Interim and Final Study Report Template for Non-Interventional Post-Authorisation Safety Studies (PASS)

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

PASS INFORMATION

Title	Finasteride and male breast cancer – a register-based nested case-control study in Denmark, Finland, and Sweden
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Product reference	- MRP number SE/H/0158/001 (Propecia) - nationally authorised products (NAP-Propecia)+(NAP-Proscar)
Procedure number	SE/H/xxxx/WS/243
Marketing authorisation holder(s)	Merck Sharp & Dohme Corp., A Subsidiary of Merck & Co., Inc. 2000 Galloping Hill Road Kenilworth, NJ 07033 U.S.A.
Joint PASS	No
Research question and objectives	The research question was to assess whether the previously reported increased incidence rate of male breast cancer among finasteride users compared to non-users might be explained by confounding factors. The main objectives were to 1) describe finasteride users compared to non-users with respect to confounding factors and 2) analyze the effect of finasteride use on breast cancer incidence while taking account of confounding factors.
Country(-ies) of study	Denmark, Finland, and Sweden
Author	PPD , Denmark
Merck Final Repository (RCAM) Date	**02-MAY-2018**

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MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Merck Sharp & Dohme Corp., A Subsidiary of Merck & Co., Inc. 2000 Galloping Hill Road Kenilworth, NJ 07033 U.S.A.
MAH contact person	PPD Associate Director Regulatory Affairs EMEA Regional Center Merck Sharp & Dohme (Europe) Inc. Clos du Lynx 5, 1200 Brussels, Belgium Tel. PPD Email. PPD

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1 ABSTRACT

Title

Finasteride and male breast cancer – a register-based nested case-control study in Denmark, Finland, and Sweden.

February 13, 2018

PPD
, Denmark

Keywords

Finasteride, breast neoplasms male, pharmacoepidemiology, registers, Nordic countries

Rationale and background

Previous studies have suggested an association between finasteride use and male breast cancer, e.g. the previous Nordic register-based stage I study reported an incidence rate ratio of 1.44 (95% confidence interval 1.11–1.88) of male breast cancer among finasteride users compared to non-users conducted by the same investigators (see section 3).

Research question and objectives

The research question was to further assess whether the increased male breast cancer incidence among finasteride users compared to non-users might be explained by confounding factors. The research objectives were twofold:

1. Describe finasteride users compared to non-users with respect to potential confounding factors (exploratory variables).
2. Analyze the effect of finasteride use on male breast cancer incidence while taking account of confounding factors decided in a directed acyclic graph (DAG) analyzing the association between finasteride use and male breast cancer.

The hypotheses were:

1. There is a systematic difference between finasteride users and non-users for potentially confounding factors previously reported to be associated with finasteride use or male breast cancer incidence.
2. The previously found increased incidence of male breast cancer among finasteride users is explained by confounding factors.

Study design

The study consisted of two substudies.

- Substudy 1 and 1A compared finasteride users (persons with at least two prescriptions of finasteride) with non-users (persons with less than 2 prescriptions of finasteride) or persons with different levels of cumulative finasteride use with respect to potential confounding factors including survey data. Entry criterion to the group of finasteride users was redemption of the second finasteride prescription.
- Substudy 2 evaluated the association between finasteride use (exposure) and male breast cancer (outcome) taking account of confounding factors. Finasteride use was included as finasteride users versus non-users and as persons with different levels of cumulative finasteride use. Country- and age-matching (year of birth) was used in substudy 2.

Setting

In substudy 1 and 1A the population comprised of all male finasteride users and a random sample of country-matched non-users in the period 1995-2014 (Denmark), 1997-2013 (Finland), and 2005-2014 (Sweden).

In substudy 2 the population comprised of all male breast cancer cases and a random sample of country- and age-matched controls during the same period.

Both studies used density sampling and were therefore matched on follow-up time.

Subjects and study size, including dropouts

In substudy 1, the number of finasteride users (2 or more redemptions) in Denmark and Finland were 139,640 men and the same number of controls (<2 redemptions of finasteride). The number of men with 2-3 packs of 98 5 mg tablets of finasteride were 119,639 men, the number of men with 4-6 packs of 98 5 mg tablets were 90,599 men, and the number of men with 7 or more packes of 98 5 mg tablets were 69,581 men . When including all three countries (Denmark, Finland and Sweden) the number of finasteride users were 246,508 men and the same number of non-users. For cumulative finasteride use 222,489 had redeemed 2-3 packs of 98 5 mg tablets, 168,908 had redeemed 4-6 packs of 98 5 mg tablets and 125,462 had redeemed 7 or more packs of 98 5 mg tablets.

In substudy 1A, the number of finasteride users who also participated in the surveys was 1,026 men and 795 controls (<2 redemptions).

In substudy 2, the number of male breast cancer cases was 680 when including Denmark and Finland and 1,005 cases when including all three countries (Denmark, Finland and Sweden). The number of controls was 29,746 men when including Denmark and Finland and 43,058 men when including all three countries.

Variables and data sources

Variables: Confounding variables were selected on the basis of a directional acyclic graph (DAGs) developed together with clinical experts: Age, country, calendar time, benign prostatic hyperplasia, estrogen therapy, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Finasteride use and male breast cancer were main variables. Several potential confounding factors were evaluated in substudy 1, e.g. benign breast disease, Klinefelter's syndrome, estrogen therapy, family history (male, female) of breast cancer, radiation exposure, alcohol intake, and socio-economic position.

Data sources: Nation-wide registers with information on prescription drugs, cancer incidence, hospital discharges, and occupation were used. Information from representative surveys on life-style factors is also included.

Results

The incidence rates of male breast cancer were between 0.70 and 1.00 per 100,000 person-years in Denmark, Finland and Sweden.

The results of substudy 1 were that several potential confounding factors were associated with higher odds of finasteride use including testicular abnormalities, obesity, radiation exposure, and higher socio-economic position. The following factors were associated with lower odds of finasteride use: estrogen therapy, living as a single man and living in an urban area. Cumulative finasteride use showed the same pattern as for binary finasteride use, with the exception of previous diagnosis of Klinefelter's syndrome, which was associated with higher odds of cumulative use of 4-6 and 7+ packs of finasteride. Except sedentary behavior being associated with decreased odds of finasteride use, lifestyle factors were not clearly associated with finasteride use although these findings may be influenced by a small sample size.

The key result of substudy 2 was that odds of exposure to finasteride was not statistically significantly different in cases of male breast cancer compared to controls (odds ratio (OR) (95% confidence interval (CI))= 1.30 (0.89-1.91) for analysis including Denmark and Finland and OR (95%CI) = 1.18 (0.84-1.65) for the analysis including all three countries. The odds ratio estimates attenuated when taking account of confounding factors decided in the DAG analyzing the association between finasteride use and male breast cancer (OR (95% CI)=1.20 (0.81-1.77) for analysis including Denmark and Finland and OR (95%CI) = 1.09 (0.77-1.53) for the analysis including all three countries). For cumulative finasteride use the OR was highest for medium users (4-6 packs) although none of the odds ratios were statistically significant.

Discussion

There was systematic difference between finasteride users and non-users with regards to confounding factors previously reported to be associated with finasteride use or male breast cancer incidence. Furthermore, the study supports that there is no statistically significant increased odds of exposure to finasteride among male breast cancer cases compared to

controls in both the age-, country- and calendar-time adjusted analysis or when taking account of confounding factors. The study showed that the adjustment for confounders decreased the odds ratio of finasteride exposure in cases relative to controls in the age-, country- and calendar-adjusted analysis.

Marketing Authorisation Holder(s)

Merck Sharp & Dohme Corp.,
A Subsidiary of Merck & Co., Inc.
2000 Galloping Hill Road
Kenilworth, NJ 07033 U.S.A.

Names and affiliations of principal investigators

PPD Denmark

2 LIST OF ABBREVIATIONS

PPD

ARIs, 5alpha-reductase inhibitors

BPH, benign prostatic hyperplasia

BRCA, Genes on chromosome 13 and 17 that normally helps suppress cell growth; certain mutations of these genes are associated with breast cancer and some other types of cancer

CRC, Case Review Committee (CRC)

DAG, directional acyclic graph

EU, The European Union

FDA, US Food and Drug Administration

ICD, International Classification of Diseases

MPHL, male pattern hair loss

PPD

PPD

eSRC, External Safety Review Committee

PPD

3 INVESTIGATORS

Principal investigator	PPD Denmark
Coordinating investigator for each country in which the study is to be performed	PPD • PPD • PPD **National scientific coordinators** • Denmark: PPD • Finland: PPD • Sweden: PPD
Sponsor contacts	PPD Sr. Scientist, Regulatory Liaison RAI - Infectious Disease Email: PPD Phone: PPD Merck & Co., Inc., Upper Gwynedd, PA USA
Other contacts	NA
Vendor/Collaborator	NA
Investigators	PPD

4 OTHER RESPONSIBLE PARTIES

Shared Responsibilities	Contact Person
Expert group	• PPD
Expert group	• PPD
eSRC	• PPD
eSRC	• PPD
eSRC	• PPD

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	Feb 2015	July 2015	-Data were extracted from several registers from all three countries and located at Statistics Denmark. -Applications to local register data administrations were approved in July 2015 for Denmark and March-Oct 2016 in Sweden and Finland, respectively. -Data started to arrive from Denmark: July 2015 (cases for substudy 1) Finland: January 2017 (cancer file) Sweden: March 2017 (substudy 1 file). -Planned dates are according to the latest signed agreement.
End of data collection	July 2017	Oct 2017	-Last data sets from Finland were received by Statistics Denmark October 2017. -Planned dates are according to the latest signed agreement.

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Milestone	Planned date	Actual date	Comments
Registration in the EU PAS register	04- May-2017	04- May-2017	
Final report of study results	April 2018	[DD-MMM-YYYY]	Planned dates are according to the latest signed agreement.

6 RATIONALE AND BACKGROUND

Finasteride is a type II 5α-reductase inhibitor and was initially approved by the US Food and Drug Administration (FDA) in 1992 under the brand name PROSCAR as a treatment for benign prostatic hyperplasia (BPH). In 1997, the FDA approved finasteride for the treatment of male pattern hair loss (MPHL), under the brand name PROPECIA.

Finasteride is available in the European Union (EU) as 1 mg and 5 mg tablets in preparations and indications as follows:

- Proscar (Finasteride 5 mg, ATC code: G04CB01) for the treatment and control of BPH in patients with an enlarged prostate to cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH. This reduces the risk of acute urinary retention and the need for BPH related surgery. The daily dose is one tablet of 5 mg.
- Propecia (Finasteride 1 mg, ATC code: D11AX10) for the treatment of men with androgenetic alopecia. Propecia stabilizes the process of androgenetic alopecia. Efficacy in bitemporal recession and end-stage hair loss has not been established. The daily dose is one tablet of 1 mg.

The annual number of newly diagnosed male breast cancer cases is around 100 in all Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) combined (Engholm 2010). Several risk factors for male breast cancer are associated with increased estrogen and decreased androgen levels. These include testicular abnormality, benign breast disease, obesity, liver cirrhosis, Klinefelter's syndrome, gynaecomastia, estrogen therapy, and occupational exposures such as work in the perfume industry, night-shift work, and in high-temperature environments (Johansen Taber 2010, Pukkala 2009).

Family history of both male and female breast cancer also affect the risk of male breast cancer. In this group genetic disposition, e.g. BRCA mutations, is associated with breast cancer (Johansen Taber 2010). Exposure to ionizing radiation is also suspected to be associated with breast cancer in men. Men with pulmonary tuberculosis, who had a large number of fluoroscopies and X-rays, have been reported to have higher incidences of breast cancer (Johansen Taber 2010). Several life-style factors associated with female breast cancer may also be associated with male breast cancer, e.g. physical inactivity and alcohol intake.

Finally, socio-economic and urban/rural differences in male breast cancer have been reported.

Some studies have investigated an association between finasteride and male breast cancer although none of the studies reported any significantly increased risk (Lee 2004, Shenoy 2010). In a case-control study of a US patients population between 2001-2009 including 339 male breast cancer cases investigated finasteride, dutasteride (i.e. a drug within the same drug class as finasteride, ATC code G04CB02), and male breast cancer and found no association between finasteride (i.e. PROSCAR dosages only) and male breast cancer (3 years or more period of observation before index date: Risk Ratio (RR) = 0.75, 95% CI: 0.27 – 2.10; 365 days cumulative therapy: RR = 1.03, 95% CI: 0.45 – 2.37) (Bird et al, 2013).

A register-based cohort stage I study with data from Denmark, Finland, Norway, and Sweden was conducted by the investigators of the present study to study the potential link between finasteride use and incident male breast cancer (Meijer et al., 2018; Study report 2012). Based on data from nation-wide registers on drug prescriptions and cancer incidence, the study reported an increased incidence of breast cancer among male users of finasteride compared to non-users (incidence rate ratio, 1.44; 95%CI, 1.11-1.88). This study was much larger than any previous study and the finding of a significantly increased incidence rate has not been reported in any of the previous studies. When restricting the analyses to Denmark and Finland with the longest observation period, an increased breast cancer incidence rate was also observed, most pronounced in Denmark. The higher prevalence of finasteride use was observed in Finland compared to Denmark. Furthermore, Danish users of finasteride had a 1.23 times higher mortality rate compared to Finnish finasteride users. These two patterns indicate that finasteride users in Denmark are more selected than in Finland, which could indicate that confounding factors may be different between the two countries. Statistical adjustment was made for age and calendar year, but concerns have been raised whether adjustment for other risk factors for breast cancer may alter the association found.

The present study is a stage II study following up on the prior stage I study examining the potential link between finasteride use and incident male breast cancer (Meijer et al., 2018). In the present study further information on confounding factors was included to compare finasteride users and non-users (investigating finasteride users defined by both a binary variable and a cumulative variable) and to evaluate whether the reported association between finasteride use and male breast cancer could be explained by confounding factors. The main analyses were performed for both Denmark and Finland to evaluate the effect of finasteride in the two countries with longest follow-up (1997-2013 for Finland and 1995-2014 for Denmark) and, alternatively, for all three countries (Denmark (1995-2014), Finland (1997-2013), and Sweden (2005-2014)). The analysis only including Finland and Denmark was performed since follow-up time was limited for Sweden which increases the influence of truncation and makes latency analyses more difficult to perform.

7 RESEARCH QUESTION AND OBJECTIVES

The research question was to further assess whether the increased male breast cancer incidence among finasteride users compared to non-users might be explained by confounding factors. The research objectives were twofold:

1. Describe finasteride users compared to non-users with respect to potential confounding factors (exploratory variables).
2. Analyze the effect of finasteride use on male breast cancer incidence while taking account of confounding factors decided in a DAG analyzing the association between finasteride use and male breast cancer.

The hypotheses were:

1. There was a systematic difference between finasteride users and non-users for potentially confounding factors previously reported to be associated with finasteride use or male breast cancer incidence.
2. The previously found increased incidence of male breast cancer among finasteride users could be explained by confounding factors.

8 AMENDMENTS AND UPDATES

See Annex 1F for Protocol Amendment dated on 10-Feb-2015, and Annex 1G for Protocol Amendment dated Jan-2018.

9 RESEARCH METHODS

9.1 Study design

The first step was developing a DAG for the association between finasteride use and male breast cancer. This development highlighted factors associated with finasteride use, factors that are a consequence of finasteride use, and factors associated with male breast cancer risk. The DAG (within the Statistical Analysis Plan (SAP) in Annex 1H) pinpointed which variables to include in the analysis of the association between finasteride use and male breast cancer (substudy 2) and which should be left out. All factors associated with finasteride use or male breast cancer was included in the descriptive substudy 1.

9.1.1 Substudy 1

In substudy 1, persons with at least two prescriptions of finasteride and persons with less than two prescriptions of finasteride and persons with different levels of cumulative finasteride use (0-1 packs of 98 tablets, 2-3 packs, 4-6 packs, and 7+ packs) were compared with respect to potential confounding factors described in section 9.4. This study utilized a new user

design by excluding finasteride users with the first redemption of finasteride within the first 6 months of registration. For each male we sample one male non-user using density sampling (Rothman 2008). Specifically, when one man redeemed his second finasteride prescription we sampled one other man alive in the same country at that particular day who had redeemed less than two finasteride prescriptions before or at that particular day. We restricted the control selection to men of age 35 and above, since the use of finasteride is almost entirely restricted to this age span. This man was given an index date and information on confounding factors was extracted for the period before the index date. Using this sampling scheme, the odds ratios estimated in the logistic regression model could be interpreted as an incidence rate ratio of finasteride use for persons exposed to confounding factors compared to non-exposed (Rothman 2002, Rothman et al., 2008). For confounders with more than two categories, the odds ratios estimated could be interpreted as incidence rate ratios for each category compared to a reference group. Several supplementary analyses were performed including alternative definitions of finasteride use, comparison of finasteride and alpha-blockers users, age-stratified analyses, and stratified on factors associated with surveillance bias and latency. The supplementary analyses are further described in section 9.7.

The matching criteria of substudy 1 were:

- Country
- Follow-up time (density sampling)

9.1.2 Substudy 1A

In substudy 1A finasteride users were compared with non-users with respect to self-reported life-style factors as obesity, alcohol intake, and physical inactivity also listed in section 9.3. In this study, we linked national surveys including self-reported information on these potential confounders with finasteride users and non-users, either defined by use of a binary or a cumulative measure of finasteride use (substudy 1 data).

9.1.3 Substudy 2

In substudy 2, the effect of either finasteride use versus non-use or cumulative finasteride use on male breast cancer was analyzed taking account of the confounding factors selected by the previously developed DAG (described in the Statistical Analysis Plan). The development of the DAG highlighted factors associated with finasteride use, factors that were a consequence of finasteride use, and factors associated with male breast cancer risk. The DAG pinpointed which variables should be included in the analysis of the association between finasteride use and male breast cancer and which should be left out. A DAG is a graphic model that depicts causal relationships between variables of interest. A DAG is thus an encoding of assumptions about the causal relationships between the variables of interest. In an epidemiologic context, one of these variables is usually called the exposure (here finasteride use), and another special variable is called the outcome (here male breast cancer). If all assumptions in the diagram are true, we can infer sets of variables for which to adjust to minimize bias.

We identified five minimal sufficient adjustment sets. A sufficient adjustment set is a set of covariates such that adjustment will minimize bias when estimating the causal effect of the exposure on the outcome. One of the minimum sufficient sets included variables, which could be measured in nation-wide registers, which was included as the adjustment set in substudy 2. The variables included age, country, calendar time, benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences.

Breast cancer cases were identified in the national cancer registers, where diagnosis of cancer is carefully evaluated by medical experts (Gjerstorff 2011). The study was a density sampled case-control study, where each male breast cancer case will be country- and age-matched to controls (Rothman 2002). We selected 50 controls per case (see calculation of minimal detectable OR in section 9.5). This substudy also utilized a new user design by excluding finasteride or dutasteride users with the first prescription redemption within the first 6 months of registration. The primary analysis excluded users of dutasteride from cases and controls. Several supplementary analyses were performed, including alternative definitions of finasteride use, combining use of finasteride and dutasteride (i.e. use of any 5alpha-reductase inhibitors (ARIs)), comparison of finasteride and alpha-blockers users, analysis nested within a cohort of patients with BPH, country-specific and age-stratified analyses, and stratifications on factors associated with surveillance bias and latency. The supplementary analyses are further described in section 9.7.

The matching criteria of substudy 2 were:

- Country
- Age
- Follow-up time (density sampling)

One supplementary analysis is the comparison of use of alpha-blocker and use of finasteride. This analysis is done by analyzing the association between finasteride use and male breast cancer among non-users of alpha-blockers and the association between alpha-blockers and male breast cancer among non-users of finasteride. If the risk estimates of finasteride and alpha-blockers on male breast cancer were comparable in these two analyses, this would have supported that unmeasured confounding by indication is present, while if the risk estimate of finasteride was stronger than alpha-blockers this would have indicated that confounding by indication did not strongly influence the association between finasteride use and male breast cancer. This analysis was only included as a supplementary analysis because the indication for treatment with alpha-blockers and finasteride may be different in the Nordic countries and because of lack of power when excluding persons exposed to either finasteride or alpha-blockers.

Another supplementary analysis was within a cohort of men with diagnosis or treatment for benign prostatic disease termed the BPH cohort. The development and definition of diagnosis and treatment of relevant benign prostatic diseases was done together with clinical experts.

9.2 Setting

The two substudies consisted of two study populations:

The substudy 1 consisted of finasteride users (at least two prescriptions of finasteride) during the study period compared with non-users (less than two prescriptions of finasteride). For each user we sampled one country-matched non-user alive and living in the populations at that given day. The study period was 1995-2014 in Denmark, 1997-2013 in Finland, and 2005-2014 in Sweden. During the analysis phase we also compared users with a higher consumption of finasteride with users with lower consumption and non-users. This was the reason for not using age-matching in this study because by age-matching we would need several non-users for the same finasteride user as the user accumulates finasteride. Instead we adjusted our analysis for differences in age.

In substudy 1A we included all finasteride users (substudy 1 data) who previously had participated in a survey. Each finasteride user was compared to sampled non-users who previously had participated in a survey. We included the most recent information on life-style factors.

The substudy 2 was designed as a density sampled case-control study (Rothman 2002). Each male breast cancer case during follow-up (1995-2014 in Denmark, 1997-2013 in Finland, and 2005-2014 in Sweden) was country- and age-matched to controls at risk of breast cancer on the date of breast cancer diagnosis (index date). For each case we sampled 50 controls.

9.3 Subjects

9.3.1 Inclusion criteria

Substudy 1

- Males residing in either Denmark, Finland, or Sweden on the index date
- Aged 35 years and older
- Finasteride user group: Men who had redeemed at least two prescriptions of finasteride in the study period (either as one group or divided into three groups, i.e. 2-3 packs of 98 tablets, 4-6 packs, and 7+ packs)
- Non-finasteride user group: Men who had redeemed less than two prescriptions of finasteride in the study period

Substudy 2

- Males residing in either Denmark, Finland, or Sweden on the index date
- Aged 35 years and older
- Cases: Men with a diagnosis of primary breast cancer
- Controls: Men without a diagnosis of breast cancer at index date

Exclusion criteria

Substudy 1

- None

Substudy 2

- Previous cancer diagnosis or treatment for cancer except non-melanoma skin cancer
- Previous prostatectomy
- Finasteride or dutasteride use (dutasteride is a drug in the same class as finasteride) within first 6 months of registration in the prescription registers (new user design).

9.4 Variables

9.4.1 Exposure

Substudy 1

In substudy 1, a range of variables were examined to evaluate differences between users and non-users of finasteride. The explanatory variables in the analysis were testicular abnormalities / disorders, benign breast disease, obesity, liver cirrhosis, Klinefelter's syndrome, estrogen therapy, occupational exposures, family history of breast cancer, radiation exposure including men treated with radiotherapy for pulmonary tuberculosis, socio-economic position, living as a single man, urban / rural differences, diabetes, and bone fractures. For substudy 1A we studied life-style related risk factors: Alcohol intake, physical inactivity, dietary intake of vegetables, and dietary intake of animal fat. Variables that might be associated with surveillance bias were also examined.

Substudy 2

The exposure variable was either redemption of two or more finasteride prescriptions and the comparison group of males with less than two prescriptions sampled from the population or cumulative prescriptions of finasteride (0-1 packs of 98 tablets of 5 mg, 2-3 packs, 4-6 packs, and 7+ packs; all finasteride prescriptions have been converted to the equivalence of packs with 98 5 mg finasteride tablets) in the period before breast cancer diagnosis..

9.4.2 Outcome

In substudy 1, the dependent variable was either redemption of two or more finasteride prescriptions and the comparison group of males with less than two prescriptions sampled from the population or cumulative finasteride use (0-1 packs of 98 tablets, 2-3 packs, 4-6 packs, and 7+ packs of finasteride).

In substudy 2, a primary breast cancer case was defined as one that was recorded in the cancer registers, as per ICD-10-CM (C50).

Information on the macro- and microscopic basis of breast cancer diagnosis is available from the Nordic cancer registers. A diagnosis in the cancer registers is based on the combination of information from the national patient registers, pathology registers and cause of death registers. The vast majority of cases listed in those registers are based on invasive examinations (surgery and autopsy) and histological confirmation. In case of incomplete or controversial information, requests for further information are sent to hospitals and physicians who failed to report complete information (Gjerstorff, 2011; Pukkala, 2011). The use of multiple data sources secures a high degree of completeness of the cancer registers.

To characterize the male breast cancer cases, a descriptive analysis was performed. This analysis consisted of information on pathology code (per microscopic-based evidence of primary malignant neoplasia of the breast which was indicated by histology and/or cytology), macroscopic diagnostics, and stage at diagnosis (local, regional and metastatic).

9.4.3 Covariates

In substudy 2, the confounding variables in the analysis were variables in the selected minimum sufficient confounder set in the DAG: benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorder and urban/rural differences (described in more detail Annex 1H: Statistical Analysis Plan (SAP)). Furthermore, variables that may be associated with surveillance bias were included: diagnosis of gynaecomastia, use of drugs or exposed to environmental agents that cause or may cause gynaecomastia, number of prescriptions, number of surgeries, number of hospital contacts, diagnosis of urinary retention, cancer stage at diagnosis, and diagnosis of benign breast disease. The variables may be associated with surveillance bias in that patients with these factors may have an increased probability of diagnosis of breast cancer because of more careful surveillance. The analyses in substudy 2 were stratified on these factors to detect whether an increased odds ratio could be explained by surveillance bias.

Information on date of birth, date of death, sex and date of immigration and emigrations were also obtained.

9.5 Data sources and measurement

The sampling populations were the Danish, Finnish, and Swedish male populations aged 35 years or older. We utilized the nation-wide registers of prescription, cancer incidence, contacts to the secondary and tertiary hospital system, the civil registration system, and registers on occupational group. The registers covered different periods, but all registers had registration for the period 1995-2014 for Denmark, 1997-2013 for Finland, and 2005-2014 for Sweden. Linkage between the registers was possible due to the unique individual identification numbers (Gissler 2004, Thygesen 2011).

Information from the prescription registers and the cancer registers have been validated (Gjerstorff 2011, Kildemoes 2011, Pukkala 2011). The national patient registers include diagnostic and treatment information for patients treated at the secondary and tertiary hospital level (Lynge 2011, Pukkala 2011). Clinical experts have been consulted on how to include this information. The codes used for constructing all variables are presented in Annex

1A. Information on date of birth, immigration, emigration, and death was obtained from the civil registration systems (Pedersen 2011, Pukkala 2011). Information on occupational status was obtained from registers on attachment to the labour market (Petersson 2011, Pukkala 2009).

We also included information from population surveys conducted in Denmark (Christensen 2012, Ekholm 2009), Finland (Pukkala 2011), and Sweden. The surveys are nation-wide representative health surveys including information on life-style factors. We linked this information to the finasteride users and non-users sampled in substudy 1A. This information was not used in substudy 2, since the overlap between breast cancer cases and the survey samples was too small.

9.5.1 Study Procedures

Not relevant for the present study.

9.6 Bias

A limitation of the study was the comparison of users with non-users, where the observed association might be influenced by confounding by indication since finasteride users would have more comorbidities and might have more contacts with medical staff. This could result in higher incidence of breast cancer diagnoses among finasteride users than among a random sample of males.

In the analyses we tried to assess this bias by stratifying the analyses by factors associated with surveillance bias, by adjusting for comorbidities, and by doing analysis of the separate effects of alpha-blockers and finasteride.

A minor limitation related to estimation of finasteride use was the prescription registers, which contain information on redeemed medications, and no information on the actual consumption of drugs. This is the reason for only categorizing persons with at least two prescriptions of finasteride as exposed, because these persons with repeated purchases of finasteride were more likely to also have used most of the drugs.

For several of the confounding factors, the information was only based on one or a few ICD-10 codes. This may have resulted in under-estimation of the true prevalence of several of the confounding factors, e.g. obesity. We think this under-estimation was not related with finasteride use thereby mimicking non-differential misclassification resulting in conservative observed associations for substudy 1. For other possible confounding factors the information was based on statistical classification systems, e.g. industrial classification systems, which may also be misclassified. We think this also resulted in an under-estimation of the association between confounding factors and finasteride use. Whether this underestimation resulted in an over- or under-estimation of the association between finasteride use and breast cancer could not be predicted.

Truncation was also a potential bias in the study meaning that we had no information on confounding factors, finasteride use, or cancer incidence before the start of registration of

each of these factors. This was most pronounced for finasteride use, since we did not know whether a finasteride user in the first year of registration in Denmark and Finland and for more than a decade in Sweden was a long-term user (prevalent user) or a first-time user (incident user). This was only a minor limitation in Denmark and Finland, since finasteride was first approved in 1992, but was important to consider for Sweden. We evaluated the influence of this limitation by excluding finasteride users in the first year of registration as a supplementary analysis to ensure that users in the second year were incident users.

In substudy 1A, only participants of the national surveys were included. This might have introduced selection bias in that the participants might not be representative of all finasteride users and non-users.

9.7 Study size

The substudy 1 included all finasteride users and a random sample of country-matched non-users. In the previous study of finasteride use and male breast cancer (Meijer et al., 2018, Study report 2012) the number of unique finasteride users (one or more prescriptions of finasteride) was 56,406 for Denmark in the period 1995-2009, 111,820 for Finland in the period 1997-2010, 22,345 for Norway in the period 2004-2009, and 79,712 for Sweden in the period 2005-2009. The study also estimated that 76-85% of the finasteride person-time was for users with at least two prescriptions of finasteride. We therefore estimated that approximately 214,000 persons had at least two prescriptions of finasteride and hence counted as finasteride users in the present study.

The minimum detectable odds ratio (OR) was calculated for different values of proportion of non-finasteride users exposed to the confounder of relevance.

If the following assumptions were made, we could calculate the minimum detectable OR:

- Power = 90%
- Alpha = 5%
- Two-sided test
- 214,000 finasteride users
- 214,000 non-users

If we varied the proportion of non-finasteride users exposed to the confounder, we could estimate the minimum detectable odds ratio (Table 1).

Table 1 Minimal detectable OR for substudy 1

The proportion of non-finasteride users exposed to the confounder	Minimum detectable OR
1% / 99%	1.102
5% / 95%	1.046
10% / 90%	1.033
25% / 75%	1.023
50%	1.020

We concluded that the power of substudy 1 was very high even when only one non-user was included per user. Even under the assumption of a power of 90% we would be able to detect odds ratios of 1.10 for very rare (or very common) confounders.

Substudy 1A included a linkage between the prescription registers and national health surveys. The Danish National Health Survey consisted of cross-sectional surveys conducted in 2000, 2005, and 2010 among persons aged 16 years and older. The number of participants in the surveys was 16,688, 14,566, and 15,165, respectively, which corresponds to approximately 0.4% of the population. Based on the previous study (Meijer et al., 2018, Study report 2012), we assumed that 3% of males were finasteride users. This meant that we could assume that approximately 240 finasteride users also would have participated in each of the surveys.

In Finland, the National FINRISK Study has been conducted since 1972 every five years, first in Eastern Finland, and later on in five areas in Finland (Helakorpi 2008; Vartiainen et al 2010). The main aim of the FINRISK Study is to collect data on and monitor cardiovascular diseases and other non-communicable diseases and risk factors among the Finnish population. Participants from each study area have been selected by using stratified random sampling. The participants were 25 to 64 years (since 1997, they were 25 to 74 years) old at baseline. In Norway, the Cohort of Norway (CONOR) includes information from about 173,000 respondents in the period from 1994 to 2003 (Næss 2008). The participants answered a questionnaire and underwent a physical examination. The Swedish Survey of Living Conditions, Statistics Sweden interviews about 10,000 respondents annually (some changes over time have occurred). Each year between 2000 and 2012 about 7,500–10,000 respondents were interviewed (respondents were 16–84 years of age).

Substudy 2 included all male breast cancer cases and a country- and age-matched sample of controls. The number of male breast cancer cases was 365 in Denmark, 236 in Finland, 101 in Norway, and 200 in Sweden in the previous study (Meijer et al., 2018, Study report 2012). The number of finasteride users who developed male breast cancer after first purchase of finasteride was 29 in Denmark, 26 in Finland, 1 in Norway, and 7 in Sweden. In this study the sample was slightly increased because of longer follow-up. We expected approximately 1000 cases in the present study. The exposure variable in substudy 2 was either finasteride use (2+ prescriptions) versus less than two prescriptions or cumulative finasteride use (0-1

packs of 98 tablets of 5 mg, 2-3 packs, 4-6 packs, and 7+ packs). We expected the 1000 cases would be distributed in the binary finasteride use categories as follows: 948 used 0-1 packs of 98 tablets and 52 used 2+ packs of 98 tablets. For the four categories of cumulative finasteride use the number of cases would be: 948 cases used 0-1 packs of 98 tablets, 20 cases used 2-3 packs, 11 cases used 4-6 packs and 21 cases used 7+ packs.

Based on the following assumptions, the minimal detectable OR for a comparison of exposure 7+ packs versus 0-1 packs could be calculated for a varying number of controls per case and assuming different proportions of exposed controls in a matched case-control study (Dupont, 1988 as implemented in STATA version 12 in the SAMPSI_MCC procedure):

- Power = 80 %
- Alpha = 5%
- Two-sided test
- Number of cases: 969
- Number of controls per case varies: 10, 25, 50, 100
- Proportion of exposure individuals among controls varied: 0.3%, 0.5%, 1%, 1.5%, 2%, 3%, 4%
- Correlation of exposure between pairs in the case-control set at 0.1

For a varying proportion of exposed controls we could estimate the minimum detectable OR for a comparison of exposure 7+ packs versus 0-1 packs of substudy 2 for 10, 25, 50 and 500 controls per case, respectively (Table 2). Similar minimum detectable OR was expected for a comparison between exposure 0-1 packs versus the two other exposure groups (2-3 packs, 4-6 packs).

Table 2 Minimal detectable OR for substudy 2

The proportion of exposed controls	Minimum detectable OR			
	1:10 controls	1:25 controls	1:50 controls	1:500 controls
0.3%	3.29	3.15	3.10	3.05
0.5%	2.69	2.59	2.56	2.53
1%	2.13	2.08	2.06	2.04
1.5%	1.91	1.86	1.85	1.84
2%	1.77	1.74	1.73	1.72
3%	1.62	1.60	1.59	1.58
4%	1.54	1.52	1.51	1.50

This analysis supported that the minimum detectable OR would not be varying remarkably by number of controls and 50 controls per case was assumed to be an adequate number of controls to include in substudy 2. The minimum detectable OR, when sampling 50 controls

per case, was estimated to range from 2.56 if 0.5% of the controls were exposed to 1.51 if 4% of the controls were exposed.

9.8 Data transformation

The outcome variable in substudy 1 was finasteride use (2+ prescriptions versus 0-1 prescriptions) and cumulative finasteride use (in three dichotomized variables: 2-3 packs of 98 5 mg tablets, 4-6 packs and 7 or more packs vs. less than 2 packs). These variables were constructed by identifying the date when these events happened. These dates were then used as index dates for the construction of the potential confounding variables.

The outcome variable in substudy 2 was male breast cancer. For each case the date of diagnosis was the index date. The control for that case got the same index date. These dates were then used as index dates for the construction of finasteride use and the confounding variables included (benign prostatic hyperplasia, estrogen therapy, Klinefelter's syndrome, educational level, testicular disorders and urban/rural differences). Finasteride use was constructed both as finasteride use (2+ prescriptions versus 0-1 prescriptions) and as cumulative finasteride use (2-3 packs of 98 5 mg tablets, 4-6 and 7+ packs) before the index date.

The construction of the potential confounding factors are described below:

Age: Age was categorized into 5-years categories (35-39 years, 40-44, …, 85-89, and 90+ years).

Calendar time: Categorized into 3-years categories (1995-1997, 1998-2000, …, 2010-2012, 2013-2014).

All diseases included as potential confounding factors were identified in the patient hospital registers among all hospital contacts with specific primary or secondary diagnosis before the index date or within the last 10 years for diabetes and bone fracture. See Annex 1A for the specific ICD-8, ICD-9 and ICD-10 codes used. The diseases included this way were testicular disorders, benign breast disease, obesity, liver cirrhosis, Klinefelter's syndrome, diabetes, and bone fractures.

All drugs included as potential confounding factors were identified in the prescription registers among all prescriptions with specific ATC-codes before the index date. See Annex 1A for specific ATC-codes. We only included prescriptions within the last 10 years before the index date and only drugs with at least two prescriptions. As a note, estrogens were defined with the ATC-codes G03A-G03X which also included testosterones. The variable estrogen therapy, which was included in the analyses, thereby also included exogenous testosterone.

Occupational exposures (occupations with high temperatures and the perfume industry) were identified in occupational registers with males occupied in specific occupations one or two years before the index date in Denmark and Sweden. In Finland, the latest census data (1990,

1995, 2000, 2005, 2010) were used to determine occupational status. See Annex 1A for specific occupational codes used.

Family history of breast cancer was identified as any breast cancer diagnosis among any family members (parents, siblings and children). In substudy 1, any family breast cancer diagnosis before index date were included, while in substudy 2 any breast cancer diagnosis throughout the study period was included. The reason was that in substudy 1 the information should be used to evaluate whether knowledge of familial breast cancer influenced prescription pattern, while in substudy 2 family history was an indicator of familial breast cancer risk.

Radiation exposure as potential confounding factor was identified in the patient registers among all contacts with specific procedure codes before index date. See Annex 1A for specific procedure codes.

Educational level was obtained from the education registers including information on education one or two years before index date in Denmark and Sweden. In Finland, the two latest census data (1990, 1995, 2000, 2005, 2010) were used to determine educational level.

Living as a single man was obtained the year before index date in Denmark and Sweden. In Finland, the latest census data (1990, 1995, 2000, 2005, 2010) were used to determine cohabitation status.

Urbanisation was obtained by information on the number of persons in the village/city where the men lived (Denmark and Finland), while in Sweden it was identified as the number of persons in the residential municipality. In Denmark, urban areas was identified as cities with more than 200 residents, in Finland the variable was whether the place of residence was in an urban settlement, while in Sweden a urban municipality was identified as one with more than 2000 residents. We included the information one or two years before index date.

Variables that may be associated with surveillance bias were constructed as follows:

Diagnoses of benign breast disease, gynecomastia and urinary retention were identified in the patient hospital registers among all hospital contacts with specific primary or secondary diagnosis before the index date. See Annex 1A for the specific ICD-8, ICD-9 and ICD-10 codes used.

Use of drugs or exposed to environmental agents that cause or may cause gynecomastia was identified in the prescription registers with specific ATC-codes before the index date. See Annex 1A for specific ATC-codes. We only included drugs with at least two prescriptions.

Number of prescriptions before index date was included as the number of days with at least one prescription redemption. We only included prescriptions within the last 10 years before the index date in Denmark and Sweden. In Finland we included all prescription redemptions before the index date without any time restriction, due to the way data was delivered by the data manager at Finnish prescription register. This variable was dichotomized into above and below the country-specific median number of prescriptions.

Number of surgeries before index date was included as the number of days with at least one surgical procedure. We only included procedures within the last 10 years before the index date. This variable was dichotomized into above and below the country-specific median number of surgeries.

Number of hospital contacts before index date was included as the number of days with at least one hospital contact. We only included contacts within the last 10 years before the index date. This variable was dichotomized into above and below the country-specific median number of hospital contacts.

Cancer stage among male breast cancer cases was included in substudy 2 and was dichotomized into local breast cancer versus regional and metastatic breast cancer.

Finally, a few additional variables were constructed:

Benign prostatic hyperplasia was based on either specific diagnoses or specific surgical procedure codes before index date. See Annex 1A for specific codes.

Use of alpha blockers was identified in the prescription registers with specific ATC-codes before the index date. See Annex 1A for specific ATC-codes. We only included males with at least two prescriptions of alpha blockers.

Dutasteride was included as at least two prescriptions of dutasteride before index date for all substudy 2 secondary analyses (but not for substudy 1 or substudy 2 primary analyses).

In the secondary analysis 4 in substudy 2 (table 2.13 and table 2.14 – Annex 1C), the exposed group was broader and included the use of both dutasteride and finasteride. Finasteride use was included as number of 5 mg tablets and dutasteride use was included as number of 0.5 mg tablets. The cumulative use was defined as number of packs with 5 mg finasteride tablets and 0.5 mg dutasteride tablets.

9.8.1 Data management

The handling of data includes seven steps.

1. All national scientific coordinators applied to relevant agencies for permission to perform the study and to get access to data, including Statistics Denmark/Statistics Finland /Statistics Sweden, and other relevant agencies to search the prescription registers for all purchases of finasteride and the cancer registers for all male breast cancer cases.
2. All national scientific coordinators facilitated the construction of the study populations:
    - Study population consisting of all finasteride users and a sample of comparable non-users.
    - Study population consisting of male breast cancer cases and controls during the study period.

- Both study populations were sampled via density sampling based on the description and SAS code derived by the Danish scientific coordinator and agreed upon by the national scientific coordinators. The code can be found in Annex 1B.

3. All national scientific coordinators are responsible of acquiring and checking the datasets and examined how the datasets could be combined with the registers: Prescription register, cancer register, national patient register, civil registration system and registers on labour force. Data control included - but was not restricted to - check for legal values for each categorical variable, check of consistency between dates (at least date of birth before all other dates and date of death after all dates), and check and advice on the handling of missing data. All national scientific coordinators produced a data control report describing the checks performed and describing how the final dataset should be constructed from the registers received including reasons for modifications and exclusions. In this process all national coordinators had to agree on the reasons for exclusion, e.g. missing value on crucial variables, chronological errors in the relation between dates, non-legal values of categorical variables, and extreme values of continuous variables.
4. The datasets from Finland and Sweden were transferred to Statistics Denmark where all subsequent data handling was done by the Danish scientific coordinator.
5. The Danish scientific coordinator linked the data as described by the document developed by all national scientific coordinators and the data sets from all countries were joined into a combined analysis dataset. Relevant variables were derived.
6. The Danish scientific coordinator assessed the data validity of all countries by logical checks, examination of extreme values, and missing data. It was important that identification numbers were maintained to facilitate linkage back to the original data sets to be able to check the data and for the sake of transparency.
7. Data analysis and evaluation of the hypotheses described above (section 8) using SAS version 9.3 was performed by the Danish scientific coordinator.

9.9 Statistical methods

9.9.1 Main summary measures

Descriptive measures were calculated to describe the Nordic populations including the sex and age structure. Incidence rates were calculated for each country by calendar year and age.

For the study population in substudy 1, descriptive measures included the potential confounding factors as mean and standard deviation for continuous variables and number and proportion for categorical variables.

For the study population in substudy 2, descriptive measures included the confounding factors identified in the DAG as mean and standard deviation for continuous variables and number and proportion for categorical variables.

9.9.2 Main statistical methods

For both substudies finasteride use was defined as either a binary variable (at least two prescriptions of finasteride versus less than two prescriptions) or a cumulative variable (2-3 packs of 98 tablets, 4-6 packs, or 7+ packs of finasteride versus less than two packs of finasteride). Moreover, both substudies included either a long follow-up time including only Denmark and Finland (1995/1997-2013/2014) or a follow-up period including the available data from all three countries (Denmark (1995-2014), Finland (1997-2013), and Sweden (2005-2014). The combination of the two different definitions of finasteride use and the two follow-up periods gave four different main analyses (A-D): A (long follow-up and binary finasteride use); B (long follow-up and cumulative finasteride use); C (available follow-up period for all three countries and binary finasteride use), and D (available follow-up period for all three countries and cumulative finasteride use).

In substudy 1, logistic regression was performed by comparing potential confounding factors for finasteride users compared to non-users and between potential confounding factors for cumulative finasteride users and non-users. The main analyses included these two definitions of finasteride use among either long follow-up data from Denmark (1995-2014) and Finland (1997-2013) or all available data including all three countries (Denmark, Finland, and Sweden (2005-2014)), i.e. analyses A-D.

In substudy 1A, the same main analyses as in substudy 1 were done, i.e. we included dependent variables as a binary variable for all three countries.

In substudy 2, conditional logistic regression were performed by comparing male breast cancer cases with controls in respect to either finasteride users versus non-users or cumulative finasteride use and including confounding factors in the analysis. We included confounding factors established by the DAG developed before substudy 1. Conditional logistic regression was performed to take account of the country- and age-matching. The analyses were either performed with long follow-up data from Denmark (1995-2014) and Finland (1997-2013) or including all available follow-up time (Denmark, Finland and Sweden (2005-2014) as described above (i.e. analyses A-D).

9.9.3 Missing values

Persons with missing values in the register of educational achievement were included in the group with low educational level as these were assumed to be persons who did not finish any education or only finished elementary school and these furthermore had been found to match this groups with regard to income level.

Persons with missing data on occupational industries were included in the group without employment in high-temperature and perfume industries. Persons with missing data on urbanization were included in the urban group.

9.9.4 Sensitivity analyses

In both substudies, a number of pre-defined sensitivity / supplementary analyses were planned.

Substudy 1:

1. Analysis stratified by age.
2. Analysis among men with diagnosis of benign prostatic hyperplasia.
3. Number of alpha-blocker users and non-users among finasteride users and non-users.
4. Analysis of years of finasteride use.
5. Analysis of years since first finasteride use.
6. Analysis only included 5 mg finasteride as finasteride users.
7. Change the requirement for new users by excluding finasteride users with first redemption of finasteride within the first 2 years of follow-up.
8. Stratification of factors associated with surveillance bias

Substudy 2:

1. Analysis stratified by age.
2. Analysis among men with diagnosis of benign prostatic hyperplasia.
3. Analysis of finasteride use (use versus non-use) among alpha-blocker non-users and alpha-blocker use (use versus non-use) among finasteride non-users.
4. Analysis of finasteride or dutasteride use.
5. Analysis of years of finasteride use.
6. Analysis of years since first finasteride use.
7. Analysis only included 5 mg finasteride as finasteride users.
8. Analysis including persons who only redeem one prescription as exposed.
9. Change the requirement for new users by excluding finasteride users with first redemption of finasteride within the first 2 years of follow-up.
10. Stratification of factors associated with surveillance bias:
    a. Analysis stratified by diagnosis of gynecomastia.
    b. Analysis stratified by use of drugs or exposure to environmental agents that cause or may cause gynecomastia.
    c. Analysis stratified by number of prescriptions.
    d. Analysis stratified by number of surgeries.
    e. Analysis stratified by number of hospital contacts.
    f. Analysis stratified by diagnosis of urinary retention.
    g. Analysis stratified by cancer stage at diagnosis.
    h. Analysis stratified by diagnosis of benign breast disease.

11. Analysis inferring lag time of 1 or 2 years between finasteride use and male breast cancer.

9.9.5 Amendments to the statistical analysis plan

Refer to 8. Amendments and updates.

9.10 Quality control

The study is register-based and data quality was therefore difficult to ascertain directly. Previous studies have evaluated the validity of the central registers, e.g. the prescription registers and the cancer registers (Jensen 2002, Kildemoes 2011, Pukkala 2011). These studies in general supported that the validity and completeness of the data sources are high.

The statistical analyses were performed on servers at Statistics Denmark. The programming was performed by two researchers independently limiting programming errors. The statistical programs were stored at the servers at Statistics Denmark.

As described above in section 9.8.1 (data management), each national scientific coordinator validated the datasets and explored how the datasets can be combined with the registers. Data control included check for legal values for each categorical variable, check of consistency between dates (at least date of birth before all other dates and date of death after all dates), and check and advice on the handling of missing data. All national scientific coordinators produced three data control reports describing the checks performed and describing how the final dataset should be constructed from the registers received including reasons for modifications and exclusions.

In the first data control, tabulations of all raw data files were conducted to find odd values and check for consistent dates.

In the second data control, the study populations for substudies 1, 1A and 2 were constructed and final datasets for all registers were established.

In the third data control, all variables were tabulated in the datasets for all substudies.

10 RESULTS

10.1 Participants

Flow chart 1 and 2 (in Annex 1D and 1E) describe the selection of study subjects for substudy 1 and 2.

In substudy 1, we included finasteride users from Denmark (1995-2014), Finland (1997-2013) and Sweden (2005-2014). We excluded rare values, men aged <35 years of age and males with a finasteride prescription the first half year of registration, ending with a study population of 246,508 cases and the same number of controls.

In substudy 2, we included male breast cancers from Denmark, Finland and Sweden and their controls. We excluded duplicates, controls with previous cancer (excluding non-melanoma skin cancer), men with previous prostatectomy, males with a finasteride prescription during the first half year of registration and males with index date before and after study period, ending with a study population of 1,009 cases and 43,549 controls. In the main analysis, we also excluded males with previous use of dutasteride, ending with a study population of 1,005 cases and 43,058 controls.

10.1.1 Protection of Human Subjects

This was an observational study with no administration of any therapeutic or prophylactic agent. Patients observed in this study would continue with the normal standard of care as provided by their personal physician. National registers of cancer, hospital contacts, and socio-economic factors, prescriptions were the sole data source.

According to Danish, Finnish, and Swedish law register-based studies can be carried out without consent from the data subjects where the processing takes place for the sole purpose of carrying out statistical or scientific studies of significant public importance and where such processing is necessary in order to carry out these studies. It is an absolute requirement that the publication of statistical or scientific results may never reveal the identity of individuals or otherwise compromise data subjects. We obtained approval by the data agencies in the three countries before data management and data analyses were performed.

10.2 Descriptive data

Please see Annex 1C tables 0.1 and 0.2 (background tables) and tables 1.1, 1.2, 2.1 and 2.2 (descriptive tables).

The incidence rate (IR) of male breast cancer was highest in Denmark (IR (95%CI)=1.00 cases/100,000 person years (0.92-1.08) and lowest in Finland (IR (95% CI) = 0.70 cases/100,000 person years (0.63-0.77)). The incidence rate increased by age. There was no clear temporal pattern.

In substudy 1 the study population in Denmark and Finland included 139,640 finasteride users and controls. Finasteride users were older (69.9 years versus 51.3 years) and had more often been diagnosed with testicular abnormalities (7.1% versus 5.1%), obesity (1.2% versus 0.8%), liver cirrhosis (1.3% versus 1.0%), used estrogen therapy (2.1% versus 1.1%), had been exposed to radiation (3.9% versus 2.0%), had lower educational level (52.7% versus 36.3%), less often lived alone (23.4% versus 25.2%), had diabetes (6.6% versus 3.5%) and bone fractures (4.0% versus 3.0%) and were less often exposed to occupational exposures (0.4% versus 1.1%) and fewer had had an event of breast cancer in the family compared to the control population (2.0% versus 3.5%).

In substudy 2, a total of 680 male breast cancer cases and 29,746 controls were included in Denmark and Finland and 1005 male breast cancer cases and 43,058 controls when also including Sweden. The proportion of finasteride users were higher among cases compared to controls (3.8% versus 2.9%). The difference in use was most pronounced for low and

medium cumulative use (0.9% versus 0.7% for low use and 0.7% versus 0.5% for medium use). A larger proportion of cases than controls had benign prostatic hyperplasia (13.2% versus 10.0), estrogen therapy (0.9% versus 0.5%), and testicular disorders (7.1% versus 6.0%), while there were only small differences for Klinefelter's syndrome, education and urban residence.

10.3 Outcome data

The study included 1009 male breast cancer cases. Of those 4 used dutasteride before index date and were excluded in the main analysis (tables 2.3 and 2.4 – Annex 1C).

In the following, the cases were further described.

ICD-10 codes:

Out of all breast cancer cases, 758 patients (75.1%) had unspecific ICD-10 code (C50.9), while 32 (3.2%) had cancer of nipple and areola (C50.0), 133 (13.2%) had cancer of central portion of breast (C50.1), 7 (0.7%) had cancer of the upper-inner quadrant of breast (C50.2), 4 (0.4%) had cancer of lower-inner quadrant of breast (C50.3), 41 (4.1%) had cancer of upper-outer quadrant of breast (C50.4), 10 (1.0%) had cancer of lower-outer quadrant of breast (C50.5), 1 (0.1%) had cancer of axillary tail of breast (C50.6), and 23 (2.3%) had cancer of overlapping sites of breast (C50.8).

Cancer stage at diagnosis:

In total 459 (45.5%) had local cancers and 446 (44.2%) had regional or metastatic cancer. 104 (10.3%) had missing values on this information.

Macroscopic diagnostics:

The majority of patients, 948 (94.0%), were diagnosed at surgery and 12 (1.2%) were diagnosed at autopsy. The remaining cases were diagnosed by clinical observation (n=14; 1.4%), endoscopic examination (n=6; 0.6%), radiologic examination (n=16; 1.6%) or had missing information on macroscopic examination (n=12; 1.2%).

Microscopic diagnostics:

The diagnosis of 985 patients (97.6%) was based on histologic or cytologic information from the primary tumor, while the diagnosis of 6 patients (0.6%) was based on histologic or cytologic information from metastasis. The remaining (1.8%) had no information on microscopic diagnostics.

10.4 Main results

The main results were tabulated in Annex 1C tables 1.3, 1.4, 2.3 and 2.4 (main results).

The main results of substudy 1 were that several potential confounding factors were associated with higher odds of finasteride use including testicular abnormalities (OR (95%CI)=1.27 (1.22-1.32)), obesity (OR (95%CI)=1.35 (1.24-1.48)), radiation exposure (OR (95%CI)=1.27 (1.20-1.34)), and higher socio-economic position (OR (95%CI)=1.40 (1.36-1.44)). The following factors are associated with lower odds of finasteride use: estrogen therapy (OR (95%CI)= 0.79 (0.73-0.84)), living as a single man (OR (95%CI)=0.93 (0.91-0.95)) and living in an urban area (OR (95%CI)=0.96 (0.94-0.99)). Cumulative finasteride use showed the same pattern as for binary finasteride use except Klinefelter's syndrome was associated with medium (4-5 packs) and high (7+ packs) cumulative use (OR (95%CI)=5.23 (1.19-23.10) and 6.52 (1.00-42.64), respectively). Lifestyle factors were not clearly associated with finasteride use although these findings may be influenced by a small sample size. Results from the analysis including Denmark and Finland and results from the analysis including all three countries were similar; OR reported above was from the analysis including Denmark and Finland which are the countries with the longest follow up (Table 1.3 – Annex 1C).

The main results of substudy 2 was that odds of exposure to finasteride was not statistically significantly different in cases of male breast cancer compared to controls either in the age-, country- and calendar time-adjusted analysis (OR (95%CI)=1.30 (0.89-1.91) when including Denmark and Finland and OR (95%CI)=1.18 (0.84-1.65) when including all three countries) or in the analysis taking account of confounding factors decided in a DAG (age, country, calendar time, benign prostatic hyperplasia, estrogen therapy, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences) analyzing the association between finasteride use and male breast cancer (OR (95%CI)=1.20 (0.81-1.77) when including Denmark and Finland and OR (95%CI)=1.09 (0.77-1.53) when including all three countries). For cumulative finasteride use the odds ratio was highest for medium users (4-6 packs, OR (95%CI)=1.38 (0.56-3.40) when including Denmark and Finland and OR (95%CI)=1.24 (0.58-2.65) when including all three countries) although none of the odds ratios are statistically significant.

10.5 Other analyses

In general, supplementary analyses conducted for substudy 1 and substudy 2 did not vary markedly from the results from in main analyses.

In substudy 1, results from the supplementary analyses supported that finasteride users and non-users are different. For example, differences between finasteride users and non-users consisted when the analysis was stratified by age, restricted to men with benign prostatic hyperplasia or men who redeemed 5 mg finasteride or excluding finasteride the first two years of drug registration.

In substudy 2, most supplementary analyses supported the main results that odds of exposure to finasteride were not statistically significantly different among male breast cancer cases and controls. A few significant results were however found, but these did not show a clear pattern. For example, the secondary analysis 6 where patients with less than 1 year or 1-2 years of finasteride use had significantly increased odds of male breast cancer (OR

(95%CI)=2.17 (1.06-4.47) and OR (95%CI)=1.8 (1.0-3.2), respectively) in the analysis of Denmark and Finland, but not in the analyses of all three countries. Likewise in secondary analysis 10 the odds of male breast cancer was significantly higher among men with low number of surgeries (OR (95%CI)= 1.96 (1.10-3.48) in the analysis of Denmark and Finland and OR=1.88 (1.08-3.28) in the analysis of all three countries. Another example is in secondary analysis 11 where the latent analysis inferring 1 year of lag time between finasteride use and male breast cancer showed increased odds of male breast cancer for low cumulative use compared to non-users in the analysis of all three countries (OR (95%CI)=1.94 (1.10-3.44), but not for the other groups of cumulative use neither in the analysis only including Denmark and Finland or when inferring 2 years of lag time between finasteride and male breast cancer. The few number of significant estimates should be seen in relation to how many analyses we have conducted and it is likely that they may be a reflection of multiple testing.

Please also see Annex 1C supplementary analyses for substudy 1 and 2.

10.6 Adverse events/adverse reactions

Definition of Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or who undergoes a protocol-specified procedure and which does not necessarily have to have a causal relationship with this treatment or procedure. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal l product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during the course of the use of the Sponsor's product in studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Definition of Serious Adverse Event

"Serious Adverse Event" (SAE) means an adverse event which is fatal or life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, or is a congenital anomaly/birth defect, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered a Serious Adverse Event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Adverse Event Reporting

If, through the conduct of this study, an investigator (or other study personnel) becomes aware of any serious adverse experience that is possibly, probably, or definitely related to an investigational or marketed product manufactured by Merck & Co., Inc., Schering Corporation, or MSP Singapore LLC, it should be reported to one of the persons on the sponsor contact information list within 24 hours of identification. The end of study report, and any interim analysis, will include aggregate listings of all SAEs and any non-serious AEs collected for finasteride and protocol-specified procedures, and will be provided to regulatory agencies as required by the Sponsor.

During the study period, no adverse events were observed or reported.

11 DISCUSSION

11.1 Key results

The key results of substudy 1 were that several potential confounding factors were associated with higher odds of finasteride use including testicular abnormalities, obesity, radiation exposure, and higher socio-economic position. The following factors were associated with lower odds of finasteride use: estrogen therapy, living as a single man and living in an urban area. Cumulative finasteride use showed the same pattern as for binary finasteride use except Klinefelter's syndrome was associated with medium and high cumulative use (for 4-6 and 7+ packs). Lifestyle factors were not clearly associated with finasteride use although these findings may be influenced by a small sample size.

The conclusion is that there are systematic differences between finasteride users and non-users with regards to confounding factors previously reported to be associated with finasteride use or male breast cancer incidence.

The key results of substudy 2 were that the odds of exposure to finasteride was not statistically significantly different among male breast cancer cases compared to controls neither in the age-, country and calendar time-adjusted analysis nor when taking account of confounding factors decided in a DAG analyzing the association between finasteride use and male breast cancer. For cumulative finasteride use the odds ratio was highest for medium users (4-6 packs) although none of the odds ratios were significant.

The majority of supplementary analyses supported the same conclusion that the odds of exposure were not statistically significantly different among male breast cancer compared to controls. A few of the supplementary analyses found significant associations between finasteride use and male breast cancer, but there was no clear pattern that supports a statistically significant association for the specific subgroups investigated.

11.2 Limitations

A limitation of the study was the comparison of users with non-users, where the observed association might have been influenced by both confounding by indication since finasteride

users might have more comorbidities and surveillance bias (ascertainment bias) since finasteride users may have more contacts with medical staff than non-users. Surveillance bias may also result from finasteride users having their breasts examined due to breast complaints since breast complaints are a known and labeled side effect of finasteride. In the analyses we captured this bias by stratifying the analyses by factors associated with surveillance bias, by adjusting for comorbidities, and by doing analysis of the separate effects of alpha-blockers and finasteride which have similar indications. The results from these sensitivity analyses confirmed that there was no statistically significant increase in the odds (or likelihood) of finasteride exposure among male breast cancer cases compared to controls.

A minor limitation related to estimation of finasteride use was the prescription registers, which contain information on redeemed medications, and no information on the actual consumption of drugs. This was the reason for only categorizing persons with at least two prescriptions of finasteride as exposed, because these persons with repeated purchases of finasteride were more likely to also have used most of the drugs. The supplementary analysis of including males with only one redemption of finasteride as exposed, showed slightly stronger risk estimates, but the conclusion was similar of no significant association between finasteride use and male breast cancer.

For several of the confounding factors, the information was only based on one or a few ICD codes. This might have resulted in under-estimation of the true prevalence of several of the confounding factors, e.g. obesity. We do not think this under-estimation was related to finasteride use thereby mimicking non-differential misclassification resulting in conservative observed associations for substudy 1. For other of the possible confounding factors the information was based on statistical classification systems, e.g. industrial classification systems, which may also be misclassified. We think this also resulted in an under-estimation of the association between confounding factors and finasteride use. This could result in incomplete adjustment of confounding and the results may therefore be biased by residual confounding. Whether this underestimation or residual confounding resulted in an over- or under-estimation of the association between finasteride use and breast cancer could not be predicted as it is related to the direction and strength of the associations between confounders on the one side and finasteride use and male breast cancer on the other side.

Truncation was also a potential bias in the study meaning that we have no information on confounding factors, finasteride use, or cancer incidence before the start of registration for each of these factors. This was most pronounced for finasteride use, since we do not know whether a finasteride user in the first years of registration in Denmark and Finland and for more than a decade in Sweden was a long-term user (prevalent user) or a first-time user (incident user). This was the reason we excluded males with a finasteride prescription during the first half year of registration. This is only a minor limitation in Denmark and Finland, since finasteride approved in 1992, but is important to consider for Sweden. Consequently, we performed the analyses for Denmark and Finland and for all three countries. The overall result was that the associations decreased when including Sweden, which may mirror truncation bias of finasteride use. We furthermore conducted a supplementary analysis excluding the first two years of registration, where we observed the same results.

The number of male breast cancer cases was limited making the analysis sensitive to small changes. The supplementary analyses were performed to further evaluate the association and to perform an analysis of sensitivity. However, the number of male breast cancer cases included in the primary analysis was reduced in some of the supplementary analyses. Consequently, the power of some of these analyses was limited.

11.3 Interpretation

Previous research has shown markedly higher prevalence of finasteride use in Finland and Sweden than in Denmark (Kjaerulff et al. 2016). In 2009, period prevalences were 18.2/1000 males in Finland and 12.0/1000 males in Sweden compared to 4.9/1000 males in Denmark. Incidence rates of finasteride use for Finland and Sweden were about three times that for Denmark in 2008–2009.

Our report adds to this descriptive study that several potential confounding factors are associated with higher odds of finasteride use including testicular abnormalities, obesity, radiation exposure, and higher socio-economic position and that other factors are associated with lower odds of finasteride use: estrogen therapy, living as a single man and living in an urban area.

These findings add to the understanding that there are systematic differences between finasteride users and non-users with regards to confounding factors previously reported to be associated with finasteride use or male breast cancer incidence. Testicular abnormalities, obesity, radiation exposure, and higher socio-economic position may all be associated with male breast cancer and the association between finasteride use and male breast cancer would be overestimated in an analysis without adjusting for these potential confounders. Contrarily, not adjusting for estrogen therapy would underestimate the association because estrogen therapy was negatively associated with finasteride use. Living as a single man and living in an urban area are factors associated with finasteride use, but it uncertain how these factors are related with male breast cancer and therefore are difficult to evaluate how they would influence the association studied.

Based on all these associations reported, it is therefore not clear how confounding would influence the association between finasteride use and male breast cancer based on the results from substudy 1. By using the DAG methodology we have included the minimum sufficient confounder set to minimize the influence of confounding factors in the adjusted analysis.

The main finding from substudy 2 was that there is no statistically significant increased odds of finasteride use among male breast cancer cases compared to controls while taking account of confounding factors. For cumulative finasteride use the odds ratio is highest for medium users (4-6 packs) although none of the odds ratios are significant.

Several supplementary analyses supported the same conclusion and analyses stratified by surveillance bias factors did not support that surveillance bias modifies the association. A few of the supplementary analyses found significant associations between finasteride use and male breast cancer, which may be a reflection of multiple testing. There is no clear pattern of

the supplementary analyses that supports statistically significant association for some specific subgroups.

Even though the main result of the study is not statistically significant, it is important to mention in this drug safety study that the confidence interval of the odds ratio also supports an increased odds of finasteride use among male breast cancer cases compared to controls. The higher bound of 1.77 in the main analysis (Table 2.3 – Annex 1C) does support that it is unlikely that the odds ratio is higher than 1.77. When interpreting this potential higher finasteride exposure among breast cancer cases, it should be acknowledged that male breast cancer is a rare disease with incidence rate between 0.70 and 1.00 per 100,000 person-years in the three Nordic countries (Table 0.2 – Annex 1C).

Previous studies of the association between finasteride use and male breast cancer are conflicting. A number of studies have indicated a possible link between finasteride use and risk of male breast cancer. One study reported no significant association but the follow-up time was only 1-3 years after exposure (Bird 2013), which may be considered a short follow-up period. In a study from United Kingdom a non-significant odds ratio at 1.08 for the association between ever use of finasteride or dutasteride, but an odds ratio at 1.29 for cumulative use for three or more years which is similar to our non-significantly increased odds ratio for medium cumulative finasteride use (Duijnhoven 2014). The previous stage I study based on Nordic register data showed a significantly increased incidence rate ratio at 1.44 (95% confidence interval 1.11-1.88) among finasteride users compared to the reference population (Meijer et al., 2018). The data sources for the previous study were similar to the present stage 2 study except that we have longer time periods and data from Norway was not included in the present study. Furthermore, in the previous study no individual-level data were available on finasteride non-users. Another difference was the exclusion criteria (see section 9.3), which is stricter in this study than the previous study where the only exclusion criterion was previous male breast cancer (i.e. the analysis was performed on incident male breast cancer). Finally, the previous study only adjusted for age, calendar time and country, while the present study carefully adjusted for several important potential confounding factors determined by DAG methodology.

The main strength of this study is that it includes nation-wide data from three countries with 1005 cases and almost 45,000 controls. It has relatively long follow-up time especially for the Danish and Finnish males, and contains individual-level data on numerous potential confounding factors for all persons included. The quality of the registers is high due to the completeness and validity of registered data (Engholm 2010; Gissler 2004; Gjerstorff 2011; Jensen 2002; Kildemoes 2011; Lynge 2011; Pedersen 2006; Pedersen 2011; Petersson 2011; Pukkala 2011).

In conclusion, the study adds to the literature of the association between finasteride use and male breast cancer in supporting that finasteride use is not associated with a statistically significant increase in the likelihood of male breast cancer when taking into account of potential confounding factors.

11.4 Generalisability

In this report, nation-wide registers with information on prescription drugs, cancer incidence, hospital discharges, and occupation were used. Information from representative surveys on life-style factors was also included. Since all registers have high completeness and high validity and all finasteride users and all male breast cancer cases were included, the results have high external validity with generalizable results to the whole Nordic male population. Furthermore, since we included information on three whole populations, the results may be applicable outside the Nordic countries.

12 OTHER INFORMATION

13 CONCLUSION

There are systematic differences between finasteride users and non-users with regards to confounding factors previously reported to be associated with finasteride use or male breast cancer incidence. Furthermore, the study supports that there is no statistically significant increased odds of exposure to finasteride among male breast cancer cases compared to controls in the age-, country- and calendar time-adjusted analysis or when taking account of confounding factors and the study supports that the adjustment of confounders decreased the odds ratio compared to the age-, country- and calendar-adjusted analysis.

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ANNEXES

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	1A	19-DEC-2017	Table with codes final
2	1B	19-DEC-2017	Sampling of controls
3	1C	19-DEC-2017	FIN Tables clean
4	1D	10-JAN-2018	Flowchart substudy1
5	1E	10-JAN-2018	Flowchart substudy 2
6	1F	15-FEB-2015	Protocol Amendment dated on 10-FEB-2015
7	1G	16-JAN-2018	Protocol Amendment dated on Jan 2018
8	1H	30-JAN-2015	SAP

Annex 2 Study protocol

(0906-162-01)

PASS information

Title	Finasteride and male breast cancer – a register-based nested case-control study in Denmark, Finland, Norway, and Sweden
Protocol version identifier	Version 162.01: 10 February 2015
Date of original protocol	Version 162.00: 12 March 2014
EU PAS register number	Study not registered
Active substance	G04CB01 and D11AX10
Medicinal product	Proscar and Propecia
Product reference	Reference number(s) of centrally authorized products and/or, if possible, of nationally authorized products subject to the study See Annex 3
Procedure number	SE/H/158/01/FU/02
Marketing authorisation holder(s)	Merck sharp & Dohme B.V., Waarderweg 39, BN 2031 Haarlem, The Netherlands
Joint PASS	No
Research question and objectives	The research question is to explore whether the previously reported increased incidence rate of male breast cancer among finasteride users compared to non-users may be explained by confounding factors. The main objectives are to 1) describe finasteride users compared to non-users with respect to confounding factors and 2) analyze the effect of finasteride use on breast cancer incidence while taking account of confounding factors.
Countries of study	Denmark, Finland, Norway, and Sweden
Author	PPD , Denmark

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Merck sharp & Dohme B.V., Waarderweg 39, BN 2031 Haarlem, The Netherlands
MAH contact person	PPD Associate Director – Regulatory Liaison Regulatory Affairs EMEA Regional Center, MSD BV Molenstraat 110, 5342 CC Oss, The Netherlands Tel: PPD Fax: PPD E-mail: PPD

1. Table of Contents

2. List of abbreviations

PPD

ARIs, 5alpha-reductase inhibitors

BPH, benign prostatic hyperplasia

BRCA, Genes on chromosome 13 and 17 that normally helps suppress cell growth; certain mutations of these genes are associated with breast cancer and some other types of cancer

CRC, Case Review Committee (CRC)

DAG, directional acyclic graph

EU, The European Union

FDA, US Food and Drug Administration

ICD, International Classification of Diseases

MPB, male pattern baldness

PPD

PPD

eSRC, External Safety Review Committee

PPD

3. Responsible parties

PPD

- PPD
- PPD

PPD

- PPD
- PPD
- PPD

National scientific coordinators

- Denmark: PPD

- Finland: PPD [redacted]
- Norway: TBD
- Sweden: PPD [redacted]

Expert group

- PPD [redacted]
- PPD [redacted]
- Additional experts will be included as the project starts

4. Abstract

Title: Finasteride and male breast cancer – a register-based nested case-control study in Denmark, Finland, Norway, and Sweden.

Rationale and background: Some previous studies have suggested an association between finasteride use and male breast cancer.

Research question and objectives: To explore whether the increased incidence rate among finasteride users compared to non-users may be explained by confounding factors. The research objectives are twofold:

1. To describe finasteride users compared to non-users with respect to potential confounding factors.
2. To analyze the effect of finasteride use on male breast cancer incidence while taking account of confounding factors that may explain the previously reported increased incidence.

Study design: The study consists of two substudies.

- Substudy 1 and 1A compare finasteride users (persons with at least two prescriptions of finasteride) with non-users (persons with less than 2 prescriptions of finasteride) or persons with different levels of cumulative finasteride use with respect to potential confounding factors including survey data. Entry criterion to the group of finasteride users is redemption of the second finasteride prescription.
- Substudy 2 evaluates the association between finasteride use (exposure) and male breast cancer (outcome) taking account of confounding factors. Finasteride use is included as finasteride users versus non-users and as persons with different levels of cumulative finasteride use. Country- and age-matching will be used in substudy 2.

Population: In substudy 1 and 1A, the population comprises of all male finasteride users and a random sample of country-matched non-users aged 35+ years in the period 1995-2013 (Denmark), 1994-2013 (Finland), 2008-2013 (Norway), and July 2005-2013 (Sweden). In substudy 2 the population comprises of all male breast cancer cases and a random sample of country- and age-matched controls during the same period. Both studies used density sampling and were therefore matched on follow-up time.

Variables: Confounding variables were selected on the basis of directional acyclic graphs (DAGs) developed together with clinical experts. Finasteride use and male breast cancer are main variables. Several potential confounding factors were evaluated, e.g. benign breast disease, Klinefelter's syndrome, estrogen therapy, family history (male, female) of breast cancer, radiation exposure, alcohol intake, and socio-economic position.

Data sources: Nation-wide registers with information on prescription drugs, cancer incidence, hospital discharges, and occupation were used. Information from representative surveys on life-style factors is also included.

Study size: In substudy 1 and 1A, all finasteride users and a random sample of country-matched non-users are included. This encompasses approximately 44,000 users in Denmark, 88,000 users in Finland, 18,000 users in Norway, and 64,000 users in Sweden. For each user, one non-user aged 35+ years from the same country will be included. Substudy 1A is based on the population in substudy 1 where survey data is available. In substudy 2, all male breast cancer cases aged 35+ years will be encompassed (i.e. approximately 1000 cases) and country and aged-matched 50 controls per case will be sampled.

Data analysis: Logistic regression models will be used in both substudies. Matching on country and follow-up time (i.e. density sampling) will be accounted for in both studies, and additionally age-matching will be is performed in substudy 2. In both substudies, men aged 35 or more years will be included. For both substudies, finasteride use will be defined as either a binary variable (at least two prescriptions of finasteride versus less than two prescriptions) or a cumulative variable (2-3 packs of 98 pills, 4-6 packs, or 7+ packs of finasteride versus less than two packs of finasteride). Moreover, both substudies will include either a long follow-up time including only Denmark and Finland (1995/1994-2013) or a follow-up period including the available data from all four countries (Denmark (1995-2013), Finland (1994-2013), Norway (2008-2013), and Sweden (July 2005-2013). The combination of the two different definitions of finasteride use and the two follow-up periods gives four different main analyses (i.e. analyses A-D). In substudy 1, the association between potential confounders and finasteride use is analyzed and in substudy 2, the association between finasteride use and breast cancer is analyzed. Supplementary analyses will be stratified by age, be performed within a benign prostatic hyperplasia cohort, will combine finasteride and dutasteride users and will compare finasteride and alpha-blockers users. Further supplementary analyses will include alternative definitions of finasteride use (years of use, years since first use, restrict exposure to only intake of 5 mg finasteride, include persons with only one redemption of finasteride as exposed and change the requirement for new users). Furthermore, the analyses will be stratified on factors associated with surveillance bias, e.g. diagnosis of gynaecomastia, stage at diagnosis, and number of hospital admissions and, finally, latency-time analyses will be performed. Analyses of both substudies will be adjusted for differences in calendar year and analyses in Substudy 2 will additionally be adjusted for confounders.

5. Amendments and updates

This protocol (Version 162.01: 10 November 2014) has gone through very minor amendments since the original protocol (Version 162.00: 12 March 2014). These minor edits have been detailed in the coverletter.

6. Milestones

Detailed in Annex 1: Study Timeline

7. Rationale and background

Finasteride is a type II 5α-reductase inhibitor and was initially approved by the US Food and Drug Administration (FDA) in 1992 under the brand name PROSCAR as a treatment for benign prostatic hyperplasia (BPH). In 1997, the FDA approved finasteride for the treatment of male pattern baldness (MPB), under the brand name PROPECIA.

Finasteride is available in the European Union (EU) as 1 mg and 5 mg tablets in preparations and indications as follows:

- Proscar (Finasteride 5 mg, ATC code: G04CB01 (G04CB04 in Finland from 1994–1996)) for the treatment and control of BPH in patients with an enlarged prostate to cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH. This reduces the risk of acute urinary retention and the need for BPH related surgery. The daily dose is one tablet of 5 mg.
- Propecia (Finasteride 1 mg, ATC code: D11AX10) for the treatment of men with male pattern hair loss to increase hair growth and prevent further hair loss. The daily dose is one tablet of 1 mg.

The annual number of newly diagnosed male breast cancer cases is around 100 in all Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) combined (Engholm 2012). Several risk factors for male breast cancer are associated with increased estrogen and decreased androgen levels. These include testicular abnormality, benign breast disease, obesity, liver cirrhosis, Klinefelter's syndrome, gynaecomastia, estrogen therapy, and occupational exposures such as work in the perfume industry, night-shift work, and in high-temperature environments (Johansen Taber 2010, Pukkala 2009). Age of the mother at birth may also increase the risk of breast cancer.

Family history of both male and female breast cancer also affect the risk of male breast cancer. In this group genetic disposition, e.g. BRCA mutations, is associated with breast cancer (Johansen Taber 2010). Exposure to ionizing radiation is also suspected to be associated with breast cancer in men. Men with pulmonary tuberculosis, who had a large number of fluoroscopies and X-rays, have been reported to have higher incidences of breast cancer. Several life-style factors associated with female breast cancer may also be associated with male breast cancer, e.g. physical inactivity and

alcohol intake. Finally, socio-economic and urban/rural differences in male breast cancer have been reported.

Some studies have investigated an association between finasteride and male breast cancer although none of the studies reported any significantly increased risk (Lee 2004, MHRA 2009, Shenoy 2010). Most recently, a case-control study of a US patients population including 339 male breast cancer cases investigated finasteride, dutasteride (i.e. a drug within the same drug class as finasteride, ATC code G04CB02), and male breast cancer and found no association between finasteride (i.e. PROSCAR™ dosages only) and male breast cancer (3 years or more period of observation before index date: RR = 0.75, 95% CI: 0.27 – 2.10; 365 days cumulative therapy: RR = 1.03, 95% CI: 0.45 – 2.37) (Bird et al, 2013). A register-based cohort study with data from Denmark, Finland, Norway, and Sweden was conducted by the applicants to study the potential link between finasteride use and incident male breast cancer (results not published) (Stage 1 Study report, unpublished). Based on data from nation-wide registers on drug prescriptions and cancer incidence, the study reported an increased incidence of breast cancer among male users of finasteride compared to non-users (incidence rate ratio, 1.44; 95%CI, 1.11-1.88). This study was much larger than any previous study and the finding of a significantly increased incidence rate has not been reported in any of the previous studies. When restricting the analyses to Denmark and Finland with the longest observation period, an increased breast cancer incidence rate was also observed, most pronounced in Denmark. Higher prevalence of finasteride use was observed in Finland compared to Denmark. Furthermore, Danish users of finasteride had a 1.23 times higher mortality rate compared to Finnish finasteride users. These two patterns indicate that finasteride users in Denmark are more selected than in Finland, which could indicate that confounding factors may be different between the two countries. Statistical adjustment was made for age and calendar year, but concerns have been raised whether adjustment for other risk factors for breast cancer may alter the association found.

In the present study further information on confounding factors will be included to compare finasteride users and non-users (investigating finasteride users defined by both a binary variable and a cumulative variable) and to evaluate whether the reported association between finasteride use and male breast cancer can be explained by confounding factors. The main analyses will be performed for both Denmark and Finland to evaluate the effect of finasteride in the two countries with longest follow-up (1994-2013 for Finland and 1995-2013 for Denmark) and, alternatively, for all four countries (Denmark (1995-2013), Finland (1994-2013), Norway (2008-2013) and Sweden (July 2005-2013)). The analysis only including Finland and Denmark will be performed since follow-up time is limited for Sweden and Norway which increases the influence of truncation and makes latency analyses more difficult to perform.

8. Research question and objectives

The research question is to further explore whether the increased male breast cancer incidence among finasteride users compared to non-users may be explained by confounding factors. The research objectives are twofold:

1. Describe finasteride users compared to non-users with respect to potential confounding factors (exploratory variables).
2. Analyze the effect of finasteride use on male breast cancer incidence while taking account of confounding factors decided in a DAG analyzing the association between finasteride use and male breast cancer.

The hypotheses are:

1. There is a systematic difference between finasteride users and non-users for potentially confounding factors previously reported to be associated with finasteride use or male breast cancer incidence.
2. The previously found increased incidence of male breast cancer among finasteride users is explained by confounding factors.

9. Research methods

9.1. Study design

The first step was developing a DAG for the association between finasteride use and male breast cancer. This development highlighted factors associated with finasteride use, factors that are a consequence of finasteride use, and factors associated with male breast cancer risk. The DAG pinpointed which variables to include in the analysis of the association between finasteride use and male breast cancer (substudy 2) and which should be left out. All factors associated with finasteride use or male breast cancer will be included in the descriptive substudy 1.

9.1.1. Substudy 1

In substudy 1, persons with at least two prescriptions of finasteride and persons with less than two prescriptions of finasteride and persons with different levels of cumulative finasteride use (0-1 packs of 98 pills, 2-3 packs, 4-6 packs, and 7+ packs) are compared with respect to potential confounding factors described in section 9.3. This study utilizes a new user design by excluding finasteride users with the first redemption of finasteride within the first 6 months of registration. For each male we sample one male non-user using density sampling (Rothman 2008). Specifically, when one man redeems his second finasteride prescription we will sample one other man alive in the same country at that particular day who has redeemed less than two finasteride prescriptions before or at that particular day. We will restrict the control selection to men of age 35 and above, since the use of finasteride is almost entirely restricted to this age span. This man will be given an index date and information on confounding factors will be extracted for the period before the index date. Using this

sampling scheme the odds ratios estimated in the logistic regression model can be interpreted as an incidence rate ratio of finasteride use for persons exposed to confounding factors compared to non-exposed (Rothman 2002, Rothman 2008). For confounders with more than two categories, the odds ratios estimated can be interpreted as incidence rate ratios for each category compared to a reference group. Several supplementary analyses will be performed including alternative definitions of finasteride use, comparison of finasteride and alpha-blockers users, age-stratified analyses, and stratified on factors associated with surveillance bias and latency. The supplementary analyses are further described in section 9.7.

The matching criteria of substudy 1 are:

- Country
- Follow-up time (density sampling)

9.1.2. Substudy 1A

In substudy 1A finasteride users will be compared with non-users with respect to self-reported life-style factors as obesity, alcohol intake, and physical inactivity also listed in section 9.3. In this study, we link national surveys including self-reported information on these potential confounders with finasteride users and non-users, either defined by use of a binary or a cumulative measure of finasteride use (substudy 1 data).

9.1.3. Substudy 2

In substudy 2, the effect of either finasteride use versus non-use or cumulative finasteride use on male breast cancer is analyzed taking account of the confounding factors selected by the previously developed DAG. In a situation where results from substudy 1 and 1A show an important imbalance between finasteride and non-finasteride users that is not yet included in the DAG, we will reconsider the DAG by including or excluding arrows as appropriate and use the updated minimum sufficient confounder set for confounder adjustment in substudy 2. Breast cancer cases will be identified in the national cancer registers, where diagnosis of cancer is carefully evaluated by medical experts (Gjerstorff 2011). The study will be a density sampled case-control study, where each male breast cancer case will be country- and age-matched to controls (Rothman 2002). We will select 50 controls per case (see calculation of minimal detectable OR in section 9.5). This substudy will also utilize a new user design by excluding finasteride or dutasteride users with the first redemption within the first 6 months of registration. The primary analysis will exclude users of dutasteride from cases and controls. Several supplementary analyses will be performed, including alternative definitions of finasteride use, combining use of finasteride and dutasteride (i.e. use of any ARI), comparison of finasteride and alpha-blockers users, analysis nested within a cohort of patients with benign prostatic hyperplasia (BPH), country-specific and age-stratified analyses, and stratified on factors associated with surveillance bias and latency. The supplementary analyses are further described in section 9.7.

The matching criteria of substudy 2 are:

- Country
- Age
- Follow-up time (density sampling)

One supplementary analysis is the comparison of use of alpha-blocker and use of finasteride. This analysis is done by analyzing the association between finasteride use and male breast cancer among non-users of alpha-blockers and the association between alpha-blockers and male breast cancer among non-users of finasteride. If the risk estimates of finasteride and alpha-blockers on male breast cancer will be comparable in these two analyses, this may support that unmeasured confounding by indication is present, while if the risk estimate of finasteride is stronger than alpha-blockers this may indicate that confounding by indication does not strongly influence the association between finasteride use and male breast cancer. This analysis is only included as a supplementary analysis because the indication for treatment with alpha-blockers and finasteride may be different in the Nordic countries and because of lack of power when excluding persons exposed to either finasteride or alpha-blockers.

Another supplementary analysis will be within a cohort of men with diagnosis or treatment for benign prostatic disease termed the benign prostatic hyperplasia (BPH) cohort. The development and definition of diagnosis and treatment of relevant benign prostatic diseases will be done together with clinical experts.

9.2. Setting

The two substudies consist of two study populations:

The substudy 1 consists of finasteride users (at least two prescriptions of finasteride) during the study period compared with non-users (less than two prescriptions of finasteride). For each user we sample one country-matched non-user alive and living in the populations at that given day. The study period is 1995-2013 in Denmark, 1994-2013 in Finland, 2008-2013 in Norway, and July 2005-2013 in Sweden. Data will be available until and including 2012 for all countries, for some countries also for 2013. Data will be applied for including 2013 and used if available. During the analysis phase we will also compare users with a higher consumption of finasteride with users with lower consumption and non-users. This is the reason for not using age-matching in this study because by age-matching we would need several non-users for the same finasteride user as the user accumulates finasteride. Instead we will adjust our analysis for differences in age.

In substudy 1A we will include all finasteride users (substudy 1 data) who previously have participated in a survey. Each finasteride user will be compared to sampled non-users who previously have participated in a survey. We will include the most recent information on life-style factors.

The substudy 2 is designed as a density sampled case-control study (Rothman 2002). Each male breast cancer case during follow-up (1995-2013 in Denmark, 1994-2013 in Finland, 2008-2013 in Norway, and July 2005-2013 in Sweden) will be country- and age-matched to controls at risk of breast cancer on the date of breast cancer diagnosis (index date). For each case we will sample 50

controls (see calculation of minimal detectable OR in section 9.5). Data will be available until and including 2012 for all countries, for some countries also for 2013. Data will be applied for including 2013 and used if available.

9.2.1. Inclusion criteria

Substudy 1

- Males residing in either Denmark, Finland, Norway, or Sweden on the index date
- Aged 35 years and older
- Finasteride user group: Men who have redeemed at least two prescriptions of finasteride in the study period (either as one group or divided into three groups, i.e. 2-3 packs of 98 pills, 4-6 packs, and 7+ packs)
- Non-finasteride user group: Men who have redeemed less than two prescriptions of finasteride in the study period

Substudy 2

- Males residing in either Denmark, Finland, Norway, or Sweden on the index date
- Aged 35 years and older
- Cases: Men with a diagnosis of primary breast cancer (see section 9.2.3 Primary breast cancer case definition)
- Controls: Men without a diagnosis of breast cancer at index date

9.2.2. Exclusion criteria

Substudy 1

- None

Substudy 2

- Previous cancer diagnosis or treatment for cancer except non-melanoma skin cancer
- Previous prostatectomy
- Finasteride or dutasteride use (dutasteride is a drug in the same class as finasteride) within first 6 months of registration in the prescription registers (new user design).

9.2.3. Primary breast cancer case definition

A primary breast cancer case will be defined as one that is recorded in the cancer registers, as per ICD-10-CM (C50).

Information on the macro- and microscopic basis of breast cancer diagnosis is available from the Nordic cancer registers. A diagnosis in the cancer registers is based on the combination of information from the national patient registers, pathology registers and cause of death registers. The vast majority of cases listed in those registers are based on invasive examinations (surgery and autopsy) and histological confirmation. In case of incomplete or controversial information, requests

for further information are sent to hospitals and physicians who failed to report complete information (Gjerstorff, 2011; Pukkala, 2011). The use of multiple data sources secures a high degree of completeness of the cancer registers.

To characterize the male breast cancer cases, a descriptive analysis will be performed. This analysis will consist of information on pathology code (per microscopic-based evidence of primary malignant neoplasia of the breast which was indicated by histology and/or cytology) and intervention against the primary breast cancer (i.e. surgery, radiation, and/or chemotherapy).

9.3. Variables

In substudy 1, the dependent variable is either redemption of two or more finasteride prescriptions and the comparison group of males with less than two prescriptions sampled from the population or cumulative finasteride use (0-1 packs of 98 pills, 2-3 packs, 4-6 packs, and 7+ packs of finasteride). Variables that may be associated with surveillance bias will also be examined. The explanatory variables in the analysis are described in Table 2. For substudy 1A we will study life-style related risk factors. In substudy 2, the outcome is first diagnosis of male breast cancer and controls are sampled from the population. The exposure variable is either redemption of two or more finasteride prescriptions and the comparison group of males with less than two prescriptions sampled from the population or cumulative prescriptions of finasteride (0-1 packs of 98 pills of 5 mg, 2-3 packs, 4-6 packs, and 7+ packs) in the period before breast cancer diagnosis. The potential confounding variables are described in Table 2, but in the analysis only variables in the selected minimum sufficient confounder set in the DAG will be included (described in more detail in Statistical Analysis Plan (SAP)). Furthermore, variables that may be associated with surveillance bias will be studied (Table 3).

For finasteride exposures, the information in the registers reflects the fact that medication prescribed has been dispensed to and paid for by the patient. Whether the medication has actually been consumed, though, is not known.

Table 2. Information on potential confounding factors that will be included in substudy 1 and may be included in the substudy 2 depending on the final DAG developed

Confounding factors	Explanation	Data source (also see Table 4)	Substudy 1 (1)	Substudy 2 (2)
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	Testicular disorders could influence the estrogen-androgen ratio increasing risk of breast cancer. The only complication is that most patients with testicular disorders will have been treated as children and this may not be available in the hospital registers	National Patient Registers, including but not limited to orchitis and cryptorchidism	Any diagnosis before finasteride use	Any diagnosis before breast cancer index date
- Benign breast disease	Benign breast disease is associated with breast cancer risk	National Patient Registers	Any diagnosis before finasteride use	Any diagnosis before breast cancer index date
- Obesity	Obesity and morbid obesity influence the estrogen-androgen ratio. We include contacts to the hospital system for morbid obesity and self-reported height and weight from nation-wide registers	National Patient Registers including the following disorders: Obesity (ICD-10, E66). Furthermore self-reported height and weight from nation-wide surveys	Any diagnosis before finasteride use or self-reported BMI before finasteride use	Only register-based diagnoses on morbid obesity included. Any diagnosis before breast cancer index date
- Liver cirrhosis	Liver cirrhosis influences the conversion of sex-hormones which could influence the breast cancer risk	National Patient Registers. Include the following disorders: Alcoholic cirrhosis of liver (ICD-10, K70.3), toxic liver disease with fibrosis and cirrhosis (K71.7), and liver fibrosis and cirrhosis (K74)	Any diagnosis before finasteride use	Any diagnosis before breast cancer index date
- Klinefelter's syndrome	Rare syndrome that causes abnormal development of the testicles due to low production of male hormones and high production of female hormones. The syndrome is a risk factor for breast cancer. Very few patients with this syndrome and may therefore not be relevant in the present study	National Patient Registers including the ICD-10 code for the syndrome-me: Q98.4	Any diagnosis before finasteride use	Any diagnosis before breast cancer index date

Table 2. Information on potential confounding factors that will be included in substudy 1 and may be included in the substudy 2 depending on the final DAG developed

Confounding factors	Explanation	Data source (also see Table 4)	Substudy 1 (1)	Substudy 2 (2)
- Estrogen therapy	Medications that may influence the exposure to estrogen will be included.	National Prescription Registers	At least two redemptions before finasteride use	At least two redemptions before breast cancer index date
- Occupational exposures	Occupational exposures in the perfume industry, in high-temperature environments and night-shift work may increase the exposure to estrogens	Denmark: Register-based labour force Finland: Censuses Norway: Censuses Sweden: Register-based labour force behavior; place of work; employer etc. (source: LISA)	Labour market affiliation in any of these occupations two calendar years before finasteride use	Labour market affiliation in any of these occupations two calendar years before breast cancer index date
Family exposures				
- Family history of breast cancer	Family history of breast cancer (male, female) is associated with breast cancer	Civil registration systems and cancer registers. The information on mothers is available for cohorts from 1960 in Denmark (Pedersen 2006) and from October 1953 in Finland. For Sweden, it is possible – in principle – to identify biological parents via RTB and then to look for each individual in the Cancer register. The Cancer registry started in 1958 in Sweden.	Any familial breast cancer diagnosis before finasteride use	Any familial breast cancer diagnosis during the whole registration period

Table 2. Information on potential confounding factors that will be included in substudy 1 and may be included in the substudy 2 depending on the final DAG developed

Confounding factors	Explanation	Data source (also see Table 4)	Substudy 1 (1)	Substudy 2 (2)
Ionizing radiation and cancer treatment				
- Radiation exposure including men treated with radiotherapy for pulmonary tuberculosis	X-rays of the chest may increase risk of breast cancer. SKS-code: UXRC including UXRC40/UXRC45 (mammography). Will also include CAT scans	National Patient Registers	Any treatment before finasteride use	Any treatment before breast cancer index date
Life-style factors				
- Alcohol intake	Alcohol intake is a risk factor for breast cancer	Nation-wide surveys	Intake five years before finasteride use	Self-reported information will not be included
- Physical inactivity	Physical inactivity is a risk factor for breast cancer	Nation-wide surveys	Activity five years before finasteride use	Self-reported information will not be included
- Dietary intake of vegetables and fruit	Vegetable and fruit intake a preventive factor for breast cancer	Nation-wide surveys	Intake five years before finasteride use	Self-reported information will not be included
- Dietary intake of animal fat	Animal fat may increase risk of breast cancer	Nation-wide surveys	Intake five years before finasteride use	Self-reported information will not be included

Table 2. Information on potential confounding factors that will be included in substudy 1 and may be included in the substudy 2 depending on the final DAG developed

Confounding factors	Explanation	Data source (also see Table 4)	Substudy 1 (1)	Substudy 2 (2)
Socio-economic differences				
- Socio-economic position	Finasteride users have higher socio-economic position. We include socio-economic position using categorizations used by the national statistical offices	Denmark: Register-based labour force Finland: Censuses Sweden: Register-based labour force data (source: LISA)	Socio-economic position the year before finasteride use	Socio-economic position the year before breast cancer index date
- Living as a single man		Civil registration systems	Cohabitation status the year before finasteride use	Cohabitation status the year before breast cancer index date
- Urban / rural differences	Men living in urban areas may experience higher breast cancer incidence, e.g. due to elevated exposure to traffic-related air pollution, light at night or higher alcohol intake	Civil registration systems	Information the year before finasteride use	Information the year before breast cancer index date
Other factors				
- Diabetes	Potentially novel finding (Brinton et al 2014)	National patient registers	Index up to 10 years before first finasteride use	Index up to 10 years before breast cancer index date
- History of bone fractures	Brinton et al 2014 (reported in this study among those diagnosed with male breast cancer at older ages)	National patient registers	Index up to 10 years before first finasteride use	Index up to 10 years before breast cancer index date

(1) This column describes how the information is included in substudy 1.
(2) This column describes how the information is included in substudy 2.

Table 3. Information on factors potentially associated with surveillance bias included in the study and data sources

Factors associated with surveillance bias	Explanation	Data source (also see Table 4)	Substudy 2
- Gynaecomastia	One side-effect of finasteride use is gyneaecomastia. Gyneaecomastia is associated with breast cancer	National Patient Registers including the ICD-10 code N62	Any diagnosis before breast cancer index date
- Use of drugs that cause gynaecomastia	Antiandrogens other than finasteride and dutasteride (bicalutamide, flutamide, nilutamide) Antihypertensives (Spironolactone) Antiretrovirals (protease inhibitors (saquinavir, indinavir, nelfinavir, ritonavir, lopinavir) and nucleoside reverse transcriptase inhibitors (stavudine, zidovudine, lamivudine) Environmental exposures (phenothrin) Exogenous hormones (estrogen, rednisone (adolescent boys)) Gastrointestinal agents (histamine$_2$-receptor blockers (cimetidine))	Prescription registers	At least two redemptions before breast cancer index date
- Number of prescriptions	Indication of morbidity	Prescription registers	Count up to 10 years before breast cancer index date
- Number of surgeries	Indication of morbidity	National Patient Registers	Any number of surgeries before breast cancer index date
- Number of admissions	Indication of morbidity	National Patient Registers	Any number of admissions before breast cancer index date
- Urinary retention	Associated with finasteride use	National patient registers	Any diagnosis before breast cancer index date
- Cancer stage	Earlier cancer stage among finasteride users may that the finasteride users were followed closer by medical staff	Cancer registers	Cancer stage of the index case

Ideally the chronological order of confounders, exposure (finasteride use), and outcome (male breast cancer diagnosis) should be that the confounding factors should be measured before the first prescription of finasteride and finasteride use should be prescribed before the breast cancer diagnosis. In accordance with the chronological order mentioned above, potential confounding factors will be measured before the first prescription of finasteride use in substudy 1 (Table 2, the "substudy 1" column). However, in substudy 2 it is not possible to measure confounders before exposure for persons without exposure, i.e. non-exposed cases and controls. Therefore, it is necessary to include confounder information during the same period as exposure collection (the "substudy 2" column). The DAG developed clarified whether a potential confounder variable indeed is a confounder or it is an intermediate variable.

The variables presented in Table 3 may be associated with surveillance bias in that patients with these factors may have an increased probability of diagnosis of breast cancer because of more careful surveillance. The analyses in substudy 2 will be stratified on these factors to detect whether an increased odds ratio could be explained by surveillance bias (see section 9.7 below).

Information on date of birth, date of death, sex and date of immigration and emigrations will also be obtained.

9.4. Data sources

The sampling populations are the Danish, Finnish, Norwegian, and Swedish male populations aged 35 years or older. We utilize the nation-wide registers of prescriptions, cancer incidence, contacts to the secondary and tertiary hospital system, the civil registration system, and registers on occupational group. The registers cover different periods (see Table 4 below), but all registers have registration for the period 1995-2013 for Denmark, 1994-2013 for Finland, 2008-2013 for Norway, and July 2005-2013 for Sweden. The limiting factor here is the year from which medical intervention codes are available (Table 4). Linkage between the registers is possible due to the unique individual identification numbers (Gissler 2004, Thygesen 2011). We will also include national health surveys conducted in each of the countries several times during follow-up.

Table 4: Registers included in the study

Country	Register	Registration period
Denmark	Prescription register	1995-2013
	Cancer register	1943-2013
	National patient register	1977-2013 (surgeries since 1977 and outpatient contacts since 1995)
	Civil registration system	1968-2013
	Register-based labour force statistics (RAS statistics)	1980-2013
	National Health Surveys	1994, 2000, 2005 and 2010
Finland	Prescription register	1994-2013
	Cancer register	1953-2013
	Hospital patient Register	1967-2013 (surgeries since 1986 and outpatient contacts since 1998)
	Civil registration system	1967-
	Censuses including information on occupational group	1995, 2000, 2005 and 2010
	National Health Surveys	1972, 1977 onwards
Norway	Prescription register	2004-2013
	Cancer register	1951-2013
	Hospital patient Register	2008-2013
	Civil registration system	1968- 2013
	Register on labour force statistics (AaNAV)	2000 (2007)- 2013
	National Health Surveys	1994-2013
Sweden	Prescription register	July 2005-2013
	Cancer register	1958-2013
	Patient Register	1987- 2013
	Civil registration system (Register over totalbefolkningen)	1968- 2013
	Register on labour force statistics (LISA)	1990- 2013
	National Health Surveys (The Swedish Survey of Living Conditions interviews)	2000-2013

Information from the prescription registers and the cancer registers have been validated (Gjerstorff 2011, Kildemoes 2011, Pukkala 2011). The national patient registers include diagnostic and treatment information for patients treated at the secondary and tertiary hospital level (Lynge 2011, Pukkala 2011). Clinical experts have been consulted on how to include this information. The codes are described above in Table 2. Information on date of birth, immigration, emigration, and death were obtained from the civil registration systems (Pedersen 2011, Pukkala 2011). Information on occupational status will be obtained from registers on attachment to the labor market (Petersson 2011, Pukkala 2009).

We will also include information from population surveys conducted in Denmark (Christensen 2012), Finland (Pukkala 2011), Norway (Næss 2008), and Sweden. The surveys are nation-wide representative health surveys including information on life-style factors. We will link this information to the finasteride users and non-users sampled in substudy 1A.

9.5. Study size

The substudy 1 includes all finasteride users and a random sample of country-matched non-users. In the previous study of finasteride use and male breast cancer (Stage 1 Study report, unpublished) the number of unique finasteride users (one or more prescriptions of finasteride) was 56,406 for Denmark in the period 1995-2009, 111,820 for Finland in the period 1997-2010, 22,345 for Norway in the period 2004-2009, and 79,712 for Sweden in the period July 2005-2009. The study also estimated that 76-85% of the finasteride person-time was for users with at least two prescriptions of finasteride. We therefore estimate that approximately 214,000 persons will have at least two prescriptions of finasteride and hence count as finasteride users in the present study.

The minimum detectable odds ratio (OR) is calculated for different values of proportion of non-finasteride users exposed to the confounder of relevance.

If we make the following assumptions, we can calculate the minimum detectable OR:

- Power = 90%
- Alpha = 5%
- Two-sided test
- 214,000 finasteride users
- 214,000 non-users

If we vary the proportion of non-finasteride users exposed to the confounder we can estimate the minimum detectable odds ratio (Table 5).

Table 5. Minimal detectable OR for substudy 1

The proportion of non-finasteride users exposed to the confounder	Minimum detectable OR
1% / 99%	1.102
5% / 95%	1.046
10% / 90%	1.033
25% / 75%	1.023
50%	1.020

We conclude that the power of substudy 1 is very high even when only one non-user is included per user. Even under the assumption of a power of 90% we will be able to detect odds ratios of 1.10 for very rare (or very common) confounders.

Substudy 1A includes a linkage between the prescription registers and national health surveys. The Danish National Health Survey consists of cross-sectional surveys conducted in 1994, 2000, 2005, and 2010 among persons aged 16 years and older. The number of participants in the surveys was 16,688, 14,566, and 15,165, respectable, which corresponds to approximately 0.4% of the population. Based on the previous study (Stage 1 Study report, unpublished), we assume that 3% of males are finasteride users. This means that we can assume that approximately 240 finasteride users also have participated in each of the surveys. In Finland, the National FINRISK Study has been conducted since 1972 every five years, first in Eastern Finland, and later on in five areas in Finland (Helakorpi 2008; Vartiainen et al 2010). The main aim of the FINRISK Study is to collect data on and monitor levels of risk factors of cardiovascular diseases and other non-communicable diseases among the Finnish population. Participants from each study area have been selected by using stratified random sampling. The participants were 25 to 64 years (since 1997 25 to 74 years) old at baseline. In Norway, the Cohort of Norway (CONOR) includes information from about 173,000 respondents in the period from 1994 to 2003 (Næss 2008). The participants answered a questionnaire and underwent a physical examination. The Swedish Survey of Living Conditions, Statistics Sweden, interviews about 10,000 respondents annually (some changes over time have occurred). Each year between 2000 and 2012 about 7,500–10,000 respondents were interviewed (respondents were 16–84 years of age).

Substudy 2 includes all male breast cancer cases and a country- and age-matched sample of controls. The number of male breast cancer cases was 365 in Denmark, 236 in Finland, 101 in Norway, and 200 in Sweden in the previous study (Stage 1 Study report, unpublished). The number of finasteride users who developed male breast cancer after first purchase of finasteride was 29 in Denmark, 26 in Finland, 1 in Norway, and 7 in Sweden. In this study, the sample will slightly increase because of longer follow-up. We expect approximately 1000 cases in the present study. The exposure variable in substudy 2 is either finasteride use (2+ prescriptions) versus less than two prescriptions or cumulative finasteride use (0-1 packs of 98 pills of 5 mg, 2-3 packs, 4-6 packs, and 7+ packs). We expect the 1000 cases will be distributed in the binary finasteride use categories as

follows: 948 used 0-1 packs of 98 pills and 52 used 2+ packs of 98 pills. For the four categories of cumulative finasteride use the number of cases will be: 948 cases used 0-1 packs of 98 pills, 20 cases used 2-3 packs, 11 cases used 4-6 packs and 21 cases used 7+ packs.

Based on the following assumptions, the minimal detectable OR for a comparison of exposure 7+ packs versus 0-1 packs can be calculated for a varying number of controls per case and assuming different proportions of exposed controls in a matched case-control study (Dupont, 1988 as implemented in STATA version 12 in the SAMPSI_MCC procedure):

- Power = 80 %
- Alpha = 5%
- Two-sided test
- Number of cases: 969
- Number of controls per case varies: 10, 25, 50, 100
- Proportion of exposure individuals among controls varies: 0.3%, 0.5%, 1%, 1.5%, 2%, 3%, 4%
- Correlation of exposure between pairs in the case-control set at 0.1

For a varying proportion of exposed controls we can estimate the minimum detectable OR for a comparison of exposure 7+ packs versus 0-1 packs of substudy 2 for 10, 25, 50 and 500 controls per case, respectively (Table 6). Similar minimum detectable OR is expected for a comparison between exposure 0-1 packs versus the two other exposure groups (2-3 packs, 4-6 packs).

Table 6. Minimal detectable OR for substudy 2

The proportion of exposed controls	Minimum detectable OR			
	1:10 controls	1:25 controls	1:50 controls	1:500 controls
0.3%	3.29	3.15	3.10	3.05
0.5%	2.69	2.59	2.56	2.53
1%	2.13	2.08	2.06	2.04
1.5%	1.91	1.86	1.85	1.84
2%	1.77	1.74	1.73	1.72
3%	1.62	1.60	1.59	1.58
4%	1.54	1.52	1.51	1.50

This analysis supports that the minimum detectable OR does not vary remarkably by number of controls and 50 controls per case is assumed to be an adequate number of controls to include in substudy 2. The minimum detectable OR, when sampling 50 controls per case, is estimated to range from 2.56 if 0.5% of the controls are exposed to 1.51 if 4% of the controls are exposed.

9.6. Data management

The handling of data includes seven steps.

1. All national scientific coordinators will apply relevant agencies for permission to perform the study and to get access to data, including Statistics Denmark/Statistics Finland/Statistics Norway/Statistics Sweden, and other relevant agencies to search the prescription registers for all purchases of finasteride and the cancer registers for all male breast cancer cases.
2. All national scientific coordinators will facilitate the construction of the study populations:
    - Study population consisting of all finasteride users and a sample of comparable non-users.
    - Study population consisting of male breast cancer cases and controls during the study period.
    - Both study populations will be sampled via density sampling based on the description and SAS code derived by the Danish scientific coordinator and agreed upon by the national scientific coordinators.
3. All national scientific coordinators are responsible of acquiring and validating the datasets and will explore how the datasets can be combined with the five registers described in section 9.4. Data control includes - but is not restricted to - check for legal values for each categorical variable, check of consistency between dates (at least date of birth before all other dates and date of death after all dates), and check and advice on the handling of missing data. All national scientific coordinators produce a data control report describing the checks performed and describing how the final dataset should be constructed from the registers received including reasons for modifications and exclusions. In this process all national coordinators have to agree on the reasons for exclusion, e.g. missing value on crucial variables, chronological errors in the relation between dates, non-legal values of categorical variables, and extreme values of continuous variables (see Statistical Analysis Plan (SAP)).
4. The datasets from Finland, Norway, and Sweden are transferred to Statistics Denmark where all subsequent data handling is done by the Danish scientific coordinator.
5. The Danish scientific coordinator links the data as described by the document developed by all national scientific coordinators and the data sets from all countries will be joined into a combined analysis dataset. Relevant variables will be derived.
6. The Danish scientific coordinator will assess the data validity of all countries by logical checks, examination of extreme values, and missing data. It is important that identification numbers are maintained to facilitate linkage back to the original data sets to be able to check the data and for the sake of transparency.
7. Data analysis and evaluation of the hypotheses described above (section 8) using SAS version 9.3 will be performed by the Danish scientific coordinator. Please also see section 9.7.

9.7. Data analysis

In the previous study (Stage 1 Study report, unpublished) we found a few inconsistencies, e.g. wrong chronology of dates and missing data for important variables. These inconsistencies accounted for

few records and were removed from the analyses. If the same pattern is observed in this study we will also remove persons with inconsistencies to ensure complete data in analysis. Initially, a DAG of the association between finasteride use and male breast cancer including potential confounders was derived by the Danish national investigators and the clinical expert group (Greenland 1999). The DAG clarified whether the potential confounders listed in Table 2 are confounders, colliders, or intermediate variables. Based on this clarification, it was decided which potential confounders will be included in substudy 2. In a situation where results from substudy 1 and 1A show an important imbalance between finasteride and non-finasteride users that is not yet included in the DAG, we will reconsider the DAG by including or excluding arrows as appropriate and use the updated minimum sufficient confounder set for confounder adjustment in substudy 2. All factors associated with finasteride use of male breast cancer will be included in the descriptive substudy 1. Please refer to Statistical Analysis Plan (SAP).

For both substudies finasteride use will be defined as either a binary variable (at least two prescriptions of finasteride versus less than two prescriptions) or a cumulative variable (2-3 packs of 98 pills, 4-6 packs, or 7+ packs of finasteride versus less than two packs of finasteride). Moreover, both substudies will include either a long follow-up time including only Denmark and Finland (1995/1994-2013) or a follow-up period including the available data from all four countries (Denmark (1995-2013), Finland (1994-2013), Norway (2008-2013), and Sweden (July 2005-2013). The combination of the two different definitions of finasteride use and the two follow-up periods gives four different main analyses (A-D) also described in Annex 4: A (long follow-up and binary finasteride use); B (long follow-up and cumulative finasteride use); C (available follow-up period for all four countries and binary finasteride use), and D (available follow-up period for all four countries and cumulative finasteride use)

In substudy 1, logistic regression will be performed by comparing potential confounding factors for finasteride users compared to non-users and between levels of cumulative finasteride use. The main analyses will include these two definitions of finasteride use among either long follow-up data from Denmark (1995-2013) and Finland (1994-2013) or all available data including all four countries (Denmark, Finland, Norway (2008-2013) and Sweden (July 2005-2013)), i.e. analyses A-D.

Ten supplementary analyses will be performed for substudy 1 (please also see Annex 4 for a table of the analyses) to further elaborate the associations between potential confounders and finasteride use:

1. Age-stratified analysis (above and below 45 years of age)
2. Analysis within the benign prostatic hyperplasia cohort
3. Analysis comparing alpha-blockers users with finasteride users
4. Include years of finasteride use as dependent variable (1-3, 4-5 and 6+ years)
5. Include years since first finasteride use as dependent variable (below 1 year, 1-2 years, 3-4 years and 5+ years)
6. Only include 5 mg finasteride as finasteride users
7. Include persons who only redeem one prescription in the user group

8. Change the requirement for new user by excluding finasteride users with first redemption of finasteride within the first 2 years of follow-up
9. Stratify the analysis by variables associated with surveillance bias
10. Latency analyses by inferring 1 and 2 years of lag time between confounding factors and finasteride use

In substudy 1A, the same main analyses as in substudy 1 will be done, i.e. we will include dependent variables as either a binary variable or as a cumulative variable in either Denmark and Finland or in all four countries (i.e. analyses A-D).

In substudy 2, conditional logistic regression will be performed by comparing male breast cancer cases with controls in respect to either finasteride users versus non-users or cumulative finasteride use and including confounding factors in the analysis. We will include confounding factors established by the DAG developed before substudy 1. We will consider using propensity score adjustment to take account of the numerous confounding factors more efficiently. The propensity score distribution will be plotted to look at overlap. If there is not sufficient overlap, then propensity score adjustment is not feasible. If the overlap is sufficient, we will use propensity score to adjust for multiple confounders. Conditional logistic regression will be performed to take account of the country- and age-matching. The analyses will either be performed with long follow-up data from Denmark (1995-2013) and Finland (1994-2013) or including all available follow-up time (Denmark, Finland, Norway (2008-2013) and Sweden (July 2005-2013) as described above (i.e. analyses A-D).

Eleven supplementary analyses will be performed for substudy 2 (please also see Annex 4 for a table of the analyses) to further elaborate the associations between finasteride use and breast cancer:

1. Age-stratified analysis (above and below 45 years of age)
2. Analysis within the benign prostatic hyperplasia cohort
3. Analysis comparing alpha-blockers users with finasteride users
4. Analysis of combined finasteride or dutasteride use (i.e. use of any ARI)
5. Include years of finasteride use as exposure (1-3, 4-5 and 6+ years)
6. Include years since first finasteride use as exposure (below 1 year, 1-2 years, 3-4 years and 5+ years)
7. Only include 5 mg finasteride as finasteride users
8. Include persons who only redeem one prescription as exposed
9. Change the requirement for new user by excluding finasteride users with first redemption of finasteride within the first 2 years of follow-up
10. Stratify the analysis by variables associated with surveillance bias
11. Perform latency analyses by inferring 1 and 2 years of lag time between exposure and confounders and breast cancer

All analyses will be programmed by two researchers independently to ensure complete agreement of the number of men, finasteride use (both binary and cumulative), number of cases, and the results of the analyses.

9.8. Quality control

The study is register-based and data quality is therefore difficult to ascertain directly. Previous studies have evaluated the validity of the central registers, e.g. the prescription registers and the cancer registers (Jensen 2002, Kildemoes 2011, Pukkala 2011). These studies in general support that the validity and completeness of the data sources are high.

The statistical analyses will be performed on servers at Statistics Denmark. The programming will be performed by two researchers independently limiting the programming errors. The statistical programs will be stored at the servers at Statistics Denmark.

9.9. Limitations of the research methods

A limitation of the study is the comparison of users with non-users, where the observed association may be influenced by confounding by indication since finasteride users will have more comorbidities and may have more contacts with medical staff. This could result in higher incidence of breast cancer among finasteride users than among a random sample of males. In the analyses, we try to capture this bias by stratifying the analyses by factors associated with surveillance bias, by adjusting for comorbidities, and by doing analysis of the separate effects of alpha-blockers and finasteride.

A minor limitation related to estimation of finasteride use is the prescription registers, which contain information on redeemed medications, and no information on the actual consumption of drugs. This is the reason for only categorizing persons with at least two prescriptions of finasteride as exposed, because these persons with repeated purchases of finasteride are more likely to also have used most of the drugs.

For several of the confounding factors, the information is only based on one or a few ICD-10 codes. This may result in under-estimation of the true prevalence of several of the confounding factors, e.g. obesity. We think this under-estimation will not be related with finasteride use thereby mimicking non-differential misclassification resulting in conservative observed associations for substudy 1. For other of the possible confounding factors the information is based on statistical classification systems, e.g. industrial classification systems, which may also be misclassified. We think this will also result in an under-estimation of the association between confounding factors and finasteride use. Whether this underestimation will result in an over- or underestimation of the association between finasteride use and breast cancer cannot be predicted.

Truncation is also a potential bias in the study meaning that we have no information on confounding factors, finasteride use, or cancer incidence before the start of registration of each of these factors. This is most pronounced for finasteride use, since we do not know whether a finasteride user in the first year of registration in Denmark and Finland and for more than a decade in Norway and Sweden is a long-term user (prevalent user) or a first-time user (incident user). This is only a minor limitation in Denmark and Finland, since finasteride was first approved in 1992, but is important to consider for Norway and Sweden. We will evaluate the influence of this limitation by excluding finasteride users in the first year of registration as a supplementary analysis to ensure that users in the second year are incident users.

In substudy 1A, only participants of the national surveys will be included. This may introduce selection bias in that the participants may not be representative of all finasteride users and non-users.

10. Protection of human subjects

This is an observational study with no administration of any therapeutic or prophylactic agent. Patients observed in this study will continue with the normal standard of care as provided by their personal physician. National registers of cancer, hospital contacts, and socio-economic factors will be the sole data source.

According to Danish, Finnish, Norwegian, and Swedish law register-based studies can be carried out without consent from the data subjects where the processing takes place for the sole purpose of carrying out statistical or scientific studies of significant public importance and where such processing is necessary in order to carry out these studies. It is an absolute requirement that the publication of statistical or scientific results may never reveal the identity of individuals or otherwise compromise data subjects. We will obtain approval by the data agencies in the four countries before data management and data analyses will be performed.

11. Management and reporting of adverse events/adverse reactions

11.1. Definition of Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or who undergoes a protocol-specified procedure and which does not necessarily have to have a causal relationship with this treatment or procedure. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal l product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor’s product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during the course of the use of the Sponsor's product in studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

11.2. Definition of Serious Adverse Event

"Serious Adverse Event" (SAE) means an adverse event which is fatal or life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, or is a congenital anomaly/birth defect, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered a Serious Adverse Event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

11.3. Adverse Event Reporting

If, through the conduct of this study, an investigator (or other study personnel) becomes aware of any serious adverse experience that is possibly, probably, or definitely related to an investigational or marketed product manufactured by Merck & Co., Inc., Schering Corporation, or MSP Singapore LLC, it should be reported to one of the persons on the sponsor contact information list within 24 hours of identification. The end of study report, and any interim analysis, will include aggregate listings of all SAEs and any non-serious AEs collected for and protocol-specified procedures, and will be provided to regulatory agencies as required by the Sponsor.

12. Plans for disseminating and communicating study results

The project will be published in a study report encompassing in detail the data sources, data management, analyses, and results. The outcomes will also be published in international peer reviewed journals if possible. The aim is to get publications in a well-perceived journal focusing on the area of research.

13. References

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Annex 1. List of stand-alone documents

Document	Document number
Stage 1 Research protocol: A multinational, observational registry-based study on a potential link between finasteride and male breast cancer in 4 Nordic countries	1
Stage 1 Study report: A multinational, observational register-based study on a potential link between Finasteride and male breast cancer in four Nordic countries	2
Study Timeline	3
Statistical Analysis Plan	4

Annex 2. ENCePP checklist for study protocols

Annex 3. Products Reference Numbers

Propecia

Member State Initials	Name of MAH	Name of Product	National Authorisation Number(s)	MR procedure number (if applicable)	Pharmaceutical form(s)	Strength(s)
AT	Merck Sharp & Dohme Ges.m.b.H	Propecia 1 mg Filmtabletten	1-24532	SE/H/0158/001	Film Coated Tablet	1 mg
CY	Merck Sharp & Dohme B.V., The Netherlands	PROPECIA	18318	N/A	Film-coated tablets	1 mg
CZ	Merck Sharp & Dohme B.V.	Propecia	87/244/99-C	N/A	Film-coated tablets	1 mg
DE	MSD SHARP & DOHME GMBH Lindenplatz 1 85540 Haar	Propecia 1 mg Filmtabletten	44270.00.00	SE/H/0158/001	Film Coated Tablets	1 mg
DK	Merck Sharp & Dohme B.V., The Netherlands	Propecia	30252	SE/H/0158/001	Film-coated tablets	1 mg
EE	Merck Sharp & Dohme OÜ	Propecia	238498	N/A	Film-coated tablet	1 mg
EL	Vianex S.A.	PROPECIA	74574/25-10-2012	SE/H/0158/001	Film-coated tablet	1 mg
ES	Merck Sharp & Dohme de España, S.A.	Propecia 1 mg comprimidos recubiertos con película	62.441	SE/H/0158/001	Film-coated tablet	1 mg
FI	Merck Sharp & Dohme B.V., The Netherlands	Propecia	13713	SE/H/0158/001	Film-coated tablets	1 mg
FR	MSD France	Propecia 1mg comprimé pelliculé	34009 349 065 4 1, 34009 349 066 0 2 34009 349 067 7 0 34009 349 068 3 1 34009 349 070 8 1	SE/H/0158/001	Film-coated tablets	1 mg
HR	Merck Sharp & Dohme d.o.o.	PROPECIA 1 mg filmom	UP/I-530-09/09-02/408	N/A	Film-coated tablets	1 mg

Proscar

PRODUCT: Proscar				
PSUR period: 19-Aug-12 to 18-Aug-13				
EU Member State	Local Product Name	Pharmaceutical Form	Strength	Authorisation number
Austria	Proscar 5 mg Tabletten	Film-coated tablets	5 mg	1-19689
Belgium	Proscar	Film-coated tablet	5 mg	922 IS 151 F3
Bulgaria	Proscar	Film-coated tablet	5mg	20011070
Croatia	Proscar 5 mg filmom obložene tablete	Film-coated tablet	5mg	UP/I-530-09/09-02/409
Cyprus	Proscar	Film-coated tablet	5mg	19539
Czech	Not registered	N/A	N/A	N/A
Denmark	Proscar	Film-coated tablet	5 mg	14514
Estonia	Not registered	N/A	N/A	N/A
Finland	Proscar	Film-coated tablet	5 mg	10751
France	Chibro-Proscar, comprimé pelliculé	Film-coated tablet	5 mg	3400933524845 (28 tablets PVC/Aluminum) 3400933524906 (28 tablets Aluminium/Aluminum) 3400933568849 (14 tablets PVC/Aluminum) 3400933568900 (14 tablets Aluminium/Aluminum) 3400933569150 (5 tablets Aluminium/Aluminum) 3400933569099 (5 tablets PVC/Aluminum) 3400937909075 (84 tablets PVC/Aluminum) 3400937909136 (90 tablets PVC/Aluminum)
Germany	Proscar 5 mg Filmtabletten	Filmcoated tablets	5 mg	42859.00.00
Greece	Proscar	FC tab	5 mg	55487/9-8-2010
Hungary	Proscar	Film-coated tablets	5 mg	OGYI-T-2186/01
Iceland	Not registered	N/A	N/A	
Ireland	Proscar 5mg Film Coated Tablet	Film coated tablets	5 mg	1286/17/1

Proscar, continued

PRODUCT: Proscar				
PSUR period: 19-Aug-12 to 18-Aug-13				
EU Member State	**Local Product Name**	**Pharmaceutical Form**	**Strength**	**Authorisation number**
Italy	Proscar 5 mg compresse rivestite con film	Film-coated tablets	5 mg	028308017 (15 tablets) 028308029 (30 tablets)
Latvia	Not registered	N/A	N/A	N/A
Liechtenstein	National via Switzerland , Proscar,	Film coated tablets	5 mg	51'774
Lithuania	Not registered	N/A	N/A	N/A
Luxembourg	Proscar	Film-coated tablet	5 mg	0483/03107721
Malta	Proscar	Film-coated tablet	5 mg	MA058/00701
Netherlands	Proscar	Film-coated tablet	5 mg	RVG 15482
Norway	Proscar	Tablets	5 mg	7841
Poland	PROSCAR	Film-coated tablets	5 mg	R/3621
Portugal	PROSCAR	Film-coated tablets	5 mg	2133189 (14) 2133288 (28) 2133387 (56)
	FINASTERIDA FROSST	Film-coated tablets	5 mg	2327484 (14) 2327583 (28) 2327682 (56)
Romania	PROSCAR	Film-coated tablets	5 mg	6268/2006/01-02
Slovakia	Not registered	N/A	N/A	N/A
Slovenia	PROSTIDE 5mg filmsko oblozene tablete	Film coated tablet	5 mg	5363-I-585/08
Spain	Proscar 5mg comprimidos con cubierta pelicular	Film coated tablet	5 mg	59.830
Sweden	Proscar	Filmcoated tablet	5 mg	11644/1991-0107
UK	Proscar 5mg film-coated TABLETS	Film-coated tablet	5 mg	PI 00025/0279

Annex 4. Overview of the data analysis
Substudy 1

Variable	Specification	Types of analysis														
		A	B	C	D		1	2	3	4	5	6	7	8	9	10
Period	Long follow-up (1994/1995-2013)	X	X													
	All periods available: Start: DK (1995), F (1994), N (2008) and S (July 2005) and end: 2013			X	X											
Country	Denmark and Finland	X	X	X	X											
	Norway and Sweden			X	X											
Dependent variable	Finasteride use versus non-use	X		X												
	Cumulative finasteride use		X		X											
Age	Age-stratified						X									
Cohort definition	Benign prostatic hyperplasia cohort							X								
	Compared to users of alpha-blockers								X							
Dependent variable	Years of use									X						
	Years since first use										X					
	Only including 5 mg finasteride											X				
	Change requirement for new users												X			
Surveillance bias	Stratified by variables associated with surveillance bias (Table 3 in protocol)													X		
Latency	Latency analyses														X	
Life-style factors	Analysis of self-reported life-style factors (substudy 1A)															X

Abbreviations: DK, Denmark; F, Finland; N, Norway; S, Sweden; ARI, 5alpha-reductase inhibitor. The letters and numbers of types of analyses refer to the analyses described in section 9.7.

Substudy 2

Variable	Specification	Types of analysis														
		A	B	C	D		1	2	3	4	5	6	7	8	9	10	11
Period	Long follow-up (1994/1995-2013)	X	X														
	All periods available: Start: DK (1995), F (1994), N (2008) and S (July 2005) and end: 2013			X	X												
Country	Denmark and Finland	X	X	X	X												
	Norway and Sweden			X	X												
Exposure	Finasteride use versus non-use	X		X													
	Cumulative finasteride use		X		X												
Age	Age-stratified						X										
Cohort definition	Benign prostatic hyperplasia cohort							X									
	Compared to users of alpha-blockers								X								
Exposure	Finasteride or dutasteride use (i.e. use of any ARI)									X							
	Years of use										X						
	Years since first use											X					
	Only including 5 mg finasteride												X				
	Persons with one prescription as exposed													X			
	Change requirement for new users														X		
Surveillance bias	Stratified by variables associated with surveillance bias (Table 3 in protocol)															X	
Latency	Latency analyses																X

Abbreviations: DK, Denmark; F, Finland; N, Norway; S, Sweden; ARI, 5alpha-reductase inhibitor. The letters and numbers of types of analyses refer to the analyses described in section 9.7.

Annex 5. QUALIFIED PERSON FOR PHARMACOVIGILANCE (QPPV)

Annex 3 Additional information

None.