REVIEW

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Total Calcium (Dietary and Supplementary) Intake and Prostate Cancer: a Systematic Review and Meta-Analysis

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Abstract

Background: Controversial results have been reported concerning the influence of calcium intake on prostate cancer risk. The aim of this study was to determine any association between total calcium (in the diet and in supplements) intake and prostate cancer. **Materials and Methods:** The present systematic review and meta-analysis study was carried out following a PRISMA guidelines. Two reviewers independently using MeSH keywords searched international databases including PubMed, Science Direct, Cochrane, EMBASE, Web of Science, CINAHL, EBSCO and search engines such as Google Scholar. The searches were performed without any time limit until May 2016. The results were pooled using a random effects model and homogeneity was confirmed using the Q test and I^2 index. Subgroup analyses was performed according to continents and study designs. The data were analyzed using STATA software version 3.2, with $p<0.05$ considered significant. **Result:** Overall, 12 studies with a total sample size of 905,046 were entered into the final meta-analysis. The main age range of the participants was 50 to 70 years. The relative risks (RR) for total calcium with total prostate cancer, localized prostate cancer, and advance prostate cancer were estimated to be 1.15 (95% CI: 1.04-3.46), 1.05 (95% CI: 0.96-1.14), and 1.15 (95% CI: 0.89-1.50), respectively. Only the relationship between total calcium and total prostate cancer was significant ($P<0.05$). **Conclusions:** High calcium intake can be considered as a risk factor for total prostate cancer. Therefore, calcium intake might be a target for prevention.

Keywords: Calcium- prostate cancer- systematic review- meta-analysis

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Introduction

Prostate cancer is a disease in which malignant cells originate from the prostate tissues. They regularly and increasingly expand and lead to an increased volume in each of the cellular components of the prostate gland. It is among the most common diagnostic neoplasm in men and the second leading cause of death from cancer following lung cancer. The incidence of this disease significantly increases after 65 years of age. Prostate cancer is the most common malignancy in America, Canada and the sixth known cancer in the world. Its incidence and prevalence rates vary in different parts of the world. In the United States of America,itis the most common cancer in men (Butler et al., 2010; Yavari, 2013-2014). It is also the second leading cause of cancer deaths among men in the United States of America. No comprehensive investigation on prostate cancer epidemiology has been carried out in Iran. In cancer recording projects, some have ranked it fifth and others ranked it's the ninth type of cancer among Iranian males. Sajadiet al. in a study conducted in five provinces Iran reported the annual incidence rate of this disease 5 per 100,000 persons and observed no difference among the aforementioned provinces (Yavari, 2013-2014). There are four types of prostate cancer. Total prostate cancer refers to all types of prostate cancer. Advance prostate cancer means that the cancer has spread outside the prostate capsule. The type of cancer is also known as metastatic cancer and it is often observed in bones and lymph nodes. Localized prostate cancer only affects a part of the prostate. Fatal prostate cancer is the leading cause of death. Some studies have shown that the possible impact of diet is associated with increased risk of prostate cancer (Wiseman, 2008). Based on clinical and laboratory documents, high intake of calcium and dairy products may increase the risk of developing prostate cancer by suppressing the production of 1,25 Dihyroxy Vitamin D3 (the active form of vitamin D3) which is independent from the Vitamin D receptors (Yavari, 2013-2014); (Ahn et al., 2007); (Park et al., 2007). Furthermore, ecological studies have reported a high correlation between calcium intake and prostate cancer risk (Ganmaa et al., 2002; Zhang and Kesteloot, 2005; Grant, 1999). But nother studies were reported not correlation between calcium intake and prostate cancer risk (Butler et al., 2010; Ahn et al., 2007;

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Park et al., 2007). A systematic review and meta-analysis study with the reviewing all documents related to a specific topic can be presented overall estimation and complete picture of the problem (Rahmati et al., 2017; Azami et al., 2017). Regarding the fact that many studies have been carried out on the relationship between total calcium and prostate cancer over the world and a number of studies have shown that calcium increases the risk of prostate cancer; however, the relationship was not significant in other studies and considering the increasing importance of the issue and high mortality rates; a systematic review and meta-analysis can put all documentation together to provide a more accurate picture of the problem in the world. The aim of this study was to determine the relationship between total calcium (diet and supplements) and prostate cancer in the world and to examine its general trend in the world by a systematic approach and meta-analysis.

Materials and Methods

Search Strategy

The current study was conducted based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Moher, Liberati, Tetzlaff, Altman, and Group, 2010).Two reviewers independently using keywords ("Calcium"[MeSH] and "Prostatic Neoplasms"[MeSH]) searched international online databases including PubMed, Science Direct, Cochrane, EMBASE, Web of Science, CINAHL, EBSCO and search engine such as Google Scholar search engine. The searches were performed without any time limit until May 2016. Moreover, the articles'' references were also examined for further studies.

Study Selection

First, all related articles (the relationship between total calcium and prostate cancer) were collected a, a list of titles and abstracts of research studies were prepared by the researchers in databanks and duplicate studies were removed.

After blinding the article's specifications (including the name of the journal and the name of the authors) by the researcher (Shoboo Rahmati), the full text of the articles was presented to the researchers (Milad Azami and Mohammad Reza HafeziAhmadi). If the article was rejected, the reason for this was noted. In the event of a dispute between the two authors, this paper was evaluated by a team of researchers.

Quality assessment

Two researchers independently examined the selected articles using an adapted version of Newcastle Ottawa Scale (NOS) for Cohort Studies and also NOS for case-control studies (Wells et al., 2010), which is a standard and an international checklist for the quality assessment of the studies. The articles that received threshold score of qualitative evaluation were enrolled in the meta-analysis process.

Inclusion and exclusion criteria

Inclusion criteria in the present study, including: Studies in which the relationship between total calcium (diet and supplements) and prostate cancer was identified, Availability of full text articles, Observational epidemiological studies and Articles was published and indexed in English abstract. Exclusion criteria include studies: prostate cancer not event as outcome and Low quality studies.

Data Extraction

To reduce the bias and errors in data collection, data extraction was independently done by two researchers using data extraction form (name, author, year of publication, country, continent, number of participants, number of follow-up years, sex, age, exposure assessment, type of exposure, dose, Relative risks (RR) or odds ratio (OR), CI (confidence interval) and matched variables). If you need to have specific questions or ambiguous articles, the author via e-mail questions need to be asked. For further information and in the case of having questions, contact the corresponding author. Information extracted by two researchers was compared and the differences were discussed. These differences were also shared by a third person and finally a consensus was reached by re-examining and comparing the obtained results.

Outcomes of Interest

The outcome of interest included prostate cancer, total prostate cancer, localized prostate cancer, advance prostate cancer, and fatal prostate cancer.

Statistical Analysis

Prostate cancer was categorized in to total prostate cancer, localized prostate cancer, advance prostate cancer, and fatal prostate cancer and their relationship with total calcium was analyzed. However, the relationship between total calcium with fatal prostate cancer was not analyzed because there were only three studies assessing this relationship. In order to analyze the subgroups, follow-up years were divided into two groups: less than 10 years and more than 10 years. The dose was divided into two groups: less than 750 mg/day and more than 750 mg/day. Furthermore, to evaluate the effect of total calcium in relation with different types of prostate cancer, the relative risk index and to evaluate the heterogeneities, the (I^2) index and Q statistic were used. I^2 index is an index that shows heterogeneities among studies, I^2 less than 25% show low heterogeneities, $\%25 < I^2 < 75\%$ moderate heterogeneity, and $I^2 > 75\%$ high heterogeneity. When Q statistics was significance we used random effect models. For the heterogeneity of studies, the random effect model was used to combine the study's results. In every study, RR or OR extracted the lower and higher limit. In studies that this index was not extracted, it was calculated through OR=ad/bc (Articles that had not the OR to use the formula) and the logarithm of OR or RR was used to polarize the effect size. Error standard was calculated by SE= 1n (upper 95% CI / lower 95% CI) / (2× 1.96). If only upper and lower limit had been reported in studies, OR= ad/bc was used. Meta-regression was used for evaluating the relation between year of study and effect size and evaluating the cause of heterogeneity of studies. Begg's

funnel plot was used to investigate publication bias and sensitivity analysis was performed to evaluate the effect of each study on the overall results. STATA software version 3.2 was used to analyze in this study and P<0.05 has been considered significance level for all analyzes.

Results

Literature Search result and characteristics of studies

A total of 165 articles were identified from the database search by two authors and 11 studies were excluded due to duplication. After screening the titles and abstracts, 120 studies were excluded because of their irrelevance to the topic. Finally, 12 studies (including 11 cohort studies and 1 case control study) with appropriate quality entered the meta-analysis (Figure 1).

The average age of majority was between 50 -70 years and also about 83%of articles had been performed in the USA (Table 1).

The relationship between calcium intake and total prostate cancer

The heterogeneity in the study was high (I^2= 59.7%, P= 0.006). In eleven studies, the combined studies using random-effects model the relationship between calcium intake and total prostate cancer showed that calcium intake increases the prostate cancer risk with a RR of 1.15 (95% CI: 1.04- 1.27) (Figure 2-A).

This relationship in cohort and case control studies was significant with RR of 1.11 (95% CI: 1.02-1.20) and OR of 2.20 (95% CI: 1.40-3.46), respectively (Figure 2-A).

Sensitivity analysis

Sensitivity analysis was performed on the impact of each study in overall results. Sensitivity analysis by removing one study at the same time was indicated that the overall RR was robust (Figure 2-B).

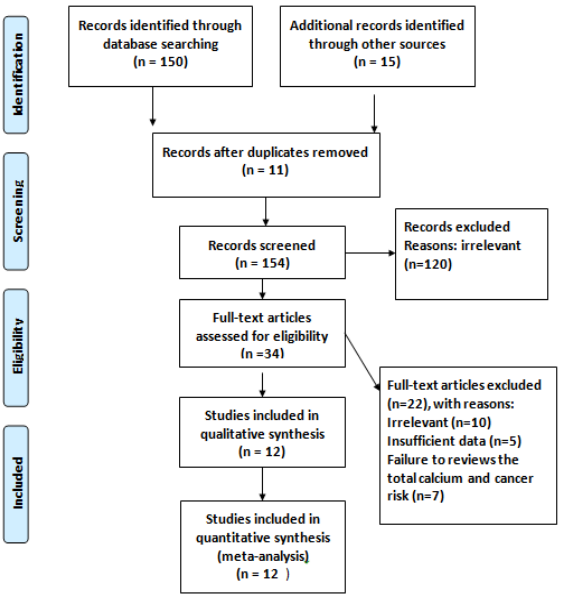


Figure 1. Entry Procedures of Studies to Meta-analysis

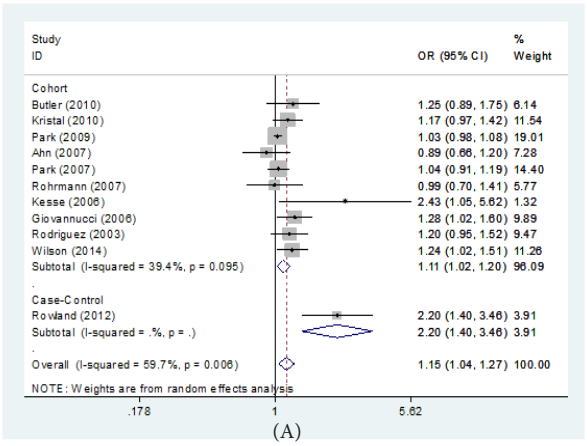


Figure 2. Forest Plot of Meta-analysis (A) and Sensitivity Analysis (B) for Relationship between Calcium Intake and Total Prostate Cancer

Subgroups analysis for relationship between calcium intake and total prostate cancer

Based on the continent

Nine, one, one study was conducted on the continents of America, Asia and Europe, respectively. RR with 95% CI for relationship between calcium intake and total prostate cancer in American, Asian and European studies was 1.13 (95% CI: 1.03-1.25), 1.25 (95% CI: 0.89-1.75), and 2.43 (95% CI: 1.05-5.62), respectively (Figure 3-A).

Based on follow-up years

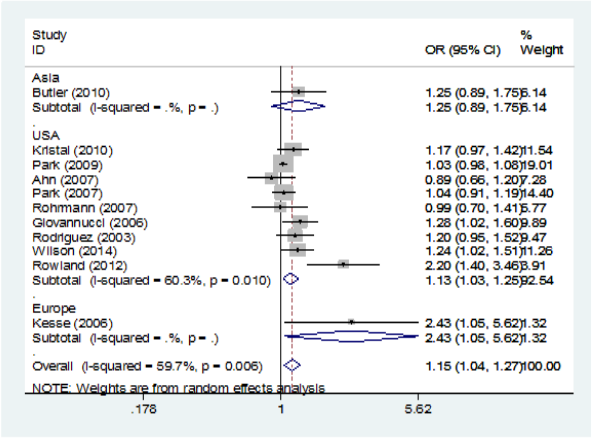
In studies with follow-up less and more than 10 years, the relationship between calcium intake and total prostate cancer was significant with the RR of 1.07 (95% CI: 0.98-1.17) and 1.22 (95% CI: 1.07-1.38), respectively (Figure 3-B).

Based on the dose of consumable

In nine studies with doses <750 Mg / day, the relationship between calcium intake and total prostate cancer was significant with the RR of 1.09 (95% CI: 1.01-1.18) and also in two studies with a dose > 750 Mg / day, this relationship was not significant with the RR of 1.59 (95 % CI: 0.91-2.78) (Figure 3-C).

Based on sample size and year of publication

According to the Table 2, there is no significant relationship between year of publication and the effect size logarithm and their regression equation is as follows:



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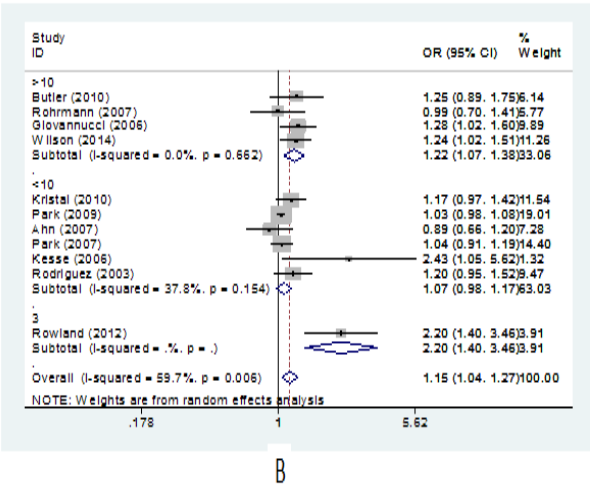

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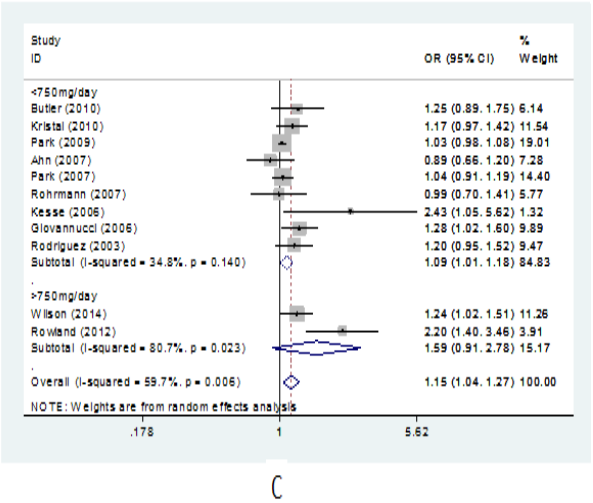


C

Figure 3. Forest Plot of the Subgroup Analysis Based on Continent (A), the Continent (B), Dose of Consumable (C) for Relationship between Calcium Intake and Total Prostate Cancer

y=-35.32+0.01x (p=.04 for the line slop). There is also no significant relationship between sample size and the effect size logarithm and their regression equation is as follows: y = 0.22-7.64x (p=.03 for the line slop) (Table 2).

The relationship between total calcium and localized prostate cancer

In eight cohort studies, the relationship between total calcium and localized prostate cancer was not significant with the RR of 1.05 (95% CI: 0.96-1.14) (Figure 4).

Subgroups analysis for relationship between total calcium and localized prostate cancer

Based on the continent

Seven and one study was conducted on the continents of America and Asia respectively. RR with 95% CI for relationship between total calcium and localized prostate cancer in Asian and American studies was estimated to be 1.43 (95% CI: 0.81-2.52) and 1.04 (95% CI: 0.95-1.13), respectively (Figure 5-A).

Based on follow-up years

In studies with follow-up less and more than 10 years, the relationship between calcium intake and Localized prostate cancer was not significant with RR of 1.04 (95% CI: 0.90-1.21) and 1.13 (95% CI: 0.96-1.34), respectively (Figure 5-B).

Based on the dose of consumable

In seven studies with doses <750 Mg / day, the relationship between calcium intake and localized prostate cancer was not significant with the RR of 1.06 (95% CI: 0.96-1.17) and also in one studies with a dose > 750 Mg / day, this relationship was not significant with RR of 1.07 (95% CI: 0.82-1.39) (Figure 5-C).

Publication Bias

The Beggs Funnel Plot was used to study the publication bias. Begg's test was showed the effect of publication bias was significant for relationship between calcium intake and total prostate cancer (P = 0.02) and the relationship between total calcium and localized prostate cancer (P = 0.03) (Figure 6).

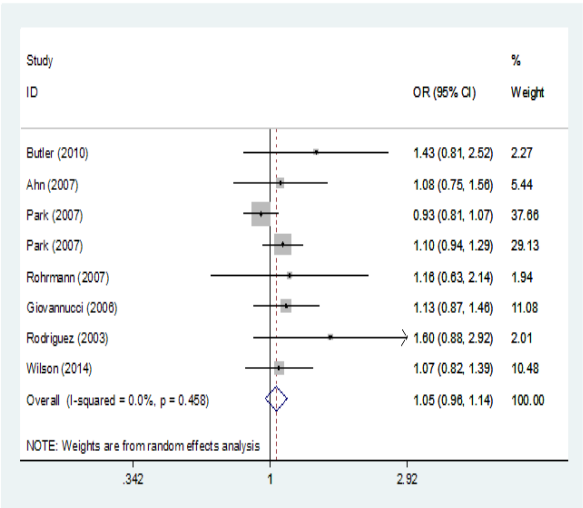
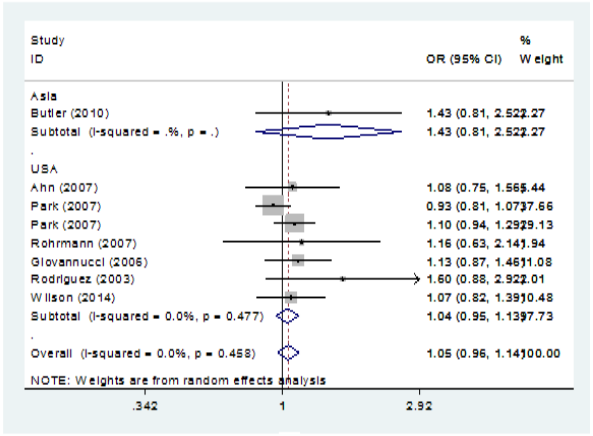


Figure 4. Forest Plot of the Relationship between Total Calcium and Localized Prostate Cancer

Table1. Characteristics of Studies Entered to Meta-Snalysis

author -publication year-reference	continent	Design	(years)	Sample size	Age	Dietary assessment	PC stage or grade	Exposure	Quantity	RR (95% CI)	Adjustment for confounders
(Butler et al., 2010)	Asia	Cohort	11	27293	45-75	FFQ	-Total pc -Localized pc -Advance pc	Total calcium	659 vs, 211mg/day	1.25 (0.89-1.74) -1.43 (0.81-2.52) -1.18 (0.75-1.87)	Age, dialect group, interview year, education, weekly supplement use
(Ahn et al., 2007)	USA	Cohort	8.9	29509	55-74	FFQ	-Total pc -Localized pc -Advance pc	Total calcium	>2001vs, <750mg/day	-0.89 0.66-1.19) -1.08 (0.75-1.56) -0.61 (0.37-1.02)	Age, race, study center, FH–PC, BMI, smoking status, physical activity, diabetes history, red meat, total energy, education, no. of screening examinations during followup
(S.-Y. Park et al., 2007)	USA	Cohort	6	293888	50-71	Validated FFQ	Localized pc -Advance pc -Fatal pc	Total calcium	>2000vs, <250mg/day	-0.93 (0.81-1.07) -1.20 (0.86-1.67) -1.05 (0.54-2.05)	Age, race/ ethnicity, education, marital status, BMI, vigorous physical activity, smoking, alcohol consumption, diabetes history, FH–PC, PSA screening, tomatoes, red meat, fish, vitamin E, ALA, total Energy….
(Giovannucci, Liu, Platz, Stampfer, and Willett, 2007)	USA	Cohort	16	47750	45-70	Validated FFQ, 131 food items	-Total pc -Localized pc -Advance pc Fatal pc	Total calcium	>2000vs, 500-749mg.day	-1.28 (1.02-1.60) -1.13 (0.88-1.47) -2.02 (1.28-3.19) -2.02 (1.14-3.58)	Age, time period, BMI at age 21 y, vigorous physical activity, height, cigarette packyears in the previous 10 y, FH–PC, diabetes, total calories, red meat, fish, ALA, zinc supplements, tomato sauce
(Rohrmann et al., 2007)	USA	Cohort	13	3892	>35	FFQ, 110 items	-Total pc -Localized pc -advance pc	Total calcium	>957vs, <685 mg/day	0.99 (0.70-1.41) -1.16 (0.63-2.15) -1.06 (0.55-2.04)	Age, energy intake, tomato products, BMI at age 21 y, SFA
(Rodriguez et al., 2003)	USA	Cohort	7	65321	50-74	Validated FFQ, 68 food items	Total pc Advance pc	Total calcium	>2000vs, <700 mg.day	1.2 (1-1.6) 1.6 (0.9-3)	Age at entry, race, FH–PC, total energy, total fat intake, education, phosphorus, total vitamin D
(Wilson, Shui, Mucci, and Giovannucci, 2014)	USA	Cohort	16	47885	49-75	FFQs with more than 130 food items	Total pc -Localized pc -Advance pc -Lether pc	Total calcium	>2000 mg.day	1.24 (1.02-1.51) -1.07 (0.82-1.39) -1.49 (1.01-2.20) -1.66 (1.09-2.53)	Age-BMI-race-smoking-diabetes-family history
(Rowland, Schwartz, John, and Ingles, 2012)	USA	Case-control	-	783	-		Total pc	Total calcium	>1059 mg.day	2.20 (1.40-3.46)	-
(Kesse et al., 2006)	Europe	cohort	7.7	2776	45-60	5 3 24-h dietary Record	-total pc	Total calcium	>1081vs, <725 mg.day	-2.43 (1.05-5.62)	Age, energy intake, tomato products, BMI at age 21 y, SFA
(Y. Park et al., 2007)	USA	cohort	8	82483	45-75	Validated FFQ, $180 food items	-Total pc -Localized pc -Advance pc	Total calcium	>1301vs, <470 mg.day	1.04 (0/91-1.20) -1.10 (0.94-1.29) -0.91 (0.65-1.28)	Age, time since cohort entry, ethnicity, FH– PC, education, BMI, smoking status, energy intake
(Qin, He, and Xu, 2009)	USA	cohort	8	293907	50-71	Validated FFQ	Total pc	Total calcium	1530vs,526mg/day	1.03 (0.98-1.08)	Age, raceethnicity, education, marital status, BMI, FH–cancer, diabetes, physical activity, ALA, alcohol, red meat, total energy, smoking, PSA test, tomatoes, selenium
(Kristal et al., 2010)	USA	Cohort	7	9559	>55	FFQ	Total pc	Total calcium	>1357vs,<689mg/day	1.17 (0.97-1.42	Age, raceethnicity, treatment arm, BMI, energy intake



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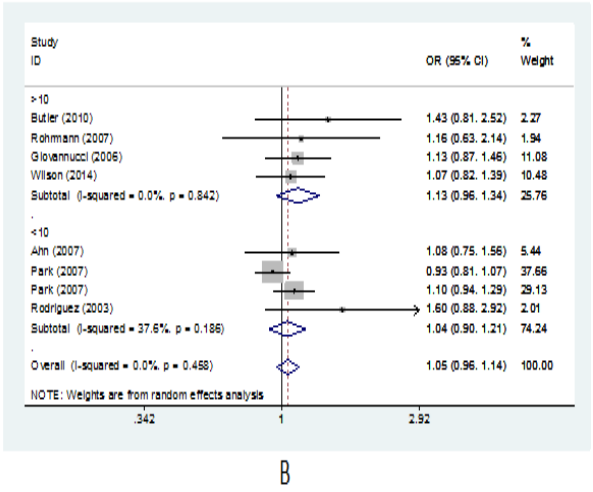

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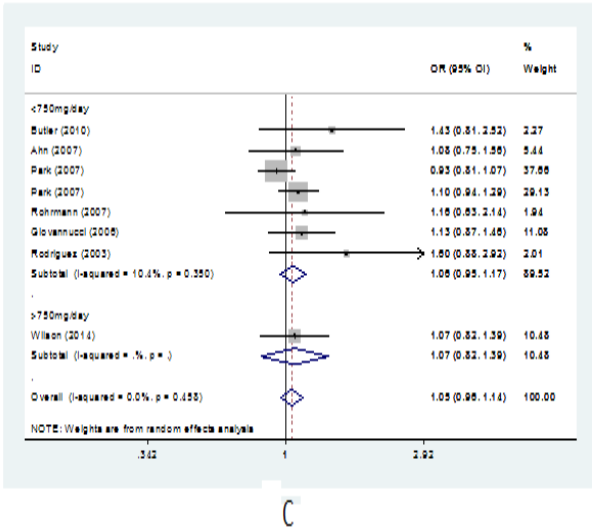

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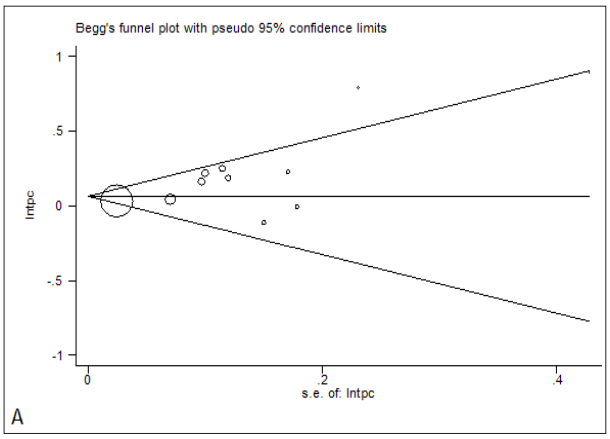
Figure 5. Forest Plot of Subgroup Analysis Based on the Continent (A), the Continent (B), Dose of Consumable (C) for Relationship between Total Calcium and Localized Prostate Cancer



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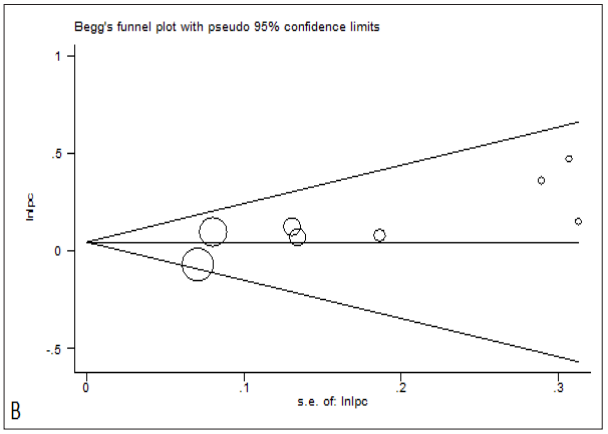

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Figure 6. Forest Plot of Publication Bias for Relationship between Calcium Intake and Total Prostate Cancer (A) and Relationship between Total Calcium and Localized Prostate Cancer (B)

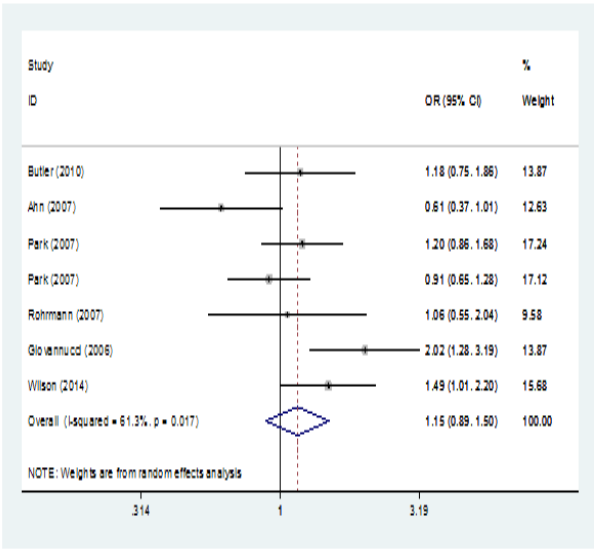

Figure 7. Forest Plot of the Relationship between Total Calcium and Advance Prostate Cancer

Table 2. The Relationship between Calcium Intake and Total Prostate Cancer by Sample Size and Year of Publication

	Coefficient	Standard error	p
Year of publication Cons	0.01	0.02	0.4
	-35.32	48.38	0.4
Sample size Cons	-7.64	7.44	0.3
	0.22	0.08	0.3

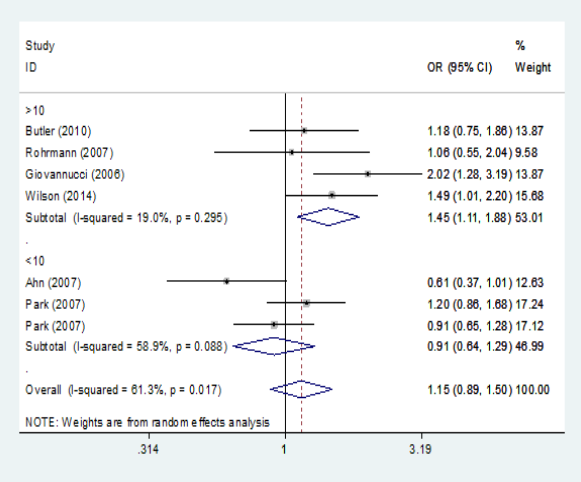

Figure 8. Forest Plot of Subgroup Analysis Based on the Continent Follow-up Years for Relationship between Total Calcium and Advance Prostate Cancer

The relationship between Total calcium and Advance prostate cancer

In seven cohort studies, the relationship between total calcium and advance prostate cancer was not significant with the RR of 1.15 (95% CI: 0.89-1.50) (Figure 7).

Subgroups analysis for relationship between total calcium and advance prostate cancer

Based on follow-up years

In studies with follow-up less than 10 the relationship between calcium intake and Advance prostate cancer was not significant with RR of 0.91 (95% CI: 0.64-1.29). In studies with follow-up more than 10 years, the relationship between calcium intake and Advance prostate cancer was significant with RR of 1.45 95% CI: 1.11-1.88) (Figure 8).

Discussion

The results of the meta-analysis study strongly showed that total calcium intake increases total prostate cancer. The analyses of sub-groups also showed that this relationship mostly is observed in the continent USA. This relationship (total calcium and prostate cancer overall) can be mostly seen in the developed countries. Of course PSA testing is of great importance in the developed countries and most studies conducted in this continent. Therefore results of the present meta-analysis study consistent to study conducted by Anue et al., (2012). Giovannucci's et al., (2007) study showed that total calcium intake increases prostate cancer risk (Ma et al., 2001).

Different studies showed that total calcium intake is mostly associated with total prostate cancer risk. In fact publication bias or small study effects can be a problem in meta-analysis of published articles and their estimation may be exaggerated. Moreover, limitations of this study include non-equal reporting of articles, publication biases, and non-publication of those articles which did not obtain a causal relationship. The assessment errors in assessing the amount of calcium were another limitation and mistake of this study. Calcium intake may be associated with other risk factors such as physical activity, smoking, alcohol consumption, meat and tomato consumption, or prostate-specific antigen (PSA) test (21, 22, 53, and 61). These risk factors act as confounding factors and the results vary in several sub-groups according to adjustment of these confounding variables.

In conclusion, results showed that total calcium intake increases the risk of total prostate cancer; however, there is a positive correlation between localized prostate cancer and advance prostate cancer, and the total calcium intake. According to the results based on the effect of calcium intake on increasing the risk of total prostate cancer, it is recommended that calcium supplements are prescribed in some cases considering their possible benefits and harms. Since no study has been conducted on the relationship between calcium intake and prostate cancer in Iran, further prospective epidemiologic studies are recommended.

Conflict of interest

The authors declare that they have no competing interests.

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