Use of warfarin and risk of urogenital cancer: a population-based, nested case-control study

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Summary

Background **Indirect evidence suggests that prolonged treatment with warfarin might be associated with a decreased incidence of urogenital cancer. We aimed to assess this association in a large population-based study.**

Methods **Beneficiaries of Saskatchewan Health who were eligible for prescription drug benefits and aged 50 years or over with no history of cancer since 1967 were enrolled into a nested, matched case-control study. 19 412 new cases of urogenital cancer diagnosed between Jan 1, 1981, and Dec 31, 2002, were identified by use of information from the Saskatchewan Cancer Agency registry. For each case, six controls, totalling 116 470, who were matched for age, sex, and time of diagnosis were selected randomly. Conditional logistic regression analysis was used to calculate adjusted incidence rates of urogenital cancer in relation to warfarin use.**

Findings **Compared with men who never used warfarin, men with 4 years of warfarin use had an adjusted incidence rate of 0·80 (95% CI [0·65–0·99]). For warfarin use 76–100% of the time, the adjusted rate ratios were 0·80 (0·66–0·96) during year 2 preceding diagnosis of prostate cancer, 0·76 (0·62–0·94) during year 3, and 0·67 (0·53–0·86) during year 4. No significant association was found between warfarin and risk of other urogenital cancers.**

Interpretation **Our results suggest that warfarin has an antitumour effect that is specific to prostate cancer. Further investigation, with more complete assessment of confounders and that addresses the effect of warfarin on mortality of prostate cancer, is warranted.**

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Introduction

Interest is growing in the anticancer properties of warfarin. Initial clinical research focused on the effect of warfarin on cancer survival.[1] Recent studies of secondary analyses of data from randomised clinical trials that used different durations of warfarin treatment for venous thromboembolism have shown mixed results of the effect of warfarin on cancer risk.[2,3] In one of these studies, patients who received 6 months of warfarin were less likely to be diagnosed with cancer than patients who received 6 weeks of warfarin (odds ratio [OR] 0·63 [95% CI 0·42–0·91]) during 8·1 years (range 6·6–9·6) of follow-up.[2] The difference between groups was mainly attributable to urogenital cancers, which included kidney, urinary bladder, prostate, ovarian, and uterine cancer (OR 0·40 [0·20–0·77]). However, data from another trial that compared 3 months to 1 year of warfarin treatment after a first episode of idiopathic deep-vein thrombosis, did not show a difference in the incidence of any cancer after a mean follow-up of 3·6 years.[3]

To investigate further the effect of warfarin on the risk of the urogenital cancers, we did a population-based, case-control study with data obtained from the Saskatchewan Cancer Agency registry and the administrative databases of Saskatchewan Health.

Methods

Participants and procedures

The source population consisted of all residents of Saskatchewan, Canada, who were aged 50 years or over, who were registered with Saskatchewan Health, and eligible for prescription drug benefits between Jan 1, 1981, and Dec 31, 2002, with no previous history of cancer since 1967 (except, because of inconsistent reporting to cancer registries, non-melanoma skin cancer, and in-situ carcinoma of the cervix).

Saskatchewan, a Canadian province with a population of around one million, has a universal publicly-funded health system, part of which, Saskatchewan Health—a provincial government department that together with regional health agencies—provides health services to over 99% of Saskatchewan residents.[4] Excluded are people whose health care is covered entirely by a federal government plan. This includes members of the Royal Canadian Mounted Police and Canadian Forces and inmates of federal penitentiaries, which account for less than 1% of the total Saskatchewan population.[4] Saskatchewan Health coordinates a wide variety of province-wide programmes, such as the Prescription Drug Plan and Medical Services, and as a result, has accumulated extensive health-care data in computerised databases. Each person registered with Saskatchewan Health is assigned a unique personal identification number, which enables electronic-record linkage between the department's databases, including the Prescription Drug Plan, and with the Saskatchewan Cancer Agency's registry.

The Saskatchewan Health Prescription Drug Plan was first introduced in 1975, and provides drug coverage to all eligible Saskatchewan residents for outpatient prescriptions, including those dispensed to residents of long-term care facilities. Residents ineligible for coverage

under the plan include around 9% of the population, mainly registered Indian people, who receive these benefits from the federal government.[4] Data in the prescription drug database between July 1, 1987, and Dec 31, 1988, were incomplete because of administrative changes to the plan during this time.

Participants of this study were entered into the source population on the latest of the following dates: the beginning of the study period (Jan 1, 1981) if they were aged 50 years or over; their 50th birthday; or date of initiation of coverage with Saskatchewan Health if aged 50 years or over. Participants exited the source population on the earliest of the following dates: at the end of the study period (Dec 31, 2002); date of diagnosis of a first urogenital tumour; date of death; or date of termination of health coverage. The most common reason for termination (other than death) was emigration from the province. We chose to study participants who were 50 years or over because they represent the population most likely to be prescribed warfarin and most at risk for urogenital cancers.

Cases of urogenital cancer were identified as all participants in the source population who were diagnosed according to the International Classification of Diseases for Oncology (ICD-O) codes[5] with any urogenital cancer (prostate (ICD-O C61), urinary bladder (ICD-O C67), kidney (ICD-O C64), ovary (ICD-O C56), or uterus (ICD-O C54 and C55), and who were registered with the Saskatchewan Cancer Agency between Jan 1, 1981, and Dec 31, 2002. Registration of cancer cases in the Saskatchewan Cancer Agency, which has been computerised since 1967, is thought to be nearly complete because provincial legislation mandates physicians to report all new cancer diagnoses to the Saskatchewan Cancer Agency and copies of all malignant pathology reports are sent to the appropriate cancer clinics.[6] These two notification processes capture about 98% of all newly diagnosed cases of cancer in the province, and an additional 1–2% of cases are identified through death certificate notifications.[6] Good concordance exists between cancer recordings in the Saskatchewan Cancer Agency registry with those in hospital charts or death certificates (kappa statistic 0·93 [95% CI 0·89–0·97]).[7]

To obtain an unbiased estimate of incidence rate ratios, incidence-density sampling was done whereby controls were selected randomly from members of the source population who were free of any cancer and at risk for developing cancer at the time of case diagnosis. Individual matching was used. For each case, six controls were selected randomly from members of the source population who were of the same age (±1 year) and sex, and who were alive and free of cancer on the date (month) of diagnosis of the corresponding case by use of a computer-generated randomisation method that was done by Saskatchewan Health. To be included in the study, both cases and controls had to have at least 5 years of continuous coverage with Saskatchewan Health before the diagnosis of cancer in the case. This ensured that sufficiently long records of drug use would be available for analysis, and that all study participants had at least 5-year treatment histories. The date of cancer diagnosis for the case was labelled as the index date for the case and the six matched controls.

Data on exposure to warfarin were compiled by use of information from the outpatient prescription drug database between the later of either first-ever coverage initiation or Jan 1, 1976, and the index date. Only the 5 years of coverage immediately preceding the index date had to be continuous. Coverage history more than 5 years earlier could be interrupted. For each warfarin prescription, the following data were provided: a unique study-specific identification number; identity of the drug; number of tablets dispensed; dose per tablet dispensed; and dispensing date. The intended duration of treatment covered by each prescription was not available. Two different approaches were used to assess exposure to warfarin preceding the index date. In the first approach, the overall exposure to warfarin in the 5-year period before the index date (ie, year –1, year –2, year –3, year –4, year –5) was characterised by two exposure indices: ever use and cumulative exposure. Ever use was defined as at least one warfarin prescription in years –2, –3, –4, or –5. In all analyses, exposure to warfarin in year –1 (the year immediately preceding the index date) was excluded from exposure calculations to avoid protopathic bias. Cumulative exposure was defined as the number of years of warfarin use during the 5-year period, while again excluding year –1, and was categorised as follows: 1-year's use was defined as one prescription in the 4-year period; 2-years' use was at least one prescription per year for 2 years; 3-years' use was at least one prescription per year for 3 years; and 4-years' use was at least one prescription per year for the 4 years –2 to –5.

The second approach assessed the timing of warfarin use on the incidence of urogenital cancers by dividing the entire coverage period into intervals. The 8-year period immediately preceding the index date was divided into 1-year periods, and the more remote coverage period before the index date was divided as follows: 9–11 years; 12–14 years; 15–17 years; and 18–20 years. Also, two exposure indices were calculated for each period: ever exposure and duration of use. Ever exposure was defined as at least one warfarin prescription in each of the constructed periods preceding the index date. The second exposure index, duration of use, was defined by dividing each of the constructed periods into 3-month intervals, and then calculating the proportion of intervals in which a warfarin prescription was dispensed. For example, in the period of 13–24 months before the index date, a warfarin prescription in one 3-month interval represented 25% duration of use for that period, a prescription in two 3-month intervals constituted 50% duration of use, a prescription in three 3-month intervals represented 75%

duration of use, and a prescription in all four intervals represented 100% duration of use for the interval. As in the cumulative warfarin-exposure analyses, warfarin use in the year immediately preceding the index date was not included in the analyses.

In all analyses, participants registered with Saskatchewan Health during the 18-month prescription gap period (July 1, 1987 to Dec 31, 1988) were deemed unexposed to warfarin during this period to keep the power of the study to a maximum—ie, we did not exclude from the analyses participants who had incomplete prescription histories as a result of this gap period.

Data on other treatments, which were thought to represent potential confounders, were also compiled from the outpatient prescription drug database, and included the treatment category and dispensing date. The treatments included: oestrogens, androgens, antioestrogens, antiandrogens, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelet agents, angiotensin-converting enzyme (ACE) inhibitors, and non-warfarin anticoagulants, such as low-molecular-weight heparin. For example, ACE inhibitors were deemed a potential confounder because they might be co-prescribed with warfarin, since hypertension—which is often treated with ACE inhibitors—is a risk factor for atrial fibrillation, the most common indication for warfarin. Furthermore, some data link ACE inhibitors to the development of prostate cancer.[8,9] Exposure to any of the potentially confounding agents depended on the exposure index under consideration, and was defined by whether a prescription for this treatment class was dispensed during the specific period.

The study protocol was approved by the Internal Review Board of the Saskatchewan Cancer Agency and the Regina Qu'Appelle Health Region Research Ethics Board. Because the study used deidentified administrative data maintained by Saskatchewan Health and deidentified administrative data by Saskatchewan Cancer Agency, no individual consent was obtained. Saskatchewan Health was responsible for the linkage, preparation, and deidentification of the datasets. Only data relevant to the study were provided for analyses.

Statistical analyses

Conditional logistic regression was used to calculate matched OR, with 95% CI, to estimate incidence rate ratios. Additionally, for exposures measured on a continuous scale, we tested for a linear trend using a formal test of trend (p trend). In all models, we controlled for the potentially confounding effects of other drugs that might be related to the occurrence of urogenital cancers. We also checked for the presence of multicollinearity of warfarin and the other drugs in the models constructed. None was found. All data management and analyses were done by use of SAS version 8.0.

	Prostate cancer		Bladder cancer		Kidney cancer		Uterine cancer		Ovarian cancer	
	Cases (n=11 502)	Controls (n=69 012)	Cases (n=3424)	Controls (n=20 544)	Cases (n=1601)	Controls (n=9605)	Cases (n=1800)	Controls (n=10 799)	Cases (n=1085)	Controls (n=6510)
Mean age at index date, years (SD)	73 (9)	73 (9)	72 (10)	72 (10)	69 (10)	69 (10)	67 (10)	67 (10)	69 (11)	69 (11)
Age distribution at index date, years (%)*										
50–59	743 (6)	4465 (6)	425 (12)	2541 (12)	312 (19)	1875 (20)	448 (25)	2688 (25)	258 (24)	1545 (24)
60–69	3288 (29)	19 741 (29)	961 (28)	5791 (28)	528 (33)	3155 (33)	628 (35)	3764 (35)	294 (27)	1770 (27)
70–79	4973 (43)	29 816 (43)	1252 (37)	7486 (36)	532 (33)	3204 (33)	491 (27)	2944 (27)	331 (31)	1987 (31)
80–89	2215 (19)	13 296 (19)	656 (19)	3950 (19)	214 (13)	1281 (13)	218 (12)	1307 (12)	173 (16)	1031 (16)
≥90	283 (2)	1694 (3)	130 (4)	776 (4)	15 (1)	90 (1)	15 (1)	96 (1)	29 (3)	177 (3)
Sex (male %)	11 502 (100)	69 012 (100)	2564 (75)	15 384 (75)	984 (61)	5904 (61)	0	0	0	0
Median prescription history, years (IQR)	17·5 (12·1–22·4)	17·5 (12·0–22·4)	16·1 (10·7–21·4)	16·1 (10·7–21·4)	16·2 (11·1–21·6)	16·1 (11·1–21·5)	15·6 (10·1–21·3)	15·6 (10·0–21·2)	15·9 (10·4–20·9)	15·8 (10·3–20·9)
Ever use of warfarin before index date (%)	856 (7)	4907 (7)	210 (6)	1227 (6)	111 (7)	517 (5)	82 (5)	469 (4)	50 (5)	296 (5)
Median number of warfarin prescriptions (IQR)	4·0 (2·0–16·0)	6·0 (2·0–22·0)	6·0 (2·0–19·0)	5·0 (2·0–17·0)	3·0 (2·0–11·0)	5·0 (2·0–20·0)	4·0 (1·0–16·0)	5·0 (2·0–20·0)	4·0 (2·0–9·0)	4·0 (2·0–16·0)
Median number of warfarin prescriptions per year of drug coverage (IQR)	0·3 (0·1–0·9)	0·3 (0·1–1·1)	0·4 (0·1–1·0)	0·3 (0·1–0·9)	0·2 (0·1–0·7)	0·3 (0·1–1·1)	0·2 (0·1–0·8)	0·3 (0·1–0·9)	0·2 (0·1–0·5)	0·2 (0·1–0·9)
Median number of warfarin tablets per prescription (IQR)	11·4 (4·8–44·0)	14·8 (4·8–57·1)	16·4 (5·5–52·4)	13·6 (4·8–46·2)	7·7 (3·8–36·8)	13·0 (5·3–61·1)	9·3 (4·5–41·5)	12·4 (4·7–45·7)	10·6 (4·6–39·1)	10·0 (4·0–41·0)

*Percentages might not add up to 100 due to rounding.

Table 1: **Characteristics of study population**

	Prostate cancer			Bladder cancer			Kidney cancer		
	Cases (n=11 502)	Controls (n=69 012)	Adjusted* incidence rate ratio (95% CI)	Cases (n=3424)	Controls (n=20 544)	Adjusted† incidence rate ratio (95% CI)	Cases (n=1601)	Controls (n=9605)	Adjusted† incidence rate ratio (95% CI)
Exposure									
Never	11 047	66 157	1·00 (reference)	3300	19 839	1·00 (reference)	1544	9305	1·00 (reference)
Ever	455	2855	0·94 (0·85–1·03)	124	705	1·04 (0·87–1·25)	57	300	0·99 (0·76–1·30)
Cumulative exposure‡									
1-year's use	228	1302	1·01 (0·89–1·16)	54	346	0·94 (0·72–1·23)	32	146	1·16 (0·81–1·65)
2-years' use	92	527	1·00 (0·82–1·23)	27	137	1·14 (0·78–1·67)	13	48	1·30 (0·75–2·25)
3-years' use	44	333	0·81 (0·60–1·09)	15	77	1·12 (0·67–1·86)	1	34	0·18 (0·03–1·31)
4-years' use	91	693	0·80 (0·65–0·99) p=0·03§	28	145	1·15 (0·79–1·68) p=0·38§	11	72	0·77 (0·42–1·40) p=0·38§

*Adjusted for NSAIDs; ACE inhibitors; other anticoagulant agents; antiplatelet medications; androgen, antiandrogen, and antioestrogen agents. †Adjusted for NSAIDs, ACE inhibitors, other anticoagulant agents, antiplatelet medications, and phenacetin. ‡Reference group is never exposure. §Trend for duration of use.

Table 2: **Incidence rate ratios for prostate, bladder, and kidney cancer according to ever use and cumulative warfarin exposure in the 5-year period before index date**

Role of the funding source

This study was funded by a peer-reviewed grant from the National Cancer Institute of Canada (number 14201). The sponsor of the study had no role in study design, data collection, data analysis, or data interpretation. Only VT and HT saw the raw data, but all authors had full access to the raw data if they wished. The corresponding author had final responsibility to submit for publication.

Results

In Jan 1, 1981, to Dec 31, 2002, 11 502 cases of prostate cancer, 3424 bladder cancer, 1601 kidney cancer, 1800 uterine cancer, and 1085 ovarian cancer were diagnosed in the source population. Table 1 shows the mean age and age distribution of the 19 412 cases and 116 470 controls, and the histories of their warfarin prescriptions. Men with prostate cancer and their matched controls had the highest prevalence of ever use of warfarin before the index date. This finding is expected because prevalence of warfarin use varies with age and sex. Generally, men have a higher use of warfarin compared with that of women, and warfarin use increases with age. In our study, the mean age of men with prostate cancer was 73 years (SD 9) and that of women with uterine cancer was 67 years (SD 10).

Tables 2 and 3 show the association between cumulative warfarin use in the 5 years preceding the index date and the incidence of each type of urogenital cancer. We found a marginally lower risk of prostate cancer for men with 4 years of warfarin use compared with those who did not receive warfarin. 4 years of warfarin use in the 5-year period immediately preceding the index date was associated with a rate ratio of 0·80 (95% CI 0·65–0·99). The statistical test for linear trend for duration of use was statistically significant (p=0·03). We did not find any statistically significant associations between the other urogenital cancers and ever or cumulative warfarin use in the 5 years preceding the index date (data not shown).

Table 4 summarises the incidence rate ratios for prostate cancer by period before diagnosis. We found a trend towards a decreasing rate ratio for prostate cancer with increasing duration of warfarin use during years 2 (p=0·0278), 3 (p=0·0181), 4 (p=0·0035), and 5 (p=0·0199) preceding the index date. For warfarin use, 76–100% of the time the rate ratio was 0·80 (0·66–0·96) during year 2, 0·76 (0·62–0·94) during year 3, 0·67 (0·53–0·86) during year 4, and 0·81 (0·62–1·04) during year 5. Increasing duration of use in the subsequent time periods was not associated with a decreased risk of prostate cancer. As in the cumulative analysis, we did not find any statistically significant associations between the timing of warfarin use and the other urogenital cancers (data not shown).

To assess the effect of assuming that participants were unexposed to warfarin during the 18-month prescription gap period, we did a sensitivity analysis by restricting the cumulative years of exposure analyses to the cohort of participants with index dates between Jan 1, 1994, and Dec 31, 2002. This analysis ensured that at least 5 years of

	Uterine cancer			Ovarian cancer		
	Cases (n=1800)	Controls (n=10 799)	Adjusted* incidence rate ratio (95% CI)	Cases (n=1085)	Controls (n=6510)	Adjusted* incidence rate ratio (95% CI)
Exposure						
Never	1754	10 538	1·00 (reference)	1062	6346	1·00 (reference)
Ever	46	261	0·98 (0·73–1·33)	23	164	0·82 (0·54–1·25)
Cumulative exposure						
1-year's use	27	128	1·16 (0·79–1·71)	12	85	0·82 (0·46–1·46)
2-years' use	8	48	0·90 (0·44–1·82)	2	23	0·58 (0·14–2·31)
3-years' use	2	31	0·40 (0·10–1·61)	1	20	0·33 (0·05–2·36)
4-years' use	9	54	0·93 (0·48–1·80) p=0·54†	8	36	1·21 (0·59–2·51) p=0·63†

*Adjusted for NSAIDs; ACE inhibitors; other anticoagulant agents; antiplatelet medications; ovulant, oral contraceptive, and antioestrogen agents. †Trend for duration of use.

Table 3: **Incidence rate ratios for uterine and ovarian cancer according to ever use and cumulative warfarin exposure in the 5-year period before index date**

exposure history without interruption was available for all participants. The resulting adjusted incidence rate ratios of prostate cancer in men with ever (rate ratio 0·94 [0·90–0·99]) and 4-years of cumulative use (0·76 [0·61–0·96]) were similar to those from the unrestricted analysis (table 2).

Discussion

To our knowledge, this is the first large population-based epidemiological study that has been specifically designed to report on the association between warfarin use and risk of urogenital cancer. Our results indicate that prolonged warfarin use was associated with a marginal decrease in risk of prostate cancer. Specifically, at least 4 years of cumulative warfarin use was associated with a significant decrease in the incidence rate ratio of prostate cancer (0·80 [95% CI 0·65–0·99]) in the incidence of prostate cancer. Also, increasing duration exposure to warfarin in years 2, 3, 4, and 5 preceding the index date was associated with a significant trend towards a decreasing rate ratio for prostate cancer during these years.

Important strengths of this study include the absence of recall bias because we used prerecorded prescription histories that were collected prospectively for all participants. Also, the likelihood of misclassification of cancer cases was low because of the reliability of the data from the cancer registry, for example, 93% of prostate cancer cases registered by the Saskatchewan Cancer Agency in Saskatchewan since 1970 have been microscopically confirmed, and for the period of 1990–94, 97% of cases have been confirmed.[10] Additionally, the likelihood of selection bias is small due to the identification of cancer cases from the Saskatchewan Cancer Agency registry, which includes almost all cancer cases in Saskatchewan, and the use of incidence-density sampling for control selection. However, because information on organ removal was not available in the databases, we cannot exclude the possibility that participants who were not at risk for cancer at the time of sampling as a result of previous organ removal (eg, hysterectomy, bilateral oopherectomy, prostatectomy) for non-cancer-related indications, might have been selected to be controls. The number of Saskatchewan residents who undergo removal of an organ for reasons other than the treatment of cancer is probably very small, therefore, we would assume that an even smaller number would have been included in our study. Consequently, given our large sample size, the effect of this selection bias is probably negligible.

As a result of database limitations and issues related to study design, warfarin exposure might have been underestimated for three reasons. First, information on in-hospital warfarin prescriptions was not available, therefore, actual consumption of warfarin might have been underestimated; this underestimation is unlikely to be by a large amount because the number of inpatient warfarin prescriptions relative to the number of outpatient warfarin prescriptions is probably very small. Nonetheless, underestimation of exposure is unlikely to be associated with cancer status, and as a result, bias the association between use of warfarin and risk of prostate cancer toward the null (non-differential misclassification). Second, warfarin use might have been underestimated in the timing but not cumulative analyses because prescription histories beyond the 5-year period preceding the index date might have been interrupted. Because only the earliest coverage initiation

Period before index date	Duration of warfarin use (%)	Cases (n=11 502)	Controls (n=69 012)	Crude incidence rate ratio (95% CI)	Adjusted* incidence rate ratio (95% CI)
Year 2 (13–24 months)	Never	11 205	67 079	1·00 (reference)	1·00 (reference)
	Ever	297	1933	0·92 (0·81–1·04)	0·91 (0·80–1·03)
	25%	65	377	1·03 (0·79–1·34)	1·01 (0·77–1·31)
	50%	60	280	1·28 (0·97–1·69)	1·26 (0·95–1·67)
	75%	42	312	0·80 (0·58–1·11)	0·79 (0·57–1·10)
	100%	130	964	0·81 (0·67–0·97)	0·80 (0·66–0·96)
	p	..	..	0·04	0·03
	Incomplete history†	0	0	..	..
Year 3 (25–36 months)	Never	11 254	67 376	1·00 (reference)	1·00 (reference)
	Ever	248	1636	0·91 (0·79–1·04)	0·89 (0·77–1·02)
	25%	67	359	1·12 (0·86–1·45)	1·07 (0·83–1·40)
	50%	39	239	0·98 (0·70–1·37)	0·94 (0·67–1·33)
	75%	42	262	0·96 (0·69–1·33)	0·94 (0·68–1·30)
	100%	100	776	0·77 (0·62–0·95)	0·76 (0· 62–0·94)
	p	..	..	0·03	0·02
	Incomplete history†	0	0	..	..
Year 4	Never	11 297	67 607	1·00 (reference)	1·00 (reference)
	Ever	205	1405	0·87 (0·75–1·01)	0·86 (0·74–0·99)
	25%	59	331	1·07 (0·81–1·41)	1·04 (0·78–1·37)
	50%	42	205	1·22 (0·88–1·71)	1·19 (0·85–1·65)
	75%	31	229	0·81 (0·56–1·18)	0·80 (0·55–1·16)
	100%	73	640	0·68 (0·53–0·87)	0·67 (0·53–0·86)
	p	..	..	0·006	0·004
	Incomplete history†	0	0	..	..
Year 5	Never	11 344	67 859	1·00 (reference)	1·00 (reference)
	Ever	158	1153	0·82 (0·69–0·97)	0·81 (0·68–0·96)
	25%	38	275	0·83 (0·59–1·16)	0·81 (0·57–1·13)
	50%	28	188	0·89 (0·60–1·32)	0·87 (0·59–1·30)
	75%	25	198	0·75 (0·50–1·14)	0·75 (0·49–1·13)
	100%	67	492	0·81 (0·63–1·05)	0·81 (0·62–1·04)
	p	..	..	0·03	0·02
	Incomplete history†	0	0	..	..
Year 6	Never	10 898	65 291	1·00 (reference)	1·00 (reference)
	Ever	148	939	0·94 (0·79–1·13)	0·92 (0·77–1·10)
	25%	44	237	1·11 (0·81–1·53)	1·08 (0·78–1·49)
	50%	25	156	0·96 (0·63–1·46)	0·93 (0·61–1·42)
	75%	26	160	0·98 (0·65–1·48)	0·96 (0·63–1·45)
	100%	53	386	0·82 (0·61–1·10)	0·81 (0·60–1·08)
	p	..	..	0·254	0·18
	Incomplete history†	456	2782	..	..

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Year 7	Never	10526	63074	1·00 (reference)	1·00 (reference)
	Ever	125	748	1·00 (0·83–1·21)	0·99 (0·81–1·19)
	25%	40	192	1·25 (0·89–1·75)	1·23 (0·87–1·73)
	50%	17	126	0·81 (0·49–1·34)	0·79 (0·48–1·32)
	75%	24	130	1·11 (0·72–1·72)	1·09 (0·71–1·69)
	100%	44	300	0·88 (0·64–1·20)	0·87 (0·63–1·19)
	p	..	..	0·62	0·53
	Incomplete history†	851	5190	..	..
Year 8	Never	10150	60872	1·00 (reference)	1·00 (reference)
	Ever	120	631	1·14 (0·94–1·39)	1·12 (0·92–1·36)
	25%	35	182	1·15 (0·80–1·65)	1·13 (0·78–1·62)
	50%	22	110	1·19 (0·75–1·88)	1·16 (0·73–1·83)
	75%	24	120	1·22 (0·78–1·89)	1·20 (0·77–1·86)
	100%	39	219	1·06 (0·76–1·50)	1·05 (0·75–1·48)
	p	..	..	0·30	0·36
	Incomplete history†	1232	7509	..	..
9–11 years	Never	8937	53503	1·00 (reference)	1·00 (reference)
	Ever	136	722	1·13 (0·94–1·36)	1·10 (0·91–1·32)
	25%	74	423	1·06 (0·83–1·36)	1·02 (0·79–1·31)
	50%	23	107	1·28 (0·81–2·01)	1·24 (0·79–1·96)
	75%	13	81	0·95 (0·53–1·72)	0·93 (0·52–1·68)
	100%	26	111	1·40 (0·91–2·14)	1·40 (0·91–2·14)
	p	..	..	0·09	0·12
	Incomplete history†	2429	14787	..	..
12–14 years	Never	7702	46085	1·00 (reference)	1·00 (reference)
	Ever	89	463	1·15 (0·92–1·45)	1·14 (0·91–1·43)
	25%	56	290	1·16 (0·87–1·55)	1·14 (0·86–1·53)
	50%	14	74	1·12 (0·63–1·98)	1·11 (0·62–1·97)
	75%	11	47	1·37 (0·71–2·64)	1·38 (0·71–2·66)
	100%	8	52	0·94 (0·45–1·99)	0·94 (0·45–1·99)
	p	..	..	0·31	0·32
	Incomplete history†	3711	22464	..	..
15–17 years	Never	6114	36382	1·00 (reference)	1·00 (reference)
	Ever	46	282	0·98 (0·72–1·34)	0·95 (0·70–1·31)
	25%	32	186	1·03 (0·71–1·50)	0·99 (0·68–1·45)
	50%	3	32	0·54 (0·17–1·77)	0·53 (0·16–1·72)
	75%	6	21	1·87 (0·75–4·68)	1·82 (0·73–4·57)
	100%	5	43	0·69 (0·28–1·75)	0·71 (0·28–1·81)
	p	..	..	0·71	0·70
	Incomplete history†	5342	32348	..	..
18–20 years	Never	4188	24939	1·00 (reference)	1·00 (reference)
	Ever	26	163	0·95 (0·62–1·44)	0·94 (0·62–1·44)
	25%	19	113	0·98 (0·60–1·60)	0·98 (0·60–1·61)
	50%	0	9	..	..
	75%	2	13	0·88 (0·20–3·92)	0·89 (0·20–4·00)
	100%	5	28	1·12 (0·43–2·91)	1·12 (0·43–2·92)
	p	..	..	0·80	0·95
	Incomplete history†	7288	43910	..	..

*Adjusted for NSAIDs; ACE inhibitors; other anticoagulant agents; antiplatelet medications; androgen, antiandrogen, and antioestrogen agents. †Participants with no coverage information available during this period.

Table 4: **Effect of timing and extent of warfarin use on risk of prostate cancer in the 20-year period before index date**

date between Jan 1, 1976, and the 5-year date before the index, was reported, any subsequent date of coverage reinitiation, for example, after migration back into the province, was not captured. However, coverage interruption is probably not significant because the most common reason for coverage termination and reinitiation is migration in and out of Saskatchewan, which has a net migration rate of 2% in favour of migration out of the province;[11] furthermore, this type of migration is more common in young adults than older adults. Lastly, underestimation of the association between warfarin and prostate cancer might have occurred because we assumed no warfarin use during the 18-month prescription gap period for patients registered with Saskatchewan Health during that period. However, our sensitivity analysis does not support this.

Our findings are consistent with those reported by Schulman and co-workers.[2] They reported that while an overall decrease in the incidence of genitourinary cancers was reported with 6 months compared with 6 weeks of warfarin (OR 0·40 [95% CI 0·20–0·77]), most of these tumours were prostate cancer.[2] A subsequent case-control study that used computerised databases from a Veterans Administration Hospital and compared warfarin use in 330 cases of bladder cancer in men and 1293 male controls did not show a statistically significant association between ever use of warfarin and bladder cancer, after adjusting for smoking and age (OR 1·27 [0·85–1·89]).[12] However, the sample size might have been too small to detect a significant effect. Additionally, in a secondary analysis of two randomised clinical trials that compared 3 months with 1 year of warfarin use to treat a first episode of idiopathic venous thrombosis in 429 patients, prolonged use of warfarin did not have an effect on overall cancer incidence (relative risk 0·71 [0·36–1·41]).[3] However, because there was no linkage to a cancer registry, prevalent cases of cancer might have been included at the start of the study, and new cases of cancer might have been missed during study follow-up (thereby leading to misclassification). Furthermore, the sample size might have been too small to observe a significant effect.

An important limitation with our study is that possible causes of prostate cancer and the other urogenital tumour types, for which information was not available in the database, were not included in the analyses. Socioeconomic and lifestyle risk factors for prostate cancer, such as ethnicity,[13] diet,[14] and less so, smoking,[15] might have confounded the association between warfarin and prostate cancer. No information on clinical conditions that could affect the development of urogenital cancer was available in the prescription database. Although diagnostic information can be derived from the Physician Services database of Saskatchewan Health, this information is less reliable because it is derived from data on physician billing, which have less complete and less-specific diagnostic coding.[4] In particular, diabetes might be an important confounder because it has been

associated with an increased risk of kidney,[16] endometrial,[17] and bladder cancer,[18] and a decreased risk of prostate cancer.[19] A meta-analysis of 17 studies assessing the effect of diabetes on prostate cancer suggested that men with diabetes are 16% (7–24) less likely to develop prostate cancer than men without diabetes.[19] Men with diabetes have an increased risk of cardiovascular disease and its complications, such as atrial fibrillation, and, therefore, warfarin might be prescribed more in men with diabetes compared with those who do not have diabetes. Consequently, diabetes might have an important confounding effect on the association between warfarin use and urogenital cancers.

We assessed confounding by other prescription medications, including aspirin and low-molecular-weight heparins. A meta-analysis of five prospective observational studies that assessed the risk of prostate cancer with aspirin suggested a summary OR of 0·85 (0·77–0·94),[20] and patterns of warfarin prescribing might be affected by the use of aspirin due to an increased risk of bleeding with concomitant use of aspirin. Low-molecular-weight heparins, which over the past decade have been prescribed with warfarin in the initial outpatient treatment of venous thrombotic disorders, have been suggested to improve survival in patients with cancer—although evidence for this finding is scarce.[21,22] No data support a chemo-preventive role for low-molecular-weight heparin, but its anticancer effects might affect cancer risk. We did not assess the use of statins on risk of urogenital cancers. Statins are prescribed in patients with cardiovascular disease and some epidemiological studies have shown an inverse association with prostate cancer,[23,24] however, five meta-analyses of 35 randomised controlled trials that were designed to assess the efficacy of statins on cardiovascular outcomes have consistently shown no effect on overall cancer risk and site-specific cancer risk;[25–29] therefore, use of statins would probably have not been an important confounder in our study.

Detection bias could have occurred because people who receive warfarin treatment are closely monitored by physicians, which can lead to more opportunity for screening of prostate cancer and early cancer detection. However, this would lead to an underestimation of a true anticancer effect of warfarin. Although no formal screening programmes exist in Canada for prostate cancer, the introduction of the prostate-specific antigen assay in Saskatchewan in 1990 resulted in a sharp increase in the reporting of the incidence of prostate cancer and, in particular, early-stage prostate cancer.[10] However, the increased detection of prostate cancer in Saskatchewan during the early 1990s is unlikely to bias our results because use of warfarin is probably not differentially associated with screening of prostate-specific antigen.

Confounding by indication remains a possibility, but no published studies exist that suggest atrial fibrillation, valvular heart disease, or stroke—the most common indications for long-term (ie, greater than 6–12 months) warfarin use—are risk factors for prostate cancer. Venous thromboembolic disease, a less common indication for long-term warfarin use, has been reported to be associated with cancer.[30] Non-experimental studies suggest that in patients with venous thromboembolic disease in whom a thrombosis risk factor is not evident, 2–10% will develop cancer within 1–2 years after a thrombosis episode.[30] However, confounding by venous thromboembolic disease would lead to underestimation of the antitumour effect of warfarin.

Our findings on the association between warfarin use and decreased risk of prostate cancer are consistent with some tumour studies in animals,[31] and biochemical explanations have been proposed to explain the anticancer effect of warfarin, including coagulation and non-coagulation-mediated mechanisms. For example, warfarin-induced inhibition of thrombin generation might alter the ability of thrombin to signal membrane receptors through a series of protease-activated receptors that are often involved in cell mitogenesis and survival. Alternatively, gas6, a vitamin K-dependent non-coagulant protein that is a ligand for Axl, a receptor tyrosine kinase, has been described to be important in the biology of prostate cancer. Axl has been shown to be overexpressed in prostate cancer, and also, DU-145 cells, an in-vitro cell line derived from prostate cancer, show gas6-Axl dependence for cell growth.[32,33] Therefore, some of the anticancer effect of warfarin might occur through inhibition of gas6 function. However, given the complexity of the biology of cancer cells, inhibition of a single mitogenic factor, such as gas6, is unlikely to completely abrogate the development of cancer. A more biologically plausible explanation is that warfarin delays growth of small and clinically silent tumours, thereby postponing the clinical presentation of cancer.

Why a protective effect was not seen with the other types of urogenital tumour is unclear, unless this effect was a result of larger numbers for prostate cancer. Another explanation could be residual confounding by unmeasured risk factors, such as diabetes, of the association between warfarin and uterine and kidney cancer. The effect of warfarin might be exerted mainly on small cancers, such as prostate cancer, which has a relatively long latency period compared with that of other cancer types, and not on those already of a size amenable to diagnosis.

Analyses based on timing and cumulative exposure to warfarin support an anticancer effect of warfarin on prostate cancer. The percent incidence reduction that was estimated in our study could be used to measure the effect of warfarin use on the lifetime probability (risk) of prostate cancer. However, since our study was a case-control study, we could not obtain a direct estimate of the absolute lifetime risk in the absence of warfarin. Because the lifetime risk of prostate cancer is substantial, this absolute risk could potentially be decreased significantly.

Therefore, further studies are needed with a more complete assessment of confounders and indications for warfarin use. Additionally, prospective studies with long follow-up should be done to assess the effect of warfarin use on survival in prostate cancer. If the association between warfarin and prostate cancer is confirmed, then mechanistic studies to identify warfarin-mediated biological processes in the development of prostate cancer should be encouraged, and clinical studies of prevention and treatment of prostate cancer pursued. Although warfarin has important bleeding complications that could preclude its widespread use for chemoprevention, targeted prophylactic treatment in high-risk individuals might be feasible, and, if improved prostate-cancer survival is shown, intervention trials in patients with prostate cancer should be done.

Contributors

VT and SRK conceived the study, and VT did the study design. JPC, SRK, MB, and JAH advised on the study protocol and planned statistical analyses. VT, JPC, SRK, JAH, and MB obtained funding. VT and HT collected data. VT, HT, and JAH directed statistical analyses. VT and HT did the statistical analyses. HT created the statistical programs and analysed data. VT, HT, MB drafted the report. All authors revised the report.

Conflicts of interest

The authors declared no conflicts of interest.

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Warfarin and prevention of prostate cancer

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In this issue of *The Lancet Oncology*, Tagalakis and co-workers[1] report intriguing results from a Canadian case-control study that suggests an association between warfarin use and decreased risk of prostate cancer. 4 years of warfarin use was associated with an adjusted incidence rate ratio of 0·80 (95% CI 0·65–0·99) for prostate cancer compared with that in men who had never used warfarin. The researchers also assessed the association between warfarin use and cancer at other sites of urogenital cancer, including the kidney, bladder, uterus, and ovaries. While no significant associations were detected for these cancer sites, the statistical precision of several risk estimates was low, and, therefore, inconclusive. The study's findings raise three key questions: first, could the risk estimates have been affected by uncontrolled confounding or other biases in the study?; second, could a biological mechanism explain the findings?; and third, do other studies support the association?

The study by Tagalakis and colleagues is based on routine data extracted from health-care databases. The accuracy of such data is well known to be affected by coding and other errors. Since the idea that warfarin might decrease cancer risk has not been extensively publicised, nondifferential misclassification of the exposure data is probably the same for cases and controls, and this misclassification would lead to an underestimation of the real effect.[2] The researchers had access to data on some potential confounding variables, but few risk factors for prostate cancer are known. The researchers did not have data on obesity, a potential risk factor for both prostate cancer and cardiovascular diseases, and, therefore, also for warfarin treatment. However, because an inverse association was found, it is unlikely that uncontrolled confounding due to obesity can explain the results. The study also did not include data on the indications for warfarin use, but confounding due to warfarin treatment for underlying diseases also cannot explain the decreased risk estimates. For example, venous thromboembolism, the main indication for warfarin treatment, is associated with an increased risk of cancer at many sites, including the prostate.[3] However, anticoagulation can cause the serious adverse effect of major bleeding;[4] therefore, patients at increased risk of bleeding, such as those with liver cirrhosis, uraemia, alcoholism, peptic ulcer, and poor compliance, are probably under-represented in those who use warfarin. Whether clinical selection for warfarin treatment is associated with decreased risk of prostate cancer is unknown, and needs to be addressed in further studies. By contrast, warfarin use is associated with visits to the doctor, which in turn, is associated with increased medical attention—and possibly increased screening of prostate-specific antigen. This increased surveillance might make warfarin use seem to have a direct association with prostate cancer.

Nonetheless, both biological and clinical evidence is available to support the findings of the Canadian study. The association between cancer and increased risk of thromboembolism is well-known. Since Trousseau reported in 1865 the occurrence of migratory thrombophlebitis in patients with cancer,[5] researchers have increasingly recognised that thromboembolism can be both a presenting sign and a complication of cancer.[6] The most compelling clinical evidence comes from Schulman and co-workers' secondary analysis of randomised trial data, which showed that patients with venous thrombosis who received 6 months of treatment with warfarin had a lower incidence of urogential cancer compared with patients treated for 6 weeks.[7] Uncontrolled confounding due to selection for treatment was not an issue in this study.

Strong evidence suggests that tumour growth is associated with a hypercoagulable state in patients with cancer who have no clinical sign of thrombosis. Studies in animals have also clearly shown that unfractionated heparin and low-molecular-weight heparin inhibit processes involved in tumour growth and metastasis.[8] Likewise, experimental evidence for the potential of anticoagulation treatment to retard tumour growth and survival has been available for more than 20 years. In a clinical trial of patients with small-cell lung cancer, Zacharski and colleagues showed that those treated with warfarin in addition to standard chemotherapy had a significantly longer progression-free and overall survival, compared with patients treated with chemotherapy alone.[9] Since then, further evidence has accrued, indicating that patients with venous thromboembolism who are treated with low-molecular-weight heparin have lower cancer mortality compared with those treated with unfractionated heparin.[10]

This good evidence suggests the potential for anticoagulation to be used for cancer chemoprevention. But first, additional observational studies and clinical trials are needed to confirm the findings of the Canadian study and to address potential uncontrolled confounding and other biases—ie, safety and efficacy. Second, the principles behind primary chemoprevention should be considered. Because of the relatively low incidence of prostate cancer, the years and numbers of patients needed to be treated to prevent one cancer case will be very high. To ensure adequate compliance, the chemoprevention regimen should have no adverse effects and be easy to administer. Warfarin treatment does not meet these requirements. Progress in cancer biology and in drug development over the next decades might improve our ability to identify high-risk patients for whom the benefit of treatment with warfarin outweighs the risk of bleeding. The study by Tagalakis and co-workers should stimulate further translational research that combines basic biology, and clinical and epidemiological expertise to assess the association between coagulation and cancer. Such efforts will probably lead to improved primary, secondary, and tertiary prevention of cancer.

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Cancer caused by x-rays—a random event?

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In the years immediately after the establishment of the State of Israel, ringworm of the scalp—tinea capitis—reached epidemic proportions in thousands of immigrant children, many from north Africa. The preferred treatment at the time was to induce temporary epilation by a dose of x-rays. The study by Flint-Richter and Sadetski[1] in this issue of *The Lancet Oncology* documents the incidence of radiation-associated brain tumours in a subset of such individuals, consisting of more than 500 families who have been followed for over 50 years.

This fascinating paper is of substantial interest in itself, but in addition, could have far-reaching and important implications on radiation protection and in every sphere of life in which radiation is used. These areas include diagnostic radiology, radiation oncology, and even the generation of nuclear power. The reason for this possibility is that this study offers solid epidemiological evidence that—at least in this population consisting partly of north-African Jews—radiation-associated cancers are clustered in certain families rather than being evenly distributed throughout the irradiated population. Specifically, if all of the children irradiated during the treatment of tinea capitis are taken in to account, the risk of developing a radiation-associated meningioma is about 1 in 100. However, in some families the risk is 4 out of 5. This is an incredible concentration of risk. Current standards of radiation protection are based entirely on the assumption that the human population is uniform in radiosensitivity—ie, that radiation carcinogenesis is a stochastic event—so that when a population is exposed to radiation, the small proportion who fall victim to a radiation-induced cancer are randomly distributed. The new data conflict with this paradigm.

Of course, we have realised for some time that a radiosensitive subpopulation might exist. The International Commission on Radiological Protection issued a voluminous report on this topic in 1999,[2] and the subject was discussed again in the Biological Effects of Ionizing Radiation (BEIR) VII report of The National Academy of Sciences.[3] Both reports concluded that certain