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

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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.

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# 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+

2001 2012

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

4,937 cutaneous malignant melanoma (MM)

Cox Proportional Hazard Models



n Ambient UV

Age as time scale + age categories + sex + education + socioeconomic 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 1 incidence in Switzerland 2 Seçkin Boz<sup>1,2</sup>, Marek Kwiatkowski<sup>1,2</sup>, Marcel Zwahlen<sup>3</sup>, Murielle Bochud<sup>4</sup>, Jean-Luc Bulliard<sup>4,8</sup>, Isabelle 3 Konzelmann<sup>5</sup>, Yvan Bergeron<sup>6</sup>, Elisabetta Rapiti<sup>7</sup>, Manuela Maspoli Conconi<sup>8</sup>, Andrea Bordoni<sup>9</sup>, Martin 4 Röösli<sup>1,2</sup>, Danielle Vienneau<sup>1,2\*</sup> 5 6 Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Allschwil, 1. 7 Switzerland 8 2. University of Basel, Basel, Switzerland 9 Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland 3. 10 Centre for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland 4. 11 5. Valais Cancer Registry, Valais Health Observatory, Sion, Switzerland 12 6. Fribourg Cancer Registry, Fribourg, Switzerland 13 7. Geneva Cancer Registry, Geneva University, Geneva, Switzerland 14 Neuchâtel Cancer Registry, Neuchâtel, Switzerland 8. 15 9. Ticino Cancer Registry, Institute of Pathology South of Switzerland, Locarno, Switzerland 16 \*Corresponding Author: 17 Danielle Vienneau (PhD) 18 Department of Epidemiology and Public Health 19 Swiss Tropical and Public Health Institute

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## 24 Conflict of interest

25 The authors declare they have nothing to disclose.

26

## 27 **1** Abstract

28 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

30 to ionizing radiation from radon. We aimed to evaluate the association between residential radon

31 exposure and melanoma and squamous cell carcinoma incidence.

32 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)

35 were identified using data from cantonal cancer registries. Long-term residential radon and ambient

36 solar ultraviolet radiation exposures were assigned to each individual's address at baseline. Cox

37 proportional hazard models with age as time scale, adjusted for canton, socioeconomic position,

38 demographic data available in the census, and outdoor occupation were applied. Total and age specific

39 effects were calculated, in the full population and in non-movers, and potential effect modifiers were

40 tested.

41 In total 4937 incident cases of melanoma occurred during an average 8.9 years of follow-up. Across

42 all ages, no increased risk of malignant melanoma or squamous cell carcinoma incidence in relation to

43 residential radon was found. An association was only observed for melanoma incidence in the

44 youngest age group of 20-29 year olds (1.68 [95% CI: 1.29, 2.19] 100 Bq/m<sup>3</sup> radon). This association

45 was mainly in women, and in those with low socio-economic position.

46 Residential radon exposure might be a relevant risk factor for melanoma, especially for young adults.

47 However, the results must be interpreted with caution as this finding is based on a relatively small

48 number of melanoma cases. Accumulation of radon is preventable, and measures to reduce exposure

49 and communicate the risks remain important to convey to the public.

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

51

## 52 **2** Introduction

Radon-222 is a naturally occurring radioactive noble gas and a product of the decay processes of 53 54 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.<sup>1,2</sup> Buildings are 55 susceptible to radon accumulation through the release of gas from building materials, diffusion from 56 57 water systems and drains, and through cracks in the foundations.<sup>3</sup> The primary contributors to indoor 58 radon concentration are local geology (granite and metamorphic rocks) and soil, with the rate of 59 transfer into buildings influenced by various factors such as ventilation, temperature differential, and building material permeability.<sup>4,5</sup> Radon has been estimated to contribute 40% of the overall annual 60 radiation exposure in Switzerland.<sup>6</sup> 61

62 The International Agency for Research on Cancer classifies radon as a Group 1 carcinogen based on 63 the evidence from early epidemiological and experimental studies on lung and respiratory track tumours.<sup>7</sup> A causal link was established between radon exposure and lung cancer based on the strong 64 evidence from occupational, case-control, general population cohorts, occupational and experimental 65 animal model studies.<sup>8-12</sup> The lung and respiratory tract are the organs that are the most affected by 66 radon exposure through inhalation, with dosimetry indicating that the skin receives the next highest 67 68 dose.<sup>13</sup> Radon and short-lived radon daughters (polonium, bismuth, and lead) emit alpha and beta particles.<sup>14</sup> These alpha and beta emitting decay products can attach to aerosol particles via 69 70 electrostatic interactions and deposit on the skin surface.<sup>15</sup> The emitted particles can travel through the skin tissue and deposit their energy.<sup>16</sup> Stem cells are located in the basal layer of the epidermis and 71 72 within range of both alpha and beta particle penetration. Alpha particles, that penetrate less deep, can 73 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). <sup>17,18</sup> Alpha particles can also induce a negative effect to cells that 74 75 are not directly irradiated via cell signalling from irradiated neighbour cells, which is called bystander effect. <sup>19</sup> For these reasons, radon and its progeny can potentially irradiate the skin, reaching the basal 76 layer of the epidermis to induce skin cancer.<sup>20,21</sup> The annual radiation dose to the skin from radon 77 exposure in indoor air at a level of 200 Bq/m<sup>3</sup> has been estimated to be 25 mSv.<sup>13</sup> It has further been 78 79 estimated that around 0.7% (0.5% to 5%) of skin cancer incidence could be attributed to the radon exposure at 20 Bq/m<sup>3</sup> level.<sup>22</sup> Lastly, a recent experimental study on mice indicate that radon exposure 80 could affect the structure of the skin, induce damage and result in dysregulation of gene expression.<sup>23</sup> 81

82 Melanoma (MM) is a type of skin cancer that develops from melanocytes in the basal layer of the

83 epidermis and has a much higher mortality rate than non-melanoma skin cancers (NMSC), specifically

84 squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).<sup>24</sup> However, the relationship between

85 residential radon exposure and skin cancers is not well understood, with conflicting results among the

86 few available studies. One of the first epidemiological studies investigating the relationship between

- 87 radon and melanoma incidence was conducted among Czech uranium miners and reported a non-
- 88 significant increased risk.<sup>25</sup> Two ecological studies conducted in southwest England found higher
- 89 incidence rates for SCC and NMSC in areas with higher radon levels.<sup>26,27</sup> A Danish study, with
- 90 modelled radon concentration at residential addresses, found an increased risk of BCC incidence, but
- 91 not other types of skin cancer.<sup>28</sup> A cohort study in the Galicia region of Spain found a statistically
- 92 significant risk of NMSC incidence for people living in homes with measured radon levels greater
- 93 than 50 Bq/m<sup>3</sup> compared to those with lower levels.<sup>29</sup> The complex nature of the relationship between
- radon exposure and skin cancer incidence may vary depending on the cancer subtype, the level and
- 95 duration of exposure, and individual susceptibility.
- 96 Prior research on the relationship between radon and skin cancer in Switzerland focused on mortality.
- 97 The first study found that radon exposure increased the risk of death from MM and all skin cancers
- 98 when the erythemal-weighted UV dose was taken into account.<sup>30</sup> With longer follow-up and updated
- 99 residential radon and ambient UV exposure models, a subsequent study showed a smaller increased
- 100 risks. The hazard ratios (HRs) and 95% confidence intervals (CIs) for 100 Bq/m<sup>3</sup> radon increase were
- 101 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
- 102 and all skin cancers combined, respectively<sup>31</sup>.
- 103 Given that deaths from melanoma represent only about 18% of incident cases,<sup>32</sup> studies on melanoma
- 104 incidence can provide more sensitive risk estimates to complement previous mortality research. We
- 105 aimed to investigate the association between radon exposure and melanoma incidence using robust,
- 106 nation-wide individual level radon and UV exposures.

## 107 **3** Methods

### 108 **3.1** Swiss National Cohort & Cancer registries

109 This study is based on a cohort constructed by combining data from selected cantonal cancer registries 110 and the Swiss National Cohort (SNC). The SNC longitudinal research platform links nation-wide 111 censuses to mortality and emigration records <sup>33</sup>. As it is census-based, involvement is mandatory and 112 the SNC captures an estimated 98.6% of the Swiss population in 2000.<sup>34</sup>

- 113 The incidence cases (detailed below) were obtained from each cantonal cancer registry (CR)
- 114 separately for the following six south-western Swiss cantons: Vaud (VD), Neuchâtel (NE), Valais
- 115 (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
- 117 were obtained through the National Institute for Cancer Epidemiology and Registration (NICER) and
- 118 each individual cancer registry. These records were transferred to the Center for Primary Care and
- 119 Public Health (Unisanté) to consolidate into a single, consistent database with all skin cancer cases.

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

125 The malignant melanoma and squamous cell cancer (C43 and C44, respectively) cases were

- 126 determined by using International Classification of Disease for Oncology, Third edition (ICD-O-3),
- 127 codes.<sup>37</sup> Using morphology codes defining the histologic composition of cancer cells within the
- 128 primary cancer, we distinguished cutaneous malignant melanoma (8720-8790), and squamous cell
- 129 carcinoma (8050-8084, 8560-8574). No *in situ* cases were included. Incident melanoma was used as
- 130 the main outcome.

### 131 **3.2** Study population & Follow-up

All adults aged 20 years and older and living in the cantons of Vaud, Neuchâtel, Valais, Geneva, 132 133 Fribourg, and Ticino were included. Given the one-time linkage with the SNC, cases within each CR 134 were included from December 4, 2000 (as the earliest possible date) to December 31 2011. The exact 135 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; 136 137 Geneva: 2000 to 2009; Fribourg: 2006 to 2011; Ticino: 2000 to 2008) (Figure S1). Most CRs were 138 registering skin cancers at the time of the 2000 census, except for Fribourg which began on January 1, 139 2006. Hence, people living in Fribourg were included in the analyses with delayed entry.

### 140 **3.3** *Exposure assessments*

We utilized the same exposure assessments for both residential radon and ambient UV exposures as in 141 the previous nationwide study on melanoma mortality in Switzerland.<sup>31</sup> Based on their residential 142 coordinates at baseline, modelled indoor radon (in Bq/m<sup>3</sup>) and ambient UV (in mW/m<sup>2</sup>) exposures 143 144 were assigned to each participant. The residential radon exposure model used here was developed using a random forest approach and is fully described elsewhere. <sup>38</sup> The model was based on ~80,000 145 146 measurements collected from 1994 to 2017 and stored in the Swiss radon database by the Federal Office for Public Health (FOPH).<sup>39</sup> The measurement dataset was divided into 5 random subsets, for a 147 148 5-fold modelling strategy to evaluate robustness (i.e. 5 models, each with 80% data were used for 149 model development and the remaining 20% for validation). The average of the 5 models was used to 150 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 151 152 2005), lithology, texture of the soil, groundwater quality and depth, terrestrial radiation, distance to the 153 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 154

showed the models to be robust, though the performance metrics indicated uncertainty (R<sup>2</sup> 0.31;
Spearman's rank correlation 0.51; root-mean-squared-error 0.74 ln Bq/m<sup>3</sup>). 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. <sup>38</sup> The residential radon
exposure distributions, including community level averages for illustrative purposes only, are shown
in Figure 1.

161 The monthly UV climatology data covering the period from 2004 until 2016 were provided by

162 MeteoSwiss with a spatial resolution of 1 x 1 km.<sup>40,41</sup> These monthly data were used to calculate an

163 annual average of the whole period and assigned to the coordinates of the participants at baseline.

164 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").<sup>42</sup>

### 167 **3.4** Statistical methods

The Cox proportional hazard model was used with age as a time scale.<sup>43</sup> All participants were 168 169 considered at risk as of the date of the census (04.12.2001), except for those in Fribourg where 170 01.01.2006 was used (cancer registry in Fribourg was created in 2005 and considered complete from 171 2006 onwards). Follow up ended on the last day of 2011 for participants living in canton Vaud, 172 Neuchâtel, and Fribourg; 2010 for Valais; 2009 for Geneva; and 2008 for Ticino. Participants were 173 followed-up until that date or until one of the following events: the first occurrence of malignant 174 melanoma, death, emigration from the country, or other loss to follow-up. The date of diagnosis was 175 only available as a month and year, thus each event was considered to have happened on the 15<sup>th</sup> day 176 of the month.

- The Cox model included residential radon exposure <sup>38</sup> and ambient UV exposure <sup>41</sup> both as continuous
  variables. It was adjusted for: canton as a fixed effect to account for differences in background
- 179 incidence of melanoma; population demographics and administrative variations between cantonal
- 180 CRs; education attainment (compulsory school, upper secondary, tertiary, unknown) because of
- 181 known differences in care-seeking;<sup>44</sup> marital status (single, married, widowed, divorced), to reflect
- 182 differences in lifestyle and culture; and Swiss-SEP <sup>36</sup> (continuous). The model was stratified by sex
- 183 (men, women), mother tongue (German, French, Italian, other), and outdoor occupation (binary:
- 184 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-
- 186 log plots and Kaplan-Meier survival curves.<sup>45</sup>
- 187 First, estimates for the overall population were derived. Biological considerations <sup>46</sup> and the previous
- 188 study for Switzerland on skin cancer mortality <sup>31</sup> 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

- 190 interaction term was introduced between radon exposure and age group to obtain age-specific
- 191 estimates. Hazard ratios and 95% confidence intervals were reported per 100 Bq/m<sup>3</sup> radon (the annual
- 192 average residential radon concentration reference level set by the WHO<sup>11</sup>) to obtain effect estimates
- 193 comparable to previous similar studies.<sup>28,30,31</sup> A sensitivity analysis was carried out on the sub-set of
- 194 non-movers identified as those who lived at the same address in both the 1990 and 2000 census (thus
- 195 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
- 197 investigated by comparing the models with and without an interaction term with radon exposure; the
- 198 reported HRs and p-values from the likelihood ratio test were calculated by age group.
- 199 The main outcome definition was incidence of primary malignant melanoma. We also conducted
- 200 secondary analyses using SCC incidence as outcome. Different to the main analysis, the secondary
- 201 analysis excluded Ticino due to lack of records for SCC, and the Fribourg follow-up was until end of
- 202 2012 (Figure S1). BCC was not investigated as a secondary outcome because it is less consistently
- 203 registered and incomplete in most cancer registries.
- 204 Individuals in cancer registries may have multiple entries if diagnosed with more than one type of skin
- 205 cancer (SCC or BCC, in addition to melanoma). Because UV exposure is the major risk factor for all
- 206 types of skin cancers, and behaviours that lead to UV exposure may change after diagnosis or
- 207 treatment, we censored upon diagnosis of other skin cancers (SCC or BCC) in a sensitivity analysis.

## 208 **4** Results

- 209 The study population comprised 1,575,923 adults living in the six studied cantons, representing 21.7
- 210 % 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
- 212 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
- 214 missing SEP index. The remaining 1,362,919 participants were included in the analysis with total of
- 215 12,120,549 person years of follow-up (average 8.9 years) and 4,937 primary malignant melanoma
- cases.
- 217 The average age of the full study population and melanoma cases were 49.1 and 55.7 years,
- 218 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
- 220 married, French speaking, and had completed upper secondary education. Approximately 4% of the
- 221 cohort were working outdoors with potential for UV exposure (Table 1). The percentages of
- 222 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,

223 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
- 225 76.4 Bq/m<sup>3</sup> with a standard deviation of 40.6 Bq/m<sup>3</sup>, approximately 20% of individuals were living in
- homes with residential radon exposure exceeding the established guideline limit of  $100 \text{ Bq/m}^3$  by
- 227 World Health Organization (Figure S3). Radon and ambient UV exposures were not correlated (r =
- 228 0.08).

229 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<sup>3</sup>. A risk increase was only found in the
- youngest age group (1.68 [1.29, 2.19] per 100 Bq/m<sup>3</sup>). Similar results were observed when the analysis
- 232 was restricted to non-movers (Table 2).
- 233 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.
- 236 In the secondary analysis, we found no association between radon exposure and SCC incidence (Table
- 237 S2). The sensitivity analysis where we also censored on the first diagnosis of SCC or BCC, if
- 238 occurring before a melanoma diagnosis, did not change the main results (Table S3 vs. Table 2).

## 239 **5 Discussion**

240 In this cohort study including cantons in Switzerland prone to radon, no association was found 241 between residential radon exposure and incidence of cutaneous malignant melanoma or squamous cell 242 carcinoma. Even the analysis restricted to non-movers, where exposure misclassification is expected to 243 be reduced, showed no association. The only increased risk for melanoma incidence in relation to 244 radon exposure was in the youngest adults (aged 20-29), and based on a relatively small number of 245 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 246 age, the association between radon exposure and melanoma incidence was stronger among women and 247 248 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.<sup>30,31</sup> 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

256 the complex relationship between exposure and the outcomes, we cannot exclude these biases. On the 257 other hand, the observed stronger effects of radon on melanoma incidence for younger adults and 258 women is consistent with the previous studies on melanoma mortality, suggesting the link between 259 radon exposure and melanoma risk should not be dismissed. For squamous cell carcinoma, however, 260 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 261 that reported statistically significant excess relative risks for BCC and SCC but not for MM.<sup>47</sup> Within 262 263 Mayak nuclear facility workers who were chronically exposed to ionizing radiation, a higher risk for BCC but not SCC was found.<sup>48</sup> Together these finding might indicate the exposure to ionizing 264 radiation is more related to risk of BCC, a notion that is supported by the findings of the Danish Diet, 265 Cancer and Health cohort study.<sup>28</sup> Unfortunately BCC incidence as an outcome could not be 266 267 considered in our analysis.

That we only saw signs of a relationship for melanoma in the young adults could relate to ionizing 268 radiation having more effect early in life.<sup>49</sup> Previous evidence supports that the carcinogenic effect of 269 ionizing radiation is age dependent, <sup>50-52</sup> but also that risks related to age at exposure can differ 270 depending on the cancer type. <sup>53</sup> Excess risks seem to decrease with age at exposure for stomach and 271 thyroid cancers, while the risk of breast and lung cancers gradually increases at older ages.<sup>54</sup> 272 Regarding skin cancer, a study among atomic bomb survivors indicated a one year of decrease in age 273 at exposure related to an 11% increase in the risk of BCC. The results, however, were inconclusive for 274 melanoma due to a low number of cases.<sup>47</sup> A similar pattern was also found in a study on BCC in 275 relation to radiation therapy. The relative risk was highest among people who received radiation 276 therapy during childhood, and the risk gradually decreased with the age at exposure.<sup>55</sup> Considering that 277 the risk from ionizing radiation does not diminish for decades for many solid cancers including skin.<sup>56</sup> 278 279 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 280 281 association among young adults who were non-movers, with exposure at baseline also reflecting 282 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 283 thinner and gradually increase from birth to adulthood. <sup>57</sup> The thickness of skin reaches its maximum 284 285 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. <sup>58</sup> 286

287 Evidence suggests that the effect of ionizing radiation is different on males and females.<sup>59</sup> The report

288 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

290 cancer compared to men when exposed to the same amount of radiation.<sup>60</sup> The susceptibility, however,

291 can vary greatly from no known differences by sex for certain solid cancers to large differences for

- 292 other cancer types. For example, a pooled cohort study among nuclear workers occupationally exposed 293 to ionizing radiation in the United States observed no significant effect modification by sex for non-294 smoking related radiogenic cancer (bone, skin, brain, breast, central nervous system, thyroid).<sup>61</sup> For 295 malignant skin cancers, a Russian cohort study among nuclear facility workers exposed to gamma-rays 296 also did not observe any modification of excess relative risk by sex.<sup>62</sup> We can only speculate that 297 higher risk of melanoma with regard to residential radon exposure observed in our study, and 298 primarily in the youngest women, might be due to women having thinner skin or spending more time
- indoor at home than men.<sup>63</sup>
- 300 Socio-economic status is also associated with melanoma incidence, with higher incidence reported in
- 301 educated high income populations.<sup>64</sup> Similarly, we observed statistically significant positive
- 302 coefficients for continuous socio-economic status and higher coefficients in those with higher attained
- 303 education (upper secondary and tertiary) compared to those in a lower category (data not shown). The
- 304 possible reasons could relate to behaviours such that people with higher socioeconomic status are
- 305 more likely to travel to destinations with higher UV exposure, such as mountains or seaside holidays,
- 306 compared to people with lower socioeconomic status,<sup>65</sup> and they are more likely to examine their skin
- 307 regularly and undergo screenings.<sup>64</sup> We saw no risk, however, in the high SEP population group in the
- 308 effect modification analysis. It may be that any small increase in risk has been masked by the
- 309 substantially higher risk from recreational UV exposure.<sup>66</sup> Instead the noted higher risk of melanoma
- 310 incidence in relation to radon exposure in the lower SEP group, especially in the younger adults, might
- 311 be explained by lower quality housing and lack of access to or the cost of remedial efforts. The
- 312 national level radon remediation survey for Switzerland revealed that the major reasons for not taking
- 313 action against high residential radon levels are the high cost of the required renovations and that radon
- 314 is not considered a health risk,<sup>39</sup> 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
- 320 systematic and can be considered as complete for all the CRs used in this study.
- 321 Still it must be acknowledged that exposure was modelled for, not measured in, every home. We also
- 322 did not have data on behaviours that may influence radon exposure, such as the amount of time spent
- 323 indoors and ventilation practices at home. Exposure misclassification due to these factors cannot be
- 324 avoided and is a limitation of this study. Future studies may be better suited to address these issues.
- 325 We also could not include adults across the whole of Switzerland, because of unavailability of
- 326 previously linked cancer registries to SNC. However, the study covered most cantons with known high
- 327 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 328 329 exposure. Further, high intensity intermittent UV exposures, especially in childhood, are known to be more important than average ambient UV exposures for melanoma risk.<sup>66</sup> Unfortunately, we did not 330 have information about personal UV exposure history and sun-related protection behaviours, which 331 332 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 333 334 individuals, only considering residential radon may not have captured the total radon exposure given that indoor exposure may also occur in occupational settings<sup>67</sup>. Future studies could also consider 335 336 other designs and exposure assessment methods, such as individual long-term radon measurements 337 possibly considering time activity, to capture both residential and occupational exposures.

## 338 6 Conclusion

339 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 340 341 early stages of adulthood, in particular for women and those with lower socio-economic position. 342 Studies involving other cantonal cancer registries within Switzerland, or elsewhere, with longer 343 follow-up would help clarify the relationship between radon exposure and skin cancer risk. From a 344 public health perspective, and based on the stronger evidence for lung cancer, radon exposure remains 345 an important risk factor for the health of the general population. Therefore, prevention and mitigation 346 of radon gas in dwellings with high radon levels should continue to be promoted by governmental 347 organizations and international agencies.

## 348 7 Authors' contribution

349 Conceptualization (DV, MR); Data curation (CB, MZ, SB, DV); Formal analysis (SB, DV, MK);

- 350 Funding acquisition (DV, MR); Investigation (All); Methodology (All); Interpretation of results (All);
- 351 Project administration (DV); Supervision (DV, MR); Roles/Writing original draft (SB, DV); Writing

352 - review & editing (All).

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

# 354 8 Funding

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

## **356 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.

## 359 10 Acknowledgements

360 We thank the Swiss Federal Statistical Office for providing mortality and census data and for the

361 support which made the Swiss National Cohort and this study possible (grant nos. 3347CO-108806,

362 33CS30\_134273 and 33CS30\_148415). We also acknowledge the members of the Swiss National

363 Cohort Study Group: Matthias Egger (Chairman of the Executive Board), Adrian Spoerri Claudia

364 Berlin, and Marcel Zwahlen (all Bern), Milo Puhan (Chairman of the Scientific Board), Matthias Bopp

365 (both Zurich), Martin Röösli (Basel), Murielle Bochud (Lausanne) and Michel Oris (Geneva). We

366 thank Martha Palacios, Fabio Barazza, Christophe Murith and Daniel Storch at the Federal Office for

367 Public Health for providing the Swiss Radon Database and expert advice and appreciate the UV

368 climatology data produced within collaboration between Centre for Primary Care and Public Health

369 (Unisanté), University of Lausanne, and Federal Office of Meteorology and Climatology MeteoSwiss.

370 Lastly, S.B. gratefully acknowledges the grant received as "Study Abroad Program" (YLSY) from the

371 Ministry of National Education, Republic of Turkey.

## 372 **11 References**

- Avrorin VV, Krasikova RN, Nefedov VD, Toropova MA. The chemistry of radon. *Russian Chemical Reviews*. 1982;51(1):12.
- 375 2. National Research Council. *Health risks of radon and other internally deposited alpha-* 376 *emitters: BEIR IV.* vol 4. National Academies Press; 1988.

377 3. Nazaroff WW. Radon transport from soil to air. *Reviews of geophysics*. 1992;30(2):137-160.

4. Ramola R, Prasad G, Gusain G, Isotopes. Estimation of indoor radon concentration based on

radon flux from soil and groundwater. *Applied Radiation*. 2011;69(9):1318-1321.

Ruano-Ravina A, Wakeford R. The increasing exposure of the global population to ionizing
 radiation. *Epidemiology*. 2020;31(2):155-159.

382 6. Roth J, Schweizer P, Gückel C. Basis of radiation protection. *Schweizerische Medizinische*383 *Wochenschrift*. 1996;126(26):1157-1171.

- 384 7. IARC. Man-made mineral fibres and radon. *IARC monographs on the evaluation of* 385 *carcinogenic risks to humans*. 1988;43
- 8. Kang JK, Seo S, Jin YW. Health Effects of Radon Exposure. Yonsei Med J. Jul
- 387 2019;60(7):597-603. doi:10.3349/ymj.2019.60.7.597
- 388 9. Sethi TK, El-Ghamry MN, Kloecker GH. Radon and lung cancer. *Clin Adv Hematol Oncol.*389 2012;10(3):157-164.
- 390 10. Darby S, Hill D, Auvinen A, et al. Radon in homes and risk of lung cancer: collaborative

analysis of individual data from 13 European case-control studies. *BMJ*. Jan 29 2005;330(7485):223.
doi:10.1136/bmj.38308.477650.63

393 11. WHO. *WHO handbook on indoor radon: a public health perspective*. World Health

Organization; 2009.

Ruano-Ravina A, Martin-Gisbert L, Kelsey K, et al. An overview on the relationship between
 residential radon and lung cancer: what we know and future research. *Clinical and Translational*

- 398 13. Kendall G, Smith T. Doses to organs and tissues from radon and its decay products. *Journal of Radiological Protection*. 2002;22(4):389.
- 400 14. Darby S, Hill D, Doll R. Radon: a likely carcinogen at all exposures. *Annals of Oncology*.
  401 2001;12(10):1341-1351.
- 402 15. Eatough JP, Henshaw DL. Radon and thoron associated dose to the basal layer of the skin.
  403 *Physics in Medicine Biology*. 1992;37(4):955.
- 404 16. Eatough J, Henshaw D. The theoretical risk of non-melanoma skin cancer from environmental
  405 radon exposure. *Journal of Radiological Protection*. 1995;15(1):45.
- 406 17. Konishi E, Yoshizawa Y. Estimation of depth of basal cell layer of skin for radiation 407 protection. *Radiation protection dosimetry*. 1985;11(1):29-33.
- 408 18. Sandby-Møller J, Poulsen T, Wulf HC. Epidermal thickness at different body sites:
- relationship to age, gender, pigmentation, blood content, skin type and smoking habits. *Acta dermato- venereologica*. 2003;83(6):410-413.
- 411 19. Brenner D, Sachs R. Do low dose-rate bystander effects influence domestic radon risks?
- 412 International Journal of Radiation Biology. 2002;78(7):593-604.
- Eatough J. Alpha-particle dosimetry for the basal layer of the skin and the radon progeny 218Po and 214-Po. *Physics in Medicine Biology*. 1997;42(10):1899.
- 415 21. Charles MW. Radon exposure of the skin: I. Biological effects. *J Radiol Prot*. Sep
- 416 2007;27(3):231-52. doi:10.1088/0952-4746/27/3/R01
- 417 22. Charles MW. Radon exposure of the skin: II. Estimation of the attributable risk for skin cancer
  418 incidence. *J Radiol Prot.* Sep 2007;27(3):253-74. doi:10.1088/0952-4746/27/3/R02
- 419 23. Mo W, Xu W, Hong M, et al. Proteomic and miRNA profiling of radon-induced skin damage
  420 in mice: FASN regulated by miRNAs. *Journal of Radiation Research*. 2022;
- 421 24. Linares MA, Zakaria A, Nizran P. Skin cancer. *Primary care: Clinics in office practice*.

422 2015;42(4):645-659.

- 423 25. Kulich M, Řeřicha V, Řeřicha R, Shore D, Sandler D. Incidence of non-lung solid cancers in
- 424 Czech uranium miners: A case–cohort study. *Environmental research*. 2011;111(3):400-405.
- 425 doi:10.1016/j.envres.2011.01.008
- 426 26. Wheeler BW, Allen J, Depledge MH, Curnow A. Radon and skin cancer in southwest
- 427 England: an ecologic study. *Epidemiology*. Jan 2012;23(1):44-52.
- 428 doi:10.1097/EDE.0b013e31823b6139
- 429 27. Wheeler BW, Kothencz G, Pollard AS. Geography of non-melanoma skin cancer and
- 430 ecological associations with environmental risk factors in England. Br J Cancer. Jul 9
- 431 2013;109(1):235-41. doi:10.1038/bjc.2013.288
- 432 28. Brauner EV, Loft S, Sorensen M, et al. Residential Radon Exposure and Skin Cancer
- 433 Incidence in a Prospective Danish Cohort. *PLoS One*. 2015;10(8):e0135642.
- 434 doi:10.1371/journal.pone.0135642
- 435 29. Barbosa-Lorenzo R, Barros-Dios JM, Aldrey MR, Caramés SC, Ruano-Ravina A. Residential
- 436 radon and cancers other than lung cancer: a cohort study in Galicia, a Spanish radon-prone area.
- 437 European journal of epidemiology. 2016;31(4):437-441.
- 438 30. Vienneau D, de Hoogh K, Hauri D, et al. Effects of Radon and UV Exposure on Skin Cancer
- 439 Mortality in Switzerland. *Environ Health Perspect*. Jun 16 2017;125(6):067009. doi:10.1289/EHP825
- 440 31. Boz S, Berlin C, Kwiatkowski M, et al. A prospective cohort analysis of residential radon and
- 441 UV exposures and malignant melanoma mortality in the Swiss population. *Environment international*.
  442 2022;169:107437.
- 443 32. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of
- incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*. 2021;
- 446 33. Bopp M, Spoerri A, Zwahlen M, et al. Cohort Profile: the Swiss National Cohort--a
- 447 longitudinal study of 6.8 million people. *Int J Epidemiol*. Apr 2009;38(2):379-84.
- 448 doi:10.1093/ije/dyn042
- 449 34. Coverage Estimation for the Swiss Population Census 2000: Estimation Methodology and
  450 Results (Swiss Federal Statistics Office) (2004).

*Oncology*. 2023:1-12.

- Journal Pre-proof
- 451 35. Plys E, Bovio N, Arveux P, et al. Research on occupational diseases in the absence of 452 occupational data: A mixed-method study among cancer registries of Western Switzerland. Swiss 453 medical weekly. 2022;152:w30127. 454 Panczak R, Galobardes B, Voorpostel M, Spoerri A, Zwahlen M, Egger M. A Swiss 36. 455 neighbourhood index of socioeconomic position: development and association with mortality. J456 Epidemiol Community Health. 2012;66(12):1129-1136. doi:10.1136/jech-2011-200699 457 37. Report WG. International rules for multiple primary cancers (ICD-0 third edition). European 458 journal of cancer prevention: the official journal of the European Cancer Prevention Organisation 459 (*ECP*). 2005;14(4):307-308. 460 38. Vienneau D, Boz S, Forlin L, et al. Residential radon-Comparative analysis of exposure models in Switzerland. Environmental pollution. 2021;271:116356. doi:10.1016/j.envpol.2020.116356 461 Barazza F, Murith C, Palacios M, Gfeller W, Christen E. A national survey on radon 462 39. remediation in Switzerland. Journal of Radiological Protection. 2017;38(1):25. 463 464 Harris TC, Vuilleumier L, Backes C, Nenes A, Vernez D. Satellite-Based Personal UV Dose 40. 465 Estimation. Atmosphere. 2021;12(2):268. Vuilleumier L, Harris T, Nenes A, Backes C, Vernez D. Developing a UV climatology for 466 41. 467 public health purposes using satellite data. Environment International. 2021;146:106177. 468 doi:10.1016/j.envint.2020.106177 469 42. Guénel P, Laforest L, Cyr D, et al. Occupational risk factors, ultraviolet radiation, and ocular 470 melanoma: a case-control study in France. Cancer Causes Control. 2001;12(5):451-459. 471 Kleinbaum DG, Klein M. The Cox proportional hazards model and its characteristics. Survival 43. 472 analysis: a self-learning text. 2012:97-159. 473 44. Buster KJ, You Z, Fouad M, Elmets C. Skin cancer risk perceptions: a comparison across 474 ethnicity, age, education, gender, and income. Journal of the American Academy of Dermatology. 475 2012;66(5):771-779. Schoenfeld D. Chi-squared goodness-of-fit tests for the proportional hazards regression model. 476 45. 477 Biometrika. 1980;67(1):145-153. 478 46. Kamiya K, Ozasa K, Akiba S, et al. Long-term effects of radiation exposure on health. The 479 lancet. 2015;386(9992):469-478. 480 Sugiyama H, Misumi M, Kishikawa M, et al. Skin cancer incidence among atomic bomb 47. 481 survivors from 1958 to 1996. Radiation Research. 2014;181(5):531-539. 482 Azizova TV, Bannikova MV, Grigoryeva ES, Rybkina VL. Risk of skin cancer by histological 48. 483 type in a cohort of workers chronically exposed to ionizing radiation. Radiation and environmental 484 biophysics. 2021;60(1):9-22. Tong J, Hei TK. Aging and age-related health effects of ionizing radiation. Radiation 485 49. 486 Medicine and Protection. 2020;1(1):15-23. 487 Crosfill M, Lindop PJ, Rotblat J. Variation of sensitivity to ionizing radiation with age. 50. 488 Nature. 1959;183(4677):1729-1730. Ritz B, Morgenstern H, Moncau J. Age at exposure modifies the effects of low-level ionizing 489 51. 490 radiation on cancer mortality in an occupational cohort. Epidemiology. 1999;10(2):135-140. 491 52. Smoll NR, Brady Z, Scurrah K, Mathews JD. Exposure to ionizing radiation and brain cancer 492 incidence: The Life Span Study cohort. Cancer epidemiology. 2016;42:60-65. 493 53. Preston D, Ron E, Tokuoka S, et al. Solid cancer incidence in atomic bomb survivors: 1958– 494 1998. Radiation research. 2007;168(1):1-64. 495 Shuryak I, Sachs R, Brenner D. A new view of radiation-induced cancer. Radiation protection 54. 496 dosimetry. 2011;143(2-4):358-364. 497 Karagas MR, McDonald JA, Greendberg ER, et al. Risk of basal cell and squamous cell skin 55. 498 cancers after ionizing radiation therapy. JNCI: Journal of the National Cancer Institute. 499 1996:88(24):1848-1853. 500 56. Shore RE. Radiation-induced skin cancer in humans. Medical and Pediatric Oncology: The 501 Official Journal of SIOP—International Society of Pediatric Oncology (Societé Internationale 502 d'Oncologie Pédiatrique. 2001;36(5):549-554. Saitoh A, Aizawa Y, Sato I, Hirano H, Sakai T, Mori M. Skin thickness in young infants and 503 57. 504 adolescents: Applications for intradermal vaccination. Vaccine. 2015;33(29):3384-3391.
- 505 58. Shuster S, BLACK MM, McVitie E. The influence of age and sex on skin thickness, skin collagen and density. *British Journal of Dermatology*. 1975;93(6):639-643.

- 507 59. Narendran N, Luzhna L, Kovalchuk O. Sex difference of radiation response in occupational 508 and accidental exposure. *Frontiers in genetics*. 2019;10:260.
- 509 60. National Research Council. *Health risks from exposure to low levels of ionizing radiation:*
- 510 BEIR VII phase 2. vol 7. National Academies Press; 2006.
- 511 61. Schubauer-Berigan MK, Daniels RD, Bertke SJ, Tseng C-Y, Richardson DB. Cancer mortality
  512 through 2005 among a pooled cohort of US nuclear workers exposed to external ionizing radiation.
- 513 *Radiation Research*. 2015;183(6):620-631.
- 514 62. Azizova TV, Bannikova MV, Grigoryeva ES, Rybkina VL. Risk of malignant skin neoplasms
- in a cohort of workers occupationally exposed to ionizing radiation at low dose rates. *PLoS One*.
  2018;13(10):e0205060.
- 517 63. Dao Jr H, Kazin RA. Gender differences in skin: a review of the literature. *Gender medicine*. 518 2007;4(4):308-328.
- 519 64. Jiang A, Rambhatla P, Eide M. Socioeconomic and lifestyle factors and melanoma: a 520 systematic review. *British Journal of Dermatology*. 2015;172(4):885-915.
- 521 65. Clarke CA, Moy LM, Swetter SM, Zadnick J, Cockburn MG. Interaction of Area-Level
- 522 Socioeconomic Status and UV Radiation on Melanoma Occurrence in CaliforniaUV, SES and
- 523 Melanoma Occurrence. *Cancer epidemiology, biomarkers & prevention.* 2010;19(11):2727-2733.
- 524 66. Erdei E, Torres SM. A new understanding in the epidemiology of melanoma. *Expert review of* 525 *anticancer therapy*. 2010;10(11):1811-1823.
- 526 67. Whicker JJ, McNaughton MW. Work to save dose: contrasting effective dose rates from radon
- 527 exposure in workplaces and residences against the backdrop of public and occupational regulatory
- 528 limits. *Health physics*. 2009;97(3):248-256.

529

|                                     | Study por        | oulation                                | Sub-set population      |                       |  |
|-------------------------------------|------------------|---|-------------------------|-----------------------|--|
| Characteristics                     | Full Cohort      | MM cases <sup>a</sup>                   | Non-movers <sup>b</sup> | MM cases <sup>a</sup> |  |
| Participants <sup>c</sup> , $n$ (%) | 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, <i>n</i> (%)       |                  |   |                         |                       |  |
| 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                   |  |

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

<sup>a</sup> MM cases: Primary invasive cutaneous melanomas (ICD-O-3: C43, 8720-8790). No in situ cases. <sup>b</sup> Non-movers: Same residential location at 1990 and 2000 censuses.

<sup>c</sup> Percentages calculated for the row.

|            | Full cohort |                           | Non-movers <sup>a</sup> |                           |  |
|------------|-------------|---------------------------|-------------------------|---------------------------|--|
|            | Cases       | HR (95% CIs) <sup>b</sup> | Cases                   | HR (95% CIs) <sup>b</sup> |  |
| 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)         |  |

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

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.

<sup>a</sup> Non-movers: Same residential location at 1990 and 2000 censuses.

<sup>b</sup> Hazard ratios (95% confidence intervals) are expressed per 100 Bq/m<sup>3</sup> radon increase.

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

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

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<sup>3</sup> radon increase.

<sup>a</sup> Based on Swiss-SEP<sup>19</sup>: 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.

<sup>b</sup> No includes those with indoor jobs and those not in paid employment.

<sup>c</sup> 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<sup>3</sup>. \*Radon exposures above 500 Bq/m<sup>3</sup> 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

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### **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:

Journal Prevention