Cancer Risk in Long-term Users of Vitamin K Antagonists: A Population-Based Case-Control Study

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Conflicts of interest

JH has participated in research projects funded by Novartis, Pfizer, Menarini, MSD, Nycomed, Astellas and Alkabello with grants paid to the institution where he was employed. JH has received fees for teaching or consulting from Nycomed, Astellas, Pfizer, Novartis, Astra Zeneca, Menarini, Leo Pharmaceuticals and Ferring. JH and SF have personally received fees for teaching from the Danish Association of Pharmaceutical Manufacturers. AP declares no conflicts of interest.

Background

Some evidence suggests that VKA-treatment could protect against development of *de novo* cancers (1;2), especially prostate cancer (3;4). A potential chemopreventive effect of VKA-drugs would have considerable public health implications.

Objective

We conducted a population-based case-control study of incident cancers in Denmark to address the question: Does long-term VKA-treatment influence the risk of developing cancer?

Table 1
The association between long-term exposure to VKA and cancer risk, overall and stratified by cancer site

Cancer type	Cases Exposed /unexposed	Controls Exposed /unexposed	Crude OR	Adjusted OR *
All malignancies	3,425 / 226,827	21,393 / 1,639,519	1.11 (1.07–1.15)	1.06 (1.02–1.10)
Buccal cavity and pharynx	61 / 6,304	497 / 46,503	0.86 (0.65–1.12)	0.81 (0.62–1.07)
Esophagus	69 / 3,100	346 / 22,628	1.40 (1.07–1.83)	1.31 (1.00–1.72)
Stomach	86 / 4,155	493 / 29,925	1.20 (0.95–1.52)	1.13 (0.89–1.43)
Colon	448 / 19,786	2,371 / 141,624	1.32 (1.19–1.46)	1.25 (1.13–1.39)
Rectum	39 / 3,918	239 / 28,202	1.15 (0.81–1.61)	1.15 (0.81–1.62)
Liver	32 / 1,887	220 / 13,768	1.02 (0.70–1.49)	0.84 (0.57–1.25)
Pancreas	74 / 4,924	465 / 35,630	1.10 (0.86–1.41)	0.96 (0.74–1.24)
Lung, bronchus and pleura	450 / 28,661	3,002 / 205,820	1.05 (0.94–1.16)	0.91 (0.82–1.01)
Melanoma of skin	123 / 11,614	758 / 85,133	1.12 (0.93–1.37)	1.15 (0.94–1.40)
Breast	362 / 37,675	1,853 / 273,828	1.38 (1.23–1.55)	1.39 (1.24–1.56)
Cervix uteri	19 / 3,506	98 / 25,813	1.36 (0.83–2.23)	1.27 (0.77–2.09)
Corpus uteri	56 / 5,878	366 / 42,089	1.04 (0.78–1.39)	1.04 (0.78–1.38)
Ovary, fallopian tube etc.	33 / 4,850	235 / 34,783	0.96 (0.66–1.38)	0.96 (0.66–1.38)
Prostate	463 / 21,700	3,707 / 154,205	0.85 (0.77–0.94)	0.86 (0.77–0.95)
Kidney	73 / 4,118	362 / 30,530	1.45 (1.12–1.88)	1.34 (1.04–1.75)
Urinary bladder	302 / 13,560	1,875 / 97,190	1.12 (0.99–1.27)	1.06 (0.94–1.21)
Brain	25 / 4,091	204 / 30,283	0.86 (0.57–1.32)	0.88 (0.58–1.35)
Non-Hodgkin lymphoma	117 / 6,968	617 / 50,681	1.32 (1.08–1.62)	1.29 (1.05–1.58)
Multiple myeloma	58 / 2,892	314 / 20,913	1.32 (0.99–1.76)	1.32 (0.99–1.77)
Leukemia	93 / 5,896	537 / 42,615	1.20 (0.96–1.50)	1.19 (0.95–1.49)
Other	442 / 31,344	2,834 / 227,356	1.08 (0.97–1.19)	1.03 (0.92–1.14)

* Adjusted for use of aspirin, NSAID, 5-α-reductase inhibitors, statins, contraceptives and hormone supplements, diagnoses of Crohn's disease, colitis ulcerosa, COPD or diabetes, and Charlson Comorbidity Index.

Data material

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.

Cases were all Danish individuals with a histologically verified primary cancer diagnosis (except non-melanoma skin cancer) between January 1, 2000 and December 31, 2009. For each case, we randomly selected eight controls, matched by gender and birth year, among all Danish citizens.

Data analysis

The analysis was performed as a conventional matched case-control study. Odds ratios (ORs) for cancer associated with VKA exposure was calculated using conditional logistic regression, with adjustment for potential confounders. In all analyses, long term VKA-use was compared to never-use of VKA. Long-term VKA-use was defined as being exposed to VKA for a cumulative period longer than three years prior to one year before the index date.

The following potential confounders were included in the regression model: a) Use of drugs known or suspected to modify the risk of some cancers; b) Prior diagnoses of diseases known or suspected to modify the risk of some cancers and c) a modified Charlson Comorbidity Index (CCI) score.

Results

We identified 238,196 eligible cases and 1,713,176 controls..

The crude OR for cancer associated with VKA use was 1.08 (95% CI, 1.06–1.10) for VKA ever-use and 1.11 (95% CI, 1.07–1.15) for long-term VKA use. The corresponding adjusted ORs were 1.04 (95% CI, 1.02–1.07) and 1.06 (95% CI, 1.02–1.10) (Table 1). The OR for prostate cancer was 0.86 (0.77-0.95)

Elevated ORs were found for cancers related to alcohol or obesity, but not tobacco- or VTE-related cancers (data not shown). Duration-response analysis yielded risk estimates close to unity. Sub-analyses according to age, gender, history of diabetes, absence of VTE, or low comorbidity showed only a slightly increased OR associated with long-term VKA exposure among those aged <60 years and among females (data not shown).

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.

Strengths:

- Study size and the nationwide approach.
- High population coverage.
- The validity of the databases used is generally high.

Limitations:

- Use of prescription data for exposure classification is associated with some misclassification.
- Our data sources did not include diagnoses made in the primary health care sector, possibly leading to misclassifications of some disease confounders.
- Possible 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.

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