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FULL PAPER

Cancer incidence after childhood irradiation for tinea capitis in a Portuguese cohort

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Objectives: Our aim was to compare cancer incidence in a cohort exposed in childhood (1950–63) to a therapeutic dose of radiation in the North of Portugal and followed-up until the end of 2012, with the incidence rates for the same age and sex in the general population.

Methods: A population-based North Region cancer registry (RORENO) was used to assess which members of the cohort developed cancer. The association between radiation exposure and overall and specific cancer sites was evaluated using standardised incidence ratios (SIR).

Results: Over the full follow-up period, 3357 individuals of the 5356 original tinea capitis (TC) cohort (63%) were retrieved in the RORENO, and 399 new cancer cases were identified, representing an increased risk of 49% when compared with the general population (SIR = 1.49; 95% CI: 1.35–1.64). The risk was slightly higher in males than in females (SIR = 1.65; 95% CI: 1.43–1.89 vs SIR = 1.35; CI = 1.17–1.55). The risk was slightly higher in the individuals exposed to a higher radiation dose (SIR = 1.78; 95% CI: 1.22–2.51 for ≥ 630 R vs SIR = 1.46; 95% CI: 1.31–1.62

for 325–475 R). In females, there was an excess cancer risk in all cancers with the higher radiation dose (SIR = 2.00; 95% CI: 1.21–3.13 for ≥ 630 R vs SIR = 1.30; 95% CI: 1.11–1.51 for 325–475 R) which was not observed in males, and for combined dose categories significantly raised SIRs for thyroid and head and neck cancer, suggesting a possible higher radiosensitivity of females. An increased risk was also observed for some cancers located far from the irradiated area.

Conclusions: The results suggest an association between radiation exposure and later increased cancer risk for cancers located near the radiation exposed area, mainly thyroid, and head and neck cancers. Further studies are necessary to disentangle possible non-radiation causes for distant cancers increased risk.

Advances in knowledge: This paper shows a possible association between childhood X-ray epilation and increased risk of cancer which was not previously investigated in the Portuguese TC cohort.

INTRODUCTION

Exposure to ionising radiation has been associated with cancer development, particularly for childhood exposure and for high doses of radiation.^{1,2} At low radiation doses, the situation is less clear and the lowest dose of x-radiation or γ -radiation for which there is good evidence of increased cancer risk has not been established.³

In occupationally exposed cohorts, such as the Chernobyl emergency workers, Kashcheev *et al*⁴ reported an increase in cancer incidence not accompanied by a concomitant increase in mortality. Contrarily, Akleyev *et al*⁵ did not find

strong evidence that chronic low-dose-rate exposure of the embryo and foetus increased solid cancer risk in childhood or adulthood. Wang *et al*⁶ found a significantly increased cancer risk in medical diagnostic X-ray workers, for breast and oesophageal cancers.

Considering medical or accidental exposures, similar results have been observed. Pauwels *et al*⁷ found an increased breast cancer risk resulting from mammography biennial screening. Eisenberg *et al*⁸ found increased cancer risk resulting from radiation exposure during cardiac imaging. Contrarily, Siegel *et al*⁹ did not find credible

evidence of imaging-related low-dose (<100 mGy) carcinogenic risk.

Other studies have demonstrated dose-related increased risks of cancers such as thyroid, breast, brain, non-melanoma skin cancer and leukaemia, with greatest risks for children irradiated early in life.¹⁰

Given this uncertainty about long-term side-effects of low-dose radiation exposure, we have attempted to assess cancer incidence in the Portuguese tinea capitis (TC) cohort.¹¹ These individuals have been exposed to X-ray scalp epilation in childhood¹² and showed an increased frequency of thyroid and basal cell carcinomas,^{12,13} as previously reported in other TC cohorts.^{14–16} The estimated doses received were as follows: on the scalp (4.8 Gy),¹⁴ bone marrow (4 Gy),¹⁷ brain (1.4–1.5 Gy),^{17,18} but lower in other organs such as skin of the face and neck (0.1–0.5 Gy),¹⁹ thyroid (0.045–0.495 Gy),^{15,17} parathyroid (0.39 Gy)²⁰ and breast (0.016 Gy).²¹

The aim of this study was to evaluate if the TC cohort presented an increased risk of developing cancer when compared with the general population.

SUBJECTS AND METHODS

Subjects

The TC scalp epilation cohort ($n = 5356$) was retrieved from the cases recorded at the former *Dispensário Central de Higiene Social do Porto* (DCHSP), between 1950 and 1963. Former studies accomplished with this cohort aimed at conducting an active search of its members. Briefly, we contacted by postal mail all the individuals whose addresses could be found by cross-linking our database with several address containing data bases (*e.g.*, phone book, hospitals and healthcare centres); addresses were retrieved for three-quarters of the cohort (74.6%). From these, 1369 individuals were clinically observed between 2006 and 2012. The clinical observation consisted of screening for skin and thyroid

cancer, all performed by the same physician.^{11,12} Other 448 individuals have in the meantime passed away.

In the present study, further attempts to identify the TC cohort elements were performed. All individuals who were not already unequivocally identified were manually searched in the National Health Service database (Portuguese acronym: RNU). This database has national coverage and all residents in the country must be registered on it in order to have access to the National Health Service care. After death, information on each deceased user is kept on the database. The search on the database was made using name and date of birth. In the cases where no date of birth was available, an age interval was used based on the age at irradiation. For some individuals of the cohort, we did not obtain precise information on age and/or they had very common names, so it was not possible to unequivocally identify the full cohort ($n = 1999$, 37.3% not identified). Demographic and radiation-related characteristics of included ($n = 3357$) and excluded ($n = 1999$) individuals are compared in Table 1.

In order to assess which individuals of the cohort developed cancer during the follow-up period (1991 to 2012), the cohort database was linked with the North Region of Portugal Cancer Registry (RORENO) database. The RNU individual identification number was used as unique key to link both databases. For cases identified in the RORENO database, topographic cancer site, histology and date of diagnosis were retrieved.

We excluded from this analysis squamous and basal cell skin carcinomas as RORENO data completeness on these tumour types was not guaranteed. The follow-up period defined for TC cohort individuals was January 1991 to December 2012, because the RORENO registry began in 1991 and 2012 corresponded to the last RORENO update at the time of the present study. Individuals who had deceased before 1991 were excluded.

Table 1. Demographic data of cohort members, found and not found in the Portuguese National Health Service database (RNU – Registo Nacional de Utentes)

Variable	Individuals found in RNU		Individuals not found in RNU		<i>p</i> -value
	<i>n</i>	%	<i>n</i>	%	
Total ($n = 5356$)	3357	62.7	1999	37.3	
Gender					
Male	1539	45.8	1016	50.8	<0.001
Female	1818	54.2	983	49.2	
Age at irradiation					
<5 year-old	596	17.8	319	16.0	0.099
≥5 year-old	2761	82.2	1680	84.0	
Irradiation dose					
325–475 R	3129	93.2	1873	93.7	0.676
≥630 R	203	6.0	115	5.8	
Unknown	25	0.7	11	0.6	

RORENO is a population-based regional cancer registry. It covers the North region of Portugal, the area of residence of most of the cohort members. Routine demographic and clinical data are collected in accordance with the Portuguese privacy policy and with approval of the Portuguese Data Protection Authority. Individual patient consent is not required for the registry data. Patient anonymity is maintained by data coding and the access to information is allowed for research purposes.

Data analysis

The association between X-ray epilation treatment and the incidence of all cancer types combined and specific types of cancer individually was evaluated using standardised incidence ratios (SIR).²² The expected number of cancer cases was obtained considering the TC cohort had the same age, sex and calendar year-specific cancer incidence rates as the general population. These rates were calculated based on the information registered in the population-based registry (RORENO). For each individual and calendar year, the person-time at risk was considered as the time between first January of that year and date of death or end of year. Since RORENO database includes multiple tumours, they have been also considered for the TC cohort individuals. SIR was obtained by dividing the observed number of cases in the TC cohort by the expected number of cases. The confidence interval associated with the SIR was calculated by applying the Wilson and Hilferty²³ approximation for chi-square percentiles.

To assess the possibility of an excess cancer risk introduced by our clinical observation (started in 2006), the data analysis was divided into two periods: January 1991–December 2005 and January 2006–December 2012. Additionally, we also divided the total cohort into two groups: previously clinically observed individuals, as described above, ($n = 1369$), and not observed individuals, ($n = 1988$). SIR for specific cancer types were calculated for total follow-up period (1991–2012) to prevent losing statistical power, except for thyroid cancer which was actively diagnosed during the 2006–2012 period.¹²

RESULTS

A significantly higher number of females was observed in the TC group of individuals tracked in the National Health Service database (RNU) comparing with the ones that were not tracked (Table 1) (54.2% vs 49.2%, $p < 0.001$). No significant differences were observed between the two groups concerning age at irradiation and radiation dose ($p = 0.099$ and $p = 0.676$, respectively).

The SIRs for cancer in the periods 1991–2005, 2006–2012 and in the full follow-up period are presented in Table 2. These results were stratified by gender and by clinically observed vs clinically non-observed patients.

Over the entire follow-up period (22 years), 399 new cancer cases were identified. An increased risk of developing any type of cancer was observed for the TC cohort, with SIRs ranging from 1.27 to 1.68 in the two periods evaluated (Table 2). In males, the increase in cancer risk was significant in both periods, but slightly higher in 2006–2012 (SIR = 1.55 and SIR = 1.73, for the former and latter periods, respectively). In females, a significant increased risk was observed in 2006–2012 (SIR = 1.64; 95% CI: 1.35–1.97) but not in 1991–2005 (SIR = 1.08; 95% CI: 0.86–1.34).

To evaluate if there was an excess risk for the individuals exposed to a higher radiation dose (due to a epilation treatment repetition whenever the hair did not fall as expected), we divided the group by radiation dose, cancer site and gender; the entire period was considered due to the small number of cases receiving a higher dose (Table 3). A slight increased risk for any cancer was observed when the dose received was ≥ 630 R comparing with a 325–475 R dose (SIR = 1.78; 95% CI: 1.21–2.51 vs SIR = 1.46; 95% CI: 1.31–1.62), which was more evident in females (SIR = 2.00; 95% CI: 1.22–3.13 vs SIR = 1.30; 95% CI: 1.11–1.51). In males no significant increase was observed, comparing with the general population, for the ≥ 630 R group. When stratifying by different cancer types, the only significant increase observed was

Table 2. Standardised incidence ratios (SIR) and 95% CIs of cancer by gender and period

Variable	1991–2005			2006–2012			1991–2012		
	n	SIR	95% CI	n	SIR	95% CI	n	SIR	95% CI
Total patients ($n = 3357$)									
Male	80	1.55	1.23–1.93	125	1.73	1.44–2.06	205	1.65	1.43–1.89
Female	81	1.08	0.86–1.34	113	1.64	1.35–1.97	194	1.35	1.17–1.55
Total	161	1.27	1.08–1.48	238	1.68	1.48–1.91	399	1.49	1.35–1.64
Observed Patients ($n = 1369$)									
Male	15	0.86	0.48–1.41	52	1.91	1.43–2.51	67	1.50	1.16–1.90
Female	38	1.17	0.83–1.60	59	1.87	1.43–2.42	97	1.51	1.23–1.85
Total	53	1.06	0.79–1.38	111	1.89	1.56–2.28	164	1.51	1.29–1.76
Non-observed Patients ($n = 1988$)									
Male	65	1.90	1.47–2.42	73	1.61	1.26–2.03	138	1.74	1.46–2.05
Female	43	1.02	0.73–1.37	54	1.44	1.08–1.88	97	1.21	0.99–1.48
Total	108	1.41	1.16–1.70	127	1.54	1.28–1.83	235	1.48	1.29–1.68

Table 3. Standardised incidence ratios (SIR) and 95% CIs of cancer by radiation dose, site and gender

Cancer site	325–475 R			≥630 R			Unknown
	n	SIR	95% CI	n	SIR	95% CI	n
Total cancers (<i>n</i> = 3332)							
Male	190	1.65	1.43–1.90	13	1.53	0.81–2.62	2
Female	173	1.30	1.11–1.51	19	2.00	1.21–3.13	2
Total	363	1.46	1.31–1.62	32	1.78	1.22–2.51	4
Head and Neck (C00–C14) ^a							
Male	14	1.45	0.79–2.44	1	1.52	0.02–8.46	0
Female	7	3.87	1.55–7.98	0	-	-	0
Total	21	1.84	1.14–2.81	1	1.28	0.02–7.12	0
Stomach (C16)							
Male	23	1.73	1.10–2.60	2	2.10	0.24–7.60	0
Female	10	1.21	0.58–2.23	1	1.73	0.02–9.64	0
Total	33	1.53	1.06–2.15	3	1.96	0.39–5.74	0
Colorectal (C18–C20)							
Male	22	1.31	0.82–1.98	0	-	-	0
Female	20	1.42	0.87–2.20	3	2.84	0.57–8.30	0
Total	42	1.36	0.98–1.84	3	1.29	0.26–3.77	0
Lung (C33–C34)							
Male	32	2.05	1.40–2.90	3	2.58	0.52–7.55	1
Female	4	0.92	0.25–2.36	0	-	-	0
Total	36	1.81	1.26–2.50	3	2.03	0.41–5.92	1
Breast (C50)							
Female	43	0.88	0.63–1.18	3	0.88	0.18–2.56	0
Prostate (C61)							
Male	31	1.96	1.33–2.78	2	1.51	0.17–5.46	0
Thyroid (C73)							
Male	8	4.16	1.79–8.19	0	-	-	0
Female	36	2.75	1.93–3.81	4	4.65	1.25–11.9	2
Total	44	2.93	2.13–3.94	4	4.05	1.09–10.4	2
Leukaemia (C91–C95, D45–D47)							
Male	2	0.95	0.11–3.43	1	6.62	0.09–36.8	0
Female	5	2.38	0.77–5.55	0	-	-	0
Total	7	1.66	0.67–3.43	1	3.32	0.04–18.5	0

ICD10 – International Classification of Diseases 10th Revision: head and neck (ICD10: C00–C14), stomach (ICD10: C16), colorectal (ICD10: C18–C20), lung (ICD10: C33–C34), breast (ICD10: C50), prostate (ICD10: C61), thyroid (ICD10: C73) and leukaemia (IC10: C91–C95, D45–D47)

^aIncludes lip, oral cavity and pharynx

for thyroid, either considering the whole group, or only females (SIR = 4.05 vs SIR = 4.65) as no males who received ≥630 R developed thyroid cancer (Table 3).

Differences were also perceived when analysing observed and non-observed individuals separately. In both the observed and non-observed groups, there was a statistically significant increased risk of developing cancer compared with the general

population. In the observed group: SIR = 1.51 (95%CI: 1.29–1.76) and in the non-observed group SIR = 1.48 (95%CI: 1.29–1.68). When analysing the risk stratified by period of observation, in the observed group the SIR was only significantly higher for the later period 2006–2012 (SIR = 1.89; 95% CI: 1.56–2.28), while in the non-observed group there was a significant increased risk in both periods (Table 2).

Figure 1. Number of observed cancer cases and standardised incidence ratios (SIR) by cancer site.

We calculated SIRs for head and neck (ICD10—International Classification of Diseases 10th Revision: C00-C14), stomach (ICD10: C16), colorectal (ICD10: C18-C20), lung (ICD10: 34), breast (ICD10: C50), prostate (ICD10: C61), thyroid cancer (ICD10: C73) and leukaemia (ICD10: C91-C95, D45-D47), for all the follow-up period (Figure 1) (Table 4). For thyroid cancer, SIRs were further stratified by period and age-group at irradiation (Table 5). Other cancers were studied, such as brain tumours but, due to small figures, they were not included in the tumour site stratification.

Increased risks were observed for all the cancer sites evaluated, with the exception of breast cancer, colorectal cancer and leukaemia. Some differences between cancer sites according to gender were observed. Head and neck cancer showed an increased risk for females (SIR = 3.60; 95% CI: 1.44–7.42) but not for males; stomach cancer showed an increased risk for males (SIR = 1.75; 95% CI: 1.13–2.58) but not for females; lung cancer showed also an increased risk for males (SIR = 2.14; 95% CI: 1.50–2.96) but not for females. For thyroid cancer the increased risk affected both genders.

Thyroid cancer was studied in more detail due to our clinical diagnosis activity, which began in 2006, comprising thyroid ultrasonography (Table 5). We observed an increased risk in the irradiated cohort in 2006–2012, both in males and females (males: SIR = 5.04; 95% CI: 1.84–11.0; females: SIR = 4.27; 95% CI: 2.92–6.03), and in younger patients (SIR = 4.75; 95% CI:

2.53–8.12) or patients irradiated at older age (SIR = 2.77; 95% CI: 1.95–3.82).

DISCUSSION

An association between TC X-ray epilation in childhood and later increased risk of malignant disease was observed in this study. The risk of an irradiated individual developing malignant non-skin tumour in the 1991–2012 period was 49% higher than the general population. This excess risk has not been described in other TC cohorts. In Japanese atomic bomb survivors, an excess of solid cancers was evident approximately 10 years after radiation exposure.²⁴ In the Swedish haemangioma cohort ($n = 14\ 351$),²⁵ subjected to an external exposure of radium-226, a total of 300 cancers were diagnosed between 1958 and 1986, with a SIR of 1.11 (95% CI: 0.99–1.24), showing no significant increase in the incidence rate of solid tumours.

The excess risk was slightly higher in 2006–2012 than in 1991–2005 which may have occurred due to our clinical observations which started in 2006 and lasted until 2012. Although these clinical observations included only skin and thyroid lesions, they may have increased cancer diagnosis due to patient's higher attention to their health. To further explore this issue, we compared observed individuals and non-observed individuals. Interestingly, observed individuals had no increased cancer risk in 1991–2005 (the period before we started the clinical observations) compared with general population, but the non-observed individuals presented an increased cancer risk in both periods.

Table 4. Standardised incidence ratios (SIR) and 95% CIs of cancer by site and gender

Cancer site	1991–2012		
	n	SIR	95% CI
Head and Neck (C00–C14) ^a			
Male	15	1.45	0.81–2.39
Female	7	3.60	1.44–7.42
Total	22	1.79	1.12–2.71
Stomach (C16)			
Male	25	1.75	1.13–2.58
Female	11	1.24	0.62–2.21
Total	36	1.55	1.09–2.15
Colorectal (C18–C20)			
Male	22	1.21	0.76–1.84
Female	23	1.51	0.96–2.27
Total	45	1.35	0.98–1.80
Lung (C33–C34)			
Male	36	2.14	1.50–2.96
Female	4	0.85	0.23–2.18
Total	40	1.86	1.33–2.53
Breast (C50)			
Female	46	0.87	0.64–1.16
Prostate (C61)			
Male	33	1.92	1.32–2.69
Thyroid (C73)			
Male	8	3.88	1.67–7.64
Female	42	2.99	2.16–4.05
Total	50	3.11	2.31–4.09
Leukaemia (C91–C95, D45–D47)			
Male	3	1.32	0.27–3.86
Female	5	2.20	0.71–5.14
Total	8	1.76	0.76–3.48

ICD10 – International Classification of Diseases 10th Revision: head and neck (ICD10: C00–C14), stomach (ICD10: C16), colorectal (ICD10: C18–C20), lung (ICD10: C33–C34), breast (ICD10: C50), prostate (ICD10: C61), thyroid (ICD10: C73) and leukaemia (IC10: C91–C95, D45–D47)

^aIncludes lip, oral cavity and pharynx

This suggests observed individuals tended to be healthier than those not participating in our observation. Several individuals refused the observation due to illness, which fits with this hypothesis. This situation is frequently observed in cardiovascular²⁶ and cancer studies²⁷ where volunteers tend to be healthier than the overall population—“healthy volunteer effect”.²⁸

Since an increased cancer risk was observed in both periods, the analysis stratified by irradiation dose, and/or by tumour site was performed considering only the entire period to avoid losing statistical power.

Only a small excess in cancer risk was observed within the higher radiation dose group comparing with the group receiving 335–475R, but only 32 cancer cases received a dose ≥ 630 R. However, when we considered the different cancer sites in individuals exposed to ≥ 630 R, we observed differences according to gender.

Gender differences in sensitivity to radiation have been approached in several studies, pointing to a possible higher radiosensitivity of females comparing with males. Lundell and Holm,²⁵ in a total of 300 cancers, including stomach, colon, pancreas, lung, female breast, uterine cervix, ovary, testis, melanoma, nervous system, thyroid, endocrine glands and lymphoma, receiving median radiation doses between 0.01 and 0.03 Gy, found a higher SIR for females—1.15 (95%CI: 1.01–1.25) than for males—0.96 (95%CI: 0.74–1.25). In atomic bomb survivors, the excess relative risk (ERR) for all solid cancers was three times higher for females than for males.²⁹ Preston *et al*³⁰ also found higher excess absolute rates for females than males (F:M ratio = 1.4; 90%CI: 1.1–1.8), but this difference disappeared when considering non-gender-specific cancers.

In our cohort, males presented a higher excess risk for all cancers when compared with females. In male emergency workers of the Chernobyl accident, Kashcheev *et al*⁴ reported a statistically significant increase in overall cancer incidence, with an average excess risk of 18%. Contrarily, Ivanov *et al*³¹ observed no increased risk for solid cancer in Russian Chernobyl male liquidators. It is necessary to clarify if whether or not there are differences in clinical radiosensitivity between males and females.³²

In our cohort, regarding specific cancer sites, males presented an excess risk of stomach and lung cancers, which was not observable in females. The higher risk of lung and stomach cancer may be related to smoking habits. In the observed individuals, females were rarely smokers, or previous smokers, comparing with males who were frequently previous smokers (data not shown). A great proportion of the cohort members (40%) came from coastal areas where the main way of living was fishing, and many males became fishermen in adult life. It has been shown that high rates of smoking are common in fishermen,³³ as well as bad eating habits³³ and chronic stress.³⁴ A higher risk for lung cancer (even after adjustment for smoking)^{35,36} and for stomach cancer has been shown among fishermen.³⁶ This may justify the observed increase in all cancers in males, which may be not related to the childhood radiation exposure, but caused by the factors above discussed.

We also observed an increased risk of prostate cancer (SIR = 1.92), one of the few solid cancers not associated with radiation exposure in most studies.^{24,37,38} Nevertheless, in a recent study, Kondo *et al*³⁹ have shown a significant association between atomic bomb radiation and prostate cancer, stating their study was the first report revealing this association. Still, this remains a controversial issue, and we cannot exclude a possible relation to non-radiation causes, as previously hypothesised for stomach and lung cancer.

Table 5. Standardised incidence ratios (SIR) and 95% CIs of cancer by age group and period for thyroid cancer

Variable	Male			Female			Total		
	n	SIR	95% CI	n	SIR	95% CI	n	SIR	95% CI
Age group									
<5 year-old	2	5.99	0.67–21.6	11	4.57	2.28–8.19	13	4.75	2.53–8.12
≥5 year-old	6	3.47	1.27–7.55	31	2.67	1.81–3.78	37	2.77	1.95–3.82
Period									
1991–2005	2	2.29	0.26–8.27	10	1.53	0.73–2.81	12	1.62	0.84–2.83
2006–2012	6	5.04	1.84–11.0	32	4.27	2.92–6.03	38	4.38	3.10–6.01
1991–2012	8	3.88	1.67–7.64	42	2.99	2.16–4.05	50	3.11	2.31–4.09

In females, we have observed a different pattern, with an excess cancer risk in all cancers with the $\geq 630\text{R}$ dose which was not observed in males. Moreover, there was also an excess risk in head and neck cancers (cancers located near to the irradiation area) which was not observed in males. We can hypothesise that this excess cancer risk in females may be attributable to the radiation exposure, contrarily to what was discussed for males. In fact, as Harbron et al⁴⁰ have shown, females have higher risk per unit dose of radiation for many organs. More recently, Narendran et al⁴¹ have reported available data suggesting that long-term radiosensitivity in females is higher than that in males receiving a comparable dose of radiation. Still, these authors state that more systematic studies are needed to elucidate the sex differences in radiation responses across the life continuum⁴¹ and other authors believe that it is necessary to clarify whether or not there are differences in clinical radiosensitivity between males and females.³²

Regarding breast cancer, no increased risk was observed in our cohort, although breast has been described as one of the most radiosensitive organs.^{42,43} In accordance with our findings, in the Swedish haemangioma cohort, this association was also not significant (SIR = 1.24, 95% CI: 0.98–1.54), even though the mean dose absorbed by the breast was 0.40 Gy,²⁵ a dose higher than the 0.016 Gy estimated for the TC cohorts.²¹ In a subsequent study, it was shown that 12% of all breast cancers were attributable to irradiation of very young girls.⁴⁴ In the Israeli TC cohort, Modan et al²¹ found an increased risk of breast cancer, but only among females aged 5 to 9 years at exposure.

In the present study, thyroid cancer was the cancer subtype with the highest risk, both in males and females, in cases irradiated with 325–475R or with $\geq 630\text{R}$ dose, and in cases irradiated before 5 years of age. This increased risk value is in accordance with what was reported in the Swedish haemangioma cohort.²⁵ In TC cohorts, such as the ones of Israel and New York, an ERR/Gy of 32 (95%CI: 14–57) and 7.7 (95%CI: 0–60), respectively, were observed.¹⁰ The thyroid gland has a high sensitivity to radiation exposure,⁴⁵ especially in children,^{46,47} as was the case. Age is an important modifier of risk for thyroid cancer, with children exposed under 5 years being significantly more prone to develop thyroid tumours.⁴⁸ This pattern of decreasing risk with increasing age may indicate a greater radiation effect during

periods of rapid cell proliferation which occur when thyroid gland is developing.⁴⁹

Nonetheless, our results must be analysed with caution, as SIRs for thyroid cancer were much higher in 2006–2012, while in the period prior to the active diagnosis activity, there was no significant increased risk. As previously discussed, increased risk may be attributable to increased screening; SIR was especially high for males in the 2006–2012 period, and thyroid cancer is not commonly screened in non-irradiated male individuals.

One of the study limitations was the inability to include some of the cancers more commonly associated with TC irradiation treatment, such as brain tumours and non-melanoma skin cancers. Although most cancers can be induced by radiation, studies demonstrate dose-related increased risks of thyroid, breast, brain, non-melanoma skin cancers and leukaemia.¹⁰ Skin cancer was not included as completeness of the RORENO database could not be guaranteed. Brain tumours have been associated with the TC epilation treatment, with a seven-fold increase in its incidence, mostly due to meningioma.^{50,51} We found few cases of brain tumour ($n = 4$), but meningioma, a benign neoplasia, is not a tumour of compulsory inclusion in RORENO. For leukaemia, one of the first malignancies associated with irradiation treatment, a SIR of 3.2 (95%CI: 1.5–6.1), was found in the Israeli TC cohort,¹⁷ but this was not observed in the present study.

The increased risk for cancer sites located away from the irradiated area, such as stomach and prostate cancer, has not been previously described in TC cohorts, but may be attributable, as previously discussed, to non-radiation causes.

The present study has some other limitations that should be mentioned. Lack of information about date of birth in the initial registry precluded finding all the cohort members in RNU, leading to exclusion of individuals with common names. Nevertheless, in the Israeli TC cohort, a similar situation occurred with the exclusion of almost half of the cohort; from the original 20 000 Israeli children treated with ionising radiation between 1946 and 1960, only 10,834 subjects were retrieved.⁵² Similarly to our study, common names were excluded; we have no reason to suppose that people with common names would have different cancer risk.

Comparison of demographic data between members found and not found in RNU showed that more females were able to be tracked. This may have occurred due to socioeconomic conditions affecting this cohort, namely a high emigration rate experienced mostly by males. Moreover, due to senior age of this cohort, some individuals may have not completed its registry on RNU, and this may have affected mainly males. Additionally, males tend to seek less health care when compared with females.⁵³

Additionally, we did not have a cohort of non-irradiated siblings for cancer incidence risk comparison, allowing a more accurate evaluation of increased cancer risk after low-dose radiation exposure for TC treatment. Using the general population as comparison group may have introduced some biases, namely different smoking and eating habits (as previously mentioned) and an eventual skewedness towards having more individuals with low income and with lower education level. In a small sample of 245 individuals of our cohort (data not shown) in which we could assess the education level, we found that the lowest level of education (0–4 years) covered 57.1% of the individuals with a mean age of 63.3 years (standard deviation 3.9 years). In the general population, the values reported by the National Statistics Institute (PorData) for this age group were 74.6% (individuals ≥ 65 years old).⁵⁴ This may lead thus to assume that the TC cohort did not have a lower level of education comparing with the general population.

Nevertheless, although low socioeconomic position may be associated with higher cancer risk, this is still a controversial issue. Gastric cancer incidence⁵⁵ and hepatocellular carcinoma⁵⁶ were found to be higher in low socioeconomic positions. Contrarily, socioeconomic status was not a risk factor for the incidence of thyroid carcinoma.⁵⁷ Data from GLOBOCAN 2012, produced by IARC (International Agency for Research on Cancer), have shown incidence rates for all cancers combined nearly twice as high in more developed than in less developed countries.⁵⁸ In the USA, a study conducted to evaluate an association

between poverty and cancer incidence only found a negligible association.⁵⁹

CONCLUSIONS

In the present study, we have shown an association between TC X-ray epilation in childhood and later increased risk of overall cancer. This excess risk is probably due to cancers located near to the radiation exposed area. Females were found to have more radiosensitivity, with an increased cancer risk for head and neck cancers, and in all cancers combined in cases receiving more than one epilation treatment. An increased risk for cancers not located in the irradiated area was also observed which may be attributable to non-radiation causes. Further investigation will be needed to clarify these effects of radiation exposure in childhood.

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