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Managing risks from radon and NORM

Deliverable 4.2

Final report on risk estimates from PUMA and Constances: risks other than lung cancer

Work Package 4

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Executive Summary

There is still no conclusive answer to the question whether radon poses a substantial risk for any other disease than lung cancer. Absorbed organ doses from inhalation of radon to organs other than lung and respiratory tract are estimated to be substantially lower than absorbed doses to the lung (at least an order of magnitude lower). Thus, potential risks are expected to be small and large studies with wide exposure ranges are needed to investigate them. Even a small excess risk may not be negligible for diseases with high prevalence in the general population and thus could have implications for radiation protection, since large populations are exposed and current radon dose conversion factors might need revision. Based on the largest study of uranium miners – the international pooled uranium miners analysis (PUMA) – and the large population-based French Constances cohort, radon-related health risks other than lung cancer were investigated in RadoNorm Task 4.2. This deliverable gives an overview of the work completed and the results obtained in this task.

PUMA combines data of seven uranium miner cohorts from five different countries in Europe and North America with mortality follow-up between 1946 and 2014. In RadoNorm, radon-related risks for mortality from solid cancers other than lung cancer (subtask 4.2.1) and cardiovascular diseases (subtask 4.2.2) were investigated. Among the almost 120,000 male miners in PUMA, 7,720 deaths from solid cancers other than lung cancer and 17,495 deaths from cardiovascular diseases were observed. The mean value of cumulative radon exposure was 191 working level month (WLM) in the PUMA cohort and ranged between 31 and 579 WLM in individual cohorts. Based on exposure-risk analyses, slightly elevated excess relative risks were found for the group of solid cancers other than lung cancer, in particular at very high radon exposures. However, no single cancer site was clearly responsible for this increase. For circulatory system diseases (CSD) and the subgroups of ischemic heart diseases or cerebrovascular diseases, no increase in mortality risk was observed with increasing cumulative radon exposure. Overall, results do not show a clear increase in risk for solid cancers other than lung cancer or CSD due to radon, neither considered in groups nor for specific diseases.

Regarding the Constances cohort (subtask 4.2.3), the first preparatory step was a systematic literature review and meta-analysis on other potential health effects of radon than lung cancer [*Henyoh et al. 2024*]. In the meta-analyses, none of the investigated exposure-risk associations reached statistical significance, although some were close to significance, justifying further investigation.

Furthermore, for a subset of about 62,000 individuals from the general population-based Constances cohort, data on radon exposure, outcomes and potential confounders were collected and prepared in an elaborate process. Based on this epidemiological database, associations between radon exposure and incidence of diseases were investigated. Preliminary results showed no statistically significant associations at this stage, although further follow-up of the cohort would be warranted to deliver its full informative potential.

Beyond that, a radon measurement campaign in homes of around 1,000 volunteers of the Constances cohort was successfully implemented. This campaign aimed at a comparison of measured vs. estimated radon concentrations in this subset of the Constances cohort and provides important information for future improvement of predictive models.

In conclusion, slightly positive statistical associations between the group of cancers other than lung cancer and radon exposure were recently observed in cohorts of uranium miners, and a review and meta-analysis suggested potential associations of radon exposure and specific cancers, even though not reaching statistical significance. However, at this stage available studies did not allow to detect unambiguously a statistically significant association between radon exposure and any specific disease other than lung cancer.

Further follow-up of existing studies is required in order to consolidate available results in the future. Additional high-quality epidemiological studies are needed to provide more definitive evidence regarding the relationship between radon exposure and health risks other than lung cancer. These studies should specifically address incidence data, low exposure levels and female populations. Especially, studies focusing on disease incidence instead of mortality allow to investigate potential associations of radon exposure for diseases showing good or improving prognosis.

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1. PUMA (RadoNorm subtasks 4.2.1 and 4.2.2)

1.1 Description of the PUMA cohort

The international pooled uranium miners analysis (PUMA) combines data of seven uranium miners cohorts from five different countries from Europe (Czech Republic, France, Germany) and North America (Canada, USA). Almost 120,000 male workers employed in uranium mining with mortality follow-up between 1946 and 2014 are included in PUMA, thereby it constitutes the world's largest study of uranium miners.

Table 1 provides an overview of the total PUMA cohort and contributing individual cohorts, a thorough description of the PUMA project can be found in *Rage et al. 2020*. Workers included in PUMA are underground miners, open pit miners and surface workers (as non-exposed internal reference group). Uranium millers are not included in the PUMA study due to substantial differences in their occupational radiation exposure profile compared with uranium miners.

Methods to assess occupational exposure to radon progeny in working level month (WLM) differ between cohorts. Individual exposure estimates were based on expert rating in the first years of uranium mining (for some cohorts), historical records of area monitoring (for all cohorts) and, if available, on personal exposure monitoring in the later years (for some cohorts) [*Rage et al. 2020*, Table 2 therein].

Regarding numbers of deaths, among the 119,709 male miners in PUMA 15,474 deaths from solid cancers, 7,720 deaths from solid cancers other than lung cancer and 17,495 deaths from cardiovascular diseases were observed during 1946-2014 (Table 1). Mean cumulative radon exposure was 191 WLM and mean annual exposure rate was 2.9 working level (WL), both with large variation between individual cohorts. The largest individual cohort in PUMA is the German "Wismut" uranium miners cohort, contributing 54,919 miners, 4,306 deaths from solid cancers other than lung cancer and 9,806 deaths from cardiovascular diseases. In comparison to other cohorts, the Wismut cohort is characterized by a rather long mean duration of employment (14 years), high mean cumulative radon exposure (304 WLM) and at the same time a comparably low mean annual exposure rate (1.9 WL). This emphasizes the importance to investigate and check heterogeneity and sensitivity of results between cohorts, particularly regarding the impact of the Wismut cohort on overall results.

PUMA aimed at investigating various research questions, with particular focus on radon-related mortality risks for lung cancer and other diseases than lung cancer. Published results comprise a comparison of mortality in PUMA miners with the general population [*Richardson et al. 2021*], radon-related lung cancer risks for PUMA miners hired in 1960 or later ("1960+ sub-cohort") [*Richardson et al. 2022*] and for all miners from the full PUMA cohort [*Kelly-Reif et al. 2023*]. Based on these results, estimates for the lifetime excess absolute risks (LEAR) in PUMA were calculated [*Kreuzer et al. 2024*], which is an important contribution to the epidemiological approach of radon dose conversion and associated assessment of uncertainties. The research questions on radon-related mortality risks for solid cancers other than lung cancer and from cardiovascular diseases were investigated as part of RadoNorm in subtasks 4.2.1 and 4.2.2.

Table 1: Description of the full PUMA cohort (PUMA total) and contributing individual cohorts (full cohorts)

Cohort	Period of follow-up	# miners	# person-years (million)	# deaths all causes	# deaths solid cancer	# deaths solid cancer without lung cancer	# deaths cardio-vascular diseases	Mean duration of employment (years)	Mean cumulative radon exposure* (WLM)	Mean annual exposure rate* (WL)
Eldorado (Canada)	1950-1999	13,574	0.42	4,044	999	482	1,381	2	122	8.3
Ontario (Canada)	1954-2007	28,546	1.01	8,572	2,489	1,243	2,803	5	31	0.9
Czech (Czech Republic)	1952-2014	9,978	0.32	5,572	1,964	788	1,875	8	73	0.8
France (France)	1946-2007	5,086	0.18	1,984	662	449	464	17	37	0.8
Wismut (Germany)	1946-2013	54,919	2.16	27,738	8,065	4,306	9,806	14	304	1.9
Colorado Plateau (USA)	1960-2005	4,137	0.12	2,964	874	262	799	4	579	11.7
New Mexico (USA)	1957-2012	3,469	0.13	1,576	421	190	367	9	90	9.6
PUMA total		119,709	4.34	52,450	15,474	7,720	17,495	10	191	2.9

WLM: Working level month, WL: Working level

* Non-exposed miners (i.e. with WLM=0) were excluded from calculation of mean values

1.2 Radon-related mortality risks in the German uranium miners cohort

Context: As a preparatory and comparable analysis for the subsequent analyses in the PUMA cohort, radon-related health risks for death from diseases other than lung cancer were investigated in the German uranium miners study with most recent follow-up data from 1946-2018 [*Fenske et al. 2025*]. Since the Wismut cohort is the largest individual cohort in PUMA, this analysis contributes to a better understanding of potential sensitivity of PUMA results regarding the impact of individual cohorts.

Methods: For the cohort of almost 59,000 former employees of the "Wismut" uranium mining company in Eastern Germany, excess relative rates (ERRs) per 100 WLM were estimated for numerous outcomes (main groups and subgroups of causes of death) based on internal Poisson regression for cumulative lagged exposure to radon progeny. Occupational exposure to radon progeny in WLM was retrospectively assessed using a comprehensive job-exposure matrix.

Results: The findings of the German uranium miners cohort indicate small increased risks for a few selected outcomes, in particular for the group of all cancers other than lung cancer (n=6,126; ERR/100 WLM = 0.014 [95% confidence interval (CI): 0.007; 0.022] and for ischemic heart diseases (n=6,182; ERR/100 WLM = 0.010 [95% CI: 0.003; 0.016]). The increase in excess relative risk was particularly observed at very high radon exposures. Regarding other cardiovascular diseases, no increase in mortality risk was observed neither for the main group of diseases of the circulatory system (n=12,263, ERR/100 WLM = 0.004 [95% CI: −0.001; 0.008]) nor for the subgroup of cerebrovascular diseases (n=2,586, ERR/100 WLM = -0.004 [95% CI: −0.012; 0.004]). Regarding radon exposure and other causes of death, no clear associations were present, including other subgroups of cardiovascular diseases, non-malignant respiratory diseases excluding pneumoconiosis, neurodegenerative diseases and many considered single cancer sites. Notably elevated but not statistically different from zero were the ERR/100 WLM estimates for myeloid leukaemia (n=114; ERR/100 WLM = 0.076 [95% CI: −0.011; 0.164]) and pharynx cancer (n=112; ERR/100 WLM = 0.070 [95% CI: −0.041; 0.182]). However, there was no single cancer site that was clearly responsible for the increased risk for the group of all cancers other than lung cancer.

Conclusion: Altogether, the study did not provide convincing evidence for an increased radon-related risk for other diseases than lung cancer, and further studies based on larger populations – such as PUMA – are needed to bring more insight.

1.3 Risk of death from solid cancers other than lung cancer in PUMA

Context: It is well established that exposure to radon and its progeny can cause lung cancer, both from occupational and residential radon studies. For cancers other than lung cancer, however, there is still no conclusive answer as to whether radon poses a substantial risk. Absorbed organ doses from inhalation of radon outside the respiratory tract are estimated to be considerably lower than that of the lung. Thus, potential risks are expected to be small and large studies with wide exposure ranges – such as the large PUMA cohort – are needed to investigate them. Even a small excess risk could have high implications for radiation protection because large populations are exposed and might be affected.

Previous PUMA analyses showed notably elevated mortality rates in miners compared to the general population for the following cancer sites: liver and gallbladder, larynx, stomach and pleura [*Richardson et al. 2021*]. For stomach and liver cancer, increased standardized mortality ratios (SMRs) have nearly consistently been observed for almost all uranium miner studies [e.g. *Darby et al. 1995*, *Kreuzer et al. 2021*]. For other solid cancer sites, however, findings are inconsistent across studies reporting SMRs or standardized incidence ratios (SIRs). Quantitative risk estimates of the relationship between radon exposure and specific diseases other than lung cancer, both from residential radon and miners or

workers studies, have recently been summarized within the scope of RadoNorm, subtask 4.2.3 [*Henyoh et al. 2024*] – see also Section 2.1.

This analysis examines the association between cumulative radon exposure and death from solid cancers other than lung cancer in the full PUMA cohort.

Methods: The present analysis was performed on the PUMA cohort described in Section 1.1. Considered causes of death in this analysis were the groups of solid cancers other than lung cancer and extrathoracic airways cancers, as well as 19 single cancer sites. Table 2 shows considered outcomes and corresponding codes according to the International Classification of Diseases (ICD), whereby different cohorts used different ICD coding mostly depending on calendar period. To calculate the linear excess relative rates (ERR) per cumulative 5-year lagged exposure to radon progeny in working level month (WLM), internal Poisson regression with baseline stratification for age, calendar year, and cohort study was used. Various sensitivity analyses examined possible heterogeneity of results between cohorts, such as analyses on the PUMA cohort without individual cohorts or on individual cohorts only.

Table 2: Considered causes of death in the analysis and corresponding codes according to the International Classification of Diseases (ICD), with different revisions depending on calendar period

ICD revision	ICD-6	ICD-7	ICD-8	ICD-9	ICD-10
Calendar period	1945–1954	1955–1964	1965–1978	1979–1999	≥ 2000
Cause of death / cancer site					
Solid cancers	140-199	140-199	140-199	140-199	C00-C80, C97
Solid cancers other than lung cancer	140-199 excl. 162-163	140-199 excl. 162.0-162.1, 162.8, 163	140-199 excl. 162	140-199 excl. 162	C00-C80 excl. C33-C34, C97
Extrathoracic airways cancers (Oral and pharynx, nose, nasal cavity, larynx)	140-148, 160, 161	140-148, 160, 161	140-149, 160, 161	140-149, 160, 161	C00-C14, C30-C32, C46.2
Oral and pharynx	140-148	140-148	140-149	140-149	C00-C14, C46.2
Pharynx	145-148	145-148	146-149	146-149	C09#, C09.0-C09.1, C09.8-C09.9, C10#, C10.0-C10.4, C10.8-C10.9, C11#, C11.0-C11.3, C11.8-C11.9, C12#, C13#, C13.0-C13.2, C13.8-C13.9, C14#, C14.0, C14.2, C14.8
Oesophagus	150	150	150	150	C15
Stomach	151	151	151	151	C16
Colon/small intestine	152-153	152-153	152-153	152-153	C17-C18
Rectum	154	154	154	154	C19-C21
Liver / gallbladder/ biliary passages	155-156	155-156	155-156,197.8	155-156	C22-C24
Liver	155	155	155	155	C22
Gallbladder / biliary passages	156	156	156,197.8	156	C23-C24
Pancreas	157	157	157	157	C25
Nose, nasal cavity	160	160	160	160	C30-C31
Larynx	161	161	161	161	C32
Pleura	162.2	162.2	163	163	C38.4
Skin (melanoma and other)	190-191	190-191	172-173	172-173	C43, C44, C46#, C46.0, C46.9
Prostate	177	177	185	185	C61
Kidney	180	180	189.0-189.2	189.0-189.2	C64-C66
Bladder	181	181	188,189.3-189.9	188, 189.3-189.9	C67-C68
Brain	193	193	191-192	191-192	C70-C72
Thyroid	194	194	193	193	C73

Results: Table 3 shows the main results. A slightly elevated estimate was found for the group of solid cancers other than lung cancer (n=7,720; ERR/100 WLM = 0.011 [95% CI: 0.004; 0.018]) – not only in the PUMA cohort, but also consistently when considering the PUMA cohort without Wismut (n=3,414; ERR/100 WLM = 0.011 [95% CI: -0.003; 0.025]) as well as the Wismut cohort in PUMA separately (n=4,306; ERR/100 WLM = 0.011 [95% CI: 0.004; 0.019]).

However, there was no single cancer site with a statistically significantly increased excess risk that could be responsible for the small increase in risk in the PUMA cohort. Furthermore, no increase in radon-related excess relative risk was present for extrathoracic airways cancers (n=581; ERR/100 WLM = 0.001 [95% CI: -0.025; 0.027]).

For the group of solid cancers other than lung cancer, Figure 1 shows relative rate (RR) estimates across categories of cumulative radon exposure in comparison with linear associations. Only the exposure categories above 1,000 WLM were associated with slightly increased RRs, and statistically significantly increased categorical estimates were only observed for the total PUMA cohort and for the Wismut cohort in PUMA.

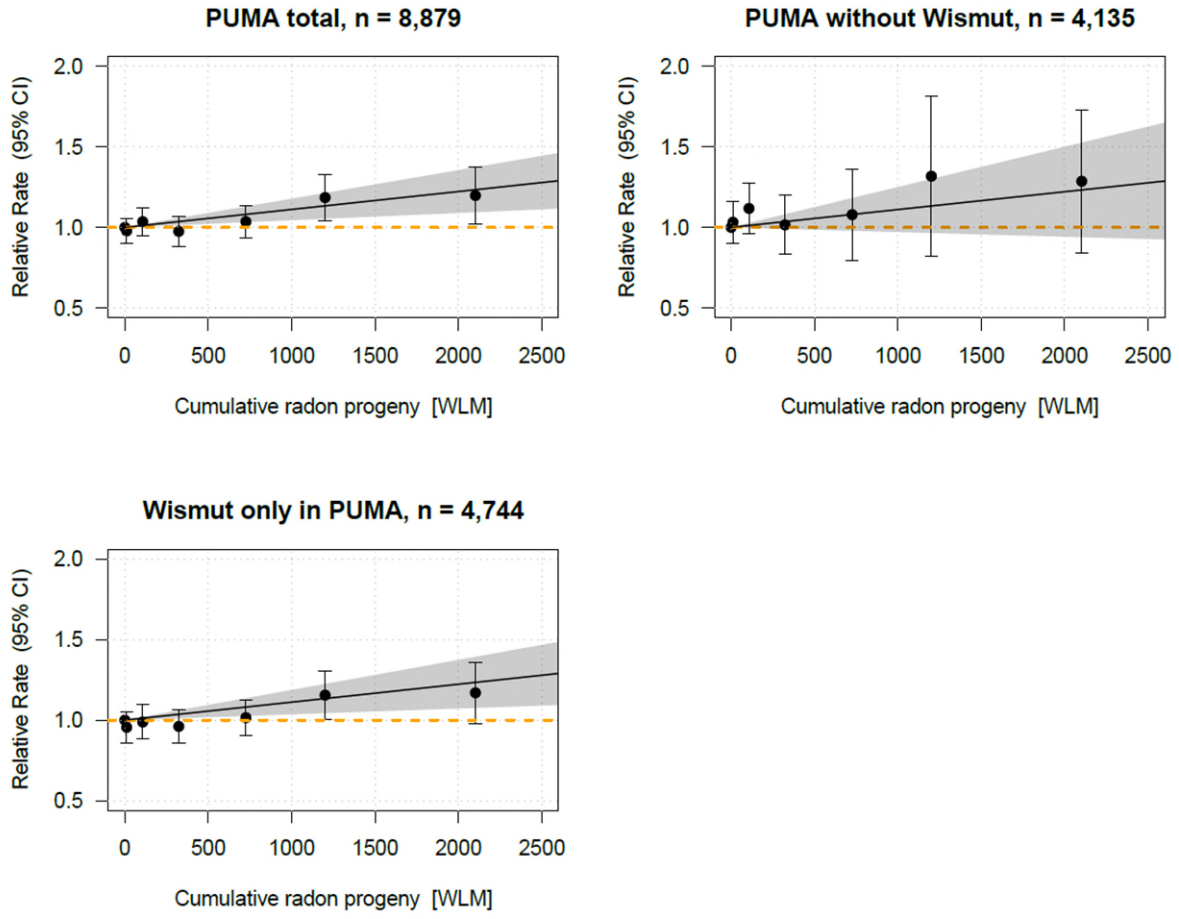

Figure 1 – Solid cancers other than lung cancer: Comparison of relative rate estimates from linear and categorical model in relation to 5-year lagged cumulative radon exposure.
ERR/100 WLM estimate from linear model displayed by black line with CI in grey. Relative rate estimates from categorical model with exposure in categories (0, >0 to <50, 50 to <200, 200 to <500, 500 to <1000, 1000 to <1500, 1500+ WLM) displayed by black dots with CIs as vertical bars. Dashed orange horizontal line corresponds to 'no association' for comparison. WLM, working level month.

Table 3: Radon-related excess relative rate estimates (ERR / 100 WLM) for solid cancers other than lung cancer in the full PUMA cohort, PUMA without Wismut and Wismut cohort only in PUMA

	PUMA total			PUMA without Wismut			Wismut cohort in PUMA		
Cause of death / cancer site	# deaths	ERR/100 WLM	95% CI	# deaths	ERR/100 WLM	95% CI	# deaths	ERR/100 WLM	95% CI
Solid cancers other than lung cancer	7,720	0.011	0.004; 0.018	3,414	0.011	-0.003; 0.025	4,306	0.011	0.004; 0.019
Extrathoracic airways cancers	581	0.001	-0.025; 0.027	313	-0.006**	-0.022; 0.011	268	0.015	-0.020; 0.051
Oral and pharynx	321	0.005	-0.035; 0.045	160	-0.006**	-0.010; -0.002	161	0.026	-0.030; 0.082
Pharynx	177	0.004	-0.048; 0.057	93	-0.005**	-0.055; 0.045	84	0.048	-0.046; 0.143
Oesophagus	352	-0.006**	-0.017; 0.006	168	-0.006**	-0.009; -0.002	184	-0.025	-0.048; -0.002
Stomach	1,064	0.015	-0.001; 0.032	352	-0.004	-0.027; 0.019	712	0.020	0.001; 0.039
Colon, small intestine	872	0.021	-0.002; 0.043	428	0.022	-0.025; 0.070	444	0.020	-0.006; 0.045
Rectum	580	0.019	-0.007; 0.046	240	0.012	-0.042; 0.066	340	0.021	-0.009; 0.050
Liver / gallbladder / biliary passages	590	0.020	-0.006; 0.047	227	0.027	-0.043; 0.097	363	0.020	-0.009; 0.049
Liver	444	0.024	-0.009; 0.056	181	0.044	-0.061; 0.149	263	0.021	-0.014; 0.056
Gallbladder / biliary passages	143	0.016	-0.029; 0.061	43	-0.006	-0.011; -0.001	100	0.017	-0.033; 0.067
Pancreas	544	0.001	-0.022; 0.025	220	0.039	-0.063; 0.140	324	-0.001	-0.025; 0.022
Nose, nasal cavity	31	0.045	-0.144; 0.235	20	-0.006	-0.405; 0.394	11	0.071	-0.179; 0.322
Larynx	229	-0.006**	-0.036; 0.025	133	-0.006**	-0.052; 0.041	96	0.002	-0.042; 0.046
Pleura	36	0.098	-0.094; 0.290	17	0.533	-0.619; 1.686	19	0.072	-0.111; 0.254
Skin (melanoma and other)	166	0.007	-0.034; 0.047	87	0.063	-0.071; 0.197	79	-0.010	-0.055; 0.035
Prostate	856	0.008	-0.010; 0.026	428	0.005	-0.023; 0.033	428	0.010	-0.013; 0.032
Kidney	346	0.014	-0.017; 0.044	103	-0.006	-0.053; 0.041	243	0.016	-0.018; 0.051
Bladder	420	0.009	-0.017; 0.035	162	0.013	-0.063; 0.089	258	0.008	-0.020; 0.036
Brain	303	-0.006**	-0.037; 0.026	159	-0.005**	-0.070; 0.060	144	-0.030	-0.052; -0.008
Thyroid gland	32	0.058	-0.104; 0.221	14	0.072	-0.512; 0.657	18	0.057	-0.111; 0.225

** Error: no convergence of model estimation

Conclusion: These preliminary results indicate a small radon-related increase in risk for solid cancers other than lung cancer, particularly present at very high radon exposures. There is no single cancer site that is clearly responsible for this increase in risk. In the scope of scientific manuscript preparation, further analyses are currently ongoing, specifically regarding heterogeneity in effects between studies, influence of individual cohorts on the overall results, and effects of low exposures or temporal patterns. Convergence problems are also tackled. Dose-response analyses based on organ doses, as provided by RadoNorm WP 3, Task 3.2, will provide further insights in the future.

1.4 Risk of death from cardiovascular diseases in PUMA

Context: Beyond the risks of cancer, the question of cardiovascular risks linked to ionizing radiation exposure arises. The underlying biological hypothesis is that damage caused by ionizing radiation can lead to inflammatory reactions or oxidative stress at the cell level and lead to inflammation, atherosclerotic plaque or stenosis at the tissue level [*Liu et al. 2022*].

An increased risk for cardiovascular disease has been associated with the exposure to ionizing radiation in some epidemiological studies. Among the survivors of the Hiroshima and Nagasaki atomic bombs (N=86,600 subjects), the excess relative risk (ERR) for death from circulatory system diseases was significantly increased (ERR/Gy = 0.14 [95% CI: 0.06; 0.22]) [*Takahashi et al. 2017*]. In the large international INWORKS cohort (INternational WORKers Study) including about 308,000 nuclear workers from France, the United Kingdom, and the United States, significantly increased risks for death from all circulatory system diseases (ERR/Sv = 0.22 [90% CI: 0.08; 0.37]), and from the subgroups of ischemic heart diseases (ERR/Sv = 0.18 [90% CI: 0.004; 0.36]) and cerebrovascular diseases (ERR/Sv = 0.50 [90% CI: 0.12; 0.94]) were observed in association with cumulative external occupational exposure to ionizing radiation [*Gillies et al. 2017*].

Consequently, the question on cardiovascular risk associated with internal exposure to radon is raised. Uranium miners constitute a relevant population because they are mainly exposed to radon during their occupational activity and, as most of the occupational studies, they are well followed in terms of administrative information and dosimetric exposure records. The French cohort of uranium miners has observed a significant increase of risk for cerebrovascular diseases among 5,086 miners (ERR/100 WLM = 0.41 [95% CI: 0.04; 1.03]) [*Rage et al. 2015*], but the German cohort did not observe any increase of circulatory system disease risk among 59,001 uranium miners (ERR/100 WLM = 0.0006 [95% CI: -0.004; 0.006]) [*Kreuzer et al. 2006*]. In an external comparison of PUMA miners with the general population, no elevated mortality rates were observed for circulatory diseases and ischemic heart diseases [*Richardson et al. 2021*]. Given these few and inconsistent results observed among uranium miners, it is necessary to conduct a larger study to increase the power of the analysis.

Methods: The present analysis was performed on the PUMA cohort described in Section 1.1.
All Circulatory System Diseases (CSD) were coded according to the International Classification of Diseases (ICD) as 330-334, 400-468 (ICD-7), 390-458 (ICD-8), 390-459 (ICD-9) and I00-I99 (ICD-10). The following two main sub-groups of CSD have also been studied: Ischemic Heart Diseases (IHD) coded as 420 (ICD-7), 410-414 (ICD-8), 410-414, 429.2 (ICD-9), and I20, I20.0-I20.1, I20.8-I20.9, I21, I21.0-I21.4, I21.9, I22, I22.0-I22.1, I22.8-I22.9, I24, I24.1, I24.8-I24.9, I25, I25.0-I25.6, I25.8-I25.9, I51.3, I51.6 (ICD-10) and Cerebrovascular Diseases (CeVD) coded as 330-334 (ICD-7), 430-438 (ICD-8), 430-438 (ICD-9) and G45, G45.0-G45.2, G45.4, G45.8-G45.9, I60, I61, I61.0-I61.6, I61.8-I61.9, I62, I62.0-I62.1, I62.9, I63, I63.0-I63.6, I63.8-I63.9, I64, I67, I69, I69.0-I69.4, I69.8 (ICD-10).

The relationships between cumulative radon exposure and the risk of CSD, IHD or CeVD were estimated by a linear excess relative risk (ERR) model with cumulative radon exposure lagged by 5 years to account for a minimum latency period between exposure and risk. The ERR model was fitted with

internal Poisson regression which uses non-exposed uranium miners (surface workers) as an internal reference group and where the baseline risk was stratified by calendar year, attained age and study cohort. Maximum likelihood parameter estimates and likelihood-based 95% confidence intervals (CIs) were calculated with the AMFIT module of Epicure. In case of non-convergence of the linear model, a log-linear model was used.

Results: A total of 17,495 deaths from CSD occurred in the PUMA cohort, including 9,746 deaths from IHD and 3,169 deaths from CeVD. The exposure-risk analysis is presented in Table 4. The risk estimate for mortality from all circulatory system disease (CSD) was ERR/100 WLM = -0.001 [95% CI: -0.005; 0.003]. For sub-categories of CSD, no association was observed for IHD mortality (ERR/100 WLM = 0.001 [95%CI: -0.004; 0.006]). The linear model did not converge to estimate the mortality risk for CeVD. The log-linear model did not show any increased risk, and a negative estimate was observed (ERR/100 WLM = -0.021 [95% CI: -0.045; -0.002]). In individual cohorts, no statistically significantly increased excess relative risk estimates were observed for any of the three considered CSD outcomes.

Conclusion: The present work constitutes the first one conducted among a very large cohort to assess the risk of circulatory system disease associated with radon exposure. Strengths of the study are its very large size, long duration of follow-up and the high availability of radon exposure information. There are also some limitations regarding the lack of incidence data and smoking data. Smoking is a known risk factor for cardiovascular diseases, however no information is available for the total PUMA cohort. Nevertheless, the RadoNorm Task 4.1 from WP 4 will provide additional information on the effect of smoking in the relationship between radon exposure and the risk of cardiovascular diseases.

The present study does not highlight any evidence of an association between cumulative radon exposure and mortality risk from circulatory system disease, neither in each individual cohort, nor in the pooled international PUMA cohort.

In conclusion, the observed results do not support an increase in the risk of death from cardiovascular disease linked to radon exposure. Supplementary sensitivity analyses assessing the risk among different categories of cumulative radon exposure, attained age or hiring period will be included in the scientific paper in preparation.

Table 4: Relationship between deaths from circulatory system diseases and cumulative radon exposure among uranium miners of the PUMA cohort

	Circulatory System Diseases (CSD)			Ischemic Heart Diseases (IHD)			Cerebrovascular Diseases (CeVD)		
	N	ERR/100 WLM [95% CI]		N	ERR/100 WLM [95% CI]		N	ERR/100 WLM [95% CI]	
Eldorado (Canada)	1,381	-0.018	[< -0.032 ; 0.002]	945	-0.017	[< -0.033 ; 0.006]	176	-0.110	[-0.390 ; 0.012]
Ontario (Canada)	2,803	-0.051	[< -0.100 ; 0.042]	1,969	-0.005	[< -0.140 ; 0.064]	334	0.140	[-0.480 ; 0.500]
Czech Republic	1,875	0.003	[-0.047 ; 0.069]	931	-0.051	[-0.098 ; 0.024]	280	0.170	[-0.072 ; 0.330]
France	464	0.088	[-0.044 ; 0.280]	167	0.020	[< -0.140 ; 0.310]	107	0.270	[-0.033 ; 0.460]
Wismut (Germany)	9,806	-0.001	[-0.005 ; 0.004]	5,002	0.002	[-0.004 ; 0.009]	2,139	-0.021	[-0.048 ; 0.000]
Colorado Plateau (USA)	799	-0.002	[< -0.006 ; 0.007]	505	0.000	[< -0.007 ; 0.013]	92	-0.019	[-0.240 ; 0.019]
New Mexico (USA)	367	0.057	[-0.075 ; 0.260]	227	0.039	[< -0.110 ; 0.300]	41	0.077	[-109.1 ; 0.330]
PUMA total	**17,495**	**-0.001**	**[-0.005 ; 0.003]**	**9,746**	**0.001**	**[-0.004 ; 0.006]**	**3,169**	**-0.021**	**[-0.045 ; -0.002]**

1.5 Summary of risk estimates from PUMA

Figure 2 gives an overview of the estimates for excess relative risk of death from solid cancers other than lung cancer and from cardiovascular diseases in PUMA. The linear ERR/100 WLM estimate for lung cancer is presented for reason of comparison of effect sizes. Without inclusion of effect modification by time since exposure, attained age and exposure rate, it should not be further interpreted. The linear ERR/100 WLM estimates for the group of solid cancers other than lung cancer and for single cancer sites other than lung cancer (Table 3) is at least an order of magnitude smaller than that for lung cancer and, therefore, matches well with estimated organ doses from biokinetic models.

Altogether, results do not show a clear increase in mortality risk for solid cancers other than lung cancer or CSD due to radon, neither considered in groups nor for subgroups of diseases.

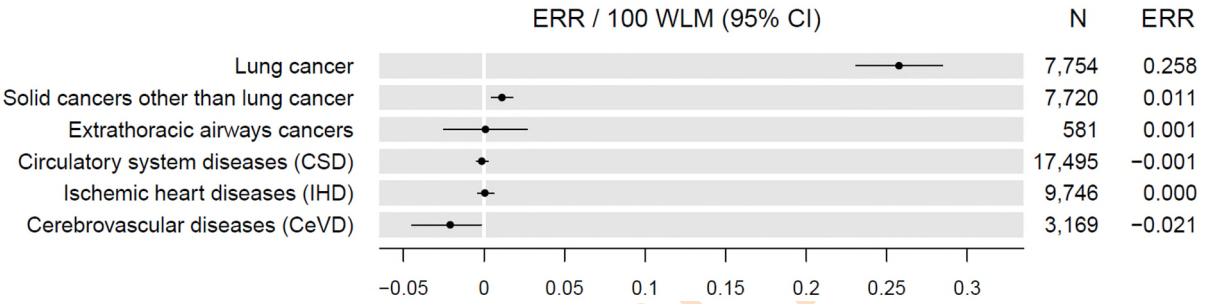

Figure 2 – Overview of PUMA estimates for risk of death from solid cancers other than lung cancer and from cardiovascular diseases.

Excess relative rate (ERR/100 WLM) estimates (black dots) together with associated 95% confidence intervals (CI, horizontal bars) and number of deaths per outcome (n) sorted by size of ERR/100 WLM in comparison with estimate from lung cancer.

Note that ERR/100 WLM estimate for lung cancer slightly differs from published estimate in Kelly-Reif et al. (2023) because of different ways of baseline stratification (here; without inclusion of duration of employment).

2. Constances (RadoNorm subtask 4.2.3)

2.1 Literature review and meta-analysis of other potential effects of radon than lung cancer

As part of a PhD thesis funded by RadoNorm and completed by Afi Henyoh – including work on the Constances cohort that will be presented in Section 2.2 – the first work conducted was a systematic literature review and a meta-analysis focusing on potential health effects of radon other than lung cancer [*Henyoh et al. 2024*].

The literature review included studies published from January 1990 to March 2023, in English and French languages, identified in several databases (PubMed, ScienceDirect, Scopus, ScieLo and HAL). Therefore, its results did not include the newer results from the Wismut and PUMA cohorts of uranium miners presented above. Studies covering both residential and occupational exposures to radon were considered, as well as all age groups (children and adults) and potential health effects other than lung cancer.

A total of 129 studies were included in the systematic review. Figure 3 shows the designs and types of exposure (residential vs. occupational) as well as the age groups (children vs. adults) covered by these studies.

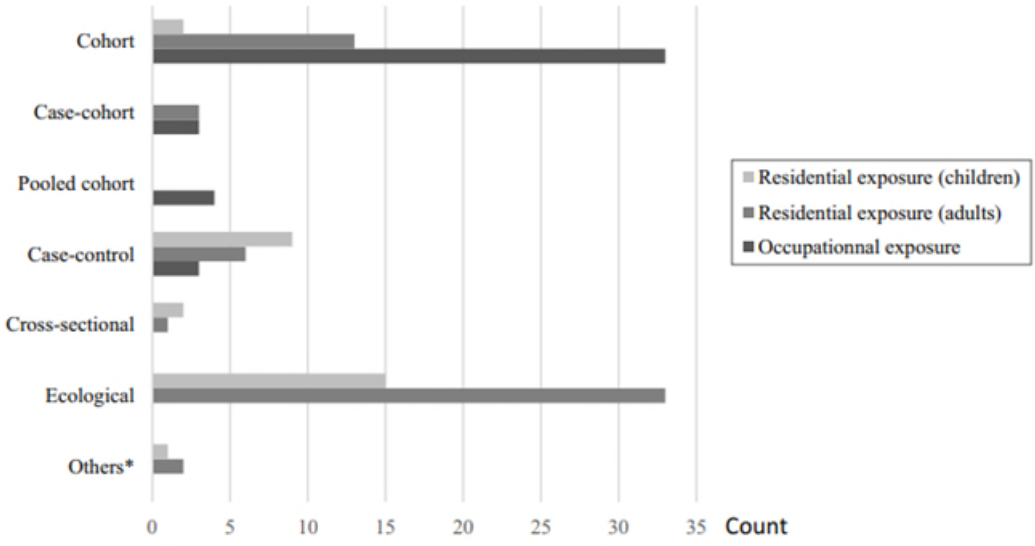

Figure 3 – Repartition of studies included in the systematic review on potential health effects of radon other than lung cancer, by exposure type and design

**"Two-design in one" studies: ecological study & case-control study; Ecological study & case-only study; Ecological study & cohort study.*

In the meta-analysis, which provides the most informative results beyond narrative review, only studies based on individual data with quantitative estimates for the association between radon exposure and health outcomes were included. This criterion excluded ecological studies based only on aggregated rather, which provide a lower weight of evidence than studies analysing individual data and for which estimates of exposure-risk associations are not directly transposable to the individual level.

In total, 40 distinct studies were included in the meta-analysis. Average weighted standardized incidence ratios (metaSIR), standardized mortality ratios (metaSMR), and risk ratios (metaRR) were estimated per 100 unit (Bq/m^3 for residential exposure or working level month for occupational exposure) increase in radon exposure by combining estimates from the eligible studies using the random-effect inverse variance method. The DerSimonian & Laird estimator was used to estimate between-study variability. For each health outcome, analyses were performed separately for miners, children, and adults in the general population.

Table 5 shows the results of the meta-analysis obtained for cancers other than lung cancer, and Table 6 shows the results for non-cancerous diseases.

For all health outcomes investigated, the results of the meta-analyses showed no statistically significant association (Tables 5 and 6), and heterogeneity was only present among occupational studies, especially between those included in the metaSIR or metaSMR analyses. However, the estimated exposure-risk associations were positive and close to the statistical significance threshold for: lymphohematological cancer incidence in children (metaRR = 1.01; 95% CI: 1.00–1.03; p = 0.08); malignant melanoma mortality among adults in the general population (metaRR = 1.10; 95% CI: 0.99–1.21; p = 0.07); liver cancer mortality among miners (metaRR = 1.04; 95% CI: 1.00–1.10; p = 0.06); intestine and rectal cancer mortality combined among miners (metaRR = 1.02; 95% CI: 1.00–1.04; p = 0.06).

In conclusion, although none of the exposure-risk associations estimated in the meta-analyses reached statistical significance, the hypothesis that radon may have other health effects apart from lung cancer could not be ruled out and call for additional research. To date, only few studies could be included in the meta-analysis for most health outcomes, especially regarding the exposure-risk relationships analyses based on incidence data. This might be an important limitation, especially for diseases with good prognosis. In addition, many studies could not clearly demonstrate proper consideration for potential confounders of the exposure-risk relationships. Therefore, more well-designed studies are needed to further investigate the question of potential health effects of radon other than lung cancer.

Table 5 – Summarized results of the meta-analysis on potential effects of radon on cancers other than lung cancer

Population	Mortality from cancer Cancer incidence	Number of studies	Cases/sample size	Meta risk ratio (95% CI) per 100 Bq/m³ or WLM[a]	P for metaRR	Cochran's Q-test p for heterogeneity	Egger's test p for publication bias
Children							
	Leukaemia	6	14,787/2,063,663	1.01 (1.00 - 1.03)	0.08	0.81	0.15
	Central nervous system tumour	4	8,262/2,024,707	1.02 (0.98 - 1.05)	0.43	0.11	0.81
Adults in the general population							
	Malignant melanoma	2	5,226/5,716,404	1.10 (0.99 - 1.21)	0.07	0.88	_
	Non-melanoma skin cancer	2	1,431/5,716,404	0.91 (0.61 - 1.34)	0.63	0.20	_
Miners							
	Leukaemia	4	545/60,835	0.99 (0.97 - 1.01)	0.50	0.43	0.78
	Lymphoma	5	161/124,327	1.02 (0.96 - 1.09)	0.45	0.87	0.27
	Extrathoracic airways	3	401/45,738	0.90 (0.74 - 1.11)	0.32	0.25	0.83
	Stomach	4	880/120,203	1.00 (0.96 - 1.04)	0.98	0.22	0.40
	Pancreas	2	296/75,223	1.00 (0.98 - 1.02)	0.98	0.82	_
	Liver	2	207/75,421	1.04 (1.00 - 1.10)	0.06	0.78	_
	Intestine and rectal	5	639/136,855	1.02 (1.00 - 1.04)	0.06	0.83	0.55
	Brain and CNS	2	120/61,632	0.98 (0.95 - 1.02)	0.32	0.81	_
	Kidney & other urinary organs	5	285/109,988	1.02 (0.99 - 1.05)	0.14	0.51	0.28

a. *Estimates were expressed in Bq/m³ for children and adults in the general population, since residential exposure was considered. Estimates were expressed in WLM for miners since occupational exposure was considered.*

Table 6 – Summarized results of the meta-analysis on potential effects of radon on diseases other than cancer

Cause of death	Number of studies	Cases/ sample size	Meta risk ratio (95%CI) per 100 WLM[a]	P for metaRR	Cochran's Q-test p for heterogeneity	Egger's test p for publication bias
All circulatory system disease	6	10,117/115,145	0.99 (0.98 - 1.01)	0.30	**0.06**	0.39
Cerebrovascular disease	4	2,151/82,673	0.984 (0.93 - 1.04)	0.55	**<0.01**	0.62
Ischemic heart disease	3	6,830/82,673	0.997 (0.99 - 1.01)	0.63	0.32	0.62
Chronic obstructive pulmonary disease	3	1,073/69,120	1.00 (0.99-1.02)	0.56	0.51	0.21

a. *Estimates were expressed in WLM here since only studies of miners could be included.*

2.2 Epidemiological analysis of radon exposure and cancer risks in the Constances cohort

2.2.1 Objectives

Because of the information gaps identified in the review and meta-analysis mentioned above on potential effects of radon on diseases other than lung cancer on the one hand, and of the lack of knowledge of effects at adult age of radon exposures received during childhood on the other hand [*UNSCEAR 2019*], the present study aimed to investigate within a general population cohort allowing to track the incidence of various diseases:

1) the association between cumulative radon exposure during childhood and late risks of various cancers in adulthood,

2) more broadly, the association between cumulative lifelong residential radon exposure and the subsequent risk of developing specific cancers.

2.2.2 Methods

2.2.2.1 Description of the CONSTANCES cohort

The CONSTANCES cohort was designed as a sample of French adults, aged 18-69 years at recruitment, randomly selected among persons registered with the general scheme of the French Social Security system (French acronym “CNAM”) that covers over 85% of French residents, following a sampling scheme stratified on age, sex, socioeconomic status and region of France. About 220,000 subjects were included over the 2012-2019 period from 20 “départements” (French administrative districts). At inclusion, the selected participants were invited to attend a partnering Health Screening Centre (HSC) for a comprehensive health examination and to complete questionnaires. Data collected from participants at inclusion include social and demographic characteristics, socioeconomic status, life events, behaviours, and occupational factors. In addition, health and social data are collected through linkage to the French national medico-administrative databases including the National health data system (Système national des données de santé, SNDS). The follow-up includes a yearly self-administered questionnaire, an annual linkage to the national medico-administrative databases, and a medical examination in the HSC every 4 years. Almost none of the people included in CONSTANCES are permanently lost to follow-up, thanks to the passive follow-up through national medico-administrative databases for the large majority of participants who gave consent.

2.2.2.2 Sample of the CONSTANCES cohort included in the present study

CONSTANCES participants eligible for inclusion in the present study were those 1) who provided their lifetime residential history retrospectively through a residential history recall campaign which mainly took place between 2019 and 2022, and 2) for whom we were able to directly reconstruct indoor radon exposure (see 2.2.2.5) over at least 80% of their lifetime period, from birth until 2022. In total, 62,448 participants were included in these analyses. Depending on the risk period of interest (related to the first or second objective of the study), some participants with a cancer diagnosis were classified as having a prevalent cancer based on their age at diagnosis and were subsequently excluded from the corresponding age-specific analyses.

2.2.2.3 Health outcome assessment

Based partly on the results of the literature review and meta-analysis presented in Section 2.1, the targeted cancer locations under study were lung, buccal and pharyngeal, stomach, liver, colon-rectum (grouped), kidney, central nervous system (CNS), female breast, cervix uteri, corpus uteri, ovary,

prostate, connective tissue, skin (melanoma and non-melanoma, separately), and blood and lymphatic system (non-Hodgkin lymphoma [NHL], leukaemia). We additionally studied all cancer locations combined, and all cancer locations combined except lung, i.e., by excluding participants diagnosed with lung cancer. All cancer cases and their corresponding age at first diagnosis were identified from both self-reported data and the SNDS.

2.2.2.4 Lifetime indoor radon exposure reconstruction in the study population

We used annual average municipality-level indoor radon concentration data, predicted all over mainland France by a geostatistical cokriging model using both radon concentration measurements in 10,843 residences and the French map of geogenic radon potential. The residences were sampled to cover all departments in mainland France [*IRSN, 2021*]. The dosimeters were placed in the main room for at least two months, and measurements were corrected for seasonal variability. The geogenic radon potential map was developed in 2010 by the IRSN and identified five classes of geologic radon potential, reflecting the ability of the geological units to produce radon gas and contribute to its transfer in the atmosphere. We reconstructed participants' lifetime yearly residential radon exposure, from birth to 2022 at the latest, by assigning the municipality-level radon average concentration to their successive home addresses. In case of multiple residences within a year, we calculated an annual weighted mean radon concentration with respect to the time spent in each residence.

2.2.2.5 Covariates selection

We used causal Directed Acyclic Graphs (DAG) to select relevant covariates to control for biases [*Tennant et al. 2021*] while studying relationships between cumulative annual radon exposure and cancer risks. For each cancer location studied, we built a specific causal DAG based on existing literature, expert knowledge, and the study population selection criteria and data-generating processes The minimum set of covariates needed to minimize biases while estimating cancer-specific risk in relation to radon exposure included birth cohort (5-year birth period for all cancers, except buccal and pharyngeal cancer where 10-year birth period was use), time-varying age, region of residence, residence characteristics, socioeconomic status (SES), and smoking status (for some cancers only). Detailed time-varying characteristics of occupied residences were not available at the time of this study. However, we assumed that birth cohort, in combination with SES and region of residence could partially capture this information, as they are predictors of the residence characteristics.

2.2.2.6 Statistical analysis

To investigate the long-term effects, precisely in adulthood, of cumulative annual average radon exposure in early life, the exposure period considered started from birth to age 15 included, and the follow-up period spanned from age 16 to the earliest among age at diagnosis of the primary targeted cancer under study or age at censoring. Censoring was defined as the earliest among age at diagnosis of a first cancer other than the targeted cancer under study diagnosis (excluding non-melanoma skin cancer if the cancer under study was not skin cancer), prophylactic mastectomy or ophorectomy (applicable for breast and ovary cancer respectively, when under study), age at death, or age on December 31, 2022. Accordingly, individuals diagnosed with cancer before age 16 were excluded from these specific analyses.

Conversely, to study the long-term effects of lifelong cumulative annual average radon exposure, both the exposure and the follow-up periods spanned from birth to the earliest among age at diagnosis of the primary targeted cancer under study or age at censoring as defined above. In both analyses, we considered a minimal latency period between cumulative radiation exposure and the potential incidence of radiation-induced cancer. Specifically, we applied a two-year lag time if the targeted cancer was leukaemia, and a ten-year lag for all other cancers.

We fitted a time-dependent Cox proportional hazards model to assess the association between cumulative annual average residential radon exposure (as a continuous variable) and the age at diagnosis of the primary targeted cancer for individual. To limit spurious findings due to multiple testing, we applied false discovery rate (FDR) correction to the p-values of the main results using the Benjamini–Hochberg method as implemented in the p.adjust() function in R. All the analyses were performed using the Survival and Splines packages in the statistical software R, version 4.4.2 (https://www.r-project.org/).

2.2.3 Main results

We obtained data for the 62,448 included participants on average for 54.3 years (standard deviation (SD) = 13.12), corresponding to 3,390,544 person-years cumulated from birth. Table 7 presents the characteristics of the participants included in the analyses at their recruitment in the CONSTANCES cohort, and at the end follow-up. Overall, 7,433 (11.9%) participants of 62,448 were diagnosed for incident primary cancer. The median age at time of censoring was 55 years (interquartile range (IQR) = 44). The median cumulative radon exposure at age 15 and at time of censoring was 876 Bq/m^3.years (IQR = 637, 1,259) and 3,110 Bq/m^3.years (IQR=2,214, 4,243), respectively. The unit "Bq/m^3.years" was used in order to reflect the cumulative nature of the exposure, and avoid misleading direct transposition of results to the radon activity concentrations measured in houses which represent a unit of intensity. For instance, living during 10 years in a house with an activity concentration of 60 Bq/m^3 would lead to an exposure of "600 Bq/m^3.years" rather than an exposure of "600 Bq/m^3".

Statistically significant interactions between radon exposure and sex were observed on the risk of colorectal cancer (p=0.035), non-melanoma skin cancer (NMSC, p=0.002), and the groups "all cancer" (p<0.001), and "all cancer, lung excluded" (p<0.001). Subsequently, the results were presented for both men and women separately for these specific cancers or groups of cancers.

Overall, we found no statistically significant association between increased residential radon exposure over the early life period and the risk of cancer in adulthood (see Table 8, left part). Similarly, no statistically significant association was found between lifelong residential radon exposure and the lifetime cancer risk (see Table 8, right part).

Table 7 – Characteristics of population from the Constances cohort included in the study of associations between radon exposure and cancers

Characteristics	Statistics for the study population (N = 62,448)
Sex, n (%)	
Male	28,481 (45.6)
Female	33,967 (54.4)
Age at recruitment (categorical), n (%)	
=29	4,494 (7.2)
]29-39]	11,813 (18.9)
]39-49]	14,630 (23.4)
]49-59]	14,389 (23.0)
>59	17,122 (27.4)
Diploma, n (%)	
No diploma/Elementary/Junior High School Certificate or equivalent	3,064 (4.9)
Vocational certificate	7,483 (12.0)
Senior high school certificate	9,009 (14.4)
Associate's or Bachelor's Degree	17,758 (28.4)
Master's Degree	24,123 (38.6)
Other diploma	126 (0.2)
Unknown	885 (1.4)
Body mass index category, n (%)	
Underweight	1,716 (2.7)
Normal	35,439 (56.7)
Overweight	24,852 (39.8)
Other	441 (0.7)
Physical activity level, n (%)	
Low	4,705 (7.5)
Moderate	38,103 (61.0)
High	17,983 (28.8)
Unknown	1,657 (2.6)
Smoking status, n (%)	
Never	30,791 (49.3)
Former or Ever	31,010 (49.7)
Unknown	647 (1.0)
Alcohol consumption (AUDIT score), n (%)	
Abstainer	1,558 (2.5)
Low-risk consumption	24,243 (38.8)
Hazardous consumption	33,968 (54.4)
Unknown	2,679 (4.3)
Age at censoring	
Median attained age (IQR)	55.00 (44, 65)
Mean attained age ± SD	54.30 ± 13.1
Deceased	
Yes, n (%)	195 (0.3)

Characteristics	Statistics for the study population (N = 62,448)
n; Median age at death (IQR)	195; 68.00 (59, 73)
n; Mean age at death ± SD	195; 64.7 ± 10.7
All cancer	
Yes, n (%)	7,433 (11.9)
n; Median age at diagnosis (IQR)	7,429; 56 (46, 64)
n; Mean age at diagnosis ± SD	7,429; 54.1 ± 12.9
Cumulative average radon exposure at age 15 (in Bq.m^{-3}.years)	
Median (IQR)	875.6 (637, 1,259)
Mean ± SD	1,024.1 ± 615.8
Cumulative average radon exposure at censoring (in Bq.m^{-3}.years)	
Median (IQR)	3,110 (2,214.1, 4,242.9)
Mean ± SD	3,412.7 ± 1,708.9

IQR: Interquartile range; SD: Standard deviation

Table 8 – Associations between cumulative annual average radon exposure and adjusted[α] cancer risk in the Constances cohort.

Cancer	Cases/person-years	Effect of exposure up to 15 years old on cancer risks at adult age		Cases/person-years	Effect of lifelong radon exposure on cancer risk estimated over the whole lifetime	
		HR (95% CI) per 1000 Bq.m^{-3}.years	p$^{\lambda}$		HR (95% CI) per 1000 Bq.m^{-3}.years	p$^{\lambda}$
All cancer in men	3143/1,145,219	1.029 (0.869; 1.219)	0.92	3159/1,572,301	1.002 (0.975; 1.031)	0.95
All cancer in women	4241/1,308,974	0.934 (0.802; 1.087)	0.85	4268/1,818,243	0.975 (0.948; 1.003)	0.46
All cancer, lung excluded in males	3025/1,141,275	1.052 (0.887; 1.247)	0.86	3040/1,568,357	1.005 (0.976; 1.034)	0.92
All cancer, lung excluded in females	4130/1,302,568	0.949 (0.814; 1.106)	0.85	4157/1,811,852	0.979 (0.952; 1.008)	0.58
Lung	170/2,466,551	0.506 (0.202; 1.263)	0.58	171/3,403,005	0.899 (0.770; 1.049)	0.61
Buccal and pharyngeal	85/2,2,466,481	1.355 (0.518; 3.540)	0.85	88/3,402,935	0.874 (0.697; 1.096)	0.73
Stomach	61/2,466,568	0.386 (0.041; 3.645)	0.85	61/3,403,022	0.905 (0.670; 1.22)	0.85
Liver	39/2,466,581	0.402 (0.108; 1.488)	0.61	40/3,403,035	0.950 (0.778; 1.160)	0.89
Colorectal in men	290/1,150,462	0.457 (0.229; 0.913)	0.29	290/1,577,572	0.918 (0.835; 1.009)	0.46
Colorectal in women	266/1,315,839	0.569 (0.293; 1.106)	0.51	267/1,825,183	0.908 (0.818; 1.009)	0.46
CNS	88/2,466,560	1.328 (0.552; 3.194)	0.85	92/3,403,014	1.073 (0.933; 1.233)	0.81
Kidney	192/2,466,507	0.872 (0.441; 1.724)	0.92	194/3,402,961	0.948 (0.839; 1.071)	0.85
Connective & soft tissue$^{\mu}$	56/2,466,460	0.815 (0.279; 2,386)	0.92	60/3,402,914	1.062 (0.889; 1.270)	0.85
Melanoma of skin$^{\mu}$	396/2,454,193	1.072 (0.691; 1.662)	0.92	396/3,390,544	1.034 (0.963; 1.111)	0.85
NMSC in men	462/1,145,219	1.290 (0.856; 1.946)	0.70	462/1,572,301	1.041 (0.972; 1.114)	0.73
NMSC in women	504/1,308,974	1.031 (0.696; 1.527)	0.95	504/1,818,243	0.981 (0.914; 1.054)	0.89
Leukaemia	147/2,466,506	1.039 (0.751; 1.439)	0.95	151/3,402,960	1.011 (0.892; 1.146)	0.95
NHL	177/2,466,457	0.985 (0.522; 1,859)	0.98	179/3,402,911	1.055 (0.955; 1.166)	0.79
Prostate$^{\mu}$	1028/1,150,191	1.290 (0,978; 1.701)	0.46	1029/1,577,301	1.024 (0.978; 1.073)	0.81
Female breast	1625/1,315,207	0.893 (0.690; 1,155)	0.85	1627/1,824,551	0.973 (0.928; 1.020	0.73
Cervix uteri	399/1,315,748	1.160 (0.774; 1.739)	0.85	399/1,825,092	1.048 (0.961; 1.143)	0.79
Corpus uteri$^{\mu}$	115/1,315,861	1.068 (0.443; 2.574)	0.95	115/1,825,205	0.971 (0.810; 1.164)	0.92
Ovary	94/1,315,846	1.291 (0.647; 2.576)	0.85	97/1,825,190	1.030 (0.876; 1.211)	0.92

[α]All the risk models were adjusted for Birth cohort, Region of residence, Diploma, and Smoking status, unless specified; HR: Hazard Ratio; CI: Confidence interval; [λ]corrected p value, with adjustment for multiple testing; [μ] the risk models were adjusted for Birth cohort, Region of residence, and Diploma; CNS: Central nervous system; NMSC: Non-melanoma skin cancer; NHL: Non-Hodgkin lymphoma;

2.2.4 Discussion: strengths and current limitations

To the best of our knowledge, this is the first study which reconstructed the entire lifetime residential radon exposure among an adult cohort, and the first study which focused on the long-term (adulthood) cancer risk associated to residential radon exposure accrued over the childhood period. Its main objectives were to investigate 1) the cancer risk in adulthood potentially associated to accrued residential radon exposure during childhood; and 2) the cancer risk potentially associated with lifelong accrued residential radon exposure. Based on follow-up until the end of year 2022 at the latest, no significant increase in cancer risk associated with residential radon exposure could be detected in this population.

Despite these strengths mentioned above, our study still currently has some limitations. The cohort was still relatively young at the end of follow-up. The median and mean ages at end of follow-up were 55 and 54.3 years, respectively. This may have limited the available statistical power to detect significant associations. Our study failed to detect the well-documented association between radon exposure and lung cancer risk [*UNSCEAR 2019*]. One of the potential explanations for this (and possibly for the lack of association with other cancers) might be a lack of power due to the relatively small number of lung cancer cases (171 primary incident cases), due to the overall young age of the cohort. Many national case-control studies on residential radon and lung cancer conducted in Europe and North America including less than 1,000 cases also failed to detect a statistically significant association between radon and lung cancer, whereas pooled analyses of these studies comprising between 4,081 to 7,148 lung cancer cases clearly detected a significant positive association [*Darby et al. 2006; Krewski et al. 2006*].

The annual radon concentration estimates we used in this study were derived from a predictive model [*IRSN 2021*]. Unfortunately, building characteristics or household ventilation habits data were not included in this model, although it is well established that these factors influence indoor radon concentration. The lack of such variables likely contributed to a limited predictive power of the model (see Section 2.3). Although we indirectly adjusted for ventilation habits through the time-varying smoking status, time-varying region of residence, birth cohort and education, and also partially for the residence characteristics by including age, education, birth cohort, and the time-varying region of residence, it is still possible that our results suffer from bias potentially introduced by error in the assessment of the radon concentration. Progress on this respect is expected in the near future, since more than 42,600 persons included in our study recently responded to a questionnaire about the characteristics of each of their residence since birth.

2.2.5 Conclusions and perspectives

Current findings must be interpreted with caution in the light of the study's current limitations. Although no significant association between radon and cancer risk could be detected in the CONSTANCES cohort to date, further investigations of the potential effects of radon on both lung cancer and other health outcomes in this and other cohorts is warranted.

Radon exposure assessment will be improved in the future by integrating additional radon measurement data and subsequently updating the geostatistical model used to predict radon concentrations. In a near future, for a subset of the cohort who responded to a dedicated questionnaire, it will also be possible to integrate building characteristics data into the models, to enhance the accuracy of radon concentration prediction at the dwelling level.

Extending the follow-up of the cohort will increase statistical power, which may eventually reveal the well-established relationship between radon exposure and lung cancer risk.

Lastly, reconstruction of other radiological exposures than radon is underway in the CONSTANCES cohort as part of the ongoing CORALE research project (radiological component of the exposome and risks of chronic diseases in the CONSTANCES cohort) to study more comprehensively the effects of radiation exposure (from radon and other radiation sources) on various diseases.

2.3 Radon measurements in the home of 1,000 Constances volunteers

During winter 2023-2024, a radon measurement campaign in the homes of participants from the study population described in Section 2.2 was carried out.

Initially, participants randomly selected from the study population described above and living in houses were contacted to propose them to participate to a radon measurement campaign. Based on the agreements received, a total of 1,007 dosimeters was sent to the participants, along with an online questionnaire about the characteristics of the houses and of the rooms in which measurements would be conducted.

Dosimeters remained in the measurement room at least 2 months during winter 2023-2024.

In total, dosimeters were sent back and successfully analysed for 984 persons, resulting in a 97% measurement success rate.

Figure 4 shows the geographic distribution of measurements conducted.

The median and arithmetic mean of measurement results were 45 Bq/m^3 and 103 Bq/m^3, respectively. Measurement results above 300 Bq/m^3 were detected in 6,5 % of the houses. Recommendations were provided to the participants currently living in these houses.

The linear correlation coefficient between measured concentrations and those estimated by the geostatistical model used in Section 2.2. was r = 0.27. Improvement of this correlation is foreseen once the geostatistical model will be improved and residence characteristics will be taken into account.

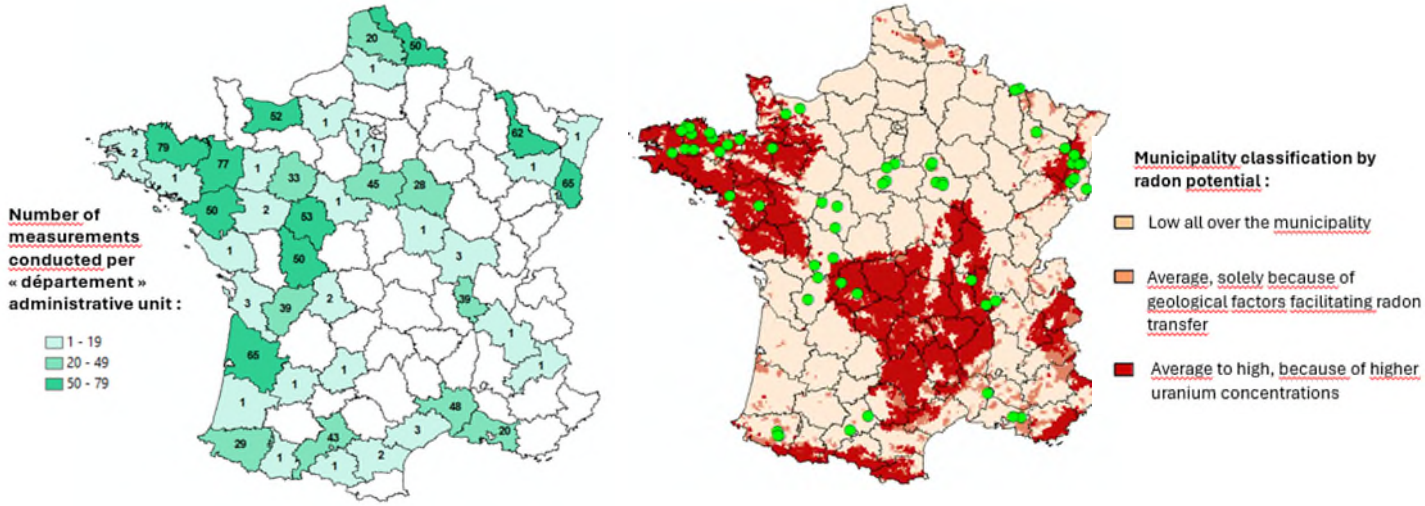

Figure 4 – Geographical distribution of the radon measurements conducted in the houses of volunteers from the Constances cohort

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