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Cancer risk in long-term users of vitamin K antagonists: A population-based case–control study

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Some evidence suggests that long-term use of vitamin K antagonists (VKAs) has a cancer chemopreventive effect. Such an effect would have considerable implications in terms of understanding tumor biology. To evaluate if long-term VKA treatment influences the risk of developing cancer, we performed a matched case–control analysis. We used data from four Danish nationwide registers. Cases were all Danish individuals with a first-time cancer diagnosis (except nonmelanoma skin cancer) between 2000 and 2009. For each case, eight controls, matched by birth year and gender, were selected from the source population by risk-set sampling. Long-term VKA use was defined as exposure to VKA for a period of 3 or more years. Conditional logistic regression was used to compute odds ratios (ORs) for cancer associated with long-term VKA exposure, adjusting for potential confounders. Prespecified subanalyses were performed for selected cancer sites, subgroups and measures of exposure. A total of 238,196 cases and 1,713,176 controls were included. The adjusted OR for cancer associated with long-term VKA exposure was 0.99 (95% CI: 0.95–1.02). Long-term VKA use was associated with increased ORs for alcohol- or obesity-related cancer sites, whereas we observed a decreased risk of prostate cancer (OR: 0.86; 95% CI: 0.78–0.95). Our study does not support a general chemopreventive effect of VKA drugs. However, in accordance with findings from previous studies, we found an inverse association between use of VKA and prostate cancer.

Heparins and vitamin K antagonists (VKA) are used routinely in cancer patients as prophylaxis for venous thromboembolism (VTE),[1,2] as VTE is a well-known complication of malignant disease.[3–6] There is solid evidence that hemostasis is involved in tumor progression and metastasis[7–9] and that heparins directly influence tumor progression.[10] Although early experimental and observational studies indicated some inhibitory effects of VKA treatment on tumor progression in small-cell lung cancer,[11,12] these findings could not be replicated in a randomized setting,[13] and the current evidence does not support a major effect of VKA treatment on cancer progression.[14,15]

There is, however, some evidence that VKA treatment protects against development or progression of cancers. In a post-trial study of the protective effect of VKA treatment on the recurrence of VTE,[16] patients who received VKA treatment for 6 months experienced a 40% reduced risk of total cancer compared to patients who received 6 weeks of VKA treatment.[17] The risk reduction was most pronounced for urological cancers. In a similar study, comparing 3 and 12 months of VKA treatment, this association was not replicated,[18] and a small case–control study focusing on bladder cancer similarly found no association.[19] Moreover, two recent cohort studies reported significantly reduced cancer risks associated with long-term VKA treatment, primarily for prostate cancer,[20,21] whereas a third cohort study using heart valve replacement as an instrumental variable for VKA treatment did not confirm the association.[22]

A potential chemopreventive effect of VKA drugs would have considerable mechanistic implications. Therefore, we conducted a population-based case–control study, using a significantly larger sample size than in previous studies, to substantially address the question: Does long-term VKA treatment influence the risk of developing cancer?

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Subjects and Methods

Our study was conducted as a population-based case–control study of incident cancers in Denmark (population about 5.6 million inhabitants) during the period January 1, 2000 to December 31, 2009.

Data sources

We used data from four nationwide registers: the Danish Cancer Registry, the Danish National Patient Register, the Danish National Prescription Registry and the Danish Civil Registration System.

The Danish Cancer Registry[23,24] has recorded incident cases of cancer on a nationwide basis since 1943 and has an accurate and almost complete ascertainment of cancer cases.[23,25] Cancer

What's new?

Vitamin K antagonists (VKA) are used routinely in cancer patients as prophylaxis for venous thromboembolism (VTE) and have been associated with a reduced risk of certain cancers when used long-term. However, other reports have refuted such an association, and this Danish matched case-control analysis further reports no relationship between VKAs and overall cancer risk. The authors did, however, uncover a statistically significant protective effect against prostate cancer, which could have important implications for understanding prostate tumor biology.

diagnoses registered in The Danish Cancer Registry were recorded according to the International Classification of Diseases (ICD) for Oncology from 1977 to 2003 (ICD-O-1-3) and the ICD-10 since 2004.

The Danish National Patient Register contains data on all hospitalizations in Denmark since 1978 and outpatient visits since 1995. Discharge/contact diagnoses are coded according to ICD-8 from 1978 to 1993 and ICD-10 since 1994. Virtually all medical care in Denmark is furnished by the public health authorities, whereby this data resource allows true population-based studies, covering all inhabitants of Denmark.[26]

The Danish National Prescription Registry[27] contains data on all prescription drugs redeemed by Danish citizens since 1995. Prescription data include the date of dispensing, the substance, brand name and quantity. The dosing information and the indication for prescribing are not recorded. Drugs are categorized according to the Anatomic Therapeutic Chemical code, a hierarchical classification system developed by the World Health Organization (WHO) for purposes of drug use statistics.[28] The drug quantity dispensed for each prescription is expressed by the defined daily dose (DDD) measure, also developed by the WHO.[28]

The Danish Civil Registration System[29] contains data on vital status (date of death) and migration to and from Denmark, which allowed us to extract controls and to keep track of all subjects.

All data sources were linked by use of a personal identification number, a unique identifier assigned to all Danish residents since 1968 that encodes gender and date of birth.[29] All linkage was performed within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes.[27]

Cases

Cases were all Danish individuals with a first-time cancer diagnosis (except nonmelanoma skin cancer) between January 1, 2000 and December 31, 2009. Nonmelanoma skin cancers were excluded as they are substantially underreported and their clinical significance is considerably less than for other cancers. We only included cases with histological confirmation of the cancer diagnosis. We further excluded cases who were not inhabitants in Denmark at the date of the cancer diagnosis (index date) or who immigrated to Denmark less than 5 years before the index date.

Controls

Controls were selected by use of a risk-set sampling strategy. For each case, we randomly selected eight controls, matched by gender and birth year, among all Danish citizens. Controls were assigned an index date identical to the date of diagnosis for the corresponding case. Exclusion criteria for cases were also applied to controls, *i.e.*, we excluded controls who had immigrated to Denmark less than 5 years before the index date or who had a cancer diagnosis before the index date. As some of these exclusions were performed after the control selection procedure, the final control:case ratio deviated slightly from 8:1. Study subjects were eligible as controls before they became cases and could be selected as controls more than once. Thereby, the computed odds ratio (OR) is an unbiased estimate of the incidence rate ratio that would have emerged from a cohort study of the source population.[30]

Exposure definition

Cases and controls were considered ever users of VKA if they had redeemed at least one prescription for any VKA more than 1 year before the index date, and long-term users if they had been exposed to VKA for a cumulative period longer than 3 years 1 year before the index date. The 1-year latency period was introduced because the risk of developing VTE is known to increase within the last year before a cancer diagnosis as a consequence of the thrombogenic effects of an as yet subclinical cancer.[4–6] Because VTEs are routinely treated with VKA, the VKA use was expected to increase among cases in the last year before the cancer diagnosis (index date), introducing reverse causation bias.[31] This would mask a genuine protective effect of VKA against cancer development.

The main problem with studies on VKA use is that treatment can be either chronic or episodic. Therefore, we performed exploratory analyses to define the duration that should be assigned to each prescription. An analysis of waiting time distributions[32] revealed that VKA prescriptions that were dispensed more than 15 weeks apart were unlikely to pertain to the same treatment episode. Thus, we assigned each VKA prescription an exposure period of 15 weeks, *i.e.*, 105 days. If the next VKA prescription occurred within this exposure period, we assumed that the treatment episode had continued. If it occurred later, we assumed that treatment had been paused. No adjustment was made for overlaps between prescriptions. Similarly, the exposure period assigned to a single prescription or the last prescription in a treatment episode was 105 days.

Data Analysis

The analysis was performed as a conventional matched case–control study. ORs for cancer associated with VKA exposure

were calculated using conditional logistic regression, with adjustment for potential confounders. In all analyses, VKA use was compared to never use of VKA.

The following potential confounders were included in the regression model: (*i*) use of drugs known or suspected to modify the risk of some cancers, including aspirin (ATC: B01AC06, N02BA01 and N02BA51), non-aspirin NSAID (M01A), 5-α-reductase inhibitors (G04CB), statins (C10AA), angiotensin-II antagonists (C09C and C09D) and contraceptives and hormone supplements (G02BB01, G03AA07, G03AA09, G03AA10, G03AA11, G03AA12, G03AA13, G03AB, G03C, G03D, G03F and G03HB01). Exposure to a confounder drug was defined by a cumulative dose of at least 500 DDD before the index date. (*ii*) Prior diagnoses of diseases known or suspected to modify the risk of some cancers, including colitis ulcerosa (ICD-8: 563.19 and 569.04; ICD-10: K51.0–K51.3) and Crohn's disease (ICD-8: 563.01; ICD-10: K50 and K51.0–K51.3), chronic obstructive pulmonary disease (COPD) (as a crude marker of heavy smoking) (ICD-8: 490.00, 491.00, 491.01 and 491.03; ICD-10: J42, J43 and J44) and diabetes [composite measure of diagnoses (ICD-8: 249.00, 249.09, 250.00 and 250.09; ICD-10: E10–E14) or any prescription for an antidiabetic (ATC-group A10)]. (*iii*) A modified Charlson comorbidity index (CCI) score,[33,34] in which each disease category has an associated weight based on the adjusted risk of 1-year mortality. To ensure comparability between cases and controls, we disregarded cancer diagnoses when computing the CCI score. We defined the levels of comorbidity as low (CCI score: 0), medium (CCI score: 1) and high (CCI score: $\geq$2).

To evaluate the potential influence from confounding life style factors not fully covered by our data sources, we categorized cancers as related to tobacco, alcohol and obesity. Cancers related to tobacco were defined as cancers of the buccal cavity and pharynx, esophagus, stomach, colon/rectum, liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, cervix, ovary, kidney, renal pelvis and ureter, urinary bladder and myeloid leukemia.[35] Cancers related to alcohol were defined as cancers of the mouth, pharynx, esophagus, colon/rectum, liver, larynx and breast.[36] Cancers related to obesity were defined as cancers of the esophagus, colon/rectum, pancreas, breast, endometrium and kidney.[37] Similarly, we defined cancers known to be strongly associated with VTE as cancers of the pancreas, ovary, liver and brain.[4]

In a subanalysis, we used a composite exposure category of long-term (>3 years) VKA treatment and a history of atrial fibrillation. Atrial fibrillation was defined as having a diagnosis of atrial fibrillation (ICD-8: 427.93; ICD-10: I48.9) or having filled a prescription for either verapamil (C08DA01) or digoxin (C01AA05), while excluding those with any previous diagnosis of VTE (ICD8: 45099, −100, −108, −109, −190, −192, −199, −300 and −309; ICD10: I80–I82).

Finally, we performed subgroup analyses specified by age, gender and different measures of comorbidity, and some exploratory analyses with modified exposure, *e.g.*, by duration of treatment and by choice of VKA.

All analyses were performed using Stata Release 12.0 (StataCorp, College Station, TX).

Results

A total of 300,890 cancer cases (except nonmelanoma skin cancer) were registered in the period of case ascertainment (2000–2009). We excluded 33,773 nonprimary cancer cases and 3,099 cancer cases diagnosed among study subject who had emigrated or immigrated within the last 5 years before index date. Finally, we excluded 25,822 cancer cases that were not histologically verified. After these exclusions, the final study population consisted of 238,196 cases and 1,713,176 controls (average of 7.2 controls per case) (Table 1). The median age of cases was 66 (interquartile range: 57–75) years, and 48.9% were male. Among cases, 11,369 (4.8%) had redeemed one or more prescriptions for VKA more than 1 year before the index date (VKA ever users) and 3,425 (1.4%) had used VKA for more than 3 years. The corresponding figures for controls were 73,657 (4.3%) and 21,393 (1.2%). Among cases and controls, 4.1 and 3.6%, respectively, were exposed to warfarin, 1.0 and 0.9% to phenprocoumon and 0.3 and 0.2% to both warfarin and phenprocoumon. All of the included confounders were more prevalent among cases than among controls, notably for comorbidity (CCI score 1: 20.3 *vs.* 17.5%; CCI score $\geq$2: 14.4 *vs.* 11.0%), use of hormone supplements (13.0 *vs.* 11.7%), COPD (6.7 *vs.* 4.3%) and diabetes (7.7 *vs.* 6.6%).

The crude OR for cancer associated with VKA use was 1.08 (95% CI: 1.06–1.10) for VKA ever users and 1.11 (95% CI: 1.07–1.15) for those who were VKA users for more than 3 years (Tables 2 and 3). The corresponding adjusted ORs were 0.98 (95% CI: 0.96–1.00) and 0.99 (95% CI: 0.95–1.02). Overall, the adjustment yielded slightly lower OR estimates.

As expected, the most frequent cancer sites were breast, colon, lung and prostate, altogether accounting for 47.6% of cases. The number of cases specified by cancer site is shown in Table 2 along with the adjusted OR for each cancer site. The adjusted ORs were slightly below unity for cancers of the buccal cavity and pharynx, liver and prostate (OR: 0.62–0.86), whereas the highest ORs were seen for cervical, colorectal and breast cancers (OR: 1.19–1.39). Elevated ORs were found for cancers related to alcohol or obesity, but not tobacco- or VTE-related cancers.

The duration-response analysis (Table 3) yielded risk estimates close to unity, with no differences between warfarin and phenprocoumon, ever use and long-term use, different durations of VKA use or for atrial fibrillation as an underlying indication for VKA. Subanalyses according to age, gender, history of diabetes, absence of VTE or low comorbidity (Table 4) showed only a slightly increased OR associated with long-term VKA exposure among females.

Finally, explorative analyses (results not shown) revealed no changes in the ORs for breast or ovarian cancer when excluding ever users of hormone supplements (OR: 1.33 and 0.85, respectively). Similarly, ORs for prostate cancer

Table 1. Characteristics of cancer cases and their matched controls

	Cases ($n = 238,196$)	Controls ($n = 1,713,176$)
Men	116,380 (48.9%)	841,437 (49.1%)
Women	121,816 (51.1%)	871,739 (50.9%)
Age (years), median (IQR)	66 (57–75)	66 (57–75)
VKA ever users	11,369 (4.8%)	73,657 (4.3%)
Warfarin	9,659 (4.1%)	62,338 (3.6%)
Phenprocoumon	2,325 (1.0%)	15,062 (0.9%)
Both	615 (0.3%)	3,743 (0.2%)
Long-term VKA users	3,425 (1.4%)	21,393 (1.2%)
Warfarin	2,632 (1.1%)	16,441 (1.0%)
Phenprocoumon	827 (0.3%)	5,171 (0.3%)
Both	34 (0.0%)	219 (0.0%)
Charlson comorbidity index (CCI) score		
CCI score = 0	155,445 (65.3%)	1,224,810 (71.5%)
CCI score = 1	48,368 (20.3%)	299,476 (17.5%)
CCI score ≥ 2	34,383 (14.4%)	188,890 (11.0%)
Drugs		
Aspirin	32,770 (13.8%)	224,690 (13.1%)
Non-aspirin NSAID	13,142 (5.5%)	89,281 (5.2%)
5-α-reductase inhibitors	1,349 (0.6%)	8,815 (0.5%)
Statins	15,245 (6.4%)	105,090 (6.1%)
AT-II-Antagonists	12,825 (5.4%)	85,638 (5.0%)
Contraceptives and hormone supplements	30,926 (13.0%)	199,632 (11.7%)
Diagnoses		
Crohn's disease	930 (0.4%)	4,715 (0.3%)
Colitis ulcerosa	1,478 (0.6%)	9,686 (0.6%)
COPD	15,916 (6.7%)	73,771 (4.3%)
Diabetes	18,453 (7.7%)	112,944 (6.6%)
Atrial fibrillation	20,966 (8.8%)	128,620 (7.5%)
Atrial fibrillation and long-term VKA	2,315 (1.0%)	14,876 (0.9%)

Abbreviations: IQR: interquartile range; VKA: vitamin K antagonists; COPD: chronic obstructive pulmonary disease.

remained unchanged when ever users of 5-α-reductase inhibitors were excluded (OR: 0.85). Long-term use of warfarin was inversely associated with prostate cancer (OR: 0.83; 95% CI: 0.73–0.93) when ever users of phenprocoumon were excluded. A slightly higher value was observed for phenprocoumon (OR: 0.94; 95% CI: 0.76–1.17) when ever users of warfarin were excluded.

Discussion

The results of the present large case–control study do not support a general chemopreventive effect of VKA drugs. However, in accordance with results from other studies, we found a reduced risk of prostate cancer associated with the use of VKA drugs.

The main strengths of the study are its size and the nationwide approach, including all diagnosed cancers in the entire Danish population for a period of 10 years. Furthermore, as almost all health care service in Denmark is undertaken by the public health care system and therefore covered by our data sources, we have high population coverage. In addition, the validity of the databases used is generally high.[24–27,29,34]

Our study also has some limitations. The use of prescription data for exposure classification is associated with some misclassification, including in-hospital treatment (in 2010, the in-hospital use of VKA constituted 1.3% of the total use of VKA in Denmark[38]) and noncompliance. Any misclassification is most likely nondifferential, *i.e.*, independent of case status, thereby leading to a conservative bias. Furthermore, we did not have prescription data before 1995 and some study subjects may have used larger amounts of possible carcinogenic or chemopreventive drugs before 1995. However, by limiting the study population to cancer diagnoses from 2000 onward, we ensured a minimum of 5 years exposure history. Furthermore, any drug effect on cancer risk is likely to diminish over time, as shown for, *e.g.*, hormone replacement therapy and breast cancer risk.[39] Our data sources did not include diagnoses made in the primary health care sector, possibly leading to misclassifications of some disease confounders. However, most of the confounder diagnoses in our study will typically require hospital treatment at some point. Furthermore, diagnoses identified from the Danish National Patient Registry have previously been shown to be valid predictors of comorbidity.[34]

Our attempt to avoid reverse causation bias by disregarding VKA use within the last year before the index date is supported by three studies, all of which reported that the occurrence of certain cancer diagnoses was elevated from 6 months to 1 year following a diagnosis of VTE.[4–6] One study suggested a slightly increased risk of up to 10 years after a VTE diagnosis.[5] In addition, we found a slightly lower risk for VTE-related than for non-VTE-related cancers. A reverse causation bias would most likely have resulted in the opposite pattern. All things considered, we thus find it unlikely that our study in any substantial degree would suffer from this source of bias.

Finally, our study might also be influenced by a healthy user/sick stopper bias, as clinicians might be hesitant to initiate VKA therapy or choose to discontinue VKA therapy in terminal or frail patients.[40] This potential bias is most likely partially accommodated by the 1-year latency period before the index date.

The subgroup analysis of tobacco-related cancers did not indicate any apparent confounding. This was to be expected, as tobacco smoking is not known to be associated with any diseases treated with VKA. For obesity- and alcohol-related

Table 2. The association between long-term (>3 years) exposure to VKA and cancer risk, overall and stratified by cancer site

Cancer type	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude OR	Adjusted OR[1]
All malignancies	3,425/226,827	21,393/1,639,519	1.11 (1.07–1.15)	0.99 (0.95–1.02)
Buccal cavity and pharynx	61/6,304	497/46,503	0.86 (0.65–1.12)	0.66 (0.50–0.86)
Esophagus	69/3,100	346/22,628	1.40 (1.07–1.83)	1.17 (0.89–1.53)
Stomach	86/4,155	493/29,925	1.20 (0.95–1.52)	0.95 (0.74–1.20)
Colon	448/19,786	2,371/141,624	1.32 (1.19–1.46)	1.19 (1.07–1.32)
Rectum	39/3,918	239/28,202	1.15 (0.81–1.61)	1.16 (0.82–1.64)
Liver	32/1,887	220/13,768	1.02 (0.70–1.49)	0.62 (0.42–0.93)
Pancreas	74/4,924	465/35,630	1.10 (0.86–1.41)	0.83 (0.65–1.08)
Lung, bronchus and pleura	450/28,661	3,002/205,820	1.05 (0.94–1.16)	0.81 (0.73–0.90)
Melanoma of skin	123/11,614	758/85,133	1.12 (0.93–1.37)	1.16 (0.96–1.42)
Breast	362/37,675	1,853/273,828	1.38 (1.23–1.55)	1.38 (1.23–1.55)
Cervix uteri	19/3,506	98/25,813	1.36 (0.83–2.23)	1.20 (0.73–1.99)
Corpus uteri	56/5,878	366/42,089	1.04 (0.78–1.39)	1.02 (0.77–1.37)
Ovary, fallopian tube, *etc.*	33/4,850	235/34,783	0.96 (0.66–1.38)	0.91 (0.63–1.31)
Prostate	463/21,700	3,707/154,205	0.85 (0.77–0.94)	0.86 (0.78–0.95)
Kidney	73/4,118	362/30,530	1.45 (1.12–1.88)	1.16 (0.89–1.50)
Urinary bladder	302/13,560	1,875/97,190	1.12 (0.99–1.27)	0.98 (0.87–1.11)
Brain	25/4,091	204/30,283	0.86 (0.57–1.32)	0.72 (0.47–1.11)
Non-Hodgkin lymphoma	117/6,968	617/50,681	1.32 (1.08–1.62)	1.14 (0.93–1.40)
Multiple myeloma	58/2,892	314/20,913	1.32 (0.99–1.76)	1.09 (0.81–1.46)
Leukemia	93/5,896	537/42,615	1.20 (0.96–1.50)	1.12 (0.89–1.41)
Other	442/31,344	2,834/227,356	1.08 (0.97–1.19)	0.94 (0.85–1.04)
All tobacco-related cancers	1,921/109,537	11,618/789,562	1.15 (1.10–1.21)	0.96 (0.91–1.01)
All non-tobacco-related cancers	1,504/117,290	9,775/849,957	1.07 (1.01–1.13)	1.02 (0.96–1.07)
All alcohol-related cancers	1,175/79,475	6,521/575,170	1.26 (1.18–1.34)	1.15 (1.08–1.23)
All non-alcohol-related cancers	2,250/147,352	14,872/1,064,349	1.05 (1.00–1.10)	0.92 (0.87–0.96)
All obesity-related cancers	1,274/86,098	6,976/622,246	1.27 (1.20–1.35)	1.19 (1.12–1.26)
All non-obesity-related cancers	2,151/140,729	14,417/1,017,273	1.03 (0.99–1.08)	0.89 (0.85–0.94)
VTE-related cancers	164/15,752	1,124/114,464	1.01 (0.86–1.20)	0.79 (0.66–0.93)
All non-VTE-related cancers	3,261/211,075	20,269/1,525,055	1.12 (1.08–1.16)	1.00 (0.96–1.04)

[1]Adjusted for use of aspirin, NSAID, 5-α-reductase inhibitors, statins and contraceptives and hormone supplements, diagnoses of Crohn's disease, colitis ulcerosa, COPD or diabetes, and Charlson comorbidity index. Abbreviations: VKA: vitamin K antagonists; VTE: venous thromboembolism.

cancers, we observed a clear association between long-term VKA use and an increase in cancer risk. However, there is significant overlap between cancer sites related to obesity and alcohol. For cancers related to alcohol but unrelated to obesity, *i.e.*, buccal cavity, pharynx and liver (Table 2), we found significantly reduced ORs. This is compatible with alcoholism and liver failure being contraindications to VKA treatment.[36] Obesity is also a plausible confounder as it is known to be associated with both cancer[37] and VTE.[41] Our findings confirm these associations, suggesting that obesity was the most significant uncontrolled confounder in our study. Our finding of a difference in the overall risk estimate according to gender is primarily a result of the differences in risk estimates for the two frequent gender-specific cancer types: breast cancer among females (OR: 1.38) and prostate cancer among men (OR: 0.86).

Two previous studies of the relationship between VKA drugs and cancer risk compared short-term VKA treatment (6–12 weeks) with longer VKA exposure (6–12 months).[16–18] Both studies can be criticized for not having a prespecified hypothesis and for comparing two active treatments, only differing in the duration of the treatment. In 2004, Blumentals *et al.* published a small case–control study[19] showing no association between VKA treatment and bladder cancer risk, which is in agreement with our findings. A cohort study of 3,231 VKA users reported an inverse association between

Table 3. The association between VKA exposure and cancer risk, specified by exposure pattern

Subgroup	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude OR	Adjusted OR[1]
VKA, ever users	11,369/226,827	73,657/1,639,519	1.08 (1.06–1.10)	0.98 (0.96–1.00)
Warfarin	9,659/226,827	62,338/1,639,519	1.09 (1.06–1.11)	0.99 (0.97–1.01)
Phenprocoumon	2,325/226,827	15,062/1,639,519	1.09 (1.04–1.14)	0.97 (0.93–1.02)
VKA, use > 3 years	3,425/226,827	21,393/1,639,519	1.11 (1.07–1.15)	0.99 (0.95–1.02)
Warfarin	2,632/226,827	16,441/1,639,519	1.11 (1.06–1.16)	0.99 (0.95–1.03)
Phenprocoumon	827/226,827	5,171/1,639,519	1.12 (1.04–1.20)	0.98 (0.91–1.06)
VKA use > 3 years and AF[2]	2,315/226,827	14,876/1,639,519	1.08 (1.03–1.13)	0.96 (0.91–1.00)
Duration of VKA use				
VKA use < 1 year	4,886/226,827	32,575/1,639,519	1.05 (1.02–1.08)	0.97 (0.94–1.00)
VKA use 1.0–2.9 years	2,988/226,827	19,272/1,639,519	1.09 (1.05–1.13)	0.99 (0.95–1.03)
VKA use 3.0–4.9 years	1,791/226,827	10,977/1,639,519	1.14 (1.08–1.20)	1.01 (0.96–1.07)
VKA use 5.0–6.9 years	934/226,827	6,024/1,639,519	1.07 (1.00–1.15)	0.95 (0.88–1.02)
VKA use 7.0–8.9 years	475/226,827	3,015/1,639,519	1.08 (0.98–1.20)	0.96 (0.87–1.06)
VKA use > 9 years	295/226,827	1,794/1,639,519	1.13 (1.00–1.28)	0.99 (0.87–1.12)

The reference for all analyses is never use of VKA. All cancer sites are included.
[1]Adjusted for use of aspirin, NSAID, 5-α-reductase inhibitors, statins and contraceptives and hormone supplements, diagnoses of Crohn's disease, colitis ulcerosa, COPD or diabetes, and Charlson comorbidity index. [2]Long-term VKA use with atrial fibrillation was compared with VKA never use without atrial fibrillation, *i.e.*, excluding those with VKA never use and atrial fibrillation. Abbreviations: VKA: vitamin K antagonists; AF: atrial fibrillation.

Table 4. The association between long-term exposure to VKA and cancer risk, specified by patient subgroup

Subgroup	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude OR	Adjusted OR[1]
All	3,425/226,827	21,393/1,639,519	1.11 (1.07–1.15)	0.99 (0.95–1.02)
Male	2,204/109,194	14,717/793,347	1.04 (1.00–1.09)	0.92 (0.88–0.97)
Female	1,221/117,633	6,676/846,172	1.26 (1.19–1.34)	1.12 (1.05–1.19)
Age < 60 years	194/71,473	1,077/541,705	1.36 (1.17–1.59)	1.05 (0.90–1.22)
Age 60–80 years	2,311/127,546	14,507/911,283	1.12 (1.07–1.17)	0.99 (0.95–1.04)
Age > 80 years	920/27,808	5,809/186,531	1.05 (0.98–1.13)	1.01 (0.94–1.08)
CCI score = 0	842/152,145	6,013/1,200,780	1.06 (0.98–1.15)	1.06 (0.98–1.15)
No history of VTE	2,858/222,785	18,217/1,619,000	1.10 (1.05–1.14)	0.97 (0.93–1.01)
Diabetes	649/16,593	3,580/102,177	1.08 (0.92–1.26)	0.99 (0.84–1.16)

All cancer sites are included.
[1]Adjusted for use of aspirin, NSAID, 5-α-reductase inhibitors, statins and contraceptives and hormone supplements, diagnoses of Crohn's disease, colitis ulcerosa, COPD or diabetes, and Charlson comorbidity index (CCI). Abbreviations: VKA: vitamin K antagonists; CCI: Charlson comorbidity index; VTE: venous thromboembolism.

long-term VKA treatment and cancer risk (RR: 0.88, 95% CI: 0.80–0.98), with an additionally reduced risk of prostate cancers (RR: 0.69, 95% CI: 0.50–0.97).[21] In that study, all study subjects with a history of VTE before enrollment were excluded. A case–control study of urogenital cancers, similar to ours in methodology, reported an incidence rate ratio of 0.80 (95% CI: 0.65–0.99) for prostate cancer with use of warfarin,[20] which is very close to our estimate of 0.83. Although this association was not seen in a recent cohort study,[22] including a subset of our study population, the association between long-term VKA exposure and prostate cancer risk has been replicated in multiple studies and warrants further evaluation.

In conclusion, we did not find any apparent association between use of VKA drugs and cancer risk overall; however, our results support the hypothesis of a protective effect of VKA drugs against prostate cancer. This association warrants further investigation and, if found causal, may have important implications for understanding tumor biology.

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