ASSOCIATION BETWEEN SELENIUM LEVEL AND BLADDER CANCER; SYSTEMATIC REVIEW AND META-ANALYSIS

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Received on 19-07-2016 Accepted on 20-08-2016

Abstract

Bladder cancer is one of the common cancers in men. The different studies have shown different results on the effects of selenium on the risk of bladder cancer. The aim of this study was to determine the association between the selenium in serum, Toenail and supplements on the one hand and the risk of bladder cancer on the other. Doing a systematic review and meta-analysis of 9 studies (4 studies on the selenium level in the toenail, 2 studies in serum and 3 studies in supplements), therefore, it was tried to achieve some exact results of the association between selenium and the bladder cancer risk. The results showed there is no publication error in the observational studies (Begger’s test = -0.71; 95% CI (-4, 2.66). In the subgroups of selenium supplement, serum and Toenail, the heterogeneity was $I^2 = 0\%$ (P value = 0.81), $I^2 = 0\%$ (P value = 0.35) and $I^2 = 1.47\%$ (P value = 0.38) and overall $I^2 = 63\%$ (P value = 0.005), respectively. The risk ratio in the studies of selenium supplements, serum and Toenail was FEM = 1.02 (P value = 0.8), FEM = 0.3 (P value<0.001) and FEM = 0.85 (P value = 0.1) and in general FEM = 0.83 (P value = 0.01) respectively. The increase of selenium in supplements does not any effect on the increase or decrease of the bladder cancer (non-significant). The increase of selenium in serum and toenail reduces (significantly) the risk of bladder cancer in first case and (non-significantly) in second case. In general, the results of this study supported the lowering effect of selenium especially in serum on the risk of bladder cancer.
Keywords: selenium, bladder cancer, serum, toenail, supplements, meta-analysis

1. Introduction

The bladder cancer is one of the common types of cancer worldwide, especially among men. The risk factors for bladder cancer include smoking (65% men and 35% women), occupational exposure, such as absorption of aromatic amines, excessive absorption of arsenic and schistosomiasis infection [2,1].

The bladder cancer is a complex disease; the polymorphisms of genes of little influence are involved in the development of this disease [3]. There are strong evidences based on which NAT 2 slow acetylation and GSTM1 null genotypes increase the risk of bladder cancer [5,4]. Although the mentioned factors are more than half of the causes of bladder cancer [6], but the still unknown factors have remained about which there is not any explanation. One of these unknown factors is the environmental pollutants. The environmental pollutants include heavy metals and trace elements that through influencing the oxidative stress mechanisms can be effective in reducing or increasing the risk of types of cancer including bladder cancer [8,7]. The trace elements such as selenium play an important role in the different intracellular processes. Lack of sustainability of these elements in the cell causes a cell dysfunction and ultimately disease [9]. The forms of non-metallic selenium consist of the selenite and the organic selenium comprises the methylselenic acid and selenomethionine [10]. Selenium has combined with amino acids; hence the name of selenoproteins [12,11]. EPA has proclaimed the reference dose of selenium for preventing the adverse effects of selenium on the health as 0.005 mg/kg-day [13]. Selenium can be both beneficial and harmful to human health. The absorption of selenium to a certain extent has the anti-cancer effects, but the excessive absorption of it causes a chronic toxicity in humans and diseases such as loss of hair and Toenail, gastrointestinal problems, skin rash, garlic breath odor, nervous system abnormalities [14] and Keshan disease and Kashin-Beck disease [15]. Several mechanisms have been proposed to explain the anti-cancer effects of selenium, including: rehabilitation of damaged DNA, induction of phase II enzymes, increase of immunity, inhibition of cell cycle, angiogenesis and the induction of apoptosis [17,16]. However it should be noted that the mechanism of rare elements in inhibition and development of cancers is very complex. Although the anti-cancer effects of selenium have not still been fully known, but the different studies have shown an inverse association of selenium level with gastrointestinal, lung and prostate cancers [20-18]. Therefore, in this study we tried to carefully evaluate the association between selenium level in the toenail, serum and supplements on the one hand and the risk of bladder cancer on the other by doing a systematic review and meta-analysis.

2. Materials and Methods
This study was a systematic review and meta-analysis on the association between the selenium level in supplement, serum and Toenail on the one hand and the risk of bladder cancer on the other. For finding the studies conducted in Iran and the world, the databases SID, Irandoc, Scopus, Pubmed and ISI Web of Science was used.

1.2. The criteria of selection and evaluating quality of studies
At first a list of titles and abstracts of all studies available on the databases mentioned by three researchers (Mi. A, Ya.F, Ha.K,) was procured in order to avoid the bias of researchers. Titles and abstracts of articles, published between 1985 and 2016, were examined independently. The search for 2 weeks from 04/15/2016 to 30/04/2016 was done and then the related studies were entered into the research process independently and by method of blinding the initial evaluation. The similar studies were excluded. The main criterion of inclusion of different articles to this study was a reference to the selenium level and the bladder cancer risk. In the second stage, the abstracts of the selected different studies were investigated by researchers using the check-list STROBE that is a standard check-list. This check-list contains 43 sections and evaluates the different and varied aspects of methodology, including the sampling methods, measurement of variables, statistical analysis and the objectives of study [21].

In this check-list the score of 40 was considered as the least achievable point and the score of 45 as the maximum one. Finally the top articles that had gained the least point (40) given to questions of check-list, were entered to the research and their data for meta-analysis were extracted. For determining the Bias Publication, the funnel plot and Egger’s test were used.

2.2. Data extraction
In this study, 9 articles (8 case-control studies and one cohort study) in all of which the almost same methodology had been used and had been completed in the period 1989 to 2012, were meta-analyzed. The important information needed to analyze the data, including information on the subject, title, method of study, type of study, study time, score of each one in the system of (NOS) [Newcastle-Ottawa scale], the risk ratio of bladder cancer, the number of cases, control and confidence level was collected.

3.2. Data synthesis and analysis
According to qualitative evaluation criterion NOS which includes Selection, Comparability and Exposure, the case-control and cohort studies were scored. In the system NOS the score range is determined from 0 to 9. In this study, the studies were classified into two groups of low score (<7) and high score (≥7).

4.2. Statistical synthesis and analysis of data
The meta-analysis of data was done by software of Comprehensive Meta-Analysis V. 2.2.064. For calculating the heterogeneity of the studies, I^2 Higgins was used. For meta-analysis, in the studies in which I^2 was greater than 50% the random effect model was used and one in which I^2 was less than 50% the fixed effect one was applied. The subgroups in this study included the qualitative score of study (high and low) and type of study. The significance level was P value <0.05.

3. Results

1.3. Identification of the relevant studies

As shown in Figure 1, in general 498 articles were obtained by searching the databases SID, Irandoc, Ovid, Scopus, Embase, ISI web of science and PubMed. Based on titles and abstracts and some other reasons, 352 articles were excluded in the stage Eligibility. From among remaining 146 articles, 137 articles including the reported correlation, hazard risk, mean missing key data for were set aside. Finally, 9 articles remained for meta-analysis. In general, from between these 9 articles 8 case-control studies and one cohort study was obtained (figure 1). 4 studies measured the selenium level in toenails, 2 studies the selenium level in serum and 3 studies that in complement.

2.3. Characteristics of the studies

General characteristics of studies such as year of publication, country, type of study, confrontation cases, cases, the age of the participants, measurement of selenium level and the results have been shown in Table 1. The range of publication years of articles was 1989 to 2012. In 9 articles 94248 participants in general (2410 patients and 91,838 controls) were detected. The average age of study participants was 62.5 year.

| Record identified through database in SID, Irandoc, Ovid, Scopus, Embase, ISI web of science and PubMed studies; (n=498) |
| Excluded on basis of title and abstract (n=311) |
| Excluded for other reason (n=41) |
| Full text article on se and pc extracted (n=146) |
| Studies excluded because they only reported correlation, hazard risk, mean (n=79), Studies excluded because they were missing key data for meta-analysis (n=25), Studies reported on se biomarkers (n=33) |
| Selenium supplement and bladder cancer (n=3) |
| Serum selenium and bladder cancer (n=2) |
| Toenail selenium and bladder cancer (n=4) |

Figure-1. Studies selection process for meta-analysis.

Table1. Characteristics of studies included in the systemic review and meta-analysis.
<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Country</th>
<th>Type of Study</th>
<th>Subj ect</th>
<th>Cas e</th>
<th>Age</th>
<th>Measureme nts of selenium</th>
<th>Odd s rati o</th>
<th>Lo w</th>
<th>Hig h</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hotaling et al</td>
<td>201 1 USA cohort</td>
<td>77050</td>
<td>330</td>
<td>50– 76</td>
<td>Selenium supplement</td>
<td>0.97</td>
<td>0.7 2</td>
<td>1.31</td>
<td>not support the use of commonly taken vitamin or mineral supplements or 6 common anti-inflammatory supplements for the chemoprevention of urothelial cell carcinoma [22]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clark et al</td>
<td>199 6 USA case-control</td>
<td>653</td>
<td>6</td>
<td>mean 63</td>
<td>Selenium supplement</td>
<td>1.27</td>
<td>0.4 4</td>
<td>3.67</td>
<td>support the hypothesis that supplemental selenium may reduce the incidence of, and mortality from, carcinomas of several sites. [23]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallace et al</td>
<td>200 9 Germany case-control</td>
<td>2048</td>
<td>857</td>
<td>25– 74</td>
<td>Toenail selenium</td>
<td>0.9</td>
<td>0.6 8</td>
<td>1.19</td>
<td>selenium is not inversely related to risk of bladder cancer overall; however, they raise the possibility that selenium may be preventive in certain molecular phenotypes of tumors. [24]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kellen et al</td>
<td>200 6 Belgium case-control</td>
<td>540</td>
<td>362</td>
<td>≥ 50</td>
<td>Serum selenium</td>
<td>0.27</td>
<td>0.1 5</td>
<td>0.47</td>
<td>an inverse association between serum selenium concentration and bladder cancer risk [25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeegers et al</td>
<td>200 2 Netherlands case-cohort</td>
<td>2890</td>
<td>431</td>
<td>55– 69</td>
<td>Toenail selenium</td>
<td>0.67</td>
<td>0.4 7</td>
<td>0.97</td>
<td>evidence is in favor of an inverse association [26]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Year</td>
<td>Country</td>
<td>Study Design</td>
<td>Participants</td>
<td>Mean Age</td>
<td>Outcome</td>
<td>Selenium Concentration</td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>p-Value</td>
<td>Reference</td>
</tr>
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<tr>
<td>Michaud et al 2005</td>
<td>USA</td>
<td>Case-control</td>
<td>446</td>
<td>222</td>
<td>Mean 62</td>
<td>Toenail selenium</td>
<td>1.17</td>
<td>0.66</td>
<td>2.07</td>
<td>[27]</td>
<td></td>
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<tr>
<td>Michaud et al 2002</td>
<td>Finland</td>
<td>Case-control</td>
<td>264</td>
<td>132</td>
<td>Mean 50-69</td>
<td>Toenail selenium</td>
<td>0.9</td>
<td>0.45</td>
<td>1.78</td>
<td>[28]</td>
<td></td>
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</tr>
<tr>
<td>Helzlsouer et al 1989</td>
<td>USA</td>
<td>Case-control</td>
<td>95</td>
<td>35</td>
<td>Mean 59</td>
<td>Serum selenium</td>
<td>0.49</td>
<td>0.16</td>
<td>1.49</td>
<td>[29]</td>
<td></td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lotan et al 2012</td>
<td>USA</td>
<td>Case-control</td>
<td>7852</td>
<td>35</td>
<td>≥ 50</td>
<td>Selenium supplement</td>
<td>1.13</td>
<td>0.70</td>
<td>1.84</td>
<td>[30]</td>
<td></td>
</tr>
</tbody>
</table>

Based on the criterion for qualitative evaluation (NOS) Newcastle-Ottawa Case scale, in the case-control and cohort studies all of them were of score higher than 7; therefore they have high quality (Tables 2 and 3).
**Table-2. Methodological Quality of Studies Included in the Final Analysis Based on the Newcastle-Ottawa Scale for Assessing the Quality of Case-Control Studies.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Selection (Score)</th>
<th>Comparability (Score)</th>
<th>Exposure (Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adequate definition of patient cases</td>
<td>Representativeness of patient cases</td>
<td>Selection of controls</td>
</tr>
<tr>
<td>Clark et al</td>
<td>1996</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Wallace et al</td>
<td>2009</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Kellen et al</td>
<td>2006</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Zeegers et al</td>
<td>2002</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Michaud et al</td>
<td>2005</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Michaud et al</td>
<td>2002</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Helzlsouer et al</td>
<td>1989</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lotan et al</td>
<td>2012</td>
<td></td>
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</tr>
</tbody>
</table>

**Table-3. Methodological quality of studies included in the final analysis based on the Newcastle-Ottawa scale for assessing the quality of cohort.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Selection (Score)</th>
<th>Comparability (Score)</th>
<th>Exposure (Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adequate definition of the exposed cohort</td>
<td>Representativeness of the non-exposed cohort</td>
<td>Selection of the non-exposed cohort</td>
</tr>
<tr>
<td>Hotaling et al</td>
<td>2011</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
The heterogeneity in subgroups of selenium supplement, serum and toenail was respectively (P value = 0.81) I^2= 0%, (P value = 0.35) I^2= 0% and (P value = 0.38) I^2= 1.47% and in general ( P value = 0.005) I^2= 63%. Since the heterogeneity in all subgroups was less than 50%, therefore for calculating the mean of risk the fixed effect model was used. The risk ratio in studies of selenium supplement, serum and toenail was respectively FEM = 1.02 (P value = 0.8), FEM = 0.3 (P value<0.001) and FEM = 0.85 (P value = 0.1). in general it was REM = 0.83 (P value = 0.01).

Results showed that an increase of selenium in supplements does not any effect in increase and decrease of the bladder cancer. The risk of bladder cancer has decreased significantly in serum. It has decreased in toenail but non-significantly (Figure 2).

Figure 2. Forest plot of meta-analysis on selenium and bladder cancer in the selenium supplements, serum selenium and toenail selenium subgroups.

The heterogeneity in studies of other countries and the United States was respectively 79%, 0% and in general 63%.

Therefore, for studies conducted in other countries the model of random effect was used and for studies of the United States the fixed effect model. The risk ratio in other countries and the United States was respectively REM = 0.71 (P value = 0.001) and FEM = 1 (P = 0.89) and in general FEM = 0.83 P value = 0.01) (Figure 3). Results of other countries showed that risk of bladder cancer reduces significantly. However, the studies done in the United States showed that selenium has not a significant effect on reducing the risk of bladder cancer. In general, the risk of bladder cancer decreased 18%, significantly.

Figure 3. Forest plot of meta-analysis on selenium and bladder cancer in the Usa and other countries.
4. Discussion

The meta-analysis results of this study showed that an increase of selenium reduces 18% of the risk of bladder cancer. Of course, the lowering effect in the studies of serum, toenail and supplement was different. Although our knowledge of the effect of selenium on bladder cancer is little, many studies have reported its protective effect on the some kinds of cancer [33-31,20,18].

The various studies of clinical trials on the use of selenium supplement had contradictory results. For example, in studies of Nutritional Prevention of Cancer (NPC) and Supplementation Vitamins et Minéraux Antioxidants there was observed a non-significant inverse association between selenium and prostate cancer as well as between selenium and vitamin E on the one hand and the prostate cancer on the other [34,32,20]. NPC also reported that due to insufficient number of incident cases the association between selenium and cancer is unknown [35]. The study of Longnecker et al and Satia et al showed that in high concentration of selenium in toenail (~0.9 μg / g) and serum (~100 μg / L), the selenium in toenail and serum had a significant correlation [37,36].

In addition, the great amount of the glutathione peroxidases and Selenoproteins P activities was observed in the concentration range of 80-95 μg / L of selenium in serum [38]. Selenium may have an anti-cancer nature mainly through selenoproteins, although its special mechanisms are not fully known. In development of colorectal cancer, the glutathione peroxidases and selenoproteins P have an antioxidant nature, especially through scavenging reactive oxy-gen species and diminishing further oxidative damage [39]. The protective nature of selenium is related also to the activities of hydrogen selenide and selenomethionine inside the cell; they can modify the proteins of thiols and mimicking methionine [40].

Due to the effectivity of selenium on apoptosis, DNA repair and carcinogen metabolism, some studies have suggested that adding it to the diet is essential. On the other hand, the oxidative stresses that are caused by exposing to arsenic, cadmium and lead can be prevented or reduced by increasing the level of selenium [40]; because these metals act as selenium antagonist [41].

The overall heterogeneity (I² =63%) of the studies was due to difference in the type of sampling (serum or toenail), smoking, type of study and the selenium level.

In this study the various studies showed different results. The cohort study of Hotaling et al showed that the long-term use of selenium supplement (6 years) does not reduce the risk of bladder cancer [22]. In a case-control study,
Lotan et al. obtained similar results [30]. The study of Michaud et al. showed the increase of level of selenium in toenail reduces the risk of bladder cancer, especially in women [28].

The inversion of funnel plot and the results of Eggers’ test showed that there is not a considerable publication error in the results of this study (Figure 4).

![Funnel plot of standard error by log adds ratio.](image)

Limitations of this study included being incomplete the subgroups, time range of studies, the disease level (primary, high grade and advanced), language of studies (except Persian and English), a difference of some confounding factors such as age, income, race, smoking status, body mass index, physical activity, the lack of studies on selenium supplements. For obtaining the association between age and the risk of bladder cancer, in some studies the exact age was not specified. Finally, the measurement errors, including difference in equipment, measurement method, the staff constitute the other limitations of this study.

5. Conclusions

The results of a systematic review and meta-analysis of nine studies showed that an increase of the selenium concentration in serum reduces significantly the risk of bladder cancer (P-value <0.05). The effect of consuming the selenium supplements as well as the selenium in toenail on the bladder cancer was not significantly lowering. In general, the results of this study supported the lowering effect of selenium on bladder cancer.

6. Acknowledgment

Students research office of Semnan university of medical sciences was supports the financial of this research (Code:7541, Date:2016/04/17).

7. References


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