

# Residential radon exposure and cancer

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## Abstract

Radon is an established human lung carcinogen naturally released as an odorless, colorless gas from soil and rocks. It is a major environmental source of ionizing radiation and can cause oxidative damage to DNA, increasing the risk of lung cancer. Although the association between radon and lung cancer is well established, the association between radon and other cancers is not. Based on reported studies, there is no consistent evidence indicating an association between radon and non-solid and solid cancers, but limited literature, heterogenous study design, and confounding variables preclude definitive conclusions. More research is needed to evaluate the association between residential radon and non-lung cancers, particularly with regard to skin cancer, central nervous system (CNS) cancer, renal, and stomach cancer, in which existing literature suggests potential associations with residential radon may exist. However, the literature largely demonstrates that lung cancer is the primary concern associated with residential radon exposure; the lack of association with non-lung cancers could reflect the lack of studies which have an adequate sample size, establish accurate levels of radon exposure, and control for confounders. These results should be considered in residential radon mitigation efforts which should focus on smokers with high radon exposures.

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## Introduction

Radon-222 (Rn-222) is a colorless, odorless gas produced from the decomposition of uranium and radium, and is naturally released from bedrock and soil.<sup>1</sup> Rn-222 is the most common isotope of radon and spontaneously ejects alpha-particles, decaying into radon “daughter radioisotopes” polonium (Po-214, Po-218), bismuth, and lead.<sup>1,2</sup> Inhalation of radon gas can result in decay products of radon becoming trapped in lung tissue. These daughter radioisotopes will continuously emit alpha particles, becoming a source of ionizing radiation. For the general population, radon gas is the leading environmental source of ionizing radiation. Ionizing radiation induces oxidative damage in DNA, including single and double-strand breaks causing genome instability, and increases the risk of lung cancer.<sup>2</sup> Radon gas concentration is measured in units of becquerels per cubic meter (Bq/m<sup>3</sup>).<sup>3</sup>

Globally, the outdoor radon concentration does not pose health risks at a level of 5 Bq/m<sup>3</sup>-15 Bq/m<sup>3</sup>.<sup>1</sup> However, as radon escapes from the ground, the gas can leak through porous house foundations, such as basements where it can concentrate to levels that pose a health hazard when inhaled. Radon exposure from building materials and water sources may also have a minor role.<sup>1</sup> While the average estimated radon concentration of 48 Bq/m<sup>3</sup> in residential homes is comparatively lower than the Environmental Protection Agency radon “action level” of 148 Bq/m<sup>3</sup>,<sup>4</sup> an estimated 8.5 million residences had radon levels exceeding this.<sup>5</sup> Furthermore, a 2019 study of residential radon levels in the Canadian provinces of Alberta and Saskatchewan found residential homes contained a mean radon level of 108 Bq/m<sup>3</sup> with 17.8% containing radon levels that exceeded 200 Bq/m<sup>3</sup>. On average, homes built after 1992 had radon levels 31.5% higher (average 142 Bq/m<sup>3</sup>, median 103 Bq/m<sup>3</sup>) than homes built before 1992 (average 108 Bq/m<sup>3</sup>, median 85 Bq/m<sup>3</sup>).<sup>6</sup> This study suggests that the modern North American Prairie residential homes have increasing levels of radon, with more recently constructed homes containing higher radon concentrations. This increase may be attributed to more ‘modern’ building metrics, such as larger square footage that allows more contact with bedrock, taller ceilings, and reduced window openings on upper floors. In addition, it is possible that the more recent use of energy-efficient home insulation during cold weather seasons also decreases air ventilation.<sup>6</sup>

## Radon association with lung cancer

Radon exposure is the second leading cause of lung cancer after smoking.<sup>4</sup> Globally, lung cancer has the highest incidence and mortality, representing 11.6% of all cancer cases and 18.4% of cancer deaths in 2018.<sup>7</sup> Increased mortality from lung disease in miners was first linked to radon exposure during the 1950s. Subsequently, studies on lung cancer risks in underground miners with occupational radon exposure were published.<sup>8</sup> These reports led to rising concerns in the general public about the possible risk of lung cancer due to radon exposure in residential areas. Many epidemiological studies have since established a major association

between lung cancer and radon exposure.<sup>9-13</sup> Lorenzo-Gonzales *et al.* recently analyzed the association between residential radon exposure and lung cancer in North-Western Spain.<sup>14</sup> Cases included patients with a histologic diagnosis of lung cancer; controls included individuals undergoing surgical procedures unrelated to smoking. Residential radon was directly measured into their homes. The odds ratio for having lung cancer significantly increased with residential radon exposure and with tobacco consumption. Analysis of the interaction between these variables indicated that individuals who had >66 pack years of smoking and >200 Bq/m<sup>3</sup> radon exposure had a 29.3% higher risk of having lung cancer. Radon is currently considered the second greatest risk factor for lung cancer by the American Cancer Society.

### Radon and non-lung cancers

While the association between radon and lung cancer is fairly well established, the link between radon and other cancers is less so. Given the ionizing effects of radon and its prevalence in the environment, it is reasonable to assume that it could be a causative factor for other types of malignancies.<sup>15</sup> Studies published from 2000 to 2021 on the association between residential radon and various non-lung cancers are reported in this review.

### Skin cancer

The association between radon and skin cancers is biologically plausible, as radon decay products can deposit on the skin and emit alpha particles, irradiating the skin's outer layers. At a radon gas level of 200 Bq/m<sup>3</sup>, the skin receives an estimated annual dose of 25 millisieverts (mSv), with mSv defined as a unit of ionizing radiation from radon decay products, compared to 35.8-159 mSv when inhaled for the lungs and <1 mSv when inhaled for the majority of other organs. Therefore, the skin receives the next highest dose from radon and radon decay products after the lungs.<sup>16</sup> Alpha particles from radon decay products Po-218 and Po-214 are capable of penetrating as deep as 47 and 70  $\mu$ m into the epidermis, respectively, potentially reaching the basal layer of skin in certain parts of the

body.<sup>17</sup> On the assumption that target cells for skin cancer induction are in the basal layer of the epidermis, theoretical calculations estimate 0.7% (95% CI:0.5, 5.0%) of skin cancers in the United Kingdom can be attributed to the nominal indoor radon level of 20 Bq/m<sup>3</sup>.<sup>18</sup>

Studies investigating the association between residential radon exposure and skin cancers are reported in Table 1. In an American Cancer Prevention Study II cohort study, there was no association between residential radon exposure and mortality due to malignant neoplasms of connective tissue (HR:1.10; 95% CI:0.80, 1.51), other skin (HR:0.70; 95% CI:0.42, 1.19), and melanomas (HR:1.08; 95% CI:0.88, 1.33).<sup>19</sup> Similarly, in a Spanish cohort study, no association between residential radon exposure and non-melanoma skin cancer was found (HR:1.5; 95% CI:0.6, 3.8).<sup>20</sup>

When associations between radon and skin cancer are observed, they can depend on the type of cancer studied. For example, in an ecologic study of South-Western England, an association between residential radon exposure and squamous cell carcinoma was found (RR:1.76; 95% CI:1.46, 2.11), but no association for basal cell carcinoma (RR:0.81; 95% CI:0.66, 1.00) or malignant melanoma (RR:0.85; 95% CI:0.65, 1.11) was found.<sup>21</sup> In contrast, a Danish cohort study reported an association between residential radon exposure and basal cell carcinoma (IRR:1.14; 95% CI:1.03, 1.27), but not squamous cell carcinoma (IRR:0.90; 95% CI:0.70, 1.37) or melanoma (IRR:1.08; 95% CI:0.77, 1.50).<sup>22</sup> Finally, a 2017 Swiss national cohort study found an association between residential radon exposure and malignant melanoma mortality (HR:1.16; 95% CI:1.04, 1.29), highlighting the conflicting results among studies.<sup>23</sup>

Ultraviolet (UV) exposure is a significant confounding factor in reported studies, given the association between UV exposure and skin cancer, and could not fully be controlled for. The Danish cohort study best controlled for UV exposure, adjusting for municipal-level mean daily hours of bright sunshine per residence, outdoor occupation, and participation in leisure-time physical activities potentially pertinent to sun exposure.<sup>22</sup> In other studies, how-

**Table 1. Studies on residential radon exposure and skin cancer risk.**

| Country        | Author                               | Study Design            | Mean Follow-Up  | Sample Size   | Exposure   | Radon Exposure Measurements   | Risk Estimate (95% CI)   |
|----------------|--------------------------------------|-------------------------|---|---|--|---|--|
| Switzerland    | Vienneau (2017) <sup>23</sup>        | Cohort                  | 7.8 years   | 5.2 million subjects; 1,900 MM cases  | Per 100 Bq/m <sup>3</sup>                                    | Address-level exposure estimated by national exposure prediction model              | HR:1.16 (1.04, 1.29)   |
| Denmark        | Bräuner (2015) <sup>22</sup>         | Cohort                  | 13.6 years  | 51,445 subjects; 3,889 cases (3,243 BCC, 317 SCC, 329 MM)   | Per 100 Bq/m <sup>3</sup>                                    | Address-level exposure estimated by validated regression model                      | BCC IRR:1.14 (1.03, 1.27)<br>SCC IRR:0.90 (0.70, 1.37)<br>MM IRR:1.08 (0.77, 1.50)   |
| Spain          | Barbosa-Lorenzo (2016) <sup>20</sup> | Cohort                  | 30.2 years  | 1933 subjects; 25 skin, except melanoma, cancer cases   | $\geq 50$ Bq/m <sup>3</sup>                                  | Bedroom-level exposure from Galicia Radon Map*                                      | HR:1.5 (0.6, 3.8)  |
| United States  | Turner (2012) <sup>19</sup>          | Cohort                  | 20.4 years  | 811,961 subjects; 2,098 cases (1,247 MM, 538 connective tissue malignant neoplasm, 313 other skin malignant neoplasm) (all mortality) | Per 100 Bq/m <sup>3</sup> radon                              | County-level exposure estimated by empirical study model                            | MM HR:1.08 (0.88, 1.33)<br>Connective Tissue Malignant Neoplasm Mortality HR:1.10 (0.80, 1.51)<br>Other Skin Malignant Neoplasm Mortality HR:0.70 (0.42, 1.19) |
| United Kingdom | Wheeler (2012) <sup>21</sup>         | Ecological Surveillance | Period: 2000-2004 (cancer incidence); 1980-2000 (radon) | 18,306 cases  | $\geq 230$ Bq/m <sup>3</sup> radon vs 0-39 Bq/m <sup>3</sup> | Postcode sector-level exposure obtained from National Radiologic Protection Board** | BCC RR:0.81 (0.66, 1.00)<br>SCC RR:1.76 (1.46, 2.11)<br>MM RR: 0.85 (0.65, 1.11)   |

CI, confidence interval; MM, malignant melanoma; HZ, hazard ratio; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; IRR, incidence rate ratio; RR, relative risk, \*Galician Radon Map measurements obtained from radon detectors placed in study participants' bedrooms for a minimum of three months, \*\*National Radiologic Protection Board radon atlas measurements were obtained through radon detectors placed in surveyed households

ever, UV exposure was not addressed at all.<sup>19,20</sup> None of the reported studies comprehensively accounted for sunshine exposure duration, particularly with regard to individual behavior and preferences. Differences in study design and variables such as UV exposure limit conclusions that can be drawn from existing literature, with additional studies needed to investigate any potential association.

### Stomach cancer

The association between groundwater radon and stomach cancer is of interest since radon is soluble in water and, when ingested, can remain in the stomach for several minutes.<sup>16</sup> Routine ingestion of water (600 L annually) containing 1000 Bq/L of radon decay products and radon gas together results in an annual dose of 1.5–50.4 mSv to the stomach, compared with 0.01–1.26 mSv to the lungs.<sup>16</sup> However, this dose is still significantly below the range for inhaled radon to the lungs (35.8–159 mSv). Furthermore, a study on alpha particles from internally incorporated plutonium found no association with stomach cancer incidence. Like plutonium, radon emits alpha particles, suggesting there may be no association between groundwater radon and stomach cancer despite apparent biological plausibility.<sup>24</sup>

Studies investigating the association between residential radon exposure and stomach cancer are reported in Table 2. In a small case-cohort study in Finland, risk of stomach cancer was not attributed to radon or other radionuclides in well water (HR:0.68; 95% CI:0.29, 1.59).<sup>25</sup> In a United States ecological study, there was an unclear association between groundwater radon and stomach cancer (IRR:1.05, 95% CI:0.99, 1.11). However, utilizing a cluster membership model quantifying exposure at the address level and estimating the odds of cancer cases belonging to clusters, study authors reported groundwater radon causes a statistically significant increase in the odds of stomach cancer cases (OR:1.24; 95% CI:1.03, 1.49).<sup>26</sup> Definitive conclusions cannot be drawn from this limited literature, but there is biological plausibility supporting a potential association.

When considering residential radon exposure in the air and stomach cancer, there is less biological plausibility compared to groundwater radon, as the stomach receives a low dose from inhaled radon and radon decay products (0.08–0.19 mSv).<sup>16</sup> Reported studies have mixed results. A large American Cancer Prevention Study II cohort study found no association with stomach cancer mortality (HR:0.85; 95% CI:0.70, 1.03), but a smaller

Spanish cohort study supported an association with stomach cancer incidence (HR:0.8; 95% CI:1.2, 98.0).<sup>19,20</sup> Conflicting results may partially be attributed to the Spanish study's smaller cohort size and the use of incidence as a parameter rather than mortality; however, this effect is limited since gastric cancer has a 31% 5-year survival rate in the United States.<sup>27</sup> In addition, both the American and Spanish cohort studies failed to address groundwater radon entirely in their study design, introducing a confounding variable. Cohort studies of uranium miners do not indicate a significant association between occupational radon exposure in the air and stomach cancer,<sup>28–31</sup> suggesting there may also be no association with residential radon exposure in the air and stomach cancer.

### Central nervous system cancer

The association between residential radon exposure and central nervous system (CNS) cancer is biologically plausible, although the rationale is not as strong as radon and other cancers of the body. Moderate-to-high doses of ionizing radiation are the only environmental risk factor for brain and CNS tumors, and radon is a major environmental source of ionizing radiation.<sup>32</sup> However, the brain receives a relatively low dose from inhaled radon and its decay products, with an annual dose at a radon gas level of 200 Bq/m<sup>3</sup> estimated to be 0.02–0.15 mSv for the brain, compared to 35.8–159 mSv for the lung.<sup>16</sup>

Studies investigating the association between residential radon exposure and CNS cancer are reported in Table 3. In a Spanish ecological study, a statistically significant positive association between residential radon exposure and brain cancer mortality was observed, particularly in females (Spearman's rho values of 0.286,  $p < 0.001$  and 0.509,  $p < 0.001$  for males and females, respectively).<sup>33</sup> Similarly, a Danish cohort study suggested a statistically significant association between long-term exposure to residential radon and primary brain tumor risk (IRR:1.96; 95% CI:1.07, 3.58).<sup>34</sup>

Conversely, in a United States ecological study of five states, a small negative association between mean county radon levels and CNS cancer incidence was observed, with 0.068 fewer cases of CNS cancer per 1 pCi/L radon ( $p < 0.0001$ ). However, in one state alone (Iowa), a small positive association was observed, with 0.022 more cases per 1 pCi/L radon ( $p = 0.006$ ). Still, study authors concluded the study did not show a link between radon and CNS cancer incidence.<sup>21</sup> In a French ecological study examining natural background radiation, there was no reported association between

**Table 2. Studies on residential radon exposure and stomach cancer risk.**

| Country       | Author                               | Study Design     | Sample Size                   | Mean Follow-Up                 | Exposure                         | Radon Exposure Measurements   | Risk Estimate (95% CI)  |
|---------------|--------------------------------------|------------------|-------------------------------|--------------------------------|----------------------------------|---|---|
| United States | Messier (2017) <sup>26</sup>         | Ecological Study | 5,218 cases                   | Surveillance Period: 1999–2009 | Per 100 Bq/L (Groundwater Radon) | Address-level exposure estimated by land-use regression and Bayesian Maximum Entropy (LUR-BME) geostatistical model | IRR:1.05 (0.99, 1.11)<br>OR (Cluster Analysis): 1.24 (1.03, 1.49) |
| Finland       | Auvinen (2005) <sup>25</sup>         | Case-Cohort      | 371 subjects, 107 cases       | Surveillance Period: 1981–1995 | Water samples from 100 Bq/L      | HR:0.68 (0.29, 1.59) wells used by study (Groundwater Radon)  | participants  |
| Spain         | Barbosa-Lorenzo (2016) <sup>20</sup> | Cohort           | 1920 subjects, 12 cases       | 30.2 years                     | ≥50 Bq/m <sup>3</sup> radon      | Bedroom-level exposures from Galicia Radon Map*   | HR:10.8 (1.2, 98.0)   |
| United States | Turner (2012) <sup>19</sup>          | Cohort           | 811,961 subjects, 1,880 cases | 20.4 years                     | Per 100 Bq/m <sup>3</sup> radon  | County-level exposure estimated by empirical study model  | HR:0.85 (0.70, 1.03)  |

CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; HR, hazard ratio, \*Galician Radon Map measurements obtained from radon detectors placed in study participants' bedrooms for a minimum of three months.

radon and childhood CNS tumor incidence (IRR:1.02; 95% CI:0.96, 1.07), and in an American Cancer Prevention Study II cohort study, no association with brain cancer mortality was reported (HR:0.98; 95% CI:0.83, 1.15).<sup>19,35</sup> This is similar to occupational studies on radon exposure in uranium miners that revealed mixed results, though the majority indicate no association.<sup>28,30,31,36</sup> Mixed results, heterogeneous study designs, and varying study populations limit definitive conclusions. More cohort studies focusing on CNS cancer incidence in an adult population are necessary to explain any association. A 2018 systematic review by Ruano-Ravina also noted that available studies were not adequate to identify an association between residential radon exposure and CNS tumors.<sup>37</sup>

### Breast cancer

Ionizing radiation has been linked to breast cancer, suggesting a potential association between radon and breast cancer.<sup>38</sup> However, breasts receive a relatively low dose from inhaled radon and its decay products, with an annual dose at a radon gas level of 200 Bq/m<sup>3</sup> estimated to be 0.02-0.15 mSv for the breast, relative to 35.8-159 mSv for the lung.<sup>16</sup>

In a Spanish cohort study, a non-significant hazard ratio of 2.4 (95% CI:0.7, 8.6) was calculated for residential radon exposure greater than or equal to 50 Bq/m<sup>3</sup> and breast cancer incidence, though study authors noted enough cases to suggest a potential association.<sup>20</sup> A larger American Cancer Prevention Study II cohort reported no association with breast cancer mortality (HR:0.91; 95% CI:0.82, 1.01).<sup>19</sup> Similarly, in a Nurses' Health Study II cohort study, increased radon exposure was not associated with overall breast cancer risk (HR:1.06; 95% CI:0.94, 1.21; p=0.30). The study did suggest that women with radon exposure greater than or equal to 74.9 Bq/m<sup>3</sup> had an elevated risk of estrogen-receptor negative/progesterone-receptor negative breast cancer compared to women with radon exposure below 27.9 Bq/m<sup>3</sup> (HR:1.38; 95% CI:0.97, 1.96; p=0.05).<sup>39</sup> In a follow-up study, it

was found the MAPK signaling and phosphocholine biosynthesis pathways, which have roles in ionizing radiation-induced tumorigenesis, were enriched in estrogen receptor-negative and adjacent-normal samples at radon levels as low as 2 pCi, supporting biological plausibility of an association (False Discovery Rate <25%).<sup>40</sup>

No significant associations were found in reported studies, and biological plausibility is only weakly supported, though two cohort studies suggest potential associations. More research is needed to investigate any potential association.

### Esophageal cancer

Ionizing radiation is a risk factor for esophageal cancer, suggesting a potential association between radon and esophageal cancer.<sup>38</sup> In an ecological study, Ruano-Ravina *et al.* found a statistically significant association between municipal median radon concentrations and esophageal cancer mortality in men, but not in women (Spearman's rho = 0.298, p<0.001 for males; Spearman's rho = -0.045, p=0.615 for females).<sup>41</sup> However, in an American Cancer Prevention Study II cohort study, no association between mortality due to malignant neoplasms of the esophagus and mean county-level residential radon concentrations for study participants was observed (HR:1.08; 95% CI:0.89, 1.30).<sup>19</sup> In addition, cohort studies in uranium miners did not find an association between esophageal cancer and occupational radon exposure.<sup>28,30,31</sup> Although an association cannot be excluded, the lack of evidence and overall low incidence of esophageal cancers in the United States suggest that additional studies will be difficult.<sup>42</sup> However, more research is needed given the lack of a definite conclusion and the heterogeneity in the available studies.

### Oropharyngeal cancer

The association between radon and oropharyngeal cancer is of particular interest due to the high dose the oropharyngeal cavity receives from radon and radon decay products. At a radon gas level of 200 Bq/m<sup>3</sup>, the extra-thoracic part of the respiratory tract (nose,

**Table 3. Studies on residential radon exposure and central nervous system cancer risk.**

| Country       | Author                              | Study Design                                     | Sample Size                      | Mean Follow-Up  | Exposure  | Radon Exposure Measurements  | Correlation/Risk Estimate (95% CI)                     |
|---------------|-------------------------------------|--|----------------------------------|---|---|--|--|
| Spain         | Ruano-Ravina <sup>33</sup> (2017)   | Brain Cancer Mortality Ecological Study          | 949 male cases, 758 female cases | Surveillance Period: 1999-2008  | 49.4% municipalities geometric mean: <100 Bq/m <sup>3</sup><br>50.6% municipalities geometric mean >100 Bq/m <sup>3</sup> | Bedroom-level exposure obtained from Galicia Radon Map*                                      | p Males: 0.164 (p=0.009)<br>p Females: 0.433 (p<0.001) |
| Denmark       | Bräuner <sup>34</sup> (2013)        | Brain Tumor Cohort Study                         | 57,053 subjects, 121 cases       | 12.6 years  | Per 100 Bq/m <sup>3</sup> radon   | Address-level exposure estimated by validated regression model                               | IRR:1.96 (1.07,3.58)                                   |
| France        | Berlivet <sup>64</sup> (2020)       | CNS Tumors in children under 15 Ecological Study | 5471 cases                       | Surveillance Period: 2000-2012  | Per 100 Bq/m <sup>3</sup> radon   | Municipality-level exposure from Institut de Radioprotection et de Sûreté Nucléaire (IRSN)** | IRR:1.02 (0.96,1.07)                                   |
| Norway        | Risco Kollerud <sup>63</sup> (2014) | Cohort Study of CNS cancer in children 0-15      | 712,674 subjects, 427 cases      | Birth to date of cancer diagnosis, death, emigration or 15 years of age | Per 100 Bq/m <sup>3</sup> radon   | Address-level exposure estimated by buffer model   | HR:1.13 (0.99-1.28)                                    |
| United States | Monastero <sup>65</sup> (2019)      | CNS cancer Ecological Study                      | 59,392 cases                     | N/A   | Per 37 Bq/m <sup>3</sup> radon  | County-level exposure from AirCheck***   | B:-0.068 (p<0.0001)                                    |
| United States | Turner <sup>19</sup> (2012)         | Malignant Brain Neoplasm Mortality Cohort Study  | 811,961 subjects, 2,232 cases    | 20.4 years  | Per 100 Bq/m <sup>3</sup> radon   | County-level exposure estimated by empirical study model                                     | HR:0.98 (0.83,1.15)                                    |

p, Spearman's Rho value; CI, confidence interval; IRR, incidence rate ratio; B, beta coefficient (binomial correlation); HR, hazard ratio; \*Galician Radon Map measurements obtained from radon detectors placed in study participants' bedrooms for a minimum of three months; \*\*IRSN conducted a national campaign on indoor radon concentration measurements between 1982 and 2003, with 10,843 measurements total; \*\*\*AirCheck is a third-party website that provides compiled radon measurements from individual homes collected by Individual National Health Association certified radon specialists, county health departments and the US EPA.



mouth, pharynx, and larynx) receive an estimated annual dose of 44.5-70.9 mSv from inhaled radon and radon decay products, comparable to the lungs (35.8-159 mSv).<sup>16</sup>

However, an American Cancer Prevention Study II cohort study reported no association between mean county-level residential radon concentrations for study participants and mortality due to malignant neoplasms of the lip, oral cavity, and pharynx (HR:0.80; 95% CI:0.59, 1.08).<sup>19</sup> This may be due in part to the use of mortality as a parameter, with 5-year overall survival rates for cancers of the oral cavity and pharynx at 66%.<sup>42</sup>

Cohort studies on uranium miners indicate small to insignificant associations between occupational radon exposure and risk of oropharyngeal cancer.<sup>28,30,31,43</sup> A systematic review of 13 cohort studies, 2 on the general population and 11 on miners, also concluded that oropharyngeal cancer incidence or mortality was not significantly associated with radon exposure in most studies, though limited quality and number of studies was noted.<sup>44</sup> Considering the strong biological plausibility, this association should not be excluded from future study.

### Kidney cancer

The association between residential radon exposure and genitourinary cancer is biologically plausible as the kidney is the organ that receives the second-highest dose from inhaled radon and radon decay products after the lungs. At an annual dose at a radon gas level of 200 Bq/m<sup>3</sup>, the kidney receives a dose of 0.54-5.20 mSv from inhaled radon and radon decay products, compared to 35.8-159 mSv when inhaled for the lung, and less than 1 mSv for most other organs.<sup>16</sup>

In a large American Cancer Prevention Study II cohort study, no association between residential radon exposure and mortality due to malignant neoplasms of the kidney was observed (HR:0.94; 95% CI:0.76, 1.16).<sup>19</sup> Similarly, in a smaller Spanish cohort study, a hazard ratio (HR) of 0.6 (95% CI:0.2, 1.9) was calculated for residential radon exposure greater than or equal to 50 Bq/m<sup>3</sup> and urinary tract cancer incidence compared to residential radon exposure less than 50 Bq/m<sup>3</sup> and found no association.<sup>20</sup> In a Finnish cohort study, ingested natural radionuclides in drilled well water were not associated with kidney cancer. For radon specifically, exposure to 130-399 Bq/L radon in groundwater had a hazard ratio of 0.64 (95% CI:0.30, 1.38) relative to a hazard ratio of 1 for less than 130 Bq/L radon in groundwater, indicating no association.<sup>45</sup>

In addition, occupational radon exposure studies of uranium miner cohorts generally do not support an association with kidney cancer, though some studies did find significant risks.<sup>28,30,31</sup> A 2018 meta-analysis of eight studies, including the American Cancer Prevention Study II cohort study reported above, 1 other general population study, and 6 uranium miner studies, found no clear association between radon and kidney cancer, consistent with the studies reported above, although study authors also could not exclude an association.<sup>46</sup> Despite apparent biological plausibility, the balance of evidence does not support an association between residential radon exposure and kidney cancer.

### Leukemia

Significant attention has been given to leukemia and radon, in part because it is theorized that small doses of radon may reach the bone marrow and induce leukemia.<sup>47</sup> At an annual dose of 200 Bq/m<sup>3</sup>, the bone marrow receives an estimated dose of 0.28 mSv<sup>16</sup>; Harley and Robbins estimated a 10-year exposure to 200 Bq/m<sup>3</sup> as 0.22-0.63 mSv.<sup>48</sup> Several studies have also examined the effect of radon on leukocytes.<sup>49-51</sup> Oestricher *et al.* noted an increased frequency of chromosomal aberration in peripheral blood lymphocytes in individuals with home radon levels of 200-1000 Bq/m<sup>3</sup>,

compared to those living in homes less than <200 Bq/m<sup>3</sup>, but this association was not observed at higher concentrations (1000-13,000 Bq/m<sup>3</sup>).<sup>52</sup> Hamza and Mohankmar observed that radon can cause chromosomal damage to lymphocytes at low doses and dose rates, but this was an *in vitro* study.<sup>53</sup> Stem cells exposure in pulmonary capillaries is another proposed mechanism.<sup>48</sup>

Results of radon and leukemia studies are mixed, with several studies finding both positive<sup>54-58</sup> and null associations.<sup>35,59-64</sup> A meta-analysis of these studies by Lu *et al.* observed a weak but positive association between radon exposure and leukemia (OR:1.37; 95% CI:1.02, 1.82), noting the difference between case-control (OR:1.22; 95% CI:1.01, 1.42) and cohort (HR:0.97; 95% CI:0.81, 1.15) studies.<sup>47</sup> Indeed, Tong *et al.* noticed the majority of surveyed ecological studies (11 out of 12) found a positive association, while the majority of case-control studies found weak or no association.<sup>65</sup> A review by Laurier *et al.* observed a similar trend.<sup>66</sup> Since case-control studies are considered the more reliable study for explaining such associations, it is suggested that these studies may be more representative of the true effect of radon on leukemia<sup>65</sup>. However, Evrard *et al.* argued that case-control studies may not be large enough to identify causal associations for leukemia and radon, since their study found indoor radon concentration would explain only 5.4% of childhood cancers.<sup>67</sup> In studies that use modeling, the type of model used can affect outcomes. For example, Toti *et al.* observed that a cohort that had previously shown a negative association between radon and leukemia showed no association upon reanalysis with a different model.<sup>68</sup> Positive associations may also be restricted to specific groups, such as age groups, sex, or cancer subtype.<sup>67,69</sup> Finally, the number of participants and cases can affect the reliability of outcomes. For example, Kohli *et al.* concluded that areas of higher radon exposure were associated with an increased risk of leukemia in children. However, their total cases of leukemia were small (n=90), with only 4 total cases in the high exposure group.<sup>54</sup>

Confounding factors have been studied in conjunction with leukemia and radon exposure. Again, the results here are mixed. For example, Oancea *et al.* found their results were not affected by latitude (a surrogate for UV exposure)<sup>56</sup>, and Ha *et al.* observed no effect from adjusting for smoking and socioeconomic factors (Table 4).<sup>70</sup> However, Raaschou-Nielsen *et al.* noted an increase in the relative risk for leukemia when data were adjusted for birth order, mother's age, traffic density, proximity high-voltage facilities (RR:1.70; 95% CI:1.08, 2.67, per 10<sup>3</sup> Bq/m<sup>3</sup>), for better geocoding precision (RR:1.64; 95% CI:1.06, 2.52), and for residence in single-family housing (RR:2.44; 95% CI:1.24, 4.81) compared to unadjusted data (RR:1.56; 95% CI:1.05, 2.30).<sup>58</sup> Bräuner *et al.* observed that exposure to nitrous oxide and traffic density may increase leukemia risk from radon.<sup>55</sup> Associations may also be specific to certain subsets of leukemia.<sup>67</sup> Ultimately, while studies are split on the association of radon and leukemia, observed risk estimates are typically very low suggesting that, if an association does exist, it is likely small.

### Thyroid cancer

To our knowledge, only four studies have examined the association between radon and thyroid cancer.<sup>71-74</sup> All studies have been ecological, and none has found an association between radon and thyroid cancer. Similarly, Ron *et al.* reviewed five cohort studies examining environmental radiation exposure and found no association with thyroid cancer.<sup>75</sup> Other studies regarding environmental radiation and thyroid cancers and neoplasms have found null,<sup>76-78</sup> and positive associations.<sup>79,80</sup> Oakland *et al.* notes that the latency between low-level radiation exposure and thyroid cancer incidence may be too lengthy to be identified by ecologic studies.<sup>71</sup>

## Lymphoma

The number of studies on lymphoma is also limited. Teras *et al.* observed statistically significant associations among women for diffuse large B-cell and follicular lymphomas and no association among men.<sup>81</sup> Ha *et al.* observed a slight association with non-Hodgkin's lymphoma in men (RR:1.01; 95% CI:0.99, 1.03) and women (RR:1.03; 95% CI:1.01, 1.06), with female children and adolescents having the highest risk (RR:1.04; 95% CI:0.99, 1.10).<sup>70</sup> Peckham *et al.* observed an association for diffuse large B-cell lymphoma (aIRR:1.73; 95% CI:1.03, 2.91), but not for Hodgkin's, Burkitt's, or total lymphomas.<sup>82</sup> However, several other studies have found no association.<sup>58,60</sup>

## Conclusions

The available literature does not support any strong associations between radon and non-lung cancers. While some studies have reported associations, results were often limited, contradictory, and inconclusive, possibly explained by differences and limitations in study design. For example, the methods to measure radon exposure ranged from radon detectors placed in study participants' bedrooms to county-level estimates assigned by zip code; the majority of studies used estimates for radon exposure rather than direct measurements. Since radon levels vary depending on geography and architecture, estimates used in existing studies may not

fully capture individual level radon exposure. Some countries, *e.g.*, Spain and United Kingdom, have higher levels of radon exposure. Consequently, studies should focus on those regions, if possible. In addition, in some countries, families tend to occupy the same dwelling from long periods of time which has the potential to increase exposure. Studies were also difficult to compare due to the inclusion of both cohort and ecological studies and the use of both cancer incidence and mortality data. Furthermore, studies, to varying degrees, failed to account for confounding variables, such as UV exposure, groundwater radon, tobacco use, *etc.* There is a strong association between tobacco use, environmental radon, and lung cancer; this association may be relevant in other cancers. Finally, ecological studies were subject to "ecological fallacy" or a faulty generalization of data based on a group to an individual.

Due to the limitations of existing literature, future investigations are needed, especially for skin, stomach, and CNS cancers. Future cohort and case-control studies, ideally with individual level radon exposure measurements by radon detectors and better control for confounding factors, are needed to conclusively confirm or negate associations between residential radon exposure and non-lung cancers. However, since the lungs are the organs that receive the largest dose from residential radon exposure, lung cancer remains the principal concern with residential radon exposure, and other associations are secondary, less significant concerns, at least based on available studies. Finally, these results should be considered when designing radon mitigation efforts, especially for cancers where only a slight risk is observed.<sup>83</sup>

**Table 4. Studies on residential radon exposure and leukemia risk.**

| Country       | Author   | Study Design              | Sample Size   | Mean Follow-Up   | Exposure  | Radon Exposure Measurements  | Risk Estimate (95% CI)  |
|---------------|--|---------------------------|---|--|---|--|---|
| Denmark       | Raaschou-Nielsen (2008) <sup>58</sup><br>2306 controls | Case-control<br>1968-1994 | 1153 cases<br>per 103 Bq/m <sup>3</sup> -yrs                  | Surveillance period  | ≥0.89 x 10 <sup>3</sup> Bq/m <sup>3</sup> -yrs;   | Address-level exposure<br>estimated by regression model                  | RR:1.31 (0.92–1.88)<br>(all leukemias)<br>RR:1.63 (1.05-2.53) (ALL only)<br>RR:1.34 (0.97–1.85)     |
| United States | Oancea (2017) <sup>56</sup>                            | Ecological                | 272 CLL cases   | Surveillance period:<br>1999-2013  | >4 pCi/l  | County-level exposure estimates  | PE:1.165 (0.440–1.891)  |
| Korea         | Ha (2017) <sup>70</sup>                                | Ecological                | 29,068 cases  | Surveillance period:<br>1989-2009 (radon);<br>1999-2008 (cancer incidence) | Per 10 Bq/m <sup>3</sup> increase<br>in radon conc.   | Indoor-level exposure<br>estimated by modeling from<br>county level data | RR:1.00 (0.98–1.02) (male),<br>0.98 (0.95–1.00) (female)  |
| Denmark       | Bräuner (2010) <sup>55</sup>                           | Case-control              | 985 childhood<br>(<15 yrs) cases<br>1,969 controls            | Surveillance period:<br>1968-1994  | Per 10 Bq/m <sup>3</sup> -years<br>increase in radon  | Address-level exposure<br>estimated by regression model                  | RR:1.48 (1.03, 2.13)  |
| Switzerland   | Hauri (2013) <sup>61</sup>                             | Cohort                    | 298 cases<br>1,287,354 total cohort                           | 2000-2008  | ≥139.9 Bq/m <sup>3</sup> )  | Address-level exposure<br>estimated by regression model                  | HR:0.95 (0.63, 1.43)  |
| Norway        | Kollerud (2014) <sup>63</sup>                          | Cohort                    | 0-15 yr old children,<br>437 cases<br>721,674 total cohort    | 1967-2009  | Per 100 Bq m <sup>3</sup><br>model  | Address-level exposure<br>estimated from buffer                          | OR:1.00 (0.87–1.14)<br>(<1 year), 0.99 (0.86–1.13)<br>(0–4 years), 0.99 (0.86–1.13)<br>(0-15 years) |
| France        | Demoury (2017) <sup>64</sup>                           | Case-control              | Childhood (<15) AL cases;<br>11,819 cases,<br>30,000 controls | 1990-2009  | Per 100 Bq/m <sup>3</sup>   | Address-level<br>exposure estimated<br>by cokriging model                | SIR:1.01 (0.91–1.12)  |
| Sweden        | Kohli (2000) <sup>54</sup>                             | Cohort                    | Childhood ALL; 90 cases;<br>53,146 total cohort               | 1979-1992  | High risk<br>(50,000 Bq/m <sup>3</sup> );<br>normal risk (10,000 – 50,000 Bq/m <sup>3</sup> ) | Commune- level radon<br>exposure risk                                    | RR:5.67 (1.06-42.27);<br>4.64 (1.29-28.26);   |

RR, relative risk; CI, confidence interval; CLL, chronic lymphocytic leukemia; ALL, acute lymphocytic leukemia; SIR, standardized incidence ratio; CML, chronic myeloid leukemia; AL, acute leukemia; AML, acute myeloid leukemia; PE, parameter estimate.

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