Eur J Dermatol 2012; 22(2): 225-30

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Article accepted on 12/18/2011

Head and neck basal cell carcinoma prevalence in individuals submitted to childhood X-ray epilation for tinea capitis treatment

Background: A higher prevalence for basal cell carcinoma (BCC) has been associated with radiation, namely with tinea capitis epilation treatment. *Objective:* To evaluate the prevalence of head and neck basal cell carcinoma (BCC) and to identify the major risk factors for BCC in individuals irradiated in childhood for tinea capitis treatment. *Methods:* We clinically observed 1,308 individuals from an original cohort of 5,356 irradiated between 1950 and 1963, registering previous skin lesions excisions and proposing for surgery all the suspicious lesions detected. In 585 participants, 47 with BCC, the skin pigmentation was measured. *Results:* The overall prevalence of BCC was 8.0% and of multiple BCC was 2.4%. Both total (14.7%) and multiple BCC (6.6%) were significantly more common in the individuals who had received a higher radiation dose. Multiple BCC was more prevalent (3.7%) in younger irradiated individuals and total BCC (9.4%) in women. Participants with BCC and without BCC presented similar skin pigmentation. *Conclusion:* Younger age at irradiation, higher dose and female gender increased the risk of developing BCC in these irradiated individuals.

Key words: basal cell carcinoma, scalp irradiation, scalp ringworm, skin pigmentation, tinea capitis, X-ray epilation

doi:10.1684/ejd.2012.1670

Tinea capitis is a fungal disease that reached epidemic proportions in the 1950s and 1960s in Portugal, similarly to other European countries [1]. As there was no oral antifungal treatment available at that time, radiation-induced epilation was used as an efficient method for tinea capitis treatment and eradication [2, 3]. This procedure, performed according to the Kienbock-Adamson method, was considered, at that time, as theoretically without risks [2]. After epilation it was easier to apply the sulphur ointment and iodine tincture that were the advised therapeutic procedures [2].

Basal cell carcinoma (BCC) is the most common skin cancer [4, 5] and a higher prevalence has been associated with radiation [6], namely with the tinea capitis epilation treatment [7-9]. It is the most frequent tumour developing on irradiated scalps [10]. An increase in BCC risk with increased radiation dose has been observed [7] and an inverse association between age at exposure and BCC risk has also been referred [11, 12]. Radiation-induced BCC is more aggressive and more prone to recurrence so these patients should be under close observation [9]. Furthermore the risk for BCC is persistently elevated 40 or more years after the first treatment [12, 13].

We had access to the registries of these treatments performed between 1950 and 1963 in the Dispensário de Higiene Social do Porto (DHSP), an institution dedicated to infectious diseases that is now closed. These registries included name, address, age, treatment date, tinea diagnosis and dose received. Most of the patients were children. Having in mind the association above referred between the radiation treatment they experienced and BCC, we decided to perform a clinical follow-up study of these individuals in order to detect these neoplasias. Our primary objectives in the present work were to evaluate the prevalence of BCC and to identify the major correlates of BCC in these individuals.

Material and methods

The DHSP files included 5,356 individuals submitted to radiation-induced epilation between 1950 and 1963 and it was possible to trace 3,522 (66%). This registration included name, address (at the time of the treatment), age, treatment date, tinea diagnosis and dose received. The majority of the individuals were 6-15 years old (70%), which reflects the scholar inspections done at the time to diagnose the disease. The standard treatment was carried out according to the Kienbock-Adamson technique [2] using one X-ray epilation session (325-400 R), but 6% of the individuals were submitted to 2 or 3 sessions. Their present addresses were obtained by checking the entire cohort in the Portugal Telecom (National Phone Company) website and in National Health Service databases. A letter was sent to all the individuals for whom a presumed present address was found, informing them about the treatment they had been submitted to and inviting them to contact us. A free

To cite this article: Boaventura P, Oliveira R, Pereira D, Soares P, Teixeira-Gomes J. Head and neck basal cell carcinoma prevalence in individuals submitted to childhood X-ray epilation for tinea capitis treatment. *Eur J Dermatol* 2012; 22(2): 225-30 doi:10.1684/ejd.2012.1670

phone line was provided for that purpose. A second letter was sent whenever the first received no reply. Of the 3,522 presumably traced individuals, 1,308 agreed to be clinically observed (participants) and 287 were deceased. The clinical examination took place between March 2006 and November 2010. It included a summarized clinical history and a detailed examination of the head and neck areas in order to detect suspicious skin lesions. Skin colour (tanned/untanned) was registered. In 585 participants, 47 with BCC, the melanin contents on the inner arm and on the forehead were measured with a DermaSpectrometer. A cervical ultrasound and a serum calcium measurement were also suggested (data not shown).

All the BCC lesions were confirmed through hospital or cancer registries (RORENO data base). A copy of the histological report of the excised lesions was requested from the pathology departments or directly from the patients. Using the information available in the histopathological reports, the following histological subtypes were considered: nodular BCC, superficial BCC, infiltrative BCC and basosquamous BCC [14, 15].

In the statistical analysis, prevalence estimates for each outcome were compared using chi-squared tests, with p-values <0.05 considered significant for each survey. We used logistic regression to explore the determinants taking BCC/multiple BCC as the dependent variable and the risk factors as independent variables. These analyses tested whether the prevalence of BCC increased (p values <0.05 were considered statistically significant), taking into account the risk factors. Analyses of the BCC data were conducted using PASW Statistics for Windows (release 18.0; IBM®, SPSS® Statistics).

All the procedures were done under strict ethical and confidentiality procedures according with the Portuguese ethical rules. The study was approved by the Ethics Committee of the Hospital Pedro Hispano and all the participants signed an informed consent.

Results

The main characteristics of participants and total cohort individuals have been reported elsewhere [16]. There was a significant difference towards younger age at time of irradiation between participants and cohort members. This may be due to the long delay between the irradiation and the actual contact, which in some situations was more than 50 years. More of the individuals who were older at the time of irradiation may have deceased, are more frequently ill, or simply are less likely to come to a clinical observation after such a long time since irradiation. There was also a significant difference towards more women between participants and cohort members. A possible explanation is that women may be more likely to come to the clinical observation as they are more concerned about their health than men [17]. The mean age of participants (±standard deviation) was 58.4 years (±4.4) (median=58).

We clinically observed 1,308 individuals from the original cohort, among whom 75 already had a BCC diagnosis. In our clinical observation, 146 participants presented suspicious undiagnosed head and neck lesions that were proposed for surgical excision, but only 87 had surgery *(table 1)*. The remaining 59 had no surgery or biopsy for the reasons presented in *Table 1*. Of the 87 lesions excised, 35 were BCCs; 29 represented new BCC patients diagnosed by us, the other 6 had already had a previous BCC excision. Considering the retrospective and prospective evaluation of BCC lesions, we had 104 participants with BCC diagnosis, 30 men and 74 women. Concerning the number of lesions, 73 participants had only one BCC; and the other 31 had multiple lesions (30%). Among participants with multiple BCCs, 19 had two tumours, 5 had three and 7 participants had four or more, leading to a total number of 165 BCC lesions in 104 participants. The mean number of lesions per patient was 1.82. We also observed 4 participants with squamous cell carcinoma (SCC), previously diagnosed, and three with melanomas (one diagnosed in the present study). One hundred and fifty-nine BCCs (96.4%) were localized on the head or neck. Ninety-nine BCCs developed on areas considered to be protected from the sun (scalp and trunk) (70.2%) and 42 on areas considered as exposed to it (face and neck) (29.8%), and for 24 cases the precise head or neck localization could not be determined. We could obtain 86 histological reports that presented information on the histological subtype *(table 2)*. The other 79 BCCs were classified as "not defined", as the histological report did not present information about the subtype or was not available. The most common subtypes were nodular (46.5%) and superficial (38.4%). Nodular subtype was more common in sun-exposed areas when compared to the other subtypes, but the differences were not significant. Univariate analysis for gender, age at irradiation, age at diagnosis, irradiation dose, untanned/tanned skin (phototypes II and III), melanin content, tinea diagnosis variables was conducted but no significant association was found with BCC subtype.

The overall prevalence of BCC (95%CI) was 8.0% (4.8-8.6) and of multiple BCC (95%CI) was 2.4% (1.6-4.1). The mean age at excision of the first lesion (±SD) was 54.3 years (±8.2). Univariate analysis for gender, age at irradiation,

Table 1. Results from the 146 suggested excisions of skin lesions

	N	(%)
Performed	87	(59.6)
Malignant tumour	37	(25.3)
• BCC	35	(24.0)
• Melanoma	1	(0.7)
• Palate malignant tumour	1	(0.7)
Benign tumour	46	(31.5)
• Actinic keratosis	1	(0.7)
• Trichoblastoma	1	(0.7)
• Trichoepithelioma	3	(2.1)
• Nevi/papillomas/traumatic lesions/seborreic keratosis	41	(28.1)
Not sent for histological analysis	4	(2.7)
Not Excised	59	(40.4)
• Lesion disappeared	4	(2.7)
• Patient refused excision	11	(7.5)
• Different medical opinion	17	(11.6)
• Waiting list for surgery	11	(7.5)
• Without information	16	(11.0)

Table 2. BCC subtype distribution according to gender, age at diagnosis, localization and BCC frequency

	Nodular n (%)	Superficial n (%)	Infiltrative n (%)	Basosquamous n (%)	Not defined	Total
Gender						
• Men	12 (50)	9 (37.5)	1 (4.2)	2 (8.3)	16	40
• Women	28 (45.2)	24 (38.7)	6 (9.7)	4 (6.5)	63	125
Age at diagnosis (mean ± SD)	54.7 ± 8.6	53.1 ± 9.1	57.0 ± 4.5	52.8 ± 9.4	52.6 ± 8.7	54.3 ± 8.2
Localization						
• Sun-protected area	25 (42.4)	24 (40.1)	6 (10.2)	4 (5.4)	40	99
• Sun-exposed area	11 (55.0)	6 (30.0)	1 (5.0)	2 (10.0)	22	42
• Not determined	4 (57.1)	3 (42.9)	0	0	17	24
BCC frequency						
• Single BCC	18 (42.9)	16 (38.1)	5 (11.9)	3 (7.1)	31	73
• Mutiple BCC	22 (50.0)	17 (38.6)	2 (4.5)	3 (6.8)	48	92
All	40 (46.5)	33 (38.4)	7 (8.1)	6 (7.0)	79	165

Table 3. Total BCC and multiple BCC prevalence and odds ratio (OR) in the 1308 participants according to gender, age at irradiation and irradiation dose

		Prevalence (%)	(% $CI_{95\%}$)	OR	(OR $CI_{95\%}$)	p-value
Total BCC						
Gender	• M	5.7	(1.2-10.2)			
	• F	9.4	(3.7-15.1)	**1.71**	(1.11-2.66)	**0.015**
Age at irradiation	• ≤5 years	8.9	(3.3-14.5)	1.21	(0.80-1.83)	0.378
	• >5 years	7.5	(2.3-12.7)			
Irradiation dose	• 325-400 R	7.5	(2.3-12.7)			
	• ≥630 R	14.7	(7.7-21.7)	**2.08**	(1.06-4.09)	**0.029**
Multiple BCC						
Gender	• M	1.5	(0.0-5.9)			
	• F	2.9	(0.0-8.9)	1.94	(0.87-4.39)	0.101
Age at irradiation	• ≤5 years	3.7	(0.0-10.5)	**2.24**	(1.1-4.57)	**0.023**
	• >5 years	1.7	(0.0-7.9)			
Irradiation dose	• 325-400 R	2.1	(0.0-7.3)			
	• ≥630 R	6.6	(0.0-15.5)	**3.25**	(1.21-8.71)	**0.013**

age at diagnosis, irradiation dose, untanned/tanned skin (phototypes II and III), melanin content, and tinea diagnosis variables was conducted and significant association was found concerning gender, age at irradiation and irradiation dose and BCC presence *(table 3).* No significant differences were found when multivariate analysis was performed. BCC was significantly more prevalent in women (9.4%) than in men (5.7%), with an increased risk to develop a BCC in women, OR (95% CI) of 1.72 (1.11-2.66). We found a significantly higher total BCC and multiple BCC prevalence in the participants who received a dose ≥630 R, (14.5% and 6.6% respectively) when compared to the ones who received the 325-400 R dose, (7.5% and 2.1% respectively). The participants who received a higher dose were more likely to develop a BCC OR (95% CI) of 2.08 (1.06-4.09), and more likely to develop a multiple BCC OR (95% CI) of 3.25 (1.21-8.71). The individuals irradiated at a younger age were more likely to develop multiple BCC, OR (95% CI) was 2.24 (1.10-4.57). The mean latency period for lesion excision was 47.2 years (±7.3). No significant differences were found in this latency period considering age at irradiation, irradiation dose and gender.

The majority of the participants were classified as phototypes II and III. Melanin content in unexposed (inner arm) and exposed (forehead) areas was similar in the participants who developed BCC when compared to the ones who did not develop BCC *(table 4),* showing normal distributions in both groups *(figure 1).*

Discussion

Radiation has been associated with a high prevalence of BCC [7-9]. In the present study we found a BCC prevalence of 8.0% in individuals irradiated in childhood for tinea capitis epilation treatment. Data concerning the prevalence of BCC in asymptomatic non-irradiated cohorts are scarce but present a low prevalence, ranging from 0.1% to 0.9% [18-20]. In previous studies, using only retrospective data, scalp irradiation for tinea capitis during childhood resulted in a 3.6 to 4 fold increased risk of BCC [7, 12]. In our study, if we consider only the BCCs previously diagnosed, the rate of BCC was 5.7%, a value that can be considered similar

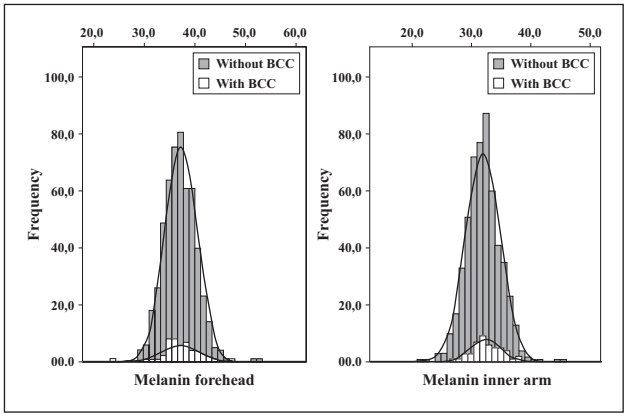

Figure 1. Melanin content distribution in the inner arm and in the forehead.

Table 4. Melanin content in the inner arm and the forehead of participants with BCC or without BCC

		Mean	(SD)	N	(%)
Total BCC					
Inner arm	With lesion	32.1	(2.5)	47	(8.0)
	Without lesion	32.0	(2.9)	538	(92.0)
Forehead	With lesion	37.4	(3.7)	47	(8.0)
	Without lesion	37.1	(3.1)	536	(92.0)
Multiple BCC					
Inner arm	With lesion	31.7	(2.7)	14	(2.0)
	Without lesion	32.0	(2.9)	571	(98.0)
Forehead	With lesion	37.8	(3.1)	14	(2.0)
	Without lesion	37.1	(3.2)	569	(98.0)

SD: Standard Deviation; N: Count

to the one found in the previous retrospective studies of similar cohorts referred above. In a small control group we are gathering (73 individuals to date; data not shown) constituted by age-matched, non-irradiated persons submitted to the same clinical protocol as the irradiated individuals, no suspicious skin lesions were found. Nevertheless, as we have only observed 24% of the entire cohort (1,308/5,356) we cannot exclude a bias towards clinically observing more individuals with BCC, although 28% of the BCC cases were diagnosed by us in participants totally unaware of their problem. A bias in opposite direction (observing fewer BCCs than the ones really present) could also be present, due to the fact that 40% of the proposed skin lesion excisions were not performed. The mean age at excision of the first lesion found in our study, 54 years, (similar for both genders), was lower than the 64-65 years referred in previous non-irradiated cohorts (of 10,000-200,000 individuals [20, 21]), but in accordance with the younger ages (39-56 years) found in other tinea capitis irradiated cohorts [10, 22-24]. The mean latency period for lesion excision in the present study was 47 years. Maalej *et al*. [24] found a shorter latency period (36 years) in a similar tinea capitis cohort, defining the latency period as the time between irradiation and cancer occurrence. In our study we considered the latency period between irradiation and surgery, as it was not easy to be certain about the time of the cancer appearance. When excision was advised in our clinical observation, some patients referred to having lesions for several years. A shorter latency period was also referred in younger irradiated tinea capitis patients [11, 25]. We did not find any significant differences in the latency period considering age at irradiation, irradiation dose and gender.
The most common BBC lesion was the nodular subtype (46.5%), followed by the superficial subtype (38.4%). In other studies from non-irradiated individuals, nodular subtype was found to be the more common histological subtype, although with variable prevalence – 45 to 78% [21, 26-28]. The value obtained in our series was similar to the one referred in the Hakverdi *et al*. [27] study but it was smaller than the values referred in the other studies. On the contrary, we had a higher prevalence of the superficial subtype. As the superficial subtype has been considered by several authors as high risk, due to its more aggressive behaviour [14, 15], we supposed that this higher prevalence found in our study could be associated with the X-ray treatment. This is in accordance with our observation that the nodular subtype was more common in sun-exposed areas when compared to the other subtypes, although the differences were not significant. However, in the Mseddi *et al*. [8, 10] studies of tinea capitis irradiated patients, the superficial type was not mentioned while the nodular subtype appeared in 74-76% of their cases. We cannot exclude, in our series, a possible bias due to the fact that the histological subtype was not defined in 47.9% of cases.
Higher radiation dose significantly increased BCC prevalence in our study *(table 3)* as would be expected. Karagas *et al*. [13] found an association between a history of radiation treatment and BCC that was particularly strong for BCCs arising within the radiation treatment field. Ron *et al*. [7] showed a dose response for BCC in their tinea capitis irradiated cohort. They also suggested that subsequent exposure to UV radiation would likely play a role in the expression of radiation-induced BCC [7].
Pigmentation characteristics, tendency to sunburn, and poor tanning ability, have all been associated with higher BCC risk [29, 30] although few studies have found epidemiological evidence. In our study we did not find a statistically significant association of these putative BCC risks factors since skin pigmentation and melanin content (non-exposed and exposed areas), were similar between the participants who developed BCC when compared to the ones who did not develop BCC. Although it was not possible to enrol all the participants in the skin melanin content analysis, the very similar values obtained for participants with BCC *vs* participants without BCC indicate that this similarity will probably be maintained if we extend the analysis to all the participants. Taken together, these results also indicate that irradiation is a much stronger risk factor that masks the eventual (lower) risk given by skin pigmentation. The similar distribution pattern of melanin content found in the two groups leads us to suggest that, in this tinea capitis irradiation setting, skin pigmentation has minimal influence on BCC risk and that there is no additive or synergistic effect with irradiation.
We found that the odds ratio for multiple BCC, but not total BCC, was significantly elevated for younger age at radiation. For total BCC, the OR increase was not statistically significant. Irradiation at young ages has been shown by

other authors as increasing BCC risk [7, 12, 13], especially if radiation occurred in early childhood [7, 12]. Multiple BCC has been referred as more common in the BCC patients who suffered childhood scalp irradiation for tinea capitis treatment [9] and maybe considered as an index of individual susceptibility [12]. So we could argue that, in our study, the younger-irradiated children were more susceptible to the more aggressive form of the radio-induced lesion, multiple BCC. Multiple BCC was observed in the present study in 30% of the patients, a value roughly similar to the 38% found by Shore *et al*. [12] in tinea capitis irradiated individuals and much higher than the 16% found by Scrivener *et al*. [21] in their cohort of 10,245 non-irradiated BCC patients.

Incidence rates for BCC have been reported to be similar in both genders [20], higher in men [5] or higher in women [21]. Ron *et al*. [7], in their tinea capitis irradiated cohort, found a BCC relative risk for females slightly higher than for males, but without reaching significance. In our study, total BCC was significantly more common in women when compared to men and that still holds true if we consider only the previously diagnosed BCCs, suggesting that women show a higher susceptibility for BCC development in this setting. Considering multiple BCC, the prevalence for women remained higher than for men, but was no longer significant (p=0.101), possibly due to the lower figures of multiple BCC (n=31). As more than half of the lesions found in women in our study (54%) were present on the face and neck, we may speculate that women were more prone to having them removed, not only for health reasons, but also for aesthetic reasons.

Concerning skin malignancies other than BCC, we found 4 SCCs, previously diagnosed, and 3 melanomas, one diagnosed by us. The low figures obtained in our study for these lesions do not allow us to have a clear "picture". Nevertheless, Karagas *et al*. [6] initially suggested that exposure to therapeutic radiation was associated with BCC but not with SCC, and lately they have shown that early exposure to radiation treatment was a risk factor for SSC but not as strong as for BCC [13]. Shore *et al*. [12] found no association between ionizing radiation exposure and cutaneous malignant melanoma.

In summary, due to the high BCC prevalence found in these Portuguese tinea capitis irradiated individuals, and showing a higher risk for multiple BCCs in the younger irradiated ones, those who are younger at the present moment, we believe that this justifies a close follow-up of this cohort. This tumour, although causing low mortality, carries considerable morbidity [31]. We agree with Meibodi *et al*. [22], that it is very important to create awareness in these tinea capitis irradiated individuals and to refer them to their physician for any suspicious lesions, namely the dermatological ones. ■

Disclosure. *Acknowledgments: We want to thank Prof. Sobrinho Simões for the valuable suggestions. The authors thank Ana Reis for proofreading. Gratefulness is also due to all the individuals that agreed to participate in this study as well as to all the physicians that provided us clinical information.*

Prize ACS-MERCK SERONO in Cancer Epidemiology, 2010

Financial support: This work was supported by a grant from Calouste Gulbenkian Foundation (ref. 76636) and FCT (project: PIC /IC /83154 /2007) and further funding from the Portuguese Foundation for Science and Technology (FCT), by a grant to P.B. (SFRH /BPD /34276 /2007). IPATIMUP is an Associate Laboratory of the Portuguese Ministry of Science, Technology and Higher Education and is partially supported by the FCT. The work was conducted with the support of Public Health Department of ARS-Norte.

Conflict of interest: none.

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