https://nephropathol.com DOI: 10.34172/jnp.2024.21539 J Nephropathol. 2024;13(2):e21539

Journal of Nephropathology

Association between calcium intake and prostate neoplasm; a systematic review and meta-analysis

Shahin Asgari Savadjani[1], Farshad Yadollahi[2], Ahmadreza Maghsoudi[3*]

[1]Department of Internal Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran
[2]Department of Internal Medicine, School of Medicine, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran
[3]Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

ARTICLE INFO

Article type:
Meta-analysis

Article history:
Received: 24 Dec. 2023
Accepted: 4 Mar. 2024
Published online: 9 Mar. 2024

Keywords:
Prostatic neoplasms
Prostate cancer
Prostate neoplasm
Calcium
Factor IV

ABSTRACT

Introduction: Prostate cancer is the second leading cause of cancer death, and the present systematic review and meta-analysis aimed to investigate the effect of calcium use on the risk of prostate cancer.
Materials and Methods: The current systematic review and meta-analysis used the PRISMA checklist. The search was conducted using databases, including Web of Science, Cochrane, ProQuest, PubMed, and Google Scholar Search Engine, without a time limit until November 22, 2023. The obtained data was analyzed using STATA 14 software.
Results: The results obtained from combining 28 observational studies and clinical trials indicated that calcium increased the risk of prostate cancer (OR: 1.10, 95% CI: 1.06, 1.13). On the other hand, cohort (OR: 1.08, 95% CI: 1.06, 1.13), cross-control (OR: 1.04, 95% CI: 0.96, 1.14), cross-sectional (OR: 1.06, 95% CI: 0.86, 1.29), and randomized controlled trial (OR: 1.21, 95% CI: 1.06, 1.39) studies indicated a relationship between calcium use and risk of prostate malignancy. Furthermore, calcium increased the risk of prostate cancer in the age group 50 to 59 years (OR: 1.16, 95% CI: 1.09, 1.24), however no considerable association was noticed between calcium administration and prostate cancer in the age group 60 to 69 years (OR: 1.03, 95% CI: 0.94, 1.13). The risk of prostate cancer in individuals who used less than 1300 mg calcium per day, those who used 1300 – 2000 mg/d, and those who taken more than 2000 mg calcium per day were (OR: 1.04, 95% CI: 1, 1.09), (OR: 1.17, 95% CI: 1.09, 1.26), and (OR: 1.29, 95% CI: 1.13, 1.48), respectively.
Conclusion: Generally, calcium administration increases the risk of prostate cancer in men by 10%, and the risk is enhanced with the increase in dosage of calcium.
Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID=CRD42023489091) and Research Registry (UIN: reviewregistry1787) website.

Implication for health policy/practice/research/medical education:
Our meta-analysis revealed that calcium intake through diet increased the risk of prostate carcinoma in men by 10%, and higher doses of calcium increased the risk of prostate neoplasm. The risk of prostate cancer in individuals who used less than 1300 mg calcium per day, those who used 1300–2000 mg/d, and those who used more than 2000 mg calcium per day were 4%, 17%, and 29%, respectively..

Please cite this paper as: Asgari Savadjani S, Yadollahi F, Maghsoudi A. Association between calcium intake and prostate neoplasm; a systematic review and meta-analysis. J Nephropathol. 2024;13(2):e21539. DOI: 10.34172/jnp.2024.21539.

Introduction

Prostate tumor is the second leading cause of tumor death among men (1), and in 2020, 1.4 million cases of prostate tumors and 375 000 deaths due to prostate tumors were reported globally (2). Various reasons play roles in the occurrence of prostate tumors. According to a study, higher age, family history, and taller heights are associated with an increased risk of prostate tumors (3). Among the environmental factors, diet plays a significant role in the etiology of chronic diseases, including prostate tumors (4). High intakes of dairy products and calcium are related to the increase of the risk of prostate tumors (4). The calcium and vitamin D of dairy products play critical roles in the pathogenesis of prostate tumors. It is assumed that high calcium consumption, along with the reduction in the concentration of vitamin D in blood circulation, increases

*Corresponding author: Ahmadreza Maghsoudi,
Email: dr_maghsoudi_md@yahoo.com, ahmaghsoudi@med.mui.ac.ir

Meta-analysis

the risk of prostate tumors (5).

A previous meta-analysis by Aune et al showed that high calcium intake through diet is a risk factor for prostate tumor occurrence compared with low calcium levels (6). On the other hand, various studies published on this subject reported inconsistent results. Some of the studies indicated that calcium use increased the risk of prostate tumors (7,8). On the contrary, several studies reported that daily calcium intake did not affect the occurrence of prostate tumors among men (9,10). Accordingly, in this systematic review and meta-analysis, we decided to explore the association between calcium consumption and the risk of prostate tumors and present a general and new conclusion.

Materials and Methods

The present study was designed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist(11), and its protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) website.

Search strategy

The search was conducted without a time limit until November 22, 2023, in databases Web of Science, Cochrane, ProQuest, PubMed, and Google Scholar Search Engine. Medical Subject Headings (Mesh) keywords "Plastic Neoplasms, Prostate Cancers, Prostate Neoplasm, Calcium, Factor IV" and their equivalents were used to search the sources. The keywords were combined using 'AND' and 'OR' operators to conduct advanced searches. In a manual search, however, a list of eligible sources was investigated. The search strategy on the Cochrane website included: Prostatic Neoplasms OR Prostate Cancers OR Prostate Neoplasm in Title Abstract Keyword AND Calcium OR Factor IV in Title Abstract Keyword.

PICO component

- Population: studies investigating the relationship between calcium intake and risk of prostate tumor.
- Intervention: calcium consumption.
- Comparison: placebo or those who didn't consume calcium.
- Outcomes: The relationship between calcium intake and risk of prostate tumor.

Inclusion criteria

Observational studies and randomized controlled trials that investigated the relationship between calcium intake and the risk of prostate tumor entered the present study.

Exclusion criteria

Duplicate studies, animal studies, posters, reviews, studies that reported qualitative results, low-quality studies, and studies published as abstracts, and also studies that lacked the required data for analysis were removed from our review list.

Quality assessment

The Cochrane Institute checklist was used to assess the quality of randomized controlled trial studies (12). The checklist comprises seven questions, each question with three options to answer: high bias risk, low bias risk, and known. Eventually, studies with four out of seven answers indicating low bias risk were considered high-quality. Newcastle-Ottawa Scale (NOS) was conducted to evaluate the observational studies (13). NOS included three views: participant selection, comparability, and outcome evaluation. In this step, studies that obtained at least six stars entered our study (as high-quality studies). In the end, two researchers assessed the disagreements regarding the answers to questions and reached the same answer after consultation.

Data extraction

Two researchers independently extracted the data. Additionally, the designed checklist for data extraction included the author's name, study design, sample size, age of the individuals in the calcium consumer group and comparison group, the amount of consumed calcium, study duration, time and location of the study, the odds ratio between calcium intake and risk of prostate neoplasm, and its 95% confidence interval (CI). The third researcher reviewed the data extracted by the previous researchers and addressed the cases of inconsistencies.

Statistical analysis

The log odds ratio (OR) of the studies was conducted to combine the studies, and the I^2 index was used to evaluate the heterogeneity. The three subcategories of the I^2 index included heterogeneity lower than 25% (low), heterogeneity between 25 and 75% (moderate), and heterogeneity higher than 75% (high), and fixed effects and random effects models were employed for low and high heterogeneities, respectively. The inter-study heterogeneity of this meta-analysis was moderate (I^2 = 54.4%). The publication bias plot was used to review the publication bias when searching the sources. Data analysis was conducted using STATA 14 software, and p-values lower than 0.05 were considered statistically significant ($P < 0.05$).

Results

Study selection

After searching for sources in the mentioned databases, 972 studies were found. Reviewing the title of the studies

indicated 425 duplicate studies, which were removed. Then, abstracts of the studies were reviewed, and 71 studies published as abstracts and without full-texts were excluded. In the next step, 69 studies were removed for lacking the required data for analysis. Eventually, 379 other studies were removed due to other exclusion criteria, and 28 high-quality studies remained (Figure 1).

Among the 28 studies eligible for entering the present meta-analysis, 12 were cohort, 10 were case-control, one was cross-sectional, and five were randomized controlled trial studies. Some studies reported the relationship between calcium intake and prostate neoplasm by the dosage of consumed calcium. Table 1 presents a part of the extracted data from these studies.

Figure 2 shows that calcium intake is a risk factor for prostate carcinoma and increases the risk of prostate neoplasm in men by up to 10% (OR: 1.10, 95% CI: 1.06, 1.1).

Table 2 shows the relationship between calcium intake and risk of prostate neoplasm in the cohort (OR: 1.08, 95% CI: 1.06, 1.13), case-control (OR: 1.04, 95% CI: 0.96, 1.14), cross-sectional (OR: 1.06, 95% CI: 0.86, 1.29), and randomized controlled trial (OR: 1.21, 95% CI: 1.06, 1.39) studies. In cohort and randomized controlled trial studies, daily calcium consumption increased the risk of prostate neoplasm in men by 8% and 21%, respectively. Nevertheless, the relationship between calcium intake and the risk of prostate carcinoma in case-control and cross-sectional studies was statistically insignificant.

Calcium intake increased the risk of prostate neoplasm in the age group 50 to 59 years (OR: 1.16, 95% CI: 1.09, 1.24) by 16%; however, there was no statistically significant relationship between calcium consumption and prostate carcinoma in the age group 60 to 69 years (OR: 1.03, 95% CI: 0.94, 1.13) (Table 2).

Different studies used different measurements for the presentation of daily calcium intake dosage. First, all units were converted into mg per liter. Then, after categorizing the studies into three groups, we concluded that men with daily calcium consumption higher than 1300 mg (OR: 1.04, 95% CI: 1, 1.09), between 1300 and 2000 (OR: 1.17, 95% CI: 1.09, 1.26), and higher than 2000 mg (OR: 1.29, 95% CI: 1.13, 1.48) faced 4%, 17%, and 29% increased risk of prostate carcinoma, respectively.

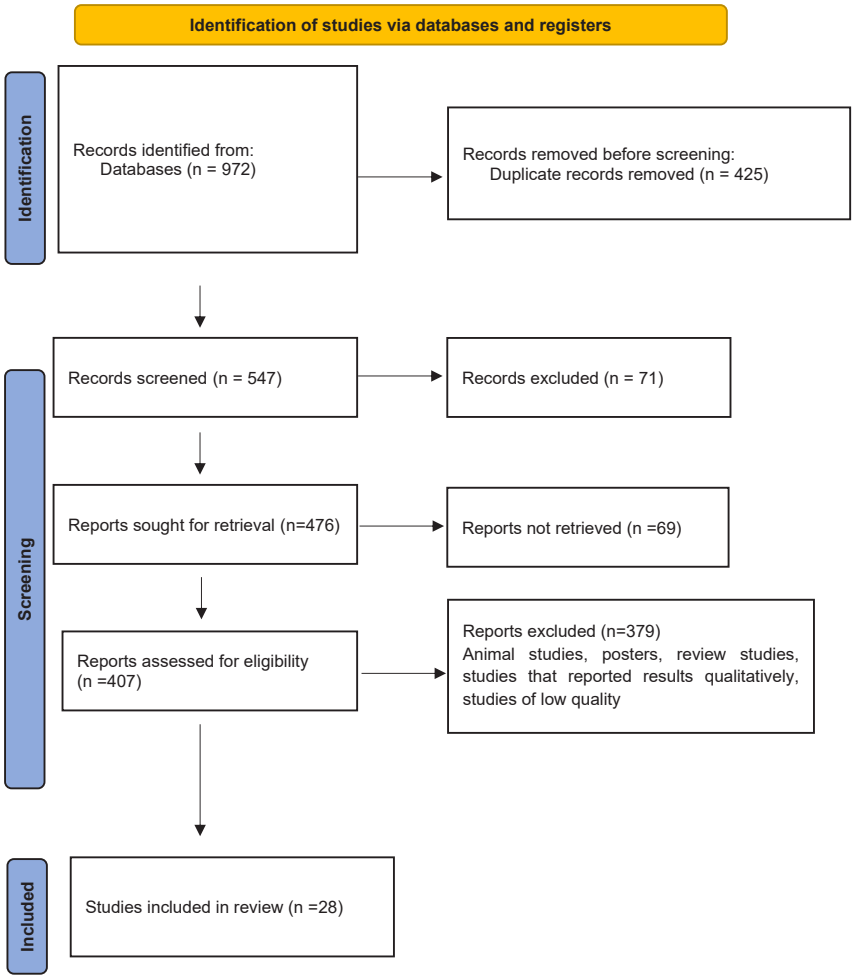

Figure 1. The flow chart of study selection (PRISMA).

Table 1. Data extracted from reviewed studies

Author, year of publication	Location	Type of study	Sample size in the calcium consuming group	Mean age in the calcium consuming group (year)	Sample size in the compare group	Sample size in the compare group (year)	Duration of study	Dosage
Watling CZ, 2023 (8)	UK	Cohort	NR	NR	NR	NR	from 2006 to 2010	1359 mg/d
Orlich MJ, 2022 (7)	USA & Canada	Cohort	NR	NR	NR	NR	2010-2014	2020 mg/d
Lan T, 2020 (14)	USA	Cohort	3548	NR	NR	NR	1996–2011	318–386 mg/1000 kcal
Lan T, 2020 (14)	USA	Cohort	3599	NR	NR	NR	1996–2011	386-487 mg/1000 kcal
Lan T, 2020 (14)	USA	Cohort	3478	NR	NR	NR	1996–2011	487-627 mg/1000 kcal
Lan T, 2020 (14)	USA	Cohort	3770	NR	NR	NR	1996–2011	>627 mg/1000 kcal
Batai K, 2017(9)	USA	Cross-sectional	165	63.8	249	58.9	2000-2014	368.8–616.0 mg/d
Batai K, 2017 (9)	USA	Cross-sectional	171	63.8	234	58.9	2000-2014	616.1–1033.3 mg/d
Batai K, 2017 (9)	USA	Cross-sectional	179	63.8	235	58.9	2000-2014	>1033.3 mg/d
Lane JA, 2017 (10)	UK	Case-control	337	63	712	62.7	NR	659 mg/d
Lane JA, 2017 (10)	UK	Case-control	328	63	721	62.7	NR	798 mg/d
Lane JA, 2017 (10)	UK	Case-control	366	63	683	62.7	NR	928 mg/d
Lane JA, 2017 (10)	UK	Case-control	324	63	725	62.7	NR	1112 mg/d
Wilson KM, 2015 (15)	USA	Cohort	119	56.3	NR	NR	1986 to 2010	>2000 mg/d
Wilson KM, 2015 (15)	USA	Cohort	365	56.3	NR	NR	1986 to 2010	1500 to <2000 mg/d
Wilson KM, 2015 (15)	USA	Cohort	551	56.3	NR	NR	1986 to 2010	1250 to <1500 mg/d
Wilson KM, 2015 (15)	USA	Cohort	1079	54.7	NR	NR	1986 to 2010	1000 to <1250 mg/d
Wilson KM, 2015 (15)	USA	Cohort	1898	54.7	NR	NR	1986 to 2010	750 to <1000 mg/d
Wilson KM, 2015 (15)	USA	Cohort	245	53.9	NR	NR	1986 to 2010	<500 mg/d
Rowland GW, 2013 (16)	USA	Case-control	536	64	274	64	between 1997 and 2005	< 604 mg/d
Rowland GW, 2013(16)	USA	Case-control	507	64	274	64	between 1997 and 2005	604–894 mg/d
Rowland GW, 2013 (16)	USA	Case-control	479	64	273	64	between 1997 and 2005	895–1258 mg/d
Rowland GW, 2012 (17)	USA	Case-control	75	62.7	59	63.5		488 – 680 mg/d

Table 1. Continued

Author, year of publication	Location	Type of study	Sample size in the calcium consuming group	Mean age in the calcium consuming group (year)	Sample size in the compare group	Sample size in the compare group (year)	Duration of study	Dosage
Rowland GW, 2012 (17)	USA	Case-control	162	62.7	61	63.5		681–1059 mg/d
Rowland GW, 2012 (17)	USA	Case-control	179	62.7	59	63.5		> 1059 mg/d
Williams CD, 2012 (18)	USA	Case-control	29	63	NR	NR	between 2007 and 2010	707.5 mg/d
Williams CD, 2012 (18)	USA	Case-control	29	63	NR	NR	between 2007 and 2010	1245.9 mg/d
Kristal AR, 2010 (19)	USA & Canada	Case-control	420	63.6	NR	NR	1994–2003	598–841 mg/d
Kristal AR, 2010 (19)	USA & Canada	Case-control	368	63.6	NR	NR	1994–2003	842–1,165 mg/d
Kristal AR, 2010 (19)	USA & Canada	Case-control	442	63.6	NR	NR	1994–2003	>1,165 mg/d
Butler LM, 2010 (20)	Singapore	Cohort	75	NR	NR	NR	between 1993 and 1998	266–371 mg/d
Butler LM, 2010 (20)	Singapore	Cohort	71	NR	NR	NR	between 1993 and 1998	372–521 mg/d
Butler LM, 2010 (20)	Singapore	Cohort	92	NR	NR	NR	between 1993 and 1998	≥523 mg/d
Raimondi S, 2010 (21)	Canada	Case-control	197	35-84	197	35-84	1989–1993	967.1–1177.8 mg/d
Raimondi S, 2010 (21)	Canada	Case-control	NR	NR	NR	NR	1989–1993	1177.9–1430.7 mg/d
Raimondi S, 2010 (21)	Canada	Case-control	NR	NR	NR	NR	1989–1993	>1430.7 mg/d
Kurahashi N, 2008 (22)	Japan	Cohort	68	55.6	NR	NR	1990-2004	403.6 mg/d
Kurahashi N, 2008 (22)	Japan	Cohort	97	56.8	NR	NR	1990-2004	521.9 mg/d
Kurahashi N, 2008 (22)	Japan	Cohort	107	58.1	NR	NR	1990-2004	725.1 mg/d
Ahn J, 2007 (23)	USA	RCT	513	55-74	NR	NR	1993 and 2001	751-1000 mg/d
Ahn J, 2007 (23)	USA	RCT	792	55-74	NR	NR	1993 and 2001	1001-1500 mg/d
Ahn J, 2007(23)	USA	RCT	2580	55-74	NR	NR	1993 and 2001	1501-2000 mg/d
Ahn J, 2007 (23)	USA	RCT	85	55-74	NR	NR	1993 and 2001	≥2001 mg/d
Mitrou PN, 2007 (24)	Finland	RCT	611	56.7	NR	NR	between 1985 and 1988	1000–1499 mg/d
Mitrou PN, 2007 (24)	Finland	RCT	402	56.7	NR	NR	between 1985 and 1988	1500–1999 mg/d
Mitrou PN, 2007 (24)	Finland	RCT	103	57.1	NR	NR	between 1985 and 1988	≥2000 mg/d

Table 1. Continued

Author, year of publication	Location	Type of study	Sample size in the calcium consuming group	Mean age in the calcium consuming group (year)	Sample size in the compare group	Sample size in the compare group (year)	Duration of study	Dosage
Park SY, 2007 (25)	USA	Cohort	925	NR	NR	NR	1993–2002	470–<692 mg/d
Park SY, 2007 (25)	USA	Cohort	949	NR	NR	NR	1993–2002	692–<935 mg/d
Park SY, 2007 (25)	USA	Cohort	936	NR	NR	NR	1993–2002	935 to <1301 mg/d
Park SY, 2007 (25)	USA	Cohort	888	NR	NR	NR	1993–2002	≥1301 mg/d
Kesse E, 2006 (26)	France	RCT	18	57.1	NR	NR	1994–1995	725–891 mg/d
Kesse E, 2006 (26)	France	RCT	24	57.1	NR	NR	1994–1995	891–1081 mg/d
Kesse E, 2006(26)	France	RCT	19	57.1	NR	NR	1994–1995	>1081 mg/d
Giovannucci E, 2006 (27)	USA	Cohort	1099	NR	NR	NR	1986-2002	750-999 mg/d
Giovannucci E, 2006 (27)	USA	Cohort	898	NR	NR	NR	1986-2002	1000-1499 mg/d
Giovannucci E, 2006 (27)	USA	Cohort	207	55.8	NR	NR	1986-2002	1500-1999 mg/d
Giovannucci E, 2006 (27)	USA	Cohort	85	55.8	NR	NR	1986-2002	≥2000 mg/d
Tavani A, 2005 (28)	Italy	Case-control	263	46-74	291	46-74	1991–2002	875.61 mg/d
Tavani A, 2005 (28)	Italy	Case-control	254	46-74	290	46-74	1991–2002	1067.6 mg/d
Tavani A, 2005 (28)	Italy	Case-control	261	46-74	290	46-74	1991–2002	1300 mg/d
Tavani A, 2005 (28)	Italy	Case-control	321	46-74	290	46-74	1991–2002	≥2000 mg/d
Tseng M, 2005 (29)	USA	Cohort	37	57.8	NR	NR	1982-1992	642.1 mg/d
Tseng M, 2005 (29)	USA	Cohort	66	57.8	NR	NR	1982-1992	920.6 mg/d
Baron JA, 2005 (30)	USA	RCT	345	61.8	327	61.8	1996-1999	1,200 mg/d
Rodriguez C, 2003 (31)	USA	Cohort	1293	NR	NR	NR	1992-1999	700–999 mg/d
Rodriguez C, 2003 (31)	USA	Cohort	835	64.4	NR	NR	1992-1999	1000–1499 mg/d
Rodriguez C, 2003 (31)	USA	Cohort	265	NR	NR	NR	1992-1999	1500–1999 mg/d
Rodriguez C, 2003 (31)	USA	Cohort	95	65.6	NR	NR	1992-1999	≥2000 mg/d
Kristal AR, 2002 (32)	USA	Case-control	605	40-64	592	40-64	1993-1996	518 mg/d

Table 1. Continued

Author, year of publication	Location	Type of study	Sample size in the calcium consuming group	Mean age in the calcium consuming group (year)	Sample size in the compare group	Sample size in the compare group (year)	Duration of study	Dosage
Kristal AR, 2002 (32)	USA	Case-control	NR	NR	NR	NR	1993-1996	672 mg/d
Kristal AR, 2002 (32)	USA	Case-control	NR	NR	NR	NR	1993-1996	850 mg/d
Kristal AR, 2002 (32)	USA	Case-control	NR	NR	NR	NR	1993-1996	1163 mg/d
Berndt SI, 2002 (33)	USA	Cohort	NR	NR	NR	NR	NR	756 mg/d
Berndt SI, 2002(33)	USA	Cohort	NR	NR	NR	NR	NR	1121 mg/d
Tavani A, 2001 (34)	Italy	Case-control	66	45-79	145	45-79	1985-1992	<471 mg/d
Tavani A, 2001 (34)	Italy	Case-control	49	45-79	163	45-79	1985-1992	<757 mg/d
Tavani A, 2001 (34)	Italy	Case-control	47	45-79	161	45-79	1985-1992	<992 mg/d
Tavani A, 2001 (34)	Italy	Case-control	69	45-79	141	45-79	1985-1992	<1691 mg/d
Chan JM, 2001(35)	USA	RCT	206	52	NR	NR	1982–1984	151–300 mg/d
Chan JM, 2001 (35)	USA	RCT	377	54	NR	NR	1982–1984	301–600 mg/d
Chan JM, 2001 (35)	USA	RCT	274	55	NR	NR	1982–1984	>600 mg/d
Giovannucci E, 1998 (36)	USA	Cohort	817	40-75	NR	NR	1986-1994	500-999 mg/d
Giovannucci E, 1998 (36)	USA	Cohort	292	40-75	NR	NR	1986-1994	100-1499 mg/d
Giovannucci E, 1998 (36)	USA	Cohort	88	40-75	NR	NR	1986-1994	1500-1999 mg/d
Giovannucci E, 1998 (36)	USA	Cohort	65	40-75	NR	NR	1986-1994	≥2000 mg/d
Chan JM, 1998 (37)	Sweden	Case-control	130	<80	134	<80	1989-1994	825-999 mg/d
Chan JM, 1998 (37)	Sweden	Case-control	138	<80	134	<80	1989-1994	1000-1182 mg/d
Chan JM, 1998 (37)	Sweden	Case-control	147	<80	134	<80	1989-1994	≥1183 mg/d

RCT: Randomized clinical trial; NR: Not reported.

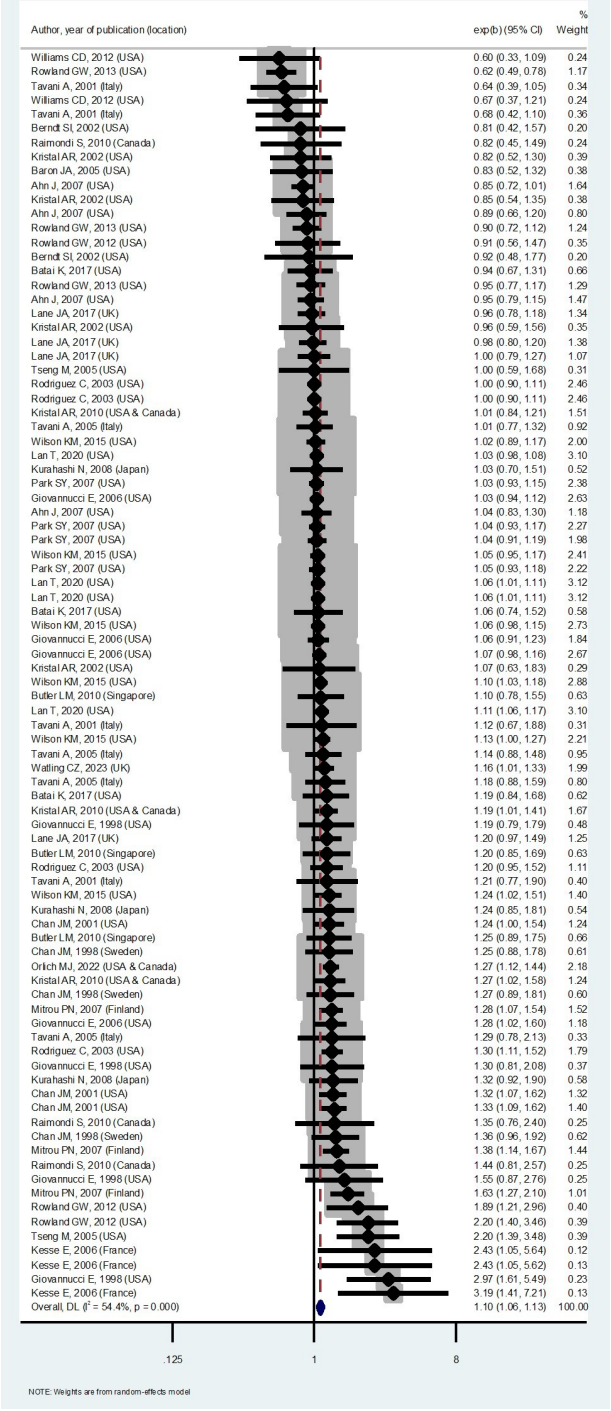

Figure 2. Forest diagram showing the relationship between calcium intake and prostate neoplasm risk and its 95% CI.

In fact, by increasing the daily calcium intake, the risk of prostate neoplasm in men increased (Table 2).

Discussion

Our meta-analysis revealed that calcium intake through diet increased the risk of prostate carcinoma in men by 10%, and higher doses of calcium increased the risk of prostate neoplasm.

Aune et al conducted a meta-analysis aimed to investigate the relationship between consuming dairy products and calcium and the risk of prostate neoplasm. Eventually, the researchers stated that calcium in the diet (for each 400 mg/d) was linked to the risk of prostate carcinoma (RR: 1.05, 95% CI: 1.02, 1.09) (6). A study by López-Plaza a et al on the relationship between the consumption of milk and dairy products and the risk of prostate carcinoma showed that the risk of prostate carcinoma increased by consuming 400 g of dairy products per day (RR: 1.07, 95% CI: 1.02, 1.12) (38). A previous meta-analysis by Gao et al reported that men with the highest dairy product (RR =1.11, 95% CI: 1.00 to 1.22) and calcium (RR: 1.39, 95% CI: 1.09 to 1.77) consumption were more exposed to prostate carcinoma that men with the lowest amount of consumption (39). In another meta-analysis aimed to explore the association among milk consumption and prostate carcinoma, Qin et al reported that daily consumption of milk, a product containing calcium, increases the risk of prostate carcinoma in men by up to 68% (OR: 1.68, 95% CI: 1.34 – 2.12) (40). Results reported by the mentioned studies were consistent with the results of the present article and confirmed our results. All of these studies indicated that daily calcium intake through diet was a potential threat to the occurrence of prostate carcinoma. Increased calcium levels might have reduced the vitamin D concentration, thereby suppressing the immune system of the body and potentially leading to prostate carcinoma.

Based on the results of a recent meta-analysis by Huncharek et al on the effect of dairy products, calcium, and vitamin D on the risk of prostate carcinoma, there was no relationship between calcium intake and increased risk of prostate carcinoma (RR: 1.04 (95% CI: 0.90 – 1.15) (41). Zhao et al studied the relationship between consuming dairy products and the risk of prostate carcinoma and reported the relationship between

Table 2. Evaluation of the relationship between calcium intake and the risk of prostate neoplasm according to the variables of study type, dosage and age group of men

Subgroups		OR (95% CI)	I^2 (%)	P value
Type of study	Cohort	1.08 (1.06, 1.13)	37.4	0.012
	Case-control	1.04 (0.96, 1.14)	55.9	<0.001
	Cross-sectional	1.06 (0.86, 1.29)	0	0.631
	RCT	1.21 (1.06, 1.39)	74.1	<0.001
Mean age (year)	50-59	1.16 (1.09, 1.24)	63.4	<0.001
	60-69	1.03 (0.94, 1.13)	65.3	<0.001
Dosage (mg/d)	<1300	1.04 (1, 1.09)	49.1	<0.001
	1300-2000	1.17 (1.09, 1.26)	22	0.261
	>2000	1.29 (1.13, 1.48)	58.8	0.017

RCT: Randomized clinical trial; CI: Confidence interval; OR: Odds ratio.

consuming dairy products and advanced prostate cancer (RR: 0.98 (95% CI: 0.94, 1.03)), non-advanced prostate cancer (RR: 1.10 (95% CI: 0.98, 1.24)), and fatal prostate carcinoma (RR: 0.92 (95% CI: 0.84, 1.00)). Generally, no noteworthy correlation was detected between consuming dairy products and the risk of prostate carcinoma in any of the mentioned groups. In terms of consumption dosage, however, consumption of 400 grams of dairy products per day increased the risk of prostate neoplasm by 2% (RR: 1.02 (95% CI: 1.00, 1.03) (42). The result of the mentioned investigation was inconsistent with our meta-analysis. Huncharek et al and Zhao et al believed that calcium intake does not affect the risk of prostate carcinoma in men. However, it must be noted that the dosage, period of calcium consumption, and the age of the consumers are among the factors that affect the relationship between calcium and prostate neoplasm and might have caused heterogeneity between the studies, consequently leading to inconsistent results. Considering the individual's age group, daily consumption of calcium to a certain amount is required for the human body and poses no threat to health. On the other hand, the sample size, number of reviewed studies, and their types too affect the outcomes.

Conclusion

Calcium intake increased the risk of prostate carcinoma, and higher doses of calcium significantly increased the risk of prostate neoplasm. Consuming excessive amounts of calcium in individuals aged 50 to 59 was a prostate carcinoma risk factor, which indicates that middle-aged individuals are at risk and must avoid consuming too much calcium in their diets. However, we recommend conducting more studies on this subject.

Limitations

The eligible studies did not report the duration of calcium consumption. Most studies did not mention the age group of the participants or reported the age as multi-decade periods, which caused the age-based analysis to lose a part of the information. Most studies did not mention the source which provided the consumed calcium. Accordingly, we failed to present an analysis based on the consumed source. We recommend addressing these limitations in future studies.

Acknowledgments

The authors would like to thanks Hamid Nasri and Hosein Mardanparvar for guidance and editing of manuscript registration on the PROSPERO website.

Authors' contribution

Conceptualization: Ahmadreza Maghsoudi.
Data curation: Farshad Yadollahi, Shahin Asgari Savadjani.
Formal analysis: All authors.
Investigation: Ahmadreza Maghsoudi.
Methodology: All authors.
Project administration: Ahmadreza Maghsoudi.
Resources: Farshad Yadollahi, Shahin Asgari Savadjani.
Software: All authors.
Supervision: Ahmadreza Maghsoudi.
Validation: Ahmadreza Maghsoudi.
Visualization: Farshad Yadollahi, Shahin Asgari Savadjani.
Writing–original draft: All authors.
Writing–review & editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study was conducted following the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website with the ID CRD42023489091, and on the Research Registry website with the Unique Identifying Number (UIN) reviewregistry1787. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Funding/Support

None.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. doi: 10.3322/caac.21492.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. doi: 10.3322/caac.21660.
3. Chan JM, Gann PH, Giovannucci EL. Role of diet in prostate cancer development and progression. J Clin Oncol. 2005;23(32):8152-60. doi: 10.1200/jco.2005.03.1492.
4. Wilson KM, Mucci LA. Diet and Lifestyle in Prostate Cancer. Adv Exp Med Biol. 2019;1210:1-27. doi: 10.1007/978-3-030-32656-2_1.
5. Hirayama T. Epidemiology of prostate cancer with special reference to the role of diet. Natl Cancer Inst Monogr. 1979(53):149-55.
6. Aune D, Navarro Rosenblatt DA, Chan DS, Vieira AR, Vieira R, Greenwood DC, et al. Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr. 2015;101(1):87-117. doi: 10.3945/ajcn.113.067157.
7. Orlich MJ, Mashchak AD, Jaceldo-Siegl K, Utt JT, Knutsen SF, Sveen LE, et al. Dairy foods, calcium intakes, and risk of

incident prostate cancer in Adventist Health Study-2. Am J Clin Nutr. 2022;116(2):314-24. doi: 10.1093/ajcn/nqac093.
8. Watling CZ, Kelly RK, Dunneram Y, Knuppel A, Piernas C, Schmidt JA, et al. Associations of intakes of total protein, protein from dairy sources, and dietary calcium with risks of colorectal, breast, and prostate cancer: a prospective analysis in UK Biobank. Br J Cancer. 2023;129(4):636-47. doi: 10.1038/s41416-023-02339-2.
9. Batai K, Murphy AB, Ruden M, Newsome J, Shah E, Dixon MA, et al. Race and BMI modify associations of calcium and vitamin D intake with prostate cancer. BMC Cancer. 2017;17(1):64. doi: 10.1186/s12885-017-3060-8.
10. Lane JA, Oliver SE, Appleby PN, Lentjes MA, Emmett P, Kuh D, et al. Prostate cancer risk related to foods, food groups, macronutrients and micronutrients derived from the UK Dietary Cohort Consortium food diaries. Eur J Clin Nutr. 2017;71(2):274-83. doi: 10.1038/ejcn.2016.162.
11. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1. doi: 10.1186/2046-4053-4-1.
12. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. doi: 10.1136/bmj.d5928.
13. Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. Ottawa: Ottawa Hospital Research Institute; 2011.
14. Lan T, Park Y, Colditz GA, Liu J, Wang M, Wu K, et al. Adolescent dairy product and calcium intake in relation to later prostate cancer risk and mortality in the NIH-AARP Diet and Health Study. Cancer Causes Control. 2020;31(10):891-904. doi: 10.1007/s10552-020-01330-z.
15. Wilson KM, Shui IM, Mucci LA, Giovannucci E. Calcium and phosphorus intake and prostate cancer risk: a 24-y follow-up study. Am J Clin Nutr. 2015;101(1):173-83. doi: 10.3945/ajcn.114.088716.
16. Rowland GW, Schwartz GG, John EM, Ingles SA. Protective effects of low calcium intake and low calcium absorption vitamin D receptor genotype in the California Collaborative Prostate Cancer Study. Cancer Epidemiol Biomarkers Prev. 2013;22(1):16-24. doi: 10.1158/1055-9965.epi-12-0922-t.
17. Rowland GW, Schwartz GG, John EM, Ingles SA. Calcium intake and prostate cancer among African Americans: effect modification by vitamin D receptor calcium absorption genotype. J Bone Miner Res. 2012;27(1):187-94. doi: 10.1002/jbmr.505.
18. Williams CD, Whitley BM, Hoyo C, Grant DJ, Schwartz GG, Presti JC Jr, et al. Dietary calcium and risk for prostate cancer: a case-control study among US veterans. Prev Chronic Dis. 2012;9:E39. doi: 10.5888/pcd9.110125.
19. Kristal AR, Arnold KB, Neuhouser ML, Goodman P, Platz EA, Albanes D, et al. Diet, supplement use, and prostate cancer risk: results from the prostate cancer prevention trial. Am J Epidemiol. 2010;172(5):566-77. doi: 10.1093/aje/kwq148.
20. Butler LM, Wong AS, Koh WP, Wang R, Yuan JM, Yu MC. Calcium intake increases risk of prostate cancer among Singapore Chinese. Cancer Res. 2010;70(12):4941-8. doi: 10.1158/0008-5472.can-09-4544.
21. Raimondi S, Mabrouk JB, Shatenstein B, Maisonneuve P, Ghadirian P. Diet and prostate cancer risk with specific focus on dairy products and dietary calcium: a case-control study. Prostate. 2010;70(10):1054-65. doi: 10.1002/pros.21139.
22. Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane AS. Dairy product, saturated fatty acid, and calcium intake and prostate cancer in a prospective cohort of Japanese men. Cancer Epidemiol Biomarkers Prev. 2008;17(4):930-7. doi: 10.1158/1055-9965.epi-07-2681.
23. Ahn J, Albanes D, Peters U, Schatzkin A, Lim U, Freedman M, et al. Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomarkers Prev. 2007;16(12):2623-30. doi: 10.1158/1055-9965.epi-07-0601.
24. Mitrou PN, Albanes D, Weinstein SJ, Pietinen P, Taylor PR, Virtamo J, et al. A prospective study of dietary calcium, dairy products and prostate cancer risk (Finland). Int J Cancer. 2007;120(11):2466-73. doi: 10.1002/ijc.22553.
25. Park SY, Murphy SP, Wilkens LR, Stram DO, Henderson BE, Kolonel LN. Calcium, vitamin D, and dairy product intake and prostate cancer risk: the Multiethnic Cohort Study. Am J Epidemiol. 2007;166(11):1259-69. doi: 10.1093/aje/kwm269.
26. Kesse E, Bertrais S, Astorg P, Jaouen A, Arnault N, Galan P, et al. Dairy products, calcium and phosphorus intake, and the risk of prostate cancer: results of the French prospective SU.VI.MAX (Supplémentation en Vitamines et Minéraux Antioxydants) study. Br J Nutr. 2006;95(3):539-45. doi: 10.1079/bjn20051670.
27. Giovannucci E, Liu Y, Stampfer MJ, Willett WC. A prospective study of calcium intake and incident and fatal prostate cancer. Cancer Epidemiol Biomarkers Prev. 2006;15(2):203-10. doi: 10.1158/1055-9965.epi-05-0586.
28. Tavani A, Bertuccio P, Bosetti C, Talamini R, Negri E, Franceschi S, et al. Dietary intake of calcium, vitamin D, phosphorus and the risk of prostate cancer. Eur Urol. 2005;48(1):27-33. doi: 10.1016/j.eururo.2005.03.023.
29. Tseng M, Breslow RA, Graubard BI, Ziegler RG. Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. Am J Clin Nutr. 2005;81(5):1147-54. doi: 10.1093/ajcn/81.5.1147.
30. Baron JA, Beach M, Wallace K, Grau MV, Sandler RS, Mandel JS, et al. Risk of prostate cancer in a randomized clinical trial of calcium supplementation. Cancer Epidemiol Biomarkers Prev. 2005;14(3):586-9. doi: 10.1158/1055-9965.epi-04-0319.
31. Rodriguez C, McCullough ML, Mondul AM, Jacobs EJ, Fakhrabadi-Shokoohi D, Giovannucci EL, et al. Calcium, dairy products, and risk of prostate cancer in a prospective cohort of United States men. Cancer Epidemiol Biomarkers

Prev. 2003;12(7):597-603.
32. Kristal AR, Cohen JH, Qu P, Stanford JL. Associations of energy, fat, calcium, and vitamin D with prostate cancer risk. Cancer Epidemiol Biomarkers Prev. 2002;11(8):719-25.
33. Berndt SI, Carter HB, Landis PK, Tucker KL, Hsieh LJ, Metter EJ, et al. Calcium intake and prostate cancer risk in a long-term aging study: the Baltimore Longitudinal Study of Aging. Urology. 2002;60(6):1118-23. doi: 10.1016/s0090-4295(02)01991-x.
34. Tavani A, Gallus S, Franceschi S, La Vecchia C. Calcium, dairy products, and the risk of prostate cancer. Prostate. 2001;48(2):118-21. doi: 10.1002/pros.1087.
35. Chan JM, Stampfer MJ, Ma J, Gann PH, Gaziano JM, Giovannucci EL. Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study. Am J Clin Nutr. 2001;74(4):549-54. doi: 10.1093/ajcn/74.4.549.
36. Giovannucci E, Rimm EB, Wolk A, Ascherio A, Stampfer MJ, Colditz GA, et al. Calcium and fructose intake in relation to risk of prostate cancer. Cancer Res. 1998;58(3):442-7.
37. Chan JM, Giovannucci E, Andersson SO, Yuen J, Adami HO, Wolk A. Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer (Sweden). Cancer Causes Control. 1998;9(6):559-66. doi: 10.1023/a:1008823601897.
38. López-Plaza B, Bermejo LM, Santurino C, Cavero-Redondo I, Álvarez-Bueno C, Gómez-Candela C. Milk and dairy product consumption and prostate cancer risk and mortality: an overview of systematic reviews and meta-analyses. Adv Nutr. 2019;10(Suppl 2):S212-23. doi: 10.1093/advances/nmz014.
39. Gao X, LaValley MP, Tucker KL. Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. J Natl Cancer Inst. 2005;97(23):1768-77. doi: 10.1093/jnci/dji402.
40. Qin LQ, Xu JY, Wang PY, Kaneko T, Hoshi K, Sato A. Milk consumption is a risk factor for prostate cancer: meta-analysis of case-control studies. Nutr Cancer. 2004;48(1):22-7. doi: 10.1207/s15327914nc4801_4.
41. Huncharek M, Muscat J, Kupelnick B. Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: a meta-analysis of 26,769 cases from 45 observational studies. Nutr Cancer. 2008;60(4):421-41. doi: 10.1080/01635580801911779.
42. Zhao Z, Wu D, Gao S, Zhou D, Zeng X, Yao Y, et al. The association between dairy products consumption and prostate cancer risk: a systematic review and meta-analysis. Br J Nutr. 2023;129(10):1714-31. doi: 10.1017/s0007114522002380.