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# Radiation dose as a risk factor for malignant melanoma following childhood cancer

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**Abstract**

The aim of this study was to determine therapy-related risk factors for the development of melanoma after childhood cancer. Among 4401 3-year survivors of a childhood cancer in eight French and British centres and 25 120 patients younger than 20 years old at first malignant neoplasm (FMN) extracted from the Nordic Cancer Registries, 16 patients developed a melanoma as a second malignant neoplasm (SMN). A cohort study of the French and British cohorts was performed. In a nested case–control study, the 16 patients who developed a melanoma as a SMN (cases) were matched with 3–5 controls in their respective cohort according to gender, age at the first cancer, the calendar year of occurrence of the first cancer and follow-up. Radiotherapy appeared to increase the risk of melanoma for local doses >15 Gy, Odds Ratio (OR) = 13 (95% Confidence Interval (CI): 0.94–174). Regarding chemotherapy, we observed an increased OR for both alkylating agents and spindle inhibitors, OR = 2.7 (95% CI: 0.5–14). Children treated for a gonadal tumour as a FMN were found to be at a higher risk of melanoma, OR = 8.7 (95% CI: 0.9–86). The adjusted OR for the local radiation dose was 1.07 (95% CI: 1.00–1.15). In conclusion, radiotherapy may contribute to an increased risk of melanoma as a SMN, but only at very high doses of low linear energy transfer radiation. Common genetic origins between gonadal tumours and malignant melanomas are likely.


## 1. Introduction

As survival following childhood cancer improves, more survivors are 'at risk' for second malignancies [1]. In large cohort studies with long follow-up times, 5–10% of children treated for a first malignancy developed subsequent tumours [2,3]. Although melanoma is rare in childhood and adolescence, recent reports indicate a rise in its incidence [4,5].

Melanoma as a second malignant neoplasm (SMN) after a first malignant neoplasm (FMN) during childhood cancer has been reported in bone marrow transplant recipients [6] and after retinoblastoma [7]. Some secondary melanomas developed in radiation fields, but it is not clear whether this was related to radiotherapy [7]. In patients treated for childhood malignancies, chemotherapy increases the number of benign naevi [8], one of the most common risk factors for melanoma in the general population [9].

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The quantification of melanoma occurrence as a SMN and its relationship, if any, with radiotherapy, chemotherapy and the type of first cancer during childhood could provide a rational basis for the design of future treatment protocols. To date, no published study has estimated the relationship between the radiotherapy dose received at a given site in the body and the risk of melanoma at that site. This paper reports on a case–control study, nested in two European cohorts of patients treated for a first cancer in childhood.

## 2. Patients and methods

### 2.1. Study population

#### 2.1.1. Nordic cohort

A cohort of childhood cancer patients was constituted of individuals diagnosed before the age of 20 years with a malignancy (solid or not), that was recorded in one of the five Nordic National Cancer Registries between 1960 and 1987. There were 25 120 individuals (13 947 males and 11 173 females) who were followed-up through December 1991 for the date of the onset of SMN, the date of death or the date of emigration, whichever occurred first. The average follow-up time was 7.5 years (range 0–32 years). The data collection and coding methods employed by each registry have been previously described in detail in Ref. [10].

#### 2.1.2. French and British cohort

A cohort of 4401, at least 3-year survivors treated for a solid cancer during childhood in eight centres in France and Great Britain, between 1942 and 1986, was constituted. Clinical and pathological characteristics of the cancer, the type of treatment and detailed information on chemotherapy were extracted from hospital clinical records by physicians. Radiotherapy data were obtained from the technical records, by clinicians or hospital physicists. All details concerning this cohort have previously been described in Ref. [2]. The cut-off date was 1 January 1993 for patients treated in French centres, and 1 January 1991 for those treated in British centres, which means that no data were collected beyond these two dates.

### 2.2. Cohort study

This cohort study focused exclusively on the French and British cohorts; results concerning the Nordic cohort have been reported in a previous publication [10]. The follow-up period was defined as the interval between the date of the diagnosis of the first cancer and the date of onset of a melanoma as a SMN or the date of the last follow-up. The expected number of melanomas as a SMN was obtained for each gender, 5-year age group and 5-year calendar period, by multiplying the reference incidence rates by the number of person-years at risk (PYR). We used the estimations of the French national cancer incidence rates for patients treated in French centres [11] and the United Kingdom national cancer incidence rates for those treated in Great Britain [12] as the reference rates. Both French and United Kingdom national cancer incidence rates were age-adjusted. The ratio between the observed number and the expected number of melanomas as a SMN, i.e. the standardised incidence rate (SIR), was calculated assuming that the number of melanomas followed a Poisson distribution [13]. Annual excess incidence (AEI) was defined as the difference between the observed and the expected number of SMN, divided by the number of person-years of follow-up. The cumulative incidence of melanoma was estimated using the Kaplan–Meier method and Greenwood's variance was used to estimate the corresponding confidence intervals (CIs). AMFIT Software was used for the cohort analysis [14]. Statistical tests were performed by comparing the deviance of nested models [13].

### 2.3. Case–control study

16 subjects had developed a melanoma as a SMN after a first cancer other than a melanoma in both cohorts, 10 in the Nordic cohort and six in the French and British cohort. Dosimetric reconstruction was not possible for one case in the Nordic cohort for whom the received dose was missing. Each of the 16 cases was matched with 3–5 controls that were randomly extracted from the cohort to which the case belonged. The matching criteria we used were gender, age at first cancer ($\pm 3$ years), the calendar year of occurrence of first cancer ($\pm 3$ years) and follow-up. These criteria are those frequently used in this type of case–control study nested in a cohort [15]. Controls were not matched for the type of first cancer to avoid over-matching, since the type of first cancer was strongly correlated with the type of treatment. Moreover, we specifically wanted to investigate the separate role of the type of first cancer. Controls had to be followed-up over a period that was at least equal to the interval between the first and the second cancer of the matched case. This period was defined as the follow-up period. Conditional logistic regression was used to analyse the risk of malignant melanoma as a function of radiation, chemotherapy and FMN [16]. The significance of various parameters was tested by comparing nested models using likelihood ratio tests in Epicure epidemiological software [14].

### 2.4. Medical record extraction

Medical records of all cases and controls were scrutinised and data extracted and collected. Predefined

registration forms were completed by investigators blinded as to whether the individual was a case or a control. The diagnoses of FMN and SMN were verified and the site and the histological type were coded. Dates for relapse(s) of FMN, as well as for all treatments of primary FMN and treatments of relapses were recorded.

#### 2.4.1. Chemotherapy agents

These were classified into five drug categories: alkylating agents and related compounds, spindle inhibitors, inhibitors of nucleotide synthesis, topoisomerase II inhibitors and other drugs. In order to quantify the total amount of drug in each chemotherapy subgroup, we converted the dose of each cytotoxic expressed in $mg/m^2$ into $mol/m^2$. We then added up the number of $mol/m^2$ for each drug category. The dose of each drug received by each case or control either as initial treatment or for recurrences of the first cancer were summed over the follow-up period.

#### 2.4.2. Radiotherapy files

These were scrutinised for relevant data. We first determined the location of the melanoma area for each case and a similar area for each matched control, in order to ascertain the radiation doses received in these areas, whatever the treated volume. Patients and their radiotherapy beam arrangements were simulated using the Dos_EG software [17]. Originally, no correction was made in Dos_EG for entrance surface dose accumulation nor for the lack of full backscatter at the exit side of the beam. As the structure of interest for melanoma is the basal cell layer located approximately 70 μm below the outer surface of the skin as well as the first millimetres of tissue, corrections were necessary when the melanoma area was included in the beam or near the beam borders. We used the investigations of a number of authors based on results using very thin dosimeters and analyses [18–20] to establish correction factors from tissue doses to skin doses [19,20]. When melanoma areas were remote from the beam borders, the discrepancy between skin and deeper doses (calculated by Dos_EG) was small, hence no correction was made and the doses calculated by Dose_EG were taken into account. The local radiation dose was defined as the cumulative absorbed dose at the site of the melanoma for the case, and at the same site for its matched controls, during the follow-up period minus 3 years corresponding to the minimal latency period, for the occurrence of a radiation-induced cancer.

## 3. Results

### 3.1. Cohort study

Of the 4401 patients in the French and British cohort, 509 (11.6%) were lost to follow-up, and 554 (12.6%) died before the end of the study. The mean follow-up duration was 15 years (range 3–48 years), and the mean age attained at the end of the follow-up period was 21 years (3–58 years). The total number of person-years at risk after 30 years of follow-up was 1380. A total of six melanomas as a SMN were observed 3 years or more after the diagnosis of the first cancer; 0 among the 1215 patients treated in British centres and 6 among the 3,186 patients treated in French centres. No melanoma was observed in the family history of any of the 6 cases and 1 case belonged to a family affected by the Recklinghausen syndrome. The overall cumulative incidence of melanoma was 0.02% (standard deviation (S.D.) = 0.02%), 10 years after the diagnosis of the first cancer, 0.09% (S.D. = 0.05%), 20 years after and 0.4% (S.D. = 0.19%) 30 years after. From the general population, a total of 0.66 melanoma were expected in the cohort, yielding a SIR of 9.1 (95% CI: 3.6–18) for melanoma as a SMN. The mean AEI per 100 000 person-years of follow-up was 7.3 (95% CI: 1.7–17). When the time since the diagnosis of the first cancer was taken into account, the AEI was found to increase, but non-significantly ($P = 0.2$) (Table 1). All melanomas occurred after radiotherapy, two of which were also treated with chemotherapy. The SIRs for patients treated with radiotherapy alone and for patients treated with radiotherapy plus chemotherapy were 6.4 (95% CI: 1.1–20) and 21 (95% CI: 6.4–48) (Table 2), respectively.

Table 1
Occurrence of melanoma as a SMN in 4401 3-year survivors of a childhood cancer according to time since diagnosis

| Time since diagnosis (years) | PYR | Second malignant neoplasms (SMN) | | Annual incidence/100 000 persons (95% CI) | | | SIR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | Observed | Expected | Total | AEI | *P* for trend | |
| 3–9 | 31 583 | 1 | 0.09 | 3.2 (0.2–14) | 3.2 (0.2–14) | | 12 (0.7–51) |
| 10–19 | 20 242 | 2 | 0.23 | 9.9 (1.6–31) | 7.9 (0.3–28) | 0.2 | 8.8 (1.5–27) |
| 20–29 | 6838 | 3 | 0.25 | 44 (11–114) | 39 (6.2–109) | | 12 (3.0–31) |
| ⩾30 | 1380 | 0 | 0.09 | – | – | | |
| All | 60 043 | 6 | 0.66 | 10.0 (4.0–20) | 7.3 (1.7–17) | | 9.1 (3.6–18) |

PYR, person years at risk; AEI, annual excess incidence; SIR, standardised incidence ratio; 95% CI, 95% Confidence Interval.

### 3.2. Case–control study

The individual characteristics of the 16 subjects who developed a melanoma after a FMN are detailed in Table 3. 4 cases were males and 12 were females (Table 4). The site of melanoma was the trunk in 6 cases, lower limb in 6 cases, head in 3 cases and no site was mentioned for 1 case. The first cancer was a tumour of the central nervous system (CNS) (4 cases), a gonadal tumour (3 cases), a Wilms' tumour (2 cases), retinoblastoma (2 cases), Hodgkin's lymphoma (2 cases), soft-tissue sarcoma (1 case), neuroblastoma (1 case) and other cancer (1 case). The mean age at the first cancer was approximately 9 years in both cases and controls with a range of (1–18) and (0–19), respectively. The mean interval between the first cancer and the occurrence of melanoma was 18 years (range 4–30 years), and the mean age at which melanoma occurred was 27 years (range 16–44 years).

12 cases (75%) and 45 controls (60%) received radiotherapy as treatment for their first cancer. The beam energies used for the treatment of the first cancer were: Cobalt-60 gamma rays, high energy X-rays, low energy X-rays and electrons, the most frequent being Cobalt (8 cases and 24 controls treated). The mean local dose was 15.5 Gy for cases (range 0.03–51) and 3.1 Gy for controls (range 0–43) (Table 4). The local dose was missing for 2 cases and 3 controls: the melanoma site was missing for 1 case so no local dose was assessed for this patient and its 3 controls who received radiotherapy. It was not possible to estimate the radiation dose for the second case. Two melanomas were adjacent to the radiation fields (corresponding local doses were 8 and 14 Gy) and three were in the radiation fields (corresponding local doses were 37, 45 and 51 Gy). The risk of melanoma was found to be linked to the local radiation dose ($P = 0.05$), although this result was borderline significant. An increasing risk of melanoma was observed

Table 2
Occurrence of melanoma as a SMN in 4401 3-year survivors of a childhood cancer according to treatment

| Treatment | Patients | PYR | Second malignant neoplasms | | Annual incidence/100 000 persons (95% CI) | | SIR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | | Observed | Expected | Total | AEI | |
| No CTor RT | 399 | 7021 | 0 | 0.11 | – | – | – |
| RT alone | 1029 | 18 681 | 2 | 0.31 | 11 (1.8–33) | 8.7 (3.7–31) | 6.4 (1.1–20) |
| CT alone | 889 | 8698 | 0 | 0.05 | – | – | – |
| CT + RT | 2084 | 25 644 | 4 | 0.19 | 16 (4.8–36) | 12 (2.1–33) | 21 (6.4–48) |

CT, chemotherapy; RT, radiotherapy.

Table 3
Individual characteristics of 16 cases of melanoma in 4401 3-year survivors of a childhood cancer

| Sex | Cohort | Diagnosis of FMN | | | Treatment of FMN | | | | | Melanoma as a SMN | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Diagnostic group | Year | Age (years) | CT | RT | Beam quality | RT dose (Gy) | Mean fraction | Year | Age (years) | Site |
| M | N | Retinoblastoma | 1964 | 1 | No | No | | | 0 | 1987 | 24 | Scapula |
| M | N | Hodgkin's lymphoma | 1962 | 17 | Yes | Yes | O/C | 51 | 17 | 1985 | 40 | Scapula |
| M | N | Gonadal tumour | 1960 | 14 | No | Yes | C | 0.09 | 24 | 1990 | 44 | Scapula |
| F | N | Gonadal tumour | 1967 | 18 | No | Yes | C | 0.03 | 20 | 1983 | 34 | Foot |
| F | N | Gonadal tumour | 1963 | 13 | No | Yes | N.A. | N.A. | | 1986 | 37 | Iliac crest |
| F | N | CNS tumour | 1965 | 9 | No | No | | | 0 | 1988 | 32 | Tibia |
| F | N | Retinoblastoma | 1969 | 2 | No | No | | | 0 | 1989 | 22 | Femur |
| F | N | Others | 1970 | 6 | No | No | | | 0 | 1986 | 22 | Mouth |
| F | N | Hodgkin's lymphoma | 1967 | 13 | Yes | Yes | C/H/E | N.A. | 20 | 1975 | 21 | N.A. |
| F | N | Neuroblastoma | 1973 | 4 | Yes | Yes | H | 0.07 | 14 | 1989 | 20 | Femur |
| F | FB | Wilms' tumour | 1965 | 1 | Yes | Yes | O/C | 8.3 | 15 | 1990 | 27 | Rib |
| F | FB | CNS tumour | 1967 | 14 | No | Yes | H | 0.3 | 16 | 1979 | 26 | Knee |
| F | FB | Wilms' tumour | 1969 | 8 | Yes | Yes | C | 14 | 19 | 1991 | 30 | Rib |
| F | FB | Soft tissue | 1971 | 3 | No | Yes | E | 45 | 15 | 1992 | 25 | Eye |
| M | FB | CNS tumour | 1974 | 13 | No | Yes | C/E | 0.03 | 12 | 1978 | 17 | Foot |
| F | FB | CNS tumour | 1979 | 3 | No | Yes | C | 37 | 22 | 1991 | 16 | Eye |

FMN, first malignant neoplasm; M, male; F, female; N, Nordic cohort; FB, French and British cohort; C, cobalt-60 gamma rays; H, high energy X-rays; O, low energy X-rays; E, electrons; NA, not available; CNS, central nervous system.

specifically for local doses >15 Gy, OR = 13 (95% CI: 0.94–174) (Table 5). When patients who received 17 fractions or less were compared with those who received more than 17 fractions of radiotherapy, fractionation of the radiation dose was found to have no effect ($\chi^2 = 0.11$, $P = 0.7$).

5 cases (31%) and 13 controls (17%) received chemotherapy. Alkylating agents were administered to 3 cases and 7 controls, whereas 4 cases and 8 controls received spindle inhibitors (Table 4). As most of the patients received both types of drugs, we decided to investigate the relationships between the risk of melanoma as a SMN and a generated chemotherapy variable defined as follows: recipients of both alkylating agents and spindle inhibitors versus all other recipients of chemotherapy. The risk of melanoma was found to increase when both alkylating agents and spindle inhibitors were used, crude OR = 2.7 (95% CI: 0.5–14) and even after adjustment for the local radiation dose, adjusted OR = 2.0 (95% CI: 0.3–14), albeit non-significantly. An increasing

Table 4
Characteristics of cases and controls

| | Cases ($n = 16$) | Controls ($n = 75$) |
|---|---|---|
| Male | 4 (25%) | 18 (24%) |
| Age in years at first cancer, mean (min–max) | 8.7 (1–18) | 8.6 (0–19) |
| Year first cancer of diagnosed, mean (min–max) | 1968 (1960–1979) | 1968 (1958–1979) |
| Morphology of first cancer | | |
| Ewing's sarcoma | 0 | 2 |
| Other bone sarcomas | 0 | 3 |
| Soft tissue | 1 | 4 |
| Neuroblastoma | 1 | 3 |
| Wilms' tumour | 2 | 14 |
| CNS tumour | 4 | 20 |
| Retinoblastoma | 2 | 5 |
| Hodgkin's lymphoma | 2 | 8 |
| Non-Hodgkin's lymphoma | 0 | 2 |
| Gonadal tumour | 3 | 3 |
| Leukaemia | 0 | 4 |
| Others | 1 | 7 |
| Radiotherapy | 12 (75%) | 45 (60%) |
| Cobalt/high energy X-rays/low energy X-rays/electrons, no. of patients[a] | 8/3/2/3 | 24/12/12/3 |
| Fractions, mean (min–max) | 18 (12–24) | 17 (4–36) |
| Total duration in days, mean (min–max) | 68 (23–198) | 37 (2–83) |
| Local dose (Gy), mean (min–max) | 15.5 (0.03–51) | 3.1 (0–43) |
| Chemotherapy | 5 (31%) | 13 (17%) |
| Mol/m$^2$, mean (min–max) | 15 (0–35) | 150 (0–641) |
| Alkylating agents, no. of patients | 3 | 7 |
| Cyclophosphamide/procarbazine/mustine, no. of patients[b] | 2/2/2 | 6/2/1 |
| Mol/m$^2$, mean (min–max) | 15 (0–35) | 36 (0–129) |
| Spindle inhibitors, no. of patients | 4 | 8 |
| Vincristine/vinblastine, no. of patients | 3/1 | 7/1 |
| Mol/m$^2$, mean (min–max) | 0.03 (0–0.08) | 0.02 (0–0.09) |
| Topoisomerase II inhibitors, no. of patients | 2 | 7 |
| Inhibitors of nucleotide synthesis, no. of patients | 0 | 5 |
| Other drugs, no. of patients | 0 | 2 |

[a] Some patients were treated with more than one type of machine.
[b] Some patients received more than one of these drugs.

Table 5
Odds Ratio (OR) of melanoma as a function of the local radiation dose

| | Cases/controls | Mean dose in controls | Unadjusted OR (95% CI) | $P$ value |
|---|---|---|---|---|
| No RT | 4/33 | 0[a] | 1[a] | 0.05[b] |
| (0–1 Gy) | 5/29 | 0.16 | 1.4 (0.28–7.0) | |
| (1–15 Gy) | 2/6 | 1.4 | 3.2 (0.37–27) | |
| >15 Gy | 3/4 | 29 | 13 (0.94–174) | |
| Unknown dose 2/3 | | | | |

[a] Reference category.
[b] Likelihood ratio test for an exponential model with the dose as a continuous variable.

Table 6
Odds ratio (OR) of melanoma as a function of radiotherapy and chemotherapy

| | Cases/controls | OR (95% CI) |
|---|---|---|
| RT−CT− | 4/25 | 1[a] |
| RT−CT+ | 0/5 | – |
| RT+CT− | 7/37 | 1.2 (0.27–5.5) |
| RT+CT+ | 5/8 | 4.6 (0.84–25) |

[a] Reference category

risk of melanoma was observed when the OR associated with radiotherapy alone, OR = 1.2 (95% CI: 0.27–5.5) was compared with that associated with chemotherapy plus radiotherapy, OR = 4.6 (95% CI: 0.84–25) (Table 6). No significant interaction was found between chemotherapy (coded as yes/no) and the local radiation dose ($P = 0.19$).

3 cases and 3 controls were treated for a gonadal tumour as the first cancer. 5 of them had an ovarian tumour whose histological type was dysgerminoma in 4 cases and granulosa cell tumour in 1 case. One patient had an embryonal carcinoma in the testicle. Children treated for a gonadal tumour as a FMN were found to be at a higher risk of melanoma as a SMN, crude OR = 8.7 (95% CI: 0.9–86), and even after adjustment for the local radiation dose, adjusted OR = 5.5 (95% CI: 0.5–57), but this increasing risk was non-significant. In a logistic model including the local radiation dose, chemotherapy and the type of first cancer simultaneously, the local radiation dose was the only factor that had a significant impact on the risk of melanoma, adjusted OR = 1.07 (95% CI: 1.00–1.15) (Table 7).

## 4. Discussion

This cohort study demonstrated that the risk of developing melanoma after a childhood cancer is 9.1-fold higher in the French and British cohort (95% CI: 3.6–18) compared with that of the general population. This result confirms the excess of melanoma as a SMN, observed in the Childhood Cancer Survivor Study cohort [1] and in the Nordic cohort [10]. In the case–control study, the risk of melanoma was found to be linked to the local radiation dose ($P = 0.05$). An increasing risk of melanoma was observed for local doses >15 Gy, OR = 13 (95% CI: 0.94–174). Chemotherapy containing alkylating agents and spindle inhibitors and/or a gonadal tumour as a FMN were found to increase the risk of melanoma, but non-significantly. In the multivariate analysis, only the local radiation dose had a significant impact on the risk of melanoma, adjusted OR = 1.07 (95% CI: 1.00–1.15), although this result was borderline significant.

Table 7
Adjusted odds ratio (OR) of melanoma as a function of the type of first cancer, local radiation dose and chemotherapy

| | OR (95% CI) | *P* value |
|---|---|---|
| Local radiation dose (per Gy) | 1.07 (1.00–1.15) | 0.05 |
| Alkylating agent and spindle inhibitor (yes/no) | 2.6 (0.3–20) | 0.35 |
| Gonadal tumour (yes/no) | 6.4 (0.5–75) | 0.14 |

As all ultraviolet (UV)-induced injury to DNA may potentially be due to ionising radiation, logically ionising radiation could be expected to cause malignant melanoma. Until now, this issue has remained controversial and no clear-cut evidence has emerged [21]. Indeed, no excess of melanoma was linked to the radiation dose in the major radio-epidemiological studies published [22]. This is the first study to produce consistent evidence for a role of the radiation dose in the risk of malignant melanoma [23].

Concerning environmental exposure to radiation, two controversies persist. The first is to determine whether constitutional and/or occupational factors have contributed to an increase in the number of malignant melanomas observed among employees at the Laurence Livermore National Laboratory [24,25]. A recent study based on the National Dose Registry of Canada has refuelled the debate [26]. The second controversy concerns employees on flights. The epidemiological studies conducted over the last 20 years provide scant consistent evidence linking malignant melanoma to radiation exposures during air travel as it appears to be difficult to separate the potential carcinogenic effect of radiation from the effects of lifestyle in this sub-population [27].

Concerning the specific issue of melanoma as a SMN, two studies focused on this subject. Licata [28] failed to show an association between ionising radiation and an increasing risk of melanoma among 164 survivors of cutaneous T-cell lymphomas followed-up over 6 years on average; results were based on six melanomas. In 1996, Corpron and colleagues reported 11 cases of melanoma as a SMN after treatment of a childhood cancer, 4 of which developed in an irradiated field after treatment of their first malignancy [7].

Several studies have examined the effects of chemotherapy on the total number of benign naevi in children. In 1990, De Wit and colleagues showed that the median number of naevocytic naevi was significantly higher in children who had received chemotherapy for haematological malignancies when compared with their healthy siblings [29]. In 1993, Green and colleagues evidenced an association between treatment for childhood cancer and acral naevi and suggested that atypical naevi may also be associated with chemotherapy in childhood [30].

A recent study showed frequent involvement of the *p16* gene and confirmed the role of the *CDK4* gene as a

melanoma-predisposing gene in familial melanoma [31]. However, human hereditary malignant melanomas account for a very small percentage (<5%) of all the melanomas [32]. Little is known about the genetic factors that mediate susceptibility to, and the outcome of, sporadic malignant melanoma. Mechanisms which predispose to sporadic malignant melanoma in adolescence are probably different from those implicated in familial forms of the disease as only two of 147 Australian adolescents with malignant melanoma presented germline variants or mutations of *CDKN2A* [32].

In our study, we found that children treated for a gonadal tumour were at a higher risk of melanoma. This result confirms a previous finding concerning the excess of melanoma following germ cell tumours [33]. If mutations of *CDKN2A* may constitute an initial event in the development of ovarian carcinoma [34], the association of a gonadal tumour with melanoma observed in our study could be explained by an initial mechanism common to the two diseases. Hereditary retinoblastoma survivors have clearly been identified as being at a higher risk of melanoma. The excess of melanoma following retinoblastoma [35], is probably due to common aetiological factors between these two tumour types: the retinoblastoma protein (pRB) is phosphorylated by CDK4 and CDK6, the two target kinases of CDKN2A.

## 5. Conclusion

The results of this study suggest a potential contribution of radiotherapy and chemotherapy to the risk of melanoma as a SMN: melanoma may be radio-induced, but only at very high doses of low linear energy transfer (LET) radiation (>15 Gy). Given the small number of cases in our study, further studies, including pooled cohorts should be set up in order to confirm these preliminary results. Survivors of a childhood malignancy should be considered at risk for developing melanoma and suspicious pigmented lesions should be carefully evaluated. Our result concerning the increased risk of melanoma after a gonadal tumour need to be confirmed.

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## References

1. Neglia JP, Friedman DL, Yasui Y, *et al*. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *J Natl Cancer Inst* 2001, **93**, 618–629.
2. de Vathaire F, Hawkins M, Campbell S, *et al*. Second malignant neoplasms after a first cancer in childhood: temporal pattern of risk according to type of treatment. *Br J Cancer* 1999, **79**, 1884–1893.
3. Hawkins MM, Stevens MC. The long-term survivors. *Br Med Bull* 1996, **52**, 898–923.
4. Hoang MT, Eichenfield LF. The rising incidence of melanoma in children and adolescents. *Dermatol Nurs* 2000, **12**, 183–188.
5. Karlsson P, Boeryd B, Sander B, Westermark P, Rosdahl I. Increasing incidence of cutaneous malignant melanoma in children and adolescents 12–19 years of age in Sweden 1973–92. *Acta Derm Venereol* 1998, **78**, 289–292.
6. Socie G, Curtis RE, Deeg HJ, *et al*. New malignant diseases after allogeneic marrow transplantation for childhood acute leukaemia. *J Clin Oncol* 2000, **18**, 348–357.
7. Corpron CA, Black CT, Ross MI, *et al*. Melanoma as a second malignant neoplasm after childhood cancer. *Am J Surg* 1996, **172**, 459–461.
8. Baird EA, McHenry PM, MacKie RM. Effect of maintenance chemotherapy in childhood on numbers of melanocytic naevi. *Br Med J* 1992, **305**, 799–801.
9. Bataille V, Bishop JA, Sasieni P, *et al*. Risk of cutaneous melanoma in relation to the numbers, types and sites of naevi: a case-control study. *Br J Cancer* 1996, **73**, 1605–1611.
10. Olsen JH, Garwicz S, Hertz H, *et al*. Second malignant neoplasms after cancer in childhood or adolescence. Nordic Society of Paediatric Haematology and Oncology Association of the Nordic Cancer Registries. *Br Med J* 1993, **307**, 1030–1036.
11. Menegoz F. *Le Cancer en France: Incidence et Mortalité. Situation en 1995. Evolution entre 1975 et 1995*. Paris, France, Reseau FRANCIM, 2000.
12. Office for National Statistics. *Cancer 1971–1997* [CDROM]. London, Office for National Statistics, 1999.
13. Breslow NE, Day NE. *Statistical Methods in Cancer Research. Volume II—The Design and Analysis of Cohort Studies. IARC Science Publication 82*. Geneva, IARC, 1987 1–406..
14. Preston DL, Lubin JH, Pierce DA. *EPICURE User's Guide*. Seattle, WA, USA, Hirosoft International Corporation, 1993.
15. Garwicz S, Anderson H, Olsen JH, *et al*. Second malignant neoplasms after cancer in childhood and adolescence: a population-based case-control study in the 5 Nordic countries. The Nordic Society for Pediatric Hematology and Oncology. The Association of the Nordic Cancer Registries. *Int J Cancer* 2000, **88**, 672–678.
16. Breslow NE, Day NE. *Statistical Methods in Cancer Research. Volume I—The Analysis of Case–Control Studies. IARC Science Publication 32*. Genova, IARC, 1980 5–338.
17. Shamsaldin A, Grimaud E, Hardiman C, Diallo I, de Vathaire F, Chavaudra J. Dose distribution throughout the body from radiotherapy for Hodgkin's disease in childhood. *Radiother Oncol* 1998, **49**, 85–90.
18. Gagnon WF, Horton JL. Physical factors affecting absorbed dose to the skin from cobalt-60 gamma rays and 25-MV x rays. *Med Phys* 1979, **6**, 285–290.
19. Starkschall G, St George FJ, Zellmer DL. Surface dose for megavoltage photon beams outside the treatment field. *Med Phys* 1983, **10**, 906–910.
20. Jackson W. Surface effects of high-energy X rays at oblique incidence. *Br J Radiol* 1971, **44**, 109–115.
21. Shore RE. Radiation-induced skin cancer in humans. *Med Pediatr Oncol* 2001, **36**, 549–554.
22. Ron E, Preston DL, Kishikawa M, *et al*. Skin tumor risk among atomic-bomb survivors in Japan. *Cancer Causes Control* 1998, **9**, 393–401.

23. Boice JD Jr, Day NE, Andersen A, *et al*. Second cancers following radiation treatment for cervical cancer. An international collaboration among cancer registries. *J Natl Cancer Inst* 1985, **74**, 955–975.
24. Austin DF, Reynolds P. Investigation of an excess of melanoma among employees of the Lawrence Livermore National Laboratory. *Am J Epidemiol* 1997, **145**, 524–531.
25. Moore DH, Patterson HW, Hatch F, *et al*. Case-control study of malignant melanoma among employees of the Lawrence Livermore National Laboratory. *Am J Ind Med* 1997, **32**, 377–391.
26. Sont WN, Zielinski JM, Ashmore JP, *et al*. First analysis of cancer incidence and occupational radiation exposure based on the National Dose Registry of Canada. *Am J Epidemiol* 2001, **153**, 309–318.
27. Boice Jr. JD, Blettner M, Auvinen A. Epidemiologic studies of pilots and aircrew. *Health Phys* 2000, **79**, 576–584.
28. Licata AG, Wilson LD, Braverman IM, Feldman AM, Kacinski BM. Malignant melanoma and other second cutaneous malignancies in cutaneous T-cell lymphoma. The influence of additional therapy after total skin electron beam radiation. *Arch Dermatol* 1995, **131**, 432–435.
29. de Wit PE, de Vaan GA, de Boo TM, Lemmens WA, Rampen FH. Prevalence of naevocytic naevi after chemotherapy for childhood cancer. *Med Pediatr Oncol* 1990, **18**, 336–338.
30. Green A, Smith P, McWhirter W, *et al*. Melanocytic naevi and melanoma in survivors of childhood cancer. *Br J Cancer* 1993, **67**, 1053–1057.
31. Soufir N, Avril MF, Chompret A, *et al*. Prevalence of p16 and CDK4 germline mutations in 48 melanoma-prone families in France. The French Familial Melanoma Study Group. *Hum Mol Genet* 1998, **7**, 209–216.
32. Youl P, Aitken J, Hayward N, *et al*. Melanoma in adolescents: a case-control study of risk factors in Queensland, Australia. *Int J Cancer* 2002, **98**, 92–98.
33. Avril MF, Chompret A, Verne-Fourment L, *et al*. Association between germ cell tumours, large numbers of naevi, atypical naevi and melanoma. *Melanoma Res* 2001, **11**, 117–122.
34. Shigemasa K, Hu C, West CM, *et al*. p16 overexpression: a potential early indicator of transformation in ovarian carcinoma. *J Soc Gynecol Investig* 1997, **4**, 95–102.
35. Eng C, Li FP, Abramson DH, *et al*. Mortality from second tumors among long-term survivors of retinoblastoma. *J Natl Cancer Inst* 1993, **85**, 1121–1128.