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Title page

Full title: Characteristics of finasteride users in comparison with non-users: a Nordic nationwide study based on individual-level data from Denmark, Finland, and Sweden

Running title: Comparison of finasteride users and non-users

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Key points:

- Results from the existing studies on the association between finasteride and male breast cancer are inconsistent and adequate confounder adjustment is crucial for obtaining unbiased results.
- This study compares finasteride users and non-users across several covariates to detect potential confounders in investigations of the association between finasteride use and risk of male breast cancer.

- Nordic nationwide registries and surveys that are structured in a similar fashion provide a unique opportunity for performing cross-national individual-level data analyses increasing the generalizability of results.
- Systematic differences between finasteride users and non-users were observed with respect to a number of potential confounders.

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Abstract

Purpose

Published epidemiological studies on the association between finasteride use and the risk of male breast cancer have been inconclusive due to methodological limitations including small number of male breast cancer cases included. Determinants of male breast cancer have been studied, but it remains unexplored whether these are also related to finasteride use and thereby constitute potential confounders. This study aimed to assess whether there are differences between finasteride users and non-users with regard to a number of potential confounders.

Methods

In total, 246,508 finasteride users (≥35 years) were identified in the prescription registries of Denmark (1995–2014), Finland (1997–2013), and Sweden (2005–2014). An equal number of non-users were sampled. The directed acyclic graph (DAG) methodology was used to identify potential confounders for the association between finasteride and male breast cancer. A logistic regression model compared finasteride users and non-users with regard to potential confounders that were measurable in registries and population surveys.

Results

Finasteride users had higher odds of testicular abnormalities (odds ratio 1.40; 95% confidence interval 1.36–1.44), obesity (1.31; 1.23–1.39), exogenous testosterone (1.61; 1.48–1.74), radiation exposure (1.22; 1.18–1.27), and diabetes (1.07; 1.04–1.10) and lower odds of occupational exposure in perfume industry or in high temperature environments (0.93; 0.87–0.99), living alone (0.89; 0.88–0.91), living in urban/suburban areas (0.97; 0.95–0.99), and physical inactivity (0.70; 0.50–0.99) compared to non-users.

Conclusions

Systematic differences between finasteride users and non-users were found emphasizing the importance of confounder adjustment of associations between finasteride and male breast cancer.

Introduction

Finasteride 5 mg was approved for treatment of symptomatic benign prostatic hyperplasia in 1992 and finasteride 1 mg was later approved for treatment of androgenetic alopecia in 1997.[1, 2] In 2009, the Medicines and Healthcare products Regulatory Agency (MHRA) summarized the evidence from case reports raising concerns as to whether finasteride use is associated with increased risk of male breast cancer.[3] Several epidemiological drug safety studies of this association did not reveal consistent conclusions and had methodological limitations often due to low number of male breast cancer cases included.[4-9] Some of the previous studies were based on relatively small and selected samples[4-6, 8] while one study based on large data sources only had limited confounder information[7]. However, confounding by indication was lower in one study as the study was restricted to men with BPH.[6] One study from the authors including data from three Nordic countries and adjusting for several confounders showed no association between finasteride use and male breast cancer.[9] The unadjusted and adjusted models did not show large differences[9] even though confounder adjustment seems important, as finasteride users are likely to be different from non-users with regard to comorbidities, socioeconomic background, demographic characteristics, and contact with the health care system. Furthermore, different utilization patterns across the Nordic countries exist[10] indicating that finasteride users may have different characteristics in the Nordic countries which is important to adjust for in cross-national association studies.

The Nordic countries have a long history of registering and monitoring data on redeemed prescriptions of drugs, cancer, in-patient and out-patient hospital contacts, and sociodemographic information on all residents.[11-14] Moreover, population surveys have been carried out continuously in the Nordic countries with information on health and health behavior among representative samples of the population.[15-18] Hence, similar registry and survey data in the Nordic countries provide a unique opportunity to perform a common data analysis and compare finasteride users and non-users with regard to potential confounders of the association between finasteride and male breast cancer.

The aim of the present study was to compare characteristics between finasteride users and non-users utilizing individual-level registry and survey data from Denmark, Finland, and Sweden in order to detect potential confounders in investigations of the association between finasteride use and risk of male breast cancer.

Methods and material

Data sources

Individual-level data were collected from registries and surveys in Denmark, Finland, and Sweden by national coordinators and transferred to Statistics Denmark for establishment of a common database. Registry data came from prescription registries, patient registries, registries of the population's education, cancer registries, occupational registries, and civil registration systems. Survey data were obtained from the Danish National Health Survey,[16, 17] National FINRISK Study,[15] and Swedish Survey of Living Conditions.[18]

Linkage of data between different data sources was feasible due to the unique personal identity code assigned to all residents at birth or immigrtion.[11, 13, 19, 20] See supplementary material for information on registers and surveys included, Table S1.

Study population and design

This study is being performed as part of a post-authorization safety study commitment to the European Union health authorities. The study used a case-control design where finasteride users were cases and non-users were controls. The case population consisted of all male finasteride users 35 years or older included in the study at the date of their second prescription redemption of finasteride (index date). We restricted the analysis to this age span since the main treatment indication would be benign prostatic hyperplasia (BPH) whereas the main treatment indication in younger ages is androgenetic alopecia. The control population consisted of density sampled country-matched non-users[21] aged 35 years or older at the index date sampled from the civil registration systems in each country, i.e., for each user one non-user was sampled at the index date of the user. Finasteride prescription redemptions were identified in the prescription registries by Anatomic Therapeutic Chemical (ATC) code G04CB01 (finasteride 5 mg) and D11AX10 (finasteride 1 mg) in the period 1 January 1995 – 31 December 2014 in Denmark, 1 January 1997 – 31 December 2013 in Finland, and 1 July 2005 – 31 December 2014 in Sweden. In the present study, both 1 mg and 5 mg finasteride redemptions were included. The Finnish prescription registry includes only subsidized drugs. Only finasteride 5 mg (and not 1 mg finasteride) is subsidized in Finland, and therefore, only 5 mg finasteride redemptions were included in Finland. Moreover, finasteride 5 mg was registered under the ATC code G04CB04 in Finland from 1994–1996 and was not included in the prescription registry in this period. Therefore, the study period in Finland started in 1997 and only included 5 mg finasteride redemptions. The prescription registries included all prescriptions redeemed at pharmacies and thereby covered the total population in Denmark, Finland, and Sweden. In-hospital administrated drugs are not included in the prescription registries; however, 99% of finasteride used in Denmark was out-of-hospital sale and this proportion was assumed to be similar in Finland and Sweden.[22] Finasteride users within the first half year after establishment of the prescription registries in each country were excluded to apply a new-user design to exclude prevalent users.[23]

Identification of covariates

Exposure variables in the present study were potential confounders for the association between finasteride and male breast cancers which were identified in the literature and by discussion with a group of experts within urology, pharmacology and epidemiology.[24] The potential confounders were identified with the aim to be included in a directed acyclic graph (DAG) from which confounders were selected and adjusted for in another study on the association between finasteride and male breast cancer by the authors.[9] The DAG is published in this paper. Whereas a range of potential determinants of male breast cancer have been reported in the literature,[25-27] less is known about determinants of finasteride use. Consequently, all potential

confounders identified from the literature and during the meeting and that were available in registries or surveys were included in the present study.

The covariates included were: exogenous testosterone (at least two prescription redemptions), estrogen therapy (at least two prescription redemptions), Klinefelter's syndrome, educational level (elementary: ≤9 years, short: 10–12 years, medium/long: >12 years), testicular disorders (e.g., hydrocele, orchitis and cryptorchidism), urbanization (urban/suburban versus rural), benign breast disease, obesity, liver cirrhosis, occupational exposures (occupied versus not occupied in perfume industry or in high-temperature environments), family history of breast cancer (breast cancer diagnosis among first degree relatives), radiation exposure (x-ray and computerized axial tomography scans of the chest), cohabitation status (living alone versus cohabiting), diabetes, bone fractures (fractures of hip, bag, wrist and upper arm), and information on diagnosis and surgical treatment of benign prostatic hyperplasia (see supplementary material for ATC and International Classification of Diseases (ICD) codes, Table S2). For men in the study population who had also participated in surveys, information on life style factors was included: alcohol intake, physical inactivity, self-reported obesity, and dietary intake of vegetables (only Denmark and Finland), or animal fat (only Denmark). Additionally, proxy variables for measuring contacts with the health care system were included (i.e., number of prescription redemptions and hospital contacts) to elucidate whether surveillance bias may be an important source of bias in studies with finasteride as the exposure.

All covariates were measured before the index date. Diabetes, bone fractures, exogenous testosterone, and estrogen therapy diagnoses and treatments within the last 10 years before index date, when available, were used, whereas any diagnosis before index date was used for the remaining diseases. In Denmark and Sweden, urbanization, occupational exposure in perfume industry or in high temperature environments, educational level, and cohabitation status were measured the year before index date and if no information was available for that year then information for the index year was used. In Finland, the same procedure was used for urbanization whereas information on occupation in perfume industry or in high temperature environments, educational level, and cohabitation status came from census data (census years: 1995, 2000, 2005, and 2010). Information from the latest census before index data was used and if information was missing for that census, information from the previous census was used. Missing information on educational level was handled as lowest educational level, missing information on living alone was handled as not living alone and missing information on urbanization was handled as living in urban area.

Statistical analysis

The association between covariates and finasteride use as a binary outcome were examined using logistic regression analysis. The covariates were testicular abnormalities / disorders, benign breast disease, obesity, liver cirrhosis, Klinefelter's syndrome, estrogen therapy, exogeneous testosterone, diabetes, history of bone fractures, radiation exposure, family history of breast cancer, socio-economic position, living alone, living in

urban/suburban area and worked in perfume industry or in high-temperature environments. The logistic regression analysis was performed to estimate odds of the covariates among finasteride users versus non-users. Odds ratio (OR) and corresponding 95% confidence interval (95% CI) were estimated. Five sensitivity analyses were performed: cumulative finasteride use as number of packages with 98 5 mg pills purchased when converting all finasteride prescription redemptions into 5 mg packs of 98 pills (0-1 packs of 98 tablets versus 2-3 packs, 4-6 packs, and 7+ packs); changing the new users definition by excluding finasteride users and non-users in the first 2 years of registration in the prescription registries; including only 5 mg finasteride as finasteride users; restricting the analyses to persons with a previous diagnosis of BPH and/or BPH surgical procedure; and stratifying the analysis by country (i.e., separate results from Denmark, Finland, and Sweden).

All analyses were performed by SAS software version 9.4.

Ethical considerations

In Denmark, Finland, and Sweden, scientific studies based on registry data can be carried out without informed consent from the subjects if the purpose is performing scientific studies of significant public health importance. Legal and ethical approvals were obtained from the relevant national data agencies required in the three countries for data from registries and survey interviews.

Results

In total, 54,750 finasteride users from Denmark, 106,164 from Finland, and 134,679 from Sweden were identified (Figure 1). In total, 49,085 finasteride users were excluded as they did not meet the new user criterion. One non-user was included per finasteride user. The final study population consisted of 246,508 users and 246,508 non-users.

---------- FIGURE 1 ----------

Finasteride users were older than non-users (mean age of 71.1 years versus 53.3 years) and a higher proportion of users had testicular abnormalities (8.2% versus 5.9%) (Table 1). A larger proportion of finasteride users compared to non-users had been exposed to radiation (4.7% versus 2.5%), had low educational level (48.1% versus 31.8%), and diabetes (8.9% versus 4.4%). In contrast, a smaller proportion of finasteride users compared to non-users were living alone (28.2% versus 33.8%).

---------- TABLE 1 ----------

Results from the fully adjusted model mutually adjusted for all potential confounders, age group, calendar year and country showed higher odds of testicular abnormalities (OR; 95% confidence interval (CI): 1.40; 1.36–1.44), obesity (1.31; 1.23–1.39), exogenous testosterone (1.61; 1.48–1.74), radiation exposure (1.22;

1.18–1.27), and diabetes (1.07; 1.04–1.10) among finasteride users compared to non-users (Table 1). Finasteride users had lower odds of occupational exposure in perfume industry or in high temperature environments (0.93; 0.87–0.99), living alone (0.89; 0.88–0.91), and living in urban/suburban areas (0.97; 0.95–0.99)). No association was found between finasteride use and any of other potential confounders that were considered (benign breast disease, liver cirrhosis, Klinefelter's syndrome, estrogen therapy, family history of breast cancer, or bone fracture).

In total, 1,821 men in the study population had participated in surveys. Only inactivity was associated with finasteride use; the odds of being inactive was lower among finasteride users than non-users (0.70; 0.50–0.99) when adjusting for all registry-based variables (except estrogen therapy, Klinefelter's syndrome, and benign breast disease due to too few observations in the survey data).

According to factors associated with health care use, finasteride users had higher odds of being in the group of men with more prescription redemptions and contacts with the hospital than the country-specific average compared to non-users (OR (95% CI) of 2.24 (2.21–2.28) and 1.78 (1.75–1.81), respectively).

Results from the two independent sensitivity analyses performed to assess the robustness of the results with changing definitions of finasteride use (i.e., cumulative use and restricting the study population to only 5 mg users) showed similar results to the main analysis (Table 2).

---------- TABLE 2 ----------

Sensitivity analyses excluding the first two years of registration or restricting the analysis to persons with BPH, respectively, showed similar results as the main analysis (Table 3). Results stratified by country generally revealed similar results for Denmark, Finland, and Sweden. However, finasteride users compared to non-users were more likely to live in urban/suburban areas in Denmark (1.16; 1.11–1.22), while the opposite result was found in Finland (0.88; 0.85-0.91). Likewise, finasteride users had higher odds of having diabetes in Denmark (1.10; 1.02–1.18) and Sweden (1.13; 1.09–1.18), whereas the odds of diabetes was lower among users than non-users in Finland (0.92; 0.87–0.97).

---------- TABLE 3 ----------

Discussion

This Nordic register-based study found systematic differences between finasteride users and non-users that may be important confounders to consider in evaluating the potential association between finasteride use and the risk of male breast cancer. Results were robust to changes in the definitions of finasteride use and to restrictions of the study population. In general, similar differences in potential confounders between finasteride use and non-users s were found in Denmark, Finland, and Sweden.

Interpretation of findings

The finding that finasteride users were different from non-users with regard to age, educational level, and comorbidities emphasizes the importance of accounting for confounding in the association between finasteride and male breast cancer or other diseases. Moreover, finasteride users had more contact with the health care system indicating that surveillance bias could influence associations between finasteride use and development of diseases.

Some differences were previously found in utilization patterns in finasteride across the Nordic countries[10]. The number of finasteride 5 mg users was markedly higher in Finland and Sweden compared to Denmark, with period prevalence in 2009 of 18.2/1000 males age 15 years or older in Finland, 12.0/1000 males in Sweden and 4.9/1000 males in Denmark. The median age at first prescription redemption was slightly different comparing the three countries with a median age of 68 years in Denmark, 70 years in Finland, and 72 years in Sweden. Hence, results from the previous study mentioned above indicated, that finasteride users might differ across the three countries, especially regarding the proportion of men using the drug. However, the present study found approximately the same determinants of finasteride use across the three countries except for few variations (i.e., urbanization and diabetes) and did not support that finasteride users had different characteristics across the countries.

The results of the study may be generalizable to other countries with similar use of finasteride as the Nordic countries. The similarities of how the determinants of finasteride use across the three countries further lend support that such associations could exist elsewhere.

Strengths and limitations

Main strengths of the study were the pooled analysis with individual-level data available for a long period of time from three countries. Similar registration procedures and data sources in the three countries enabled harmonization of the variable definitions and made it feasible to construct a common dataset. Hence, the study included a large sample based on a source population consisting of the total population from three countries. Another merit of the study was the overall high validity of the diagnoses in the national patient registries and the completeness of drug data in the prescription registries.[22, 28-31] In addition, it was possible to obtain data on a wide range of the potential confounders in the nationwide registries and representative national survey.

Study limitations included the unknown drug compliance, since data reflected purchased and not consumed drugs. However, including finasteride users at their second prescription redemption increases the likelihood that these were in fact finasteride users. Moreover, covariates measuring diseases or conditions that were not necessarily treated in the hospital (e.g., diabetes and obesity) may be underreported in our data meaning that the identified groups of patients were likely to represent the most severe cases. Information on self-reported factors was obtained from surveys, which only included a small proportion of the study population. These

results may have been influenced by non-response bias. In Finland, only information on 5 mg finasteride use was available, which could result in misclassification in that 1 mg users could be classified as non-users.

This study examined the association between finasteride use and a wide range of potential confounders. Consequently, several statistical tests were performed with the risk of committing a type 1 error. Moreover, this study had statistical power to observe small differences between finasteride users and non-user that may not be of clinical relevance (e.g., differences in diabetes, occupational exposure in perfume industry or in high temperature environment and living in urban/suburban areas). As the study was designed as a case-control study it is not possible to calculate the absolute differences between finasteride users and non-users and this is a limitation of the study.

Perspectives

Harmonization of data across countries is challenging and time consuming. A review of studies based on data from the prescription databases in the Nordic countries found that less than 1% (4 out of 515 studies) of the identified studies between 2005–2010 were based on data from more than one country.[31] This study also demonstrates the great potential in merging individual-level data from registries and surveys across the Nordic countries to obtain a common database.

Conclusion

The characteristics of finasteride users differs from that of non-users according to a number of covariates that may be associated with male breast cancer and other diseases. Hence, in observational studies evaluating the relationship between finasteride exposure and male breast cancer it is essential to adjust for such confounders.

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Conflict of interest

TMK, AKE, EP, KBo, KS, PI, KBr, JH, and LCT declare: no conflict of interest. As Partners as well as Scientific Director and Managing Director with ApEHR, AG and ME have been involved in observational register-based studies performed on a consultative basis for Merck Sharp & Dohme Corp.

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Tables

Table 1. Characteristics of male finasteride users and non-users with respect to potential confounding factors and association between potential confounding factors and finasteride use. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Numbers (%) if nothing else is stated

	Users	**Non-users**	**Age-, year- and country-adjusted** *OR (95% CI)*	**Fully adjusted** † *OR (95% CI)*
N	246,508	246,508		
Age, *mean (standard deviation)*	71.1 (10.2)	53.3 (14.7)		
Testicular-abnormalities /disorders	20,280 (8.2)	14,577 (5.9)	1.42 (1.38-1.46)	1.40 (1.36-1.44)
Benign breast disease	297 (0.1)	280 (0.1)	1.11 (0.89-1.37)	1.09 (0.88-1.35)
Obesity	3,438 (1.4)	2,369 (1.0)	1.35 (1.27-1.43)	1.31 (1.23-1.39)
Liver cirrhosis	2,970 (1.2)	2,308 (0.9)	1.02 (0.96-1.09)	1.00 (0.94-1.07)
Klinefelter's syndrome	17 (0.0)	44 (0.0)	1.29 (0.63-2.64)	0.87 (0.42-1.80)
Estrogen therapy	114 (0.1)	52 (0.0)	1.55 (1.04-2.32)	1.44 (0.96-2.14)
Exogenous testosterone	2,946 (1.2)	1,255 (0.5)	1.71 (1.58-1.85)	1.61 (1.48-1.74)
Diabetes	22,045 (8.9)	10,772 (4.4)	1.09 (1.06-1.12)	1.07 (1.04-1.10)
History of bone fractures	11,361 (4.6)	8,165 (3.3)	0.99 (0.95-1.02)	0.99 (0.96-1.03)
Radiation exposure	11,481 (4.7)	6,083 (2.5)	1.24 (1.20-1.29)	1.22 (1.18-1.27)
Family history of breast cancer	11,193 (4.5)	13,235 (5.4)	1.01 (0.98-1.04)	1.00 (0.97-1.04)
Socio-economic position				
Low (≤9 years of education)	118,661 (48.1)	78,290 (31.8)	1.00 (ref)	1.00 (ref)
Medium (10-12 years of education)	74,892 (30.4)	104,527 (42.4)	1.09 (1.07-1.11)	1.08 (1.06-1.10)
High (>12 years of education)	52,955 (21.5)	63,691 (25.8)	1.29 (1.26-1.31)	1.28 (1.26-1.31)
Living alone	69,605 (28.2)	83,328 (33.8)	0.88 (0.87-0.89)	0.89 (0.88-0.91)
Living in urban/suburban area	194,755 (79.0)	200,857 (81.5)	1.00 (0.99-1.02)	0.97 (0.95-0.99)
Worked in perfume industry or in high-temperature environments	2,426 (1.0)	4,248 (1.7)	0.89 (0.84-0.95)	0.93 (0.87-0.99)

OR=Odds ratio, 95%CI=95% confidence interval

†Model mutually adjusted for all included variables, age group (5-year categories), calendar year (3-year intervals) and country.

‡ Compared to the reference group with low educational level (≤9 years of education)

Table 2. Two sensitivity analyses of association between potential confounding factors and finasteride use with alternative definition of finasteride use: (1) cumulative use and (2) only including 5 mg finasteride use.

	Cumulative use †			Only 5 mg †
	2-3 packs	**4-6 packs**	**7+ packs**	
N (users/non-users)	222,489/246,508	168,908/246,508	125,462/246,508	243,683/246,424
	OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*
Testicular-abnormalities /disorders	1.42 (1.38-1.46)	1.44 (1.40-1.49)	1.46 (1.41-1.51)	1.41 (1.37-1.45)
Benign breast disease	1.07 (0.85-1.34)	1.06 (0.83-1.36)	1.11 (0.85-1.45)	1.10 (0.88-1.37)
Obesity	1.34 (1.25-1.43)	1.39 (1.30-1.49)	1.42 (1.32-1.53)	1.33 (1.25-1.42)
Liver cirrhosis	0.99 (0.93-1.06)	1.00 (0.93-1.08)	0.96 (0.89-1.04)	0.99 (0.93-1.06)
Klinefelter's syndrome	0.82 (0.37-1.78)	1.22 (0.52-2.86)	1.49 (0.53-4.15)	1.00 (1.48-2.11)
Estrogen therapy	1.43 (0.95-2.16)	1.08 (0.72-1.62)	0.88 (0.56-1.39)	1.20 (0.81-1.78)
Exogenous testosterone	1.55 (1.43-1.69)	1.48 (1.35-1.61)	1.40 (1.28-1.54)	1.54 (1.42-1.67)
Diabetes	1.08 (1.05-1.11)	1.10 (1.07-1.13)	1.12 (1.09-1.16)	1.08 (1.05-1.11)
History of bone fractures	1.00 (0.96-1.03)	1.00 (0.96-1.04)	0.99 (0.95-1.03)	1.00 (0.96-1.03)
Radiation exposure	1.22 (1.17-1.26)	1.20 (1.16-1.25)	1.20 (1.15-1.25)	1.23 (1.19-1.28)
Family history of breast cancer	1.02 (0.98-1.05)	1.02 (0.99-1.06)	1.06 (1.02-1.10)	1.01 (0.98-1.05)
Socio-economic position				
Medium (10-12 years of education) ‡	1.10 (1.08-1.12)	1.12 (1.10-1.14)	1.17 (1.14-1.19)	1.10 (1.08-1.12)
High (>12 years of education) ‡	1.29 (1.26-1.32)	1.31 (1.28-1.34)	1.36 (1.33-1.40)	1.26 (1.24-1.29)
Living alone	0.87 (0.86-0.89)	0.86 (0.84-0.88)	0.85 (0.83-0.87)	0.87 (0.85-0.88)
Living in urban/suburban area	0.96 (0.95-0.98)	0.95 (0.93-0.97)	0.95 (0.93-0.97)	0.96 (0.94-0.97)
Worked in perfume industry or in high-temperature environments	0.94 (0.88-1.00)	0.93 (0.87-1.00)	0.95 (0.87-1.03)	0.93 (0.88-1.00)

OR=Odds ratio, 95%CI=95% confidence interval

†Model mutually adjusted for all included variables, age group (5-year categories), calendar year (3-year intervals) and country.

‡ Compared to the reference group with low educational level ((≤9 years of education)

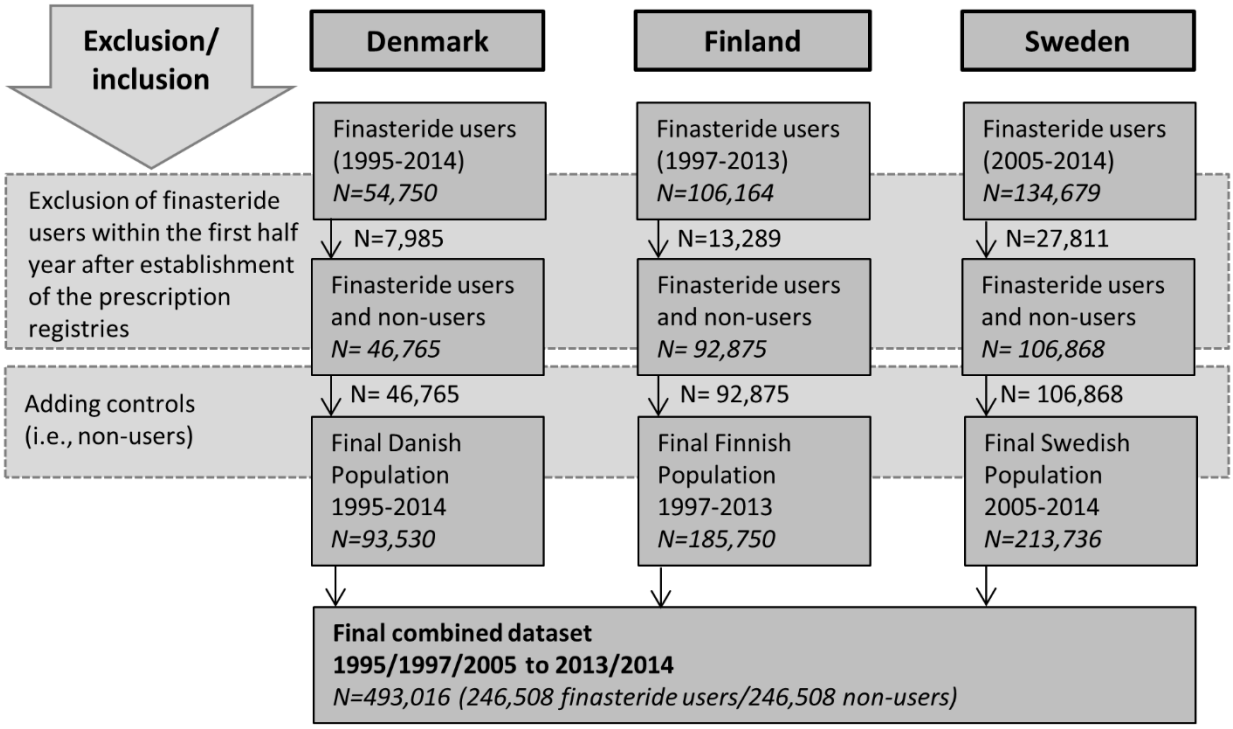
Table 3. Three sensitivity analyses of association between potential confounding factors and finasteride use with restricting and stratifying the study population: excluding prescription redemption in the first 2 years of registration; restricting the analyses to persons with BPH; and country-specific estimates for Denmark, Finland and Sweden.

	Excluding first two years of registration†	BPH cohort†	Country specific analysis†		
			Denmark	Finland	Sweden
N (users/non-users)	*212,988/245,292*	*99,671/13,827*	*46,765/46,765*	*92,875/92,875*	*106,868/106,868*
	OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*
Testicular-abnormalities /disorders	1.42 (1.38-1.46)	0.88 (0.83-0.93)	1.28 (1.21-1.36)	1.23 (1.16-1.30)	1.58 (1.51-1.64)
Benign breast disease	1.06 (0.85-1.33)	1.00 (0.61-1.65)	1.31 (0.94-1.84)	1.04 (0.74-1.47)	0.92 (0.56-1.50)
Obesity	1.30 (1.22-1.39)	1.32 (1.12-1.56)	1.43 (1.26-1.64)	1.20 (1.05-1.35)	1.31 (1.20-1.43)
Liver cirrhosis	0.99 (0.92-1.06)	0.92 (0.78-1.08)	0.99 (0.85-1.15)	0.95 (0.86-1.05)	1.04 (0.94-1.15)
Klinefelter's syndrome	0.84 (0.40-1.76)	NA	0.80 (0.08-8.25)	4.04 (0.69-13.45)	0.65 (0.27-1.55)
Estrogen therapy	1.42 (0.94-2.15)	0.48 (0.26-0.88)	4.05 (1.96-8.40)	0.54 (0.25-1.16)	0.95 (0.52-1.73)
Exogenous testosterone	1.63 (1.50-1.78)	0.97 (0.81-1.15)	1.64 (1.16-2.30)	1.53 (1.38-1.70)	1.59 (1.38-1.83)
Diabetes	1.08 (1.05-1.11)	0.97 (0.91-1.02)	1.10 (1.02-1.18)	0.92 (0.87-0.97)	1.13 (1.09-1.18)
History of bone fractures	1.01 (0.97-1.04)	0.88 (0.82-0.95)	1.00 (0.92-1.08)	0.97 (0.90-1.03)	0.99 (0.94-1.04)
Radiation exposure	1.19 (1.14-1.23)	1.01 (0.94-1.09)	1.27 (1.17-1.37)	1.16 (1.07-1.25)	1.18 (1.12-1.24)
Family history of breast cancer	1.02 (0.99-1.06)	0.95 (0.87-1.03)	0.83 (0.70-0.99)	1.07 (1.00-1.14)	1.01 (0.98-1.05)
Socio-economic position					
Medium (10-12 years) ‡	1.12 (1.10-1.14)	1.06 (1.01-1.11)	1.06 (1.02-1.10)	1.20 (1.17-1.24)	1.03 (1.00-1.06)
High (>12 years) ‡	1.31 (1.28-1.34)	1.08 (1.02-1.13)	1.37 (1.31-1.44)	1.44 (1.39-1.49)	1.17 (1.14-1.21)
Living alone	0.89 (0.88-0.91)	0.98 (0.94-1.02)	0.89 (0.86-0.93)	0.95 (0.92-0.97)	0.89 (0.87-0.91)
Living in urban/suburban area one year before	0.97 (0.95-0.99)	0.91 (0.87-0.95)	1.16 (1.11-1.22)	0.88 (0.85-0.91)	1.00 (0.97-1.02)
Worked in perfume industry or in high-temperature environments	0.97 (0.91-1.04)	1.14 (0.93-1.40)	0.86 (0.72-1.03)	1.21 (1.03-1.42)	0.87 (0.81-0.94)

OR=Odds ratio, 95%CI=95% confidence interval, NA=not available as the model could not converge when for the variable Klinefelter's syndrome was included.
† Model mutually adjusted for all included variables, age group (5-year categories), calendar year (3-year intervals) and country.
‡ Compared to the reference group with low educational level ((≤9 years of education)

Figure legends

Figure 1. Overview of the study population



Supplementary material

Table S1. Registers and surveys included as data sources

Country	Register	Registration period
Denmark	Prescription register	1995-
	Cancer register	1943-
	National patient register	1977- (surgeries since 1977 and outpatient contacts since 1995)
	Civil registration system	1968-
	Register-based labour force statistics (RAS statistics)	1980-
	Danish National Health Survey	1994, 2000, 2005 and 2010
Finland	Prescription register	1997- †
	Cancer register	1953-
	National patient register	1967- (surgeries since 1986 and outpatient contacts since 1998)
	Civil registration system	1967-
	Censuses including information on occupational group	1995, 2000, 2005 and 2010
	National FINRISK Study	2000 and 2011
Sweden	Prescription register	2005-
	Cancer register	1958-
	National patient register	1987-
	Civil registration system	1968-
	Register on labour force statistics (LISA)	1990- 2013
	Swedish Survey of Living Conditions	

† Only finasteride 5 mg (and not 1 mg finasteride) is subsidized in Finland, and therefore, only 5 mg finasteride redemptions were included in Finland. Moreover, finasteride 5 mg was registered under the ATC code G04CB04 in Finland from 1994–1996 and was not included in the prescription registry in this period. Therefore, the study period in Finland started in 1997 and only included 5 mg finasteride redemptions.

Table S2. Anatomic Therapeutic Chemical (ATC) and International Classification of Diseases (ICD)-8, -9, -10, hospital procedure, and surgical procedure codes used for finasteride and covariates the three countries

Variable	Registry	Classification system	Denmark	Finland	Sweden
Finasteride	Prescription registry	ATC	G04CB01 (5mg), D11AX10 (1mg)		
Testicular abnormalities/disorders	Patient registry	ICD-8	257, 603, 604, 605, 606, 607		
		ICD-9	---	603, 604, 606, 607, 608, 7786A	603, 604, 606, 607, 608, 778G
		ICD-10	N43-N51, P83.5		
Benign prostatic hyperplasia	Patient registry	ICD-8	600		
		ICD-9	---	6000	600
		ICD-10	N40		
		NOMESCO codes	KEA-KEW		
Benign breast disease	Patient registry	ICD-8	610, 611		
		ICD-9	---	217	
		ICD-10	D24		
Obesity	Patient registry	ICD-8	No codes available		
		ICD-9	---	2780A, 2781A, 2788A	278A
		ICD-10	E65, E66		
Liver cirrhosis	Patient registry	ICD-8	570-573		
		ICD-9	---	570-573	
		ICD-10	K70-K77		
Klinefelter's syndrom	Patient registry	ICD-8	No codes available		
		ICD-9	---	7587A, 7588B, 7588E	758H, 758W-758X
		ICD-10	Q98		
diabetes	Patient registry	ICD-8	249, 250		
		ICD-9	---	249, 250	
		ICD-10	E10-E14		
Bone fracture	Patient registry	ICD-8	820, 805, 812, 813		
		ICD-9	---	820, 821, 805.2, 805.4, 805.8, 813.4, 813.5, 812	820, 821, 805C, 805E, 805W, 813E, 813F, 812A, 812B
		ICD-10	S72, S32, S52, S42		
Radiation exposure	Patient registry	Procedure codes	UXRC10, UXRC12, UXCC00-UXCC77	AX099, GD1AA, GD1AD, HA0, PJ020, QX099, WFO, WA, XX7	AA066-AA068, AD027-AD034, AE007-AE016, AF053, AG036-AG043, AH003, AJ038-AJ050, AK020-AK025, AM007, AN051-AN075, AN090, AV005, AV006, AV035, AV036, DA031, DJ007, DV040, AA011-AA017, AB001, AB054, AC004, AD005-AD007, AE001-

					AE003, AF017, AF018, AG007-AG009, AH001, AJ004-AJ013, AK002-AK004, AL002, AN009-AN029, AV013, ZV046
Estrogen therapy	Prescription registry	ATC	G03C, G03FA, G03FB, G03HB, L02AA		
Exogenous testosterone	Prescription registry	ATC	G03BA03		
Family history of breast cancer	Population registry (first degree relatives) and cancer registry	ICD-7	170		
		ICD-10	C50		

ICD = International Classification of Diseases, ATC = Anatomic Therapeutic Chemical, NOMESCO = Nordic Medical Statistics Committees Classification of Surgical Procedures