RESEARCH COMMUNICATION

Residential Radon and Lung Cancer Risk: An Updated Meta-analysis of Case-control Studies

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Abstract

Background: Numbers of epidemiological studies assessing residential radon exposure and risk of lung cancer have yielded inconsistent results. Methods: We therefore performed a meta-analysis of relevant published case-control studies searched in the PubMed database through July 2011 to examine the association. The combined odds ratio (OR) were calculated using fixed- or random-effects models. Subgroup and dose-response analyses were also performed. Results: We identified 22 case-control studies of residential radon and lung cancer risk involving 13,380 cases and 21,102 controls. The combined OR of lung cancer for the highest with the lowest exposure was 1.29 (95% CI 1.10-1.51). Dose-response analysis showed that every 100 Bq/m³ increment in residential radon exposure was associated with a significant 7% increase in lung cancer risk. Subgroup analysis displayed a more pronounced association in the studies conducted in Europe. Studies restricted to female or non-smokers demonstrated weakened associations between exposure and lung cancer. Conclusions: This meta-analysis provides new evidence supporting the conclusion that residential exposure to radon can significantly increase the risk of lung cancer in a dose-response manner.

Keywords: Residential radon - lung cancer - radiation - case-control study - meta-analysis

Introduction

Lung cancer was the most commonly diagnosed cancer as well as the leading cause of cancer death globally. It accounts for 13% (1.6 million) of the total cancer cases and 18% (1.4 million) of the cancer deaths in 2008 (Jemal et al., 2011). Although the majority of lung cancer cases can be attributed to active cigarette smoking, radon exposure was also an important contributor to the total burden of lung cancer. In USA, it suggested that 10-15% of the total lung cancer deaths could be attributed to residential radon exposure, making radon the second leading cause of lung cancer death after smoke (NRC 1999). In 1988, the International Agency for Research on Cancer (IARC1998) determined that radon was a cause of human lung cancer. Radon gas is formed during the decay series of uranium-238, a naturally occurring radioactive mineral found in rocks and soils. The fist line of evidence of radon and lung cancer came from occupational studies on miners, especially uranium miners, exposed to high levels of radon (Radford et al., 1984; Howe et al., 1986). Using various modeling approaches, results of lung cancer risk in miners were used to project lung cancer risk for general population exposed to residential radon. However, such direct extrapolation from these studies is uncertain because of the major differences between working in underground conditions and living in houses (Al-zoughool and Krewski, 2009).

Thus, many studies have been conducted to estimate the risk of residential radon in the general population. To date, about 20 case-control studies of residential radon and lung cancer have been completed with inconsistent results. To summarize these results, meta-analysis of lung caner risk from residential radon was performed by Lubin (1995) and was supplemented by Pavia (2003). Both analyses supported the positive association of residential radon with lung cancer risk, with pooled estimated odds ratio (OR) of 1.14 (95% confidence internal CI, 1.0-1.3) and 1.24 (95% CI 1.11-1.38), respectively, based on exposure at 150 Bg/m3. However, significant unexplained heterogeneity across studies and lack of subgroup and sensitivity analyses in both studies suggested the necessity for proper improvement of the meta-analysis. Furthermore, some new case-control studies, most of which found no significant effect, emerged since then (Baysson et al., 2004; Bochicchio et al., 2005; Wichmann et al., 2005; Sandler et al. Thompson et al., 2008; Wilcox et al., 2008). Therefore, we systematically evaluated the association of residential radon with lung cancer risk by conducting an updated meta-analysis.

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Materials and Methods

Search strategy

This meta-analysis was performed and reported in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). The PubMed database through July 2011 was searched for published studies in English language using search terms "radon" in combination with "lung cancer". In addition, a manual search using reference lists of original articles and recent reviews was performed. Each published paper was independently reviewed and relevant information was extracted by two authors (Zhang and Sun).

Study selection

Studies that met the following criteria were eligible for the meta-analysis: 1) they were designed and executed as case control study; 2) the main exposure of interest was residential radon, which was determined by certain alpha-track radon detector and was expressed as time-weighted mean (Bq/m³); 3) the outcome of interest was lung cancer incidence (fatal and/or non-fatal); 4) OR with corresponding 95% CI for the highest versus lowest category of residential radon exposure were reported or appropriate data were provided to calculate these values. If the same population was studied in more than one study, we included the study with the largest subjects.

Data extraction

The following study characteristics were recorded: 1) first author's name, publication year and country of origin; 2) number of participants in the case and control groups; 3) participant characteristics including age range, sex and smoking situation; 4) radon dosimetry including detector equipment, placement, duration and time when subjects lived before enrollment; 5) statistical adjustment for the main confounding factors of interest; 6) OR from the most fully adjusted model for the highest versus the lowest exposure and their corresponding 95% CI.

Statistical analysis

The OR was used as the common measure of association between residential radon exposure and lung cancer. The homogeneity of OR across studies was tested using the Q test at the P<0.10 level of significance. The I^2 statistic was also calculated, which measures the percentage of the total variation across studies that are due to heterogeneity, rather than chance (Higgins and Thompson, 2002). Either a fixed-effects or, in the presence of heterogeneity, a random-effect model was used to calculate the pooled estimated OR. We conducted subgroup analyses stratified by geographic region, characteristic of subjects and radon dosimetry to assess the impacts of these variables on outcomes. We also conducted a sensitivity analysis to investigate the influence of a single study on the overall risk estimate by omitting one study in each turn.

In addition, we quantified dose-response association of residential radon exposure with lung cancer risk by the method of Greenland and Longnecker (1992). This analysis was restricted to the studies reporting three or more exposure levels and providing the data for categories of median radon exposure level, number of cases and controls and adjusted logarithm of the OR with its standard error. When the median value was not reported, we used the midpoint of each category. For an open-ended upper category, the exposure level was estimated by assuming the same amplitude as the previous category.

To assess the publication bias, both Egger linear regression test and Begg rank correlation test were performed (Begg and Mazumdar, 1994; Egger et al., 1997). All analyses were performed using STATA version 10.0 (StataCorp, College Station, TX, USA). A P<0.05 was considered to be statistically significant, unless otherwise specified.

Results

Literature search

A flow chart showing the study selection is presented in Figure 1. We initially identified 1192 citations from PubMed and 227 potentially eligible studies remained for screening. Among them, most were excluded after abstract because they were occupational studies on miners, no case control studies, no relevant exposure or endpoint, and reviews. After assessing the full-text of the 38 relevant articles, we identified 22 eligible studies for meta-analysis (Blot et al., 1990; Schoenberg et al., 1990; Pershagen et al.,1992, 1994; Alavanja et al., 1994, 1999; Létourneau et al., 1994; Auvinen et al., 1996; Ruosteenoja et al., 1996; Darby et al., 1998; Field et al., 2000; Sobue et al., 2000; Lagarde et al., 2001; Pisa et al., 2001; Barros-Dios et al., 2002; Wang et al., 2002; Baysson et al., 2004; Bochicchio et al., 2005; Wichmann et al., 2005; Sandler et al., 2006; Thompson et al., 2008; Wilcox et al., 2008). Seven studies were excluded for previous mete-analysis (Lubin and Boice, 1997; Pavia et al., 2003) and combined analysis in Europe, North America or China (Lubin et al., 1994; Darby et al., 2005; Krewski et al., 2005; Wang et al., 2005; Darby et al., 2006). Four studies were excluded because
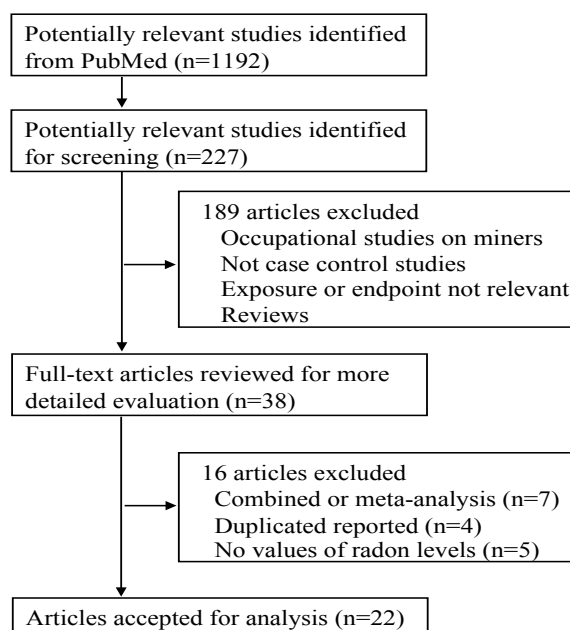

Figure 1. Flow Chart of Study Selection

Table 1. Characteristics of Case-control Studies of Residential Radon Exposure and Lung Cancer Risk

Author	Year	Sex	Location	Age (yrs)	Case/Control (n)	Quantile	Exposure comparison (Bq/m³)	Odds Ratio (95% CI)	Adjustment
Blot	1990	F	China	30-69	308/356	4	> 296 vs <74	0.7 (0.4-.3)	Age, education, smoking, and indoor air pollution
Schoenberg	1990	F	USA	All	480/442	4	148-418 vs <37	4.2 (0.99-17.5)	Age, smoking, occupation, and respondent type
Pershagen	1992	F	Sweden	All	210/209	4	≥151 vs <75	1.7 (1-2.4)	Age and smoking
Alavanja	1994	F	USA	30-84	538/1183	5	>91 vs <30	1.2 (0.9-1.7)	Age and smoking
Létourneau	1994	M/F	Canada	35-80	738/738	4	≥200 vs <25	0.77 (0.34-1.73)	Age, sex, smoking, and education
Pershagen	1994	M/F	Sweden	35-74	1360/2847	5	>400 vs ≤50	1.8 (1.1-2.9)	Age, sex, smoking, occupation, area of residence
Auvinen	1996	M/F	Finland	All	517/517	5	>400 vs ≤49	1.15 (0.69-1.93)	Age, sex, and smoking
Ruosteenoja	1996	M	Finland	0-64	164/331	3	≥ 187 ≤95	1.5 (0.8-2.9)	Age, sex, smoking, and indoor air quality
Darby	1998	M/F	UK	<75	982/3185	6	≥400 vs <25	1.79 (0.74-4.33)	Age, sex, smoking, area of residence, and social class
Alavanja	1999	F	USA	30-84	247/299	5	≥148 vs <37	0.71 (0.3-1.3)	Age, education, smoking, previous lung disease, and vegetable consumption
Field	2000	F	USA	40-84	413/614	5	>228 vs ≤57	1.79 (0.99-3.26)	Age, smoking, and education
Sobue	2000	M/F	Japan	≥40	28/35	4	≥100 vs ≤24	0.25 (0.03-2.33)	Age, sex, smoking, and occupational history
Lagarde	2001	M/F	Sweden	>29	258/487	4	>140 vs <50	1.55 (0.88-2.73)	Age, sex, passive smoking, area of current residence, and socioeconomic status
Pisa	2001	M/F	Italy	All	138/291	5	≥200 vs <40	1.0 (0.3-3.1)	Age, sex, and smoking
Barros-Dios	2002	M/F	Spain	≥35	163/241	4	≥148 vs <36.9	2.96 (1.29-6.79)	Age, sex, and family history
Wang	2002	M/F	China	30-75	768/1659	6	≥300 vs <100	1.58 (1.1-2.3)	Age, sex, prefecture, smoking, and socioeconomic factors
Baysson	2004	M/F	France	<75	486/984	5	>400 vs <50	1.11 (0.59-2.09)	Age, sex, region, smoking, and occupational exposure to asbestos and carcinogens
Bochicchio	2005	M/F	Italy	35-90	384/404	5	>400 vs <50	2.89 (0.45-18.6)	Age, sex, area of residence, smoking, and dietary variables
Wichmann	2005	M/F	Germany	24-75	2963/4232	4	≥140 vs <50	1.4 (1.03-1.89)	Age, sex, region, smoking, and occupational asbestos exposure
Sandler	2006	M/F	USA	40-79	1474/1911	4	≥53 vs <18	1 (0.93-1.07)	Age, sex, and smoking
Thompson	2008	M/F	USA	>40	200/397	6	≥250 vs <25	2.5 (0.47-13.46)	Age, smoking, residency, job exposure, income, and education
Wilcox	2008	M/F	USA	All	561/740	6	≥150 vs <25	0.76 (0.36-1.61)	Age, sex, and smoking

of duplicate or overlap reports. For example, separate studies from Eastern and Western Germany (Kreienbrock et al., 2001; Kreuzer et al., 2003) were excluded because Wichmann (2005) study in the present meta-analysis involved cases of two areas. We further excluded 5 studies, in which residential radon was not determined by alpha-track radon detector. For example, recent study conducted in Hong Kong expressed radon exposure as residential radon exposure index (Chiu et al., 2010).

Study characteristics

The characteristics of 22 case control studies are presented in the Table 1. These studies were published between 1990 and 2008. Eleven studies were conducted in Europe, 8 in North-America (7 in the United States and 1 in Canada), 2 in China and 1 in Japan. The number of case ranged from 28 to 2963, with a sum of 13380. The number of control ranged from 35 to 4232, with a sum of 21102. Of the included studies, the majority was population-base control, whereas three were hospital-based control (Baysson et al., 2004; Bochicchio et al., 2005; Thompson et al., 2008) and one combined population and hospital subjects as control (Darby et al., 1998). Half studies ascertained lung cancers from national/local cancer registries and the other half from hospitals. Two studies used lung cancer death from registry as cases (Sobue et al., 2000; Pisa et al., 2001). All of the studies adjusted for age and smoking. Sex was adjusted in the studies

with subjects containing both genders except Thompson (2008) study. For radon dosimetry, 17 studies placed two detectors in the home (bedroom and living room). Radon was measured for 1 year in 15 studies and others less than 1 year. Exposure window occupied during the 5- to 30-year period was reported to be most relevant time interval with respect to lung cancer risk due to radon (Krewski et al., 2005). Among these studies, 15 studies clearly described that they measured the radon exposure in the dwelling where subjects lived before 5 years of enrollment.

Main analysis

The multivariable adjusted ORs of lung cancer in relation to residential radon exposure from individual studies and the combined OR were presented in Figure 2. Among 22 studies, the magnitude of OR largely varied from 0.25 to 4.20. Positive association between residential radon exposure and lung cancer was detected in 15 studies with 6 reaching statistical significance. Because modest heterogeneity among studies was observed (P = 0.026, I² = 40.6%), a random-effect model was used to calculate the pooled estimated OR. Overall, the combined OR of lung cancer for the highest with the lowest exposure was 1.29 (95% CI 1.10-1.51).

Dose-response analysis

Five studies (Pershagen et al., 1992; Létourneau et al., 1994; Field et al., 2000; Sandler et al., 2006; Thompson et
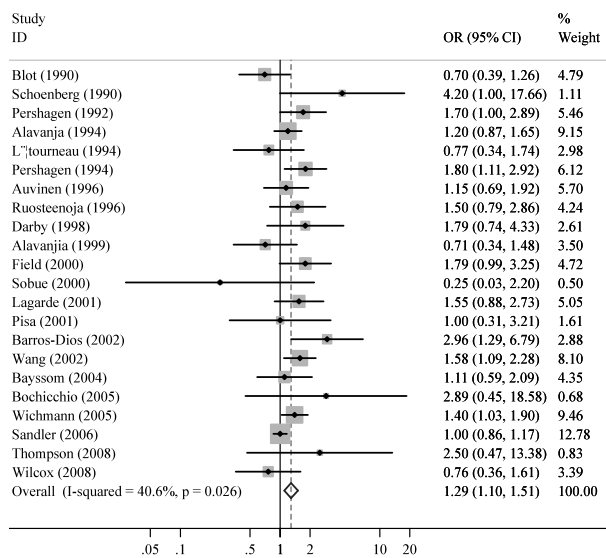
Study ID		OR (95% CI)	% Weight
Blot (1990)		0.70 (0.39, 1.26)	4.79
Schoenberg (1990)		4.20 (1.00, 17.66)	1.11
Pershagen (1992)		1.70 (1.00, 2.89)	5.46
Alavanja (1994)		1.20 (0.87, 1.65)	9.15
L"tourneau (1994)		0.77 (0.34, 1.74)	2.98
Pershagen (1994)		1.80 (1.11, 2.92)	6.12
Auvinen (1996)		1.15 (0.69, 1.92)	5.70
Ruosteenoja (1996)		1.50 (0.79, 2.86)	4.24
Darby (1998)		1.79 (0.74, 4.33)	2.61
Alavanjia (1999)		0.71 (0.34, 1.48)	3.50
Field (2000)		1.79 (0.99, 3.25)	4.72
Sobue (2000)		0.25 (0.03, 2.20)	0.50
Lagarde (2001)		1.55 (0.88, 2.73)	5.05
Pisa (2001)		1.00 (0.31, 3.21)	1.61
Barros-Dios (2002)		2.96 (1.29, 6.79)	2.88
Wang (2002)		1.58 (1.09, 2.28)	8.10
Bayssom (2004)		1.11 (0.59, 2.09)	4.35
Bochicchio (2005)		2.89 (0.45, 18.58)	0.68
Wichmann (2005)		1.40 (1.03, 1.90)	9.46
Sandler (2006)		1.00 (0.86, 1.17)	12.78
Thompson (2008)		2.50 (0.47, 13.38)	0.83
Wilcox (2008)		0.76 (0.36, 1.61)	3.39
Overall (I-squared = 40.6%, p = 0.026)		1.29 (1.10, 1.51)	100.00

.05 .1 .5 1 2 10 20

Figure 2. Forrest Plot of Case-control Studies Examining Residential Radon Exposure and Lung Cancer Rrisk

Table 2. Subgroup Analyses Relating Residential Radon Exposure to Lung Cancer by Characteristics of Study Designs and Populations

	No.	OR (95% CI)	P for heterogeneity	I^2 (%)
Total	22	1.29 (1.10-1.51)	0.03	40.6
Area of studies conducted				
Europe	11	1.50 (1.26-1.78)	0.77	0
North-America	8	1.10 (0.87-1.40)	0.14	36.8
Characteristic of subjects				
Females	9	1.18 (0.92-1.51)	0.12	37.5
Non-smokers	8	1.22 (0.97-1.54)	0.43	0.2
Radon dosimetry				
1 year measurement	15	1.16 (0.97-1.38)	0.07	38.3
In 5-30-year exposure time widow	15	1.35 (1.10-1.66)	0.01	54.2

al., 2008;) were not eligible for the dose-response analysis because they did not provide the required data (eg, the number of cases in each category). The dose-response analysis of the remaining 17 studies showed that the risk of lung cancer increased significantly, on average, by 7% for every 100 Bq/m³ increment in residential radon exposure (OR: 1.07; 95% CI: 1.04-1.10; P for trend<0.001), and little evidence of heterogeneity was found (P = 0.55).

Subgroup and sensitivity analyses

Table 2 shows the results of subgroup analyses stratified by geographic region, characteristic of subjects, and radon dosimetry. For geographic region, a significantly positive association of residential radon exposure with lung cancer risk was observed in the studies conducted in Europe but not in the studies conducted in North-America. The heterogeneity among total studies disappeared by subgroup in Europe (P=0.77) and North-America (P=0.14). Studies restricted to female or non-smokers weakened association between exposure and lung cancer with no heterogeneity among studies. Because of small number of male data, and variation and possible misclassification of smoking categories in smokers, we did not calculate their combined ORs. For radon dosimetry, the

association was somewhat stronger when the measurement was in 5-30-year exposure time widow.

Sensitivity analyses investigating the influence of a single study on the overall risk estimate by omitting one study in each turn suggested the overall risk estimates did not substantially modified by any single study, with a range from 1.26 (95% CI: 1.07-1.48) to 1.34 (95% CI: 1.14-1.57). Of note, the heterogeneity was still observed after omitting one study in each turn, except Sandler study was omitted (P=0.13).

Publication bias

There was no evidence of publication bias with regard to residential radon exposure to lung cancer risk, as suggested by Begg rank correlation test (P=0.87) and Egger linear regression test (P=0.15).

Discussion

The present meta-analysis provided evidence that residential radon exposure was associated with a significantly increased risk for lung cancer. Compared with the lowest category, people exposed to highest one of residential radon experienced 29% higher risk of lung cancer. The risk of lung cancer increased by 7% for every 100 Bq/m³ radon increment.

Notwithstanding consistent with the earlier combined analysis and meta-analyses; our findings provided additional information and knowledge different from previous results. Combined analyses combined 13 European case-control studies (Darby et al., 2005, 2006), 7 North American case-control studies (Krewski et al., 2005), 2 Chinese studies (Wang et al., 1996) and the last one combined three studies from Sweden, USA and China (Lubin et al., 1994). Although these combined analyses have advantages in terms of the pooling of original data from individual studies, they only focused on certain region of continents or optionally selected some studies for analysis. Compared with the previous meta-analysis (Pavia et al., 2003), the present analysis identified and included six more studies through an updated search. The enlarged sample size enhanced the power to detect a significant difference and provide more precise estimates of the radon effects. Based on the evidence from 22 independent case-control studies including a wide range of geographical locations and participant characteristics, our comprehensive analysis indicated a sound validity to be extrapolated to general population. In addition to the larger samples included, the present study was performed strictly according to the guidelines recommended by MOOSE (Stroup et al., 2000). In some of the previous meta-analyses (Lubin et al., 1997; Pavia et al., 2003), detailed information such as assessment criteria and publication bias was often missed, which may impair the value of analysis. Also, we used the different method for dose-response analysis based on widely accepted method in STATA software (Greenland and Longnecker, 1992). Furthermore, our result is in agreement with the recent USA cohort study where a significant positive linear trend was observed between categories of radon concentrations and lung cancer mortality (Turner et al., 2011). Although

cohort study is more effective than case-control study, it was not included in this meta-analysis since they belong to different study designs.

We observed heterogeneity across the studies in association of residential radon exposure with lung cancer risk, which also existed in previous meta-analysis. This is not surprising given the difference in countries that the study was conducted, characteristics of populations investigated, and adjustment for important confounding factors among others. As indicated by our subgroup analyses, area where study was conducted may contribute to the observed heterogeneity, as evidenced in the heterogeneity in total analysis disappeared when studies were divided by Europe and North-America. We further investigated the potential sources of heterogeneity across studies by sensitivity analyses. When the Sandler study (2006) was ruled out, no heterogeneity was found in the combined OR of the remaining studies. However, the heterogeneity changed little if other studies were removed instead of the Sandler study in which the highest category was only ≥53 Bq/m^3, a much lower exposure level than that in other studies. Thus, the selection of different category among studies may, at least in part, contribute to the heterogeneity of the present meta-analysis.

Female and nonsmoker were subgrouped to observe specific subject characteristics different from miner studies in which participants mostly involved men smokers. The result of relatively lower combined ORs in female and nonsmokers is inconsistent with a previous meta-analysis in that the combined OR for women was slightly higher (1.29, 95% CI 1.04-1.60) than that for total subjects (1.24, 95% CI 1.11-1.38) based on exposure at 150 Bg/m^3 (Pavia et al., 2003). The negative association between residential radon exposure in nonsmokers or women and lung cancer risk is supported by the fact that smoking has been confirmed as the most striking cause of lung cancer and women are among the populations with lower percentage of smoking than men. However, the benefit from the non-smoking could be partly offset by cooking emission, which was found to be an independent risk factor for women lung cancer (Chui et al., 2010). Furthermore, small number of the subgroup also limited further increment of test power in the study.

We used a linear, non-threshold model to perform dose-response analysis and found a significant increase of lung cancer risk with the increment of residential radon exposure, which is consistent with the previous meta-analysis and combined analysis (Pavia et al., 2003; Darby et al., 2005). In a combined analysis of 13 European case-control studies, Darby (2005) reported a significant dose-response relation even below currently action levels. In spite of the findings, the use of linear, no-threshold model has been often questioned. The Biological Effects of Ionizing Radiation (BEIR) VI committee adopted the linear no-threshold assumption based on current understanding of the mechanisms of radon-induced lung cancer, but recognized that this understanding is incomplete and therefore the evidence for this assumption is not conclusive (EPA 2003). Among the case-control studies included in the present meta-analysis, only the Thompson study (2008) showed a striking protective or

hormetic effect on lung cancer at low radon exposure. And it is consented that to reduce residential radon to the lowest possible level would be beneficial anyhow (Turner et al., 2011).

It is generally considered that radon exposure from 5 to 25 years in the lifetime is necessary for lung cancer to develop. Our study supports this view by showing a stronger association when the measurement was conducted in this exposure time widow. In a combined analysis of 7 North American case-control studies, restriction of subjects residing in one or two residences during the 5- to 30-year exposure time window increased the summary excess OR from 0.11 to 0.21 (95% CI 0.03-0.51) (Krewski et al., 2005). However, measurements of residential radon exposure during the 5- to 30-year period are subject to substantial uncertainty. The BEIR VI report claimed that the apparent inconsistency in findings among case-control studies was largely a consequence of exposure misclassification and random variability in radon levels (NRC, 1999). These uncertainties can arise because of the measurements during a short period of time, non-representative samples, and even the use of different track detectors. Apparently, the exposure measurement is a major issue to be taken consideration in the future study.

The precise mechanism of lung cancer induced by radon is not fully understood but may involve both genetic and epigenetic pathways in the process of neoplastic conversion. Cytogenetic studies demonstrated that radon and its decay products could induce genetic damage in forms of micronuclei formation, chromosomal aberrations, and loss of control to cell proliferation (Lutze et al., 1992; Jostes, 1996). At molecular level, exposure to radon and alpha particles may lead to hypoxanthine-guanine phosphoribosyl transferase (hprt) gene mutations that ranged from complete deletion of the gene, partial deletions to gene rearrangements (Lutze et al. 1992). Occupational studies on uranium miners also showed that about 31% of lung cancers contained the same mutation at codon 249 of the p53 gene (Vahakangas et al. 1992; Taylor et al. 1994). These genetic and cytogenetic changes attributed to radon have been reported to be linear and dose-dependent in many in vitro and in vivo experiments.

Although not the first one, our updated meta-analysis provides new evidence supporting the conclusion that residential exposure to radon can significantly increase the risk of lung cancer in a dose-response manner. This update is imperative for the welfare of public health since indoor radon levels have been reported elevating over the past decades in some developing countries over the world.

Acknowledgements

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