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Is use of vitamin K antagonists associated with the risk of prostate cancer?
A meta-analysis

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Abstract

Background: Vitamin K antagonists (VKAs) may have potential antitumor effects in prostate cancer. However, the findings of observational studies are inconsistent. The purpose of the present study was to estimate the quantitative association between VKAs use and prostate cancer risk by combining the results of all eligible observational studies.

Methods: PubMed and Web of Science database were searched from inception until May, 2018. A DerSimonian random-effects model was used to combine the studies. Study heterogeneity was measured using the chi-squared and I^2 statistics.

Results: Six eligible studies were eventually included in our meta-analysis. There was an inverse but not statistically significant association between ever use of VKAs and the risk of prostate cancer (relative risk [RR] 0.84, 95% confidence interval [CI] 0.70–1.01, $P = .063$) with large heterogeneity across studies ($P < .001$ for heterogeneity, $I^2 = 94.6\%$). When analysis restricted to long term of VKAs user (>3 years), the pooled risk estimate was 0.83 (0.77–0.90) without obvious heterogeneity ($P = .597$, $I^2 = 0.0\%$).

Conclusion: This meta-analysis indicates that VKAs use may be associated with a decreased risk of prostate cancer, especially in long-term users.

Abbreviations: CI = confidence interval, NOS = Newcastle-Ottawa Scale, OR = odds ratio, RR = relative risk, VKAs = vitamin K antagonists.

Keywords: meta-analysis, prostate cancer, risk, vitamin K antagonist

1. Introduction

Prostate cancer is one of the most common cancers that affect the male population worldwide.[1] According to Torre report published in 2015, there were 1,111,700 new cases and 307,500 deaths estimated to have occurred in 2012.[2] Well-established risk factors for prostate cancer include increased age, race/ethnicity (African–American or Jamaican), and a positive family history.[3] Additional but less established risk factors include physical activity, body mass index, and some dietary factors.[4–7]

Emerging studies have indicated that the coagulation cascade and thrombocytes implicated in the development and progression of cancer, and that anticoagulant drugs could in theory improve prognosis.[8,9] For instance, activated platelets release secretory factors, such as proangiogenic regulatory proteins, chemokines, and microparticles within the microenvironment, to promote tumor growth and metastasis.[10] In addition, thrombocytes coating circulating tumor cells offer a physical shield around tumor cells and, and thereby protecting from immune elimination.[10,11] Vitamin K antagonists (VKAs) are widely used anticoagulants worldwide for a range of indications, including atrial fibrillation, prosthetic heart valves, and venous thromboembolism.[12,13] There is evidence that VKAs, especially warfarin, have strong antitumor and anti-metastatic effects in different experimental cancer model systems.[14,15] Also, in observational studies, such as case-control and cohort studies, the potential relationship between VKAs use and prostate cancer risk has been investigated with inconsistent findings.[16,17]

Up to now, no meta-analysis has been published regarding the relationship between VKAs use and prostate cancer risk. The purpose of the present study was to estimate the quantitative association between VKAs use and prostate cancer risk by performing a meta-analysis of case-control and cohort studies.

2. Materials and methods

2.1. Search strategy

Two investigators (JDL and HZM) independently performed an electronic literature search using PubMed and Web of Science

databases from their inception until May 15, 2018 for studies comparing the incidence of prostate cancer between VKAs users and non-users. There was no restriction on publication language or date. The following keywords were used in search strategy: ("anticoagulants" OR "vitamin K antagonist" OR "warfarin" OR "coumadin") and ("prostate cancer" OR "prostate neoplasm"). Reference lists of included publications, as well as those relevant reviews, were examined for identification of additional potentially relevant studies. This study was approved by the Institutional Ethics Committee of the First Affiliated Hospital of Zhejiang University.

2.2. Study selection

We included observational studies comparing data on prostate cancer risk between VKAs users and non-users. Studies were included if that reported incidence of prostate cancer, included patients treated with VKAs, and compared VKAs users with non-users. Studies were excluded if they did not provide the information of VKAs used, were animal or cell line studies, did not compare VKAs users with non-users, or did not report data about prostate cancer. This systematic review was performed in accordance with the indications of Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[18]

2.3. Study quality assessment

A 9-star Newcastle-Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was used to evaluate the quality of each selected study by 2 independent reviewers (JDL and HZM). NOS judges a study based on 3 subscales: selection (4 items), comparability (1 item), and exposure/outcome (3 items). Each item is awarded 1 point, except for comparability (2 points). A study with ≥7 awarded points is considered as high quality.

2.4. Data extraction

Two authors (JDL and HZM) independently extracted data from the selected studies into a standardized pre-defined form. Any disagreement was resolved by consensus. The following information were extracted: study population characteristics (e.g., sample size, average age of population), duration of follow-up (for cohort studies), region in which the study was performed, parameters related to VKA therapy (e.g., anticoagulation duration, type of VKAs), matched or adjusted variables in study design and analysis, and methods of exposure and outcome assessment.

2.5. Statistical analysis

The primary outcome was the prevalence or incidence of prostate cancer, comparing VKAs ever users with never users. Considering
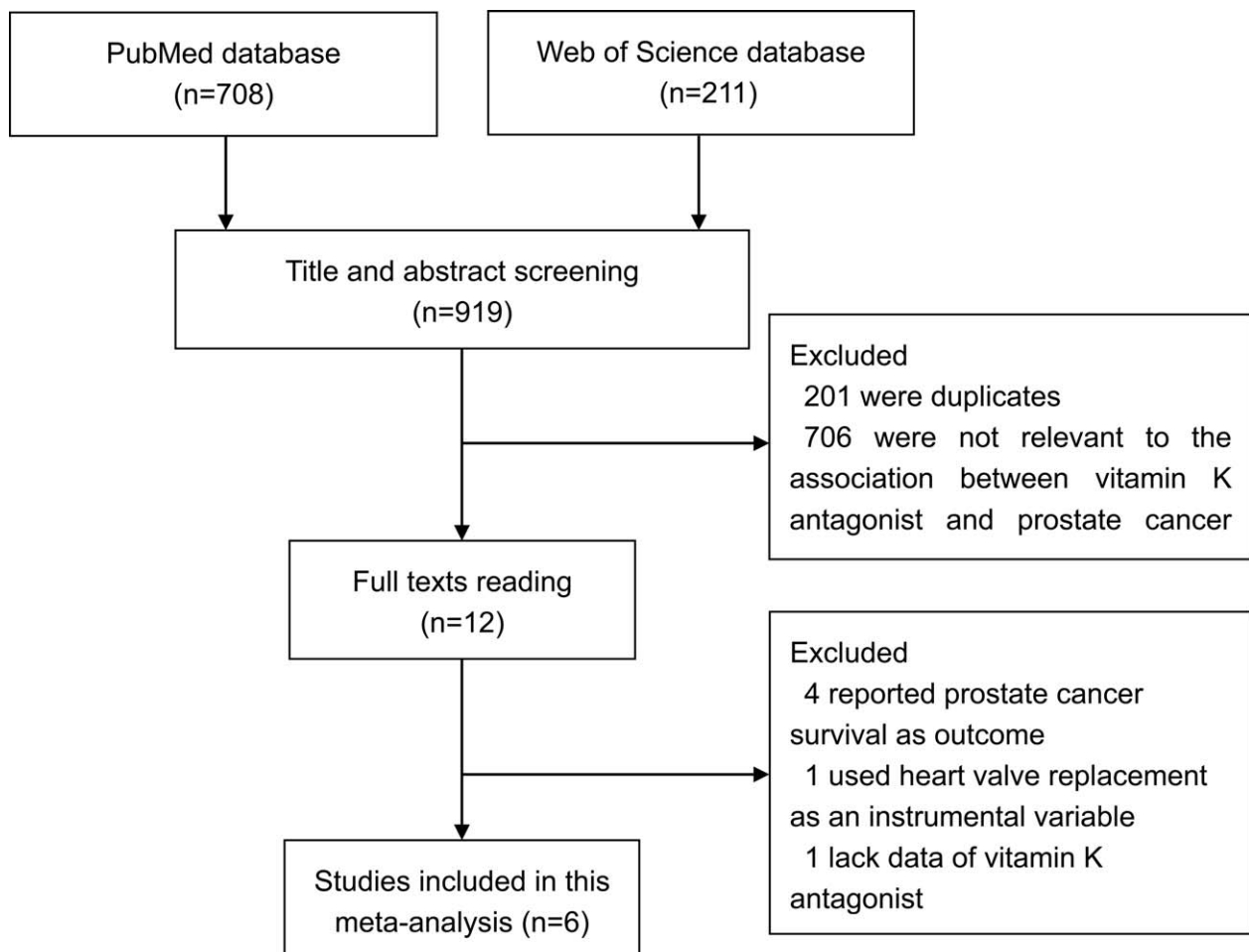

Figure 1. Flow diagram of study selection process.

prostate cancer is a rare disease, the odds ratio (OR) is a close estimator of the relative risk (RR). RR with its 95% confidence interval (CI) was used for summary analysis.

The meta-analysis was performed using STATA 10.0 (Stata-Corp, College Station, TX). When combining studies, the DerSimonian random-effects model[19] was used to account for study heterogeneity. Study heterogeneity was measured using the chi-squared and I^2 statistics, with chi-squared $P \leq .1$ and $I^2 \geq 50\%$ indicating the presence of significant heterogeneity.[20] Because anticoagulation exposure duration could mediate the effect of VKAs on prostate cancer, we also performed preplanned sensitivity (divided according to the duration of VKAs use) analysis. A funnel plot was inspected visually to assess the possibility of publication bias.

3. Results

3.1. Literature search and study characteristics

The detailed steps of literature search are presented in Fig. 1. After excluding 201 duplicates and 706 studies that were obviously not relevant (e.g., reviews, non-human studies, and studies concerning other types of cancer), 12 studies were assessed by full text reading. Four studies that reported survival as outcome, 1 study that reported heart valve replacement as exposure, and 1 study that was lack of enough data were further removed. Six eligible studies[16,17,21–24] were eventually included in this meta-analysis of the association between VKAs use and prostate cancer risk. These studies (3 cohort, 1 nested case-control, and 2 case-control studies) were performed in Canada (n=2) and Europe (n=4). All of the included studies were published between 2007 and 2017. Assessment of exposure and outcome was mainly based on medical records or databases. The study quality scores, assessed by the NOS, ranged from 6 to 8. Table 1 shows the characteristics of each study included in this meta-analysis.

3.2. Overall and subgroup analysis

The multivariable-adjusted RRs for each study and for the combination of all included studies are shown in Fig. 2. Six studies were included in the summary analysis. Pooled risk estimate was calculated with a DerSimonian random-effects model. There was an inverse but not statistically significant association of ever use of VKAs with the risk of prostate cancer (RR 0.84, 95% CI 0.70–1.01, P=.063). Statistically significant heterogeneity was observed across studies (P<.001 for heterogeneity, I^2=94.6%).

Next, we performed subgroup analyses by study design and geographical region. When stratified by study region, the RRs (95% CIs) were 0.93 (0.85–1.02) and 0.82 (0.64–1.05) for studies performed in North America and Europe, respectively. In the subgroup analyses separated by study design, a more pronounced association was detected in case-control studies (RR 0.85, 95% CI 0.78–0.94) than that in cohort studies (RR 0.84, 95% CI 0.85–1.09).

3.3. Sensitivity analysis

We firstly evaluated the impact of each study on the combined RR by repeating the meta-analysis after omitting each study in turn. The summary RRs (95% CIs) ranged from 0.80 (0.67–0.94) to 0.91 (0.80–1.03) by omitting the studies by Kinnunen et al.[16] and Haaland et al.[21], respectively (Fig. 3). In addition, we evaluated the effect of long-term use of VKAs on the risk of prostate cancer. Four studies[17,22–24] provided data for VKAs use >3 years and the pooled risk estimate of these studies using a DerSimonian random-effects model was 0.83 (0.77–0.90) without obvious heterogeneity (P=.597, I^2=0.0%) (Fig. 4). Considering reverse causation bias, we included studies with at least 6-month latency period. Four studies[17,21–23] were eligible and the pooled risk estimate using a DerSimonian random-effects model was 0.75 (0.64–0.89) with significant heterogeneity across studies (P=.002, I^2=80.3%).

Study	RR (95% CI)	Weight(%)
Haaland (2017)	0.69 (0.65, 0.72)	19.91
Kinnunen (2016)	1.06 (0.98, 1.15)	19.49
Blanc–Lapierre (2014)	0.76 (0.50, 1.16)	9.95
Pottegård (2013)	0.86 (0.78, 0.95)	19.13
Pengo (2011)	0.69 (0.50, 0.97)	12.33
Tagalakis (2007)	0.94 (0.85, 1.03)	19.19
Overall (I−squared = 94.6%, p < 0.001)	0.84 (0.70, 1.01)	100.00

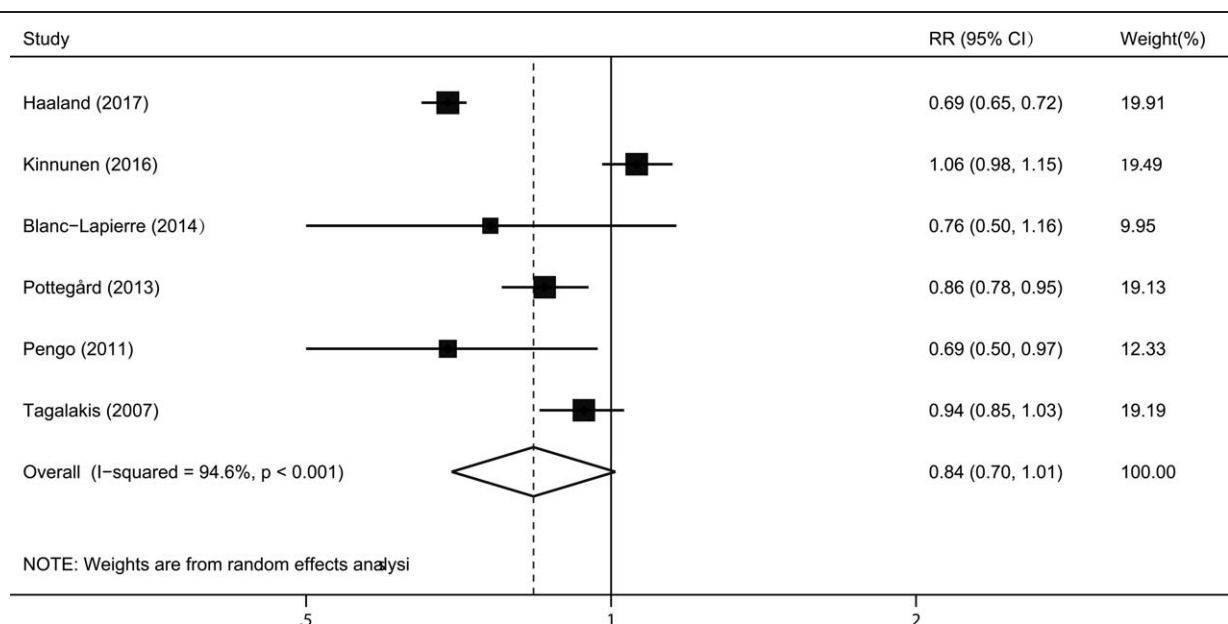NOTE: Weights are from random effects analysi

Figure 2. Relative risk for incident prostate cancer in vitamin K antagonists users compared with non-users.

Table 1

Main characteristics of studies included in this meta-analysis.

Author, year	Design	Country	Study name/source	Follow-up	No. of cases	No. of controls/participates	Exposure assessment	Outcome assessment	NOS	Matched or adjusted variables
Haaland, 2017	Cohort	Norway	Norwegian National Registry	2006–2012 (6.15 y)	NA	1,256,725	Norwegian Prescription Database	Cancer Registry of Norway	7	Age
Kinnunen, 2016	Cohort	Finland	FinRSPC	1995–2009	6537	78,615	National medication reimbursement database	Finnish Cancer Registry	7	Age, use of other drugs and the screening trial arm
Blanc-Lapierre, 2014	Case-control	Canada	PROtEuS	NA	1588	1618	Face-to-face interview	Primary histologically confirmed	8	Age, ethnicity, 5-year prostate cancer screening frequency, family history of prostate cancer, education, diabetes, body mass index and statin use
Pottegård, 2013	Case-control	Denmark	Danish nationwide registers	NA	22,163	157,912	Danish National Prescription Registry	Danish Cancer Registry	7	Age, use of aspirin, NSAID, 5-a-reductase inhibitors, statins and contraceptives and hormone supplements, diagnoses of Crohn disease, colitis ulcerosa, COPD or diabetes, and Charlson comorbidity index
Pengo, 2011	Cohort	Italy	Veneto Region	1996–2007 8.2 y	185	30,771	Public Health Service system	Public Health Service system	6	Age and time to event
Tagalakis, 2007	Nested case-control	Canada	Saskatchewan Health	1981–2002	11,502	69,012	Saskatchewan Cancer Agency's Prescription Drug Plan	registry	7	Age, NSAIDs, ACE inhibitors, other anticoagulant agents, antiplatelet medications, androgen, antiandrogen, and antioestrogen agents

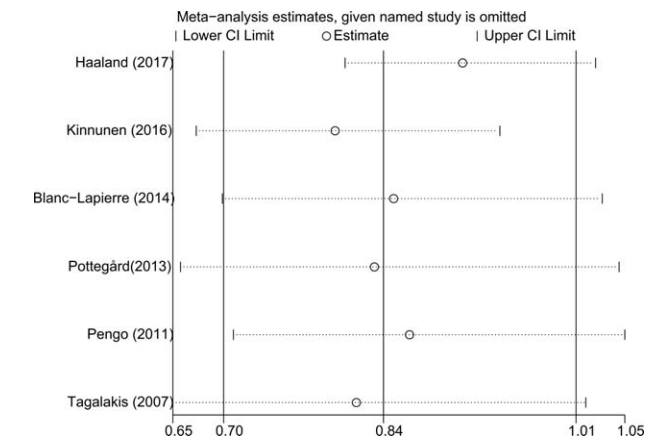NA = not available, No. = number, NOS = Newcastle-Ottawa Scale, y = year.

Figure 3. Sensitivity analysis was performed by repeating the meta-analysis after omitting each study in turn.

3.4. Publication bias

A funnel plot (Fig. 5) is a scatter plot of the studies included in this meta-analysis (represented by black dots) in a space defined by effect size (on the x-axis; scale displayed on top of the plot) and standard error (on the y-axis). A certain degree of asymmetry was observed on funnel plot, which indicated that some publication bias might exist.

4. Discussion

This systematic review and meta-analysis summarized the results of observational studies on the relationship between use of VKAs and prostate cancer risk, including 3 cohort studies, 1 nested case-control studies, and 2 case-control studies. The summary results indicated that VKAs use might be associated with a reduced risk of prostate cancer, especially for those long-term users.

Obvious heterogeneity was observed among the selected studies, which would weaken the findings of this study. The heterogeneity might attribute to the differences in study design, population source, the method of exposure, and outcome assessment, and so on. However, in the analysis of long-term VKAs users, there was no significant heterogeneity and the pooled effect size estimate was statistically significant. We speculated that when analysis restricted to certain population, the heterogeneity was reduced.

An inverse association between VKAs use and prostate cancer risk is biologically plausible. Choo et al[25] reported that fucoidan had anticancer effects on prostate cancer cells through inhibition of PI3K/Akt and MAPK pathway. The study by Rui et al[26] indicated that fucoidan had anti-tumor and anti-angiogenic effects in both cell-based assays and mouse xenograft model by regulating JAK-STAT3 pathway. Tew et al[27] found that vitamin K epoxide reductase (VKOR) expression was not expressed or expressed at very low levels in cancerous cells compared with that in benign human prostate epithelial cells, implying a possible role for VKOR in mediating the effect of VKAs on prostate cancer risk. Neubauer et al[28] found that warfarin had dose-dependent inhibitory effect of on the metastasis of the PAIII prostatic adenocarcinoma in the rat. All these findings imply a new concept that VKAs are potential chemopreventive and chemotherapeutic agents for prostate cancer.

In our meta-analysis, an inverse but not statistically significant association was observed in overall analysis. By contrast, in
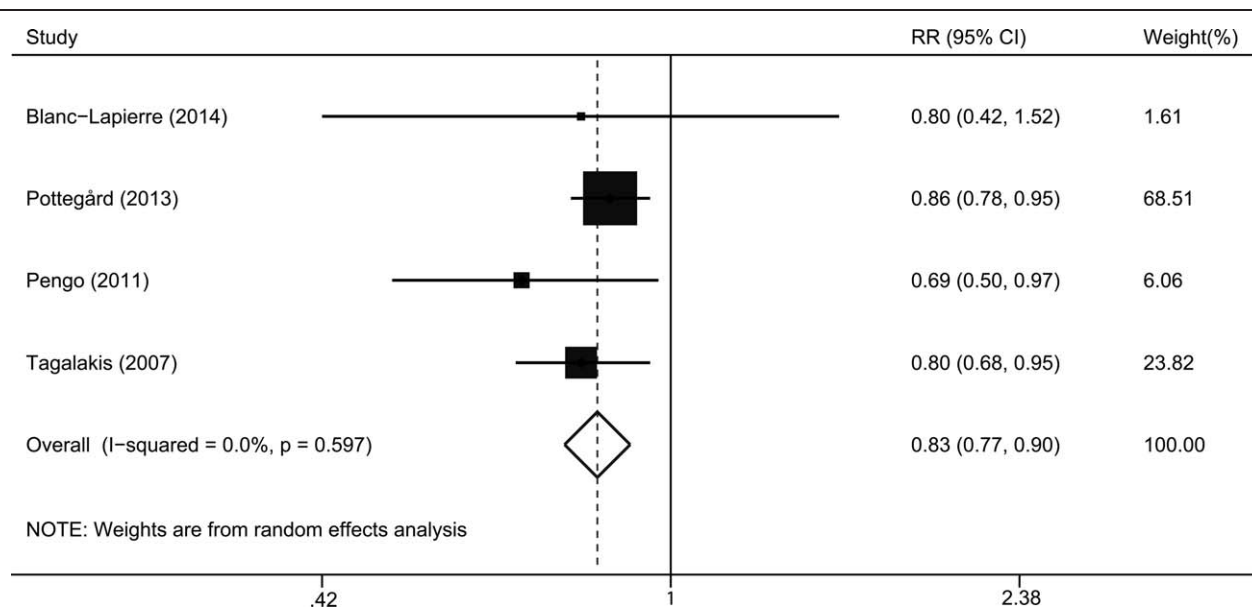
Figure 4. Relative risk for incident prostate cancer in long term vitamin K antagonists users.

sensitivity analysis, we observed that long-term VKAs users had a significant reduced risk of prostate cancer, which indicated that chronic use of VKAs, instead of short-term VKAs use, had a protective effect on prostate cancer. In addition, venous thrombosis embolism (VTE) has been reported to be associated with cancer incidence.[29,30] In our study, when analysis restricted to studies with a 6-month latency period, we also found a significant inverse association between VKAs exposure and prostate cancer risk, which implied a less possibility of reverse causation. However, these secondary analyses were based on sub-population and hence the findings should be treated with caution.

Several important limitations should to be considered in interpreting the findings of current meta-analysis. First, the quality of a meta-analysis mainly depended on the included studies. A meta-analysis is unable to solve the problem of inadequate control of all known confounders in original studies. Second, the current evidence on this association remains limited. Only 6 studies were eligible for this meta-analysis. Third, we

could not quantify a dose–response association since dose data were not available in most included studies. Fourth, patients treated with VAKs are under increased medical surveillance, which may cause detection bias. Lastly, although we have performed a comprehensive literature search, some inevitable publication bias may exist, because gray literature (i.e., conference abstracts) is difficult to find and small negative studies are less likely to be published.

5. Conclusion

This meta-analysis indicates that VKAs use may be associated with a decreased risk of prostate cancer, especially in long-term users. Further large well designed randomized controlled trials with long follow-up are warranted to further evaluate the impact of VKAs use on the risk of prostate cancer.

Author contributions

Conceptualization: Jin-Dan Luo, Jie Luo, Jun Chen, Hong-Zhou Meng.
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Validation: Jin-Dan Luo, Hong-Zhou Meng.
Visualization: Jin-Dan Luo, Hong-Zhou Meng.
Writing – original draft: Jin-Dan Luo, Jie Luo.
Writing – review & editing: Jin-Dan Luo, Hong-Zhou Meng.
Project administration: Jun Chen, Hong-Zhou Meng.
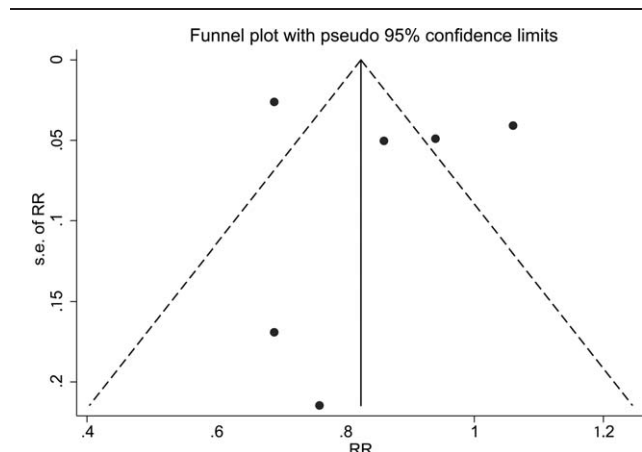**Funding acquisition:** Hong-Zhou Meng.

Figure 5. A funnel plots of studies assessing incident prostate cancer in vitamin K antagonists users compared with non-users.

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