Indoor Radon Exposure and Risk of Childhood Leukemia: A Systematic Review and Meta-analysis

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Background: Radon, a naturally occurring radioactive gas, is a known carcinogen for lung cancer, but its role in leukemia remains less understood. This systematic review and meta-analysis aimed to evaluate the association between radon exposure and the risk of leukemia.

Methods: We conducted a systematic review of case-control and cross-sectional studies to investigate the link between radon exposure and leukemia risk. Studies were selected based on specific criteria, including validated radon exposure assessments and quantitative risk estimates. A comprehensive search across PubMed, Scopus, and Web of Science identified 743 articles, with 11 studies meeting the inclusion criteria. Data were extracted using a standardized form, and the Joanna Briggs Institute (JBI) critical appraisal tool assessed study quality. Meta-analysis was performed using a random-effects model to account for study heterogeneity.

Results: The meta-analysis of 11 studies yielded a pooled odds ratio (OR) of 1.57 (95% CI: 0.77–2.38), suggesting a potential positive association between radon exposure and leukemia risk. However, this association was not statistically significant, as the confidence interval included the null value of 1. Substantial heterogeneity was observed across studies (I^2 = 99.54%, $p < 0.001$). Sensitivity analyses indicated that no single study disproportionately influenced the pooled estimate. Funnel plot inspection and statistical tests (Egger’s and

Begg's) revealed no evidence of publication bias.

Conclusion: This meta-analysis suggests a potential association between radon exposure and leukemia risk, though the evidence is not statistically significant. The observed heterogeneity underscores the need for further research with standardized methods and larger sample sizes to clarify the relationship between radon exposure and leukemia. Future studies should focus on improving exposure assessment and exploring underlying biological mechanisms.

Introduction

Radon is a naturally occurring radioactive gas formed from the decay of uranium in the earth's crust [1]. Due to its odorless, colorless, and tasteless nature, radon is often undetectable without the use of specialized equipment [2, 3]. Its presence is particularly notable in indoor environments where it can accumulate to significant levels, posing a potential health risk to inhabitants. The International Agency for Research on Cancer (IARC) has classified radon as a Group 1 carcinogen, establishing a robust link between radon exposure and an increased risk of lung cancer [4]. This classification underscores the serious health implications of radon exposure and has prompted extensive research into its effects on various forms of cancer.

Leukemia, a heterogeneous group of hematologic malignancies characterized by the abnormal proliferation of blood cells, represents a major public health concern [5]. It encompasses several subtypes, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML) [6]. The etiology of leukemia is multifactorial, with genetic [7], environmental [8], and lifestyle factors [8] contributing to its development. Among environmental factors, exposure to ionizing radiation is a well-established risk factor for leukemia, particularly in individuals with high levels of exposure, such as those undergoing radiation therapy or living near nuclear facilities [9].

Despite the known association between ionizing radiation and leukemia, the specific role of radon exposure in the etiology of leukemia remains less clear. While radon is a known carcinogen for lung cancer [10], its impact on leukemia has not been as thoroughly investigated. Existing epidemiological studies on this topic have produced mixed results, with some research suggesting a possible link between radon exposure and an increased risk of leukemia, while other studies find no significant association. The variability in findings may be attributed to differences in study design, radon exposure measurement techniques, and population characteristics.

This systematic review and meta-analysis aim to address the uncertainty surrounding the association between radon exposure and leukemia risk. By systematically reviewing and synthesizing data from a range of studies, we seek to provide a clearer understanding of this relationship. Our objective is to aggregate the available evidence, identify patterns or inconsistencies, and offer a more precise estimate of the risk associated with radon exposure. The outcomes of this review are intended to inform public health policies, guide preventive strategies, and highlight areas for future research on the environmental determinants of leukemia.

Materials and Methods

Study Design and Selection Criteria

A comprehensive detail of the protocol of this study has been already published [11]. In conducting this systematic review and meta-analysis, a thorough and targeted approach was employed to ensure the relevance and reliability of the included studies. Initially, various study designs were considered, including cohort studies, case-control studies, and cross-sectional studies. However,

upon further review, it was determined that cohort studies did not meet the specific criteria required for this review. This was primarily due to the fact that cohort studies either did not provide the detailed risk estimates needed or did not include the specific measurements of radon exposure relevant to our analysis.

As a result, the review focused primarily on case-control and cross-sectional studies. Case-control studies were selected for their ability to compare individuals with leukemia to those without the disease, thereby providing insights into differences in radon exposure levels between these groups. Cross-sectional studies were also included as they offered valuable data on the prevalence of leukemia and radon exposure at a single point in time, which was crucial for understanding the association between radon exposure and leukemia risk.

The inclusion criteria required studies to involve human participants of any age, gender, or ethnicity and to assess radon exposure using validated methods, such as environmental or occupational measurements. Studies needed to report on the incidence or risk of leukemia, encompassing various subtypes such as acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, or chronic myeloid leukemia. Only studies providing quantitative risk estimates such as odds ratios, relative risks, or hazard ratios with corresponding confidence intervals were included. To maintain the quality of the review, only peer-reviewed studies published in English were considered, excluding non-peer-reviewed sources like conference abstracts or opinion pieces.

The selection process involved a comprehensive screening of titles and abstracts followed by a detailed review of full-text articles to ensure they met the defined criteria. Data from eligible studies were systematically extracted using a standardized form to ensure consistency in capturing study characteristics, exposure details, and outcome measures. The quality of each study was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools, which provided a framework for evaluating potential biases and the reliability of the findings. This structured approach ensured that the studies included in the review were methodologically sound and provided a robust basis for assessing the association between radon exposure and leukemia risk.

Search Strategy

A comprehensive literature search was performed across three major databases: PubMed, Scopus, and Web of Science (WOS). The search terms used were:

• PubMed: 142 articles

(“Radon”) AND (“Leukemia” OR “blood cancer” OR “hematological malignancies” OR “acute lymphoblastic leukemia” OR “acute myeloid leukemia” OR “chronic lymphocytic leukemia” OR “chronic myeloid leukemia”)

• Scopus: 289 articles

TITLE-ABS-KEY (radon) AND TITLE-ABS-KEY

(leukemia OR “blood cancer” OR “hematological malignancies” OR “acute lymphoblastic leukemia” OR “acute myeloid leukemia” OR “chronic lymphocytic leukemia” OR “chronic myeloid leukemia”)

• WOS: 312 articles

• (TS=(Radon)) AND TS=(Leukemia OR “blood cancer” OR “hematological malignancies” OR “acute lymphoblastic leukemia” OR “acute myeloid leukemia” OR “chronic lymphocytic leukemia” OR “chronic myeloid leukemia”)

Information Selection and Extraction

Study Selection Process

The study selection process was designed to ensure a thorough and systematic review of the literature. Initially, a comprehensive search strategy was employed across multiple databases to identify studies relevant to the association between radon exposure and leukemia risk. The search yielded a large number of articles, which were then subjected to an initial screening based on titles and abstracts to determine their relevance. Studies that met the preliminary criteria were selected for full-text review. During this stage, articles were assessed against the predefined inclusion and exclusion criteria to confirm their eligibility for inclusion in the review. Studies were included if they involved human participants, assessed radon exposure with validated methods, reported on leukemia risk, and provided quantitative estimates of association. Those not meeting these criteria were excluded.

Data Extraction Process

For the studies that met the inclusion criteria, a standardized data extraction form was used to systematically collect relevant information. This form was designed to ensure consistency and accuracy in capturing data across studies. The extraction process involved two main components:

1. Study Characteristics and Exposure Assessment: Key details such as author (s), publication year, study design, sample size, and geographical location were recorded.

2. Outcome Measures and Quality Assessment: Data on leukemia outcomes were carefully extracted, focusing on the type of leukemia (e.g., acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, or chronic myeloid leukemia) and the reported risk estimates, such as odds ratios (OR), relative risks (RR), or hazard ratios (HR) with corresponding 95% confidence intervals (CI). The quality of each study was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools. This assessment evaluated potential biases and the methodological rigor of the studies.

To ensure the accuracy and reliability of the data extracted, the process was conducted by multiple reviewers. Any discrepancies between reviewers were resolved through discussion and, if necessary, by consulting a third reviewer. This rigorous approach aimed to provide a comprehensive and accurate synthesis of the evidence on the association between radon exposure and leukemia risk.

Results

Identification and Selection of Studies

A thorough and systematic search of the literature identified a total of 743 studies that explored the association between radon exposure and leukemia. The search strategy involved multiple databases and followed stringent inclusion and exclusion criteria. These criteria focused on studies that examined the relationship between radon exposure and leukemia, were case-control in design, provided adequate quantitative data (such as odds ratios or relative risk estimates), and included relevant exposure assessments for radon. After screening the titles and abstracts, followed by a detailed full-text review, 11 studies [12-21] were deemed eligible for inclusion in the meta-analysis. Reasons for study exclusion are detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 1).

Figure 1. Flow Chart of Systematic Review and Meta-analysis, Radon Exposure and Childhood Leukemia.

These 11 case-control studies spanned diverse geographical regions, with variability in the population sizes, radon exposure measurement techniques, and study setting (Table 1) and with variability in the population sizes (Table 2).

Reference	Year	Quality Score	Country	Study Design	Leukemia Subtype	Age Range	Exposure Assessment-Measurement Method	Diagnostic Criteria Used	Reported Results (Odds Ratio and 95% Confidence Intervals)
Jay H. Lubin [12]	1998	Low Risk	US	Case Control	ALL	0-15	Radon detectors	Not Mentioned	1.734(0.97-2.03)
U. Kaletsch [13]	1999	Low Risk	Germany	Case Control	ALL	0-15	questionnaire and a telephone interview	German ChildhoodCancer Registry	1.33(0.32-5.33)
M Steinbuch[14]	1999	Low Risk	US	Case Control	AML	0-18	parental occupational history and interview	complete medical historyand interview	1.033(0.742-1.437)
A.F. Maged[15]	2000	Low Risk	Egypt	Case Control	ALL	14-□□□□□	Interview	Clinical History	5.76(2.64-12.55)
UKCCS [16]*2	2002	Low Risk	UK	Case Control	ALL	0-15	Interview	Clinical History	0.97(0.896-1.049)
S. Yoshinaga[17]	2005	Low Risk	Japan	Case Control	ALL & AML	0-15	Measured *1	Interview survey	1.04(0.69-1.58)
Anne-Sophie Evrard (AML) [18]	2006	Low Risk	France	Ecological Study	AML	0-15	Measured	National Registry of Childhood Leukemia and Lymphoma	1.19(1.03-1.38)
Anne-Sophie Evrard (ALL) [18]	2006	Low Risk	France	Ecological Study	ALL	0-15	Measured	National Registry of Childhood Leukemia and Lymphoma	1.01(0.94-1.08)
Elvira VaclavikBra¨uner [19]	2010	Low Risk	Denmark	Case Control	All Subtypes	0-15	Measured	Danish Cancer Registry	1.48(1.03-2.13)
Gerald M. Kendall [20]	2013	Low Risk	GreatBritain	Case Control	All subtypes	0-14	Survey and Measured	National Registry of Childhood Tumours	1.12(0.88-1.43)
Nikkilä A [21]	2020	Low Risk	Finland	Case Control	ALL & AML	□□□□□-02	Measured	Finnish Cancer Registry & Clinical History	0.81(0.29-2.25)

Table 1. The Result of Included Studies on the Relationship between Radon Exposure and Risk of Leukemia.

*1, Measured means people have estimate the Radon amount by using special tools. *2, UK Childhood Cancer Study Investigators

Reference	Leukemia Subtypes	Number of cases	Number of controls	Sample size(No. of

	Studied			cases + No. of controls)
Jay H. Lubin [12]	ALL	505	443	948
U. Kaletsch [13]	ALL	82	209	291
M Steinbuch [14]	AML	173	254	427
A.F. Maged [15]	ALL	500	110	610
UKCCS [16]	ALL	2 226	3 773	5 999
S. Yoshinaga [17]	ALL & AML	255	248	503
Anne-Sophie Evrard(AML) [18]	AML	346	-	-
Anne-Sophie Evrard(ALL) [18]	ALL	4 346	-	-
Elvira VaclavikBra¨uner [19]	All Subtypes	985	1 969	2 954
Gerald M. Kendall [20]	All subtypes	27 447	36 793	64 240
Nikkilä A [21]	ALL & AML	1 093	3 279	4 372

Table 2. Patients with Leukemia According to their Occupational Exposure from Studies Included in the Meta -analysis.

Despite this variation, all selected studies met the rigorous inclusion criteria and were evaluated for quality and risk of bias using the Joanna Briggs Institute (JBI) appraisal tool, ensuring that only methodologically sound studies were included.

Quality Assessment

The quality of each of the included studies was systematically assessed using the JBI critical appraisal checklist. This tool was used to evaluate key aspects of study quality, including the clarity and accuracy of radon exposure measurement, appropriate case-control matching, proper handling of potential confounders, and sufficient follow-up periods where relevant. All 11 studies were found to have a low risk of bias, suggesting that they adhered to robust methodological standards.

Particular attention was given to the methods of radon exposure assessment, as this is a key factor influencing the reliability of the results. The studies used a combination of residential radon measurements and modeling based on geological surveys, ensuring that radon exposure was accurately assessed. Most studies also appropriately matched cases and controls or adjusted for important confounding variables such as smoking, age, and residential location. This high level of methodological quality across the studies supports the reliability of the pooled results.

Overall Meta-analysis

The overall meta-analysis combined data from the 11 included studies using a random-effects model to account for the significant heterogeneity observed across the studies. The pooled odds ratio (OR) for the association between radon exposure and leukemia was 1.57 (95% CI: 0.77–2.38). This result suggests that, while the point estimate indicates a potential positive association between radon exposure and leukemia, it is not statistically significant, as the confidence interval crosses the null value of 1. The z-test ($z = 3.82$, $p = 0.00$) further confirmed that the association does not reach statistical significance. The forest plot illustrating individual study effect sizes and the overall summary estimate is presented in Figure 1. The range of effect sizes across the studies indicates that some studies found a stronger association between radon exposure and leukemia, while others reported a weaker or non-existent relationship. This variability is captured by the random-effects model, which assumes that the true effect size may vary between studies due to differences in study populations, radon exposure levels, and methodologies (Figure 2).

Figure 2. Meta-analysis of Radon Exposure and Risk of Leukemia.

Heterogeneity and Sensitivity Analysis

A high level of heterogeneity was observed in the analysis, with a between-study variance (T^2) of 1.77, indicating considerable variability in effect sizes among studies. The I^2 statistic was calculated to be 99.54%, showing that nearly all observed variation in effect sizes was due to heterogeneity rather than random chance. Additionally, H^2 was calculated as 215.76, further supporting the presence of significant heterogeneity. The Q-test for heterogeneity ($Q(10) = 168.06$, $p < 0.001$) confirmed statistically significant heterogeneity, suggesting that the studies differed in ways potentially influencing the observed association between radon exposure and leukemia risk.

This heterogeneity may stem from differences in study populations, varying radon exposure levels, and the methods used to measure exposure. For example, while some studies relied on direct measurements of radon levels in residential homes, others used regional radon exposure estimates, potentially contributing to variability in effect sizes.

To further explore the sources of heterogeneity, a Galbraith plot (Figure 3) was generated.

Figure 3. Galbraith Plot, Demonstrating Heterogeneity.

This plot helps identify studies that deviate from the overall trend; those falling outside the expected confidence intervals may be outliers or studies disproportionately contributing to heterogeneity. This visualization provides insights into potential moderators of the radon-leukemia association.

To assess publication bias, a funnel plot (Figure 4) was created. Ideally, in the absence of publication bias, this plot should resemble a symmetrical, inverted funnel shape.

Figure 4. Funnel Plot, Observed and Imputed Studies.

Any asymmetry in the plot might suggest publication bias or other biases affecting the findings. Although slight asymmetry was visually observed, further statistical testing (e.g., Egger's test) is recommended for confirmation.

Although four imputed studies were initially identified, further investigation found no additional studies meeting the criteria.

A sensitivity analysis was conducted to evaluate the robustness of the results by systematically excluding individual studies to examine their influence on the overall pooled estimate. The stability of the pooled odds ratio across exclusions indicated that the findings were robust and not disproportionately impacted by any single study. This suggests that the meta-analysis results are reliable and not driven by outliers or highly influential studies.

Publication Bias

Publication bias, which can occur when smaller studies with negative or non-significant findings are less likely to be published, was evaluated using both Egger's regression test and Begg's test. Egger's regression test yielded a β_1 of 1.80 (SE = 2.108, z = 0.85, p = 0.3944), while Begg's

test produced a Kendall's score of 15.00 (SE = 12.845, z = 1.09, p = 0.2758). Both tests showed no

significant evidence of small-study effects or publication bias, as the p-values were not statistically significant.

To further assess the presence of publication bias, a nonparametric trim-and-fill analysis was conducted. This method imputes hypothetical missing studies to evaluate the effect of potential publication bias on the pooled estimate. In this analysis, no studies were imputed, and the pooled OR remained unchanged at 1.57 (95% CI: 0.77–2.38). This suggests that publication bias is unlikely to have influenced the results, and the findings of the meta-analysis can be considered robust and unbiased.

Here's a refined version that ties the results more closely with the findings in your subgroup analysis:

Subgroup Analysis

To investigate potential temporal variations in the association between radon exposure and leukemia risk, we conducted a subgroup analysis using the publication year as the variable. A random-effects model was employed to address the substantial heterogeneity observed among studies, accounting for both within- and between-study variations.

The heterogeneity statistics were notably high, with (R^2 = 1.77), (I^2 = 99.54%), and (H^2 = 215.76), underscoring significant variability across studies. The Cochran's (Q)- test for heterogeneity ((Q (10) = 168.06), ($p < 0.001$)) confirmed this extensive heterogeneity, suggesting that publication year could be a meaningful moderator in the relationship between radon exposure and leukemia risk. Furthermore, the test of effect sizes against the null hypothesis of zero association ((z = 3.82), ($p < 0.001$)) indicated a significant overall positive association between radon exposure and leukemia risk.

Subgroup analysis based on publication year showed marked differences between time periods, with a statistically significant test for group differences ((QB = 162.86), ($p < 0.001$)). These results imply that studies from different time periods yield varying effect sizes, suggesting potential shifts in the impact of radon exposure on leukemia risk across years. Earlier studies in the analysis generally reported higher effect estimates, which may reflect differences in study design, exposure assessment methods, or population characteristics over time. This temporal trend could also be due to improved detection and control measures in more recent studies, potentially leading to lower observed risks in recent publications.

The significance of the subgroup effect reinforces the need to consider the time period as a critical factor in evaluating radon's impact on leukemia. These findings suggest that temporal changes such as advancements in exposure assessment or variations in regional radon levels may influence study outcomes. Further investigation into these factors is warranted to better understand and interpret the influence of radon exposure on leukemia risk across different eras.

Discussion

This systematic review and meta-analysis aimed to clarify the association between radon exposure and the risk of leukemia by synthesizing data from 11 case-control studies. Radon, a known carcinogen for lung cancer, has a less clear relationship with leukemia. Our meta-analysis provides an aggregated estimate of this association and sheds light on several important aspects.

The overall pooled odds ratio (OR) for the association between radon exposure and leukemia was 1.57 (95% CI: 0.77–2.38). This result suggests a potential positive association, indicating that

higher levels of radon exposure might be linked to an increased risk of leukemia. However, since the confidence interval includes the null value of 1, the association does not achieve statistical significance. This lack of significance implies that while there is a potential risk, the evidence is not robust enough to make definitive conclusions about the link between radon exposure and leukemia.

The substantial variability in effect sizes across the included studies is noteworthy. Some studies found a stronger association between radon exposure and leukemia, while others did not find any significant relationship. This heterogeneity can be attributed to several factors, including differences in study design and methodologies for measuring radon exposure. Variations in how radon exposure was assessed ranging from direct residential measurements to regional estimates could influence the results. Additionally, differences in study populations, such as demographic characteristics and geographic locations, might also contribute to the observed variability in effect sizes.

The high level of heterogeneity, as indicated by an I^2 statistic of 99.54%, suggests significant differences in study findings. Sensitivity analyses showed that the overall pooled estimate was stable and not disproportionately influenced by any single study, reinforcing the robustness of the results despite this heterogeneity. The variability in study results highlights the need for more standardized methods in future research to achieve more consistent findings.

An evaluation of publication bias using Egger’s regression test, Begg’s test, and trim-and-fill analysis did not reveal significant evidence of small-study effects or publication bias. This indicates that the meta-analysis results are likely robust and not unduly influenced by the publication of smaller studies with non-significant findings. The absence of publication bias supports the reliability of our findings.

The results of this meta-analysis add to the ongoing discussion about the potential link between radon exposure and leukemia. While there is some evidence suggesting a possible association, the lack of statistical significance underscores the need for further research. Future studies should aim to improve exposure assessment methods, increase sample sizes to enhance statistical power, and explore potential biological mechanisms underlying the association. Longitudinal studies could also provide valuable insights into the long-term effects of radon exposure on leukemia risk.

In conclusion, while this meta-analysis suggests a potential association between radon exposure and leukemia, the evidence is not conclusive. The observed variability and lack of statistical significance highlight the need for further investigation to better understand the potential health risks associated with radon exposure.

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Statement of Transparency and Principals

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute.

• Study’s data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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