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Risk of melanoma following adulthood cancer: A case-control study

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Abstract

Melanoma is a severe skin cancer related to sun exposure. Whether this malignancy is linked to exposure to ionising radiation during adulthood is still controversial. This case-control study examined the risk of melanoma following treatment for an adulthood first malignant neoplasm (FMN). Cases were patients who presented with cutaneous melanoma after a first cancer in adulthood. Controls (3 per case) were patients free of melanoma, matched for age, duration of follow-up since the FMN, type of FMN, and followed in the same institution. A total of 57 cases and 171 controls were included. In the final multivariate analysis, no risk of melanoma was associated with radiotherapy (odds ratio (OR) for 1 Gy = 1.01, 95% confidence interval (95%CI) 0.96–1.07) nor hormonotherapy, whereas chemotherapy use (OR = 2.3, 95%CI 0.93–5.6) and having a history of familial cancer (OR = 2.8, 95%CI 1.3–5.9) exhibited a nearly significant risk. In conclusion, unlike the evidence for risk of exposure to ionising radiation during childhood, we did not substantiate a risk for association of melanoma with exposure to ionising radiation during adulthood. The risk associated with chemotherapy should justify the implementation of skin surveillance for early detection of melanoma in these patients.

Keywords: Melanoma; Neoplasms, second primary; Neoplasms, radiation-induced; Anti-neoplastic combined chemotherapy protocols

1. Introduction

In European populations, cutaneous melanoma is the solid tumour with the highest increase in incidence over the past two decades. Risk factors for melanoma include both constitutional and environmental factors. Exposure to intense and repeated ultraviolet (UV) radiation is considered to be the main environmental risk factor for developing melanoma [1]. The melanoma risk associated with non-UV radiation is less clear. Controversial data have emerged from several investigations among the Lawrence Livermore Laboratory employees [2–4] about environmental radiation and the risk of melanoma.

Whether melanoma risk is increased in immunocompromised patients is still controversial [5,6]. The risk may vary according to the cause and duration of immunodeficiency. However, there is evidence that chemotherapy does increase the number of nevi in children [7,8], as does immunodeficiency in adults [9].

We recently demonstrated in a cohort study that chemotherapy, especially with spindle cell inhibitors and alkylating agents, and radiotherapy to treat a first malignant neoplasm increases the subsequent risk of melanoma in children [10].

As cutaneous melanoma is easily detectable by clinical screening, it is of importance further to assess

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melanoma risk in adults treated for a first malignant neoplasm (FMN), in order to offer these patients lifelong surveillance and screening. We report the results of a retrospective cohort study analysing the melanoma risk as a second malignant neoplasm (SMN) associated with radiotherapy and chemotherapy for a FMN.

2. Patients and methods

2.1. Selection of patients

A total of 66 patients were registered in the computerised records of Gustave Roussy Institute as having developed a cutaneous melanoma between 1977 and 1999 as a SMN following an adulthood FMN. Of these, 9 were excluded from the study, 2 because their melanoma occurred less than 6 months after FMN diagnosis, 2 because they had a history of malignancy before the 'first' malignancy was recorded and 5 because no usable medical record was available. Hence, a total of 57 cases were included in the case-control study.

2.2. Case-control study

Each of the 57 patients who developed a malignant melanoma as a SMN was matched with 3 controls randomly extracted from the records of Gustave Roussy Institute. The matching criteria were sex, age at first cancer (±3 years) and type of FMN. Controls had to be followed-up over a period of at least equal to the interval between the first cancer and melanoma of the matched case. This period was defined as the follow-up period.

2.3. Medical record extraction

Medical records of all cases and controls were scrutinised and data extracted. Pre-defined registration forms for FMN information were completed by specialised investigators blinded for case/control status. The diagnoses of FMN and SMN were verified and the site and 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.

Chemotherapy agents were classified into five drug categories: electrophilic agents and related compounds, spindle inhibitors, inhibitors of nucleotide synthesis, topoisomerase II inhibitors and other drugs. The dose of each drug received by each case or control either as initial treatment or for recurrences of the first cancer were summed-up over the follow-up period.

Radiotherapy files were scrutinised for relevant data. First the location of the melanoma area for each case, and a similar area for each matched control was determined, in order to ascertain the radiation doses received in these areas, whatever the treated volume. Patients and their radiotherapy beam arrangements were simulated using Dos_EG software [11]. 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 to establish correction factors from tissue doses to skin doses [12–14]. 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 Dos_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.

2.4. Statistical methods

Conditional logistic regression was used to analyse the risk of malignant melanoma as a function of radiation, chemotherapy and hormonotherapy [15]. The significance of various parameters was tested by comparing nested models using likelihood ratio tests. SAS® V8.2 and Epicure software [16] were used.

3. Results

The individual characteristics of the 57 cases regarding the FMN are presented in Table 1 (with the same percentages for the 171 controls). The FMN involved

Table 1
Characteristics of the first malignant neoplasm (FMN) in the 57 cases

First cancer characteristics	Cases($n = 57$)	
	n	%
Year first cancer diagnosed		
Mean (min–max)	1984 (1971–1996)	
Age at first cancer (years)		
Mean (min–max)	49 (17–80)	
Gender (female)	63	36
Type of first cancer		
Breast	21	37
Uterus	10	18
ENT	6	11
Lymphoma	6	11
Thyroid	4	7
Skin	3	5
Testis	3	5
Miscellaneous	4	7

ENT, ear-nose-throat.

the breast (37%), uterus (18%), ear, nose and throat (ENT) (11%), lymph nodes (11%), thyroid (7%), skin (epidermoid carcinoma 5%), testis (5%) and miscellaneous other organs (7%). The mean age at FMN diagnosis was 49 years in both cases and controls, with a range of 17–80 and 14–80 years, respectively. Melanoma occurred on average 8 years after FMN diagnosis (range 1–26 years), at an average age of 56 years (range 19–85 years). The site of melanoma was the head and neck in 7 cases, upper limb in 11 cases, lower limb in 18 cases and trunk in 21 cases (Fig. 1). Other characteristics of melanomas are presented in Table 2.

A total of 41 cases (72%) and 120 controls (70%) had received radiotherapy for treatment of their first cancer. The majority had received external beam therapy, i.e. cobalt-60 γ-rays, high-energy X-rays, low-energy X-rays or electrons, the most frequent being high-energy X-rays (Table 3). Twenty-four percent of the patients had received brachytherapy or 131-iodine. The local dose was not estimable for 5 cases and 13 controls, mainly because part or all of the radiotherapy was not performed in our institute or because the technical records of radiotherapy were missing. Among patients who received radiotherapy and for whom the radiation dose could be estimated, the mean local dose was 5.4 Gy for cases (range 0.005–48 Gy) and 4.6 Gy for controls (range 0.001–47 Gy). The risk of melanoma was found not to be linked to the local radiation dose ($P = 0.8$) (Table 4), this result remaining the same when restricting the analysis to the melanoma occurring 5 years or more after radiotherapy ($P = 0.9$) and when adjusting for chemotherapy ($P = 0.8$) (Table 4). The average excess of relative risk per Gy to the skin was estimated to be 0.014 (95% confidence interval (95%CI) – 0.03–0.07). No interaction between dose–response for radiation and the type of FMN was evidenced (test for interaction, $P > 0.7$ whatever the FMN).

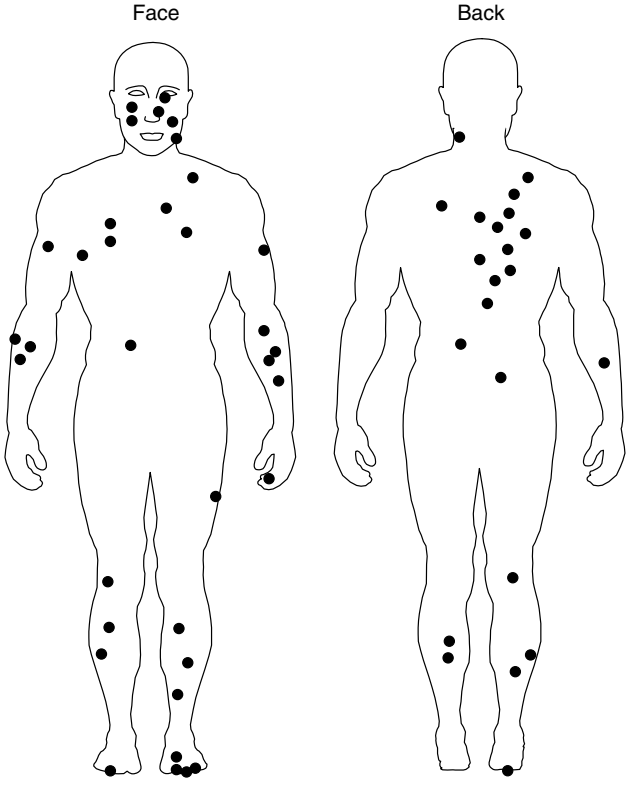

Fig. 1. Localisation of melanomas in the 57 cases.

Table 2
Characteristics of melanoma as a second malignant neoplasm (SMN)

Melanoma characteristics	Cases ($n = 57$)
Year of diagnosis	
Mean (min–max)	1991 (1977–1998)
Age at diagnosis of melanoma (years)	
Mean (min–max)	56 (19–85)
Delay elapsed since first cancer (years)	
Mean (min–max)	8 (1–26)
Histological subtype	% (*n*)
Superficial spreading	53 (30)
Nodular	28 (16)
Acral lentiginous	5 (3)
Lentigo maligna	4 (2)
Not classifiable	11 (6)
UICC stage at diagnosis	% (*n*)
I	84 (48)
II	14 (8)
III	2 (1)
Breslow index (mm)	
Mean (min–max)	1.5 (0–10)

UICC, International Union Against Cancer.

Twenty cases (35%) and 48 controls (26%) had received chemotherapy. As a whole, chemotherapy administration was associated with an odds ratio (OR) of 1.7 (95%CI 0.8–3.7) of melanoma, which remained stable (OR = 1.8, 95%CI 0.6–5.3) when the analysis was restricted to melanomas which occurred more than 5 years after FMN. When adjusting for local dose of radiation, hormonotherapy and familial history of melanoma, the risk associated with the administration of chemotherapy almost reached significance (OR = 2.3, 95%CI 0.93–5.6), whether or not the analysis was restricted to melanomas which occurred more than 5 years after FMN. No significant interaction was found between chemotherapy and the local radiation dose effect, or between those of chemotherapy and hormonotherapy. None of the individual drugs were significantly associated with melanoma in multivariate analysis, either in frequency of use (Table 5), or in dose used, except for vinblastine which was used slightly more in cases than in controls (OR = 48.1, 95%CI 0.8–79) after adjusting for the other drugs.

Seven cases (12%) and 24 controls (14%) were given hormonotherapy for their FMN. Hormonotherapy had been given for breast cancer in 27 patients and for prostate cancer in four. Twenty-five received anti-oestrogens, 4 received anti-androgens and 7 received lutein-

Table 3
Characteristics of the 57 cases of melanoma and 171 controls

First cancer treatment	Cases ($n = 57$)	Controls ($n = 171$)
Surgery	84% (48)	82% (141)
Chemotherapy	35% (20)	28% (48)
Electrophilic agents	90% (18)	94% (45)
Spindle inhibitors	55% (11)	56% (27)
Topo-isomerase II inhibitors	80% (16)	71% (34)
Inhibitors of nucleotide synthesis	55% (11)	60% (29)
Radiotherapy	72% (41)	70% (120)
External beam radiotherapy	78% (32)	76% (91)
Low-energy X-rays, cobalt, high-energy X-rays, electrons	14%, 36%, 68%, 50%	0%, 51%, 64%, 51%
Missing information	3	9
Local dose of radiation (Gy) mean (min–max)	7.3 (0.005–48)	5.9 (0.006–47)
Fractions; mean (min–max)	29 (6–66)	32 (10–70)
Total duration (days); mean (min–max)	60 (14–188)	55 (14–112)
Brachytherapy	17% (7)	18% (21)
Missing information	2	3
Local dose of radiation (Gy) mean (min–max)	0.4 (0.02–0.8)	1.7 (0.001–23)
131-iodine	5% (2)	7% (8)
Missing information	0	1
Cumulative activity (mCi) mean (min–max)	127 (4–250)	159 (1–700)
Combined radiotherapy (RT) and chemotherapy (CT)		
No RT no CT	21% (12)	22% (37)
RT no CT	44% (25)	50% (86)
CT no RT	7% (4)	8% (14)
RT CT	28% (16)	20% (34)
Hormonotherapy	12% (7)	14% (24)
Anti-oestrogens	11% (6)	11% (19)
Duration (months)		
Mean (min–max)	23 (4–42)	36 (1–138)
Others	4% (2)	3% (5)

Table 4
Odds ratio (OR) of melanoma as a function of the local radiation dose

Local radiation dose[a] (Gy)	Cases/controls	Mean dose in controls (Gy)	Unadjusted OR (95%CI)	Unadjusted OR (95%CI), > years of follow-up	Adjusted[c] OR (95%CI)
0	12/48	0	1[b]	1[b]	1[b]
0–1	23/72	0.2	1.3 (0.5–3.3)	1.5 (0.4–4.0)	2.8 (0.9–8.7)
1–5	3/12	2.7	0.9 (0.2–4.5)	0.3 (0.02–6.0)	1.4 (0.2–8.2)
5–20	4/10	10.8	1.4 (0.3–6.1)	0.7 (0.08–5.7)	1.8 (0.4–8.5)
>20	3/12	28.2	0.8 (0.1–6.1)	0.4 (0.03–4.3)	0.8 (0.1–4.8)
Unknown	8/14	–	1.7 (0.5–6.0)	0.8 (0.2–4.0)	3.3 (0.7–15.5)

CI, confidence interval.
[a] Radiation dose to the site of the melanoma or the corresponding site of the matched controls.
[b] Reference category.
[c] Adjusted for familial history of melanoma (yes/no) and for administration of chemotherapy (yes/no) and hormonotherapy (yes/no).

ising hormone-releasing hormone (LHRH) analogues. Median duration of hormonotherapy was 32 months (range 4–67) and 29 months (range 1–138), respectively, in cases and controls. Neither hormonotherapy use ($P = 0.4$) nor duration of hormonotherapy ($P = 0.5$) was associated with melanoma.

A familial history of cancer was mentioned for 23 cases (40%) and 42 controls (25%). Among 103 first-degree relatives with a history of cancer, the main sites were breast (36%), digestive tract (23%), urological (10), pulmonary (8%), ear-nose-throat (7%), uterus (7%), and others (11%). A familial history of cancer was a risk factor for developing melanoma as a SMN (OR = 2.4, 95%CI 1.2–5.0), such an history being associated with a risk of melanoma of (OR = 2.8, 95%CI 1.3–5.9) when adjusting for treatments (Table 6). No interaction was evidenced between a history of familial cancer and any of the treatments.

The risks associated with local radiation dose, chemotherapy, hormonotherapy and familial history of cancer were similar in the 29 strata of patients who were more than 50 years at first cancer diagnosis and in the 28 ones of younger patients, respectively, *P*-values between 0.3 and 0.5 for all interaction tests. The role of these fac-

Table 5
Chemotherapy received by 57 cases melanoma as SMN and 171 controls

	Cases				Controls				Crude estimates		Adjusted estimates	
	n	%	Mean dose (mg)	(min–max)	*n*	%	Mean dose (mg)	(min–max)	OR	(95%CI)	OR	(95%CI)
Electrophilic agents	18	32			45	26			1.5	(0.7–3.6)		
Bleomycin	3	5	213	(75–325)	8	5	158	(15–400)	1.3	(0.2–9.1)		
Caryolysine	1	2	56	(56–56)	7	4	64	(20–100)				
Dacarbazine	2	4	2200	(1700–2700)	3	2	6917	(500–15,000)	3.0	(0.3–36)		
Cyclophosphamide	16	28	6681	(2400–19,200)	33	19	7496	(43–24,850)	2.5	(0.9–6.5)	1.2	(0.2–6.3)
Procarbazine	1	2	850	(850–850)	8	5	9138	(2400–20,100)				
Platinum	5	9	870	(480–1450)	10	6	1064	(100–4650)	1.9	(0.5–7.2)		
Topoisomerase II inhibitors	16	28			34	20			2.2	(0.9–5.4)		
Actinomycine	2	4	5254	(8–10,500)	3	2	11,500	(4500–19,500)				
Adriamycine	14	25	369	(120–540)	28	16	452	(40–960)	2.5	(0.9–6.8)	1.9	(0.4–10.6)
Epirubicine	1	2	440	(440–440)	2	1	525	(480–570)	1.7	(0.1–31)		
VP16	2	2	1800	(900–2700)	9	5	2782	(640–6300)	0.6	(0.1–3.3)		
Spindle inhibitors	11	19			27	16			1.7	(0.5–5.3)		
Vinblastine	5	9	103	(16–294)	5	3	78	(50–120)	9.8	(1.1–90)	8.1	(0.8–79.1)
Vincristine	7	12	10	(6–18)	25	15	14	(3–40)	0.6	(0.2–2.4)		
Vindesine	1	2	9	(9–9)	3	2	43	(16–88)	1.0	(0.1–9.6)		
Inhibitors of nucleotide synthesis	11	19			29	17			1.3	(0.5–3.7)		
5-fluorouracil	7	12	4086	(2700–5100)	20	12	15,048	(600–109,600)	1.1	(0.3–3.4)		
Aracytine	2	4	1850	(1600–2100)	4	2	13,350	(120–22,600)	3.0	(0.2–48)		
Methotrexate	4	7	267	(23–600)	12	7	1197	(16–6475)	1.0	(0.2–6.3)		

Table 6
Risk factors of melanoma as a SMN

Risk factor	Relative risk of melanoma	
	Crude OR (95%CI)	Adjusted OR[a](95%CI)
Familial history of melanoma (yes/no)	2.4 (1.2–5.0)	2.8 (1.3–5.9)
Local radiation dose (+1 Gy)	1.02 (0.97–1.07)	1.01 (0.96–1.07)
Chemotherapy (yes/no)	1.7 (0.8–3.7)	2.3 (0.93–5.6)
Hormonotherapy (yes/no)	0.7 (0.2–2.7)	0.3 (0.13–1.9)

OR, odds ratio.
[a] Adjusted for the others factors in the table.

tors in the risk of subsequent melanoma were similar in males ($n = 21$) and females ($n = 36$), in patients who developed a melanoma of Breslow less than 1 mm ($n = 28$) and in those with a Breslow of 1 mm or more ($n = 23$), this last information being unknown for six patients.

4. Discussion

In this case-control study, we analysed whether the treatment for a FMN could be a risk factor for developing cutaneous melanoma. Chemotherapy administration and familial history of cancer appear to be significant risk factors for developing a subsequent melanoma, while neither radiotherapy nor hormonotherapy were evidenced to increase the risk of melanoma as a SMN.

One of the potential drawbacks of the study design is overmatching, as cases and controls were matched not only for sex, age at FMN, date of FMN and duration of follow-up, but also for FMN type. However, we chose to match for FMN type, because the dose range for radiotherapy and doses of chemotherapy agents seemed to be large enough (due to occurrence of relapses) to demonstrate differences between cases and controls. Non-matching for FMN type could have led to associations to the FMN type rather than focusing on radiotherapy and chemotherapy characteristics. Secondly, constitutional factors (skin complexion, hair colour, number and type of nevi) are known essential risk factors for developing cutaneous melanoma; these subject characteristics were not available in medical records for controls, and therefore could not be studied jointly with FMN treatment characteristics.

Although exposure to ultraviolet (UV) radiation is considered the main environmental risk factor for melanoma, the wavelengths responsible for tumour formation are still unknown. The risk of developing melanoma associated with environmental ionising radiation is controversial and no clear-cut evidence has emerged [17]. As melanoma incidence is low, especially in Asian people, information from cancer surveillance registries of atomic bomb survivors is of lesser interest than for other malignancies [18]. Whether melanoma risk can be linked to ionising radiation in the workplace during adulthood is still controversial [2–4,19], as the effects of lifestyle are difficult to take into account. Lastly, data from surveillance of airline cabin crews are also

controversial regarding risk of melanoma due to occupational exposure. A significantly increased risk of melanoma among pilots and aircrew has been found in most epidemiological studies [20–27]. Although exposure to the sun is higher in flight attendants than in the general population, this difference has been investigated in only one study, which failed to evidence a substantial difference [28]. Thus, respective aetiological responsibilities of increased recreational sun exposure and occupational exposure to ionising radiation needs further investigation.

In this context, studies dedicated to second malignant neoplasm in people treated with radiation for a FMN can provide relevant information. Melanoma was not found in excess after radiotherapy for cervical cancer [29]. Our study adds further data favouring the absence of an association between exposure to ionising radiation during adulthood and risk of cutaneous melanoma. We were able to estimate precisely the skin radiation dose at the site of melanoma and compare this with the radiation dose received at the same site in a control population.

By contrast, in children treated for a FMN, we previously demonstrated a ninefold (95%CI 3.6–18) increase in melanoma risk compared with the general population and this risk was found to be linked to the high local radiation dose [10]. However, because of ongoing development in children, the baseline risk for any type of second malignancy in children and in adults are very different. Of note, even for melanoma occurring during adulthood, evidence from epidemiological studies favours the hypothesis of UV-induced damage occurring in childhood [1].

The effects of chemotherapy during adulthood on melanoma development had previously never been questioned. In our study, we demonstrated a link between the use of chemotherapeutic agents and subsequent melanoma development, which persisted after adjustment for familial cancer history and other treatments used for the FMN. This modest increase in risk was close to statistical significance and should be noted. No specific drug was found to account for this risk, although the subgroup of patients who had received vinblastine for their FMN exhibited a higher risk, which was close to significance. However, owing to the possibility of chance findings, the very low number of patients in this subgroup, the absence of risk for other drugs of the same class, and the absence of specific biological rational accounting for this finding, this association should not be over-interpreted. Chemotherapy has been demonstrated to increase the number of nevi, which represent the melanocytic benign counterpart of melanoma [7,8]. In adults, long-term immunosuppression has also been demonstrated to be linked with a larger number of nevi [9]. Whether these treatments truly increase the number of nevi or only accelerate a genetically programmed development of nevi during childhood and adulthood is unknown. As melanoma is relatively easy to detect, our results suggest that cancer patients treated with chemotherapy should have their skin regularly examined in order to detect the occurrence of melanoma.

In conclusion, the results of this case-control study on the risk of melanoma after radiotherapy and chemotherapy treatment are twofold: we did not find evidence of an increased risk of melanoma related to radiotherapy and the risk associated with chemotherapy justifies the implementation of skin surveillance in order to detect melanoma early in these patients.

Conflict of interest statement

None declared.

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References

1. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B* 2001, **63**, 8–18.
2. 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.
3. Donald WM, Moore DN, Seward JP, *et al*. Cancer incidence rates among Lawrence Livermore National Laboratory (LLNL) employees: 1974–1997. *Am J Ind Med* 2004, **45**, 24–33.
4. 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.
5. Jensen P, Hansen S, Moller B, *et al*. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol* 1999, **40**, 177–186.
6. Lindelof B, Sigurgeirsson B, Gabel H, *et al*. Incidence of skin cancer in 5356 patients following organ transplantation. *Br J Dermatol* 2000, **143**, 513–519.
7. de Wit PE, de Vaan GA, de Boo TM, *et al*. Prevalence of naevocytic naevi after chemotherapy for childhood cancer. *Med Pediatr Oncol* 1990, **18**, 336–338.
8. Green A, Smith P, McWhirter W, *et al*. Melanocytic naevi and melanoma in survivors of childhood cancer. *Br J Cancer* 1993, **67**, 1053–1057.
9. Grob JJ, Bastuji-Garin S, Vaillant L, *et al*. Excess of nevi related to immunodeficiency: a study in HIV-infected patients and renal transplant recipients. *J Invest Dermatol* 1996, **107**, 94–697.
10. Guerin S, Dupuy A, Anderson H, *et al*. Radiation dose as a risk factor for malignant melanoma following childhood cancer. *Eur J Cancer* 2003, **39**, 379–2386.
11. Shamsaldin A, Grimaud E, Hardiman C, *et al*. Dose distribution throughout the body from radiotherapy for Hodgkin's disease in childhood. *Radiother Oncol* 1998, **49**, 85–90.

12. 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.
13. Jackson W. Surface effects of high-energy X-rays at oblique incidence. *Br J Radiol* 1971, **44**, 109–115.
14. Starkschall G, St George FJ, Zellmer DL. Surface dose for megavoltage photon beams outside the treatment field. *Med Phys* 1983, **10**, 906–910.
15. Breslow NE, Day NE. Statistical methods in cancer research. Volume I – the analysis of case-control studies. *IARC Sci Publ*, 5–338.
16. Preston DL, Lubin JH, Pierce DA. *EPICURE User's guide*. Seattle, WA, Hirosoft International Corporation, 1993.
17. Shore RE. Radiation-induced skin cancer in humans. *Med Pediatr Oncol* 2001, **36**, 549–554.
18. Ron E, Preston DL, Kishikawa M, *et al*. Skin tumor risk among atomic-bomb survivors in Japan. *Cancer Causes Control* 1998, **9**, 393–401.
19. 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.
20. Boice Jr JD, Blettner M, Auvinen A. Epidemiologic studies of pilots and aircrew. *Health Phys* 2000, **79**, 576–584.
21. Ballard T, Lagorio S, De Angelis G, *et al*. Cancer incidence and mortality among flight personnel: a meta-analysis. *Aviat Space Environ Med* 2000, **71**, 216–224.
22. Rafnsson V, Tulinius H, Jonasson JG, *et al*. Risk of breast cancer in female flight attendants: a population-based study (Iceland). *Cancer Causes Control* 2001, **12**, 95–101.
23. Reynolds P, Cone J, Layefsky M, *et al*. Cancer incidence in California flight attendants (United States). *Cancer Causes Control* 2002, **13**, 317–324.
24. Langner I, Blettner M, Gundestrup M, *et al*. Cosmic radiation and cancer mortality among airline pilots: results from a European cohort study (ESCAPE). *Radiat Environ Biophys* 2004, **42**, 247–256.
25. Blettner M, Zeeb H, Auvinen A, *et al*. Mortality from cancer and other causes among male airline cockpit crew in Europe. *Int J Cancer* 2003, **106**, 946–952.
26. Pukkala E, Aspholm R, Auvinen A, *et al*. Cancer incidence among 10,211 airline pilots: a Nordic study. *Aviat Space Environ Med* 2003, **74**, 699–706.
27. Zeeb H, Blettner M, Langner I, *et al*. Mortality from cancer and other causes among airline cabin attendants in Europe: a collaborative cohort study in eight countries. *Am J Epidemiol* 2003, **158**, 35–46.
28. Linnersjo N, Hammar B, Dammstrom G, *et al*. Cancer incidence in airline cabin crew: experience from Sweden. *Occup Environ Med* 2003, **60**, 810–814.
29. Boice Jr JD, 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.