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SELENIUM AND LUNG CANCER: A SYSTEMATIC REVIEW, META-ANALYSIS AND META-REGRESSION

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Abstract

Lung cancer is the most common cause of death in the world. Selenium is one of the elements that are recommended for the treatment of lung cancer. Therefore, in this study by carrying out a systematic review and a meta-analysis we tried to evaluate the relationship between selenium in serum, toenail and supplements and the risk of lung cancer. After searching the databases SID, Irandoc, Scopus, Pubmed and ISI Web of Science with the check-list of STROBE, 15 studies were estimated by meta-analysis. The variables affecting the heterogeneity of studies were determined by the method of moment base. The heterogeneity of studies was moderate (I^2 = 70.5%, P value <0.001). Hence the meta-analysis was conducted on the basis of the random effect model. The mean of ratio of lung cancer in studies of selenium supplements was equal to OR = 0.82 (95% CI: 0.47-1.42, P value = 0.5), in the studies of selenium in serum it was equal to OR=0.7 (95% CI: 0.45-1.07, P value = 0.1) and in the studies of selenium in the toenail it was equal to OR= 0.59 (95% CI: 0.28-1.24, P value = 0.17).

Generally speaking, the risk of lung cancer is significantly reduced by selenium [OR = 0.71 (95% CI: 0.52-0.97, p value = 0.03)].In fact the selenium reduces29% of the risk of lung cancer, significantly. There was not observed any publication error in studies (Beggar's test: z- value = 0.24; P value = 0.8).The meta-regression showed that the study

location, the measurement of selenium and the type of study have a significant effect on heterogeneity. The results supported the lowering effect of selenium on the risk of lung cancer.

Keywords:

Selenium, lung cancer, supplement, toenail, serum, systematic review, meta-analysis

1. Introduction

Despite our knowledge of the molecular carcinogenesis and the use of new methods of treatment, the lung cancer is the most common cause of mortality in the world [1].It has been estimated that the 1.04 million new cases of lung cancer occur annually in the world [2].As with most diseases for preventing the lung cancer, the risk factors involved in lung cancer should be eliminated or reduced. In spite of the fact that smoking is the most prominent cause of this disease (90%), it cannot be disregarded the role of risk factors such as occupational confrontation (asbestosis),home radon and certain dietary constituents [3].The rare elements play an important role in the various intracellular processes. Lack of sustainability of these elements in the cell causes a cell dysfunction and ultimately disease [4].One of these rare elements is selenium. The non-metallic forms of selenium include selenite and the organic selenium is the selenomethionine and methylselenic acid [5].Selenium has been combined with amino acids; hence the term of selenoproteins [7 ,6].The human body can produce 25 types of selenoproteins [8].EPA has declared the reference dose of selenium to prevent its adverse effects on the health as 0.005 mg/kg-day [9].Some of these selenoproteins have directly an antioxidant capacity at low concentrations. In addition, reproducing and activating the antioxidants with low molecular weight (vitamins E, C and Q10)the selenoproteins have indirectly an antioxidant activity [10].

Selenoproteins in high concentrations become pro-oxidant with a growth control property. The antioxidant and oxidant nature of selenoproteins is dependent on the concentration and redox potential (Figure 1) [11].

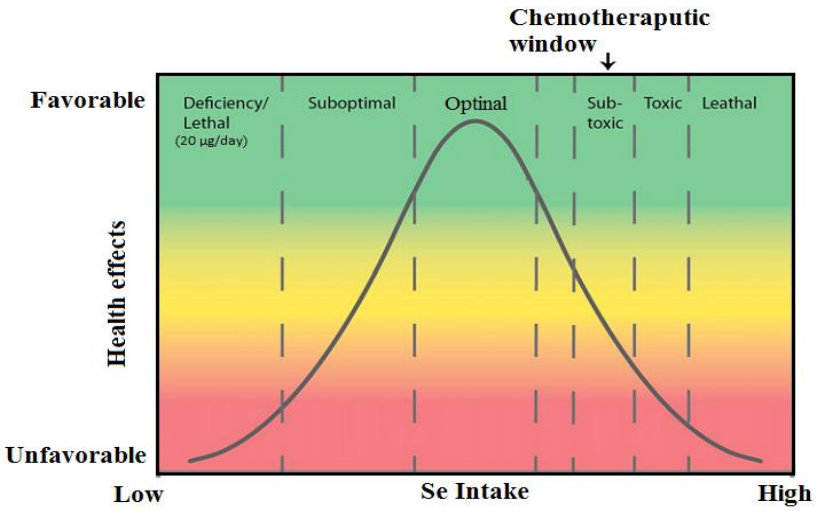

Fig. 1 A general biological response curve, dose dependent effects of selenium compounds.

As said before, the absorption of selenium to a certain extent has the anti-cancer effects, but an excessive absorption of selenium causes the chronic toxicity in human and causes diseases such as loss of hair and toenails, gastrointestinal problems, skin rash, garlic breath odor, nervous system abnormalities [12], Keshan disease and Kashin-Beck disease [13].The laboratory studies on animals have shown that selenium can reduce the development of cancers [14].Some human ecological studies have reported the relationship between the low level of selenium and the increase in mortality resulting from cancer [16 ,15].Several mechanisms have been proposed to explain the anticancer effects of selenium which include: rehabilitation of damaged DNA, induction of phase II enzymes, increase of immunity system power, inhibition of cell cycle, angiogenesis and the induction of apoptosis [18 ,17].But it should be noted that the role and mechanism of rare elements in inhibition and development of cancers is very complex. Several cross-sectional and prospective studies have reported a risk decrease of lung cancer with increasing selenium [20 ,19]but some other studies have not confirmed these results [21].For example, a prospective study in Netherland has reported the relative risk of lung cancer as 0.5 (95%CI: 0.3-0.81) RR = for selenium of toenail[22].But in a cross-sectional (case-control)study in the United States there was not observed any relationship between selenium and risk of lung cancer RR = 1.2 (95%CI: 0.77-1.88) [23].In a study the risk ratio has been adjusted: after taking selenium supplement for 5 years of follow-up it was equal to HR=0.56 (95%CI:0.31-1.01) [24].In a study that was carried out after this one, after three years of additional follow-up the risk ratio increased HR=0.74 (95%CI:0.44-1.24) [25].Nutritional Prevention of Cancer (NPC) has reported that taking 200 μg/day of selenium for 4.5 years reduces the incidence of lung cancer by 46% [26].The reasons for this difference in the results of the studies could include a difference in the period of study, the control group, the level of confrontation, the study population or other differences in designing study. Therefore, by carrying out a systematic review, meta-analysis and meta-regression in this study we attempted to evaluate carefully the relationship between the selenium in serum, toenail and supplements with the risk of lung cancer.

2. Materials and Methods

This study was a systematic review and meta-analysis of studies on the relationship between the selenium in serum, toenail and supplements with the risk of lung cancer. In order to find studies conducted in Iran and the world, the databases SID, Irandoc, Scopus, Pubmed and ISI Web of Science were used.

1.2. The criteria of selection and evaluating quality of studies

At first a list of titles and an abstract of all studies available in databases mentioned by three researchers (Ya.F, Ha.K, Ab.B) was developed to avoid the probable bias of researchers. The related titles were analyzed independently then the

search in the studies that were published between the dates 1980 and 2016 was done. The search was done for 3 weeks from the date of 18/01/2016 to 09/02/2016 and then the related studies were entered into the investigation process separately and by the method of blinding of the initial evaluation. The similar studies were excluded. The main criterion of inclusion of the different articles to this study was a referring to the relation of selenium concentration in serum, toenail and supplement with the lung cancer risk.

The investigations that were only the initial researches, or were on the treatment, determining the clinical characteristics, clinical decision-making and other investigations alien to the lung cancer were excluded from the study. In the second stage an abstract of different selected studies was evaluated by the researcher using a check-list of STROBE[1] that is a standard check-list. This check-list contains 43 sections and evaluates the different aspects of methodology, including sampling methods, measurement of variables, statistical analysis and objectives of the study [27].In this check-list, the minimum achievable score was considered to be the score 40 and a maximum one the score 45.

Finally the top articles that had gotten the minimum score (40) of the check-list questions, were entered into research and their data were extracted for the meta-analysis. For determining the sensitivity of study or Publication Bias, the Funnel Plot and Egger's and Begg-Mazumdar test were used. To determine the effect of other variables on the heterogeneity, the meta-regression was used [28].

2.2.Data extraction

In this study, 15 articles in all of which nearly the same methodology was used and had been carried out from 1987 to 2013 were evaluated. The other needed important information for analyzing the data, including information on the subject, title, methodological information, including the way of study, type of study, time of study, the risk ratio, sex, selenium concentration in serum, toenail and supplements, sample size and confidence level were collected.

3.2. Data synthesis and analysis

All Statistical analyses were performed by the software Comprehensive Meta-Analysis V. 2.2.064.In this analysis, for determining the heterogeneity the statistics t^2, I^2 were calculated by using Method of Moment base.After being determined the moderate heterogeneity in the studies (I^2> 50%), based on Random effect model we attempted to calculate the risk ratio mean.

Being carried out the initial analysis, for determining the relationship between selenium and lung cancer the accumulation diagram in the random model was used. Using meta-regression method, the effects of variables of

samples size, the time of study, place of study, type of study, the selenium sub-group (serum, toenail and supplements) that were suspected of causing heterogeneity in the study, were investigated. The significance level for co-variances of studies was P value<0.05.

3. Results

Fifteen studies with 15791 participants and 2438 cases were investigated by meta-analysis (Table 1). In databases ISI, Pubmed, Scopus, Irandoc and Sid 476 studies were observed. Due to the difference in the title or abstract and some other reasons, 414 studies were excluded. Due to the shortage of data (2 studies) or for determining the correlation or risk ratio (19 studies) and Biomarker report (7 studies), 28 studies were excluded from the meta-analysis. Finally 15 studies including three studies of toenail, 8 studies of serum and 4 supplement studies that had examined the relationship between selenium and prostate cancer were surveyed by meta-analysis (Figure 2).

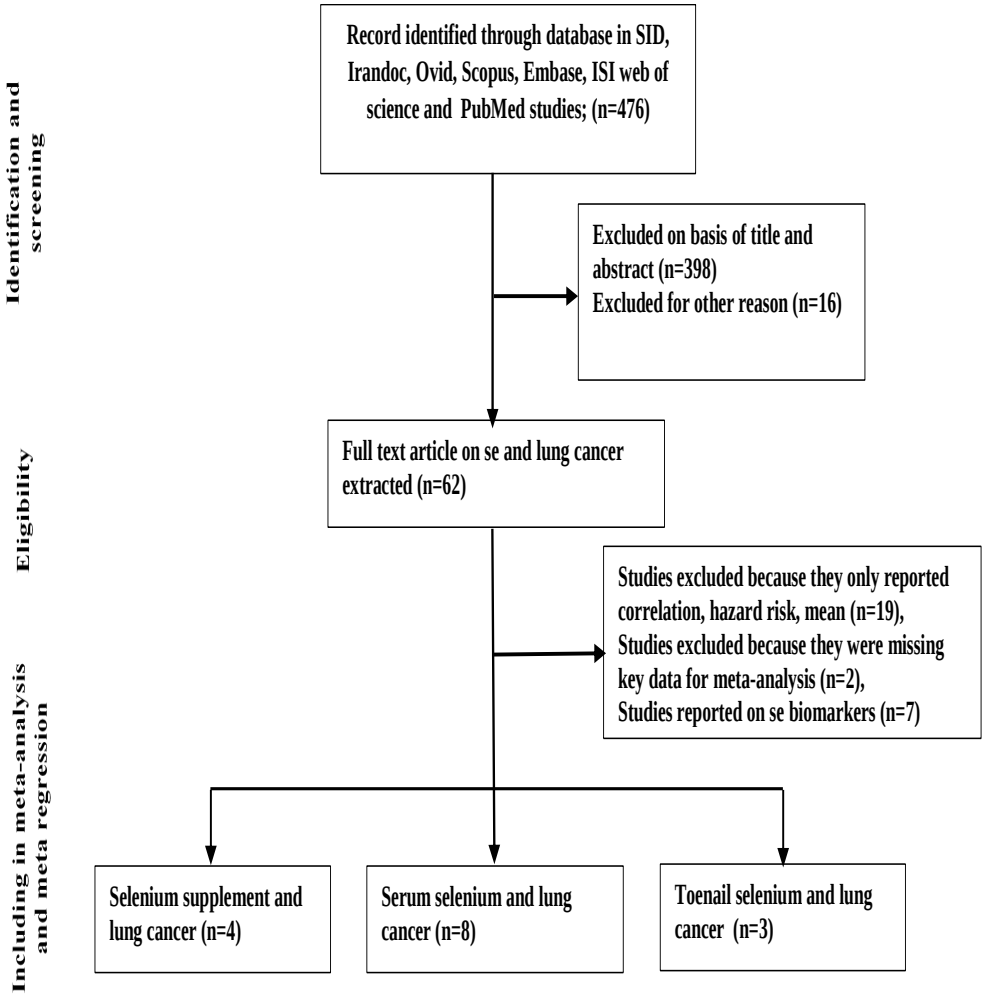

Figure 2. Studies selection process for meta-analysis.

The highest and lowest risk ratios were related to the study of Lippman et al (OR=1.12)in studies of a selenium supplement, Clark et al (OR=0.56), Kabuto et al (OR=1.8) and Jaworska et al (OR=0.1)in serum studies, Garland et al (OR=1.96) and Van del Brandt et al (OR=0.4)in toenail studies, respectively (Table 1).

Table1. Characteristics of studies included in the systemic review and meta-analysis

First Author	Year	Country	Type of study	Subject	Case	Age	Gender	Measurements of selenium	Odds ratio	Low	High	Outcome	Ref
Jablonska et al	2008	Poland	Case-control	612	325	30–78	M and F	Serum selenium	1.21	0.67	2.2	It appears that among smoking individuals, those with the Sep15 1125 AA genotype may benefit most from a higher Se intake, whereas in those with the GG or GA genotype, a higher Se status may increase the risk for lung cancer	[29]
Kabuto et al	1994	Japan	Case-control	30	27	59–60	M and F	Serum selenium	0.56	0.2	5.88	These exploratory findings add to limited data available from other reports showing slightly increased risks of lung cancer associated with low blood levels of selenium, but suggest little association with either lung or stomach cancer	[30]

												across normal selenium or zinc ranges in this Japanese population	
Jaworska et al	2013	Poland	Case-control	172	86	Mean 61.6	M and F	Serum selenium	0.1	0.03	0.34	A selenium level below 60 mg/l is associated with a high risk of both lung and laryngeal cancer	[31]
Ratnasinghe et al	2000	China	Case-control	324	108	35–74	Men	Serum selenium	1.2	0.6	2.4	Although there were no significant overall associations between prospectively collected serum alphatocopherol, gamma-tocopherol or selenium and incidence of lung cancer, results from this study suggest that higher alpha-tocopherol levels may be protective in men less than 60 years old and in those who do not drink alcohol	[32]

Goodman et al	2001	USA	Case-control	712	356	45–74	Men	Serum selenium	1.2	0.77	1.88	In the CARET population of current and former smokers consuming an ad libitum diet, the serum concentration of selenium was not a risk factor for either lung cancer or prostate cancer.	[23]
Knekt et al	1998	Finland	Case-control	285	95	Mean 57	M and F	Serum selenium	0.41	0.17	0.94	In accordance with the hypothesis, the findings suggest that very low selenium status may contribute to the risk of lung cancer	[19]
Knekt et al	1990	Finland	Cohort	N/A	153	15–99	Men	Serum selenium	0.66	0.37	1.19	These findings are in agreement with the hypothesis that low selenium intake may increase the risk of some cancers among men	[33]

Garland et al	1995	USA	Case-control	94	47	30–55	Women	Toenail selenium	1.95	0.41	9.28	Toenail selenium levels were not inversely associated with cancer risk in this study. Implications: These data, in conjunction with previous findings of no association between toenail selenium status and breast cancer risk, strongly suggest that higher selenium intake within the range consumed by most U.S. women (as reflected by toenail selenium levels) is not protective against overall cancer incidence in women	[34]
Lippman et al	2009	USA and Canada	Case-control	8696	67	≥ 50	Men	Selenium supplement	1.12	0.73	1.72	Selenium or vitamin E, alone or in combination at the doses and formulations used, did not prevent prostate cancer in this population of relatively healthy men.	[35]

Clark et al	1996	USA	Case-control	659	35	Mean 63	M and F	Selenium supplement	0.56	0.31	1.01	Selenium treatment did not protect against development of basal or squamous cell carcinomas of the skin. However, results from secondary end-point analyses support the hypothesis that supplemental selenium may reduce the incidence of, and mortality from, carcinomas of several sites. These effects of selenium require confirmation in an independent trial of appropriate design before new public health recommendations regarding selenium supplementation can be made	[24]

Van den Brandt et al	1993	Netherlands	Cohort	3345	384	55–69	M and F	Toenail selenium	0.4	0.27	0.59	The results of this study support an inverse association between selenium status and lung cancer and suggest a modification of the effect of selenium by the antioxidants β-carotene and vitamin C	[22]
Gromadzinska et al	2003	Poland	Case-control	362	152	43–78	M and F	Serum selenium	0.33	0.18	0.6	A more precise exposure assessment is required to identify the association between lung cancer incidence and occupational exposure to carcinogens	[6]
Zhou et al	1999	China	Case-control	N/A	290	30–60	Women	Selenium supplement	0.76	0.47	1.15	The apparent effects of these nutrients persisted after adjusting for cigarette smoking; suggesting that they may function as protective factors to reduce the risk for lung cancer in Chinese women	[36]

Kromhout et al	1987	Netherlands	Cohort	N/A	63	30–55	Men	Selenium supplement	0.98	0.41	2.36	Essential antioxidant micronutrients such as beta-carotene and ascorbic acid may modify lung cancer risk, with the latter possibly being more preventive than the former. Intakes of the 3 nutrients were related to lung cancer mortality, but not to mortality from other cancer types	[37]
Hartman et al	2002	Finland	Case-control	500	250	50–69	Men	toenail selenium	0.61	0.27	1.41	Low selenium status may be associated with increased risk for lung cancer	[38]

The effective variable in the heterogeneity of studies was identified by the meta-regression model. Thus the co-variances of the place of study, time of study, type of study, sample size and measurement of selenium were analyzed by meta-regression analysis and by method of Moment base. The results of meta-regression showed that the place of study, the measurement of selenium and the type of study have a significant effect on heterogeneity. After taking into account the effect of co-variances of study time, place, sample size, type of study and the measurement of selenium, the T^2 value was 0.24, 0.04, 0.26, 0.17 and 0.19, respectively (Table 2).

Table-2: Meta-regression analysis of covariances in the studies.

	Adjusted		t^2
Covariances	Coefficient	p-value	
Date	-38	0.12	0.24
Location	-0.12	<0.001	0.04
Number sample	-0.22	0.14	0.26
Measurements of Selenium[1]	-0.37	0.04	0.19
Type of study	0.45	<0.001	0.17

The mean of the ratio of lung cancer risk in the selenium supplement studies was equal to OR = 0.82 (95% CI: 0.47-1.42, P value = 0.5), in studies of selenium in serum it was equal to OR = 0.7 (95% CI: 0.45-1.07, P value = 0.1) and in studies of selenium in toenail it was equal to OR = 0.59 (95% CI: 0.28-1.24, P value = 0.17).

In general, the results of the meta-analysis showed that selenium reduces significantly the risk of lung cancer (OR = 0.71 (95% CI: 0.52-0.97, p value = 0.03 (Fig. 3).In fact selenium reduces significantly the risk of lung cancer by 29%.Heterogeneity of studies was moderate (I^2 = 70.5%, P value <0.001).

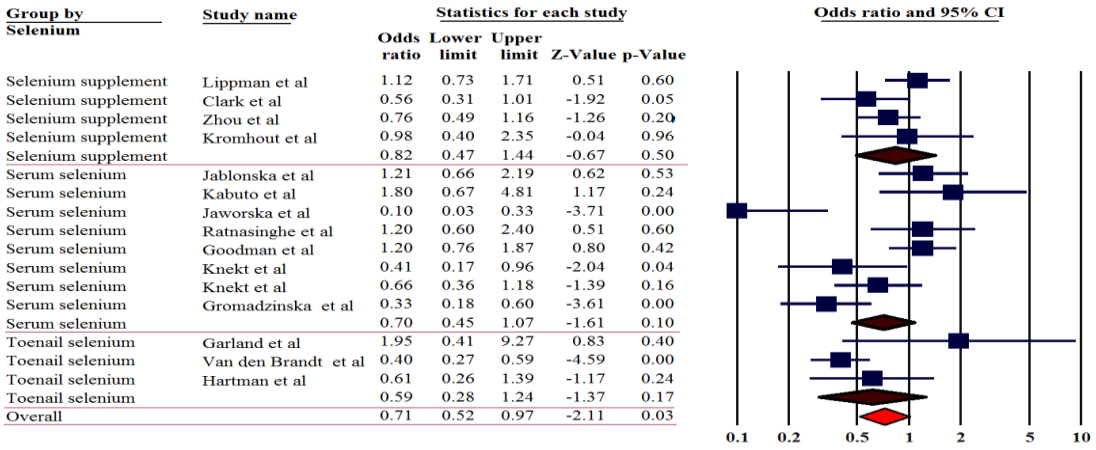

Figure-3: Forest plot of meta-analysis on selenium and prostate cancer in the selenium supplements, serum selenium and toenail selenium subgroups.

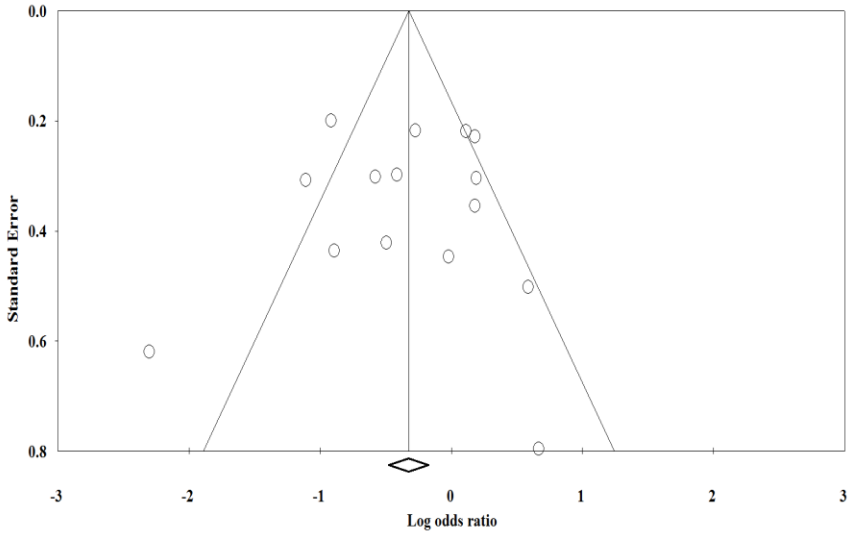

Figure-4: Funnel plot of standard error by log adds ratio.

Reversibility of the funnel diagram showed the absence of publication error (Figure 4). The statistical tests also confirmed this. (Begger's test: z - value =0.24; P value = 0.8; Egger's test: t-value=0.11, P value= 0.9).

4. Discussion

The results of our study showed that while in the random effect model the lowering effect of selenium on the risk of lung cancer was not significant in serum, toenail and supplement separately, but selenium in general reduces significantly 29% of the risk of lung cancer (P value= 0.03).

1.4. Comparison of studies

Nutritional Prevention of Cancer Studies has proven that the selenium supply with alow serum level (<106 ng/mL) reduces the risk of lung cancer [25].Another study showed that a low serum selenium level (~70.4 ng/mL) has some beneficial effects on leukopenia, hematological toxicity and nephrotoxicity [39].Also in the treatment of cancer the selenium reduces the toxicity and side effects associated with radio therapy and cisplatin [39].

In the studies of Jaworska et al [31], Gromadzinska et al[40], Hartman et al [38], Knekt et al [33], van den Brandt et al [22] and Knekt et al [33] the results showed that with an increase of selenium the risk of lung cancer is reduced, but in other studies the similar results were not achieved.

In contrast to our study, the study of Lippman et al showed that the use of a selenium supplement increases the risk of lung cancer by 12% [35]. One criticism on the study of Lippman et al is that in this study only one type of supplement from several selenium supplements has been used. Studies have shown that a selenium supplement contains two organic

forms of L-selenomethionine and selenium-methyl L-selenocysteine and an inorganic form of sodium selenite; they have revealed different mechanisms [43-41].

In the study of Ratnasinghe et al also there was observed a non-significant positive correlation between seleniumserum level and the risk of lung cancer (selenium serum level in the cases was 1% greater than control limit) [32]. Study of Hartman et al showed that the risk of lung cancer in the individuals with low level of serum selenium was higher [38].

The study of Knekt et alshowed that the risk of lung cancer in smokers who have low level of serum selenium is higher [19].

In general, Khuri et al [44]and Goodman et al [23] suggested that selenium plays an important role in lung cancer chemotherapy. Selenium in plasma concentration ng/ml 106 below reduces effectively the incidence of lung cancer. However, the additional studies are necessary for examining the selenium supplements alone and in combination with each other to prevent lung cancer. Anti-cancer effect of selenium on cancer cells is done by the multiple potential mechanisms.

In a system of antioxidants, the selenium exists asselenoproteins such as glutathione peroxidase and thioredoxin reductase; it reduces the risk of cancer through reducing damage to DNA or increasing the vulnerability of DNA [45].But other studies have shown that the difference of the chemotherapy effect depends upon the selenium level. For example, the risk of lung cancer in individuals with lower baseline selenium status was less while in individuals with higher serum level it was higher [46].

Study of Reid et al also showed that the incidence of lung cancer in individuals who used a selenium supplement did not significantly decrease in the total population; but in individuals with low baseline selenium it was decreased significantly [25].

2.4. Limitations of the study

Limitations of this study included the difference of some confounding factorsin studies such as age, income, race, smoking status, body mass index and physical activity.

The time range of studies, the disease level (primary, high and advanced), language of studies (except Persian and English), measurement errors including the difference in equipment and the measurement method were also amongst the limitations of this study.

5. Conclusions

The results of a systematic review and meta-analysis of 15 studies showed that in general by increasing the seleniumin serum, toenail and supplements the risk of prostate cancer is significantly reduced (P VALUE <0.05).The results of this study supported the reduction of the risk of lung cancer with increasing selenium.

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