IJC
International Journal of Cancer

Use of vitamin K antagonists and risk of prostate cancer: Meta–analysis and nationwide case–control study

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Use of vitamin K antagonists (VKAs) has been suggested to reduce the risk of prostate cancer. We conducted a nested case–control study using Danish demographic and health data registries and summarized existing evidence in a meta-analysis. The case–control study included all Danish men aged 40–85 years with incident histologically verified prostate adenocarcinoma between 2005 and 2015 (cases). For each case, we selected 10 age–matched controls. We used conditional logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CI) for prostate cancer associated with long–term VKA use adjusted for concomitant drug use, medical history and socioeconomic status. Among 38,832 prostate cancer cases, 1,089 (2.8%) had used VKAs for 3 or more years compared to 10,803 (2.8%) controls yielding a crude OR of 1.01 (95% CI, 0.95–1.08). Multivariable adjustment for covariates had limited influence on the association (OR, 1.03; 95% CI, 0.97–1.10). We observed no dose–response relationship (e.g. OR for 5–10 years of use, 1.06 95% CI, 0.97–1.16). We included 8 studies in the meta–analysis reporting effect estimates from 0.51 (95% CI, 0.23–1.13) to 1.10 (95% CI, 0.94–1.40). Using random effect methods, a pooled effect estimate of 0.86 (95% CI, 0.70–1.05) was obtained; however, there was considerable across–study heterogeneity (I^2: 93.9%). In conclusion, we did not observe a reduced risk of prostate cancer associated with VKA use in this nationwide study and, taken together with previous study findings, a major protective effect of VKAs against prostate cancer seems unlikely.

Introduction

Prostate cancer is the most common non–skin cancer among men in western countries and the incidence continues to rise.[1] The etiology of prostate cancer remains largely unknown and only non–modifiable risk factors have been firmly established (age, genetic factors and ethnicity).[1,2] Consequently, identification of preventive factors for prostate cancer would have a huge impact on public health.

In 2000, a secondary analysis of a randomized controlled trial sparked interest in a possible antineoplastic effect of vitamin K antagonists (VKAs). The authors reported a lower incidence of urogenital cancers in patients treated with VKAs for 6 months compared to patients treated for 6 weeks.[3] This finding was followed by observational studies reporting 20–30% reductions in prostate cancer risk with VKA use[4–7] as well as studies reporting neutral associations.[8–10] In laboratory studies, VKAs have been demonstrated to inhibit Axl–receptor signaling involved in cell growth regulation and to reduce transcriptional activity of the androgen receptor in prostate cancer cells.[11,12]

Given the conflicting epidemiological findings and the potential implications for development of drugs for prevention or treatment of prostate cancer, we conducted a systematic review of the literature, examined the association between VKA use and prostate cancer risk in a nationwide nested case–control study, and pooled the risk estimates from previous and the present study in a meta–analysis.

Key words: anticoagulant drugs, warfarin, prostate cancer, risk factors, case–control studies
Additional Supporting Information may be found in the online version of this article.
Conflict of interest: The authors report no conflicts of interest.
DOI: 10.1002/ijc.31886
History: Received 25 Apr 2018; Accepted 7 Sep 2018; Online 24 Sep 2018
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Methods

Systematic review and meta-analysis

We conducted a systematic review to summarize existing evidence on use of vitamin K antagonists (VKAs) and risk of prostate cancer. We searched PubMed, Embase, and Cochrane Library from inception until April 2018 with no restrictions on language or publication date. We combined free-text (title, subheading, abstract) with thesaurus terms related to prostate cancer and VKA treatment. Appendix B, Supporting Information provides a detailed description of the applied search strategy. Eligible studies included human participants, presented

What's new?

Vitamin K antagonists potentially exert antineoplastic effects on prostate cancer cells and may reduce prostate cancer risk. However, findings from observational studies are conflicting. In the present nationwide study of incident prostate cancers among men in Denmark from 2005–2015, the authors found no evidence linking long–term use of vitamin K antagonists, specifically warfarin and phenprocoumon, to prostate cancer risk. In a systematic review and meta-analysis, the authors reported a high degree of heterogeneity among existing studies. In conclusion, the available evidence did not support a major protective effect of vitamin K antagonists against prostate cancer.

empirical data on VKA use, and reported associations between VKA use and prostate cancer. Titles and abstracts were screened for relevance by 2 medical doctors (KBK and PHJ) independently and disagreements were resolved by consensus. We cross–reference searched all publications selected for full–text screening. Data was extracted by KBK and PHJ independently using a pre-defined data extraction sheet with information on author, year of publication, study design, study setting, study size, exposure definition, confounders, statistical methods, and effect estimates with 95% confidence intervals. For studies reporting effect estimates for several categories of cumulative VKA exposure, we reported those closest to 3 or more years of VKA use corresponding to the main exposure of the present case–control study. For the meta–analysis, we pooled the adjusted effect estimates from the studies identified in the systematic review and the present study using DerSimonian and Laird random effects methods and assessed heterogeneity using Cochran's Q and the I^2–statistic.[13] We further stratified the studies by effect estimate as we analyzed studies reporting risk ratios (RR) or odds ratios (OR) and studies reporting hazard ratios (HR) or incidence rate ratios (IRR) separately. Because the present study partially included the same population as a previous study on VKA use and risk of selected cancers in Denmark,[5] the previous study was omitted from the meta–analysis. Further, we carried out a *post hoc* sensitivity analysis excluding a study with high risk of immortal time bias.[4,14,15]

Case–control study

We conducted a nationwide case–control study comparing use of VKAs in patients with incident prostate cancer (cases) to use in men in the general population without cancer (population controls). Using conditional logistic regression, we estimated ORs for prostate cancer associated with VKA use.

Data sources

We retrieved data from the Danish National Prescription Registry,[16] Danish Cancer Registry,[17] Danish National Patient Registry,[18] Danish Civil Registration System,[19] and Statistics Denmark.[20] Appendix C, Supporting Information provides a detailed description of these registries. The registries were linked individually by the unique Danish Civil Registration Number assigned to all Danish residents.[19] The Danish National Health Care System guarantees free access to medical care and partial reimbursement of prescribed drugs, and this system allows for practically complete identification of individual–level demographic and health registry data for the entire Danish population.

Study population

We sampled our study participants from a nationwide cohort of all Danish men aged 40–85 years. We further required that participants were without previous cancer (except non–melanoma skin cancer) and had resided continuously in Denmark 10 years preceding enrollment. Using the Danish Cancer Registry,[17] we identified all incident, histologically verified prostate cancer cases during Jan 1, 2005 to Dec 31, 2015. For each case, we randomly selected 10 age–matched controls on the date of diagnosis (index date) by risk–set sampling. Participants were eligible for sampling as controls before they became cases. Thereby, the calculated ORs are estimates of the IRRs from a cohort study of the underlying source population.[21]

Exposure

Assessment of VKA use was based on filled prescriptions of warfarin and phenprocoumon recorded in the Danish National Prescription Registry.[16] Our *a priori* main exposure was defined as 3 or more years of VKA use. Furthermore, we modeled exposure as ever–use (at least 1 filled VKA prescription) and, to evaluate any dose–response relationship, as an ordinal variable according to cumulative duration of use (< 1, 1–3, 3–5, 5–10 and > 10 years). To define the duration assigned to each prescription fill, we fitted a reverse waiting time distribution (rWTD) model for warfarin and phenprocoumon prescriptions filled in 2005 adjusting for age and number of pills redeemed (100, 200, 300+).[22] If the next prescription for VKAs occurred within the duration defined by the rWTD model, we assumed that the treatment episode had continued. If it occurred later, we assumed that treatment had been paused. Similarly, the duration assigned to a single prescription and the last prescription was the estimated duration for that given age and package size in the rWTD model. Hereafter, we cumulated the duration of all VKA treatment episodes for each individual. We disregarded all VKA use 2 years prior to the index date (i.e. applied a lag–time of 2 years) to avoid reverse causation bias.[23]

Covariates

Potential confounders included (i) age and calendar time (inherent adjustment by study design); (ii) use of drugs with suggested protective effect against prostate cancer including 5α–reductase inhibitors, α–blocking agents, statins, aspirin and other non–steroidal anti–inflammatory drugs (NSAIDs), angiotensin–converting enzyme inhibitors and angiotensin II receptor blockers;[24–26] (iii) history of type 2 diabetes, ischemic heart disease, congestive heart disease, or chronic obstructive pulmonary disease;[27] (iv) history of conditions with relative contraindication for VKA use including moderate/severe liver disease, moderate/severe kidney disease, heavy alcohol use, gastrointestinal bleeding, and intracranial hemorrhage; and, lastly, (v) highest achieved education as a measure of socio-economic status. Exposure to potential confounding drugs was defined as having filled 2 or more prescriptions on separate dates. A history of potential confounding conditions was based on primary or secondary discharge/ambulatory diagnoses and/or filled prescriptions of drugs used primarily for these conditions (Appendix D, Supporting Information). For all covariates, we introduced a 2–year lag–time as for the primary exposure variable.

Data analysis

We used conditional logistic regression to estimate ORs for prostate cancer associated with VKA use compared to never–use. We evaluated the presence of a dose–response relationship by including duration of treatment as an ordinal variable in conditional logistic regression analyses and by modeling duration of treatment as a continuous variable in unconditional logistic regression analyses. In the unconditional logistic regression analyses, we estimated the incremental OR from each 1–year increase in duration of use and adjusted for age and calendar time as the matching was broken.

Supplementary and sensitivity analyses

Our main exposure was use of any VKA, however, we carried out analyses for warfarin and phenprocoumon separately in sensitivity analyses. In order to evaluate potential effect measure modification, we stratified the main analyses according to age, calendar time, clinical stage based on the TNM classification (Appendix D, Supporting Information),[28] and modified Charlson Comorbidity Index scores (excluding cancer diagnoses).[29] To examine whether the association varied by the presumed primary indication for anticoagulant therapy, we defined a combined exposure measure of VKA use and a diagnosis of atrial fibrillation/atrial flutter or venous thromboembolism. Further, we applied a new–user design by excluding all study subjects having filled a prescription for VKAs during 1995–1996 from our source population. Finally, we varied the length of the lag–time (i.e., the period prior to index date disregarded in the VKA exposure assessment) from 0 to 60 months.

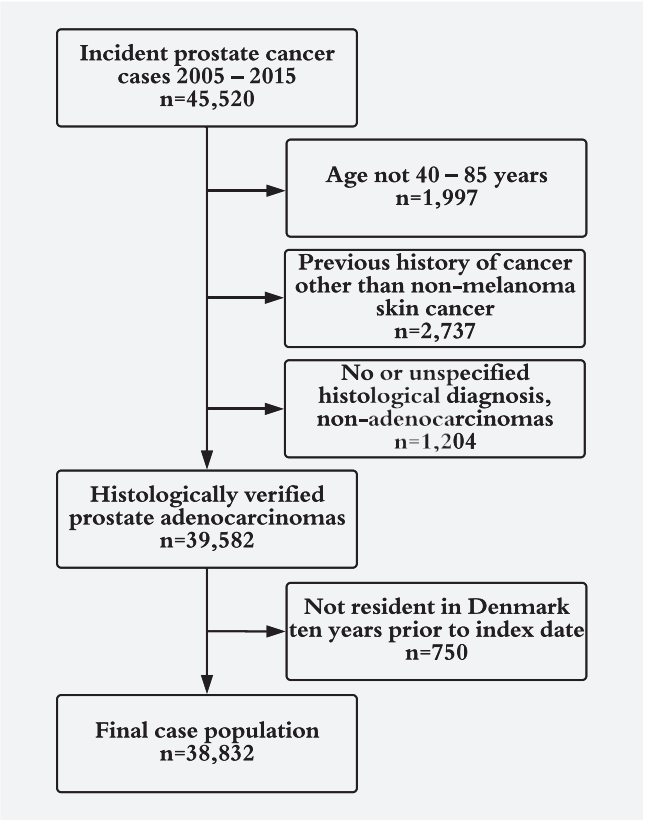

Figure 1. Selection of prostate cancer cases.

Other

All analyses were performed using STATA Release 14.2 (StataCorp, College Station, TX). The Danish Data Protection Agency and Statistics Denmark's Scientific Board approved the study. According to Danish law, ethical approval is not required for registry–based studies.

Results

Case–control study

We included 38,832 prostate cancer cases and 388,320 population controls (Fig. 1). Characteristics were largely similar between cases and controls (Table 1). Among cases, 1,089 (2.8%) were long–term users of VKAs compared to 10,803 (2.8%) among controls, yielding a crude OR of 1.01 (95% CI: 0.95–1.08) (Table 2). Multivariable adjustment for covariates had limited influence on the association (OR, 1.03; 95% CI: 0.97–1.10). We observed no apparent dose–response relationship with ORs of 1.08 (95% CI: 1.02–1.15) for less than 1 year of use and 1.06 (95% CI: 0.97–1.16) for 5 to 10 years of use (Table 2). Likewise, modeling VKA use as a continuous variable resulted in an adjusted incremental OR for each 1–year increase in cumulative duration of use of 1.00 (95% CI: 0.99–1.01, p–value for trend: 0.98).

We identified no apparent effect measure modification by age, modified Charlson Comorbidity Index score, or clinical

Table 1. Characteristics of prostate cancer cases and controls

Characteristic	Cases (n = 38,832)	Controls (n = 388,320)
Age		
Median (IQR, years)	69 (64–75)	69 (64–75)
<65 years	10,191 (26%)	101,910 (26%)
65–75 years	19,594 (50%)	195,940 (50%)
>75 years	9,047 (23%)	90,470 (23%)
Clinical stage (%)[1]		
Localized	23,868 (61%)	NA
Advanced	4,920 (13%)	NA
Unknown	10,044 (26%)	NA
Use of VKA (%)		
Non–use	35,912 (92%)	359,543 (93%)
Ever–use	2,920 (7.5%)	28,777 (7.4%)
Long–term use[2]	1,089 (2.8%)	10,803 (2.8%)
Modified Charlson Comorbidity Index[3] (%)		
0	26,166 (67%)	253,379 (65%)
1	7,323 (19%)	74,342 (19%)
2	2,995 (7.7%)	30,802 (7.9%)
≥3	2,348 (6.0%)	29,797 (7.7%)
Drug use (%)		
5α–reductase inhibitors	1,419 (3.7%)	12,498 (3.2%)
α–blockers	4,062 (10%)	32,081 (8.3%)
Statins	9,989 (26%)	102,701 (26%)
Acetylsalicylic acid	10,313 (27%)	106,521 (27%)
Non–aspirin NSAIDs	21,607 (56%)	205,167 (53%)
ACE inhibitors	9,308 (24%)	94,873 (24%)
ARBs	5,537 (14%)	51,941 (13%)
Medical history (%)		
Diabetes mellitus type 2	2,934 (7.6%)	37,941 (9.8%)
COPD	2,108 (5.4%)	22,190 (5.7%)
Ischemic heart disease or congestive heart failure	6,502 (17%)	68,389 (18%)
Conditions that may contraindicate VKA use	4,647 (12%)	51,493 (13%)
Highest achieved education, years (%)		
Short (7–10)	11,810 (30%)	130,485 (34%)
Medium (11–13)	16,709 (43%)	162,249 (42%)
Long (>13)	9,169 (24%)	78,304 (20%)
Unknown	1,144 (2.9%)	17,282 (4.5%)

Abbreviations: IQR, interquartile range; VKA, vitamin K antagonists; NSAIDs, non–steroidal anti–inflammatory drugs; ACE, angiotensin–converting enzyme inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease.
[1]Defined using TNM codes, please see Appendix D, Supporting Information for details.
[2]Defined as 3 or more years of cumulative duration of use.
[3]Cancer diagnoses were excluded from the Charlson Comorbidity Index.

stage (Table 3). ORs seemed to differ slightly with calendar time ranging from 0.93 (95% CI: 0.82–1.06) for 2005–2008 and 1.11 (95% CI: 1.01–1.22) for 2012–2015.

The analyses combining VKA use with diagnoses of either atrial fibrillation/flutter (OR, 1.04; 95% CI: 0.96–1.12) or venous thromboembolism (OR, 1.11; 95% CI: 0.95–1.30) yielded neutral associations (Appendix A, Supporting Information). The new–user analysis yielded an OR of 1.04 (95% CI: 0.97–1.12) and varying the lag–time from zero months to 60 months did not influence the observed associations (Appendix A, Supporting Information).

Systematic review and meta-analysis

We screened 2,389 titles and abstracts and selected 29 studies for full–text screening (Appendix B, Supporting Information). Of these, 6 studies were included.[4–9] We excluded 18 studies that did not report original data, e.g. reviews or comments 4 studies that reported outcomes unrelated to prostate cancer risk, e.g. prostate cancer survival, and 1 study that reported a composite outcome of urogenital malignancies but not prostate cancer specifically.[30] We identified 2 eligible studies from cross–referencing[3,10] resulting in a total of 8 included studies; 7 observational studies[4–10] and 1 secondary analysis of data from a randomized controlled trial.[3] In the secondary analysis of the randomized trial, patients were assigned to either 6 weeks (n = 419) or 6 months (n = 435) of VKA therapy after first occurrence of venous thromboembolic disease and followed for occurrence of cancer for a mean of 8.1 years from recruitment.[3] In the 6 week arm, 17 patients were diagnosed with prostate cancer during follow–up compared to 9 patients in the 6 month arm yielding a crude RR of 0.51 (95% CI, 0.23–1.13). The observational studies comprised 4 cohort studies and 3 case–control studies and varied substantially regarding patient selection, exposure definition, covariate adjustment, and outcome ascertainment. Key features of the included studies are described in Appendix B, Supporting Information.

After exclusion of a study with a population partly shared by the present study,[5] a total of 8 studies were included in the meta-analysis. The reported effect estimates ranged from 0.51 (95% CI, 0.23–1.13) to 1.10 (95% CI, 0.94–1.40) with considerable across–study heterogeneity (I^2: 93.9%) (Fig. 2). The pooled effect estimate using random effect methods was 0.86 (95% CI, 0.70–1.05). When stratifying by type of effect estimate, heterogeneity was smaller for studies reporting ORs or RRs (I^2: 64.2%) compared to studies reporting HRs or IRRs (I^2: 93.0%). The *post hoc* sensitivity analysis that excluded a study with high risk of immortal time bias[4] showed less heterogeneity for studies reporting rate ratios (I^2: 66.8%) as well as less overall heterogeneity (I^2: 58.4%) (Appendix B, Supporting Information). The pooled effect estimate of this analysis was 0.94 (95% CI, 0.83–1.07).

Discussion

We aimed to summarize existing evidence on the association between VKA use and prostate cancer risk and to examine

Table 2. Odds ratios for prostate cancer associated with vitamin K antagonist (VKA) use compared to non-use

Exposure to VKA	Cases	Controls	Crude OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Non–use	35,912	359,543	1.0 (ref.)	1.0 (ref.)
Ever–use	2,920	28,777	1.02 (0.98–1.06)	1.03 (0.99–1.07)
Long–term use[3]	1,089	10,803	1.01 (0.95–1.08)	1.03 (0.97–1.10)
Cumulative duration (years)				
‹1	1,202	11,171	1.07 (1.01–1.14)	1.08 (1.02–1.15)
1–3	629	6,803	0.93 (0.86–1.01)	0.94 (0.86–1.02)
3–5	403	4,074	0.99 (0.89–1.10)	1.01 (0.91–1.12)
5–10	553	5,314	1.04 (0.95–1.14)	1.06 (0.97–1.16)
›10	133	1,415	0.94 (0.79–1.13)	0.98 (0.81–1.17)

Abbreviations: OR, odds ratio; CI, confidence interval.
[1]Adjusted for age and calendar time (by design).
[2]Adjusted for age, calendar time, and other covariates (see "Covariates").
[3]Defined as 3 or more years of cumulative duration.

Table 3. Odds ratios for prostate cancer associated with 3 or more years of vitamin K antagonist use compared to non-use by patient subgroups

Subgroup	Cases exposed/ unexposed	Controls exposed/ unexposed	Crude OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Age				
‹65 years	96/9,830	811/98,797	1.19 (0.96–1.48)	1.18 (0.95–1.47)
65–75 years	532/18,148	5,238/181,802	1.02 (0.93–1.12)	1.06 (0.97–1.16)
›75 years	461/7,934	4,754/78,944	0.97 (0.88–1.07)	0.98 (0.89–1.09)
Calendar period				
2005–2008	259/12,167	2,794/121,349	0.93 (0.81–1.05)	0.93 (0.82–1.06)
2009–2011	309/10,205	3,146/102,324	0.99 (0.88–1.12)	1.00 (0.89–1.13)
2012–2015	521/13,540	4,863/135,870	1.08 (0.98–1.18)	1.11 (1.01–1.22)
Clinical stage[3]				
Localized	573/22,267	5,931/222,269	0.97 (0.88–1.05)	1.00 (0.91–1.09)
Advanced	153/4,526	1,516/45,269	1.02 (0.86–1.21)	1.04 (0.87–1.24)
Unknown	363/9,119	3,356/92,005	1.09 (0.98–1.22)	1.09 (0.97–1.22)
Modified Charlson Comorbidity Index[4]				
0	392/24,990	3,484/243,206	1.08 (0.97–1.21)	1.05 (0.94–1.17)
1	314/6,522	3,061/66,318	0.99 (0.85–1.15)	1.00 (0.86–1.16)
2	181/2,538	1,860/26,154	1.14 (0.88–1.49)	1.25 (0.95–1.64)
≥3	202/1,862	2,398/23,865	1.12 (0.86–1.47)	1.13 (0.86–1.48)

Abbreviations: OR, odds ratio; CI, confidence interval
[1]Adjusted for age and calendar time (by design).
[2]Adjusted for age, calendar time, and other covariates (see "Covariates").
[3]Defined using TNM codes, please see Appendix D, Supporting Information for details.
[4]Cancer diagnoses was excluded from the Charlson Comorbidity Index.

whether VKA use was associated with a reduced prostate cancer risk in a nested case–control study including all Danish incident prostate cancer cases during 2005–2015. In our case–control study, we did not observe an association between VKA use and prostate cancer risk and we identified no apparent dose–response relationship in analyses with up to 10 or more years of VKA use. In the meta-analysis, we obtained a pooled effect estimate of 0.86 (95% CI, 0.70–1.05), however, the reported associations between VKA use and prostate cancer risk remain conflicting and are derived from studies with a high degree of heterogeneity in several key features, including study design, exposure definition, confounder adjustment, and outcome assessment.

Strengths of our study include the nationwide approach using validated registry data which allowed for identification of virtually all men diagnosed with prostate cancer in the study period and a well–defined base population. Prostate cancer diagnoses were based on the Danish Cancer Registry

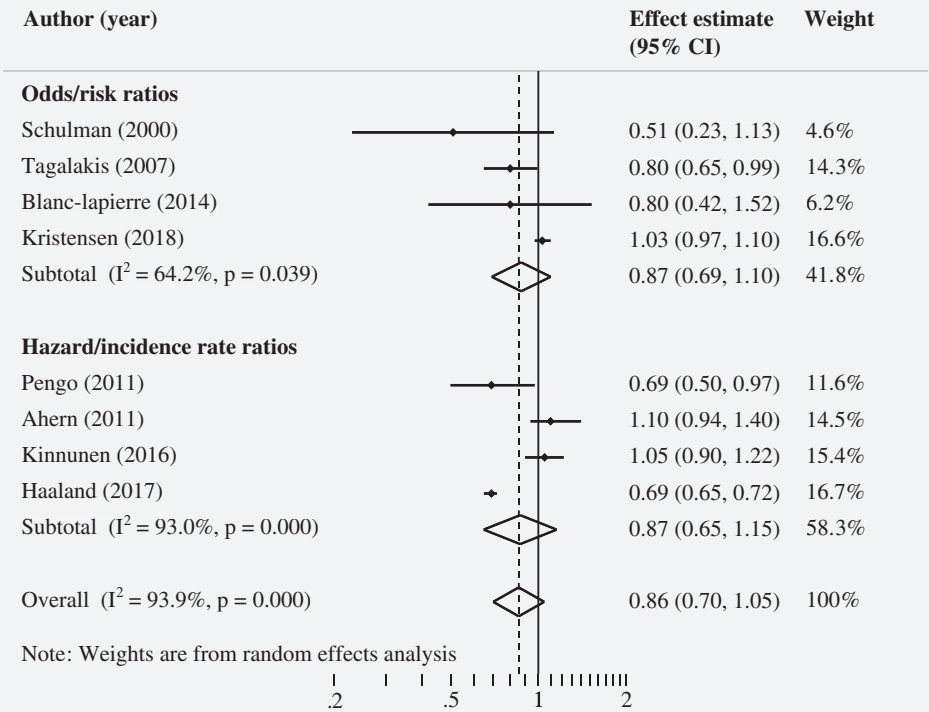

Figure 2. Forest plot of effect estimates with 95% confidence intervals for vitamin K antagonist use associated with prostate cancer stratified by odds/risk ratios and hazard/incidence rate ratios.

known to have high accuracy and completeness with histological verification of all cases further enhancing case validity.[17] Furthermore, the use of the patient and prescription registries allowed us to account for several potential confounding factors and a minimum of ten years of exposure and covariate data was available for all study subjects.[16,18] Limitations include lack of information on lifestyle factors. However, only non–modifiable risk factors for prostate cancer (age, ethnicity, genetic predisposition) have been firmly established.[31] Assessment of drug use by prescription data is associated with some misclassification as in–hospital treatment is not available and non–compliance cannot be quantified. However, the primary care setting accounted for 98.2% of the total sales of VKAs in Denmark during 1996–2015.[32]

Patients treated with VKAs are monitored routinely and may be more likely to undergo screening for prostate cancer than non–users. This may lead to underestimation of a potential protective effect of VKAs against prostate cancer. We did not have data on prostate-specific antigen (PSA) measurements to account for screening frequency directly. However, when stratifying by clinical stage, we found that ORs for VKA use associated with prostate cancer were similar for localized and advanced disease. Two previous studies included data on screening frequency and/or cancer grade. A Canadian case–control study reported that VKA users were screened more frequently in the 5 years prior to index date than non–users (60.8% of VKA–users screened 4 times or more *vs.* 39.2% among non–users).[9] However, adjusting for screening frequency did not lower the effect estimates for prostate cancer risk associated with VKA use compared to the unadjusted analyses. Further, ORs for ever–use of VKA was 0.80 (95% CI, 0.50–1.28) for low grade prostate cancer and 0.70 (95% CI, 0.37–1.34) for high grade prostate cancer similar to the OR for all cancers of 0.76 (95% CI, 0.50–1.16). In a cohort study of men randomized to screening with PSA measurements in 4 year intervals or to no intervention, the HRs associating current VKA use with prostate cancer was 1.01 (95% CI, 0.87–1.17) for men in the screening arm and 1.15 (95% CI, 1.02–1.30) for men in the control arm.[8] However, adjusting for screening arm in the multivariate analyses did not lower the HR compared to the age–adjusted HR. Similar HRs were reported for 2–5 years of VKA use associated with overall prostate cancer (1.05, 95% CI 0.90–1.22), high–grade cancer (1.10, 95% CI 0.88–1.37), and metastasized cancer 1.03 (95% CI, 0.56–1.89).

Another possible source of bias was confounding by indication, however, ORs were similar when we examined VKA use with atrial fibrillation/flutter as presumed indication compared to patients with thromboembolic disease as presumed indication. We addressed reverse causation bias (anticoagulant therapy prescribed for thromboembolic disease caused by a cancer not yet diagnosed) by introducing a lag–time of 2 years.

In sensitivity analyses, varying the lag–time from 0 to 60 months did not alter the obtained ORs, indicating that reverse causation bias probably did not play a major role in our study.

We identified 8 studies in our systematic review of which 1 was a secondary analysis of data from a randomized trial.[3] As a randomized controlled trial, known and unknown confounders were initially accounted for by design. However, this balance likely deviated over the post–intervention follow–up period. Moreover, the study was not powered to detect differences in cancer incidence as reflected in the wide confidence interval (RR 0.51, 95% CI, 0.23–1.13). In 2007, a nested case–control study including 455 exposed prostate cancer cases reported an OR for ever–use of VKAs of 0.94 (95% CI: 0.85–1.03) and an OR for 4 years of use of 0.80 (95% CI: 0.65–0.99).[7] In a Danish case–control study from 2000 to 2009 including 463 exposed prostate cancer cases, we observed an OR for 3 or more years of VKA use of 0.86 (95% CI: 0.78–0.95).[5] The reduced risk estimate in the previous study could, at least partly, be due to changes in clinical diagnoses of prostate cancer and/or VKA use over time, as we did observe a tendency toward increasing ORs with time when stratifying by calendar period. In 2016, a cohort study with 1,210 exposed cases reported a HR of 1.11 (95% CI: 1.01–1.22) for current VKA use and 1.05 (95% CI: 0.90–1.22) for 2 to 5 years of use.[8] Most recently, a cohort study including 1,699 exposed cases reported an IRR of 0.69 (95% CI: 0.65–0.72) for 6 or more months of VKA use,[4] however, this study was prone to immortal time bias as the exposure definition seemed to be dependent on future cancer status.[14,15] Because of the risk of bias pertaining specifically to this cohort study,[4] we decided to perform a *post hoc* sensitivity analysis where this study was excluded from the meta–analysis.

We included 8 studies in the meta–analysis and found a pooled effect estimate of 0.86 (95% CI, 0.70–1.05). A major limitation of our meta–analysis was the considerable heterogeneity between studies. Some heterogeneity was explained by inherent differences between ORs, RRs– and rate–ratios but also by differences in study design, study populations, covariate adjustment, exposure definition, and outcome ascertainment. We used a random effects model to obtain a pooled estimate, however, the pooled estimate should be interpreted with caution given the considerable degree of heterogeneity.

In conclusion, evidence on VKA use and prostate cancer risk is conflicting. The available evidence does not indicate any major protective effect of VKA use against prostate cancer and we found no evidence of a reduced risk of prostate cancer associated with VKA use in our nationwide study on incident prostate cancers in Denmark 2005–2015. Several biological mechanisms for VKAs compatible with anti–neoplastic properties against prostate cancer have been proposed. However, given previous findings and the findings of the current study, it does not appear that these observations translate into any major protective effect of VKA use against prostate cancer in a clinical setting.

Author's contributions

Conception of the work: AP, KBK, SF.
Literature search: KBK, PHJ.
Data analysis: KBK, AP.
Drafting the article: KBK, AP.
Critical revision of the article: All authors.
Final approval of the version to be published: All authors.

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