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RESEARCH ARTICLE

# Impact of serum vitamin D level on risk of bladder cancer: a systemic review and meta-analysis

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**Abstract** Vitamin D has important biological functions including modulation of the immune system and anti-cancer effects. There was no conclusive finding of the impact of serum vitamin D level on bladder cancer risk. A systemic review and meta-analysis was performed to assess the impact of serum 25-hydroxyvitamin D level on bladder cancer risk. The pooled relative risk (RR) with 95 % confidence interval (95%CI) was used to assess the impact of serum 25-hydroxyvitamin D level on bladder cancer risk. A total of 89,610 participants and 2238 bladder cancer cases were finally included into the meta-analysis. There was no obvious heterogeneity among those included studies ($I^2$=0 %). Meta-analysis total included studies which showed that a high serum 25-hydroxyvitamin D level could obviously decrease risk of bladder cancer (RR=0.75, 95%CI 0.65–0.87, $P$<0.001). In addition, the pooled RRs were not significantly changed by excluding any single study. The findings from the meta-analysis suggest an obvious protective effect of vitamin D against bladder cancer. Individuals with higher serum 25-hydroxyvitamin D levels suffer from less risk of subsequent bladder cancer.

**Keywords** Bladder cancer · Vitamin D · Risk · Meta-analysis

## Introduction

Bladder cancer is a common cancer in the world, which causes about 170,000 deaths each year and results in health problems [1]. Bladder cancer is the fourth most common cancer diagnosed among men and the ninth most common cancer among women in the USA [2]. There are several risk factors identified for bladder cancer and several protective factors of bladder cancer. Cigarette smoking and occupational exposure to certain chemical carcinogens are two common risk factors, while physical activity is associated with decreased risk of bladder cancer [3–5]. Vitamin D is a group of fat-soluble secosteroids and has important roles in human bodies [6, 7]. Vitamin D is first known for its traditional role in bone metabolism, but it has other important biological functions including modulation of the immune system and anti-cancer effects [8, 9]. Vitamin D can be hydroxylated to 25-hydroxyvitamin D in the liver which is the circulating form of vitamin D [10]. Vitamin D has been proven to have anti-cancer effects, and a number of epidemiologic studies have shown the suppressing effects of vitamin D on cancer risk [11, 12]. Some studies have provided strong evidence for the protective effects of vitamin D against colorectal cancer and breast cancer [13–15]. There were also several studies published to assess the impact of serum vitamin D level on bladder cancer risk [16–20]. However, there was no conclusive finding on the impact of serum vitamin D level on bladder cancer risk. Thus, there was no evidence for the association between serum 25-hydroxyvitamin D levels and risk of bladder cancer. A systemic review and meta-analysis was performed to assess the impact of serum 25-hydroxyvitamin D level on bladder cancer risk.

## Methods

### Literature search and inclusion criteria

We performed a literature search in PubMed, EMBASE, and Web of Science databases. Google was also searched to find other unpublished studies on the impact of serum vitamin D level on bladder cancer risk. Annual meeting abstracts of

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American Society of Clinical Oncology (ASCO) in 2013 and 2014 were also searched to find additional studies. There was no language limitation in our study, and the last search was updated on August 20, 2014. The following keywords were used in the meta-analysis: 25-hydroxyvitamin D, vitamin D, or 25(OH)D and bladder cancer or bladder carcinoma. The references of relevant reviews on the association between serum 25-hydroxyvitamin D levels and bladder cancer risk were also checked for other eligible studies not indexed in common databases above. The studies identified from literature search were first assessed for eligibility by reading titles and abstracts. Preliminarily included studies were further assessed by reading full-text articles (Fig. 1).

The inclusion criteria in the meta-analysis were the following: (1) cohort studies, nested case–control studies, or case–control studies; (2) assessing the association between serum 25-hydroxyvitamin D levels and bladder cancer risk; (3) the outcome was the development of bladder cancer or bladder cancer-related mortality; and (4) reporting relative risks (RRs) or hazard ratios (HR) with 95 % confidence intervals (95%CIs) for bladder cancer. Reviews or studies without usable data were all excluded. For multiple reports from the same study, only the article with the largest dataset was included into the meta-analysis.

### Data extraction

The data extraction was performed by two authors independently, and disagreement was resolved by discussion and consensus. The following data were extracted from each included study: first author, publication year, study design, country, number of participants, duration of follow-up, number of bladder cancer cases, and adjusted RRs with 95%CIs of bladder cancer according to serum 25-hydroxyvitamin D levels.

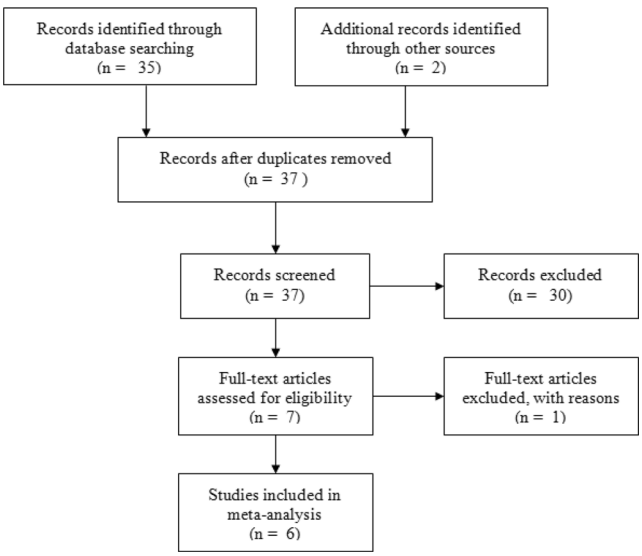


**Fig. 1** Flow diagram showing study selection in the meta-analysis

### Statistical analysis

The cutoff values for the high category or low category of serum 25-hydroxyvitamin D levels were different obviously [16, 18–20]. To maintain uniformity, the RRs with 95 %CIs comparing the highest category with the lowest category of serum 25-hydroxyvitamin D levels were used in the meta-analysis. Heterogeneity was assessed by the $I^2$ statistic, and $I^2$ more than 50 % indicated that obvious between-study heterogeneity existed in the meta-analysis [21]. When there was obvious between-study heterogeneity existing in the meta-analysis, the RRs with 95 %CIs were pooled using a random effect model [22]. When there was no obvious between-study heterogeneity existing in the meta-analysis, the RRs with 95 %CIs were pooled using a fixed effect model [23]. Subgroup analysis was performed by gender (men, women, or mixed). In the sensitivity analysis, the pooled RRs were calculated and compared by excluding any single study. Risk of publication bias was assessed by visual inspection of funnel plot. In addition, Egger's regression test was also used to assess risk of publication bias at the $P<0.05$ level of significance [24]. Trim and fill method was further used to assess risk of publication bias [25]. Statistical analyses were performed using Stata 12.0 (StataCorp, College Station, Texas, USA). Statistical significance of the pooled RRs was taken as two-sided $P<0.05$.

## Results

### Study characteristics

The literature search yielded 32 abstracts, and one study was identified from relevant reviews. After reading the titles and abstracts, 25 studies were removed and 7 potentially relevant studies were preliminarily included [4, 16–20, 26]. After full-text assessment, two articles were further excluded [4, 26]. Thus, five studies were finally included into the meta-analysis [16–20]. There were two cohort studies [16, 18], two nested case–control studies [19, 20], and one case–control study [17]. Those five studies included a total of 89,610 participants and 2238 cases of bladder cancer. Table 1 showed the details on the study design, study populations, time of follow-up, and covariates adjusted for risk estimates of those five studies. All studies were performed in developed countries. There were two studies from the USA and three studies from European countries. There were two studies in men participants and three studies in mixed participants, but there were no relevant studies in women participants (Table 1). All studies provided

**Table 1** Characteristics of five included studies in the meta-analysis

| Study | Study design | Country | Participants | Time of follow-up (years) | Cases of bladder cancer | Adjusted factors |
|---|---|---|---|---|---|---|
| Giovannucci [16] | Prospective cohort | USA | 47,800 | 14 | 382 | Age, height, smoking history, and intakes of total calories, alcohol, red meat, calcium, retinol, and total fruits and vegetables |
| Mondul [20, 26] | Nested case–control | Finland | 29,133 | 12 | 250 | Age and date of baseline blood draw and adjusted for number of cigarettes per day and years of smoking |
| Mondul [19] | Nested case–control | USA | 733 | 13 | 369 | Matching factors, smoking status, pack-years of smoking, dairy consumption, use of aspirin or ibuprofen, and mutually and blood pressure |
| Amaral [17] | Case–control | Spain | 2153 | NA | 1125 | Age, sex, region, smoking status, and season of blood collection |
| Afzal [18] | Prospective cohort | Denmark | 9791 | 28 | 112 | Age, sex, pack-years, body mass index, alcohol consumption, leisure time and work-related physical activity, and duration of education |

the adjusted RRs, though the adjusted confounders were different (Table 1).

### 25-Hydroxyvitamin D levels and bladder cancer

There was no obvious heterogeneity among those included studies ($I^2$=0 %). Meta-analysis total included studies showed that a high serum 25-hydroxyvitamin D level could obviously decrease risk of bladder cancer (RR=0.75, 95%CI 0.65–0.87, $P$<0.001; Fig. 2). In addition, the pooled RRs were not significantly changed by excluding any single study (figure not shown).

Meta-analysis of those three studies in mixed participants found that a high serum 25-hydroxyvitamin D level was significantly associated with decreased risk of bladder cancer (RR=0.73, 95%CI 0.59–0.91, $P$=0.005, $I^2$=24.8 %). Meta-analysis of two studies in men showed that a high serum 25-hydroxyvitamin D level tended to be associated with decreased risk of bladder cancer (RR=0.77, 95%CI 0.53–1.10, $P$=0.151, $I^2$=17.1 %). Subgroup analysis in women was not performed owing to the lack of relevant studies.

There was no evidence of asymmetry in the funnel plot (Fig. 3). In addition, the $P$ value from Egger's linear regression test was 0.57, which further provided evidence for the low risk of publication bias in the meta-analysis. Trim and fill method was further used to assess risk of publication bias, but no missing data were added (Fig. 4). Thus, there was no risk of publication bias in the meta-analysis.

## Discussion

Previous studies suggest that vitamin D can protect against several cancers, but there is no evidence for the association between serum 25-hydroxyvitamin D levels and risk of bladder cancer. Though several studies were published to assess the association between serum 25-hydroxyvitamin D levels and risk of bladder cancer, most of them failed to identify a strong relationship between serum 25-hydroxyvitamin D levels and bladder cancer. To comprehensively assess the effect of serum 25-hydroxyvitamin D level in the development of bladder cancer, a meta-analysis of studies was performed. It was the first meta-analysis of the association between serum 25-hydroxyvitamin D levels and bladder cancer risk. Five studies with a total of 89,610 participants were finally included into the meta-analysis [16–20]. The findings suggest that a high serum 25-hydroxyvitamin D level is associated with decreased risk of bladder cancer, while a low level of serum 25-hydroxyvitamin D is a risk factor of bladder cancer (Fig. 2). The findings from the meta-analysis provide new evidence for the anti-cancer effect of vitamin D.

Among all those five included studies, four studies were prospective studies, which had high quality and could provide a correct estimation on the association between serum 25-hydroxyvitamin D levels and bladder cancer risk. In addition, there was no heterogeneity existing in the meta-analysis, which suggested a consistent estimation of bladder cancer risk by different serum 25-hydroxyvitamin D levels in the included studies. Thus, the lack of heterogeneity showed the

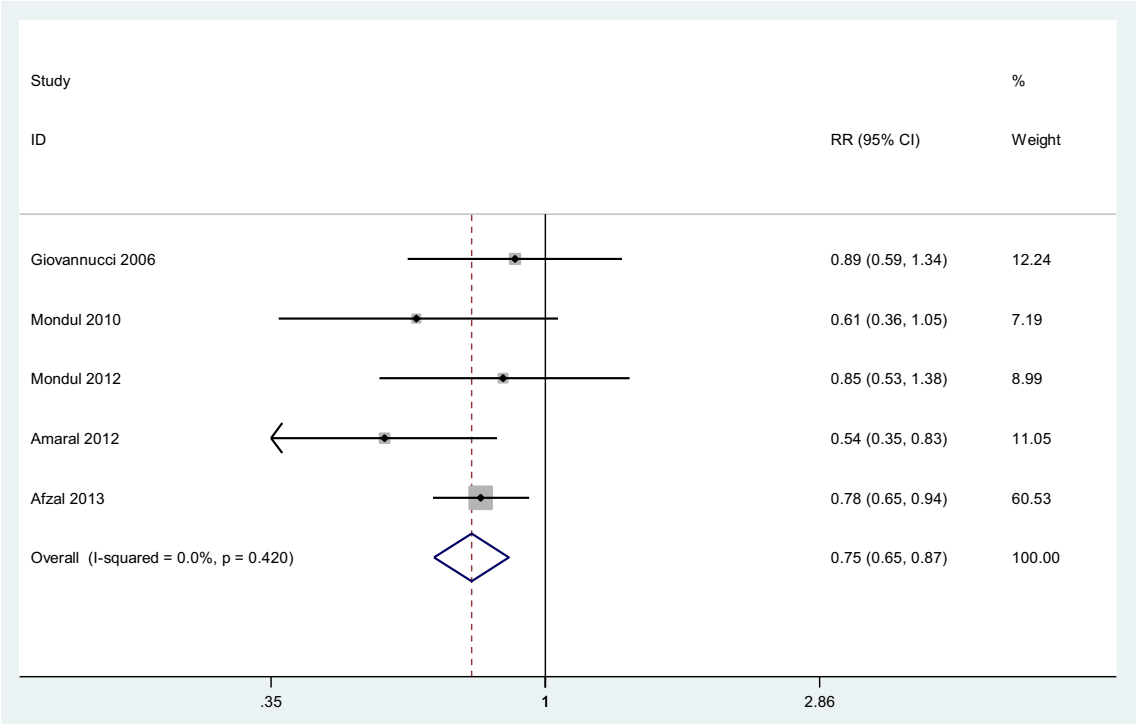


**Fig. 2** High serum 25-hydroxyvitamin D level could obviously decrease risk of bladder cancer

creditability of the pooled results. In addition, the pooled RRs were not significantly altered in the sensitivity analysis, which further indicated the robustness of the pooled estimates in the meta-analysis.

Animal and in vitro studies have shown that vitamin D can suppress tumor progression by reducing cell proliferation and invasiveness and stimulating apoptosis [27, 28]. One laboratory study showed that chemoprevention with vitamin D effectively reduced the tumor promoting effect of tobacco carcinogens in the mouse bladder [27]. Recent studies suggest that high levels of serum 25-hydroxyvitamin D have suppressing effects on the development of colorectal cancer and breast cancer [13, 15, 29]. The findings from this present meta-analysis suggest that high serum 25-hydroxyvitamin D levels were significantly associated with decreased risk of bladder cancer compared with low serum 25-hydroxyvitamin D levels. The findings from the meta-analysis are consistent with previous animal and in vitro experimental studies suggesting that greater exposure to vitamin D could have a role in protecting against bladder cancer. However, there are no trials proving that the dietary supplement of vitamin D can decrease the risk of bladder cancer in

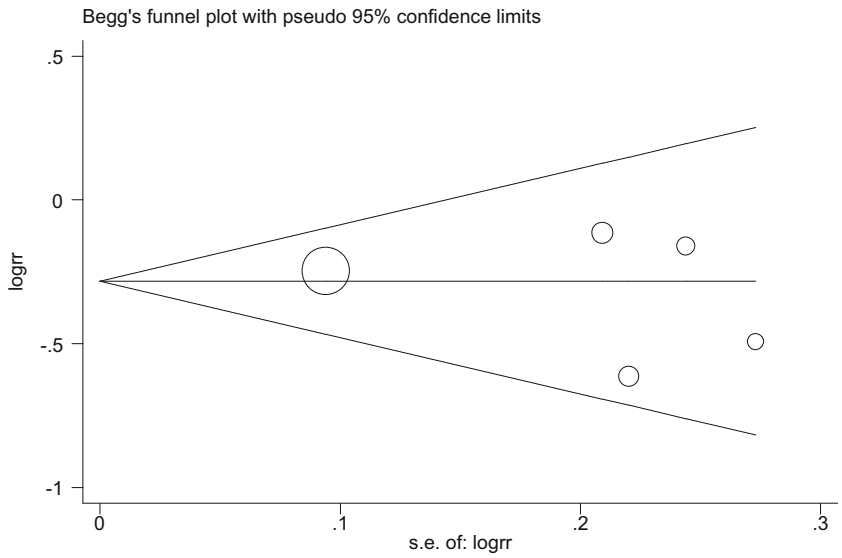


**Fig. 3** Funnel plot showed no evidence of asymmetry in the meta-analysis

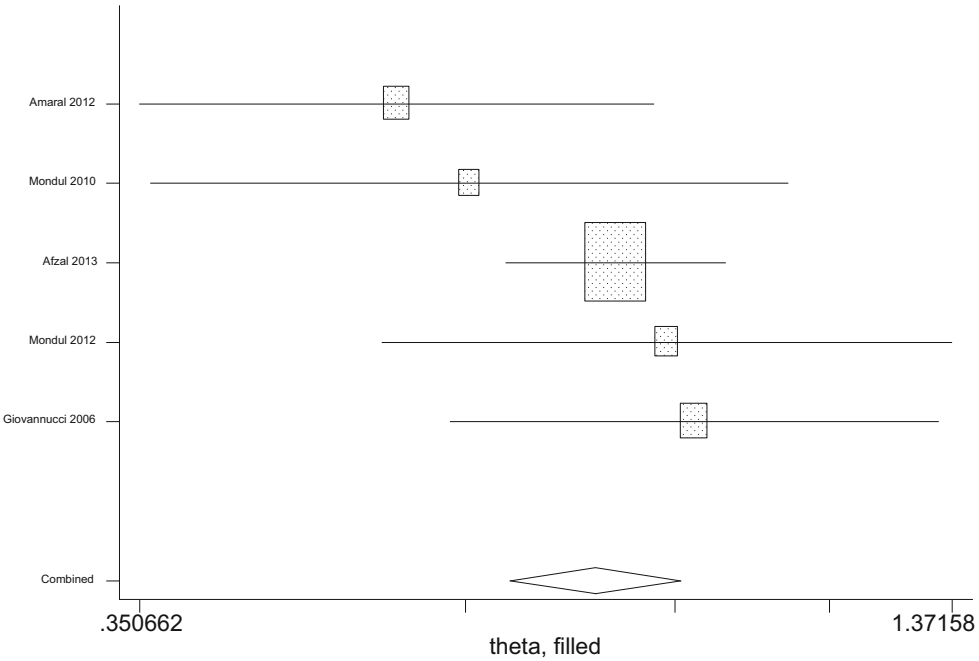


**Fig. 4** Trim and fill analysis showed no missing data in the meta-analysis

individuals with vitamin D deficiency. Further trials are needed to test whether dietary supplement of vitamin D can decrease risk of bladder cancer in individuals with vitamin D deficiency [30, 31].

Similar to other meta-analyses, our meta-analysis also had several limitations. Firstly, there were only five eligible studies in the meta-analysis, and there was no relevant study focusing on the effect of serum 25-hydroxyvitamin D levels on bladder cancer risk in women. Future studies with a well-design sample and large sample size are needed to further identify the protective effect of serum 25-hydroxyvitamin D levels against bladder cancer risk, especially the possible effect in women. Secondly, all included studies in the meta-analysis were from whites' populations; the conclusion may not be generalized to other ethnic groups. Further prospective studies are needed to identify the possible protective effect of serum 25-hydroxyvitamin D against bladder cancer risk in Asian or African populations. Finally, there were only five studies in the meta-analysis. More studies with a well-design sample and large sample size are needed to further identify the protective effect of serum 25-hydroxyvitamin D against bladder cancer.

In conclusion, the findings from the meta-analysis suggest an obvious protective effect of vitamin D against bladder cancer. Individuals with higher serum 25-hydroxyvitamin D levels suffer from less risk of subsequent bladder cancer. In addition, more studies with a well-design sample and large sample size are needed to further identify the protective effect of 25-hydroxyvitamin D against bladder cancer.

**Conflicts of interest** None

## References

1. Apolo AB, Hoffman V, Kaag MG, Latini DM, Lee CT, Rosenberg JE, et al. Summary of the 8th annual bladder cancer think tank: collaborating to move research forward. Urol Oncol. 2014.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60:277–300.
3. Keimling M, Behrens G, Schmid D, Jochem C, Leitzmann MF. The association between physical activity and bladder cancer: systematic review and meta-analysis. Br J Cancer. 2014;110:1862–70.
4. Mohr SB, Garland CF, Gorham ED, Grant WB, Garland FC. Ultraviolet b irradiance and incidence rates of bladder cancer in 174 countries. Am J Prev Med. 2010;38:296–302.
5. Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. Lancet. 2009;374:239–49.
6. Albert PJ, Proal AD, Marshall TG. Vitamin D: the alternative hypothesis. Autoimmun Rev. 2009;8:639–44.
7. Dixon KM, Mason RS. Vitamin D. Int J Biochem Cell Biol. 2009;41:982–5.
8. Plum LA, DeLuca HF. Vitamin D, disease and therapeutic opportunities. Nat Rev Drug Discov. 2010;9:941–55.
9. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol. 2008;8:685–98.
10. Bikle D. Nonclassic actions of vitamin D. J Clin Endocrinol Metab. 2009;94:26–34.
11. Bischoff-Ferrari HA. Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. Adv Exp Med Biol. 2014;810:500–25.
12. Ordonez Mena JM, Brenner H. Vitamin D and cancer: an overview on epidemiological studies. Adv Exp Med Biol. 2014;810:17–32.
13. Lee JE, Li H, Chan AT, et al. Circulating levels of vitamin D and colon and rectal cancer: the physicians' health study and a meta-analysis of prospective studies. Cancer Prev Res (Phila). 2011;4:735–43.
14. Ordonez-Mena JM, Schottker B, Haug U, et al. Serum 25-hydroxyvitamin D and cancer risk in older adults: results from a large German prospective cohort study. Cancer Epidemiol Biomarkers Prev. 2013;22:905–16.

15. Kim Y, Je Y. Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: a meta-analysis. Br J Cancer. 2014;110:2772–84.
16. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst. 2006;98:451–9.
17. Amaral AF, Mendez-Pertuz M, Munoz A, et al. Plasma 25-hydroxyvitamin D(3) and bladder cancer risk according to tumor stage and FGFR3 status: a mechanism-based epidemiological study. J Natl Cancer Inst. 2012;104:1897–904.
18. Afzal S, Bojesen SE, Nordestgaard BG. Low plasma 25-hydroxyvitamin D and risk of tobacco-related cancer. Clin Chem. 2013;59:771–80.
19. Mondul AM, Weinstein SJ, Horst RL, Purdue M, Albanes D. Serum vitamin D and risk of bladder cancer in the prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial. Cancer Epidemiol Biomarkers Prev. 2012;21:1222–5.
20. Mondul AM, Weinstein SJ, Virtamo J, Albanes D. Influence of vitamin D binding protein on the association between circulating vitamin D and risk of bladder cancer. Br J Cancer. 2012;107:1589–94.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.
23. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22:719–48.
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.
25. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. Stat Med. 2007;26:4544–62.
26. Mondul AM, Weinstein SJ, Mannisto S, et al. Serum vitamin D and risk of bladder cancer. Cancer Res. 2010;70:9218–23.
27. Pommergaard HC, Burcharth J, Rosenberg J, Raskov H. Oral chemoprevention with acetyl salicylic acid, vitamin D and calcium reduces the risk of tobacco carcinogen-induced bladder tumors in mice. Cancer Invest. 2013;31:490–3.
28. Krishnan AV, Feldman D. Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. Annu Rev Pharmacol Toxicol. 2011;51:311–36.
29. Chen P, Li M, Gu X, et al. Higher blood 25(OH)D level may reduce the breast cancer risk: evidence from a Chinese population based case–control study and meta-analysis of the observational studies. PLoS One. 2013;8:e49312.
30. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;155:827–38.
31. Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. Lancet Diabetes Endocrinol. 2014;2:307–20.