ISSN: 0975-766X
CODEN: IJPTFI
Available through Online *Review Article*
www.ijptonline.com

RELATIONSHIP BETWEEN EXPOSURE TO RADON AND THE RISK OF LUNG CANCER; SYSTEMATIC REVIEW AND META-ANALYSIS UPDATED TO 2015

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Received on 22-07-2016 *Accepted on 30-08-2016*

Abstract

Radon 222 is a radioactive isotope with a half-life of 3.825 days, which is colorless and odorless and it endangers human health in the long run by emitting alpha radiation during the decay. Many studies have been done on the effects of inhaling Radon on lung cancer risk and most studies show that inhalation of radon increases the risk of lung cancer. Therefore, in this study, it has been tried to provide accurate results on the relationship between the inhalation of Radon and the risk of lung cancer by adding new case-control studies performed by 2015. The databases of ISI, Pubmed, Scopus, Iran doc and SID were used to find the studies in Iran and the world. The studies were searched from 1990 to 2015 with the use of checklist STROBE. The studies which obtained the least score, were entered at the stage of meta-analysis.

The quality of the studies was determined based on system scale Newcastle – Ottawa. 24 papers (24 case-control studies), totally 50784 participants (20138 cases and 30646 controls) were specified. The measurement period was between 3 to 12 months. The mean concentration of Radon that the cases were exposed was 103.4±54 and 80.3±44 Bq/m3. The meta-analysis of 24 case-control studies showed that there is a significant relationship between the exposure to radon and the risk of lung cancer (OR=1.46, 95% CI (1.23-1.72), P value<0.001). Also, the heterogeneity of the studies was high (I^2=65%, p=<0.001). Egger's test showed that (Beta:1.43, 95%(0.7-2.12) there was a

significant error propagation between the studies (p value<0.001). The results of this study support the increased risk of lung cancer caused by the inhalation of radon.

Keyword: Radon, air, lung cancer, systematic review and meta-analysis.

1. Introduction

Radon222 and its daughters Po^{214} and Po^{218} are the main and final products of decay of Uranium chain 235 that can be spread from various sources such as surface water and groundwater, soil, igneous (granites) and sedimentary rocks [1-3]. Also, radon 222 is aradioactive isotope with a half-life of radon 3.825 days which is colorless and odorless and it endangers human health in the long run by emitting alpha radiation during the decay[4-6].Based on information provided by National Radiation Protection Board (NRPB), 85% of the effective dose received by humans is from natural exposure and 15 percent of it is from synthetic exposure (manmade) [7]. After smoking, the leading cause of death from lung cancer if radon gas [8,9]. America Environmental Protection Agency (EPA) announced that the deaths caused by the radon of indoor air is nearly 21000 people per year which is 10 times higher than the deaths caused by air pollution[10]. Also, it was estimated that radon can be a cause of 30% of deaths caused by lung cancer among non-smokers [11].

EPA and WHO suggested the concentrations of 148 Bq/m^3 and 100 Bq/m^3 for the radon of indoor air, respectively [10,12]. The global average concentrations of radon in the indoor and outdoor air are 48 Bq/m^3 and 15 Bq/m^3, respectively [13]. Lung cancer is the first cause of death from cancer in the world with 1.4 million deaths in 2008 and 1.6 million incidences [14]. In Europe, it was the first cause of death in men and the second cause of death with the breast cancer in women [15].

Smoking is the leading cause of lung cancer [16] and the incidence of lung cancer among non-smokers is 25% [17]. Also, other causes such as household radon [18,19], occupational exposure (asbestos, silica, cadmium, chromium, nickel and beryllium), exposure to the tobacco of environment [20], some of the waste at certain times [21]can be involved in lung cancer. In recent years, numerous meta-analysis studies examined the relationship between radon and lung cancer risk. For example, at the concentration of $100Bq/m^3$, the chance ratio of the studies in Europe, North America and China was 1.08 (1.03-1.15), 1.11(1.00-1.28) and 1.33 (1.01-1.36), respectively [22]. Several studies have been performed on the concentration of radon in drinking water and the risk of lung cancer [23,24].

Thus, recently, WHO recommended the concentration less than 100 Bq/m^3 for the radon of indoor air according to Laughlin et al. and Carneiro et al [25,26]. The systematic and meta-analysis studies have been done by 2014

meanwhile, no new studies have been done in this field. Therefore, in this study, it has tried to enter the new case-control studies performed by 2015 at the stage of meta-analysis and the results will be evaluated on the quality of studies.

2. Materials and methods

This research is a systematic and meta-analysis study on the relationship between inhalation of radon and risk of lung cancer. The databases of ISI Web of Science, Pubmed, Scopus, Irandoc and SID were used to find the studies in Iran and the world.

The selection and the quality evaluation criteria of the studies

Firstly, a list of all studies' titles and abstracts included in the mentioned databases was provided by three researchers (Ya.F, Ha.K,Ya.Z) to prevent the bias of researchers. The related titles were investigated independently and, then the studies published between the dates 1990 and 2015 were searched. The search was done for two weeks from 15.04.2016 to 30.04.2016, then the related studies were evaluated initially by blinding method and entered in the research process independently. Cohort's studies were excluded from the study. In this research, the inclusion criterion of different studies is that the inhalation of radon and the risk of cancer were noted. The studies were not of the earlier studies or the studies were performed on the field of clinical decision-making or unrelated investigations to the lung cancer were excluded from the study. In the second stage, the abstracts of the selected studies were investigated with the use of checklist STROBE[1] which is a standard checklist. This checklist includes 43 various sections and investigates various aspects of methodology, including sampling methods, measurements, statistical analysis and objectives of the study [27]. In this checklist, the minimum score is 40 and the maximum one is 45. Finally, the top studies which have gained 40 scores based on checklist, were entered in the research and their data was extracted for meta-analysis. Funnel Plot and Egger's test were used to determine the Bias Publication [28].

Data extraction

In this study, 24 articles (case-control studies) were investigated that their methodologies were almost the same and all of them were performed in 1990-2015. The important required data for data analysis including the information related to the issue, title, research method, research type, study time, study location, type and concentration of radon, the number of cases and controls, measurement period, the number of measurement devices, the score of each study in the NOS (Newcastle – Ottawa Scale) system, chance ratio of lung cancer, sample size and confidence level were collected.

According to NOS qualitative evaluation criteria which includes Selection, Comparability and Exposure, case-control studies were scored. In the NOS system the score range is from 0 to 9. The studies were classified to low score (<7) and high score (≥7) [29].

3. Results

1.3. Identification of relevant studies

At this stage, totally, 1798 studies were found by researching in the databases of SID, Irandoc, Scopus, Embase, ISI web of science and PubMed. According to Title and abstract, Duplicates removed, review, editorial, protocol, Nonhuman, radon as an exposure and lung cancer as a concern, 1576 article were excluded at the stage of Eligibility. Of 222 remaining articles, 125 studies were residential and 97 studies were occupational. 198 studies were excluded from meta-analysis due to some reasons such as lack of data and analysis of the indicators HR, RR and so on. Finally, 24 studies (24 case-control studies) in which chance ratio was calculated, were entered in the stage of meta-analysis (Figure1).

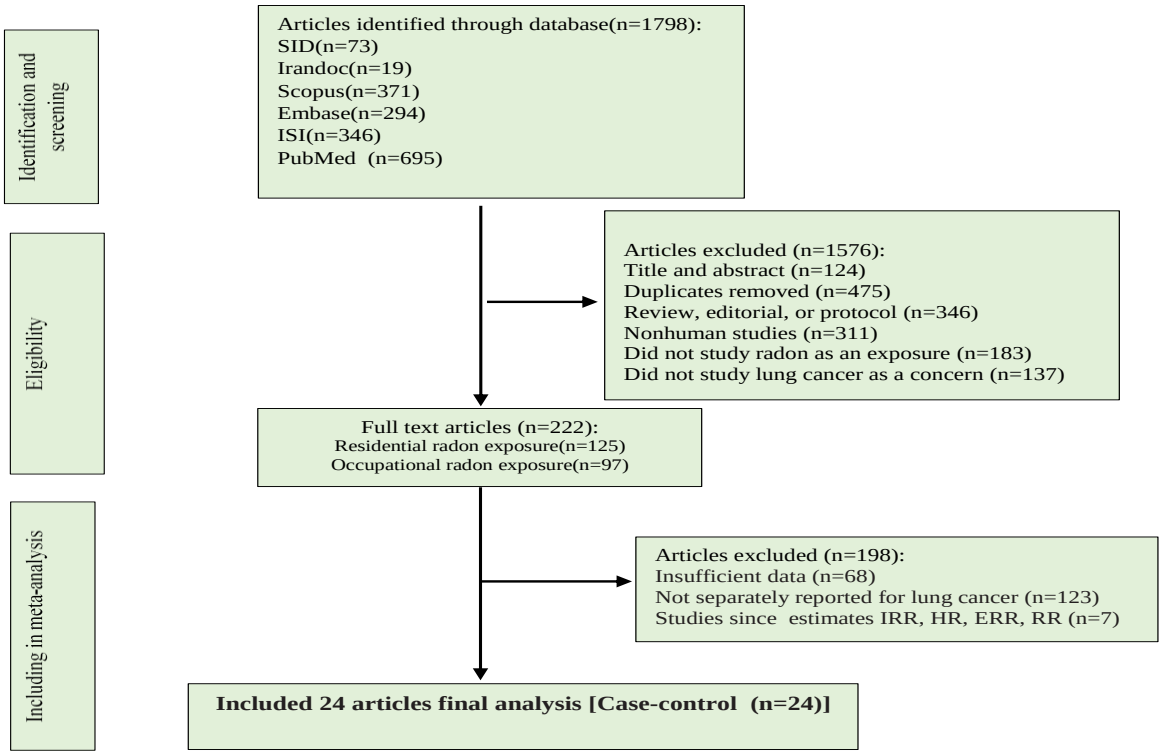

Figure1. Flow diagram for identification of relevant case-control studies.

2.3. Characteristics of the studies

General characteristics such as the year of publication, country, measurement period, the number of cases and controls, gender, the number of detectors, radon concentration in cases and controls, and the results are shown in Table 1. The scope of the study was from 1990 to 2015. 6 studies were about women, one study was on men and 17 studies were on both genders.

Table-1. General characteristics radon and lung cancer studies evaluated for meta-analysis.

	First author	Date	Case	Control	OR	Low	High		Countries	Sex	Duration of radon measurements (months)	Number of alpha track detector used	Concentration of radon (Bq/m3)		Outcome	REF
													case	control		
1	Blot et al	1990	308	356	0.7	0.3	1.6	0.95	China	Female	12	2	85		High radon levels may have overestimated the overall risks of lung cancer associated with levels typically seen in homes in this Chinese city	[30]
2	Schoenberg et al	1990	433	402	4.2	0.99	17.5	0.95	United States	Female	12	2	NA[1]		For lung cancer risk with estimated cumulative radon exposure was slightly weaker	[31]
3	Pershagen et al	1992	210	209	1.7	1	2.9	0.95	Sweden	Female	3	2	128		Further studies are needed to clarify the level of risk associated with exposure to residential radon	[32]
4	Létourneau et al	1994	738	738	0.77	0.34	1.73	0.95	Canada	Both	12	2	120		No Increase in the relative risk for any of the histologic types of lung cancer observed among the cases was detected in relation to	[33]

[1] Not applicable

														cumulative exposure to radon	
5	Pershagen et al	1994	1360	2847	1.8	1.1	2.91	0.95	Sweden	Both	3	2	107	Interaction between radon exposure and smoking with regard to lung cancer exceeded additively and was closer to a multiplicative effect	[34]
6	Auvinen et al	1996	517	517	1.15	0.69	1.93	0.95	Finland	Both	12	1	103	96	Indicate increased risk of lung cancer from indoor radon exposure	[35]
7	Ruosteenoja et al	1996	291	495	1.5	0.8	2.9	0.95	Finland	Male	12	1	213	increase in risk was not statistically significant	[36]
8	Darby et al	1998	960	3126	1.79	0.74	4.33	0.95	United Kingdom	Both	6	2	58	56	risk of lung cancer associated with residential radon exposure is about the size that has been postulated on the basis of the studies of miners exposed to radon.	[37]
9	Alavanja et al	1994	247	299	1.66	1	2.61	0.95	United States	Female	12	2	57	60	association between lung cancer and the exposure to domestic levels of radon was not convincingly demonstrated	[38]
10	Field et al	2000	413	614	1.79	0.99	3.26	0.95	United States	Female	12	3	100	89	observed risk estimates suggest that cumulative ambient radon exposure presents an important environmental health hazard	[39]

11	Pisa et al	2001	138	291	1	0.3	3.1	0.95	Italy	Both	12	1	NA		association between radon and lung cancer, as determined with a multiplicative model, was found only among male smokers	[40]
12	Barros-Dios et al	2002	163	241	2.96	1.29	6.79	0.95	Spain	Both	3	1	75	66	even at concentrations far below official guideline levels, radon may lead to a 2.5-fold rise in the risk of lung cancer	[41]
13	Wang et al	2002	768	1659	1.58	1.1	2.3	0.95	China	Both	12	2	230	222	increased estimates by 50%. Results support increased lung cancer risks with indoor radon exposures that may equal or exceed extrapolations based on miner data	[42]
14	Baysson et al	2004	486	984	1.11	0.59	2.09	0.95	France	Both	6	2	83	80	presence of a small excess lung cancer risk associated with indoor radon exposure after precise adjustment on smoking	[43]
15	Bochicchio et al	2005	384	405	2.89	0.45	18.6	0.95	Italy	Both	6	2	113	102	an association, although generally not statistically significant, between residential radon and lung cancer with both categorical and continuous analyses	[44]
16	Wichmann et al	2005	2963	4232	1.4	1.03	1.89	0.95	Germany	Both	12	2	61	60	residential radon is a relevant risk factor for	[45]

															lung cancer	
17	Sandler et al	2006	1474	1911	1	0.93	1.07	0.95	United States	Both	12	2	40	45	no evidence of an increased risk for lung cancer at the exposure levels observed	[46]
18	Thompson et al	2008	200	397	2.5	0.47	13.46	0.95	United States	Both	12	2	68	66	in comparison to high-school dropouts have a significant reduction in cancer risk after controlling for smoking, years of residency, and job exposures	[47]
19	Wilcox et al	2008	561	740	0.76	0.36	1.61	0.95	United States	Both	12	1	46	46	consistent with an earlier population-based study of radon and lung cancer among New Jersey women, and with the North American pooling of case control radon seven studies	[48]
20	Barros-Dios et al	2012	349	513	2.21	1.33	3.69	0.95	Spain	Both	3–6	1	NA		airborne radon even at low concentrations poses a risk of developing lung cancer, with tobacco habit increasing considerably this risk	[49]
21	Torres-Durán et al	2015	192	329	2.19	1.44	3.33	0.95	Spain	Both	3	1	200		An association between residential radon exposure and environmental tobacco smoke on the risk of lung cancer might	[50]

														exist	
22	Hystad et al	2014	2390	3507	1.12	1.02	1.22	0.95	United States	Both	3	1	81.3	78.6	radon is an important risk factor for lung cancer and that risks are unevenly distributed across Canada	[51]
23	Krewski et al	2006	4081	5281	1.37	0.91	2.06	0.95	Canada	Both	12	1	55.4	58.1	an association between residential radon and lung cancer risk, a finding predicted by extrapolation of results from occupational studies of radon-exposedunderground miners	[52]
24	Alavanja et al	1999	512	553	3.33	1.5	7.5	0.95	United States	Female	60	2	148		exposure to domestic levels of radon was not convincingly associated with lung cancer risk among nonsmoking women in Missouri.	[53]

These 24 studies generally had 50784 participants (20138 cases and 30646 controls). The measurement period was between 3 to 12 months. The mean concentration of Radon the cases were exposed was 103.4±54 and 80.3±44 Bq/m^3. According to NOS qualitative evaluation criteria, the studies by Bochicchio et al. and Wilcox et al. (2 studies) obtained the low score and 22 other studies obtained high score (Table2).

Table-2. Score cohort studies base on Newcastle-Ottawa Scale system.

		Selection (score)				Comparability (score)			Exposure (score)		
Study	Adequate Definition of Patient Cases	Representativeness of Patient Cases	Selection of Controls	Definition of Controls		Control for Important Factor or Additional Factor		Ascertainment of Exposure (blinding)	Same Method of Ascertainment for Participants	Non response Rate *	Total Score†
Blot et al	1	1	1	0		1		1	1	1	7
Schoenberg et al	1	1	1	0		2		1	1	0	7
Pershagen et al	1	1	1	0		1		1	1	1	7
Létourneau et al	1	1	1	0		2		1	1	0	7
Pershagen et al	1	1	1	0		2		1	1	0	7
Auvinen et al	1	1	1	0		2		1	1	1	8
Ruosteenoja et al	1	1	1	1		2		0	1	1	8
Darby et al	1	1	1	1		2		0	1	0	7
Alavanja et al	1	1	1	1		2		1	1	1	9
Field et al	1	1	1	0		2		0	1	0	6
Pisa et al	1	1	1	1		2		0	1	0	7
Barros-Dios et al	1	1	1	1		2		0	1	0	7
Wang et al	1	1	1	1		2		1	1	0	8
Baysson et al	1	1	1	1		1		1	1	0	7
Bochicchio et al	1	1	0	1		1		1	1	0	6
Wichmann et al	1	1	1	1		2		1	1	0	8
Sandler et al	1	1	1	1		2		1	1	0	8
Thompson et al	1	1	1	1		1		1	1	0	7
Wilcox et al	1	1	0	1		1		1	1	0	6
Barros-Dios et al	1	1	1	1		1		1	1	0	7
Torres-Durán et al	1	1	1	1		2		1	1	1	9
Hystad et al	1	1	1	1		1		1	1	0	7
Krewski et al	1	1	1	1		2		1	1	0	8
Alavanja et al	1	1	1	1		2		1	1	0	8

3.3. Meta-analysis of the studies

The heterogeneity of the studies was high (I^2=65% , p=<0.001), so, the model Random Effect was used for meta-analysis. The meta-analysis of 24 studies showed that there is a significant relationship between the exposure to air radon and the risk of lung cancer (OR=1.46 , 95%CI(1.23-1.72), P value<0.001) (Figure2). The data of the studies performed in 10 countries was meta-analyzed. The highest and lowest risk of lung cancer caused by exposure to radon were related to China (OR=0.91, 95%CI(0.48-1.75)) and France (OR=2.81, 95%CI(0.41-20.16)). Most studies were done in the United States, the results showed that exposure to radon increases the risk of lung cancer by 71% significantly (Figure 2).

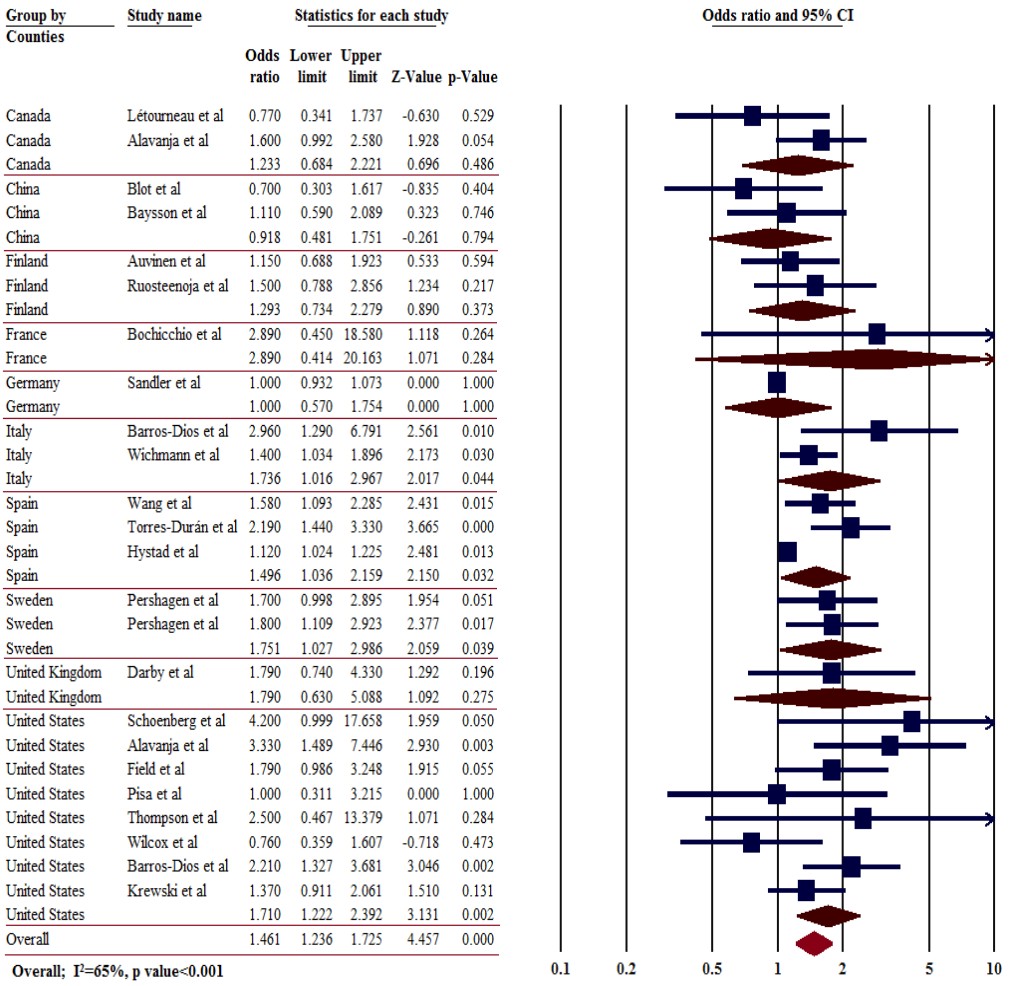

Figure 2. Forest plot of meta-analysis on radon exposure and lung cancer in the countries.

The risk of lung cancer in the studies performed on both gender (OR=1.38,95%CI(1.19-1.61), Pvalue<0.001) was reported less than one in the studies performed on women (OR=1.69,95%CI(1.18-2.42), Pvalue=0.004) and men (OR=1.5,95%CI(0.71-3.19), P value=0.29) separately (Figure3). Reverse funnel showed that there is no error propagation but Egger's test (Beta:1.43, 95%(0.7-2.12)) showed that there is a significant error propagation between the studies on the exposure to radon and lung cancer (p value<0.001) (Figure4).

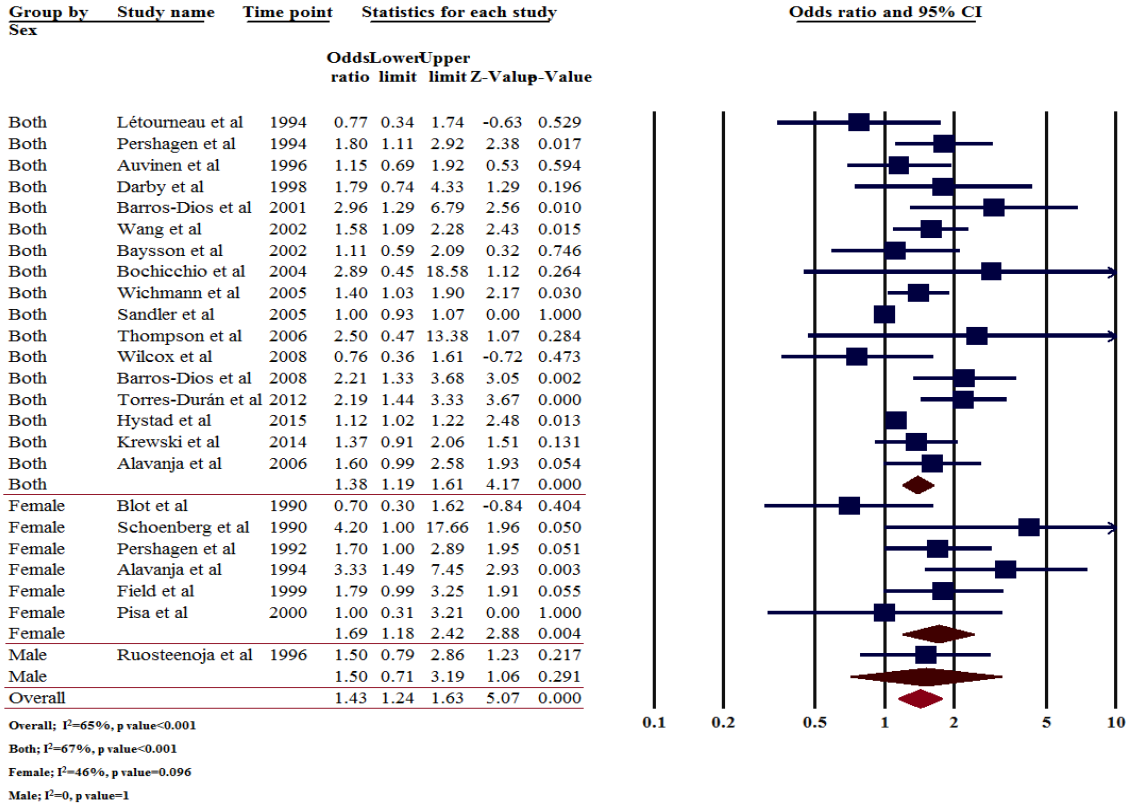

Figure 3. Forest plot of meta-analysis on radon exposure and lung cancer in groups sex.

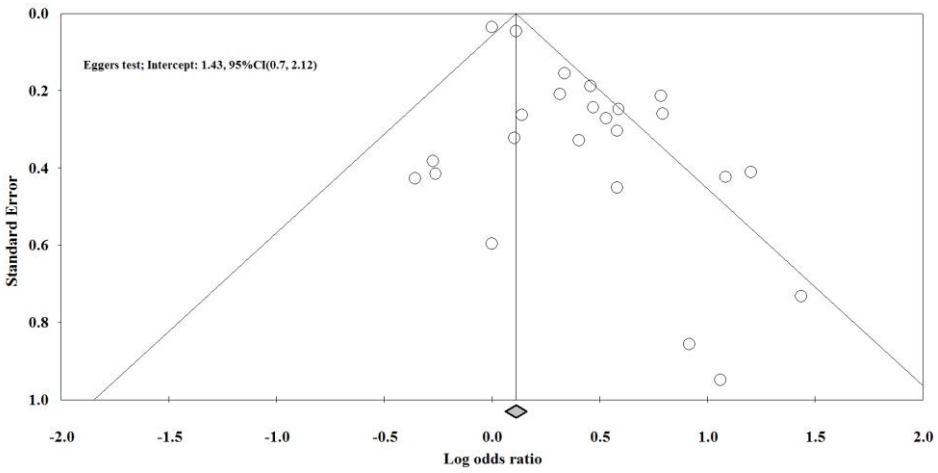

Figure 4. Funnel plot of the studies included in the meta-analysis.

4. Discussion

This systemic and meta-analysis study was performed to update the relationship between the exposure to radon and the risk of lung cancer by 2015. The results show that the exposure to radon increases the risk of lung cancer by 46%. No significant relationship was observed between the concentration of radon and the risk of lung cancer. In the studies by Schoenberg et al., Bochicchio et al., Barros-Dios et al. and Alavanja et al. that the risk of lung cancer was reported high, the mean concentrations of radon were not more than ones in other studies [31,41,44,53].

The risk of lung cancer was more in the control groups which exposed to less radon. In 65% of the studies, the concentration of radon was more than the standard of EPA (148Bq/m^3) [54] and in 35% of them, it was more than the

Europe standard (200 Bq/m^3) [55]. The study of Sheen et al. showed that for every 100 increased lung cancer risk, the risk of lung cancer increases in non-smoker subgroups by 4 to 28 % [36]. So, the risk of lung cancer caused by the expose to radon increases. In addition to radon, other variables such as occupational expose (asbestos and so on) or smoking can be examined. For every increase of 100 lung cancer risk 4 to 28 percent increased risk of lung cancer in non-smokers subgroups increases [56]. The risk of lung cancer caused by exposure to radon increases. In addition to intervening variables such as radon exposure (asbestos, etc.) or smoking can be examined. Although radon concentration is a risk factor for lung cancer, but there are a few studies on the effects of radon on non-smoker groups.

Systemic review study by Torres-Durán et al. showed that the risk of lung cancer caused by the exposure to radon is high in non-smokers [57]. Another study by Torres-Durán et al. showed that that the risk of lung cancer caused by the exposure to radon in non-smokers is higher than it in smokers [50].

On the other hand, the study by Lo et al. and also the study by Kreuzer et al. showed that 78.2% and 79.9% of the cancers among women is lung cancer [58,59]. As shown in figure3, the risk of lung cancer in subgroup of women and the subgroup of both genders (men and women) significantly increased with the expose to radon but in the study by Ruosteenoj et al., no increased risk of lung cancer was reported [36]. Of course, it is needed to study on men in terms this issue particularly to precisely conclude about the different effect of radon on men and women. On the other hand, the risk of lung cancer from radon in drinking water was not investigated in the studies. Radon in drinking water can increase the risk of lung cancer in addition to the risk of gastric cancer [23,60].

Limitations of the study

Although the results of this study show the relationship between the exposure to radon and the risk of lung cancer, but, there are some limitation in this studies as follows: excluding the study by Cohort, language limitation (except English and Persian), excluding the studies which used the blinding method, the studies are not classified to residential and occupational subgroups and the subgroups of smokers and non-smokers, excluding the studies which didn't match the variables such as the study by Aune et al. and Jin et al [61,62], the concentration of radon was not mentioned in some studies such as the study by Schoenberg et al., relatively high heterogeneity due to differences in research methods and the classification of radon concentration. On the other hand, the latency period of lung cancer caused by exposure to radon is 5 to 25 years and there was no previous information from the residents in many studies [63]. Also, some studies used thegeographical information to estimate the radon concentration [64].

5. Conclusion

The results of a systematic review and meta-analysis of 24 case-control studies on the radon and risk of lung cancer by 2015 showed that the exposure to radon increases the risk of lung cancer significantly (p value <0.001).

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