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A prospective cohort analysis of residential radon and UV exposures and malignant melanoma mortality in the Swiss population

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ABSTRACT

Background: Radon is a radioactive noble gas naturally found in the earth crust that can accumulate in buildings. In addition to lung cancer, alpha particles emitted by radon may contribute to the risk of skin cancer. We evaluated the association between residential radon exposure and skin cancer mortality, over a fifteen year period, taking residential ultra-violet (UV) exposure into account.

Methods: We included 4.9 million adults from the Swiss National Cohort. Hazard ratios for melanoma mortality were estimated using Cox proportional hazard models (20+ years old; follow-up 2001–2015). Long-term modelled residential radon and ambient UV exposures were assigned at baseline, and included together in the Cox models. With age as a time scale, models were adjusted for calendar time, sex, marital status, education, mother tongue, socioeconomic position, and occupational environment with potential for UV exposure. Age specific hazard ratios were derived. Effect modification, sensitivity analyses and the shape of the exposure response, as well as secondary analysis using other outcome definitions, were investigated.

Results: During follow-up (average of 13.6 years), 3,979 melanoma deaths were observed. Associations declined with age, with an adjusted hazard ratio per 100 Bq/m^3 radon at age 60 of 1.10 (95% CI: 0.99, 1.23). The dose–response showed an approximate linear trend between the minimum and mean radon exposure of 75 Bq/m^3. Having outdoor occupation significantly increased the risk of melanoma mortality associated with UV exposure compared to indoor jobs. Analysis restricted to the last five years of follow-up showed similar results compared to the main analysis. Similar associations were found for mortality from melanoma and non-melanoma skin cancer combined.

Conclusion: With double the follow-up time, this study confirmed the previously observed association between residential radon exposure and melanoma and non-melanoma skin cancer mortality in Switzerland. Accumulation of radon indoors is preventable and of public health importance.

1. Introduction

Radon is a radioactive noble gas naturally found in the earth crust as a consequence of uranium decay. During its half-life of 3.8 days, radon gas diffuses into soil, air, water sources, and the atmosphere from cracks between geological plates, faults, and the soil air (National Research Council, 1988). Subsequently, radon can enter buildings and homes through contact with the ground i.e., gaseous radon in the soil air diffuses from crawl space and cracks in the basement walls and transfers through air and via water systems and drains (Ramola et al., 2011). Ultimately, these processes can result in an accumulation of radon in buildings leading to radiation exposure.

Exposure to radon is responsible for nearly half of the effective dose of radiation received by the population worldwide. The lungs and respiratory tract are the most exposed organs, and a causal relationship between lung cancer and radon exposure is well established by

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experimental and epidemiological studies (IARC; Darby et al., 2005). Studies also showed that radiation from alpha particles emitted by radon and its progeny can penetrate to the skin's basal layer (Eatough, 1997; Eatough and Henshaw, 1992). Based on dosimetry calculations, the annual dose of radon to the skin at 200 Bq/m^3 is 25 mSv (Kendall and Smith, 2002), which also makes skin a relatively highly exposed organ in the human body.

In one of the earliest studies that investigated the relationship between skin cancer and radon exposure, an estimated 0.5%–5.0% of incident skin cancer cases were attributable to exposure to residential radon level at 20 Bq/m3 (Charles, 2007). Published in 2012, Wheeler et al. (2012) conducted an ecologic study in southwest England, and found higher incidence rates for squamous cell carcinoma (SCC) in the areas (i.e., postcode sectors) with mean radon levels higher than 230 Bq/m^3 compared to those lower than 39 Bq/m^3. In the same year, Turner et al. (2012) reported hazard ratios (HRs) of 1.08 (95% CI: 0.88, 1.33) and 0.70 (95% CI: 0.42, 1.19) per 100 Bq/m^3 in mean county-level radon in the United States for malignant melanoma (MM) and non-melanoma skin cancer (NMSC) mortality, respectively. A subsequent study by Wheeler et al. (2013) found that regional differences in cancer registration only partly explained the substantial geographic variation in rates, and suggested an unknown fraction of the variation might be explained by radon. A more recent cohort study in Denmark, using modelled radon exposure at the residential address, reported an association of 1.14 (95% CI: 1.03, 1.27) per 100 Bq/m^3 between radon exposure and incidence of basal cell carcinoma (BCC), but no association for SCC or MM (Brauner et al., 2015). A study carried out in the radon prone area Galicia, Spain, investigated associations between individually assigned radon exposure and cancers other than lung cancer and reported a non-significant HR of 1.5 (95% CI: 0.6, 3.8) for NMSC in the subjects that had radon concentrations more than 50 Bq/m^3 in their dwellings compared to persons with less than 50 Bq/m^3 (Barbosa-Lorenzo, 2016). A study conducted in Switzerland (Vienneau et al., 2017), also using modelled residential radon, found significant associations between increased radon exposure and mortality from MM and all skin cancers combined (HR [95% CI]:1.16 [1.02, 1.25] and 1.17 [1.06, 1.29] per 100 Bq/m^3, respectively) using data from the Swiss National Cohort from 2000 until 2008.

We aimed to follow-up these previous findings by expanding the study period up to 2015. We investigated the association between residential radon and mortality from MM, non-melanoma and all skin cancers combined in a large cohort while accounting for residential UV exposure and other important covariates in Switzerland. We further investigated the shape of the exposure–response relationship.

2. Methods

2.1. Study population

This study was based on the Swiss National Cohort (SNC), linking national censuses, emigration and mortality data (Bopp, 2009; Spoerri et al., 2010; Renaud, 2000). Use of the SNC was approved by the Ethics Committees of the Cantons of Zurich and Bern (Contract No. 170393). Because participation in the census is mandatory, the SNC includes an estimated 98.6% of the entire resident population at year 2000. It contains a wide range of personal information (e.g., date of birth, sex, civil status, occupation and job position, mother tongue), household information (e.g., type, neighbourhood index of socioeconomic position (Swiss-SEP) (Panczak et al., 2012), and information on buildings (e.g., geographical coordinates, number of floors, construction period). The outcomes in the SNC are cause-specific mortalities based on death certificates (W.H.O., 2004). Before 2010, a probabilistic linkage was used to integrate the census, emigration and mortality data within the SNC whereas from 2010 onwards a deterministic linkage based on personal identifier is used.

In this study, the population comprised adults 20 years and older on 01.01.2001 who were followed for a maximum of 15 years (until the end of 2015). The age restriction was applied due to the small number of skin cancer deaths below age 20, and to avoid complexity caused by fundamental differences between adult and paediatric cancers.

The definitive primary cause of death from malignant melanoma (MM, ICD-10 code C43) was considered as the main outcome in this study. Non-melanoma skin cancers (NMSC, ICD-10 code C44) and mortality from all skin cancer types (SC: combined MM and NMSC) were also analysed in secondary analyses.

2.2. Exposure assessment

Modelled long-term exposure to indoor radon and ambient UV were assigned to all participants at their home location. The residential radon exposure models are detailed in Vienneau et al. (2021), which utilized 79,598 radon measurements between 1997 and 2017 in households across the country recorded in the Swiss National Radon Database. These measurements, together with building specific information (construction period, floor of dwelling), variables related to physical properties of geographical location (type of rocks, distance to nearest fault, soil texture etc.) and measurement epoch (before or after 2005; to account a change in the Swiss monitoring strategy to focus on radon prone areas after 2005), were used to develop radon prediction models based on a random forest and a linear model for comparison (Fig. S1). As detailed in Vienneau et al. (2021), the random forest radon model was determined to be superior based on performance statistics in a hold out validation and was used as the primary model here; the linear model was only used in sensitivity analyses. Subsequently, the estimated residential radon exposure in Bq/m^3 was applied to the study population at baseline (2001) based on the geographical coordinates of their home location, and the floor of the dwelling. For sensitivity analyses, we recalculated radon exposure for all participants at 2011 using the variables based on their residential addresses (building and geographical information). As the radon model also included measurement epoch, radon exposure changed for all participants including non-movers.

Monthly UV data were provided by MeteoSwiss as 1x1 km grids. These originated from their models of hourly solar UV in W/m^2 taking the altitude of Switzerland, cloudiness, aerosol distribution and ozone concentration in the atmosphere into account (Harris et al., 2021). The original models were validated using the measurements from three meteorological stations across Switzerland (Vuilleumier, 2021). The average of 12 years, the period between 2004 and 2016, were calculated from the monthly grids and used to assign UV exposure at home locations. Similar to radon, for sensitivity analyses we updated exposure for participants at 2011.

A job-exposure-matrix (JEM) was used from Guénel et al. (2001) to determine if a job included frequent outside activities, which may lead to UV exposure. The JEM contains categorical UV intensity information for all job codes available at 5-digit level in International Standard Classification of Occupations (ISCO)-68 version, which we previously recoded to ISCO-88 for matching to the SNC (Vienneau et al., 2017). Subsequently, occupational environment with potential for UV exposure was created as a 3-level categorical variable at baseline (indoor or outdoor for those employed, and not in paid employment or retired).

2.3. Statistical analysis

Cox proportional hazard models were used to analyse the relationship between skin cancer and residential radon and ambient solar UV exposures. Individuals aged between 20 and 99 years old at baseline (starting on 01.01.2001) were included, and age was introduced as the underlying time scale in the Cox model. The individuals were observed until death from skin cancer, loss of follow-up, emigration, death from other causes or end of follow-up on 31.12.2015, which ever happened first.

All statistical models included both residential radon and UV

exposures. The cohort was split into 5-year periods based on calendar year to account for time trends during the follow-up. Two base models were defined, with the only difference being the interaction term. The base models thus included both exposures, one of the interaction terms (age × exposure [radon or UV]), and were stratified by sex and the 5-year periods. The interaction terms were used to obtain age specific hazard ratios (at 30, 45, 60 and 75 years), to understand the effect of age. The adjusted model further included *a priori* potential covariates, which were marital status (categorical: single, married, widowed and divorced), educational level (categorical: low = compulsory or less, medium = upper secondary, high = tertiary, and not known), neighbourhood index of socioeconomic index (continuous [was obtained from Panczak et al. (2012)), mother tongue (categorical: German, French, Italian and other) and occupational environment (indoor, outdoor and not in paid employment or retired). All of the above mentioned variables were added to the models at baseline. Additional potential covariates including job position (categorical: low = unskilled employees and workers, medium = supervisors/low level management and skilled labour, high = top management and independent professions, senior management, unknown = unemployed, job seeking, retired), type of area (categorical: urban, intermediate, rural), nationality (binary: Swiss, non-Swiss), religion (categorical: Christian, other faiths, no affiliation) were tested but not included in the model. Proportional hazard assumptions were checked by using Schoelfeld residuals. Hazard ratios were reported per 100 Bq/m^3 radon and per 1 mW/m^2 UV with 95% confidence intervals. The increment of 100 Bq/m^3 for radon was used to facilitate comparison with previous studies (Brauner et al., 2015; Vienneau et al., 2017) and to obtain effect estimates for the recommended radon level by World Health Organization (WHO, 2009). HRs were also reported per inter-quartile range (IQR) to obtain comparable HR for both residential radon and UV exposures. Non-linear relationship between residential radon and melanoma deaths were explored graphically by using natural spline functions with 3 degrees of freedom. The Akaike's Information Criterion (AIC) was used for comparison to the linear model. A categorical analysis based on quartiles of radon exposure was also done.

Effect modification was also explored for melanoma mortality. We used an interaction term between exposure and each of the following: sex, mother tongue, educational level, civil status, and occupational environment. Then we compared the model with/without the interaction term using the likelihood ratio and Wald's tests (p-value less than 0.10).

Secondary analyses included investigating other outcome definitions as primary cause of death, specifically NMSC and all skin cancer (SC: combined MM + NMSC).

Additional sensitivity analyses included consideration of time-varying exposure, implemented by updating the exposure for participants at 2011. Further, we used an alternative radon exposure prediction model available in Vienneau et al. (2021), specifically the linear model instead of the random forest model. We also conducted an analysis for non-movers, defined as living in the same location at baseline (01.01.2001) and the prior census (05.12.1990), such that exposure was valid for at least ten years prior to baseline. Lastly, a new cohort focused on the latter part of the SNC, which was not included in the previous publication (Vienneau et al., 2017) was constructed for 01.01.2011 to 31.12.2015 with all adults who were older than 20 years on 01.01.2011. We set the entry date to 01.01.2011, as the date that the SNC switched from a probabilistic to deterministic linkage between census, mortality, and emigration databases using a unique identifier.

The Cox models were developed in STATA software (Version 16.1 MP) (StataCorp, Stata Statistical Software: Release 16., 2019), while the dose–response were visualized in R using "survival" and "spline" packages (Therneau, 2020).

3. Results

Among 7,273,343 individuals available at baseline on 01.01.2001, 599,126 (8.2%) were excluded due to lack of linkage to 2010 census (because of a mismatch between the former probabilistic and current deterministic linkage in the SNC), and 1,599,118 (22.0%) were excluded due to age restrictions. We further excluded 268,547 (3.7%) individuals because of missing information on residential address or socioeconomic position, or because they were living in non-residential buildings such as hotels and senior housing. The remaining 4,904,443 individuals were followed-up with an average 13.6 years and 66 million person-years of observation time. We identified 3,979 deaths from MM (0.08% of the baseline population, 0.47% of total deaths).

The mean age was 49.1 years for the whole cohort and non-movers were older (56.8 years). A higher proportion of melanoma deaths occurred among males (59%). 64% of the cohort were married, followed by 21% who were single. German speaking individuals represented about 64% of the cohort. Only 23% of the participants had low education level. 4% of individuals had an outdoor occupation with possible UV exposure. Most of the characteristics among non-movers and the whole population were similar expect for age and marital status (Table 1). Population characteristics for cases of death from secondary outcomes (NMSC, and all skin cancer combined) are shown in Table S1. The average exposure and standard deviation (SD) of the whole cohort was 75.9 (32.0) Bq/m^3 for radon and 19.0 (1.1) mW/m^2 for UV (Table 1, Fig. S2). We found little correlation between radon and UV exposures ($r = 0.13$).

The associations between radon and UV exposures and melanoma mortality for different ages in mutually adjusted models is shown in Table 2. Though not statically significant at all ages, associations with both exposures were stronger in younger compared to older ages. HRs at age 60 were 1.10 (95% CI: 0.99, 1.23) per 100 Bq/m^3 radon and 1.05 (95% CI: 1.01, 1.09) per 1 mW/m^2 UV exposure. The dose–response curve for residential radon exposure and MM deaths showed a linear trend from the minimum radon exposure until around 75 Bq/m^3, which is very close to the mean value of cohort. Beyond that level of radon, the HRs flattened and showed little change (Fig. 1, Fig. S3 shows linear model superimposed on the spline). The AIC were remarkably similar, with a value of 80071.17 and 80071.60 for the linear and natural spline with 3 df, respectively. The categorical model also indicated a risk increase followed by flattening in the higher exposure range, but overall was not inconsistent with a linear model given the width of the confidence intervals (Table S2).

In the time-varying exposure analysis (Table 3) in which exposures were updated at 2011, associations were almost identical compared to main analysis. The correlation between radon exposure at baseline and at 2011 was 0.83 among movers and 0.97 among non-movers. Substituting the radon exposure modelled with the more simple linear regression, instead of the random forest, marginally increased the HRs at age 60 in the fully adjusted model for MM (HRs [95% CI]: 1.14 [1.00, 1.29]). The non-movers analysis showed slightly higher HRs for residential radon exposure, though with wider confidence intervals. Exposure to UV resulted higher HRs compared to residential radon exposure when HRs were expressed as IQR (Table S3).

When investigating different death outcomes, at age 60 the HRs (95% CI) per 100 Bq/m^3 for residential radon exposure were 1.06 (0.75, 1.49) and 1.09 (0.99, 1.21) for NMSC and SC, respectively (Table 3). UV exposure was significantly associated with both MM and SC.

There was little evidence of effect modification of the exposure-outcome association in the main model, except for occupational environment in relation to UV exposure only. Having an outdoor occupation increased the effect of UV exposure, with a higher risk of melanoma mortality (age 60 HRs [95% CI]: 1.27 [1.10, 1.46] vs 1.03 [0.99, 1.06] with indoor occupation at baseline) (Table S4).

The new cohort based on those over 20 years old at 2011 and followed for 5 years generally showed similar results for radon exposure

Table 1
Population characteristics in the cohort and amongst malignant melanoma deaths.

Characteristics	Cohort		Deaths from MM[c]
	Full study sample	Non-movers[b]	
Participants, n (%)	4,904,443 (100)	2,424,382 (49.4)	3,979 (0.08)
Age			
Mean (SD)	49.1 (17.0)	56.8 (16.3)	62.7 (14.5)
Sex, n (%)			
Men	2,356,193 (48.0)	1,143,456 (47.2)	2,349 (59.0)
Women	2,548,250 (52.0)	1,280,926 (52.8)	1,630 (41.0)
Civil status, n (%)			
Single	1,048,442 (21.4)	389,494 (16.1)	426 (10.7)
Married	3,143,151 (64.1)	1,637,374 (67.5)	2,761 (69.4)
Widowed	347,941 (7.1)	259,580 (10.7)	505 (12.7)
Divorced	364,909 (7.4)	137,934 (5.7)	287 (7.2)
Mother tongue, n (%)			
German	3,160,716 (64.4)	1,658,408 (68.4)	2,914 (73.2)
French	961,929 (19.6)	482,517 (19.9)	708 (17.8)
Italian	353,478 (7.2)	190,678 (7.9)	256 (6.4)
Other	428,320 (8.7)	92,779 (3.8)	101 (2.5)
Education level[a]			
Low	1,152,616 (23.5)	659,333 (27.2)	987 (24.8)
Medium	2,612,849 (53.3)	1,326,836 (54.7)	2,075 (52.1)
High	1,013,917 (20.7)	415,689 (17.1)	871 (21.9)
Not known	125,061 (2.5)	22,524 (0.9)	46 (1.2)
Occupational environment, n (%)			
Indoor	2,920,404 (59.5)	1,171,683 (48.3)	1,528 (38.4)
Outdoor	214,673 (4.4)	113,291 (4.7)	136 (3.4)
Not in paid employment or retired	1,769,366 (36.1)	1,139,408 (47.0)	2,315 (58.2)
Radon exposure, Bq/m^3			
Mean (SD)	75.9 (32.0)	79.2 (34.3)	78.6 (34.0)
Range	25.6–1154.1	25.7–1154.1	27.9–500.1
Interquartile range	32.9	36.0	34.0
UV exposure, mW/m^2			
Mean (SD)	19.0 (1.1)	19.0 (1.1)	19.0 (1.1)
Range	17.4–29.1	17.4–28.5	17.3–24.6
Interquartile range	1.6	1.6	1.5

[a] Highest completed education; low = compulsory (primary and lower secondary) or less, medium = upper secondary, high = tertiary.
[b] Non-movers have the same residential addresses between 1990 and 2001.
[c] MM: malignant melanoma as the definitive primary cause of death.

Table 2
Association of radon and UV exposure and melanoma mortality in mutually adjusted models, for different ages.

Age	Radon[a] (per 100 Bq/m^3)	UV[a] (per 1 mW/m^2)
30	1.24 (0.95, 1.60)	1.11 (1.01, 1.22)
45	1.17 (0.98, 1.39)	1.08 (1.01, 1.15)
60	1.10 (0.99, 1.23)	1.05 (1.01, 1.09)
75	1.04 (0.94, 1.16)	1.02 (0.98, 1.06)

Note: Adjusted model included: radon and UV exposures, age as time scale, strata for 5 years of calendar time and sex, and were adjusted for civil status, mother tongue, education level, socio-economic index, occupational environment, and included an interaction term between age and one of the exposures (centred age * exposure).
[a] Hazard ratios and 95% confidence intervals in brackets.

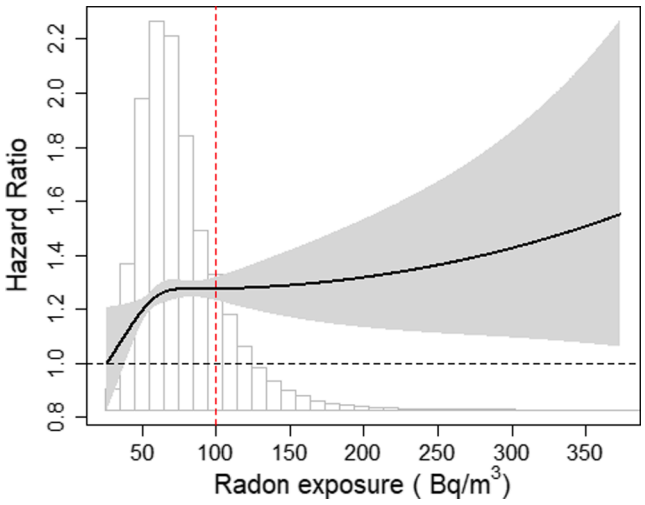

Fig. 1. Dose-response curve of radon exposure and malignant melanoma mortality, age 60. Natural spline with three degrees of freedom (black line), showing the 95% confidence intervals (grey area). Vertical dashed red line indicates the guideline limit of 100 Bq/m^3 radon concentration. Background bars show the distribution radon exposures. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Sensitivity analyses on radon and UV exposure and melanoma mortality and secondary analyses for other outcome definitions, age 60.

Analysis[a]	Deaths	Radon (per 100 Bq/m^3) HRs (95% CIs)	UV (per 1 mW/m^2) HRs (95% CIs)
Main			
MM	3979	1.10 (0.99, 1.23)	1.05 (1.01, 1.09)
Sensitivity analyses for MM			
Time-varying exposure updated at year 2011	3979	1.09 (0.98, 1.21)	1.05 (1.01, 1.10)
Substitute radon exposure with linear model	3979	1.14 (1.00, 1.29)	1.04 (1.00, 1.07)
Non-movers between 1991 and 2001[b]	2805	1.14 (1.00, 1.30)	1.07 (1.01, 1.13)
Secondary analyses for other outcome definitions			
NMSC	1118	1.06 (0.75, 1.49)	1.09 (0.96, 1.23)
SC (MM + NMSC)	5097	1.09 (0.99, 1.21)	1.06 (1.02, 1.10)

Note: Adjusted models included: radon and UV exposures, age as time scale, the interaction term between age and one of the exposures (centred age 60 * exposure), strata for 5 years of calendar time and sex, and were adjusted for civil status, mother tongue, education level, socio-economic index, and occupational environment.
[a] MM: malignant melanoma, NMSC: non-melanoma skin cancer, SC: skin cancer.
[b] Total population in non-movers analysis was 2,424,382.

compared to the main analysis (Table 4). Slightly higher HRs were observed for UV in relation to MM, NMSC and SC in the new cohort. The HR derived using the new cohort, however, had notably larger confidence intervals.

4. Discussion

In this Swiss-wide study, we found a borderline significant association between residential radon exposure and melanoma mortality (HRs [95% CI]: 1.10 [0.99, 1.23] per 100 Bq/m^3, at age 60) after accounting for long-term residential UV exposure and other important covariates.

Table 4
Analysis in the new cohort (2011–2015), associations of radon and UV exposure and different mortality outcomes, age 60.

		Radon[a] (per 100 Bq/m^3)		UV[a] (per 1 mW/m^2)	
Outcome	Deaths	Base model[b]	Adjusted model[c]	Base model[b]	Adjusted model[c]
Main (follow-up 2001–2015)					
MM	3979	1.12 (1.01, 1.24)	1.10 (0.99, 1.23)	1.00 (0.96, 1.03)	1.05 (1.01, 1.09)
New cohort (follow-up 2011–2015)					
MM	1418	1.16 (0.99, 1.36)	1.10 (0.92, 1.31)	1.02 (0.96, 1.08)	1.08 (1.01, 1.16)
NMSC	466	1.11 (0.65, 1.92)	1.11 (0.63, 1.95)	1.10 (0.92, 1.31)	1.15 (0.94, 1.41)
SC (MM + NMSC)	1884	1.15 (0.98, 1.34)	1.09 (0.91, 1.30)	1.03 (0.97, 1.09)	1.10 (1.03, 1.17)

Note: The new cohort contains 4,826,745 individuals. MM: malignant melanoma, NMSC: non-melanoma skin cancer, SC: skin cancer.
[a] Hazard ratios and 95% confidence intervals are in brackets.
[b] Base model included: radon and UV exposures, age as time scale, the interaction term between centred age and one of the exposures (age at 60 * exposure), strata for 5 years of calendar time and sex.
[c] Adjusted model included: radon and UV exposures, age as time scale, the interaction term (age at 60 * exposure), strata for 5 years of calendar time and sex, and were adjusted for civil status, mother tongue, education level, socio-economic index, and occupational environment.

Long-term residential UV exposure was associated with increased melanoma mortality (HRs [95% CI]: 1.05 [1.01, 1.09] per 1 mW/m^2, at age 60). Expressed as interquartile range (IQR) to obtain comparable effects, the HRs for radon exposure were lower than for UV exposure (Table S2). This finding corroborates the well-known evidence that cumulative UV exposure is the main causal factor for skin cancer (Rastrelli et al., 2014; Didona et al., 2018). Our findings for radon support a previous study conducted in Switzerland (Vienneau et al., 2017), that reported HRs of 1.16 (95% CI: 1.05, 1.28) per 100 Bq/m^3 radon. Thus, with an extended eight years of follow-up and new exposure models, we confirmed and updated the risk estimates. We also independently validated our findings using newer data not included in the previous study, with a sensitivity analysis focusing on a cohort of individuals 20 years and older starting in 2011. Finally, we investigated the shape of the exposure–response relationship.

The main difference between this and the previous Swiss study (Vienneau et al., 2017) is the extended follow-up in the SNC necessitating new exposure models to better capture the long term exposures. For residential radon exposure, Vienneau et al. (2017) used the model developed by Hauri et al. (2012), based on 44,631 measurements from the Swiss Radon Database between 1994 and 2004. In this study, an updated radon model was developed with almost twice the number of measurements from the same Swiss Radon Database recorded between 1994 and 2017 and improved prediction performance. Moreover, the UV exposure model was also updated with better resolution data from MeteoSwiss (Vuilleumier, 2021). Both studies have in common the use of individually assigned exposure models for both residential radon and UV exposures.

The hazard ratios of both radon and UV exposures in relation to melanoma mortality decreased with age, with a stronger trend for radon. It is well established that sensitivity to radiation is highest in younger ages, thus our findings are in line with existing knowledge (Tong and Hei, 2020; Wakeford, 2004). Additionally, several occupational cohort studies on workers exposed to ionizing radiation found an increasing carcinogenic effect with age and thus a U-shape relationship has been proposed with lowest radiation sensitivity in the middle age (Richardson and Wing, 1999; Ritz et al., 1999). We did not observe such an increase in risk at older ages but exposures in these occupational settings are typically much higher than would be expected from residential radon, which may explain the discrepancy.

We were also interested in the shape of the exposure response for the association between radon and MM. The natural spline was steeper in the lower exposure range with a flattening at higher levels. A similar pattern was indicated by the categorical analysis. While this shape clearly suggests the linear model underestimates the dose response in the lower exposure range, we found no strong statistical evidence to distinguish between the linear and natural spline models. Regardless of the exact shape, all model specifications point to a harmful effect of radon exposure. We focussed on and reported the linear no-threshold model which is easier to interpret and to compare to previous studies.

To the best of our knowledge, only a few studies have investigated the relationship between radon exposure and skin cancer (Wheeler et al., 2012; Turner et al., 2012; Wheeler et al., 2013; Brauner et al., 2015; Barbosa-Lorenzo, 2016; Vienneau et al., 2017). In those studies conducted elsewhere, the average radon concentrations were generally lower than the radon levels in Switzerland. Many were also based on incidence, which is preferable for etiological studies considering that most melanoma and skin cancer patients can be cured, thus are not captured in our mortality-based study. ICD-10 coding also does not enable distinction of BCC from SCC. Still we found borderline statistically significant association between radon exposure and deaths from SC (MM and NMSC combined) with a HR, at age 60, of 1.09 (95% CI: 0.99, 1.21) per 100 Bq/m^3. However, no association was found for NMSC alone (HRs [95% CI]: 1.06 [0.75, 1.49]), with the wide confidence interval possibly due to the small number of deaths during follow-up or non-differential outcome misclassification.

Since the exposures were assigned to individuals based on their residential addresses at baseline, any change in residency after the cohort start date may slightly alter the radon and UV exposures later in the follow-up. However, our sensitivity analysis within the subset of persons who have not moved between 1990 and 2001 showed similar results as the main findings (Table 3), with a slight increase in the HR point estimates for radon and MM as expected due to reduced exposure misclassification and better consideration of the cancer induction period. This was also observed previously by Barbosa-Lorenzo et al. (2016), where persons who had lived at the same address for at least 50 years had a HR of 2.7 (95% CI: 1.2, 6.5) for residential radon ($\geq$50 Bq/m^3 vs $<$50 Bq/m^3) for non-lung cancer mortality while in the whole cohort including movers the HR was 1.2 (95% CI: 0.9, 1.6). In other sensitivity analyses, we found very similar HRs for both exposures when updating the exposures and location at 2011 (i.e., time-varying exposure) (Table 3). This is not unexpected given the high correlation between exposures at the two time points. The HR point estimate from the new cohort (2011–2015), which included only the latter part of the SNC with deterministic linkage and data not included in our previous study, was also the same as the main finding for radon exposure and MM mortality. It should be noted that wider confidence intervals were observed for both exposures due to smaller number of outcomes.

We did not observe any effect modification for radon in relation to the occupational environment variable, but found higher point estimates with wide and overlapping confidence intervals for outdoor workers compared to people who work indoors. Assuming no correlation between work and home radon, indoor workers likely have additional radon exposure from their work place, which contributes to exposure misclassification in their residential radon exposure compared to outdoor workers. It should also be noted that the occupational environment variable is crude, as it was derived from a JEM for occupational UV exposure and ocular melanoma (Guénel et al., 2001) assigned at

baseline, and we lacked information on the duration of the occupation. The JEM did not define indoor vs outdoor occupation per se thus is even more crude for radon. Further, we did not have any information on whether individuals prefer to spend time indoors or outdoors when not working. We observed higher HRs for melanoma mortality in relation to UV exposure among people who had jobs that typically occurred in an outdoor working environment compared to indoors. There was no statistical indication that the effect of either exposure was modified by sex; however, the risk of melanoma mortality from radon was higher in women vs men, while the risk from residential UV was higher for men vs women. A possible explanation for the higher melanoma mortality risk in men from UV radiation would be higher percentage of men work outdoors with higher UV exposure. Although women are more likely to suntan (Hansen and Bentzen, 2014), women are also typically more aware of the risks and more likely to take sun protective measures compared to men (Görig et al., 2018). Additionally, men are more likely to underestimate the risks of sun exposure and have higher rates of reported sunburns (Haluza et al., 2015). We can only speculate that higher melanoma mortality risk in women from radon might be explained by behavioural differences between genders. A study from Germany showed that mean time spent indoors is higher in women compared to men at 25 and 65 years of age (Brasche and Bischof, 2005), thus the duration of exposure to residential radon may be higher. Another explanation might be that women are more sensitive than men to long-term exposure to ionizing radiation and more likely to suffer from radiation-induced cancers (Narendran et al., 2019). However, these studies are based on cancer sites where the baseline risk levels differ greatly between men and women. Also, there is no evidence on radiation induced melanoma risk difference according to sex (Shore, 2001).

The strengths of the present study are the census-based individual data that include information on demographics and dwellings, with a long follow-up. Further the large population of this study provides enough statistical power to detect small effects. We also used updated exposure prediction models, and assigned exposures to each individual based on their geo-location and floor of residence. The main limitation is the use of mortality rather than incidence from melanoma, with deaths reflecting only 7.3% of incident melanoma cases in Switzerland (IARC, 2020). This percentage is even smaller (less than 1%) for other types of skin cancer (IARC, 2020). The potential for outcome misclassification due to the use of death certification may also be an issue, however an evaluation for Switzerland indicated 95% agreement between hospital discharge records and death statistics for skin melanoma (Zellweger et al., 2019). Further study based on incidence of melanoma and non-melanoma skin cancer is warranted to thoroughly assess the role of residential exposure to radon in Switzerland. We also used long-term average ambient UV, as the measure of residential UV exposure, which is more representative of chronic sun exposure. Ambient UV, however, represents only around one-fifth of the lifetime UV exposure received by individuals (Dadvand et al., 2011), and for MM, acute and intermittent exposure is more relevant. Furthermore, our cohort has no information about vacation destinations and sun bathing behaviours of the individuals. Considering that the number of persons engaging in outdoor activities in Switzerland is relatively high compared to other European countries (Cavill et al., 2006; FSO, 2012), the UV exposure model used in our study does not fully represent the variations in the population. We also lack information on sun protective behaviours and natural shading which can substantially decrease the amount of UV that is received by individuals (Ackermann, 2016). We also did not have time activity data to indicate how long individuals are typically at home vs at work or in outdoor environments where exposure to both radon and UV may differ. For radon, the modelled residential concentrations might not fully capture the radiation dose received by residents due to personal ventilation behaviour which can modify the indoor radon concentration (Chenari et al., 2016). These types of exposure measurement error, however, typically underestimate effects. Additionally, for radon decay products to potentially induce skin cancer, direct exposure of uncovered and thinner parts of the skin is needed (Eatough and Henshaw, 1992). Information on clothing behaviours, which would also be relevant for UV exposure, were not available in this national cohort based on administrative data.

5. Conclusion

Limited information is available on the effect of residential radon exposure on the risk of skin cancer. The results of this nationwide prospective cohort study suggest that residential radon exposure is a relevant risk factor for melanoma even when taking long term-average residential UV exposure into account. Hence, increasing public awareness of radon and its risks on human health and interventions to reduce existing residential radon levels via built-in solutions applicable to the dwellings are essential from a public health perspective. Further studies, including those on incidence and in populations with additional individual-level behaviour data, are necessary to have a better understanding of the effect of residential radon on skin cancer.

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CRediT authorship contribution statement

Seçkin Boz: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Claudia Berlin:** Data curation, Investigation, Methodology, Writing – review & editing. **Marek Kwiatkowski:** Investigation, Methodology, Writing – review & editing. **Murielle Bochud:** Investigation, Methodology, Writing – review & editing. **Jean-Luc Bulliard:** Investigation, Methodology, Writing – review & editing. **Marcel Zwahlen:** Data curation, Investigation, Methodology, Writing – review & editing. **Martin Röösli:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. **Danielle Vienneau:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing 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.

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Appendix A. Supplementary material

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