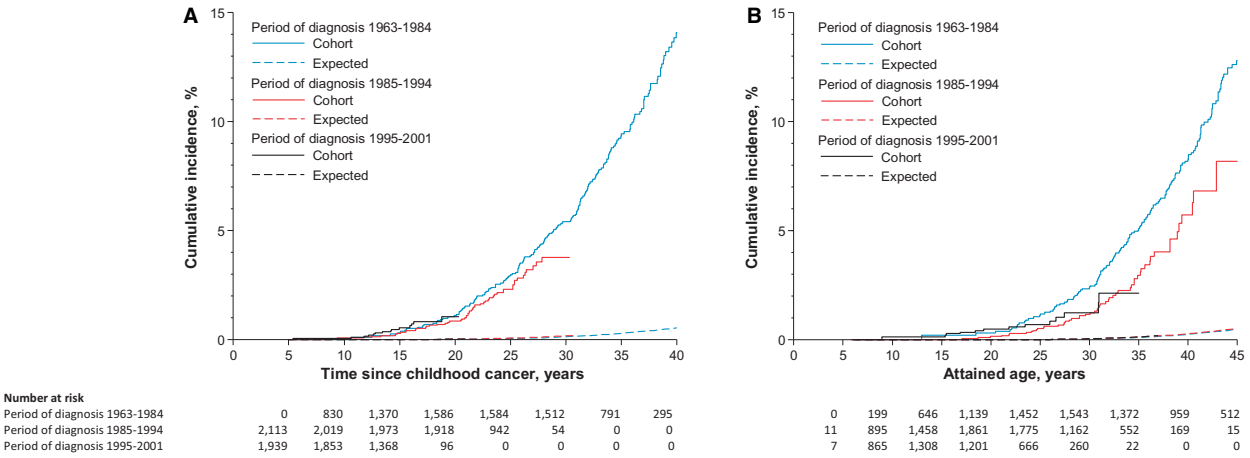

Figure 2. Cumulative incidence of basal cell carcinoma in 5-year childhood cancer survivors of the DCOG-LATER cohort and expected cumulative incidence from the general population according to period of childhood cancer diagnosis. **A)** Cumulative incidence with time since childhood cancer diagnosis as the time scale. **B)** Cumulative incidence with attained age as the time scale. Cumulative incidences were estimated in the presence of death as a competing risk and compared between subgroups of survivors with pairwise Pepe-Mori tests. Pepe-Mori test *P* values for comparison of cumulative incidences at 15 years since childhood cancer for each childhood cancer diagnosis period are as follows: .89 for 1963–1984 vs 1985–1994, .32 for 1963–1984 vs 1995–2001, and .24 for 1985–1994 vs 1995–2001. Pepe-Mori test *P* values for comparison of cumulative incidences at attained age 25 years for each childhood cancer diagnosis period are as follows: .05 for 1963–1984 vs 1985–1994, .37 for 1963–1984 vs 1995–2001, and .31 for 1985–1994 vs 1995–2001. All statistical tests were two-sided.

capitis patients and are compatible with increased radiosensitivity at a younger age (13–15). Of all chemotherapy groups tested, only vinca alkaloids appeared associated with elevated BCC risk. We observed no dose-response relationship, and no clear association with skin cancer was found in previous studies. Therefore, a cautious interpretation is warranted.

Risk of melanoma was also increased compared with the general population, in line with findings by others (2,7,25–27). We did not identify any statistically significant risk factor for melanoma consistent with data from the North American Childhood Cancer Survivor Study (27), though among French/British CCSs, a weak radiotherapy dose response was reported (6).

We found a sevenfold increased risk of SCC among survivors compared with the general population and, in univariate comparisons (owing to small sample issues), HCT and TBI appeared to be risk factors. Without multivariable adjustments, HCT represents a composite surrogate variable for several underlying factors (eg, TBI). Nonetheless, a role of HCT is plausible because SCC is a well-known disease among immunocompromised populations, including posttransplant graft-versus-host disease

Table 4. Multivariable Cox regression analyses for risk of BCC*

Model	No. total	No. of cases	HR (95% CI)
Model 1			
Sex			
Male	3269	141	1.00 (Ref)
Female	2574	118	0.98 (0.77 to 1.26)
Age at diagnosis, y			
0–4	2641	98	1.00 (Ref)
5–9	1583	65	0.58 (0.42 to 0.81)
10–17	1619	96	0.54 (0.39 to 0.73)
Treatment			
Surgery only	573	7	1.00 (Ref)
CT, no RT	2898	12	0.48 (0.19 to 1.23)
RT, no CT	445	32	3.32 (1.46 to 7.57)
CT + head/neck RT (no trunk RT)†	637	81	6.34 (2.92 to 13.77)
CT + trunk RT (no head/neck RT)†	436	33	3.97 (1.75 to 9.01)
CT + head/neck RT + trunk RT, no TBI	451	58	10.23 (4.65 to 22.53)
CT + TBI	210	28	19.67 (8.51 to 45.46)
CT + other RT‡	111	7	5.60 (1.95 to 16.02)
Model 2§			
RT to skin compartment of BCC	‖		
No	—	44	1.00 (ref)
Yes	—	200	14.32 10.10 to 20.29)
Alkylating agents			
No	2820	128	1.00 (ref)
Yes	2987	130	1.01 (0.76 to 1.36)
Anthracyclines			
No	3152	152	1.00 (ref)
Yes	2655	106	1.08 (0.80 to 1.47)
Epipodophyllotoxins			
No	4573	208	1.00 (ref)
Yes	1232	50	1.43 (0.99 to 2.09)
Vinca alkaloids			
No	1 599	55	1.00 (ref)
Yes	4210	203	1.54 (1.04 to 2.27)
Platinum agents			
No	5035	250	1.00 (ref)
Yes	770	8	0.69 (0.33 to 1.47)
Antimetabolites			
No	3087	105	1.00 (ref)
Yes	2721	153	1.22 (0.88 to 1.68)
Model 3¶			
Irradiated surface area of skin compartment of BCC	‖		
No RT to skin compartment of BCC	—	44	0.10 (0.05 to 0.19)
1–25%	—	47	1.00 (ref)
26–75%	—	75	1.99 (1.24 to 3.20)
76–100%	—	78	2.16 (1.33 to 3.53)
Age at diagnosis among those with RT to skin compartment of BCC, y	‖		
1–4	—	76	1.00 (ref)
5–9	—	55	0.62 (0.43 to 0.90)
10+	—	69	0.53 (0.37 to 0.77)
RT dose in compartment where BCC developed (per 10 Gy)	‖	—	1.06 (0.95 to 1.20)
Model 4¶			
RT to skin compartment of BCC/time since childhood cancer diagnosis, y	‖		
No/<20	—	7	1.00 (ref)
No/20+	—	37	3.17 (1.31 to 7.66)
Yes/<20	—	40	20.37 (8.99 to 46.18)
Yes/20+	—	160	42.20 (18.11 to 98.33)
Model 5#			
RT to skin compartment of BCC/sun-exposed skin area	‖		
No	—	44	1.00 (ref)
Yes/no sun-exposed area	—	65	13.33 (8.27 to 21.50)
Yes/sun-exposed area	—	135	15.52 (9.21 to 26.15)

*BCC = basal cell carcinoma; CI = confidence interval; CT = chemotherapy; Gy = Gray; HR = hazard ratio; RT = radiotherapy.
†With or without brachytherapy, radioisotopes, or RT extremities.
‡Other RT includes radioisotopes, brachytherapy, and RT extremities.
§Model was additionally adjusted for sex and age at diagnosis.
‖Not applicable because for noncases, we used the segment of the corresponding case in each risk set, that is, different segments are used for noncases depending on the risk sets to which they contribute. See Methods section.
¶Model was additionally adjusted for sex, alkylating agents (yes vs no), anthracyclines (yes vs no), epipodophyllotoxins (yes vs no), vinca alkaloids (yes vs no), platinum agents (yes vs no), and antimetabolites (yes vs no).
#Model was additionally adjusted for sex, age at diagnosis (0–4 y; 5–9 y; 10–17 y), alkylating agents (yes vs no), anthracyclines (yes vs no), epipodophyllotoxins (yes vs no), vinca alkaloids (yes vs no), platinum agents (yes vs no), and antimetabolites (yes vs no).

(28), solid organ transplant recipients (29), and HIV-positive patients (30).

A major strength of our study is the combination of detailed treatment information, a large cohort size, and information on melanoma, SCC, and BCC from record linkages. BCC and sometimes SCC are often excluded from studies on subsequent cancer risk because most cancer registries do not routinely collect data on keratinocyte skin cancers. PALGA-linkage enabled attainment of objective data on histologically confirmed keratinocyte skin cancer. We assessed the effect of radiotherapy in the skin compartment where the skin tumor occurred rather than relying on crude indicators of radiotherapy (eg yes vs no) used in most previous cohort studies, and, for the first time to our knowledge, we assessed the potential impact of crude indicators of skin surface area exposure to radiotherapy and skin cancer risk, accounting for prescribed radiation dose.

Limitations of our study are the small chance of missed BCC cases with the PALGA linkage, because a minority subgroup of BCCs, the superficial BCCs, are sometimes treated topically without histologic confirmation (31). This may affect the number of BCCs per patient, but not the number of patients with a first BCC because these are generally biopsied as recommended by the Dutch BCC guideline (32). Furthermore, there is a slight chance of false-positive findings with the PALGA linkage on family name, gender, and birth date due to administrative twins. PALGA achieved nationwide coverage during 1990, so we did not have reliable information on skin cancers occurring before 1990. By including only follow-up time since 1990 and

because most skin cancers occurred more than 20 years after childhood cancer, a follow-up interval that nearly all cohort members reached after 1990, we are confident that the impact on the estimates caused by left truncation is minimal. Also, it is plausible that increased awareness among survivors and their caregivers, as well as medical follow-up at survivorship clinics, have increased the likelihood of early detection (33). This likely explains part of the elevated skin cancer risks vs the general population, as is also illustrated by the elevated SIR of BCC in the surgery only group that suggests an overestimation of the risks due to increased awareness and possibly also due to elevated BCC susceptibility factors among CCSs. Finally, we have no information on ultraviolet radiation (UV) exposure and number of sunburns in childhood, important risk factors, especially for BCC and melanoma (34). Prior UV exposure or skin sensitivity to UV light may modify the ionizing radiation-related risk. Our sensitivity analysis to evaluate the role of radiotherapy in sun-exposed skin areas vs other skin areas found no statistically significant differences regarding radiotherapy-related BCC risk, in line with other studies in different settings (9,14,15).

Currently, most CCSs in the Netherlands are under medical surveillance at one of the late effects outpatient clinics, the frequency of which depends on prior therapy and is most intense for survivors with a history of any radiotherapy. These visits include a full-body skin examination to screen for suspicious lesions and to educate survivors about risks associated with sun exposure and how to perform self-examination of the skin (33).

In conclusion, CCSs who received radiation treatments experience a strongly increased risk of BCC, which appears to increase with a larger in-field skin surface area exposed. Moreover, patients affected with BCC often develop more BCCs later on. These findings support the need for awareness by survivors, parents, and medical professionals. Most importantly, health professionals who take care of CCSs should be trained by dermatology experts to recognize suspicious skin lesions, and survivors who received radiotherapy should be educated to be alert for local skin changes in order to timely seek medical attention for skin lesions that may be potentially malignant.

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Affiliations of authors: Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands (JCT, JLK, LCK, MMvdH-E, DB, HJvdP, CMR); Department of Pediatric Oncology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands (JCT, JLK, LCK, CMK); Department of Pediatric Oncology/Hematology, University of Groningen/Beatrix Children's Hospital/University Medical Center Groningen, Groningen, the Netherlands (WJET); Department of Pediatric Oncology/Hematology, Sophia Children's Hospital/Erasmus Medical Center, Rotterdam, the Netherlands (MMvdH); Department of Hematology, Radboud University Medical Center, Nijmegen, the Netherlands (JJL); Department of Pediatric Oncology and Hematology, Wilhelmina Children's Hospital/University Medical Center Utrecht, Utrecht, the Netherlands (BV); Department of Pediatric Oncology/Hematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands (EvD-dB); Department of Dermatology, Erasmus University Medical Center, Rotterdam, the Netherlands (TN); Department of Epidemiology and Biostatistics, The Netherlands Cancer Institute, Amsterdam, the Netherlands (MH, FEvL); Dutch Childhood Oncology Group, Utrecht, the Netherlands (NH); Department of Radiation Oncology, University of Groningen/University Medical Center Groningen, Groningen, the Netherlands (WVD).

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The DCOG-LATER Study Group for skin cancers includes the listed authors and the following collaborators: HN Caron (Emma Children's Hospital/Academic Medical Center, Amsterdam), LA Daniëls (Leiden University Medical Center, Leiden), AH Bruggink (PALGA Foundation, Houten), MA Grootenhuis (Princess Máxima Center for Pediatric Oncology, Utrecht), JG den Hartogh (Dutch Childhood Cancer Parent Organisation (VOKK), Nieuwegein), M van der Heiden-van der Loo (Dutch Childhood Oncology Group, Utrecht), MWM Jaspers (Academic Medical Center, Amsterdam), SJCMM Neggers (Erasmus Medical Center, Rotterdam), and M Schaapveld (The Netherlands Cancer Institute, Amsterdam).

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