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Association between vitamin D and bladder neoplasm; a systematic review and meta-analysis

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ABSTRACT

Introduction: Bladder neoplasm ranks as the second most prevalent reproductive system malignancy worldwide. On the other hand, the vitamin D as an anti-cancer agent has been a subject of long-standing speculation. Hence, the objective of this study is to explore the correlation between vitamin D and bladder neoplasm risk.

Materials and Methods: This systematic review and meta-analysis were designed following the PRISMA checklist. Eligible studies were identified through searches on ProQuest, PubMed, Web of Science, Google Scholar, and Cochrane, with no time restrictions until November 18, 2023. Data analysis was conducted utilizing the STATA 14 software.

Results: Serum vitamin D levels less than 50 nmol/L increased the risk of bladder neoplasm (OR: 1.33; 95% CI: 1.08, 1.64), muscle-invasive bladder cancer (MIBC) (OR: 2.73; 95% CI: 1.80, 4.14) and non-muscle invasive bladder cancer (NMIBC) (OR: 1.87 (95% CI: 1.39, 2.52)). However, the risk of bladder neoplasm in people whose serum vitamin D level was less than 50 nmol/L did not increase with age. Vitamin D serum levels greater than or equal to 50 nmol/L in people aged 40 to 49 (OR: 0.51; 95% CI: 0.27, 0.99) prevented bladder neoplasm, but no significant association was seen in people over 50 years old. In addition, there was no significant association between daily vitamin D intake and the risk of bladder neoplasm (OR: 1.13; 95% CI: 0.63, 2.06).

Conclusion: The serum vitamin D less than 50 nmol/L was correlated with bladder cancer risk increasing, including MIBC and NMIBC.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (CRD42023487519) and Research Registry (UIN: reviewregistry1754) Websites.

Implication for health policy/practice/research/medical education:
Individuals with a serum level of vitamin D less than 50 nmol/L were found to have a 33% increased risk of bladder tumor and an 87% increased risk of non-muscle invasive bladder neoplasm. Additionally, the risk of muscle-invasive bladder cancer was approximately 1.7 times higher in individuals who had vitamin D levels < 50 nmol/L compared to those in the compare group..

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Meta-analysis

Introduction

Bladder cancer, the second most common genital malignancy worldwide after prostate cancer (1), exhibits a higher incidence in men compared to women (3 to 4 times), with the risk increasing with age (2,3). Alongside genetic predisposition, lifestyle, environmental factors, and occupational exposure contribute to the development of bladder neoplasm (4). Adhering to dietary recommendations can potentially prevent up to one-third of bladder neoplasm cases, as stated by the US National Cancer Institute (5). The majority of bladder cancer cases belong to the urothelial carcinoma subtype, with approximately 75% being non-muscle invasive bladder cancer (NMIBC) (6). NMIBC tends to progress to muscle-invasive bladder cancer (MIBC) (7).

Vitamin D is a fat-soluble vitamin obtainable through food or dietary supplements (8). A deficiency is defined as a serum concentration of 25-OH (hydroxy) vitamin D below 50 nmol/L (9,10). Vitamin D deficiency is relatively common, particularly in regions with limited solar radiation, such as northern latitudes (11). Functioning as a hormone-like micronutrient, vitamin D plays a role in various biological activities, including cell proliferation, apoptosis, angiogenesis, and immune response, making it a potential anticancer agent (12-14).

Research conducted in the recent past has delved into the various actions of vitamin D beyond its role in the skeletal system. These studies have shed light on the potential associations with autoimmune disorders, infectious diseases, cardiovascular diseases, cancers, and neurological disorders, uncovering the possible underlying mechanisms (15,16). Other studies have also indicated that higher vitamin D levels may be linked to reduced tumor mortality and overall mortality (17,18). Therefore, the primary aim of this present study was to examine the correlation between vitamin D and bladder neoplasm by utilizing a systematic review and meta-analysis methodology.

Materials and Methods

This systematic review and meta-analysis study was designed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (19), and the study protocol was registered on the PROSPERO website.

Research strategy

Eligible studies were recognized through wide-ranging searches conducted on PubMed, ProQuest, Cochrane, Web of Science, and Google Scholar. The search was carried out until November 18, 2023, without any time restrictions. Keywords and their equivalents were utilized, including "Vitamin D, 25-Hydroxyvitamin D 2, Ercalcidiol, Urinary Bladder Neoplasm, Bladder Tumor, Bladder Cancer". These keywords were combined using operators (AND, OR) to perform an advanced search. Additionally, a manual search was performed by evaluating the list of sources containing eligible studies. Search strategy on the Cochrane website: Urinary Bladder Neoplasm OR Bladder Tumor OR Bladder Cancer in Title Abstract Keyword AND Vitamin D OR "25-Hydroxyvitamin D 2" OR Ercalcidiol in Title Abstract Keyword.

PICO component

The population comprised the studies assessing the correlation between bladder neoplasia and Vitamin D. The intervention undertaken was the administration of vitamin D, while the comparison group was composed of individuals not given vitamin D, acting as the placebo group. The outcomes observed were the relationship between vitamin D and the risk of bladder neoplasm.

Inclusion and exclusion criteria

Our study included investigations that evaluated the correlation between vitamin D and the risk of bladder neoplasm. However, certain studies were excluded from our review list, such as in vitro studies, repeated studies, animal model studies, systematic review and meta-analysis studies, low-quality studies, conference studies, studies with unavailable full text, and studies lacking the necessary data for analysis.

Quality assessment

In this article, the evaluation of randomized controlled trials (RCTs) was conducted using the Cochrane Institute checklist (20). This checklist consists of seven questions, each offering three response options; unclear, low risk of bias, and high risk of bias. For inclusion in our study, any study that received a low risk of bias rating for at least four questions was considered. The Newcastle-Ottawa scale (NOS) was employed to assess observational studies (21). The NOS evaluates three aspects: selection of participants, comparability, and outcome evaluation. Studies that achieved a minimum score of six stars on the NOS were deemed high-quality and included in our study. In cases where there were disagreements in the answers to the questions, the two researchers collaborated and reached a consensus through consultation with each other.

Data extraction

Data extraction was done by two researchers separately. The checklist designed for data extraction includes the first author name, the type of study, sample size, and the age of the target group and the comparison group, the place and time of the study, the serum level of vitamin D, the odds ratio of the relationship between vitamin D and the risk of bladder tumor, as well as its 95% confidence interval. The third researcher checked the extracted data and resolved the inconsistencies.

Data extraction was conducted independently by two researchers. A comprehensive checklist was developed for this purpose, encompassing information such as the

first author's name, study type, sample size and the age of target and comparison groups, study location and duration, serum vitamin D levels, the odds ratio of the relationship between vitamin D and bladder tumor risk, and the corresponding 95% confidence interval. To ensure accuracy and consistency, a third researcher reviewed the extracted data and resolved any discrepancies that were identified by the initial two researchers.

Statistical analysis

To synthesize the studies, we employed the logarithm of the odds ratios (ORs) and assessed heterogeneity using the I^2 index. The I^2 index categorizes heterogeneity as follows: less than 25% signifies low heterogeneity, 25% to 75% means moderate heterogeneity, and over 75% indicates severe heterogeneity. We utilized a random effects model due to the high heterogeneity among the studies. Furthermore, we conducted a meta-regression to explore the association between the impact of vitamin D on bladder neoplasm risk and the sample size. We utilized a publication bias chart to examine publication bias during the source search phase. Data analysis was conducted utilizing the STATA 14 software, with statistical significance being delineated as a P-value less than 0.05.

Results

The selection of studies

After completing the search phase, a total of 543 studies were obtained from the mentioned databases. Subsequently, the abstracts of these studies were reviewed, resulting in the exclusion of 52 studies due to the unavailability of their full text. Among the remaining 290 studies, 46 were further excluded as they lacked sufficient data for data analysis, leaving a final count of 244 studies. Additionally, based on other exclusion criteria, an additional 231 studies were excluded. As a result, 13 studies qualified and proceeded to the systematic review and meta-analysis stages (Figure 1).

Out of the 13 eligible studies, nine studies (sample size: 4415 individuals) assessed the association between serum vitamin D levels and the risk of bladder tumor. The remaining four studies (totaling 523 844 individuals) evaluated the association between daily vitamin D intake and bladder tumor risk. Amongst these studies, 7 were case-control studies, 4 were cohort studies, and 2 were RCTs. Table 1 presents some information pertaining to these studies.

The association between serum vitamin D levels below 50 nmol/L and the risk of bladder cancer

In general, a serum level of vitamin D below 50 nmol/L was found to increase the risk of bladder tumor (OR: 1.33; 95% CI: 1.08, 1.64). However, upon reviewing different types of studies, we have determined that there is no statistically significant association between a low vitamin D serum level (below 50 nmol/L) and the risk of bladder tumor in cohort studies (OR: 1.38; 95% CI: 0.88, 2.16), case-control

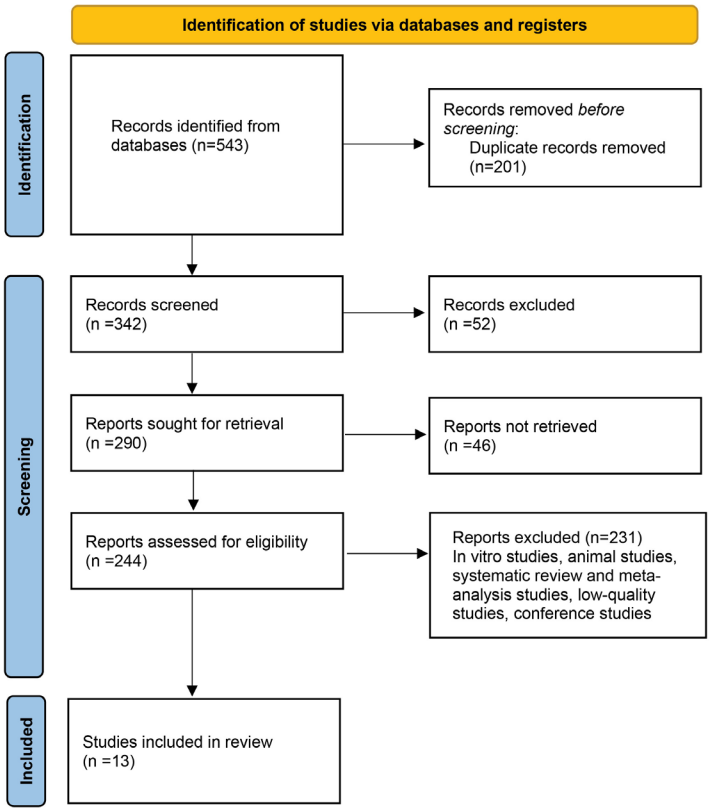

Figure 1. The flow chart of study selection.

Table 1. Baseline characteristics of included study

Author, year of publication	Location	Design of study	Number of people in target group	Mean age of people in target group	Number of people in compare group	Mean age of people in compare group	Vitamin D serum level
Wu E, 2023 (22)	UK	Cohort	214	55.5	NR	NR	<25 nmol/L
Abdelgawad A, 2022 (23)	Egypt	Cohort	84	62	31	62	16.47 ng/mL
Hektoen HH, 2021 (24)	Norway	Case-Control	34	43	52	43	≥100 nmol/L
Hektoen HH, 2021 (24)	Norway	Case-Control	102	44	115	44	75–99 nmol/L
Hektoen HH, 2021 (24)	Norway	Case-Control	61	44	68	44	<50 nmol/L
Ben Fradj MK, 2016 (25)	Tunis	Case-Control	79	64.8	69	63.3	30 - 49.99 nmol/L
Ben Fradj MK, 2016 (25)	Tunis	Case-Control	126	64.8	87	63.3	<30 nmol/L
Afzal S, 2013 (26)	Denmark	Cohort	112	≥20	NR	NR	37 nmol/L
Amaral AF, 2012 (27)	Spain	Case-Control	229	20-81	227	20-81	20.00–29.99 ng/mL
Amaral AF, 2012 (27)	Spain	Case-Control	219	20-81	212	20-81	15.00–19.99 ng/mL
Amaral AF, 2012 (27)	Spain	Case-Control	280	20-81	255	20-81	10.00–14.99 ng/mL
Amaral AF, 2012 (27)	Spain	Case-Control	346	20-81	260	20-81	<10.00 ng/mL
Mondul AM, 2012 (28)	USA	Randomized, double-blind, placebo controlled, primary prevention trial	69	58	63	58	19 to <29 nmol/L
Mondul AM, 2012 (28)	USA	Randomized, double-blind, placebo controlled, primary prevention trial	54	59	63	59	29 to <44 nmol/L
Mondul AM, 2012 (28)	USA	Randomized, double-blind, placebo controlled, primary prevention trial	44	59	57	59	≥44 nmol/L
Mondul AM, 2012 (29)	USA	Case-Control	16	64	17	64	<25 nmol/L

Table 1. Continued

Author, year of publication	Location	Design of study	Number of people in target group	Mean age of people in target group	Number of people in compare group	Mean age of people in compare group	Vitamin D serum level
Mondul AM, 2012 (29)	USA	Case-Control	54	64	63	64	25 to <37.5
Mondul AM, 2012 (29)	USA	Case-Control	92	64	79	64	37.5 to <50
Mondul AM, 2012 (29)	USA	Case-Control	49	64	64	64	≥75
Mondul AM, 2010 (30)	USA	Randomized, double-blind, placebo controlled, primary prevention trial	83	59	73	59	<25 nmol/L
Mondul AM, 2010 (30)	USA	Randomized, double-blind, placebo controlled, primary prevention trial	61	59	52	59	25 to <37.5
Mondul AM, 2010 (30)	USA	Randomized, double-blind, placebo controlled, primary prevention trial	54	59	46	59	37.5 to <50
Boot IW, 2023 (31)	Europe, America, Asia and Australia	Cohort	1994	≥18	518002	≥18	High
Boot IW, 2023 (31)	Europe, America, Asia and Australia	Cohort	NR	NR	NR	NR	Moderate
Brinkman MT, 2010 (32)	USA	Case-Control	72	62	60	60.7	171.75–388.90
Brinkman MT, 2010 (32)	USA	Case-Control	100	62	60	60.7	388.91–641.12
Brinkman MT, 2010 (32)	USA	Case-Control	61	62	60	60.7	≥641.13
Brinkman MT, 2011 (33)	USA	Case-Control	58	67.6	125	64.2	2.1–3.7 (μg/d)
Brinkman MT, 2011 (33)	USA	Case-Control	72	67.6	126	64.2	≥3.8 (μg/d)
Leung HW, 2016 (34)	Taiwan	Case-Control	334	NR	2719	NR	Vitamin D3 intake vs non-user

NR, Not reported.

studies (OR: 1.38 (95% CI: 0.98, 1.94)), and randomized controlled trials (OR: 1.24; 95% CI: 0.82, 1.90) (Figure 2).

In Figure 3, we divided the participants in the studies into three age groups. The results revealed that in the age group of 40 to 49 years (OR: 0.64; 95% CI: 0.40, 1.02), 50 to 59 years (OR: 1.17; 95% CI: 0.80, 1.70), and 60 to 69 years (OR: 1.54; 95% CI: 0.96, 2.49), there was no statistically significant association between a vitamin D serum level below 50 nmol/L and the risk of bladder tumor, meaning that for individuals with a serum level of vitamin D below 50 nmol/L, increasing age did not affect their risk of bladder tumor.

Based on the findings presented in Figure 4, it can be concluded that in the countries of Egypt (OR: 2.13; 95% CI: 1.52, 2.99), Tunisia (OR: 3.06; 95% CI: 1.88, 4.96), and Spain (OR: 1.71; 95% CI: 1.33, 2.19), a serum level of vitamin D below 50 nmol/L increased the risk of bladder cancer. However, in the countries of the UK (OR: 0.80; 95% CI: 0.41, 1.57), Norway (OR: 0.64; 95% CI: 0.40, 1.02), and the USA (OR: 1.10; 95% CI: 0.83, 1.47), a low serum level of vitamin D had no effect on bladder tumor.

Furthermore, a serum level of vitamin D below 50 nmol/L significantly increased the risk of MIBC (OR: 2.73; 95% CI: 1.80, 4.14) and NMIBC (OR: 1.87; 95% CI: 1.39, 2.52) as shown in Figures 5 and 6.

The association between serum vitamin D levels greater than or equal to 50 nmol/L and the risk of bladder tumor

There was no statistically significant link between having a serum vitamin D level greater than or equal to 50 nmol/L and bladder tumor in general (OR: 0.71; 95% CI: 0.47, 1.07). This finding was consistent across different types of studies. Both case-control studies (OR: 0.72; 95% CI: 0.44, 1.19) and randomized controlled trials (OR: 0.66; 95% CI: 0.36, 1.20) failed to demonstrate a significant association between having a serum vitamin D level greater than or equal to 50 nmol/L and bladder tumor (Figure 7).

In individuals aged 40 to 49, a serum vitamin D level greater than or equal to 50 nmol/L was found to be preventive against bladder tumor (OR: 0.51; 95% CI: 0.27, 0.99). However, this effect was not statistically significant in individuals aged 50 to 59 (OR: 0.66; 95% CI: 0.36, 1.20) and those aged 60 to 69 years (OR: 0.71; 95% CI: 0.46, 1.09) in terms of reducing the risk of bladder tumor (Figure 8).

When it comes to different countries, having a serum vitamin D level greater than or equal to 50 nmol/L was found to prevent bladder tumor in Norway (OR: 0.51; 95% CI: 0.27, 0.99) and the United States (OR: 0.69; 95% CI: 0.49, 0.98). However, there was no significant association between having a serum vitamin D level greater than or equal to 50 nmol/L and bladder tumor in Spain (OR: 1.40; 95% CI: 0.92, 2.14) (Figure 9).

The association between daily vitamin D consumption and bladder tumor risk

Overall, the findings suggest that there was no substantial association observed between the daily intake of vitamin D and the risk of developing bladder tumor (OR: 1.13; 95% CI: 0.63, 2.06) (Figure 10).

Additional analysis

The meta-regression analysis demonstrated no statistically significant association between "the effect of vitamin D on the risk of bladder neoplasm" and the number of samples

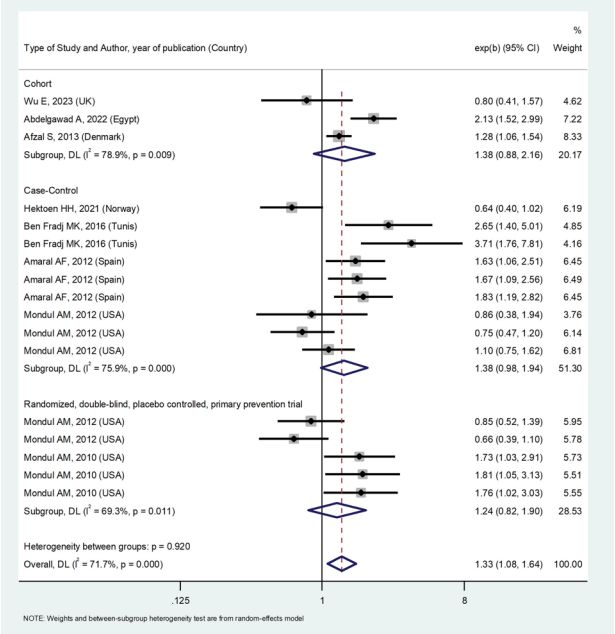

Figure 2. Forest plot of the association between serum vitamin D level <50 nmol/L and risk of bladder neoplasm by design of studies.

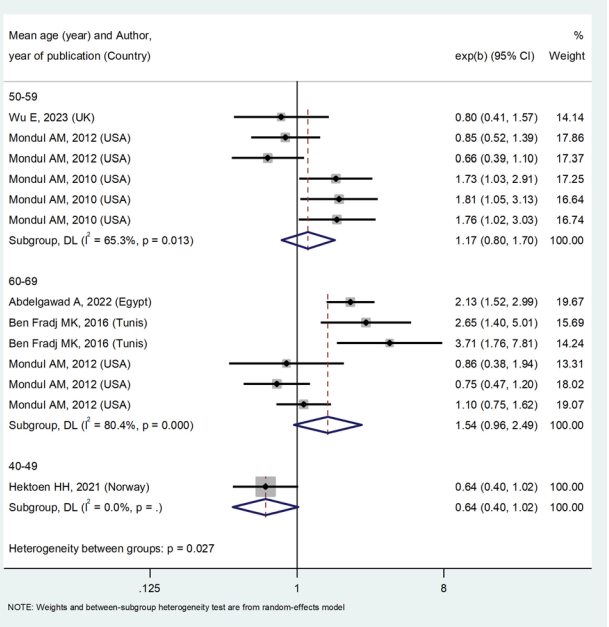

Figure 3. Forest plot of the association between serum vitamin D level <50 nmol/L and risk of bladder neoplasm by mean age.

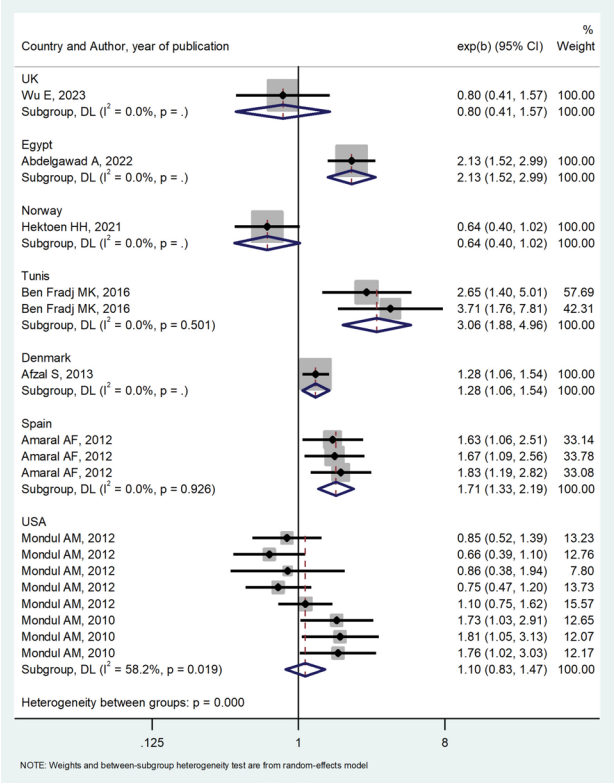

Figure 4. Forest plot of the association between serum vitamin D level <50 nmol/L and risk of bladder neoplasm by country.

(*P* value=0.068), indicating that the findings of this meta-analysis were not influenced by the sample size of the included studies (Figure 11).

Furthermore, the publication bias analysis showed no statistically significant findings (*P* value=0.582), suggesting that all published studies on the association between vitamin D and the risk of bladder neoplasm were thoroughly reviewed during the phase of searching for relevant sources. The search for resources was conducted without any bias or specific direction (Figure 12).

Discussion

Our study revealed that individuals with serum vitamin D < 50 nmol/L are high- risk for developing bladder cancers, including both MIBC and NMIBC.

In an extensive systematic review comprising six studies, Dunn et al revealed a noteworthy correlation of vitamin D and bladder neoplasm risk (35). Parallel findings were presented in our study, aligning with Zhang and colleagues' meta-analysis of seven studies, which reported a risk ratio of bladder tumor for the lowest versus the highest levels of B vitamin D (RR: 1.34, 95% CI: 1.17-1.53) (36). It is important to note that Zhang and colleagues' meta-analysis only encompassed studies published until 2015, while our study screened and evaluated studies published until 2023. Furthermore, our study delved into the influence of age variables, geographic location, and study type on the correlation of vitamin D and bladder neoplasm risk. Additionally, we investigated the association between vitamin D levels below 50nmol/L and the risks of MIBC and NMIBC, aspects that were not examined in Zhang and colleagues' meta-analysis. Comparatively, despite Dunn and colleagues' study yielding similar outcomes to our current study, it should be acknowledged that Dunn

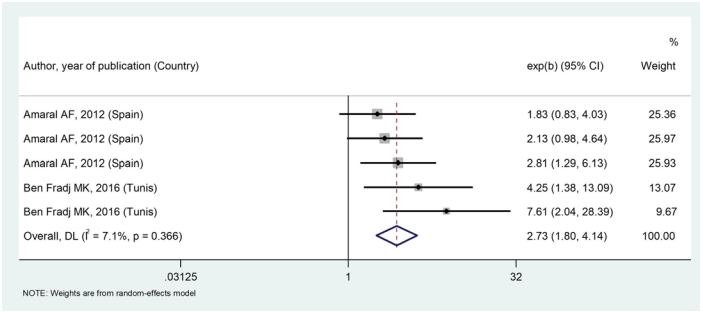

Figure 5. Forest plot of the association between serum vitamin D level<50 nmol/L and risk of MIBC.

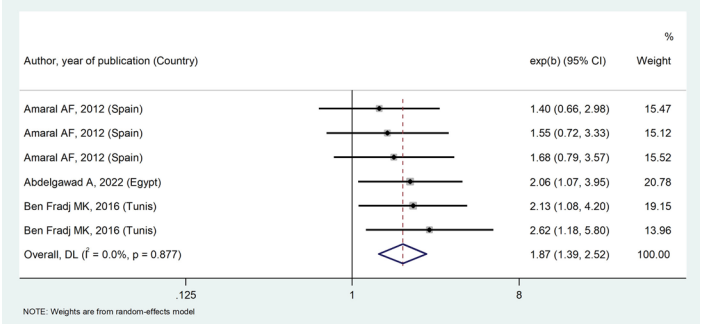

Figure 6. Forest plot of the association between serum vitamin D level<50 nmol/L and risk of NMIBC.

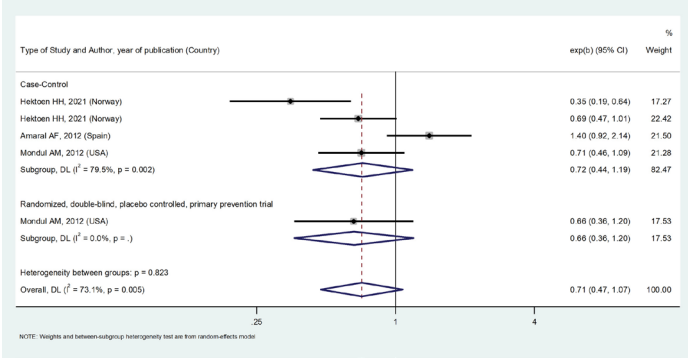

Figure 7. Forest plot of the association between serum vitamin D level ≥50 nmol/L and risk of bladder neoplasm by design of studies.

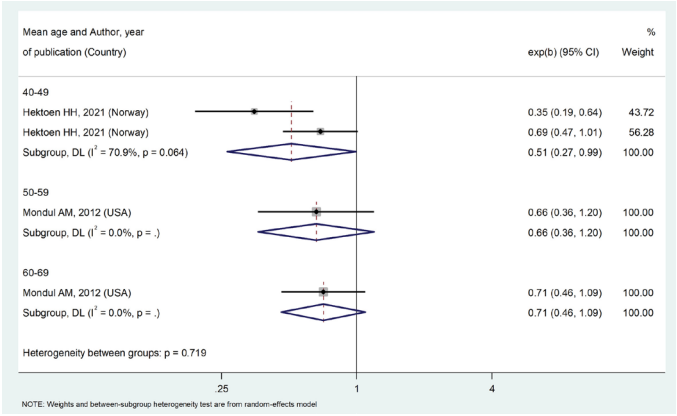

Figure 8. Forest plot of the association between serum vitamin D level>=50 nmol/L and risk of bladder neoplasm by mean age.

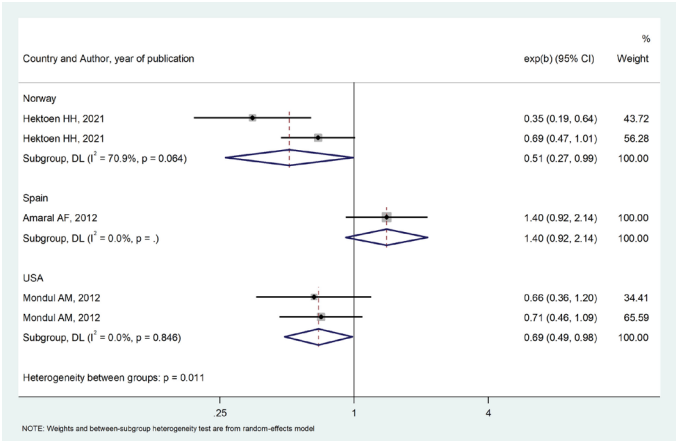

Figure 9. Forest plot of the association between serum vitamin D level>=50 nmol/L and risk of bladder neoplasm by country.

and colleagues' study was solely a systematic review, while ours encompassed both a systematic review and meta-analysis. Moreover, the scope of Dunn and colleagues' study consisted of six studies, whereas we expanded our investigation to encompass an extensive 13 studies.

In a meta-analysis performed by Goulão et al, they examined the impact of vitamin D supplementation on the occurrence and mortality rates of neoplasm. Ultimately, the researchers reached the conclusion that there was no connection between vitamin D supplementation and the incidence of neoplasm (RR: 1.03; 95% CI: 0.91, 1.15), as well as neoplasm mortality (RR: 0.85; 95% CI: 0.70, 1.04)

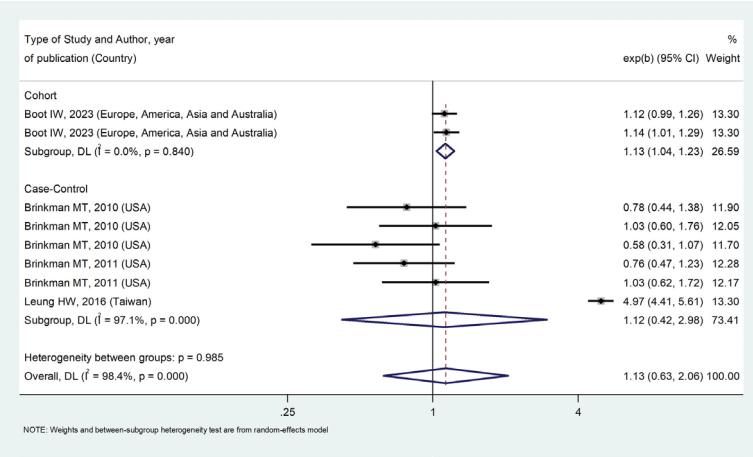

Figure 10. Forest plot of the association between vitamin D intake and risk of bladder neoplasm.

(37). In a meta-analysis, Chen et al found that for every 100 units per day increase in vitamin D intake through diet and supplementation, the relative risk of bladder neoplasm was (RR: 0.99, 95% CI: 0.95-1.03). Additionally, for each 10 nmol/L increase in circulating vitamin D, the relative risk of bladder neoplasm was (RR: 0.95, 95% CI: 0.90-1.00) (38). Our study also found no statistically significant association between daily vitamin D intake and bladder neoplasm risk, as well as between an increase in serum vitamin D levels above 50 nmol/L and bladder neoplasm risk. These findings confirm the results of Chen's study. It is worth noting that some of the studies reviewed in our meta-analysis reported serum vitamin D levels exceeding 100 nmol/L. This variability between studies may have introduced heterogeneity, and consequently, a significant association between high serum vitamin D levels and a reduced risk of bladder neoplasm was not observed in general.

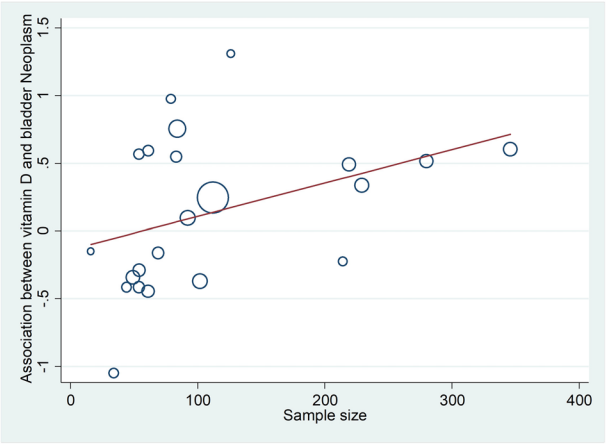

Figure 11. The meta-regression diagram showing the association between vitamin D and risk of bladder cancer by sample size.

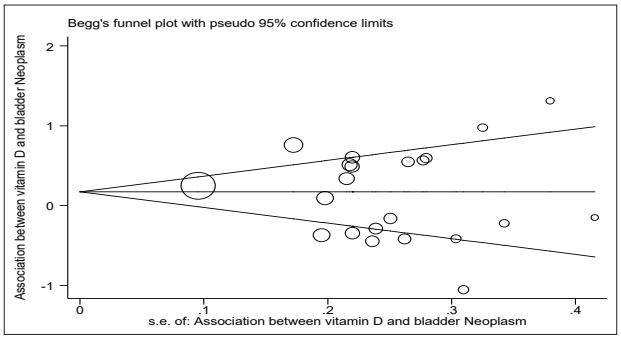

Figure 12. Publication bias diagram.

In their research, Zhao et al demonstrated that individuals with vitamin D levels exceeding 75 nmol/L had a reduced risk of bladder neoplasm compared to those with levels less than 25 nmol/L (OR = 0.68 (0.52 to 0.87) (39). Similarly, Liao et al conducted a meta-analysis that revealed high serum 25-hydroxy vitamin D levels to be associated with a decrease in bladder neoplasm risk (RR: 0.75, 95% CI 0.65-0.87) (40). In our own study, we observed a notable reduction in bladder neoplasm risk among individuals aged 40 to 49 years with high serum vitamin D levels (above 50 nmol/L). However, this association was not observed in individuals over 50 years old. It is important to note that while our study compared high vitamin D levels to normal levels, Zhao et al and Liao and colleagues' research compared high levels to low levels. Furthermore, the cut-off point and definition of high vitamin D levels varied across studies. Our study utilized a cut-off point of 50 nmol/L, whereas Zhao and colleagues' study used a cut-off point of 75 nmol/L.

In the meta-analysis conducted by Wu et al, the results indicated that individuals with higher levels of vitamin D had a reduced risk of developing renal cell neoplasm compared to those with lower levels of vitamin D (RR: 0.76, 95% CI: 0.64-0.89, *P*=0.001) (41). On the other hand, Gao and colleagues conducted a meta-analysis of 19 studies and found that higher concentrations of vitamin D were associated with an increased risk of prostate cancer (RR = 1.15, 95% CI: 1.06–1.24) (42). These findings from

studies by Wu et al and Gao et al contrasted with the results obtained in our study. It is important to note that Wu and colleagues' study focused on the association of high vitamin D levels with renal cell cancer, while the study conducted by Gao et al examined the association between high vitamin D levels and prostate cancer risk. In our study, we specifically evaluated the association between vitamin D and bladder cancer risk. The variation in the types of diseases studied may account for the discrepancy in findings between these studies.

Moving on to the limitations of our study, we were unable to assess the impact of serum vitamin D levels on bladder tumor risk in both men and women due to the limited number of eligible studies. Additionally, the studies investigating the effects of high vitamin D levels (≥50 nmol/L) on bladder tumor risk did not allow us to evaluate the potential association with MIBC and NMIBC separately. Furthermore, the dosage of daily vitamin D consumption in the studies varied, with some studies quantitatively expressing the dosage while others relied on qualitative descriptions.

Conclusion

There was no significant link between the daily vitamin D intake and the risk of bladder tumor, which may not be a surprise, considering that we do not have information about the specific amount of vitamin D received throughout the day. However, the study did reveal some noteworthy findings. Individuals with a serum level of vitamin D below 50 nmol/L were found to have a 33% increased risk of bladder tumor and an 87% increased risk of NMIBC (non-muscle invasive bladder cancer). Additionally, the risk of MIBC (muscle-invasive bladder cancer) was approximately 1.7 times higher in individuals with a serum vitamin D level below 50 nmol/L compared to those in the compare group. Therefore, it can be concluded that vitamin D deficiency is a significant risk factor for developing bladder tumor, both NMIBC and MIBC. Interestingly, the risk of bladder tumor did not increase with age in individuals with a serum vitamin D level below 50 nmol/L. Moreover, a vitamin D serum level equal to or above 50 nmol/L was found to reduce the risk of bladder tumor by 49% in individuals between the ages of 40 and 49, whereas no significant association was observed in those above 50 years old. Based on these findings, it is strongly recommended that individuals with a vitamin D deficiency take it seriously and ensure adequate intake to prevent the occurrence of serious diseases such as bladder neoplasm.

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website with (ID: CRD42023487519) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1754). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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