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ORIGINAL ARTICLE

Domestic radon exposure and risk of childhood leukemia: A meta-analysis

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Summary

Purpose: *This meta-analysis evaluated the potential influence of environmental radon exposure on childhood leukemia.*

Methods: *We searched comprehensive electronic databases from PubMed, EMBASE, and Cochrane Library to identify studies evaluating the association between radon and leukemia.*

Results: *Ten eligible studies published from 1995 to 2014 were enrolled. Of these 10 studies, 8 were case-control studies (involving 10803 cases and 16202 controls) and 2 were cohort studies (involving 1,428 cases). Overall results as odds ratio (OR) with the corresponding 95% confidence intervals (95%CI) for case-control studies and fully adjusted hazard ratio (HR) with corresponding 95%CI for cohort studies were identified. A positive but weak association was found between radon exposure and childhood leukemia in case-control studies (summary OR 1.22, 95%CI 1.01-1.42) rather than cohort studies (summary HR 0.97, 95%CI 0.81-1.15). Heterogeneity or publication bias was not observed. Moreover, overall ORs were not changed by removing any single study, suggesting the stability and reliability of conclusions.*

Conclusions: *Future prospective studies with well-controlled confounders are needed to verify the conclusion.*

Key words: *leukemia, radiation, childhood, radon, meta-analysis*

Introduction

The mortality of childhood cancer ranks second in children in developed countries following accidents [1,2]. In 1970-1999, the incidence of childhood malignancies annually rose by about 1% in Europe [3-5], which did not slow down in the first 5 years after 2000 [6]. In 1992-2007, there was an annual increase by 0.5% in the USA [6]. Globally, cases account for 30% of childhood malignancies. The etiology and pathogenesis of childhood leukemia are poorly understood [7,8]. It is generally believed that genetic and environmental factors are involved in childhood leukemia [9].

It has been clearly established that acute or repeated exposure to high dose ionizing radiation induces leukemia. The risks of developing cancer following protracted exposure to very low levels of radiation, such as those due to background radiation, are still in dispute. The risk of cancer after long-term exposure to very low-level radiation (i.e. background radiation) remains controversial.

As a natural radioactive gas released from soil, Radon gas (radon-222) can be concentrated indoor. Radon and its α-particle-emitting decay products are the primary sources of the natural exposure to ionizing radiation in the population [10]. Inhaled dose of radon is mostly deposited in the airway, thus radon exposure increases the risk for lung cancer [11,12]. A minor part of an inhaled dose can reach the red bone marrow [13-15] and the brain [15]. Owing to the high fat content of red bone marrow, radon gas is believed to damage stem cells [16] and enhance susceptibility to childhood leukemia [17].

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Stjernfeldt et al [18] firstly reported a case-control study on indoor radon and childhood leukemia in 1987. Later, many ecological studies and case-control studies have been reported. Potential influence of radon exposure on elevating the incidence of childhood acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML) are reported in some ecological studies as well. These data are analyzed from geographical units instead of individuals, which should be cautiously explained [10]. Conclusions on the influence of radon exposure to childhood leukemia are inconsistent [10,16], either with the association [19,20] or not [18,21-26]. A meta-analysis of case-control studies was conducted by Tong et al [16] to uncover the influence of radon exposure on childhood leukemia. The combined OR for calculating the lowest exposure of radon on the highest incidence of childhood leukemia was 1.37 (95%CI 1.02-1.82), suggesting a weak association. Since this paper was reported, another large sample size case-control study [23] and two cohort studies [27,28] about indoor radon and childhood leukemia have been published. The present article aimed to summarize previous studies and to extend current knowledge by inclusion of novel data and interpretation.

Methods

Literature search

Literature was searched in PubMed and Web of Science on 31 January 2019. Key words searched were as follows: "radon, leukemia". References of eligible articles were reviewed as well. Studies were limited to English language and human subjects. Abstracts and unpublished reports were excluded.

Eligibility criteria and study selection

Two investigators were responsible to independently search eligible studies and resolve any discrepancy by discussion. Inclusion criteria were: 1) Cohort or case-control studies designed with leukemia incidence as the outcome; 2) 95%CIs or data to calculate it were provided; 3) Baseline characteristics of childhood leukemia patients were provided. Ecological studies, case reports, editorials, comments, letters, news, perspectives and studies on mechanisms were excluded.

Data extraction and classification

Study characteristics data were extracted in a standardized data collection form from each included study. First author, year of publication, study region, subtype of leukemia, number of case/control, radon exposure level, RR or OR, and 95%CI in case-control studies were recorded. Fully adjusted HR with corresponding 95%CI instead of RR or OR were extracted in cohort studies.

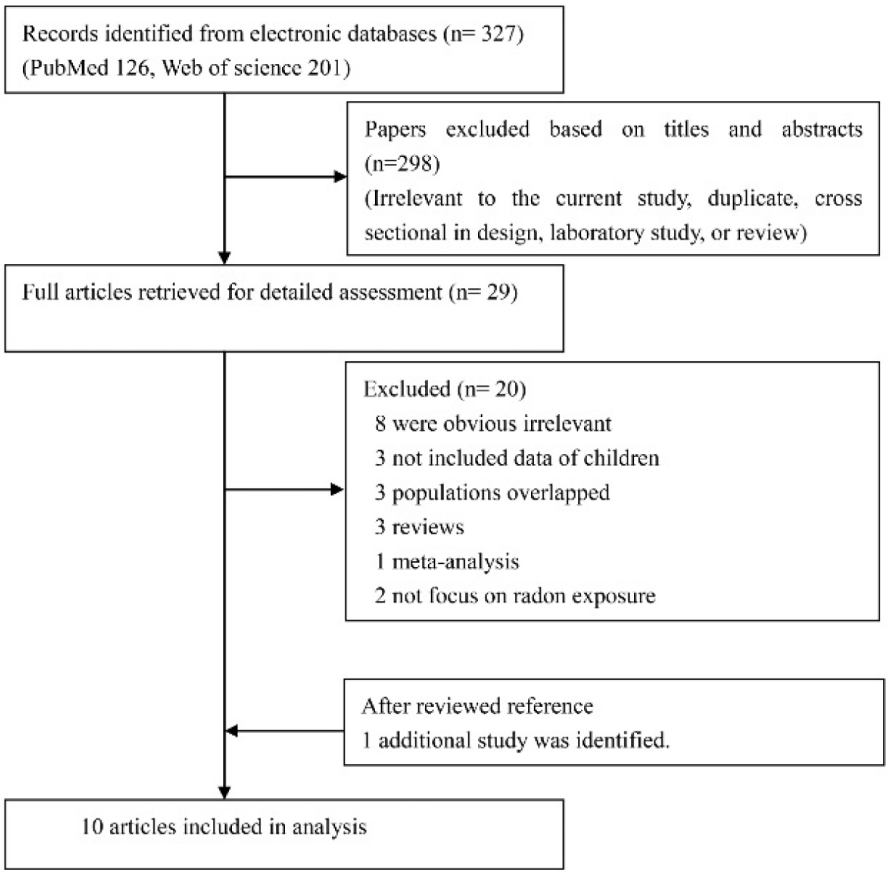

Figure 1. Literature search and study selection protocol used in this meta-analysis.

Considering that childhood leukemia is rare, the RR was utilized as the same as OR.

Statistics

Overall results as OR comparing the highest with the lowest category of radon exposure and the corresponding 95%CI for case-control studies were performed. However, the two cohort studies analyzed by Cox regression should take into account the time to diagnosis. Fully adjusted HR with corresponding 95%CI were the overall results. Heterogeneity test across studies by Q test was applied before the results were pooled. In addition, heterogeneity was quantified by I^2 test, which described the percentage of total variation across studies due to

Table 1. Characteristics of studies of indoor radon exposure and childhood leukemia

Author	*Location*	*Type of leukemia*	*Age (yr)*	*Case/control (n)*	*Exposure (Bq/m3)*	*OR (95% CI)*
Case-control studies of indoor radon exposure and childhood leukemia						
Lubin et al. 1998	United States	Acute lymphoblastic leukemia	< 15	505/443	< 37	1.00
					37–73	1.22 (0.8–1.9)
					74–147	0.82 (0.5–1.4)
					> 148	1.02 (0.5–2.0)
Kaletsch et al. 1999	Germany	Acute leukemia	< 15	82/209	< 70	1.00
					≥ 70	1.30 (0.32–5.33)
Steinbuch et al. 1999	United States/ Canada	Acute myeloid leukemia	< 18	173/254	< 37	1.00
					3 7–100	1.2 (0.7–1.8)
					>100	1.1 (0.6–2.0)
Maged et al. 2000	Egypt	Acute lymphoblastic leukemia	2-14	50/110	< 40	1.00
					40–60	4.64 (1.2–18)
					60–90	7.42 (2–27.3)
					> 90	5.42 (1.3–21.1)
UKCCS 2002	United Kingdom	Acute lymphoblastic leukemia	< 15	805/1306	< 25	1.00
					25–49	0.80 (0.64–0.99)
					50–99	1.06 (0.79–1.44)
					100–199	0.57 (0.29–1.12)
					≥ 200	0.81 (0.28–2.36)
Yoshinaga et al. 2005	Japan	Acute lymphoblastic leukemia + Acute myeloid leukemia	< 15	255/248	< 20	1.00
					20–49	1.00 (0.62–1.62)
					50–99	1.57 (0.47–5.22)
					≥ 100	2.05 (0.18–23.4)
Raaschou-Nielsen 2008	Denmark	Acute lymphoblastic leukemia	< 14	860/1720	< 0.26×10^3	1.00
					$0.26–0.89\times10^3$	1.21 (0.98–1.49)
					> 0.89×10^3	1.63 (1.05–2.53)
Kendall et al. 2013	Great Britain	Lymphoid leukemia +Acute myeloid leukemia + Other leukemia	< 14	9058/11912	1000 Bq/m^3 - years rise	1.12 (0.88 1.43)
Author	*Location*	*Type of leukemia*	*Age (yr)*	*Exposure (Bq/m^3)*	*No. of cases (Person-years)*	*Fully adjusted HR* (95% CI)*
Cohort studies of indoor radon exposure and childhood leukemia						
Hauri et al. 2013	Switzerland	All leukemia	< 16	< 77.7	525 (3,838,101)	Reference
				77.7–139.9	373 (3,034,923)	0.89 (0.78, 1.02)
				≥ 139.9	99 (754,623)	0.93 (0.74, 1.16)
				per 100 Bq/m^3	997	0.99 (0.85, 1.14)
Kollerud et al 2014	Oslo region Norway	All leukemia	< 15	<50	95 (not given)	Reference
				50–100	209 (not given)	0.97 (0.76–1.25)
				>100	127 (not given)	1.02 (0.78–1.34)
				Per 100 Bq/m^3		1.00 (0.87–1.15)

HR: hazard ratio, OR: odds ratio. *Adjusted for parity, birth weight, sex, congenital malformations, family income, mother and father's level of education.

heterogeneity rather than chance. If the heterogeneity was statistically significant, a random-effect model was used to obtain a pooled estimate of the OR; otherwise, the fix-effect model was performed. All p values reported were two-sided and p<0.05 was considered statistically significant. Egger's and Begg's tests were conducted to assess publication bias. Meta-analyses were conducted separately by study design using the fixed effects model. The survival curves were plotted using the Kaplan-Meier method and differences were assessed using log-rank test. All meta-analyses were done using STATA software (version 11; STATA Corporation, College Station, TX, USA).

Results

Included studies and study characteristics

Initially, 327 abstracts were screened and identified, and 29 potentially appropriate studies were retrieved for more detailed evaluation. After reviewing the full text, 18 articles were excluded. Of the remaining 11 studies [19-25,27-30], three articles [19,29,30] had overlapping data on leukemia risk with radon exposure separately, and the one with the highest quality was enrolled. References cited by all 29 studies were manually reviewed and one additional study [26] was identified. Thus, 10 studies in total were included. Of these 10 studies, 8 were case-control studies [19-26] (involving 10803 cases and 16202 controls) and 2 were cohort studies [27,28] (involving 1,428 cases). Detailed search diagram is shown in Figure 1. Subjects in the eligible studies were from United States, Germany, Canada, Egypt, United Kingdom, Japan, Denmark, Switzerland and Norway. Baseline information of the 10 eligible articles are presented in Table 1.

Radon exposure and childhood leukemia

Results from studies on environmental radon exposure in relation to childhood leukemia risk were inconsistent. The ORs for each study and results of our meta-analysis in childhood leukemia are presented in Figure 2. Meta-analyses were separately conducted by study design. No statistically heterogeneity was detected amongst those case-control studies (p=0.362, I^2=8.8%) and cohort studies (p=0.607, I^2=0.0%), so the fixed-effects model was used. The influence of radon exposure on child-

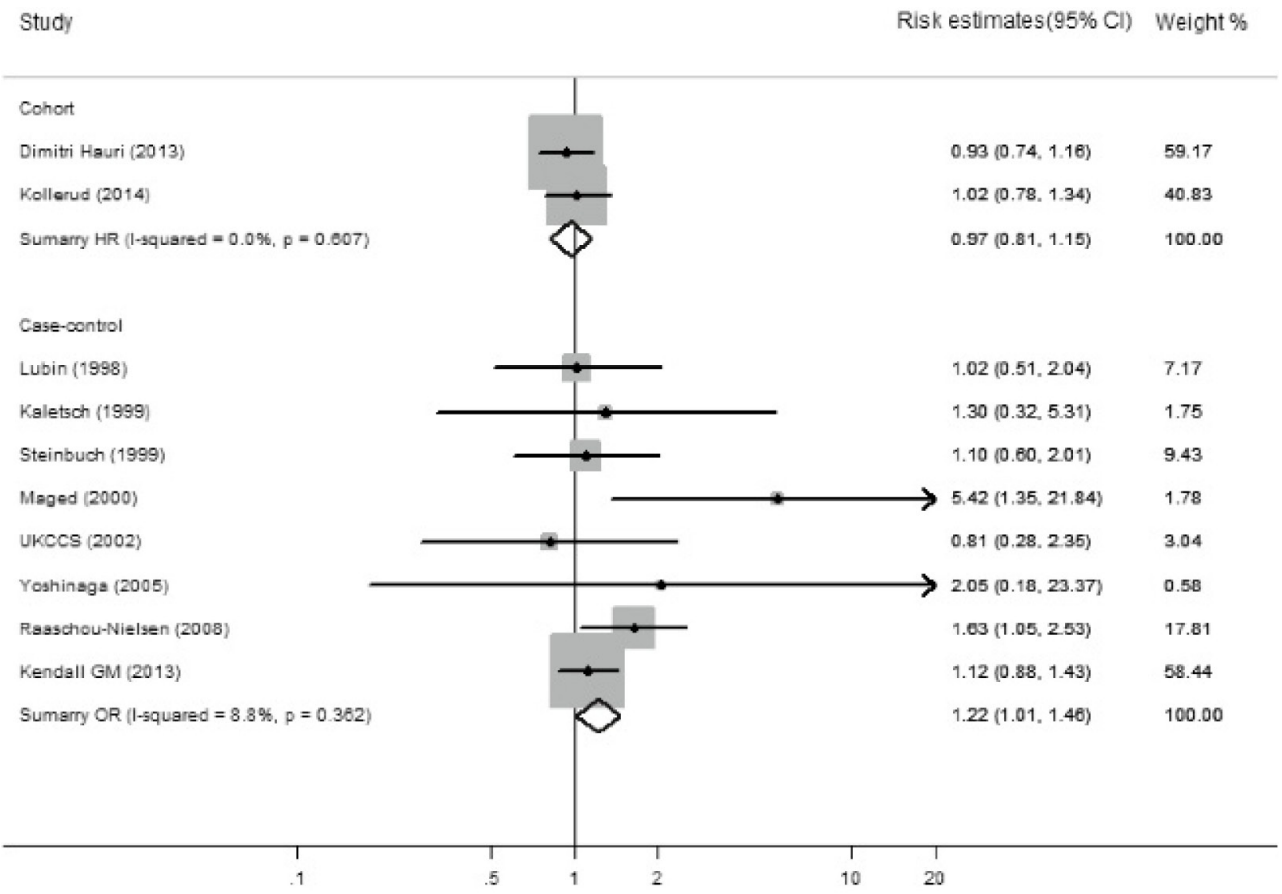

Figure 2. Forest plots of the odds ratio (OR) with 95% confidence intervals (CIs) for overall childhood leukemia risk. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study specific weight.

hood leukemia was reverse in case-control studies (summary OR 1.22, 95%CI 1.01-1.42) and cohort studies (summary HR 0.97, 95%CI 0.81-1.15).

Sensitivity analysis and publication bias

Sensitivity analysis was done by removing one study each time and re-calculating the results. No individual study was found to alter the overall ORs, demonstrating the stability and reliability of our results. In addition, Begg's (p=0.371) (Figure 3) and Egger's tests (p=0.596) (Figure 4) did not show publication bias for case-control studies.

Discussion

As the inhaled radon is mostly deposited in the airways, radon exposure is generally considered to increase the risk for lung cancer [11,12]. The precise

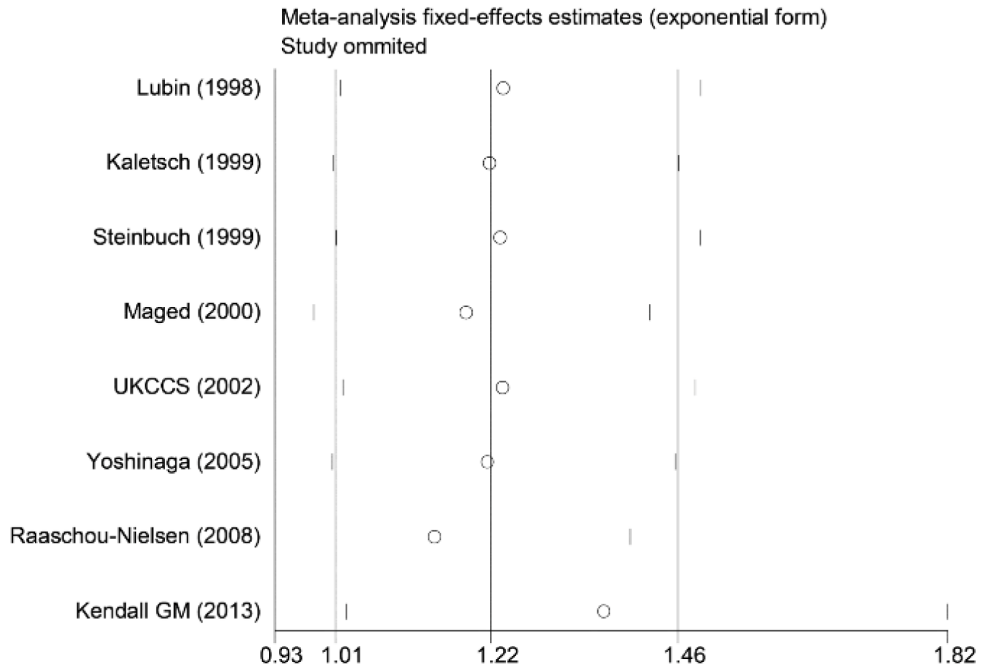

Figure 3. Results of the sensitivity analysis examining childhood leukemia risk in indoor radon expose populations.

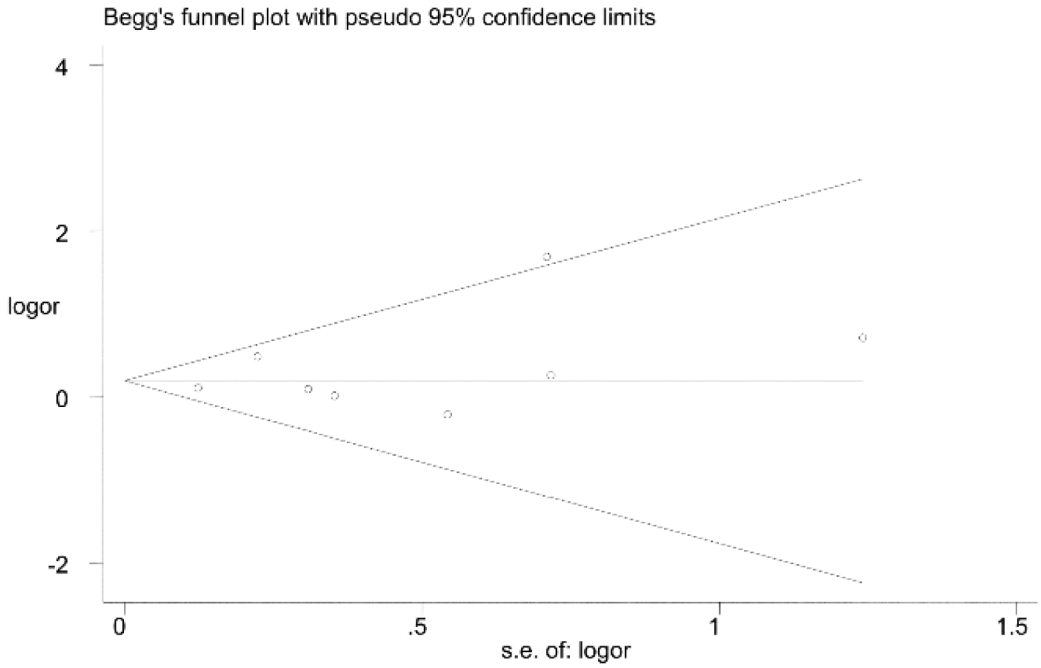

Figure 4. Begg's funnel plot to detect publication bias in overall populations. Each circle represents a separate study for the indicated association.

mechanism on the increased incidence of leukemia due to radon exposure is unknown. Richardson et al [13] suggested that a minor part of an inhaled dose can be distributed to the red bone marrow [14,15]. It has been assumed that dissolved radon gas in fatty tissues damages stem cells, eventually resulting in ALL [16]. A relative study indicated the background level of DNA damage in circulating lymphocytes may be explained by increased indoor concentration of radon [31]. Recently, low-dose target exposure of radon on human lymphocytes has been reported to cause genomic instability [32].

Published ecological studies identically concluded the influence of geographic exposure of radon on leukemia risk [33]. However, their conclusions do not withstand the close scrutiny. In addition, domestic radon concentrations vary even in the same neighborhood owing to different building structures and ventilation habits. Case-control and cohort investigations are generally believed to be reliable for validating the potential influence.

Two case-control studies found a positive association between radon exposure with leukemia [19,20]. Two recent cohort studies and six case-control studies [21-26], indicated no association. To provide an updated quantitative evaluation on radon exposure and leukemia, we conducted this meta-analysis. As far as we know, our study is the first meta-analysis to include data of cohort studies. We found a positive but weak association between radon exposure and childhood leukemia in case-control studies. Nevertheless, cohort studies did not support this association.

Several limitations in this study are noteworthy: 1) Most subjects were from western countries, with only one Asian country (Japan) [26] and African country (Egypt) [20] involved. Non-English written studies and unpublished data could potentially influence the results. 2) Subject races, examination methods, sample sizes, onset age of leukemia and exposure during pregnancy were not taken into account. 3) Subtype of leukemia and dosage of radon exposure were not available for further subgroup analyses. 4) The potential for exposure misclassification in different studies.

Conclusions

In conclusion, this meta-analysis found a positive but weak influence of radon exposure on childhood leukemia in case-control studies. The cohort studies failed to confirm this conclusion. Future prospective studies with well-controlled confounders and more statistical power are required to validate this conclusion.

Conflict of interests

The authors declare no conflict of interests.

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