Cholesterol-Lowering Drugs and Prostate Cancer Risk: A Population-based Case-Control Study

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Abstract

Background: **Previous studies have shown that statin use may reduce prostate cancer risk. In the current study, we evaluated the association between serum cholesterol–lowering medication use and prostate cancer risk at the population level.**

Materials and Methods: **All newly diagnosed prostate cancer cases in Finland during 1995 to 2002 and matched controls (24,723 case control pairs) were identified from the Finnish Cancer Registry and the Population Register Center, respectively. Detailed information on cholesterol-lowering drug purchases during the study period was obtained from the prescription database of the Social Insurance Institution of Finland.**

Results: **After adjustment for potential confounders, having ever-use of any statin was associated with marginally elevated overall prostate cancer risk [odds ratio (OR), 1.07; 95% confidence interval (95% CI), 1.00-1.16]. However, none of the statins was associated with the overall prostate cancer risk when analyzed separately. On the other hand, the risk of advanced prostate cancer was decreased among users of atorvastatin, lovastatin, and simvastatin (OR 0.61, 95% CI 0.37-0.98; OR 0.61, 95% CI 0.43-0.85; and OR 0.78, 95% CI 0.61-1.01, respectively). The risk was not affected among users of other cholesterol drug groups.**

Conclusions: **Our large population-based study showed no evidence for reduced overall prostate cancer risk among users of cholesterol-lowering drugs, whereas the risk of advanced cancer was decreased among statin users.**

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Introduction

Prostate cancer is the most common malignancy among men in most countries (1). It is also among the three most common causes of cancer death in most Western countries (1). Nevertheless, prostate cancer is usually a slowly growing cancer with a long latency period. Autopsy studies show that a quarter of men in their 40s and up to 40% of men ages 80 years or older harbor indolent local malignant lesions of the prostate (2, 3). The slow growth rate of prostate cancer provides a window of opportunity to influence different stages of carcinogenesis, making prostate cancer an attractive target for chemoprevention. Environmental factors strongly influence prostate cancer risk as shown by the Asian immigrants in North America. Asian men traditionally have a low prostate cancer risk, although the prevalence of latent prostate cancer precursors is comparable with that of the population in the Western countries (4). However, among Asian immigrants in North America, the risk of clinical cancer increases toward that of the Western population with years of residence, and also in Asia, the incidence of prostate cancer is rising partly due to the Westernization of life-styles (4).

A group of cholesterol-lowering drugs, 3-hydroxy-3-methylglutaryl CoA reductase inhibitors (statins), have shown promise in chemoprevention of prostate cancer. Multiple statins have been reported to inhibit prostate cancer cell proliferation *in vitro* by induction of cell cycle arrest and apoptosis (5, 6). Recently, a large prospective cohort study reported decreased risk of advanced prostate cancer among statin users, whereas the overall prostate cancer risk was unaffected (7). Other observational studies have suggested reduced risk for also overall prostate cancer in statin users (8, 9). However, recent meta-analyses of randomized trials of statins (10-12), along with other observational studies (13-16), have revealed no association with the cancer of the prostate or of any other site.

Of the other types of cholesterol-lowering drugs, fibrate use has not been found to affect cancer risk (8), although they are reported to cause neoplasia in rodents (17). The only study, to our knowledge, estimating cancer incidence in resin users concluded that statin users are 28% less likely to be diagnosed with any type of cancer than the users of resins (13). No reports of acipimox effect on cancer risk have been published.

This study was undertaken to evaluate prostate cancer risk among the users of cholesterol-lowering drugs at the population level.

Materials and Methods

Study Design. All newly diagnosed prostate cancer cases in Finland during 1995 to 2002 (25,029 men) were

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identified through the Finnish Cancer Registry. Data in the Finnish Cancer Registry are collected through mandatory notifications of all the cancer diagnoses made by all the Finnish health care units. Thus, it is a population-based, nationwide register with coverage of >99% of all prostate cancer patients in Finland (18). The register information includes the primary site of cancer, histology, date, and method of diagnosis. Information on the stage of prostate cancer was available in 55% of the cases (13,616 patients). Of these, 73% were localized. There were no substantial differences in median age between cases with or without information on stage (Table 1). However, the majority of cases without information on stage were diagnosed during the latter half of the study period, whereas the distribution of years of diagnosis was more even among the cases with stage (Table 1). The registry does not record differentiation, such as Gleason score, nor serum prostate-specific antigen (PSA) values.

Practically all the cases were histologically confirmed (99.3 %). Also, cases with the diagnosis based solely on clinical (0.4 %), radiological (0.3 %), or specific laboratory findings (0.02% of cases) were included. A total of 185 cases (0.7 %) with an unknown method of diagnosis were excluded.

The controls were individually matched on the age and geographic area of the cases at the time of the diagnosis. The Population Register Center of Finland selected 24,723 male controls, of whom a total of 963 were subsequently diagnosed with prostate cancer during the study period. Thus, these men appeared twice in the analysis, first as a control and later as a case in another matched case control pair. The population size in Finnish municipalities ranges from <200 to 560,000 (19). Thus, matched controls could not be found from the same municipality for 121 cases in the oldest age group, resulting in their exclusion from the analyses. A total of 24,723 case control pairs were included in the analyses.

After approval from the ethics committee of the Pirkanmaa health care district, Finland (ETL R03290), obtaining informed consent from the study population was not required due to the large size of the population and to the part of the population that is unattainable (deceased or emigrated) by the time of the study.

Table 1. Characteristics of cases in the study population of all newly diagnosed prostate cancer cases in Finland in 1995 to 2002 and their individually matched controls

	Prostate cancer stage		
	No information	Localized	Advanced
Median age (y)	69	67	69
Year of diagnosis (%*)			
1995	7.0	10.7	13.0
1996	7.8	11.8	16.8
1997	8.7	13.8	14.4
1998	10.3	14.1	14.2
1999	11.6	13.6	12.5
2000	17.1	10.8	10.4
2001	15.6	14.1	10.5
2002	21.8	11.1	8.1

*Percentage distribution of cases by year of diagnosis.

Table 2. Prevalence of medication usage among the study population of all newly diagnosed prostate cancer cases in Finland in 1995 to 2002 and their individually matched controls

Cholesterol drug use	Cases		Controls	
	n	% of total	*n*	% of total
Total number	24,723	100	24,723	100
Statin use				
Yes	2,622	10.6	2,439	9.9
No	22,101	89.4	22,284	90.1
Fibrate use				
Yes	220	0.9	211	0.9
No	24,503	99.1	24,512	99.1
Usage of other cholesterol drugs*				
Yes	61	0.2	52	0.2
No	24,662	99.8	24,671	99.8
Antidiabetic medication use				
Yes	2,201	8.9	2,406	9.7
No	22,522	91.1	22,317	90.3
Antihypertensive drug use				
Yes	12,648	51.2	11,866	48.0
No	12,075	48.8	12,857	52.0

*Includes users of resins and acipimox.

The information on cholesterol-lowering medication prescribed to the study population and reimbursed by the Social Insurance Institution of Finland (SII) during 1995 to 2002 was obtained from the comprehensive nationwide prescription database of the SII. All cholesterol-lowering drugs in use in Finland during the study period, with the exception of nicotinic acid, were reimbursable and available through a physician's prescription only, thus comprehensively documented by the database. The database provided detailed information on the quantity and time of the medication purchases for each person in the study population for a maximum of 8 years. The drugs in clinical use in Finland during the study period were statins (atorvastatin since 1998, cerivastatin from 1999 to 2001, fluvastatin since 1996, lovastatin, pravastatin, and simvastatin), fibrates (bezafibrate, clofibrate until 1998, fenofibrate since 2002, and gemfibrozil), resins (cholestyramin and cholestipol), and acipimox (until 1999). Also guar gum was used as a lipid-lowering agent in Finland during the study period. However, the main indication for usage was type 2 diabetes. Thus, guar gum was categorized as an antidiabetic drug.

The SII is a governmental agency operating under the Ministry of Health, financed through tax revenues. As part of the national public health insurance, the SII provides reimbursements for the cost of medicines prescribed by a physician (with the exception of hospital inpatients; ref. 20).

The prescription database covers all reimbursements paid by the SII. For the drugs approved as reimbursable, the reimbursement (50-100%, depending on the severity of the disease) is available for all Finnish citizens for every purchase of the drug (20). However, not all drugs are approved as reimbursable, thus not covered in the prescription database. The beneficiary with a drug prescription can either claim the reimbursement directly from the SII or pay a subsidized price at the pharmacy. The margin is reimbursed to pharmacy by the SII either directly or through an occupational health care fund.

Table 3. Overall prostate cancer risk and the risk of advanced cancer among users of the distinct cholesterol-lowering drugs

	Overall prostate cancer		Advanced prostate cancer	
	No. discordant pairs*	OR† (95% CI)	No. discordant pairs	OR† (95% CI)
All cholesterol-lowering drugs	2,369/2,235	1.06 (1.00-1.13)	202/259	0.76 (0.64-0.91)
All statins	2,253/2,067	1.07 (1.00-1.16)	196/255	0.75 (0.62-0.91)
Atorvastatin	452/407	1.10 (0.97-1.25)	26/43	0.61 (0.37-0.98)
Fluvastatin	437/428	0.99 (0.87-1.12)	48/46	1.04 (0.71-1.54)
Lovastatin	568/521	1.06 (0.94-1.18)	51/82	0.61 (0.43-0.85)
Pravastatin	181/160	1.11 (0.90-1.35)	11/15	0.72 (0.38-1.36)
Simvastatin	1,103/1,050	1.03 (0.95-1.12)	94/119	0.78 (0.61-1.01)
All fibrates	120/113	1.05 (0.86-1.27)	9/12	0.74 (0.41-1.36)
Bezafibrate	64/57	1.09 (0.83-1.44)	6/6	1.00 (0.44-2.25)
Gemfibrozil	56/52	1.05 (0.80-1.38)	4/5	0.87 (0.36-2.11)
Other cholesterol-lowering drugs‡	28/24	1.16 (0.80-1.68)	4/3	1.15 (0.40-3.33)

NOTE: Study population of all newly diagnosed prostate cancer cases in Finland in 1995 to 2002 and their individually matched controls.
*As conditional logistic regression is the analysis method, the number of case-control pairs discordant to statin use is reported. Case: user-control: nonuser/Case: nonuser-control: user.
†Adjusted for age, usage of diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, metformin, sulfonylureas, and human insulin.
‡Includes resin and acipimox user.

Approximately, 90% of all reimbursements are paid to the pharmacies, 2% through an occupational health care fund, and 8% directly to the customer.

The defined daily doses (DDD) recommended by the WHO (21) were used to quantify usage of cholesterol-lowering drugs. For each year of the study period, the cumulative usage (in milligrams) for each drug was calculated based an all purchases made that year. The yearly usage was divided with the quantity corresponding to one DDD. The total number of DDDs used for each drug during the study period was obtained as the sum of the yearly DDDs. Total DDDs for all statins, fibrates, and other lipid-lowering drugs (resins and acipimox) were combined to obtain cumulative quantity of statins, fibrates, or the other lipid-lowering drugs used during the study period. For the subjects who changed prescriptions, e.g., from fibrates to statins, the cumulative quantity was calculated for each drug and the subject contributed both as a fibrate and a statin user.

Statistical Analysis. All medication reimbursements before the month of diagnosis were included in the analyses, regardless of the length of use. For controls, the month of diagnosis of their matched case was used as the reference month for medication use.

A conditional logistic regression model was used to estimate the crude odds ratios (OR) and likelihood-based 95% confidence intervals (95% CI) for ORs of prostate cancer related to medication use in STATA 8.2 software. Additionally, a stepwise logistic regression analysis was done to obtain the ORs adjusted for age, place of residence, antidiabetic drug use, and antihypertensive drug use. Only variables with an α of <0.20 were included in the model. As a result, in the multivariable analysis, the OR of prostate cancer among cholesterol-lowering drug users was adjusted for age and usage of diuretics, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, metformin, sulfonylureas, and human insulin. All reported ORs

Table 4. Prostate cancer risk among statin users by quartiles of total cumulative quantity of medication usage

Prostate cancer risk	No. discordant pairs*	Crude OR (95% CI)	Adjusted OR† (95% CI)
Overall			
All statin users	2,253/2,067	1.09 (1.02-1.15)	1.07 (1.00-1.16)
14-167 DDD‡	576/533	1.08 (0.96-1.22)	1.06 (0.94-1.19)
168-446 DDD	559/527	1.06 (0.97-1.15)	1.04 (0.95-1.13)
447-914 DDD	558/526	1.06 (0.95-1.20)	1.05 (0.93-1.18)
915-6,781 DDD	560/483	1.16 (1.03-1.31)	1.13 (1.00-1.28)
Advanced			
All statin users	196/272	0.72 (0.60-0.87)	0.75 (0.62-0.91)
14-167 DDD	66/73	0.91 (0.65-1.27)	0.94 (0.67-1.31)
168-446 DDD	46/71	0.65 (0.45-0.94)	0.68 (0.47-0.99)
447-914 DDD	44/71	0.62 (0.43-0.90)	0.64 (0.44-0.94)
915-6,781 DDD	40/56	0.71 (0.48-1.07)	0.74 (0.49-1.11)
		$P_{trend} < 0.001$	$P_{trend} = 0.001$

NOTE: Study population of all newly diagnosed prostate cancer cases in Finland in 1995 to 2002 and their individually matched controls.
*As conditional logistic regression is the analysis method, number of case-control pairs discordant to statin use is reported. Case: user-control: nonuser/Case: nonuser-control: user.
†Adjusted for age, usage of diuretics, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, metformin, sulfonylureas, and human insulin.
‡Cumulative quantity of statins purchased during the observed time period.

in this article are multivariable adjusted, unless otherwise stated.

To study the time and dose dependency between medication use and prostate cancer risk, an analysis was done, which included only the medication purchases occurring during a period of 4 to 8 years before the diagnosis or the reference month. Based on the quantity of purchases during this time, the medication users were divided into two categories (1-1,460 DDD and 1,461 DDD or more). The cut point of 1,460 DDD was chosen empirically as it corresponds to 4 years of usage (1 DDD/day), and it allowed a meaningful number of observations in both categories. For these analyses of exposure time windows only, the case-control pairs with the exposure information available for the entire analyzed time period were included (e.g., as information on medication usage was available since the beginning of 1995, case control pairs with the reference year 1996 had information on a maximum of 2 years of medication use, thus excluded from the exposure time window analyses). Nonusers were used as the reference group in all analyses.

Results

Due to individual matching, the age distribution was identical for the cases and controls (median age, 68 years; range, 20-96 years for both groups). Statins were the most commonly used cholesterol-lowering drugs. During 1995 to 2002, 10.6% of the cases and 9.9% of the controls had used any quantity of at least one statin (Table 2). The most commonly used statin was simvastatin (prevalence of use, 5.1% in the total study population), followed by atorvastatin, fluvastatin, and lovastatin (2.5%, 2.0%, and 2.0%, respectively). Prevalences for usage of fibrates or the other lipid-lowering drugs (resins and acipimox) were 0.9% and 0.2%, respectively (Table 2). The prevalence of statin use was slightly lower (9.4% versus 12.1%), whereas prevalence of usage for fibrates (0.8% versus 0.9 %) and the other lipid-lowering drugs (0.3% versus 0.2 %) was relatively similar among men with and without information on stage, respectively.

Ever-use of any cholesterol-lowering drug was associated with a slightly elevated overall prostate cancer risk (OR 1.06, 95% CI 1.00-1.13; Table 3). In a separate analysis of the drug categories, an increased risk was observed only among statin users (OR 1.07, 95% CI 1.00-1.16; Table 3). However, the risk was not affected among users of any single statin when analyzed separately. When statin users were stratified by the total cumulative quantity of statin doses purchased during the whole study period, the overall risk of prostate cancer was elevated only in the group which had purchased 915 to 6,781 DDD (Table 4).

The risk of advanced prostate cancer, on the other hand, was reduced among statin users (OR 0.75, 95% CI 0.62-0.91; Table 3). There was a significant, but not quite linear, dose-response association in the risk of advanced prostate cancer among statin users (Table 4). When analyzed separately, the risk was decreased among users of atorvastatin (OR 0.61, 95% CI 0.37-0.98), lovastatin (OR 0.61, 95% CI 0.43-0.85), and simvastatin (OR 0.78, 95% CI 0.61-1.01; Table 3).

In the time- and dose-dependency analysis, the overall prostate cancer risk and risk of localized cancer were not affected among statin users in any of the usage categories or within any observed time period (Table 5). However, the OR of advanced prostate cancer was systematically below one within each time period, although statistical significance was not reached in most categories (Table 5).

The overall prostate cancer risk was increased only in the youngest age group of statin users, i.e., men ages 60 years or less. Nevertheless, the risk difference between the age groups was not statistically significant (data not shown).

Neither the overall usage of fibrates or the other lipid-lowering drugs nor use of any single drug in the two drug groups affected the overall prostate cancer risk (Table 3). The effect was insignificant regardless of the total quantity of usage. Stratification by the total cumulative quantity of DDDs purchased did not associate with prostate cancer risk or stage (results not shown).

Discussion

Our results show no overall protective effect of statins or the other cholesterol-lowering drugs against prostate cancer regardless of the quantity or timing of medication use.

The overall prostate cancer risk was slightly increased among statin users. Hypercholesterolemia, currently the only indication for statin usage, has been reported to be associated with increased prostate cancer risk in a case-control study (22). Cholesterol has also been reported to promote prostate carcinogenesis *in vitro* (23). However, if hypercholesterolemia accounted for the increased overall prostate cancer risk in statin users, a similar increase would be expected also among users of the other cholesterol-lowering drugs, which was not the case. More likely, the observation is due to the more active use of health services among statin users and resulting increased surveillance especially at the initiation of the treatment.

The risk of advanced cancer was decreased among statin users in a dose-dependent manner. These findings concur with the results of the recently reported cohort study by Platz et al. (7). Previously lower incidence of poorly differentiated prostate cancer has been reported in statin users (8). These findings suggest an effect at a late stage of carcinogenesis, such as tumor progression, which is plausible, given the known effect of statins on prostate cancer cell cycle and apoptosis (5, 6). The risk of advanced cancer seemed to be modestly decreased also among fibrate users (Table 3), which suggests that hypercholesterolemia could be linked with decreased risk of advanced prostate cancer. However, low number of cases impeded these analyses, and the effect was not significant.

Compared with the cohort study by Platz et al. (7), our study population was larger and we had more detailed information on medication exposure, being able to separately analyze the risks for users of distinct statins and for users of cholesterol-lowering drugs other than statins. Additionally, we were able to estimate the effect of timing and dosage of statin use on prostate cancer risk. Case-control studies are frequently limited by recall bias, but it did not affect our results, as the exposure data were obtained from a registry unaffected by the disease status.

On the other hand, unlike the cohort study, we did not have data on possible confounding factors, such as obesity and Western style high-fat diet; both established

Table 5. Prostate cancer risk and stage among statin users stratified by the cumulative quantity of medication purchases

Prostate cancer risk	Length of the observed time period			
	4 y		5 y	
	*n**	OR† (95% CI)	*n*	OR (95% CI)
Overall				
1-1,460 DDD‡	1,695/1,599	1.06 (0.99-1.14)	1,293/1,231	1.05 (0.97-1.14)
≥1,461 DDD	171/141	1.21 (0.96-1.54)	180/145	1.24 (0.99-1.55)
Localized				
1-1,460 DDD	620/569	1.09 (0.97-1.23)	456/400	1.14 (0.99-1.30)
≥1,461 DDD	73/57	1.27 (0.87-1.25)	73/57	1.29 (0.90-1.84)
Advanced				
1-1,460 DDD	123/176	0.70 (0.55-0.89)	85/125	0.68 (0.51-0.90)
≥1,461 DDD	10/13	0.78 (0.34-1.80)	9/13	0.70 (0.30-1.66)

NOTE: Study population of all newly diagnosed prostate cancer cases in Finland in 1995 to 2002 and their individually matched controls.
*Number of case-control pairs discordant to medication usage: Case: user-control: nonuser/Case: nonuser-control: user.
†Adjusted for age, usage of diuretics, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, metformin, sulfonylureas, and human insulin.
‡The cumulative quantity of statins purchased during the observed time period; 1,460 DDD used as a cut point as it corresponds to 4 y of usage if a person used regularly 1 DDD/d.

risk factors for hypercholesterolemia (24, 25). Obesity and high-fat diet possibly influence prostate cancer risk (26, 27) and serum levels of PSA, the primary method of prostate cancer diagnosis (28). However, their role as prostate cancer risk factors is not firmly established.

Lack of association between statin use and overall prostate cancer risk also concurs with the results from the recent meta-analysis of randomized clinical trials of cardiovascular disease prevention, with cancer as a secondary end-point (10) and with previous smaller observational studies (13-16). However, only 305 prostate cancer cases were available for the meta-analysis, and the follow-up time in the majority of the studies included in the meta-analysis was 4 years or less preceding the diagnosis (10). Thus, our study is based on a larger population and longer follow-up.

Due to the comprehensive national health care registers of Finland, we were able to carry out a large population-based case-control study with minimal influence of chance or selection bias. Also, being able to obtain the detailed exposure information in an objective fashion from the SII prescription database allowed us to evaluate cholesterol-lowering drug use accurately and in an unbiased fashion. The average consumption of statins in Finnish men in the same age group during 2001 to 2002 versus the overall consumption in the study population during the same time period was 47.95 DDD (29) versus 46.13 DDD per 1,000 persons per day, respectively. Similarly, consumption of fibrates was 0.69 DDD versus 0.86 DDD per 1,000 persons per day and the other lipid-lowering drugs 0.12 DDD versus 0.10 DDD per 1,000 persons per day. The comparable medication usage in our study population and the overall Finnish population shows the representativeness of the study. Naturally, the actual administration was up to the men's discretion and was, thus, not recorded.

All categories of cholesterol-lowering drugs were available in Finland only through a physician's prescription during the study period. Thus, the purchases are comprehensively documented by SII through the pharmaceutical reimbursement system. The only exception was nicotinic acid, which was not approved by the SII and not recorded by the prescription database (average consumption in 1999, 0.02 DDD/1,000/day; ref. 29). Some exposure misclassification was likely caused by the fact that information on medication purchases was available only since 1995, although lovastatin, pravastatin, simvastatin, bezafibrate, gemfibrozil, cholestipol, cholestyramin, and acipimox were licensed in Finland earlier. Thus, some of the users of these drugs may have longer history of use than appeared in our study. This may weaken the observed association. However, the distortion is likely to be small, as the estimates based on the cases diagnosed during the early period (with less complete coverage of recent use) gave similar results than analyses based on later cases.

The main limitation of our study is the absence of information on serum PSA testing among the study population. The prevalence of latent prostate cancer is already high among men in their 40s (2, 3). Epidemiologic and pathologic studies strongly suggest that more latent cancers are being found after the introduction of serum PSA testing (30). Medical treatment of high serum cholesterol is used for the primary and secondary prevention of cardiovascular disease. Thus, the men using these medications are likely to have some medical condition requiring its use, such as coronary artery disease, or to be generally more health conscious. As a result, the men using cholesterol-lowering medication are probably more active users of health services, which could result also in more frequent serum PSA determinations and digital rectal examinations. Because routine prostate cancer screening with the PSA test is not recommended in Finland and the prevalence of opportunistic screening is <20% annually (31), it is plausible that more latent prostate cancers are found among the medication users due to more active PSA testing compared with nonusers. This would falsely increase the observed OR of the overall prostate cancer for medication users and mask a possible protective effect of medication use. Additionally, prolonged statin use has been suggested to lower serum PSA level (32). This in turn would

Table 5. Prostate cancer risk and stage among statin users stratified by the cumulative quantity of medication purchases (Cont'd)

Length of the observed time period					
6 y		7 y		8 y	
n	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
912/885	1.03 (0.94-1.14)	464/483	0.96 (0.84-1.09)	427/436	0.98 (0.76-1.11)
180/146	1.23 (0.98-1.54)	128/102	1.26 (0.97-1.65)	103/83	1.24 (0.95-1.62)
333/292	1.14 (0.97-1.34)	144/138	1.04 (0.82-1.32)	132/128	1.03 (0.79-1.34)
66/52	1.26 (0.86-1.83)	36/34	1.07 (0.64-1.80)	31/28	1.10 (0.72-1.91)
54/76	0.71 (0.49-1.02)	26/43	0.61 (0.36-1.03)	18/28	0.65 (0.33-1.02)
11/13	0.82 (0.36-1.85)	6/8	0.73 (0.24-2.23)	3/4	0.71 (0.22-2.39)

reduce the number of prostate cancer diagnoses among the statin users, as lower number of prostate biopsies due to elevated PSA levels would be made.

The detection bias described above likely affects the incidence of both localized cancers and advanced cancers. However, presumably the risk estimate for localized cancer is more biased as advanced prostate cancer often causes symptoms (like lower urinary tract symptoms or pain from bone metastases), and thus, its diagnosis is not solely dependent on PSA testing. On the other hand, the men with advanced cancer could have been less active users of health services and therefore less likely to use statins. This could be one reason for the lower occurrence of advanced cases in the nonusers of statin. However, if this was a significant bias, it likely would have led to decreased risk of advanced cancer among users of other cholesterol-lowering drugs as well, which was not the case.

Our analyses on prostate cancer stage among cholesterol-lowering drug users were somewhat impeded by the information of stage being available only for slightly more than half of the cases. There were no substantial differences in age between the cases with or without information on stage (Table 1). However, majority of the cases without stage were diagnosed during the latter half of the study period. Compared with men with advanced cancer, greater proportion of men with localized cancer was diagnosed in 2001 and 2002 (Table 1). This difference likely reflects the increasing prevalence of opportunistic PSA screening in Finland, resulting in increased proportion of early PSA-detected cancers. For these cancers, complete staging, including bone scan, is not routinely done. Prevalence of statin usage was lower among the cases with stage, which could have diminished the observed association between prostate cancer stage and statin use.

Age and ethnicity are well known risk factors for prostate cancer (33). We controlled the confounding effect of age by individual matching of cases and controls. However, no significant effect modification by age was observed. We did not have information on the race of our study subjects. However, confounding by ethnicity is minimal due to the homogeneity of the Finnish population with over 98% of the population being Caucasian (34). The inherited predisposition for prostate cancer is a strong risk factor. Information of family history was not available in our study population. However, heredity is estimated to account for only minor proportion of susceptibility to prostate cancer (35), 5% to 10% of all Finnish prostate cancers (36). To generate confounding, hereditary factors would also need to be associated with cholesterol-lowering medication, for which there is little indication.

The results of our large population-based study show no association between use of cholesterol-lowering drugs and overall prostate cancer risk in a population that is not routinely screened for prostate cancer. However, the risk of advanced prostate cancer was decreased in statin users but not among users of other cholesterol-lowering drugs. Our findings are consistent with the recent results in this field. However, as varying PSA testing activity among the study populations can introduce detection bias, studies that evaluate prostate cancer risk among statin users while effectively controlling for serum PSA testing are highly needed.

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