Journal Pre-proof

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PII: S0013-9351(23)02626-9

DOI: https://doi.org/10.1016/j.envres.2023.117822

Reference: YENRS 117822

To appear in: *Environmental Research*

Received Date: 7 September 2023

Revised Date: 18 October 2023

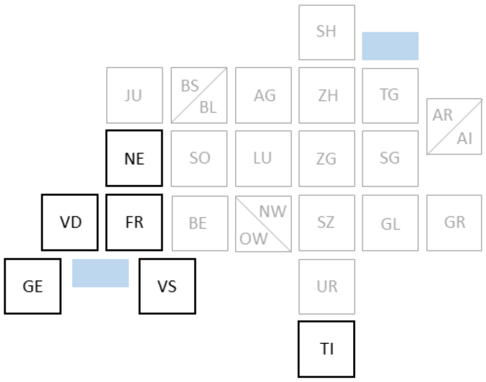
Accepted Date: 28 November 2023

Please cite this article as: Boz, Seç., Kwiatkowski, M., Zwahlen, M., Bochud, M., Bulliard, J.-L., Konzelmann, I., Bergeron, Y., Rapiti, E., Maspoli Conconi, M., Bordoni, A., Röösli, M., Vienneau, D., A cohort analysis of residential radon exposure and melanoma incidence in Switzerland, *Environmental Research* (2024), doi: https://doi.org/10.1016/j.envres.2023.117822.

Authors' contribution

Conceptualization (DV, MR); Data curation (CB, MZ, SB, DV); Formal analysis (SB, DV, MK); Funding acquisition (DV, MR); Investigation (All); Methodology (All); Interpretation of results (All); Project administration (DV); Supervision (DV, MR); Roles/Writing - original draft (SB, DV); Writing - review & editing (All).

All authors discussed and agreed on the final version of the paper.

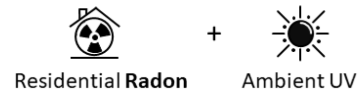


Six Swiss cantons, **1.3** million residents aged 20+

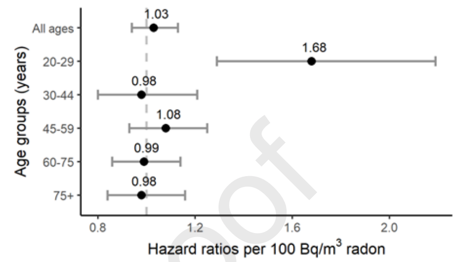
12 million person-years, average **9** years of follow-up

4,937 cutaneous malignant **melanoma (MM)**

Cox Proportional Hazard Models



Age as time scale + age categories + sex + education + socio-economic status + marital status + mother tongue + outdoor occupation + cancer registry ID



- No increased risk of MM incidence from residential radon
- Increased risk for MM incidence among young adults
- Radon exposure might be a potential risk factor in the early stages of adulthood

A cohort analysis of residential radon exposure and melanoma incidence in Switzerland

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Conflict of interest

The authors declare they have nothing to disclose.

1 Abstract

Radon is a radioactive noble gas found in Earth's crust. It accumulates in buildings, and account for approximately half the ionizing radiation dose received by humans. The skin is considerably exposed to ionizing radiation from radon. We aimed to evaluate the association between residential radon exposure and melanoma and squamous cell carcinoma incidence.

The study included 1.3 million adults (20 years and older) from the Swiss National Cohort who were residents of the cantons of Vaud, Neuchâtel, Valais, Geneva, Fribourg, and Ticino at the study baseline (04.12.2000). Cases of primary tumours of skin (melanoma and squamous cell carcinoma) were identified using data from cantonal cancer registries. Long-term residential radon and ambient solar ultraviolet radiation exposures were assigned to each individual's address at baseline. Cox proportional hazard models with age as time scale, adjusted for canton, socioeconomic position, demographic data available in the census, and outdoor occupation were applied. Total and age specific effects were calculated, in the full population and in non-movers, and potential effect modifiers were tested.

In total 4937 incident cases of melanoma occurred during an average 8.9 years of follow-up. Across all ages, no increased risk of malignant melanoma or squamous cell carcinoma incidence in relation to residential radon was found. An association was only observed for melanoma incidence in the youngest age group of 20-29 year olds (1.68 [95% CI: 1.29, 2.19] 100 Bq/m^3 radon). This association was mainly in women, and in those with low socio-economic position.

Residential radon exposure might be a relevant risk factor for melanoma, especially for young adults. However, the results must be interpreted with caution as this finding is based on a relatively small number of melanoma cases. Accumulation of radon is preventable, and measures to reduce exposure and communicate the risks remain important to convey to the public.

Keywords: radon, incidence, melanoma, squamous cell carcinoma, prospective cohort

2 Introduction

Radon-222 is a naturally occurring radioactive noble gas and a product of the decay processes of uranium found in the Earth's crust. It has a half-life of 3.8 days and readily diffuses into its surroundings, becoming widespread and releasing radioactive particles in the process.[1,2] Buildings are susceptible to radon accumulation through the release of gas from building materials, diffusion from water systems and drains, and through cracks in the foundations.[3] The primary contributors to indoor radon concentration are local geology (granite and metamorphic rocks) and soil, with the rate of transfer into buildings influenced by various factors such as ventilation, temperature differential, and building material permeability.[4,5] Radon has been estimated to contribute 40% of the overall annual radiation exposure in Switzerland.[6]

The International Agency for Research on Cancer classifies radon as a Group 1 carcinogen based on the evidence from early epidemiological and experimental studies on lung and respiratory track tumours.[7] A causal link was established between radon exposure and lung cancer based on the strong evidence from occupational, case-control, general population cohorts, occupational and experimental animal model studies.[8-12] The lung and respiratory tract are the organs that are the most affected by radon exposure through inhalation, with dosimetry indicating that the skin receives the next highest dose.[13] Radon and short-lived radon daughters (polonium, bismuth, and lead) emit alpha and beta particles.[14] These alpha and beta emitting decay products can attach to aerosol particles via electrostatic interactions and deposit on the skin surface.[15] The emitted particles can travel through the skin tissue and deposit their energy. [16] Stem cells are located in the basal layer of the epidermis and within range of both alpha and beta particle penetration. Alpha particles, that penetrate less deep, can still irradiate the basal layer especially in thinner parts of the skin, such as face, forearms and frontal trunk (on average 40, 50 and 70 µm). [17,18] Alpha particles can also induce a negative effect to cells that are not directly irradiated via cell signalling from irradiated neighbour cells, which is called bystander effect. [19] For these reasons, radon and its progeny can potentially irradiate the skin, reaching the basal layer of the epidermis to induce skin cancer.[20,21] The annual radiation dose to the skin from radon exposure in indoor air at a level of 200 Bq/m^3 has been estimated to be 25 mSv.[13] It has further been estimated that around 0.7% (0.5% to 5%) of skin cancer incidence could be attributed to the radon exposure at 20 Bq/m^3 level.[22] Lastly, a recent experimental study on mice indicate that radon exposure could affect the structure of the skin, induce damage and result in dysregulation of gene expression. [23]

Melanoma (MM) is a type of skin cancer that develops from melanocytes in the basal layer of the epidermis and has a much higher mortality rate than non-melanoma skin cancers (NMSC), specifically squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).[24] However, the relationship between residential radon exposure and skin cancers is not well understood, with conflicting results among the few available studies. One of the first epidemiological studies investigating the relationship between radon and melanoma incidence was conducted among Czech uranium miners and reported a non-significant increased risk.[25] Two ecological studies conducted in southwest England found higher incidence rates for SCC and NMSC in areas with higher radon levels.[26,27] A Danish study, with modelled radon concentration at residential addresses, found an increased risk of BCC incidence, but not other types of skin cancer.[28] A cohort study in the Galicia region of Spain found a statistically significant risk of NMSC incidence for people living in homes with measured radon levels greater than 50 Bq/m^3 compared to those with lower levels.[29] The complex nature of the relationship between radon exposure and skin cancer incidence may vary depending on the cancer subtype, the level and duration of exposure, and individual susceptibility.

Prior research on the relationship between radon and skin cancer in Switzerland focused on mortality. The first study found that radon exposure increased the risk of death from MM and all skin cancers when the erythemal-weighted UV dose was taken into account.[30] With longer follow-up and updated residential radon and ambient UV exposure models, a subsequent study showed a smaller increased risks. The hazard ratios (HRs) and 95% confidence intervals (CIs) for 100 Bq/m^3 radon increase were 1.10 (95% CI: 0.99, 1.23), 1.06 (95% CI: 0.75, 1.49) and 1.09 (95% CI: 0.99, 1.21) for MM, NMSC and all skin cancers combined, respectively[31].

Given that deaths from melanoma represent only about 18% of incident cases,[32] studies on melanoma incidence can provide more sensitive risk estimates to complement previous mortality research. We aimed to investigate the association between radon exposure and melanoma incidence using robust, nation-wide individual level radon and UV exposures.

3 Methods

3.1 Swiss National Cohort & Cancer registries

This study is based on a cohort constructed by combining data from selected cantonal cancer registries and the Swiss National Cohort (SNC). The SNC longitudinal research platform links nation-wide censuses to mortality and emigration records [33]. As it is census-based, involvement is mandatory and the SNC captures an estimated 98.6% of the Swiss population in 2000.[34]

The incidence cases (detailed below) were obtained from each cantonal cancer registry (CR) separately for the following six south-western Swiss cantons: Vaud (VD), Neuchâtel (NE), Valais (VS), Geneva (GE), Fribourg (FR), and Ticino (TI). These CRs were selected due to available linked records to the SNC and relatively high radon levels within these cantons. Permissions to use the data were obtained through the National Institute for Cancer Epidemiology and Registration (NICER) and each individual cancer registry. These records were transferred to the Center for Primary Care and Public Health (Unisanté) to consolidate into a single, consistent database with all skin cancer cases.

Through a prior project by the Institute of Social and Preventive Medicine at the University of Bern, cancer registry data were probabilistically linked to the December 4, 2000 census records within the SNC.[35] Thus, this study leverages this existing CR-to-SNC linkage to acquire the full population within each canton and the necessary variables including residential coordinates, mortality and emigration records, demographic information, and a socio-economic position index (Swiss-SEP).[36]

The malignant melanoma and squamous cell cancer (C43 and C44, respectively) cases were determined by using International Classification of Disease for Oncology, Third edition (ICD-O-3), codes.[37] Using morphology codes defining the histologic composition of cancer cells within the primary cancer, we distinguished cutaneous malignant melanoma (8720-8790), and squamous cell carcinoma (8050-8084, 8560-8574). No *in situ* cases were included. Incident melanoma was used as the main outcome.

3.2 Study population & Follow-up

All adults aged 20 years and older and living in the cantons of Vaud, Neuchâtel, Valais, Geneva, Fribourg, and Ticino were included. Given the one-time linkage with the SNC, cases within each CR were included from December 4, 2000 (as the earliest possible date) to December 31 2011. The exact date range for each CR differed depending on both the availability of the one-time linkage to the SNC and the registration processes of the registry (Vaud, Neuchâtel: 2000 to 2011; Valais: 2000 to 2010; Geneva: 2000 to 2009; Fribourg: 2006 to 2011; Ticino: 2000 to 2008) (Figure S1). Most CRs were registering skin cancers at the time of the 2000 census, except for Fribourg which began on January 1, 2006. Hence, people living in Fribourg were included in the analyses with delayed entry.

3.3 Exposure assessments

We utilized the same exposure assessments for both residential radon and ambient UV exposures as in the previous nationwide study on melanoma mortality in Switzerland.[31] Based on their residential coordinates at baseline, modelled indoor radon (in Bq/m^3) and ambient UV (in mW/m^2) exposures were assigned to each participant. The residential radon exposure model used here was developed using a random forest approach and is fully described elsewhere. [38] The model was based on ~80,000 measurements collected from 1994 to 2017 and stored in the Swiss radon database by the Federal Office for Public Health (FOPH).[39] The measurement dataset was divided into 5 random subsets, for a 5-fold modelling strategy to evaluate robustness (i.e. 5 models, each with 80% data were used for model development and the remaining 20% for validation). The average of the 5 models was used to obtain the final predicted residential radon levels. A range of geographical and building information were used as predictors specifically: season of measurement and measurement epoch (before or after 2005), lithology, texture of the soil, groundwater quality and depth, terrestrial radiation, distance to the nearest geological fault, altitude, type of the building, construction period, floor of the household dwelling, canton of the residence and degree of urban of the area. The five-fold modelling strategy showed the models to be robust, though the performance metrics indicated uncertainty (R^2 0.31; Spearman's rank correlation 0.51; root-mean-squared-error 0.74 ln Bq/m^3). Further diagnostics also suggest some exposure misclassification, as the model tended to underestimate residential radon concentrations at lower radon levels and overestimate at higher radon levels. [38] The residential radon exposure distributions, including community level averages for illustrative purposes only, are shown in Figure 1.

The monthly UV climatology data covering the period from 2004 until 2016 were provided by MeteoSwiss with a spatial resolution of 1 x 1 km.[40,41] These monthly data were used to calculate an annual average of the whole period and assigned to the coordinates of the participants at baseline. Additionally, a job-exposure matrix was linked to ISCO-88 codes within SNC to determine whether an individual had a job with the potential for UV exposure from the sun (also referred to as "outdoor occupation").[42]

3.4 Statistical methods

The Cox proportional hazard model was used with age as a time scale.[43] All participants were considered at risk as of the date of the census (04.12.2001), except for those in Fribourg where 01.01.2006 was used (cancer registry in Fribourg was created in 2005 and considered complete from 2006 onwards). Follow up ended on the last day of 2011 for participants living in canton Vaud, Neuchâtel, and Fribourg; 2010 for Valais; 2009 for Geneva; and 2008 for Ticino. Participants were followed-up until that date or until one of the following events: the first occurrence of malignant melanoma, death, emigration from the country, or other loss to follow-up. The date of diagnosis was only available as a month and year, thus each event was considered to have happened on the 15th day of the month.

The Cox model included residential radon exposure [38] and ambient UV exposure [41] both as continuous variables. It was adjusted for: canton as a fixed effect to account for differences in background incidence of melanoma; population demographics and administrative variations between cantonal CRs; education attainment (compulsory school, upper secondary, tertiary, unknown) because of known differences in care-seeking;[44] marital status (single, married, widowed, divorced), to reflect differences in lifestyle and culture; and Swiss-SEP [36] (continuous). The model was stratified by sex (men, women), mother tongue (German, French, Italian, other), and outdoor occupation (binary: indoor job not exposed to UV in work place, not employed or retired vs. working outdoors) in order to allow different baseline hazards. The proportional hazard assumptions were tested visually using log-log plots and Kaplan-Meier survival curves.[45]

First, estimates for the overall population were derived. Biological considerations [46] and the previous study for Switzerland on skin cancer mortality [31] indicated that radon effect may vary with age. We thus split the data into the following age groups: 20-29, 30-44, 45-59, 60-74, 75 and older, and an interaction term was introduced between radon exposure and age group to obtain age-specific estimates. Hazard ratios and 95% confidence intervals were reported per 100 Bq/m^3 radon (the annual average residential radon concentration reference level set by the WHO [11]) to obtain effect estimates comparable to previous similar studies.[28,30,31] A sensitivity analysis was carried out on the sub-set of non-movers identified as those who lived at the same address in both the 1990 and 2000 census (thus 10 years prior to earliest start date). Effect modification by sex, socio-economic position (converted to binary using the arithmetic mean of the continuous variable), and outdoor occupation were also investigated by comparing the models with and without an interaction term with radon exposure; the reported HRs and p-values from the likelihood ratio test were calculated by age group.

The main outcome definition was incidence of primary malignant melanoma. We also conducted secondary analyses using SCC incidence as outcome. Different to the main analysis, the secondary analysis excluded Ticino due to lack of records for SCC, and the Fribourg follow-up was until end of 2012 (Figure S1). BCC was not investigated as a secondary outcome because it is less consistently registered and incomplete in most cancer registries.

Individuals in cancer registries may have multiple entries if diagnosed with more than one type of skin cancer (SCC or BCC, in addition to melanoma). Because UV exposure is the major risk factor for all types of skin cancers, and behaviours that lead to UV exposure may change after diagnosis or treatment, we censored upon diagnosis of other skin cancers (SCC or BCC) in a sensitivity analysis.

4 Results

The study population comprised 1,575,923 adults living in the six studied cantons, representing 21.7 % of the Swiss population in 2000 (Figure S2). We excluded 113,530 (7.7%) because of failed linkage to the consecutive census in 2010. We further excluded 49,225 (3.1%) because of missing geographical coordinates for their home location, 49,433 (3.1%) because they were living in non-residential buildings (such as hospices and retirement homes), and 816 (0.1%) individuals because of missing SEP index. The remaining 1,362,919 participants were included in the analysis with total of 12,120,549 person years of follow-up (average 8.9 years) and 4,937 primary malignant melanoma cases.

The average age of the full study population and melanoma cases were 49.1 and 55.7 years, respectively. Almost half (48.7%) were non-movers prior to baseline, 53.8% of whom were women and on average older compared to the full study population. On average, individuals in the cohort were married, French speaking, and had completed upper secondary education. Approximately 4% of the cohort were working outdoors with potential for UV exposure (Table 1). The percentages of population within age groups were 14.1, 34.4, 27.3, 18.1 and 9.1 for age groups 20-29, 30-44, 45-59, 60-74, 75 and older, respectively. The proportion of cases was highest in 60-75 years old group (1,578 [32.0%]) and lowest in youngest age category (110 [2.2%]) (Table S1). The mean radon exposure was 76.4 Bq/m^3 with a standard deviation of 40.6 Bq/m^3, approximately 20% of individuals were living in homes with residential radon exposure exceeding the established guideline limit of 100 Bq/m^3 by World Health Organization (Figure S3). Radon and ambient UV exposures were not correlated (r = 0.08).

We observed no association between radon exposure and melanoma across all age groups, with a hazard ratio of 1.03 (95% CIs: 0.94, 1.13) per 100 Bq/m^3. A risk increase was only found in the youngest age group (1.68 [1.29, 2.19] per 100 Bq/m^3). Similar results were observed when the analysis was restricted to non-movers (Table 2).

None of the variables we tested modified the effect of radon exposure on melanoma incidence for all ages combined (Table 3). The noted association in the youngest age group seemed to be mainly in women and in those with lower socio-economic position, with no association in their counter parts.

In the secondary analysis, we found no association between radon exposure and SCC incidence (Table S2). The sensitivity analysis where we also censored on the first diagnosis of SCC or BCC, if occurring before a melanoma diagnosis, did not change the main results (Table S3 vs. Table 2).

5 Discussion

In this cohort study including cantons in Switzerland prone to radon, no association was found between residential radon exposure and incidence of cutaneous malignant melanoma or squamous cell carcinoma. Even the analysis restricted to non-movers, where exposure misclassification is expected to be reduced, showed no association. The only increased risk for melanoma incidence in relation to radon exposure was in the youngest adults (aged 20-29), and based on a relatively small number of cases (2.2% of all cases) thus should be should be interpreted with caution. The association in young adults remained when restricting the analysis to the non-movers. In addition to the modifying effect of age, the association between radon exposure and melanoma incidence was stronger among women and in individuals with lower socio-economic status.

Previous analyses in the entire population in Switzerland on the relationship between residential radon and melanoma mortality found positive associations.[30,31] One possible explanation for the lack of association with incidence might be that while the people living in the Alpine regions have higher radon exposure they also could have lower access to health care due to infrastructure and be less inclined towards regular screening. Thus, they may be diagnosed in the later stages of prognosis compared to those living in urban settings, inducing survival bias in the previous study (or a diagnosis bias in the present study). With no further possibility to untangle the all confounding factors affecting the complex relationship between exposure and the outcomes, we cannot exclude these biases. On the other hand, the observed stronger effects of radon on melanoma incidence for younger adults and women is consistent with the previous studies on melanoma mortality, suggesting the link between radon exposure and melanoma risk should not be dismissed. For squamous cell carcinoma, however, we found no increased risk with increase in residential radon levels. This is contrary to a previous study on skin cancer incidence and ionizing radiation dose conducted within atomic bomb survivors that reported statistically significant excess relative risks for BCC and SCC but not for MM. [47] Within Mayak nuclear facility workers who were chronically exposed to ionizing radiation, a higher risk for BCC but not SCC was found.[48] Together these finding might indicate the exposure to ionizing radiation is more related to risk of BCC, a notion that is supported by the findings of the Danish Diet, Cancer and Health cohort study.[28] Unfortunately BCC incidence as an outcome could not be considered in our analysis.

That we only saw signs of a relationship for melanoma in the young adults could relate to ionizing radiation having more effect early in life. [49] Previous evidence supports that the carcinogenic effect of ionizing radiation is age dependent, [50-52] but also that risks related to age at exposure can differ depending on the cancer type. [53] Excess risks seem to decrease with age at exposure for stomach and thyroid cancers, while the risk of breast and lung cancers gradually increases at older ages.[54] Regarding skin cancer, a study among atomic bomb survivors indicated a one year of decrease in age at exposure related to an 11% increase in the risk of BCC. The results, however, were inconclusive for melanoma due to a low number of cases.[47] A similar pattern was also found in a study on BCC in relation to radiation therapy. The relative risk was highest among people who received radiation therapy during childhood, and the risk gradually decreased with the age at exposure.[55] Considering that the risk from ionizing radiation does not diminish for decades for many solid cancers including skin,[56] exposure at very young ages extends the period to develop carcinogenesis and increases the opportunity to detect an adverse outcome. This fits with our observation of a slightly stronger association among young adults who were non-movers, with exposure at baseline also reflecting residential exposure during childhood with less uncertainty. It may be that ionizing radiation from residential radon has more effect on the skin when exposed early in life because the skin of infants is thinner and gradually increase from birth to adulthood. [57] The thickness of skin reaches its maximum around 25 and 35 years of age, then slowly loses its elasticity and moisture content while remaining the same thickness until the very old age. [58]

Evidence suggests that the effect of ionizing radiation is different on males and females.[59] The report published by the National Research Council in 2006 investigating the biological effect of ionizing radiation (BEIR VII, phase 2) showed that women are more likely to develop cancer or die from cancer compared to men when exposed to the same amount of radiation.[60] The susceptibility, however, can vary greatly from no known differences by sex for certain solid cancers to large differences for other cancer types. For example, a pooled cohort study among nuclear workers occupationally exposed to ionizing radiation in the United States observed no significant effect modification by sex for non-smoking related radiogenic cancer (bone, skin, brain, breast, central nervous system, thyroid).[61] For malignant skin cancers, a Russian cohort study among nuclear facility workers exposed to gamma-rays also did not observe any modification of excess relative risk by sex.[62] We can only speculate that higher risk of melanoma with regard to residential radon exposure observed in our study, and primarily in the youngest women, might be due to women having thinner skin or spending more time indoor at home than men.[63]

Socio-economic status is also associated with melanoma incidence, with higher incidence reported in educated high income populations.[64] Similarly, we observed statistically significant positive coefficients for continuous socio-economic status and higher coefficients in those with higher attained education (upper secondary and tertiary) compared to those in a lower category (data not shown). The possible reasons could relate to behaviours such that people with higher socioeconomic status are more likely to travel to destinations with higher UV exposure, such as mountains or seaside holidays, compared to people with lower socioeconomic status,[65] and they are more likely to examine their skin regularly and undergo screenings.[64] We saw no risk, however, in the high SEP population group in the effect modification analysis. It may be that any small increase in risk has been masked by the substantially higher risk from recreational UV exposure.[66] Instead the noted higher risk of melanoma incidence in relation to radon exposure in the lower SEP group, especially in the younger adults, might be explained by lower quality housing and lack of access to or the cost of remedial efforts. The national level radon remediation survey for Switzerland revealed that the major reasons for not taking action against high residential radon levels are the high cost of the required renovations and that radon is not considered a health risk,[39] the latter which may also differ according to SEP.

The strength of this analysis is that it is a large prospective cohort study, with an average of 9 years of follow-up. Residential radon and ambient UV exposures were assigned to every individual's addresses at baseline. The exposure assessment for radon was from a model to predict residential (i.e. household) levels, built on a very large number of measurements across the country, allowing for detailed spatial modelling including by floor of dwelling. Moreover, the registration of incident melanoma cases is systematic and can be considered as complete for all the CRs used in this study.

Still it must be acknowledged that exposure was modelled for, not measured in, every home. We also did not have data on behaviours that may influence radon exposure, such as the amount of time spent indoors and ventilation practices at home. Exposure misclassification due to these factors cannot be avoided and is a limitation of this study. Future studies may be better suited to address these issues. We also could not include adults across the whole of Switzerland, because of unavailability of previously linked cancer registries to SNC. However, the study covered most cantons with known high spatial variability of radon levels. Another potential limitation is the relatively coarse model used adjusted for long-term average ambient UV exposure, with a 1 x 1 km which represents an ecological exposure. Further, high intensity intermittent UV exposures, especially in childhood, are known to be more important than average ambient UV exposures for melanoma risk.[66] Unfortunately, we did not have information about personal UV exposure history and sun-related protection behaviours, which can markedly affect the dose from ambient UV. Finally, it should be noted that the only positive association was based on a small number of cases within young adults. Furthermore, for some individuals, only considering residential radon may not have captured the total radon exposure given that indoor exposure may also occur in occupational settings[67]. Future studies could also consider other designs and exposure assessment methods, such as individual long-term radon measurements possibly considering time activity, to capture both residential and occupational exposures.

6 Conclusion

The overall results provide little evidence for an association between residential radon exposure and melanoma incidence. Nevertheless, residential radon exposure might be a potential risk factor in the early stages of adulthood, in particular for women and those with lower socio-economic position. Studies involving other cantonal cancer registries within Switzerland, or elsewhere, with longer follow-up would help clarify the relationship between radon exposure and skin cancer risk. From a public health perspective, and based on the stronger evidence for lung cancer, radon exposure remains an important risk factor for the health of the general population. Therefore, prevention and mitigation of radon gas in dwellings with high radon levels should continue to be promoted by governmental organizations and international agencies.

7 Authors' contribution

Conceptualization (DV, MR); Data curation (CB, MZ, SB, DV); Formal analysis (SB, DV, MK); Funding acquisition (DV, MR); Investigation (All); Methodology (All); Interpretation of results (All); Project administration (DV); Supervision (DV, MR); Roles/Writing - original draft (SB, DV); Writing - review & editing (All).

All authors discussed and agreed on the final version of the paper.

8 Funding

This work was supported by the Swiss Cancer Research Foundation (grant no. KFS-4116-02-2017).

9 Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

10 Acknowledgements

We thank the Swiss Federal Statistical Office for providing mortality and census data and for the support which made the Swiss National Cohort and this study possible (grant nos. 3347CO-108806, 33CS30_134273 and 33CS30_148415). We also acknowledge the members of the Swiss National Cohort Study Group: Matthias Egger (Chairman of the Executive Board), Adrian Spoerri Claudia Berlin, and Marcel Zwahlen (all Bern), Milo Puhan (Chairman of the Scientific Board), Matthias Bopp (both Zurich), Martin Röösli (Basel), Murielle Bochud (Lausanne) and Michel Oris (Geneva). We thank Martha Palacios, Fabio Barazza, Christophe Murith and Daniel Storch at the Federal Office for Public Health for providing the Swiss Radon Database and expert advice and appreciate the UV climatology data produced within collaboration between Centre for Primary Care and Public Health (Unisanté), University of Lausanne, and Federal Office of Meteorology and Climatology MeteoSwiss. Lastly, S.B. gratefully acknowledges the grant received as "Study Abroad Program" (YLSY) from the Ministry of National Education, Republic of Turkey.

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Table 1: Population characteristics of the full cohort and non-movers, including for malignant melanoma cases.

	Study population		Sub-set population	
Characteristics	Full Cohort	MM cases[a]	Non-movers[b]	MM cases[a]
Participants[c], *n* (%)	1,362,919 (100)	4,937 (0.4)	663,167 (48.7)	3,122 (0.2)
Age				
Mean (SD)	49.1 (17.1)	55.7 (16.0)	56.7 (16.7)	60.8 (14.2)
Sex, *n* (%)				
Men	645,158 (47.3)	2,485 (50.3)	306,697 (46.3)	1,662 (53.2)
Women	717,761 (52.7)	2,452 (49.7)	356,470 (53.8)	1,460 (46.8)
Civil status, *n* (%)				
Single	294,986 (21.6)	691 (14.0)	117,028 (17.6)	325 (10.4)
Married	861,766 (63.2)	3,400 (68.9)	432,807 (65.3)	2,262 (72.5)
Widowed	98,344 (7.2)	439 (8.9)	72,138 (10.7)	334 (10.7)
Divorced	107,823 (7.9)	407 (8.2)	41,194 (6.2)	201 (6.4)
Mother tongue, *n* (%)				
German	162,863 (11.19)	631 (12.8)	89,516 (13.5)	440 (14.1)
French	844,628 (62.0)	3,430 (69.5)	420,885 (63.5)	2,163 (69.3)
Italian	223,588 (16.4)	606 (12.3)	122,978 (18.5)	398 (12.7)
Other	131,840 (9.7)	270 (5.5)	29,788 (4.5)	121 (3.9)
Education level, *n* (%)				
Low (compulsory school)	369,464 (27.1)	970 (19.6)	209,818 (31.6)	709 (22.7)
Medium (upper secondary)	652,357 (47.9)	2,498 (50.6)	326,647 (49.3)	1,600 (51.2)
High (tertiary)	300,348 (22.0)	1,415 (28.7)	120,094 (18.1)	794 (25.4)
Not known	40,750 (3.0)	54 (1.1)	6,608 (1.0)	19 (0.6)
Outdoor occupation, *n* (%)				
No	1,308,650 (96.0)	4,788 (97.0)	636,802 (96.0)	3,019 (96.7)
Yes	54,269 (4.0)	149 (3.0)	26,365 (4.0)	103 (3.3)
Swiss-SEP				
Mean (SD)	60.0 (10.5)	62.4 (10.5)	59.8 (10.4)	62.1 (10.5)
Range	5.9 – 97.2	25.5 – 91.4	5.9 – 97.3	25.5 – 91.4
Interquartile range	14.4	15.0	14.2	15.3
Radon exposure, Bq/m3				
Mean (SD)	76.4 (40.6)	75.8 (44.4)	80.4 (43.5)	78.1 (48.8)
Range	25.6 – 1154.1	27.0 – 1065.4	25.7 – 1154.1	27.5 – 1065.4
Interquartile range	43.3	40.0	46.7	41.1
UV exposure, mW/m2				
Mean (SD)	20.3 (0.8)	20.3 (0.8)	20.3 (0.8)	20.3 (0.8)
Range	18.2 – 29.1	18.5 – 26.3	18.2 – 26.6	18.5 – 26.3
Interquartile range	0.6	0.5	0.6	0.5

[a] MM cases: Primary invasive cutaneous melanomas (ICD-O-3: C43, 8720-8790). No in situ cases.
[b] Non-movers: Same residential location at 1990 and 2000 censuses.
[c] Percentages calculated for the row.

Table 2: Association between residential radon exposure and melanoma incidence among the full cohort and non-movers, by age

	Full cohort		Non-movers[a]	
	Cases	HR (95% CIs)[b]	Cases	HR (95% CIs)[b]
All ages	4,937	1.03 (0.94, 1.13)	3,122	1.01 (0.91, 1.13)
Age groups				
20-29	110	1.68 (1.29, 2.19)	56	1.73 (1.34, 2.25)
30-44	861	0.98 (0.80, 1.21)	213	0.92 (0.63, 1.33)
45-59	1273	1.08 (0.93, 1.25)	696	1.06 (0.88, 1.28)
60-74	1578	0.99 (0.86, 1.14)	1224	0.94 (0.80, 1.11)
75+	1115	0.98 (0.84, 1.16)	933	0.98 (0.82, 1.17)

Note: For entire cohort, models used age as time scale, included radon exposure, and adjusted for ambient UV exposure, sex, canton, socio-economic position, education, marital status, mother tongue, and outdoor occupation. For different age group, an interaction term between radon exposure and age groups was introduced.
[a] Non-movers: Same residential location at 1990 and 2000 censuses.
[b] Hazard ratios (95% confidence intervals) are expressed per 100 Bq/m^3 radon increase.

Table 3: Modification of the association between radon exposure and melanoma incidence, for full cohort, by age

	Sex		Socio-economic position[a]		Outdoor occupation	
	Men	Women	Low	High	No[b]	Yes
All ages	1.01 (0.90, 1.13)	1.06 (0.94, 1.19)	1.05 (0.96, 1.16)	1.00 (0.89, 1.11)	1.04 (0.95, 1.14)	0.84 (0.57, 1.24)
Age groups						
20-29	1.04 (0.42, 2.47)	1.84 (1.43, 2.37)	1.70 (1.32, 2.20)	0.90 (0.50, 1.64)	1.68 (1.29, 2.19)	NA[c]
30-44	1.10 (0.82, 1.46)	0.89 (0.68, 1,18)	0.91 (0.74, 1.13)	1.11 (0.88, 1.40)	1.01 (0.82, 1.24)	0.58 (0.18, 1.85)
45-59	1.16 (0.96, 1.40)	1.00 (0.81, 1.23)	1.04 (0.89, 1.21)	1.12 (0.95, 1.33)	1.09 (0.93, 1.27)	1.05 (0.67, 1.65)
60-74	0.89 (0.74, 1.08)	1.10 (0.91, 1.33)	0.92 (0.80, 1.07)	1.07 (0.91, 1.25)	1.00 (0.87, 1.16)	0.67 (0.31, 1.46)
75+	0.96 (0.78, 1.18)	1.01 (0.80, 1.28)	0.93 (0.78, 1.10)	1.07 (0.90, 1.28)	0.99 (0.84, 1.16)	0.59 (0.02, 17.4)

Notes: Models used age as time scale, included radon exposure, and adjusted for ambient UV exposure, sex, canton, socio-economic position, education, marital status, mother tongue, and outdoor occupation.
Effect modification was evaluated using an interaction term between radon exposure and each potential effect modifier. For the age group analyses, three-way interaction terms were used between radon exposure, age group and the potential effect modifier.
Hazard ratios (95% confidence intervals) are expressed per 100 Bq/m^3 radon increase.
[a] Based on Swiss-SEP[19]: Low and high means the neighbourhood socioeconomic index value is lower than 60 and equal or higher than 60, respectively. 60 is the mean value of the cohort.
[b] No includes those with indoor jobs and those not in paid employment.
[c] Not applicable because of no observed cases in that group.

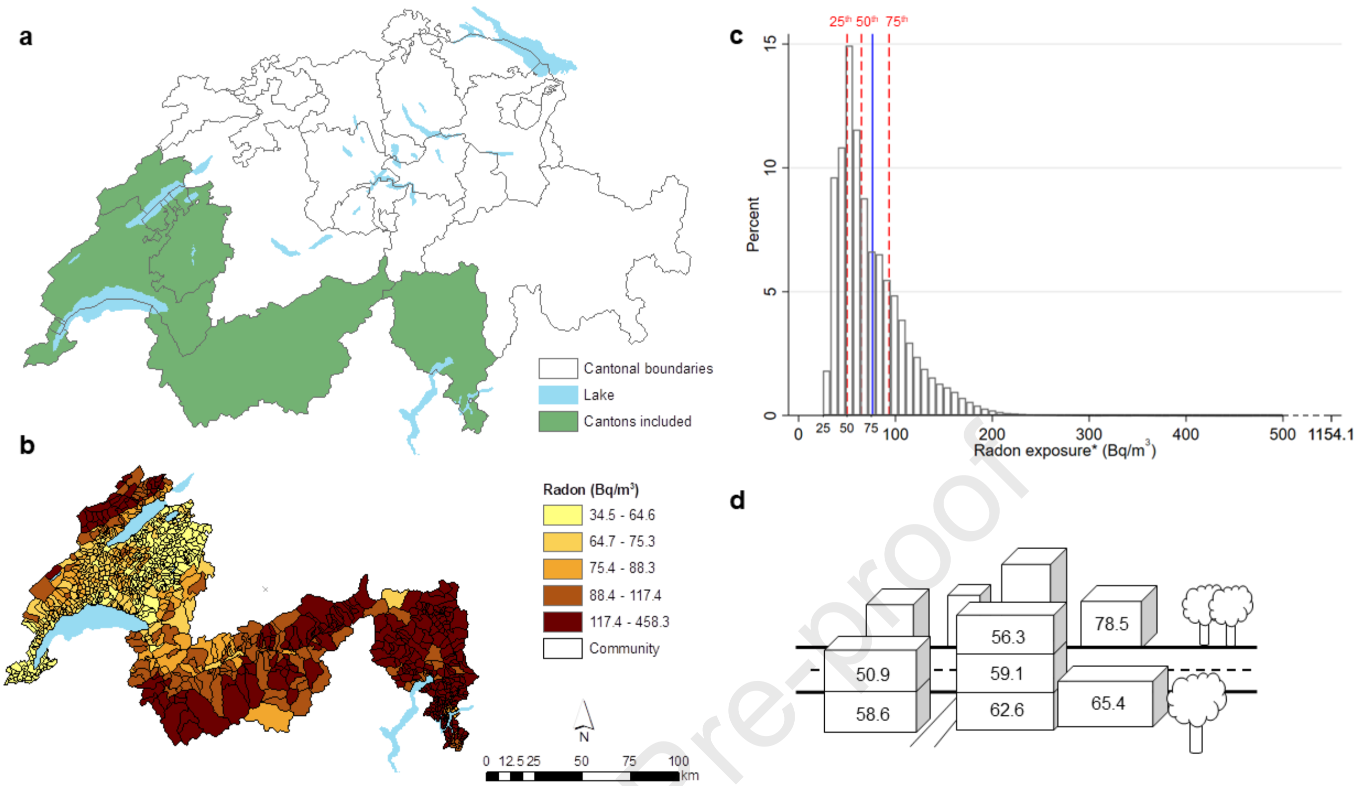

Figure 1: (a) Switzerland showing the cantonal boundaries and six included cantons. (b) Residential (household level) radon exposure averaged at community level within six cantons. Quintiles were used to categorize the radon levels. (c) Exposure distribution of residential radon for the study population at baseline. Red vertical lines represent the percentiles. Blue vertical line shows the mean value equal to 76.3 Bq/m^3. *Radon exposures above 500 Bq/m^3 were omitted to obtain a clear visualization. (d) Schematic of the residential radon levels by household, showing differences by household floor in the same building and between neighbouring buildings.

Highlights

- No overall increased risk of MM or SCC incidence in relation to residential radon
- Residential radon was associated with MM incidence among young adults
- Risk for young adults was stronger among women and those with lower SES
- Radon exposure might be a potential risk factor in the early stages of adulthood

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: