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Skin cancer in survivors of childhood and adolescent cancer

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ABSTRACT

The incidence of basal cell carcinoma (BCC) has been related to ionizing radiation, particularly for exposure occurring at young age. In this study, we considered the incidence of second skin neoplasms in long-term survivors from childhood cancer. We considered second primary cancers occurring among 776 subjects (436 males, 340 females) with first primary cancer diagnosed before age 20 years, between 1974 and 2001, in the Swiss Cantons of Vaud and Neuchâtel (786,000 inhabitants). Five BCC were observed versus 0.43 expected (standardized incidence ratio: 11.6, 95% confidence interval: 3.7–27.1). No case of cutaneous squamous cell carcinoma, nor of malignant melanoma was observed. The estimated radiation doses at 1 mm through the skin ranged between 7 and 27 Sv. These data confirm that BCC are strongly related to ionizing radiation exposure in childhood. All the BCC were located within the radiation field, thus indicating that ionizing radiation is the key aetiological factor, even in the absence of any meaningful interaction with UV.

1. Introduction

The incidence of basal cell carcinomas (BCC) is increased among atomic-bomb survivors in Hiroshima and Nagasaki.[1] Although the overall relative risk (RR) of BCC in the Life Span Study (LSS) cohort of 79972 people with dose estimates was only 1.26, an approximately 10-fold excess risk was observed in subjects exposed to $\geqslant$2 Sv. The RR was also inversely and strongly related to age at exposure, with excess RR per Sv of 21 in those exposed before age 10; of 6.7 for those at age 10–19; of 1.7 at age 20–39; and of 0.7 at age $\geqslant$40. The excess absolute risk of BCC per unit surface area related to atomic-bomb radiation, but did not differ between UV-exposed and unexposed parts of the body.[2] No excess was observed for squamous cell skin cancer (SCC), while the results were compatible with some excess risk for cutaneous malignant melanoma (CMM) and Bowen's tumour, but the data were inadequate for any meaningful inference.[1]

Studies from the USA[3] and Israel[4] have shown excess skin cancer in children irradiated for *tinea capitis* or thymic enlargement,[5] although the dose-risk relation and the effect of low doses remain unclear.[6] Among adults, in a cohort study of 1805 participants in a skin cancer prevention trial in the USA, followed-up for an average of 4 years, the RR for time to first new BCC associated with previous radiation therapy was 1.7 and that of total BCC was 2.3, while no excess was observed for SCC.[7] A population-based case-control study on 592 cases of BCC and 289 of SCC aged 25–74, and on 536 controls from New Hampshire found RRs of 3.30 for BCC and of 2.94 for SCC among therapeutically irradiated subjects on

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the site of tumour occurrence. For both histologies, the RR was higher when radiation therapy was performed under age 20. Information on radiation therapy, however, was self-reported, and hence subject to recall bias, and the apparent excess risk of SCC was restricted to UV exposed areas.[8]

The incidence of BCC, but not of SCC, was significantly elevated in a cohort of 65304 US white radiologic technologists (RR: 1.42, 2.04 and 2.16 among subjects who first worked, respectively, during the 1950s, the 1940s and before as compared to those first employed after 1960, and hence likely exposed to lower doses), and the RRs were not modified by UV exposure, although was significantly stronger among individuals with lighter eye and hair colour.[9]

Most survivors of childhood cancer have been heavily exposed to radiation. We considered, therefore, the incidence of second neoplasms in long-term survivors from childhood cancer, using data from the cancer Registries of Vaud and Neuchâtel, Switzerland. Careful monitoring and systematic pathologic examination of skin lesions has long been performed in these populations,[10] thus allowing the computation of valid and accurate measures of expected numbers of events.

2. Materials and methods

The present series comprised 776 (436 males, 340 females) first primary cancers diagnosed in patients aged <20 years between 1974 and 2001 in the Swiss Cancer Registries of Vaud and Neuchâtel (covering 786,000 inhabitants in 2000).[11,12] These included 193 cases of leukaemias, 107 of brain neoplasms, 62 of Hodgkin's disease, 57 of bone and joints neoplasms, 50 of non-Hodgkin's lymphomas, 47 of soft tissue neoplasms, 32 of testicular cancers, and 228 of miscellaneous other neoplasms. The registries are tumour based, and multiple primary malignancies found in the same person are entered separately. The information available includes socio-demographic characteristics of the patient (age, gender), the primary site and histological type of all tumours according to the standard International Classification of Diseases for Oncology, Ninth Revision (ICD-O-9),[13] and the dates of diagnoses. The rate of histological confirmation was 94% and median age was 10.2 years at diagnosis of the first primary tumour. Cases known only through death certificates amount to fewer than 5% of the average number of cases registered per year.

Patients were routinely followed up to the end of 2001 (total follow-up period, 1974–2001) through linkage with cancer registration[14] for the occurrence of a BCC diagnosed as a second primary, migration or death, for a total of 6283 person-years (3422 for males, 2861 for females) of observation.

Cumulative risk was computed using the standard life-table approach. Computation of expected numbers was based on site-, quinquennial age- and calendar-year specific incidence rates multiplied by the observed number of person-year at risk. The significance of the observed/expected ratios (standardized incidence ratio, SIR) and the corresponding 95% confidence intervals (CI) was based on the exact Poisson distribution.[15]

For the determination of the dose delivered to the skin basal cell layer by radiation therapy, we took into account the build-up effect associated with high-energy X-ray beams. Because the secondary electrons may travel some distance before coming to rest, the distribution of energy transferred from X-rays to secondary electrons can be different to the distribution of energy deposited (absorbed dose) in the tissue. At high photon energies, only a small amount of dose is deposited in the skin and superficial tissues.

Dose delivered in the first few millimetres of tissue was measured with an ionising chamber for a 6 MV beam of a linear accelerator, a cobalt-60 unit and a 250 kV X-ray tube. Since the field sizes used to treat the patients in the study were not known, measurements were made for $5 \times 5\ cm^2$ and $20 \times 20\ cm^2$ fields. These sizes represent the minimum and maximum probable beam sizes for the patient studied. The dose to the basal cell layer of the skin was determined from these measurements for each patient.[16,17] The estimated dose is the sum of the dose delivered by the anterior–posterior beam (entrance dose) and the posterior–anterior beam (exit dose), assuming that the prescribed dose is a mid-distance in the patient.

3. Results

Over the period considered, five BCC (2 in males, 3 in females) were observed in subjects diagnosed with a first primary cancer at age <20, versus 0.43 expected, corresponding to a SIR of 11.6 (95% confidence interval (CI), 3.7–27.1). The SIR was 10.3 in males and 12.8 in females, 40.5 for the first primary cancer diagnosed at age <10 (2 BCC), and 7.9 for those (1 BCC in males, 2 in females) diagnosed at age 10–19. All five second BCC were diagnosed $\geqslant$10 years following diagnosis of first primary (SIR: 14.9). No case of SCC or CMM was observed.

Table 1 gives the summary of demographic, clinical characteristics and radiation history of the 5 cases of BCC. This series comprised three cases of Hodgkin's disease diagnosed at ages 16 and 17, one cerebral astrocytoma, and one non-Hodgkin's lymphoma. All of these received radiation treatment, with estimated radiation doses at 1 mm through the skin ranging between 7 and 27 Sv. All the BCC were located within the radiation field.

4. Discussion

The present data confirm that basal cell carcinomas are related to ionizing radiation, and that the RRs are grossly elevated (over 10-fold) for exposure occurring at younger age. All five cases that developed basal cell skin cancers were exposed to high skin doses. The study also confirms the absence of excess risk of SCC, for at least 20 years, as reported from findings of: the LSS cohort of A-bomb survivors;[2] the US cohort of radiologic technologists;[9] several studies of treatment of benign conditions in adulthood;[1,3] and therapy of malignant conditions in adults.[4,6,7] However, the issue of long-term effects on SCC still remains unclear.[8] The RRs of the present study on children were however larger than the approximately 2- to 3-fold excess observed after radiation therapy in adults,[7] although the CI was wide, given the small absolute number of BCC.

Although the population studied has long been carefully monitored for skin neoplasms, all skin lesions being systematically excised,[10] underestimation may be present in the

Table 1 – Summary of demographic, clinical characteristics, and radiation history of the 5 young patients diagnosed with basal cell carcinoma following a first primary at age <20

Case No.	Sex	First primary				Second primary skin BCC		Vital status
		Age at diagnosis	Type of neoplasm, calendar year of diagnosis	Radiation therapy	Estimated skin dose (Sv)	Age at diagnosis	Anatomical site	
1	F	3	Vermis, astrocytoma, 1974	Cobalt therapy (assumed), assumed standard regimen of 50 Gy	27	30	Retro-auricular	Alive
2	M	5	B-cell NHL, stage III, 1980	Betatron 35 MeV (assumed), assumed dose of 12 Gy	7	20	Supra-clavicular	Alive
3	F	16	HD-NS, 1977	Cobalt therapy; mediastinum, cervical, supra-clavicular: 4500 R; axillae: 4000 R	24	36	Back	Alive
4	F	16	HD-NS, stage IIAa, 1976	Cobalt therapy; mediastinum, supra-clavicular, cervical, axillae: 4000 R	21	34	Back	Alive
5	M	17	HD-NS, stage I, 1985	LINAC 6 MeV; mantle ant.: 44 Gy; jugal bilateral: 40 Gy	23	34	Face	Deceased, age 34

Vaud and Neuchâtel Cancer Registries, 1974–2001.
BCC, basal cell carcinoma; Gy, Gray; HD, Hodgkin's disease; LINAC, linear accelerator; NHL, non-Hodgkin's lymphoma; NOS, not otherwise specified; NS, nodular sclerosis; and Sv, Sievert.

computation of expected numbers. Since subjects who had a childhood cancer may have selective access to medical examination, they may have more frequent diagnosis of BCC. Given the young age of this cohort however, it is unlikely that such bias may have materially influenced any of the estimates, and can hardly explain the over 10-fold excess risk observed. The lack of excess risk of SCC is also an indication of the absence of major registration bias of skin cancers in this population.

These excess risks of BCC, but not of SCC, have been related to the fact that over two thirds of the proliferating stem cells are located in the basal layer of the epidermis, which is consequently more radiosensitive.[1,18,19] All the BCC were in irradiated parts of the body, thus indicating that ionizing radiation is the key aetiological factor, even in the absence of any meaningful interaction with UV.[9]

Conflict of interest statement

None declared.

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REFERENCES

1. Ron E, Preston DL, Kishikawa M, et al. Skin tumour risk among atomic-bomb survivors in Japan. *Cancer Causes Control* 1998;**9**:393–401.
2. Kishikawa M, Koyama K, Iseki M, et al. Histologic characteristics of skin cancer in Hiroshima and Nagasaki: background incidence and radiation effects. *Int J Cancer* 2005;**117**:363–9.
3. Shore RE, Albert RE, Reed M, et al. Skin cancer incidence among children irradiated for ringworm of the scalp. *Radiat Res* 1984;**100**:192–204.
4. Ron E, Modan B, Preston DL, et al. Radiation-induced skin carcinomas of the head and neck. *Radiat Res* 1991;**125**: 318–25.
5. Hildreth NG, Shore RE, Hempelmann LH, et al. Risk of extrathyroid tumours following radiation treatment in infancy for thymic enlargement. *Radiat Res* 1985;**102**:378–91.
6. Shore RE. Overview of radiation-induced skin cancer in humans. *Int J Radiat Biol* 1990;**57**:809–27.
7. Karagas MR, McDonald JA, Greeneberg ER, et al. Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. *J Natl Cancer Inst* 1996;**88**:1848–53.
8. Lichter MD, Karagas MR, Mott LA, et al. Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. The New Hampshire Skin Cancer Study Group. *Arch Dermatol* 2000;136:1007–1011.
9. Yoshinaga S, Hauptmann M, Sigurdson A, et al. Nonmelanoma skin cancer in relation to ionizing radiation exposure among U.S. radiologic technologists. *Int J Cancer* 2005;**115**:828–34.
10. Levi F, Franceschi S, Te VC, et al. Trends of skin cancer in the Canton of Vaud, 1976–92. *Br J Cancer* 1995;**72**:1047–53.
11. Levi F, Erler G, Choffat R, et al. Statistics from the Registry of the Canton of Neuchâtel, Switzerland; 1993–1996. In: Parkin DM, Ferlay J, Teppo L, Thomas DB, editors. *Cancer incidence in*

five continents, vol. VIII, Lyon: International Agency for Research on Cancer; 2002. p. 452–53. [IARC Scient Publ. No. 155].
12. Levi F, Te VC, Randimbison L. Statistics from the Registry of the Canton of Vaud, Switzerland; 1993–1996. In: Parkin DM, Ferlay J, Teppo L, Thomas DB, editors. *Cancer incidence in five continents*, vol. VIII, Lyon: International Agency for Research on Cancer; 2002. p. 460–61. [IARC Scient Publ. No. 155].
13. World Health Organization. International Classification of Diseases for Oncology, ICD-O-9. Geneva: World Health Organization; 1976. p. 131.
14. Levi F, Randimbison L, Te VC, et al. Multiple primary cancers in the Vaud Cancer Registry, Switzerland, 1974–89. *Br J Cancer* 1993;**67**:391–5.
15. Breslow NE, Day NE. Statistical methods in cancer research, The design and analysis of cohort studies, vol. II, Geneva: World Heath Organization; 1987. [IARC Scient. Publ. No. 82].
16. Purdy JA. Buildup/surface dose and exit dose measurement for a 6 MV linear accelerator. *Med Phys* 1986;**13**:259–62.
17. McCullough EC. A measurement and analysis of buildup region dose for open fields photon beams (Cobalt-60 through 24 MV). *Med Dos* 1994;**19**:5–14.
18. Allen AC. Skin. In: Kissane M, editor. *Anderson's pathology*, vol. 2, 9th ed. St. Louis, MO (USA): C.V. Mosby Company; 1990. p. 1781–800.
19. Murphy GF, Elder DE. *Atlas of tumour pathology. Non-melanocytic Tumours of the Skin*. Washington, DC (USA): Armed Forces Institute of Pathology; 1991. p. 11–60.