ANNEX 1A TABLE WITH CODES

Type of variable	Derived variable	Codes or definition	Substudy 1	Substudy 2
Main variable of interest	Finasteride use (both dichotomous and cumulative use)	**ATC code:** G04CB01 – finasteride 5 mg **ATC code:** D11AX10 - finasteride 1 mg	X	X
Main outcome of interest	Male breast cancer in the study period	**ICD-10-CM:** C50 **ICD-7:** 170		X
Covariates from the national patient register	Testicular abnormalties/disorders(including but not limited to orchitis and cryptorchidism)	**ICD-8:** 257 Testicular dysfunction 603 Hydrocele 604 Orchitis and epididymitis 605 Redundant prepuce and phimosis 606 Sterility, male 607 Other diseases of male genital organs **ICD-9:** Sweden and Finland: 603, 604, 606, 607, 608, Sweden: 778G, Finland: 7786A **ICD-10:** N43-N51 (Hydroceles, spermatoceles, male sterility, infections in the male genitals) P83.5 (Hydroceles at birth)	X	X
	Benign prostatic hyperplasia (diagnosis and treatment)	**ICD-8:** 600 Hyperplasia of prostate **ICD-9:** Sweden: 600, Finland: 6000 (benign hyperplasia prostatae) **ICD-10:** N40 (BPH) **Danish procedure codes (treatment):** KKEA-KKEW	X	X
	Benign breast disease	**ICD-8:** 610 Chronic cystic disease of breast 611 Other diseases of breast **ICD-9:** 217 (Benign neoplasm of breast) **ICD-10:** D24 (Benign neoplasm of breast)	X	X
	Obesity	**ICD-8:** No codes found **ICD-9:** Sweden: 278A, Finland: 2780A, 2781A, 2788A **ICD-10:** E65,E66	X	X
	Liver cirrhosis	**ICD-8:** 570 Acute and subacute necrosis of liver 571 Cirrhosis of liver 572 Suppurative hepatitis and liver abscess 573 Other diseases of liver **ICD-9:** 570-573 **ICD-10:** K70 - K77 (Diseases of the liver and failure of the liver)	X	X
	Klinefelter's syndrome	**ICD-8:** No codes found **ICD-9:** Sweden: 758H, Finland: 7587A (Klinefelt´s syndrome); Sweden: 758.W-758X, Finland: 7588B, 7588E (other cond. due to sex chromosome) **ICD-10:** Q98 (Klinefelter´s syndrome and other disorders of the genome in males)	X	X
	Radiation exposure (including men treated with radiotherapy for pulmonary tuberculosis)	Danish procedure codes: UXRC10 (X-ray of the chest) UXRC12 (X-ray of the chest with contrast fluid) UXCC00 - UXCC77 (CAT scan of chest) Finnish procedure codes: AX099, GD1AA, GD1AD, HA0**, PJ020, QX099, WFO**, WA***, XX7** Swedish procedure codes: AA066-AA068, AD027-AD034, AE007-AE016, AF053, AG036-AG043, AH003, AJ038-AJ050, AK020-AK025, AM007, AN051-AN075, AN090, AV005, AV006, AV035, AV036, DA031, DJ007, DV040, AA011-AA017, AB001, AB054, AC004, AD005-AD007, AE001-AE003, AF017, AF018, AG007-AG009, AH001, AJ004-AJ013, AK002-AK004, AL002, AN009-AN029, AV013, ZV046	X	X
	Diabetes	**ICD-8:** 249, 250 **ICD-9:** 249, 250 **ICD-10:** E10-E14	X	X
	History of bone fracture	**ICD-8:** 820 (Hipfractures) 805 (Fractures of the back) 813 (Fractures of the wrist) 812 (Fractures of the upper arm) **ICD-9:** Sweden: 820, -821 (Hipfractures) 805C, 805E, 805W (Fractures of the back) 813E, -813F (Fractures of the wrist) 812A,812 B (Fractures of the upper arm) Finland: 820, 821 (Hipfractures) 805.2, 805.4, 805.8 (Fractures of the back) 813.4, 813.5 (Fractures of the wrist) 812 (Fracture of the upper arm) **ICD-10:** S72 (Hipfractures) S32 (Fractures of the back) S52 (Fractures of the wrist) S42 (Fractures of the upper arm)	X	X
	Gynaecomastia	**ICD-8:** No code **ICD-9:** No code **ICD-10:** N62 (Gynaecomasty)	X	X
	Number of surgeries	All surgical procedure codes	X	X
	Number of admissions	All in-hospital admissions	X	X
	Urinary retention	**ICD-8:** 596 Other diseases of bladder; 789 Abnormal urinary constituents of unspecified cause **ICD-9:** Sweden: 788B, 788C, 788D, Finland: 7881A, 7882A **ICD-10**: R33 (uninary retention)	X	X

Type of variable	Derived variable		Codes or definition	Substudy 1	Substudy 2
Covariates from the prescription register	Dutasteride use		**ATC code:** G04CB02		X
	α-blockers		**ATC code:** Denmark and Sweden: C02CA04 – Doxazosin G04CA03 – Terazosin Finland: C02CA G04CA	X	X
	Estrogen therapy		**ATC code:** G03A-G03X - Estrogens L02AA-L02AE - Hormone therapy in cancer treatment	X	X
	Use of drugs or exposure to environmental agents that cause or may cause gynaecomastia	Drugs other than finasteride and dutasteride that cause gynaecomastia	**ATC code:** L02BB03 – Bicalatamide L02BB01 – Flutamide L02BB02 – Nilutamide	X	X
		Anti-hypertensives	**ATC code:** C03DA01 - Spironolactone		
		Direct acting antivirals	**ATC code:** J05AE01- Saquinavir J05AE02 - Indinavir J05AE03 - Ritonavir J05AE04 - Nelfinavir J05AR10 - lopinavir & ritonavir J05AE05 - Amprenavir J05AE07 - Fosamprenavir J05AE08 - Atazanavir (nucl.rev.transc.inhib.) J05AE09 - Tipranovir J05AE10 - Darunavir J05AE11 - Teleprevir J05AE12 - Boceprevir J05AF01 – Zidovudine J05AF04 - Stavudine J05AF05 - Lamivudine J05AR01 - Zidovudine & Lamivudine J05AR02 - Lamivudine & Abacavir J05AR04 - Zidivudine, Lamivudir & Abacavir J05AR05 - zidivudine, Lamivudine & Nevirapine J05AR07 - Stavudine, Lamivudine & Nevirapine J05AR11 - Lamivudine, Tenofir disopoxil & Efavirenz		
		Phenothrin	**ATC code:** P03AC03 - Phenotrim P03AC53 - Phenotrim combinations		
		Exogeneous hormones	**ATC code:** G03CA- G03CX - Estrogen		
			ATC code: H02AB07 - Prednisone		
		Gastrointestinal agents	**ATC code:** A02BA01 - Cimetidine A02BA53 - Cimetidine combinations		
		anti-hormones	**ATC code:** L02BA01-03 - Anti-estrogens L02BB01-04 - Antiandrogens L02BG01-06 - Aromatase inhibitors L02BX - Other hormone antagonists and related agents		
	Number of prescription		All ATC	X	X
Other covariates from registers	Occupational exposure. Perfume industry, high-temperature environments and night shift work Denmark: Register-based labour force Finland: Censuses Norway: Censuses Sweden: Register-based labour force behavior; place of work; employer etc. (source: LISA)		Denmark. Uses the variable branche_kode Perfume industry: 245110, 245200, 930210, 930220, 244100, 244200 High-temperature: 271000, 273500, 274100, 274200, 274300, 274400, 274500, 272100, 275100, 275200, 275300, 275400, 284000, 752500 Finland. Variable amko in 1990 and variable ammattikoodi in 1995, 2000, 2005 and 2010 Perfume industry: amko: 840, 841 and ammattikoodi: 5141, 8221 High-temperature: amko: 630-633, 639, 655, 800 and ammattikoodi: 5161, 7212, 7221, 8121-8123, 8152, 8162 Sweden: Variable Ssyk4 (Standard för svensk yrkesklassificiering 96): Perfume industry: 5141, 5151 High temperature: 7221,7322,8111, 8121, 8122, 8123, 8125, 8221	X	X
	Socioeconomic position		Years of education	X	X
	Family history of breast cancer		Family (first degree-relatives)	X	X
			Cancer diagnosis among relatives (Breast cancer as per code ICD-10-CM: C50 and ICD-7: 170)		
	Living as a single man		Denmark: Variable familie_type = 5 Finland: Variable pety = . Sweden: Variable single=1 if living alone, single=0 if married or living with a partner.	X	X
	Urban and rural differences		Denmark: Variable bystoerrelseskode. Values 1-10 is urban and value 13 is rural. Finland: Variable taajama_k2. Value 1 is urban and value 0 is rural. Sweden: Variable urban (see Danish classification of urbanization, for Sweden variable urban is based on population size of municipality).	X	X
	Cancer history for controls (in order to exclude those with previous cancer as done among male breast cancer cases)		All cancers (except non-melanoma skin cancer) for controls		X
Other covariates from surveys	CPR-number/pnr		Country specific codes	X	
	Height				
	Weight				
	Alcohol intake				
	Smoking				

Type of variable	Derived variable	Codes or definition	Substudy 1	Substudy 2
	Physical inactivity			
	Dietary intake of fruit and vegetables			
	Dietary intake of animal fat			

ANNEX 1B SAMPLING OF CONTROLS

Annex 1B_Sampling of controls_19DEC2017.txt

```
*************************************************************************************************************
*       Generelt udtræksprogram til dannelses af kontrol populationer. I programmet skal angives:
*
*       1)- match kriterier


*
*       2) - antallet af kontroller pr. case

                                                                                                        *
*       NB


*
*       Hvis der ikke kan findes kontroller nok tages ALLE dem ud der opfylder match kriterier (Kan evt være tilfældet for meget gamle peroner)      *
*       Forlæbsregisteret er endnu ikke færdigdannet, så programmet er pt. ikke testet
                                                *
*************************************************************************************************************

* seed start - Just a positive number should be put here to set the seed ;
%let seedstart=234 ;

* Hvor mange kontroller ønskes der pr. case?;
%let antalk=100;

* Visse personer har ugyldige cpr-numre. De vælges fra;
data pop;
set projekt.pop_case;
if tjek="0";
run;

* Alle med gyldige cpr numre der fra befolkningens forløbsregiser (BEFFOR) kan potentielt indgå som kontroller;
data kpop1;
beffor.beffor2014 (keep=pnr where=(pnr^=" "));
run;


* Antal cases;
proc sql noprint;
        select count(*) into :antalcases from pop;
quit;

%macro kontrolgruppe;

proc delete
        data=kontrol;
run;

%do i=1 %to &antalcases.;
* For hver case lægges matchkriterier i makrovariable;
data _null_;
set pop;
if _n_=&i then do;
call symput ("pnr_casae",pnr);
call symput ("foed_aar",foed_aar);
call symput ("koen",koen);
call symput ("indexdato",indexdato);
```

```
end;
run;


* •     Alle i bruttopopulationen er mulige kontroller, bortset fra personer der
også er cases og som har indexdato <=indexdato for den case der udtrækkes kontroller
for;
data kpop_tmp;
merge kpop&i.(in=in_brutto where=( (status="aktiv") and (&indexdato.>= startdato)
and (&indexdato.< slutdato) ) pop(in=in_case where=(indexdato<=&indexdato.));
by pnr;
if not in_case then output;
run;


* Der udvælges nu antalk (=antal kontroller) observationer ved Simple Random
Sampling ud fra det relevante stratum af alle potentielle kontrolgruppepersoner
URS;
* Se SAS-dokumentation for denne proc på:
http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#sur
veyselect_toc.htm;

proc surveyselect OUTHITS data=kpop_tmp method=URS seed=(&seedstart)+2**&i.
n=&antalk out=kontrol1_&i. noprint;
where foed_aar="&foed_aar." and koen="&koen.";
run;

data kontrol2_&i;
set kontrol1_&i;
label pnr="Kontrol-PNR" pnr_case="Case-PNR";
pnr_case="&pnr_case.";
run;

* De udvalgte lægges over i en samlet kontrolgruppe;
proc append base=kontrol data=kontrol2_&i;
run;

* De udtrukne kontrolpersoner ligger i et datasæt, der nu kan slettes;
proc datasets lib=work noprint;
delete kpop&i kontrol1_&i kontrol2_&i;
quit;
%end;
%mend;

%kontrolgruppe;
```

ANNEX 1C FIN TABLES CLEAN

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

Tables

Version 1: 25 September 2014

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PPD

- PPD
- PPD

PPD

- PPD
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- PPD

National scientific coordinators

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- Finland: PPD
- Norway: TBD
- Sweden: PPD

Expert group

- PPD Denmark
- PPD Denmark

Additional experts will be included as the project starts

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Background tables

Table 0.1. Descriptive analysis of the Nordic populations by country, age and sex by 1st January 2010

	Denmark	Finland	Sweden
Population size	5,534,738	5,351,427	9,340,682
Men, *n (%)*	2,743,286 (49.6)	2,625,067 (49.1)	4,649,014(49.8)
Age, *n (%)*			
- 0-34	1,192,453 (43.5)	1,140,985 (43.5)	2,022,577 (43.5)
- 35-64	1,151,086 (42.0)	1,108,744 (42.2)	1,872,829 (40.3)
- 65+	399,747 (14.6)	375,338 (14.3)	753,608 (16.2)

Source: Nordic Co-operation: Nordic Statistics. Webpage: http://www.norden.org/da/fakta-om-norden/tal-og-statistik. Choose Nordic Statistics >> Population >> Population size and change >> CITI01: Population 1 January by reporting country, time, citizenship, sex and age.

Table 0.1 shows the total population size, male proportion and age distribution in Denmark, Finland and Sweden.

Table 0.2. Descriptive analysis of breast cancer incidence in the Nordic male population by country and calendar time

	Denmark	Finland	Sweden
Number of cases, *n*	560	376	797
Incidence rate per 100,000 person-years	1.00 (0.92-1.08)	0.70 (0.63-0.77)	0.84 (0.78-0.90)
Incidence rate by age per 100,000 person-years			
- 0-34	0.03 (0.01-0.06)	0.02 (0.01-0.06)	0.01 (0.01-0.03)
- 35-64	0.74 (0.64-0.86)	0.71 (0.61-0.83)	0.71 (0.63-0.81)
- 65+	4.94 (4.47-5.46)	2.94 (2.56-3.37)	3.53 (3.24-3.85)
Incidence rate by calendar time per 100,000 person-years			
- 1994-1999	0.92 (0.78-1.08)	0.54 (0.43-0.67)	0.76 (0.66-0.87)
- 2000-2004	1.00 (0.85-1.19)	0.58 (0.46-0.73)	0.86 (0.75-1.00)
- 2005-2009	0.83 (0.69-1.00)	0.74 (0.61-0.90)	0.88 (0.77-1.01)
- 2010-2013	1.24 (1.07-1.44)	0.94 (0.79-1.12)	0.88 (0.76-1.00)

Source: Information for this table is obtained from the NORDCAN database (Engholm G, Ferlay J, Christensen N, Kejs AMT, Hertzum-Larsen R, Johannesen TB, Khan S, Leinonen MK, Ólafsdóttir E, Petersen T, Schmidt LKH, Trykker H, Storm HH. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 7.3 (08.07.2016). Association of the Nordic Cancer Registries. Danish Cancer Society).

Table 0.2 shows the incidence rate of male breast cancer in Denmark, Finland and Sweden overall and stratified by age and calendar year. The incidence rate is highest in Denmark and lowest in Finland. The incidence rate increases by age. There is no clear temporal pattern.

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Substudy 1

Objective: Describe finasteride users compared to non-users with respect to potential confounding factors

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Table 1.1. Descriptive analysis of male finasteride users (both finasteride use versus non-use and cumulative finasteride use versus non-use) with respect to potential confounding factors. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Numbers (%) if nothing else is stated

Potential confounding factors	Finasteride users				Finasteride non-users
	User	Cumulative use (3)			
	2+ redemptions	2-3 packs	4-6 packs	7+ packs	<2 redemptions
N	139,640	119,629	90,599	69,581	139,640
Age, *mean (standard deviation)*	69.9 (10.2)	70.5 (9.8)	71.4 (9.4)	72.3 (9.0)	51.3 (15.0)
Increased estrogen and decreased androgen levels					
- Testicular-abnormalities /disorders	9,963 (7.1)	8,785 (7.3)	6,827 (7.5)	5,336 (7.7)	7,541 (5.4)
- Benign breast disease	254 (0.2)	209 (0.2)	159 (0.2)	126 (0.2)	213 (0.2)
- Obesity	1,729 (1.2)	1,589 (1.3)	1,237 (1.4)	955 (1.4)	1,072 (0.8)
- Liver cirrhosis	1,751 (1.3)	1,520 (1.3)	1,196 (1.3)	894 (1.3)	1,385 (1.0)
- Klinefelter's syndrome	5 (0.0)	3 (0.0)	4 (0.0)	<3 (-)	14 (0.0)
- Estrogen therapy	2,906 (2.1)	2,558 (2.1)	2,018 (2.2)	1,553 (2.2)	1,586 (1.1)
- Occupational exposures (1)	611 (0.4)	487 (0.4)	329 (0.4)	212 (0.3)	1,559 (1.1)
Family exposures					
- Family history of breast cancer	2,822 (2.0)	2,543 (2.1)	1,978 (2.2)	1,551 (2.2)	4,922 (3.5)
Ionizing radiation and cancer treatment					
- Radiation exposure (2)	5,469 (3.9)	5,264 (4.4)	4,121 (4.6)	3,259 (4.7)	2,753 (2.0)
Socio-economic differences					
- Socio-economic position					
- Low (<9 years of education)	73,542 (52.7)	62,551 (52.3)	47,891 (52.9)	37,164 (53.4)	50,746 (36.3)
- Medium (10-12 years of education)	37,140 (26.6)	31,531 (26.4)	23,185 (25.6)	17,403 (25.0)	56,283 (40.3)
- High (>12 years of education)	28,958 (20.7)	25,547 (21.4)	19,523 (21.6)	15,014 (21.6)	32,611 (23.4)
- Living as a single man	32,690 (23.4)	27,995 (23.4)	21,272 (23.5)	16,648 (23.9)	35,187 (25.2)
- Living in urban area	113,834 (81.5)	97,629 (81.6)	73,845 (81.5)	56,805 (81.6)	116,866 (83.7)
Other factors					

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Table 1.1. Descriptive analysis of male finasteride users (both finasteride use versus non-use and cumulative finasteride use versus non-use) with respect to potential confounding factors. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Numbers (%) if nothing else is stated

Potential confounding factors	Finasteride users				Finasteride non-users
	User	Cumulative use (3)			
	2+ redemptions	2-3 packs	4-6 packs	7+ packs	<2 redemptions
- Diabetes	9,272 (6.6)	8,367 (7.0)	6,683 (7.4)	5,387 (7.7)	4,878 (3.5)
- History of bone fractures	5,582 (4.0)	4,950 (4.1)	3,827 (4.2)	3,022 (4.3)	4,203 (3.0)

(1) Having worked in perfume industry or in high-temperature environment.

(2) Including men treated with radiotherapy for pulmonary tuberculosis.

(3) One pack defined as 98 pills of 5 mg.

Table 1.1 is a descriptive table of finasteride users (binary and cumulative use) compared to the control population in Denmark and Finland. The study population includes 139,640 finasteride users and controls. Finasteride users are older and have more often been diagnosed with testicular abnormalities, obesity, liver cirrhosis, use estrogen therapy, have been exposed to radiation, have lower educational level, less often live alone, have diabetes and bone fractures and are less often exposed to occupational exposures and fewer have had an event of breast cancer in the family compared to the control population.

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Table 1.2. Descriptive analysis of male finasteride users (finasteride use versus non-use and cumulative finasteride use versus non-use) with respect to potential confounding factors. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Numbers (%) if nothing else is stated

Potential confounding factors	Finasteride users				Finasteride non-users
	User	Cumulative use			
	2+ redemptions	2-3 packs	4-6 packs	7+ packs	<2 redemptions
N	246,508	222,489	168,908	125,462	246,508
Age, *mean (standard deviation)*	71.1 (10.2)	71.7 (9.7)	72.5 (9.3)	73.4 (9.0)	53.3 (14.7)
Increased estrogen and decreased androgen levels					
- Testicular-abnormalities /disorders	20,280 (8.2)	18,813 (8.5)	14,865 (8.8)	11,397 (9.1)	14,577 (5.9)
- Benign breast disease	297 (0.1)	250 (0.1)	192 (0.1)	150 (0.1)	280 (0.1)
- Obesity	3,438 (1.4)	3,261 (1.5)	2,612 (1.6)	1,979 (1.6)	2,369 (1.0)
- Liver cirrhosis	2,970 (1.2)	2,692 (1.2)	2,104 (1.3)	1,537 (1.2)	2,308 (0.9)
- Klinefelter's syndrome	17 (0.0)	15 (0.0)	13 (0.0)	9 (0.0)	44 (0.0)
- Estrogen therapy	3,573 (1.5)	3,205 (1.4)	2,567 (1.5)	1,910 (1.5)	2,406 (1.0)
- Occupational exposures (1)	2,426 (1.0)	2,242 (1.0)	1,641 (1.0)	1,139 (0.9)	4,248 (1.7)
Family exposures					
- Family history of breast cancer	11,193 (4.5)	10,691 (4.8)	8,160 (4.8)	6,075 (4.8)	13,235 (5.4)
Ionizing radiation and cancer treatment					
- Radiation exposure (2)	11,481 (4.7)	11,170 (5.0)	9,028 (5.3)	7,214 (5.8)	6,083 (2.5)
Socio-economic differences					
- Socio-economic position					
- Low (<9 years of education)	118,661 (48.1)	106,070 (47.7)	80,970 (47.9)	60,149 (47.9)	78,290 (31.8)
- Medium (10-12 years of education)	74,892 (30.4)	67,952 (30.5)	50,926 (30.2)	37,581 (30.0)	104,527 (42.4)
- High (>12 years of education)	52,955 (21.5)	48,467 (21.8)	37,012 (21.9)	27,732 (22.1)	63,691 (25.8)
- Living as a single man	69,605 (28.2)	63,237 (28.4)	48,029 (28.4)	35,589 (28.4)	83,328 (33.8)
- Living in urban area	194,755 (79.0)	175,384 (78.8)	133,063 (78.8)	99,090 (79.0)	200,857 (81.5)
Other factors					

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Table 1.2. Descriptive analysis of male finasteride users (finasteride use versus non-use and cumulative finasteride use versus non-use) with respect to potential confounding factors. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Numbers (%) if nothing else is stated

Potential confounding factors	Finasteride users				Finasteride non-users
	User	Cumulative use			
	2+ redemptions	2-3 packs	4-6 packs	7+ packs	<2 redemptions
- Diabetes	22,045 (8.9)	20.859 (9.4)	16,747 (9.9)	12,969 (10.3)	10,772 (4.4)
- History of bone fractures	11,361 (4.6)	10,562 (4.8)	8,333 (4.9)	6,355 (5.1)	8,165 (3.3)

(1) Having worked in perfume industry or in high-temperature environment.

(2) Including men treated with radiotherapy for pulmonary tuberculosis.

(3) One pack defined as 98 pills of 5 mg.

Table 1.2 is a descriptive table of finasteride users (binary and cumulative use) compared to the control population in all three countries. The study population includes 246,508 finasteride users and controls. Finasteride users are older and more often have testicular abnormalities, obesity, liver cirrhosis, use estrogen therapy, are exposed to radiation, have lower educational level, less often live in urban areas, less often live alone, have diabetes and bone fractures and are less often exposed to occupational exposures and have less often a family history of breast cancer than the control population.

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Table 1.3. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014.

	Age-, year- and country-adjusted				Adjusted (1)			
	2+ redemp	2-3 packs	4-6 packs	7+ packs	2+ redemp	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities /disorders	1.26 (1.21-1.31)	1.27 (1.22-1.32)	1.26 (1.20-1.32)	1.24 (1.18-1.30)	1.27 (1.22-1.32)	1.27 (1.22-1.33)	1.27 (1.21-1.32)	1.25 (1.19-1.31)
- Benign breast disease	1.19 (0.94-1.51)	1.16 (0.90-1.49)	1.11 (0.85-1.46)	1.14 (0.85-1.53)	1.20 (0.94-1.52)	1.17 (0.91-1.51)	1.14 (0.87-1.49)	1.16 (0.87-1.56)
- Obesity	1.33 (1.22-1.46)	1.38 (1.26-1.51)	1.42 (1.29-1.56)	1.43 (1.29-1.59)	1.35 (1.24-1.48)	1.40 (1.28-1.54)	1.44 (1.30-1.59)	1.45 (1.30-1.62)
- Liver cirrhosis	0.96 (0.89-1.05)	0.95 (0.87-1.04)	0.98 (0.89-1.07)	0.93 (0.84-1.03)	0.96 (0.88-1.05)	0.95 (0.87-1.04)	0.98 (0.89-1.08)	0.93 (0.84-1.03)
- Klinefelter's syndrome	2.51 (0.73-8.59)	1.76 (0.38-8.10)	4.15 (0.96-18.00)	4.92 (0.75-32.37)	2.85 (0.83-9.83)	2.06 (0.44-9.69)	5.23 (1.19-23.10)	6.52 (1.00-42.64)
- Estrogen therapy	0.82 (0.76-0.88)	0.77 (0.72-0.83)	0.71 (0.66-0.77)	0.66 (0.61-0.72)	0.79 (0.73-0.84)	0.74 (0.69-0.80)	0.69 (0.64-0.74)	0.64 (0.59-0.69)
- Occupational exposures (2)	1.05 (0.93-1.18)	1.05 (0.92-1.20)	1.06 (0.91-1.23)	1.07 (0.89-1.28)	1.08 (0.96-1.21)	1.09 (0.95-1.24)	1.09 (0.94-1.27)	1.10 (0.92-1.31)
Family exposures								
- Family history of breast cancer	1.06 (1.00-1.13)	1.07 (1.00-1.14)	1.10 (1.02-1.18)	1.12 (1.04-1.22)	1.05 (0.98-1.11)	1.05 (0.99-1.12)	1.08 (1.01-1.16)	1.11 (1.02-1.20)
Ionizing radiation and cancer treatment								
- Radiation exposure (3)	1.27 (1.21-1.34)	1.28 (1.22-1.36)	1.26 (1.19-1.33)	1.22 (1.14-1.29)	1.27 (1.20-1.34)	1.28 (1.21-1.35)	1.25 (1.18-1.33)	1.21 (1.14-1.29)
Socio-economic differences								
- Socio-economic position								
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years)	1.12 (1.09-1.15)	1.15 (1.12-1.18)	1.17 (1.14-1.20)	1.18 (1.15-1.22)	1.12 (1.09-1.14)	1.15 (1.12-1.17)	1.17 (1.14-1.20)	1.18 (1.15-1.22)
- High (>12 years of education)	1.39 (1.36-1.43)	1.44 (1.40-1.48)	1.46 (1.41-1.50)	1.46 (1.42-1.51)	1.40 (1.36-1.44)	1.44 (1.40-1.49)	1.47 (1.42-1.51)	1.47 (1.42-1.52)
- Living as single man year before	0.91 (0.89-	0.89 (0.87-	0.87 (0.85-0.89)	0.86 (0.84-0.89)	0.93 (0.91-	0.91 (0.89-	0.89 (0.87-0.92)	0.89 (0.86-0.91)

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	0.93)	0.91)			0.95)	0.93)		
- Living in urban area 1 year before	1.00 (0.97-1.02)	1.00 (0.97-1.03)	0.99 (0.96-1.01)	0.99 (0.96-1.02)	0.96 (0.94-0.99)	0.96 (0.93-0.98)	0.94 (0.91-0.97)	0.94 (0.91-0.97)
Other factors								
- Diabetes	0.98 (0.94-1.02)	0.98 (0.94-1.03)	1.00 (0.96-1.04)	1.01 (0.96-1.06)	0.97 (0.93-1.01)	0.97 (0.93-1.02)	0.99 (0.95-1.03)	1.01 (0.96-1.06)
- History of bone fractures	0.97 (0.93-1.02)	0.97 (0.93-1.03)	0.96 (0.91-1.01)	0.93 (0.88-0.99)	0.98 (0.94-1.03)	0.99 (0.94-1.04)	0.97 (0.92-1.03)	0.95 (0.90-1.01)

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

(2) Having worked in perfume industry or in high-temperature environment.

(3) Including men treated with radiotherapy for pulmonary tuberculosis.

Table 1.3 shows the association between potential confounding factors and finasteride use both in age-, year- and country adjusted models and mutually adjusted models. The full adjustment only has minor influence on the odds ratios. The following potential confounding factors are associated with higher odds of finasteride use: testicular abnormalities, obesity, radiation exposure, and higher socio-economic position. The following factors are 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, but Klinefelter's syndrome was found to be positively associated with finasteride use in this analysis (i.e., cumulative use of 4-6 and 7+ packs).

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Table 1.4. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

	Age-, year- and country-adjusted				Adjusted (1)			
	2+ redemp	2-3 packs	4-6 packs	7+ packs	2+ redemp	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities /disorders	1.42 (1.38-1.46)	1.43 (1.39-1.48)	1.46 (1.41-1.50)	1.48 (1.43-1.53)	1.42 (1.38-1.46)	1.43 (1.39-1.47)	1.46 (1.41-1.50)	1.47 (1.42-1.52)
- Benign breast disease	1.11 (0.89-1.37)	1.08 (0.86-1.35)	1.07 (0.83-1.37)	1.11 (0.85-1.45)	1.11 (0.90-1.37)	1.09 (0.87-1.37)	1.09 (0.85-1.39)	1.14 (0.87-1.48)
- Obesity	1.35 (1.27-1.43)	1.38 (1.29-1.47)	1.45 (1.35-1.55)	1.47 (1.37-1.59)	1.32 (1.24-1.40)	1.35 (1.26-1.44)	1.40 (1.31-1.50)	1.43 (1.32-1.54)
- Liver cirrhosis	1.02 (0.96-1.09)	1.01 (0.94-1.08)	1.02 (0.95-1.09)	0.98 (0.91-1.06)	1.01 (0.94-1.07)	0.99 (0.93-1.06)	1.00 (0.93-1.08)	0.96 (0.89-1.04)
- Klinefelter's syndrome	1.29 (0.63-2.64)	1.19 (0.55-2.60)	1.76 (0.75-4.11)	2.10 (0.76-5.78)	1.35 (0.66-2.76)	1.25 (0.57-2.71)	1.89 (0.81-4.39)	2.14 (0.77-5.96)
- Estrogen therapy	0.57 (0.54-0.61)	0.54 (0.51-0.57)	0.52 (0.48-0.55)	0.47 (0.44-0.50)	0.56 (0.52-0.59)	0.52 (0.49-0.55)	0.50 (0.47-0.53)	0.46 (0.43-0.49)
- Occupational exposures (2)	0.89 (0.84-0.95)	0.90 (0.84-0.96)	0.89 (0.83-0.96)	0.90 (0.83-0.98)	0.93 (0.87-0.99)	0.94 (0.88-1.00)	0.93 (0.87-1.00)	0.95 (0.87-1.03)
Family exposures								
- Family history of breast cancer	1.01 (0.98-1.04)	1.02 (0.99-1.06)	1.03 (0.99-1.07)	1.07 (1.02-1.11)	1.00 (0.97-1.04)	1.02 (0.98-1.05)	1.02 (0.99-1.06)	1.06 (1.02-1.10)
Ionizing radiation and cancer treatment								
- Radiation exposure (3)	1.24 (1.20-1.29)	1.24 (1.19-1.29)	1.23 (1.18-1.28)	1.22 (1.17-1.27)	1.23 (1.19-1.28)	1.23 (1.19-1.28)	1.22 (1.17-1.27)	1.21 (1.16-1.26)
Socio-economic differences								
- Socio-economic position								
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years)	1.09 (1.07-1.11)	1.11 (1.09-1.13)	1.13 (1.10-1.15)	1.17 (1.15-1.20)	1.08 (1.07-1.10)	1.10 (1.08-1.12)	1.12 (1.10-1.15)	1.17 (1.15-1.19)
- High (>12 years of education)	1.29 (1.26-1.31)	1.30 (1.27-1.33)	1.32 (1.29-1.35)	1.37 (1.33-1.40)	1.29 (1.26-1.31)	1.30 (1.27-1.33)	1.32 (1.29-1.35)	1.37 (1.34-1.41)
- Living as a single man year before	0.88 (0.87-0.89)	0.86 (0.85-0.88)	0.85 (0.84-0.87)	0.84 (0.82-0.85)	0.89 (0.88-0.91)	0.87 (0.86-0.89)	0.86 (0.85-0.88)	0.85 (0.83-0.87)

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- Living in urban area one year before	1.00 (0.99-1.02)	1.00 (0.98-1.01)	0.99 (0.97-1.01)	0.99 (0.97-1.01)	0.97 (0.95-0.99)	0.96 (0.95-0.98)	0.95 (0.93-0.97)	0.95 (0.93-0.97)
Other factors								
- Diabetes	1.09 (1.06-1.12)	1.10 (1.07-1.13)	1.12 (1.09-1.16)	1.14 (1.11-1.18)	1.08 (1.05-1.11)	1.08 (1.05-1.11)	1.10 (1.07-1.14)	1.13 (1.09-1.16)
- History of bone fractures	0.99 (0.95-1.02)	0.99 (0.96-1.03)	0.99 (0.96-1.03)	0.98 (0.94-1.02)	0.99 (0.96-1.03)	1.00 (0.96-1.04)	1.00 (0.96-1.04)	0.99 (0.95-1.03)

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

(2) Having worked in perfume industry or in high-temperature environment.

(3) Including men treated with radiotherapy for pulmonary tuberculosis.

Table 1.4 includes Sweden. Overall, the associations are similar to the results reported in Table 1.3 with the following differences: Estrogen therapy shows even lower odds ratio, occupational exposure is associated with lower odds of finasteride use (only for 2+ redemptions), socio-economic position shows less strong increased odds ratio and diabetes are associated with increased finasteride use.

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Supplementary analysis 1

Table 1.5. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1995/1997 to 2013/2014. Analysis stratified by age.

	Below age 65 years (1)				65 years and older (1)			
	2+ redemp	2-3 packs	4-6 packs	7+ packs	2+ redemp	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities /disorders	1.46 (1.37-1.56)	1.50 (1.40-1.60)	1.51 (1.40-1.64)	1.55 (1.41-1.70)	1.15 (1.09-1.21)	1.16 (1.10-1.22)	1.17 (1.11-1.23)	1.15 (1.09-1.22)
- Benign breast disease	1.22 (0.86-1.73)	1.18 (0.80-1.75)	1.05 (0.65-1.70)	1.13 (0.67-1.93)	1.18 (0.85-1.63)	1.19 (0.85-1.65)	1.20 (0.86-1.69)	1.19 (0.83-1.70)
- Obesity	1.25 (1.10-1.42)	1.31 (1.14-1.50)	1.37 (1.17-1.59)	1.40 (1.18-1.66)	1.41 (1.24-1.61)	1.43 (1.25-1.62)	1.43 (1.25-1.64)	1.42 (1.23-1.63)
- Liver cirrhosis	1.01 (0.90-1.14)	1.01 (0.88-1.15)	1.04 (0.90-1.20)	0.96 (0.81-1.15)	0.92 (0.81-1.03)	0.91 (0.81-1.02)	0.94 (0.83-1.07)	0.90 (0.79-1.03)
- Klinefelter's syndrome	1.46 (0.42-5.09)	1.03 (0.20-5.23)	2.56 (0.52-12.50)	3.60 (0.51-25.58)	NA	NA	NA	NA
- Estrogen therapy	2.26 (1.98-2.57)	2.10 (1.83-2.41)	1.86 (1.59-2.17)	1.82 (1.53-2.17)	0.53 (0.49-0.57)	0.53 (0.49-0.58)	0.54 (0.50-0.59)	0.52 (0.47-0.56)
- Occupational exposures (2)	1.07 (0.94-1.21)	1.08 (0.94-1.25)	1.06 (0.90-1.26)	1.13 (0.92-1.38)	1.24 (0.88-1.75)	1.22 (0.86-1.74)	1.34 (0.94-1.92)	1.08 (0.73-1.59)
Family exposures								
- Family history of breast cancer	1.03 (0.96-1.11)	1.03 (0.95-1.11)	1.07 (0.98-1.17)	1.09 (0.98-1.21)	1.01 (0.90-1.13)	1.02 (0.91-1.15)	1.04 (0.93-1.17)	1.09 (0.97-1.23)
Ionizing radiation and cancer treatment								
- Radiation exposure (3)	1.27 (1.15-1.41)	1.32 (1.19-1.46)	1.30 (1.16-1.46)	1.27 (1.11-1.46)	1.27 (1.19-1.35)	1.25 (1.18-1.34)	1.22 (1.15-1.31)	1.18 (1.10-1.27)
Socio-economic differences								
- Socio-economic position								
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years)	1.10 (1.06-1.14)	1.14 (1.10-1.18)	1.16 (1.11-1.21)	1.17 (1.11-1.23)	1.16 (1.12-1.20)	1.16 (1.12-1.20)	1.18 (1.13-1.22)	1.19 (1.14-1.23)
- High (>12 years of education)	1.45 (1.39-	1.51 (1.45-	1.50 (1.43-1.58)	1.48 (1.40-1.56)	1.33 (1.28-1.38)	1.37 (1.31-	1.42 (1.37-	1.46 (1.40-

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	1.50)	1.57)				1.42)	1.48)	1.52)
- Living as a single man year before	0.97 (0.94-1.01)	0.93 (0.90-0.97)	0.91 (0.87-0.95)	0.87 (0.83-0.92)	0.89 (0.87-0.92)	0.89 (0.86-0.92)	0.88 (0.85-0.91)	0.89 (0.86-0.92)
- Living in urban area 1 year before	1.00 (0.97-1.04)	0.99 (0.95-1.03)	0.97 (0.92-1.01)	0.97 (0.92-1.02)	0.92 (0.88-0.95)	0.92 (0.89-0.96)	0.92 (0.88-0.95)	0.92 (0.88-0.95)
Other factors								
- Diabetes	1.05 (0.98-1.14)	1.07 (0.99-1.16)	1.10 (1.01-1.20)	1.15 (1.04-1.27)	0.94 (0.89-0.98)	0.95 (0.90-0.99)	0.96 (0.92-1.01)	0.98 (0.92-1.03)
- History of bone fractures	1.04 (0.96-1.13)	1.07 (0.98-1.17)	1.06 (0.95-1.17)	0.97 (0.86-1.10)	0.95 (0.90-1.01)	0.95 (0.89-1.01)	0.94 (0.88-1.01)	0.95 (0.89-1.01)

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

(2) Having worked in perfume industry or in high-temperature environment.

(3) Including men treated with radiotherapy for pulmonary tuberculosis.

NA, Parameter estimates for Klinefelter's syndrome could not be estimated due to too few individuals with the syndrome

Table 1.5 shows age-stratified analyses. Generally, the odds ratios are similar for both age-groups although with some variations. The variables showing clear differences between the age-groups are testicular abnormalities showing stronger estimates for men below 65 years, living in urban areas being associated with lower odds of finasteride use among men above 65 years, but not among men below 65 year and estrogen therapy showing increased odds ratio among men below 65 years and decreased odds ratio among men above age 65 years.

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Table 1.6. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Analysis stratified by age.

	Below age 65 years (1)				65 years and older (1)			
	2+ redemp	2-3 packs	4-6 packs	7+ packs	2+ redemp	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities /disorders	1.54 (1.48-1.61)	1.59 (1.51-1.67)	1.63 (1.54-1.73)	1.69 (1.58-1.81)	1.34 (1.30-1.39)	1.35 (1.30-1.40)	1.39 (1.34-1.44)	1.41 (1.36-1.47)
- Benign breast disease	1.12 (0.82-1.53)	1.09 (0.77-1.54)	1.07 (0.71-1.61)	1.22 (0.77-1.93)	1.12 (0.84-1.51)	1.13 (0.84-1.53)	1.15 (0.85-1.57)	1.13 (0.82-1.57)
- Obesity	1.32 (1.21-1.45)	1.37 (1.25-1.51)	1.47 (1.32-1.64)	1.53 (1.35-1.74)	1.30 (1.19-1.42)	1.30 (1.19-1.42)	1.33 (1.22-1.46)	1.35 (1.23-1.49)
- Liver cirrhosis	1.05 (0.95-1.16)	1.03 (0.93-1.15)	1.05 (0.93-1.18)	1.01 (0.88-1.16)	0.96 (0.88-1.04)	0.95 (0.87-1.04)	0.97 (0.88-1.06)	0.93 (0.84-1.02)
- Klinefelter's syndrome	0.94 (0.39-2.23)	0.84 (0.31-2.31)	1.39 (0.48-4.03)	2.25 (0.66-7.62)	1.58 (0.34-7.37)	1.60 (0.34-7.46)	1.67 (0.34-8.14)	1.38 (0.26-7.26)
- Estrogen therapy	2.04 (1.80-2.30)	1.87 (1.64-2.13)	1.69 (1.46-1.96)	1.62 (1.37-1.91)	0.40 (0.38-0.43)	0.40 (0.38-0.43)	0.41 (0.39-0.44)	0.39 (0.36-0.42)
- Occupational exposures (2)	0.94 (0.86-1.03)	0.96 (0.87-1.05)	0.93 (0.83-1.04)	1.04 (0.91-1.20)	0.91 (0.82-1.00)	0.91 (0.83-1.00)	0.92 (0.84-1.02)	0.89 (0.80-0.99)
Family exposures								
- Family history of breast cancer	0.98 (0.93-1.02)	1.00 (0.95-1.05)	1.02 (0.96-1.08)	1.07 (1.00-1.15)	1.00 (0.96-1.05)	1.01 (0.96-1.06)	1.01 (0.97-1.06)	1.05 (1.00-1.10)
Ionizing radiation and cancer treatment								
- Radiation exposure (3)	1.26 (1.17-1.35)	1.26 (1.17-1.35)	1.25 (1.15-1.35)	1.24 (1.12-1.37)	1.23 (1.18-1.28)	1.22 (1.17-1.27)	1.20 (1.15-1.26)	1.19 (1.14-1.25)
Socio-economic differences								
- Socio-economic position								
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	1.05 (1.02-1.08)	1.08 (1.05-1.11)	1.09 (1.06-1.13)	1.10 (1.06-1.15)	1.11 (1.09-1.14)	1.12 (1.09-1.14)	1.13 (1.11-1.16)	1.18 (1.15-1.21)
- High (>12 years of education)	1.35 (1.31-1.39)	1.36 (1.32-1.41)	1.36 (1.31-1.41)	1.36 (1.30-1.42)	1.22 (1.19-1.25)	1.24 (1.21-1.27)	1.29 (1.25-1.33)	1.37 (1.33-1.41)
- Living as a single man year before	0.95 (0.93-	0.90 (0.88-	0.88 (0.85-	0.85 (0.82-	0.87 (0.86-0.89)	0.87 (0.85-	0.87 (0.85-	0.87 (0.85-

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	0.97)	0.93)	0.91)	0.88)		0.89)	0.89)	0.89)
- Living in urban area one year before	1.02 (0.99-1.05)	1.00 (0.97-1.03)	0.98 (0.95-1.02)	0.99 (0.95-1.03)	0.94 (0.92-0.96)	0.94 (0.92-0.97)	0.94 (0.91-0.96)	0.93 (0.91-0.96)
Other factors								
- Diabetes	1.15 (1.09-1.21)	1.18 (1.12-1.25)	1.20 (1.13-1.28)	1.22 (1.13-1.31)	1.03 (1.00-1.07)	1.04 (1.01-1.07)	1.07 (1.03-1.10)	1.09 (1.06-1.13)
- History of bone fractures	1.02 (0.96-1.09)	1.05 (0.98-1.12)	1.03 (0.96-1.12)	1.00 (0.91-1.10)	0.98 (0.93-1.02)	0.97 (0.93-1.02)	0.98 (0.94-1.03)	0.98 (0.94-1.03)

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

(2) Having worked in perfume industry or in high-temperature environment.

(3) Including men treated with radiotherapy for pulmonary tuberculosis.

Table 1.6 shows age-stratified analyses including Denmark, Finland and Sweden. Generally, the odds ratios are similar for both age-groups although with some variations. The variables showing clear differences between the age-groups are testicular abnormalities showing stronger estimates for men below 65 years, and estrogen therapy showing increased odds ratio among men below 65 years and decreased odds ratio among men above age 65 years, diabetes is stronger associated with high odds of finasteride use among men below 65 years than men aged 65 years and above and living in urban areas is associated with lower odds of finasteride use among men aged 65 years and above, but not in the younger age group.

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Supplementary analysis 2

Table 1.7. Number of finasteride users and non-users within the benign prostatic hyperplasia cohort. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

	Finasteride users	Finasteride non-users
Denmark	15,459 (88.1%)	2,096 (11.9%)
Finland	28,249 (82.8%)	5,871 (17.2%)
Sweden	55,963 (90.5%)	5,860 (9.5%)

Table 1.7 shows the number of finasteride users and non-users in the benign prostatic hyperplasia cohort of 131,157 men stratified by country. When restricting the study population to include only men who have had a diagnosis of the benign prostatic hyperplasia, the majority of men are finasteride users in all three countries.

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Table 1.8. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2014. Analysis nested within the benign prostatic hyperplasia cohort.

	Adjusted (1)			
	2+ redemp	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities /disorders	0.86 (0.79-0.93)	0.86 (0.79-0.93)	0.85 (0.79-0.93)	0.86 (0.79-0.93)
- Benign breast disease	1.11 (0.64-1.91)	1.15 (0.66-1.99)	1.07 (0.61-1.88)	1.01 (0.57-1.82)
- Obesity	1.29 (1.03-1.60)	1.25 (1.00-1.57)	1.29 (1.03-1.62)	1.29 (1.02-1.62)
- Liver cirrhosis	0.89 (0.73-1.09)	0.89 (0.72-1.09)	0.91 (0.74-1.12)	0.85 (0.68-1.05)
- Klinefelter's syndrome	NA	NA	NA	NA
- Estrogen therapy	0.35 (0.31-0.39)	0.33 (0.30-0.37)	0.33 (0.30-0.37)	0.32 (0.28-0.36)
- Occupational exposures (2)	1.17 (0.72-1.90)	1.23 (0.75-2.00)	1.23 (0.75-2.02)	1.14 (0.68-1.92)
Family exposures				
- Family history of breast cancer	1.02 (0.86-1.21)	1.01 (0.86-1.20)	1.02 (0.86-1.21)	1.05 (0.88-1.24)
Ionizing radiation and cancer treatment				
- Radiation exposure (3)	1.08 (0.97-1.20)	1.07 (0.96-1.19)	1.07 (0.96-1.20)	1.05 (0.94-1.17)
Socio-economic differences				
- Socio-economic position				
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	1.14 (1.07-1.22)	1.14 (1.07-1.21)	1.16 (1.08-1.23)	1.17 (1.10-1.26)
- High (>12 years of education)	1.18 (1.10-1.26)	1.19 (1.11-1.28)	1.21 (1.13-1.30)	1.26 (1.17-1.36)
- Living as a single man year before	1.01 (0.95-1.06)	1.00 (0.95-1.06)	0.98 (0.93-1.04)	1.00 (0.94-1.06)
- Living in urban area one year before	0.86 (0.81-0.92)	0.87 (0.82-0.93)	0.88 (0.82-0.94)	0.88 (0.82-0.95)
Other factors				
- Diabetes	0.88 (0.80-0.95)	0.90 (0.83-0.98)	0.93 (0.85-1.01)	0.94 (0.86-1.02)
- History of bone fractures	0.81 (0.73-0.90)	0.81 (0.73-0.89)	0.80 (0.72-0.89)	0.81 (0.72-0.90)

(1) Model mutually adjusted for all included variables, age group (5-year categories), calendar year (3-year intervals) and country except Klinefelter's syndrome.

(2) Having worked in perfume industry or in high-temperature environment.

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(3) Including men treated with radiotherapy for pulmonary tuberculosis.
NA, model could not converge when the variable Klinefelter's syndrome was included.

In the benign prostatic hyperplasia cohort (Table 1.8) the following variables are associated with increased odds ratio of finasteride use: Obesity and high socio-economic position, while testicular abnormalities, estrogen therapy, living in urban area, diabetes and bone fractures are associated with decreased odds ratio of finasteride use.

Table 1.9. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Analysis nested within the benign prostatic hyperplasia cohort

	Below age 65 years (1)			
	2+ redemp	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities /disorders	0.89 (0.84-0.94)	0.89 (0.84-0.94)	0.90 (0.85-0.96)	0.92 (0.86-0.97)
- Benign breast disease	1.05 (0.64-1.73)	1.07 (0.65-1.78)	1.04 (0.62-1.74)	1.00 (0.59-1.69)
- Obesity	1.34 (1.14-1.58)	1.32 (1.12-1.56)	1.38 (1.17-1.63)	1.41 (1.19-1.68)
- Liver cirrhosis	0.92 (0.78-1.08)	0.92 (0.78-1.08)	0.92 (0.79-1.08)	0.88 (0.75-1.04)
- Klinefelter's syndrome	NA	NA	NA	NA
- Estrogen therapy	0.23 (0.21-0.25)	0.22 (0.20-0.24)	0.23 (0.21-0.25)	0.21 (0.19-0.24)
- Occupational exposures (2)	1.14 (0.93-1.40)	1.16 (0.95-1.42)	1.15 (0.93-1.41)	1.16 (0.94-1.43)
Family exposures				
- Family history of breast cancer	0.94 (0.87-1.03)	0.94 (0.87-1.03)	0.94 (0.87-1.03)	0.97 (0.89-1.06)
Ionizing radiation and cancer treatment				
- Radiation exposure (3)	1.02 (0.95-1.11)	1.02 (0.94-1.10)	1.02 (0.94-1.10)	1.02 (0.94-1.10)
Socio-economic differences				
- Socio-economic position				
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	1.06 (1.02-1.11)	1.06 (1.02-1.11)	1.07 (1.03-1.12)	1.12 (1.07-1.18)
- High (>12 years of education)	1.09 (1.03-1.14)	1.10 (1.04-1.15)	1.11 (1.06-1.17)	1.19 (1.13-1.25)
- Living as a single man year before	0.98 (0.94-1.02)	0.98 (0.94-1.02)	0.97 (0.93-1.01)	0.96 (0.92-1.00)

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- Living in urban area one year before	0.91 (0.87-0.95)	0.91 (0.87-0.95)	0.92 (0.88-0.96)	0.92 (0.87-0.96)
Other factors				
- Diabetes	0.98 (0.92-1.04)	0.99 (0.93-1.05)	1.02 (0.96-1.08)	1.05 (0.98-1.11)
- History of bone fractures	0.89 (0.83-0.96)	0.89 (0.82-0.96)	0.89 (0.82-0.96)	0.90 (0.83-0.97)

(1) Model mutually adjusted for all included variables, age group (5-year categories), calendar year (3-year intervals) and country except Klinefelter's syndrome.

(2) Having worked in perfume industry or in high-temperature environment.

(3) Including men treated with radiotherapy for pulmonary tuberculosis.

NA, model could not converge when for the variable Klinefelter's syndrome was included.

When including Sweden (Table 1.9), the results are similar to Table 1.8, but with some variations. Diabetes is no longer associated with finasteride use and the association between socioeconomic position and odds of finasteride becomes weaker when including data from Sweden.

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Supplementary analysis 3

Table 1.10. Number of alpha-blocker users among finasteride users and non-users. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

	Finasteride users		Finasteride non-users	
	Alpha-blocker users	Alpha-blocker non-users	Alpha-blocker users	Alpha-blocker non-users
Denmark	19,080 (40.8%)	27,685 (59.2%)	1,573 (3.4%)	45,192 (96.6%)
Finland	44,948 (48.4%)	47,927 (51.6%)	6,367 (6.9%)	86,508 (93.1%)
Sweden	46,113 (43.1%)	60,755 (56.9%)	2,952 (2.8%)	103,916 (97.2%)

Table 1.10 shows the number of alpha-blocker users and non-users stratified by finasteride users and non-users. The table shows that alpha-blockers are more often used among finasteride users with small variation across countries (i.e., 48.4% of finasteride users in Finland have used alpha-blockers where this number is 40.8% in Denmark and 43.1% in Sweden).

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Supplementary analysis 4

Table 1.13. Association between potential confounding factors and finasteride use (years of finasteride use). Denmark and Finland from 1995/1997 to 2013/2014.

	Years of finasteride use (1)		
	1-3 years	4-5 years	6+ years
Increased estrogen and decreased androgen levels			
- Testicular-abnormalities / disorders	1.27 (1.22-1.32)	1.21 (1.14-1.28)	1.18 (1.11-1.26)
- Benign breast disease	1.20 (0.94-1.52)	0.97 (0.67-1.39)	0.95 (0.61-1.47)
- Obesity	1.35 (1.24-1.48)	1.52 (1.34-1.73)	1.51 (1.30-1.75)
- Liver cirrhosis	0.96 (0.88-1.05)	1.00 (0.88-1.13)	1.00 (0.87-1.16)
- Klinefelter's syndrome	2.85 (0.83-9.83)	7.68 (0.49-119.56)	18.97 (0.98-367.01)
- Estrogen therapy	0.79 (0.73-0.84)	0.52 (0.47-0.57)	0.43 (0.38-0.48)
- Occupational exposures (2)	1.08 (0.96-1.21)	1.24 (0.97-1.58)	1.32 (0.96-1.83)
Family exposures			
- Family history of breast cancer	1.05 (0.98-1.11)	1.17 (1.07-1.29)	1.25 (1.12-1.39)
Ionizing radiation and cancer treatment			
- Radiation exposure (3)	1.27 (1.20-1.34)	1.13 (1.05-1.21)	1.02 (0.94-1.10)
Socio-economic differences			
- Socio-economic position			
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	1.12 (1.09-1.14)	1.18 (1.14-1.22)	1.20 (1.14-1.25)
- High (>12 years of education)	1.40 (1.36-1.44)	1.50 (1.45-1.56)	1.58 (1.51-1.65)
- Living as a single man year before	0.93 (0.91-0.95)	0.85 (0.83-0.88)	0.83 (0.80-0.87)
- Living in urban area one year before	0.96 (0.94-0.99)	0.93 (0.90-0.97)	0.90 (0.86-0.94)
Other factors			
- Diabetes	0.97 (0.93-1.01)	0.96 (0.91-1.02)	0.89 (0.84-0.95)
- History of bone fractures	0.98 (0.94-1.03)	0.91 (0.85-0.97)	0.86 (0.80-0.94)

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

(2) Having worked in perfume industry or in high-temperature environment.

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(3) Including men treated with radiotherapy for pulmonary tuberculosis.

Table 1.13 shows the association between potential confounding factors and years of finasteride use. The following potential confounding factors are stronger associated with long-term finasteride use compared to short-term use: Obesity, Klinefelter's syndrome, family history of breast cancer, and high socio-economic position, while testicular disorders and radiation exposure are stronger associated with short-term finasteride use. Estrogen therapy, living as a single man, living in urban area and bone fracture are associated with decreased odds ratio of finasteride use, which becomes stronger for long-term finasteride use.

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Table 1.14. Association between potential confounding factors and finasteride use (years of finasteride use). Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

	Years of finasteride use (1)		
	1-3 years	4-5 years	6+ years
Increased estrogen and decreased androgen levels			
- Testicular-abnormalities / disorders	1.42 (1.38-1.46)	1.46 (1.40-1.52)	1.38 (1.31-1.45)
- Benign breast disease	1.11 (0.90-1.37)	1.05 (0.75-1.46)	1.05 (0.68-1.60)
- Obesity	1.32 (1.24-1.40)	1.46 (1.33-1.60)	1.43 (1.27-1.61)
- Liver cirrhosis	1.01 (0.94-1.07)	0.98 (0.88-1.08)	0.99 (0.88-1.13)
- Klinefelter's syndrome	1.35 (0.66-2.76)	2.64 (0.64-10.90)	4.19 (0.67-26.32)
- Estrogen therapy	0.56 (0.52-0.59)	0.40 (0.37-0.43)	0.37 (0.34-0.41)
- Occupational exposures (2)	0.93 (0.87-0.99)	1.01 (0.91-1.13)	0.99 (0.84-1.17)
Family exposures			
- Family history of breast cancer	1.00 (0.97-1.04)	1.10 (1.05-1.16)	1.13 (1.05-1.22)
Ionizing radiation and cancer treatment			
- Radiation exposure (3)	1.23 (1.19-1.28)	1.08 (1.02-1.13)	1.00 (0.94-1.06)
Socio-economic differences			
- Socio-economic position			
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	1.08 (1.07-1.10)	1.20 (1.17-1.24)	1.22 (1.18-1.27)
- High (>12 years of education)	1.29 (1.26-1.31)	1.44 (1.40-1.48)	1.54 (1.48-1.60)
- Living as a single man year before	0.89 (0.88-0.91)	0.84 (0.82-0.86)	0.83 (0.81-0.86)
- Living in urban area one year before	0.97 (0.95-0.99)	0.94 (0.92-0.97)	0.90 (0.87-0.94)
Other factors			
- Diabetes	1.08 (1.05-1.11)	1.11 (1.07-1.15)	1.04 (0.99-1.09)
- History of bone fractures	0.99 (0.96-1.03)	0.97 (0.93-1.03)	0.93 (0.87-1.00)

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

(2) Having worked in perfume industry or in high-temperature environment.

(3) Including men treated with radiotherapy for pulmonary tuberculosis.

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Table 1.14 also includes Sweden in the analysis of potential confounding factors and years of finasteride use. Family history of breast cancer and high socio-economic position are stronger associated with long-term finasteride use compared to short-term use, while radiation exposure is stronger associated with short-term finasteride use. Estrogen therapy, living as a single man and living in urban area are associated with decreased odds ratio of finasteride use, which becomes stronger for long-term finasteride use. Testicular disorders, obesity and diabetes are associated with increased odds of finasteride use among both short- and long-term users.

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Table 1.15. Association between potential confounding factors and finasteride use (years since first finasteride use). Denmark and Finland from 1995/1997 to 2013/2014.

	Years since first finasteride use (1)			
	<1 year	**1-2 years**	**3-4 years**	**5+ years**
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	1.25 (1.20-1.30)	1.39 (1.24-1.55)	1.53 (1.28-1.83)	1.39 (1.19-1.63)
- Benign breast disease	1.18 (0.93-1.50)	0.84 (0.37-1.93)	0.79 (0.19-3.26)	2.35 (1.06-5.21)
- Obesity	1.37 (1.25-1.50)	1.19 (0.89-1.60)	1.21 (0.74-1.98)	1.47 (1.04-2.07)
- Liver cirrhosis	0.96 (0.88-1.05)	0.94 (0.72-1.23)	0.56 (0.31-1.03)	1.11 (0.76-1.62)
- Klinefelter's syndrome	NA	NA	NA	NA
- Estrogen therapy	0.76 (0.71-0.81)	0.98 (0.82-1.17)	0.64 (0.45-0.91)	0.71 (0.53-0.95)
- Occupational exposures (2)	1.07 (0.95-1.21)	1.14 (0.76-1.70)	1.26 (0.56-2.85)	0.67 (0.21-2.10)
Family exposures				
- Family history of breast cancer	1.06 (1.00-1.13)	0.92 (0.75-1.11)	1.01 (0.70-1.45)	1.04 (0.75-1.43)
Ionizing radiation and cancer treatment				
- Radiation exposure (3)	1.27 (1.21-1.35)	1.23 (1.05-1.44)	1.51 (1.18-1.92)	1.47 (1.24-1.74)
Socio-economic differences				
- Socio-economic position				
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	1.12 (1.10-1.15)	1.16 (1.07-1.25)	1.06 (0.93-1.22)	1.16 (1.04-1.31)
- High (>12 years of education)	1.36 (1.33-1.40)	1.68 (1.56-1.82)	1.50 (1.31-1.72)	1.40 (1.23-1.58)
- Living as a single man year before	0.92 (0.90-0.94)	1.03 (0.96-1.10)	0.90 (0.79-1.02)	0.86 (0.77-0.96)
- Living in urban area one year before	0.95 (0.93-0.98)	1.03 (0.95-1.11)	0.90 (0.78-1.03)	0.88 (0.78-0.99)
Other factors				
- Diabetes	0.98 (0.94-1.02)	0.71 (0.62-0.82)	0.75 (0.60-0.94)	0.84 (0.71-1.00)
- History of bone fractures	0.98 (0.93-1.03)	1.01 (0.87-1.18)	1.17 (0.93-1.49)	0.97 (0.78-1.20)

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(1) Model mutually adjusted for all included variables, age group (5-year categories), calendar year (3-year intervals) and country except Klinefelter's syndrome.
(2) Having worked in perfume industry or in high-temperature environment.
(3) Including men treated with radiotherapy for pulmonary tuberculosis.
NA, model could not converge when the variable Klinefelter's syndrome was included.

Table 1.15 shows the association between potential confounding factors and years since first finasteride use. For most variables the association is similar for different time periods between first and second finasteride prescription redemption. Testicular abnormalities, radiation exposure and high socioeconomic position are associated with increased risk of finasteride use across all time periods between first and second prescription redemption.

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Table 1.16. Association between potential confounding factors and finasteride use (years since first finasteride use). Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

	Years since first finasteride use (1)			
	<1 year	1-2 years	3-4 years	5+ years
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	1.40 (1.36-1.44)	1.58 (1.46-1.72)	1.66 (1.45-1.91)	1.54 (1.34-1.77)
- Benign breast disease	1.09 (0.87-1.35)	1.08 (0.55-2.13)	0.74 (0.18-3.04)	2.36 (1.07-5.21)
- Obesity	1.33 (1.25-1.42)	1.10 (0.88-1.38)	1.17 (0.80-1.71)	1.48 (1.08-2.03)
- Liver cirrhosis	1.01 (0.94-1.08)	0.95 (0.76-1.18)	0.55 (0.33-0.91)	1.00 (0.69-1.45)
- Klinefelter's syndrome	NA	NA	NA	NA
- Estrogen therapy	0.54 (0.51-0.57)	0.75 (0.64-0.89)	0.53 (0.38-0.73)	0.65 (0.49-0.86)
- Occupational exposures (2)	0.94 (0.88-1.00)	0.85 (0.66-1.09)	0.87 (0.54-1.41)	0.70 (0.33-1.49)
Family exposures				
- Family history of breast cancer	1.01 (0.98-1.04)	0.87 (0.77-0.98)	1.06 (0.86-1.30)	0.90 (0.69-1.17)
Ionizing radiation and cancer treatment				
- Radiation exposure (3)	1.23 (1.19-1.28)	1.31 (1.17-1.46)	1.46 (1.23-1.74)	1.39 (1.19-1.63)
Socio-economic differences				
- Socio-economic position				
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	1.09 (1.07-1.11)	1.14 (1.07-1.21)	1.12 (1.01-1.24)	1.17 (1.05-1.30)
- High (>12 years of education)	1.26 (1.23-1.28)	1.63 (1.54-1.74)	1.48 (1.33-1.66)	1.39 (1.24-1.56)
- Living as a single man year before	0.88 (0.87-0.90)	1.04 (0.99-1.10)	0.91 (0.83-1.00)	0.86 (0.78-0.95)
- Living in urban area one year before	0.96 (0.95-0.98)	1.09 (1.02-1.16)	0.91 (0.82-1.01)	0.89 (0.80-1.00)
Other factors				
- Diabetes	1.09 (1.06-1.12)	0.82 (0.74-0.90)	0.81 (0.69-0.95)	0.88 (0.75-1.03)
- History of bone fractures	0.99 (0.96-1.03)	1.04 (0.93-1.16)	1.20 (1.00-1.44)	0.96 (0.79-1.17)

(1) Model mutually adjusted for all included variables, age group (5-year categories), calendar year (3-year intervals) and country except Klinefelter's syndrome.

(2) Having worked in perfume industry or in high-temperature environment.

(3) Including men treated with radiotherapy for pulmonary tuberculosis.

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NA, model could not converge when the variable Klinefelter's syndrome was included.

Table 1.16 includes Sweden and shows the same pattern as Tabel 1.15 although some odds ratios become stronger, e.g. for testicular abnormalities and radiation exposure.

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Table 1.17. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1995/1997 to 2013/2014. Only included 5 mg finasteride as finasteride users.

	Finasteride use (1)			
	2+ redemp	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	1.27 (1.22-1.32)	1.28 (1.22-1.33)	1.27 (1.21-1.33)	1.25 (1.19-1.31)
- Benign breast disease	1.21 (0.95-1.54)	1.16 (0.90-1.50)	1.14 (0.86-1.50)	1.17 (0.87-1.57)
- Obesity	1.39 (1.27-1.52)	1.42 (1.29-1.56)	1.45 (1.31-1.60)	1.46 (1.31-1.63)
- Liver cirrhosis	0.95 (0.87-1.03)	0.95 (0.87-1.04)	0.98 (0.89-1.08)	0.93 (0.84-1.04)
- Klinefelter's syndrome	3.42 (0.94-12.43)	2.20 (0.46-10.67)	5.71 (1.25-26.01)	6.91 (1.04-46.06)
- Estrogen therapy	0.75 (0.70-0.81)	0.73 (0.68-0.78)	0.67 (0.62-0.73)	0.63 (0.58-0.68)
- Occupational exposures (2)	1.04 (0.92-1.18)	1.07 (0.94-1.22)	1.09 (0.94-1.27)	1.11 (0.93-1.33)
Family exposures				
- Family history of breast cancer	1.04 (0.98-1.11)	1.05 (0.98-1.12)	1.08 (1.00-1.16)	1.10 (1.02-1.19)
Ionizing radiation and cancer treatment				
- Radiation exposure (3)	1.30 (1.23-1.37)	1.29 (1.22-1.36)	1.26 (1.19-1.34)	1.22 (1.15-1.30)
Socio-economic differences				
- Socio-economic position				
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	1.14 (1.11-1.17)	1.15 (1.12-1.18)	1.17 (1.14-1.21)	1.19 (1.15-1.22)
- High (>12 years of education)	1.40 (1.36-1.44)	1.44 (1.40-1.48)	1.46 (1.41-1.50)	1.47 (1.42-1.52)
- Living as a single man year before	0.91 (0.89-0.93)	0.90 (0.88-0.92)	0.89 (0.86-0.91)	0.88 (0.86-0.91)
- Living in urban area one year before	0.95 (0.93-0.98)	0.95 (0.93-0.98)	0.94 (0.91-0.96)	0.94 (0.91-0.97)
Other factors				
- Diabetes	0.97 (0.93-1.01)	0.98 (0.94-1.02)	0.99 (0.95-1.04)	1.01 (0.96-1.06)
- History of bone fractures	0.99 (0.94-1.04)	0.99 (0.94-1.04)	0.98 (0.92-1.03)	0.95 (0.90-1.01)

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(1) Model mutually adjusted for all included variables, age group (5-year categories), calendar year (3-year intervals) and country.
(2) Having worked in perfume industry or in high-temperature environment.
(3) Including men treated with radiotherapy for pulmonary tuberculosis.

Table 1.17 only includes 5 mg finasteride as finasteride users in Denmark and Finland (n=138,308). The results are similar to the main analysis (Table 1.3).

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Table 1.18. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Only included 5 mg finasteride as finasteride users.

	Finasteride use (1)			
	2+ redemp	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	1.42 (1.38-1.46)	1.43 (1.39-1.48)	1.46 (1.41-1.51)	1.47 (1.42-1.52)
- Benign breast disease	1.12 (0.90-1.40)	1.09 (0.87-1.37)	1.09 (0.85-1.40)	1.14 (0.87-1.50)
- Obesity	1.34 (1.26-1.43)	1.36 (1.27-1.45)	1.41 (1.32-1.51)	1.43 (1.33-1.54)
- Liver cirrhosis	1.00 (0.93-1.06)	0.99 (0.93-1.06)	1.00 (0.93-1.08)	0.97 (0.89-1.05)
- Klinefelter's syndrome	1.50 (0.71-3.15)	1.30 (0.59-2.85)	1.97 (0.84-4.62)	2.18 (0.78-6.13)
- Estrogen therapy	0.53 (0.50-0.56)	0.51 (0.48-0.54)	0.49 (0.46-0.53)	0.45 (0.42-0.48)
- Occupational exposures (2)	0.94 (0.88-1.00)	0.94 (0.88-1.01)	0.94 (0.87-1.01)	0.95 (0.88-1.04)
Family exposures				
- Family history of breast cancer	1.02 (0.98-1.05)	1.02 (0.99-1.05)	1.03 (0.99-1.06)	1.06 (1.02-1.10)
Ionizing radiation and cancer treatment				
- Radiation exposure (3)	1.25 (1.20-1.29)	1.24 (1.19-1.29)	1.23 (1.18-1.28)	1.21 (1.16-1.26)
Socio-economic differences				
- Socio-economic position				
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	1.10 (1.09-1.12)	1.11 (1.09-1.13)	1.13 (1.11-1.15)	1.17 (1.15-1.20)
- High (>12 years of education)	1.27 (1.24-1.29)	1.29 (1.26-1.31)	1.31 (1.28-1.34)	1.37 (1.34-1.40)
- Living as a single man year before	0.87 (0.85-0.88)	0.86 (0.85-0.88)	0.86 (0.84-0.87)	0.85 (0.83-0.86)
- Living in urban area one year before	0.96 (0.94-0.97)	0.96 (0.94-0.98)	0.95 (0.93-0.97)	0.95 (0.93-0.97)
Other factors				
- Diabetes	1.08 (1.05-1.11)	1.09 (1.06-1.12)	1.11 (1.07-1.14)	1.13 (1.09-1.16)
- History of bone fractures	1.00 (0.96-1.04)	1.00 (0.96-1.04)	1.00 (0.96-1.04)	0.99 (0.95-1.03)

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(1) Model mutually adjusted for all included variables, age group (5-year categories), calendar year (3-year intervals) and country.
(2) Having worked in perfume industry or in high-temperature environment.
(3) Including men treated with radiotherapy for pulmonary tuberculosis.

Table 1.18 only includes 5 mg finasteride as finasteride users for all three countries (n=243,683). The results are similar to the main analysis (Table 1.4).

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Supplementary analysis 7

Table 1.19. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1997/1999 to 2013/2014. Changed the requirement for new users by excluding finasteride users with first redemption of finasteride within the first 2 years of follow-up.

	Finasteride use (1)			
	2+ redemp	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	1.28 (1.23-1.33)	1.28 (1.23-1.34)	1.27 (1.22-1.33)	1.25 (1.19-1.31)
- Benign breast disease	1.13 (0.88-1.45)	1.12 (0.86-1.46)	1.07 (0.80-1.42)	1.11 (0.81-1.51)
- Obesity	1.34 (1.22-1.47)	1.38 (1.26-1.52)	1.42 (1.28-1.57)	1.43 (1.28-1.59)
- Liver cirrhosis	0.96 (0.88-1.05)	0.95 (0.86-1.04)	0.98 (0.89-1.09)	0.92 (0.82-1.02)
- Klinefelter's syndrome	2.74 (0.80-9.37)	2.01 (0.43-9.42)	4.38 (0.88-21.79)	4.48 (0.45-44.46)
- Estrogen therapy	0.80 (0.75-0.86)	0.75 (0.69-0.81)	0.68 (0.63-0.74)	0.63 (0.58-0.69)
- Occupational exposures (2)	1.08 (0.95-1.22)	1.08 (0.94-1.24)	1.10 (0.93-1.29)	1.14 (0.95-1.38)
Family exposures				
- Family history of breast cancer	1.05 (0.98-1.11)	1.05 (0.99-1.12)	1.08 (1.01-1.16)	1.11 (1.03-1.20)
Ionizing radiation and cancer treatment				
- Radiation exposure (3)	1.25 (1.18-1.32)	1.26 (1.19-1.33)	1.23 (1.16-1.31)	1.18 (1.11-1.26)
Socio-economic differences				
- Socio-economic position				
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	1.13 (1.10-1.15)	1.15 (1.12-1.18)	1.16 (1.13-1.20)	1.16 (1.13-1.20)
- High (>12 years of education)	1.39 (1.35-1.43)	1.43 (1.39-1.47)	1.44 (1.39-1.48)	1.42 (1.37-1.47)
- Living as a single man year before	0.94 (0.91-0.96)	0.92 (0.89-0.94)	0.90 (0.87-0.92)	0.89 (0.86-0.91)
- Living in urban area one year before	0.97 (0.94-0.99)	0.96 (0.93-0.99)	0.94 (0.91-0.97)	0.94 (0.91-0.97)
Other factors				
- Diabetes	0.97 (0.93-1.01)	0.98 (0.94-1.02)	0.99 (0.95-1.04)	1.01 (0.96-1.06)
- History of bone fractures	1.00 (0.95-1.05)	1.00 (0.95-1.06)	0.98 (0.93-1.04)	0.97 (0.91-1.03)

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(1) Model mutually adjusted for all included variables, age group (5-year categories), calendar year (3-year intervals) and country.
(2) Having worked in perfume industry or in high-temperature environment.
(3) Including men treated with radiotherapy for pulmonary tuberculosis.

Table 1.19 excluded males with the first finasteride redemption of finasteride within the first 2 years of follow-up in Denmark and Finland (n=120,935). The results are similar to the main analysis (Table 1.3).

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Table 1.20. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark (1997), Finland (1999) and Sweden (2007) to 2013/2014. Changed the requirement for new users by excluding finasteride users with first redemption of finasteride within the first 2 years of follow-up.

	Finasteride use (1)			
	2+ redemp	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	1.43 (1.39-1.48)	1.45 (1.40-1.49)	1.47 (1.42-1.52)	1.48 (1.43-1.53)
- Benign breast disease	1.08 (0.86-1.35)	1.08 (0.85-1.37)	1.07 (0.82-1.38)	1.13 (0.85-1.50)
- Obesity	1.32 (1.23-1.40)	1.34 (1.26-1.44)	1.41 (1.32-1.52)	1.44 (1.33-1.56)
- Liver cirrhosis	0.99 (0.92-1.06)	0.98 (0.91-1.05)	1.00 (0.92-1.07)	0.94 (0.86-1.02)
- Klinefelter's syndrome	1.33 (0.64-2.77)	1.18 (0.53-2.62)	1.57 (0.64-3.87)	1.56 (0.51-4.84)
- Estrogen therapy	0.56 (0.53-0.59)	0.52 (0.49-0.55)	0.49 (0.46-0.53)	0.45 (0.42-0.48)
- Occupational exposures (2)	0.97 (0.91-1.04)	0.98 (0.91-1.05)	0.97 (0.90-1.04)	0.98 (0.90-1.07)
Family exposures				
- Family history of breast cancer	1.03 (0.99-1.06)	1.03 (1.00-1.07)	1.04 (1.01-1.08)	1.08 (1.04-1.13)
Ionizing radiation and cancer treatment				
- Radiation exposure (3)	1.20 (1.15-1.24)	1.20 (1.15-1.24)	1.19 (1.14-1.24)	1.18 (1.13-1.23)
Socio-economic differences				
- Socio-economic position				
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	1.12 (1.10-1.14)	1.14 (1.12-1.16)	1.16 (1.14-1.18)	1.17 (1.15-1.20)
- High (>12 years of education)	1.32 (1.29-1.34)	1.33 (1.30-1.36)	1.35 (1.32-1.38)	1.36 (1.32-1.39)
- Living as a single man year before	0.89 (0.88-0.91)	0.88 (0.86-0.89)	0.87 (0.85-0.88)	0.85 (0.83-0.87)
- Living in urban area one year before	0.97 (0.95-0.99)	0.96 (0.94-0.98)	0.95 (0.93-0.97)	0.95 (0.93-0.97)
Other factors				
- Diabetes	1.09 (1.06-1.12)	1.10 (1.06-1.13)	1.12 (1.08-1.15)	1.14 (1.10-1.18)
- History of bone fractures	1.01 (0.97-1.05)	1.01 (0.97-1.05)	1.01 (0.97-1.05)	0.99 (0.95-1.04)

Confidential

(1) Model mutually adjusted for all included variables, age group (5-year categories), calendar year (3-year intervals) and country.
(2) Having worked in perfume industry or in high-temperature environment.
(3) Including men treated with radiotherapy for pulmonary tuberculosis.

Table 1.20 includes Sweden in the analysis excluding finasteride use the first 2 years of follow-up (n=212,988). The results are similar to the main analysis (Table 1.4).

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Supplementary analysis 8

Table 1.21. Association between factors associated with surveillance bias and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1995/1997 to 2013/2014. Analysis stratified by factors associated with surveillance bias

	Finasteride use (1)			
	2+ redemp	2-3 packs	4-6 packs	7+ packs
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Men with diagnosis of gynecomastia	1.39 (1.13-1.70)	1.43 (1.16-1.77)	1.51 (1.21-1.88)	1.75 (1.39-2.20)
Men using drugs or exposed to environmental agents	1.05 (1.00-1.10)	1.06 (1.01-1.11)	1.07 (1.02-1.12)	1.06 (1.01-1.12)
Men with high number of prescriptions	2.25 (2.20-2.31)	2.18 (2.13-2.24)	1.97 (1.92-2.03)	1.64 (1.59-1.69)
Men with high number of surgeries	1.51 (1.47-1.54)	1.52 (1.49-1.56)	1.56 (1.52-1.60)	1.57 (1.53-1.61)
Men with high number of hospital contacts	1.65 (1.62-1.69)	1.68 (1.64-1.72)	1.75 (1.71-1.79)	1.79 (1.75-1.84)
Men with urinary retention	1.96 (1.87-2.05)	1.95 (1.86-2.05)	1.82 (1.73-1.92)	1.65 (1.56-1.74)
Men with benign breast disease	1.20 (0.94-1.52)	1.17 (0.91-1.51)	1.14 (0.87-1.49)	1.16 (0.87-1.56)

(1) Model adjusted for all potential confounders: Testicular-abnormalities/disorders, obesity, liver cirrhosis, Klinefelter's syndrome, estrogen therapy, occupational exposures, radiation exposure, socio-economic position, living as a single man, living in urban area, diabetes, history of bone fractures, age group (5-year categories), calendar year (3-year intervals) and country.

Table 1.21 shows the association between factors associated with surveillance bias and finasteride use. Men with diagnosis of gynecomastia, men with high number of prescriptions, surgeries and hospital contacts, men with urinary retention and men with benign breast disease have increased odds ratios of finasteride use. The association between high number of prescription redemptions and finasteride use was weaker for those having redeemed 7 packs of finasteride or more compared to those who have redeemed 2-3 packs or 4-6 packs. Drugs or exposed to environmental agents are not associated with finasteride use.

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Table 1.22. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Analysis stratified by factors associated with surveillance bias

	Finasteride use (1)			
	2+ redemp	2-3 packs	4-6 packs	7+ packs
Men with diagnosis of gynecomastia	1.26 (1.09-1.47)	1.28 (1.10-1.48)	1.27 (1.08-1.49)	1.51 (1.28-1.78)
Men using drugs or exposed to environmental agents	2.02 (1.96-2.09)	2.08 (2.01-2.14)	2.30 (2.22-2.38)	2.55 (2.47-2.65)
Men with high number of prescriptions	2.27 (2.23-2.31)	2.30 (2.26-2.34)	2.58 (2.53-2.63)	2.74 (2.68-2.81)
Men with high number of surgeries	1.80 (1.78-1.83)	1.84 (1.81-1.87)	1.97 (1.93-2.00)	2.02 (1.98-2.06)
Men with high number of hospital contacts	1.80 (1.77-1.83)	1.83 (1.80-1.86)	1.96 (1.93-2.00)	2.07 (2.03-2.12)
Men with urinary retention	3.20 (3.10-3.32)	3.23 (3.12-3.35)	3.06 (2.95-3.17)	2.77 (2.67-2.88)
Men with benign breast disease	1.11 (0.90-1.37)	1.09 (0.87-1.37)	1.09 (0.85-1.39)	1.14 (0.87-1.48)

(1) Model adjusted for all potential confounders: Testicular-abnormalities/disorders, obesity, liver cirrhosis, Klinefelter's syndrome, estrogen therapy, occupational exposures, radiation exposure, socio-economic position, living as a single man, living in urban area, diabetes, history of bone fractures, age group (5-year categories), calendar year (3-year intervals) and country.

Table 1.22 includes Sweden and in general shows stronger odds of finasteride use for factors associated with surveillance bias compared to Table 1.21 and the variable on drugs or exposed to environmental agents is also associated with finasteride use when including Sweden.

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Supplementary analysis 10 (substudy 1A)

Objective: Same objective as substudy 1 but including self-reported lifestyle factors.

Table 1A.1. Descriptive analysis of male finasteride users (both finasteride use versus non-use and cumulative finasteride use versus non-use) with respect to self-reported potential confounding factors measured up to five years before finasteride use from surveys. Males aged 35 years and above in Denmark, Finland and Sweden. Numbers (%).

	Finasteride users (1)	Finasteride non-users
- Obesity (BMI)		
- ≤ 30	847 (86.0)	652 (84.0)
- > 30	138 (14.0)	124 (16.0)
- missing	41	19
- Alcohol intake (drinks/week)		
- ≤ 21	269 (86.5)	248 (86.7)
- > 21	42 (13.5)	38 (13.3)
- missing	715	509
- Physical activity		
- sedentary	139 (15.1)	127 (18.3)
- physical active	784 (85.0)	568 (81.7)
- missing	103	100
- Dietary intake of vegetables (2)		
- less than daily	114 (56.2)	105 (55.3)
- vegetables daily	89 (43.8)	85 (44.7)
- missing	76	55
- Dietary intake of animal fat (3)		
- less than daily	25 (47.2)	15 (38.5)
- animal fat daily	28 (52.8)	24 (61.5)
- missing	93	80

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(1) Finasteride users: Redeemed at least two prescriptions of finasteride. Non-users men who have redeemed less than two prescriptions.
(2) Data on dietary factors are not available in Sweden. This analysis is only performed for Denmark and Finland.
(3) Data on dietary factors are not available in Sweden and data on animal fat is not frequency based in Finland. This analysis is only performed for Denmark.

Table 1A.1 shows only small differences between finasteride users and non-users with regard to self-reported potential confounders.

Table 1A.3. Association between potential self-reported confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

	Age-, year- and country-adjusted	Adjusted (1)
	2+ redemp	2+ redemp
- Obesity (BMI)		
- ≤ 30	1.00 (ref)	1.00 (ref)
- > 30	0.86 (0.62-1.19)	0.91 (0.65-1.27)
- Alcohol intake (drinks/week)		
- ≤ 21	1.00 (ref)	1.00 (ref)
- > 21	1.05 (0.58-1.92)	1.16 (0.62-2.15)
- Physical activity		
- sedentary	0.69 (0.49-0.97)	0.71 (0.50-0.99)
- physical active	1.00 (ref)	1.00 (ref)
- Dietary intake of fruit and vegetables		
- less than daily	NA	NA
- fruit and/or vegetables daily	NA	NA
- Dietary intake of animal fat		
- less than daily	NA	NA
- animal fat daily	NA	NA

(1) Model adjusted for all register-based variables, age group (5-year categories), calendar year (3-year intervals) and country except Klinefelter's syndrome and benign breast disease because of few observations. In the analysis of self-reported obesity, no adjustment for register-based obesity was done.

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NA, estimates not reported since model could not convergence.

Table 1A.3 shows that obesity and alcohol intake are not associated with finasteride use, while sedentary behavior is associated with decreased odds ratio of finasteride use.

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Substudy 2

Objective: Analyze the effect of finasteride use on male breast cancer incidence while taking account of confounding factors decided in a directional acyclic graph (DAG).

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Table 2.1. Descriptive analysis of male breast cancer cases and controls with respect to potential confounding factors. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Numbers (%) if nothing else is stated

	Breast cancer cases (n=680)	Controls (n=29,746)
Finasteride use		
Non-user (<2 redemptions)	650 (95.6)	28,812 (96.9)
User (2+ redemptions)	30 (4.4)	934 (3.1)
Non-user (<2 packs of 98 5 mg pills)	659 (96.9)	29,005 (97.5)
Cumulative use low (2-3 packs)	6 (0.9)	199 (0.7)
Cumulative use medium (4-6 packs)	5 (0.7)	133 (0.5)
Cumulative use high (7+ packs)	10 (1.5)	409 (1.4)
Age, *mean (standard deviation)*	67.2 (11.9)	66.3 (11.8)
Benign prostatic hyperplasia	91 (13.4)	2,959 (10.0)
Estrogen therapy	9 (1.3)	217 (0.7)
Klinefelter's syndrome	0 (0.0)	<3 (-)
Socioeconomic position		
Low educational level	314 (46.2)	13,733 (46.2)
Medium educational level	227 (33.4)	10,503 (35.3)
High educational level	139 (20.4)	5,510 (18.5)
Testicular disorders	51 (7.5)	1,797 (6.0)
Urban	571 (84.0)	25,150 (84.6)

Note: As in the primary analysis, dutasteride users before index date are excluded.

In Denmark and Finland, a total of 680 male breast cancer cases and 29,746 controls are included (Table 2.1). The proportion of finasteride users are higher among cases (4.4%) compared to controls (3.1%). The difference in use is most pronounced for low and medium cumulative use. Benign prostatic hyperplasia, estrogen therapy, and testicular disorders are more prevalent among cases than controls, while there are only small differences for Klinefelter's syndrome, education and urban residence.

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Table 2.2. Descriptive analysis of male breast cancer cases and controls with respect to potential confounding factors. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Numbers (%) if nothing else is stated

	Breast cancer cases (n=1005)	Controls (n=43,058)
Finasteride use		
Non-user (<2 redemptions)	967 (96.2)	41,800 (97.1)
User (2+ redemptions)	38 (3.8)	1,258 (2.9)
Non-user (<2 packs of 98 5 mg pills)	977 (97.2)	42,004 (97.6)
Cumulative use low (2-3 packs)	9 (0.9)	290 (0.7)
Cumulative use medium (4-6 packs)	7 (0.7)	200 (0.5)
Cumulative use high (7+ packs)	12 (1.2)	564 (1.3)
Age, *mean (standard deviation)*	67.6 (12.3)	66.3 (12.2)
Benign prostatic hyperplasia	133 (13.2)	4,304 (10.0)
Estrogen therapy	9 (0.9)	225 (0.5)
Klinefelter's syndrome	0 (0.0)	6 (0.0)
Socioeconomic position		
Low educational level	447 (44.5)	18,942 (44.0)
Medium educational level	346 (34.4)	15,585 (36.2)
High educational level	212 (21.1)	8,531 (19.8)
Testicular disorders	71 (7.1)	2,562 (6.0)
Urban	830 (82.6)	35,269 (81.9)

As in the primary analysis, dutasteride users before index date are excluded.

In Denmark, Finland and Sweden, a total of 1005 male breast cancer cases and 43,058 controls are included (Table 2.2). The proportion of finasteride users are higher among cases (3.8%) compared to controls (2.9%). The difference in use is most pronounced for low and medium cumulative use. Benign prostatic hyperplasia, estrogen therapy, and testicular disorders are more prevalent among cases than controls.

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Table 2.3. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer excluding dutasteride users before index date. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	650	28,812	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	30	934	1.30 (0.89-1.91)	1.20 (0.81-1.77)
Non-user (<2 packs of 98 5 mg pills)	659	29,005	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	6	199	1.28 (0.56-2.90)	1.16 (0.51-2.64)
Cumulative use medium (4-6 packs)	5	133	1.51 (0.62-3.72)	1.38 (0.56-3.40)
Cumulative use high (7+ packs)	10	409	0.93 (0.49-1.77)	0.85 (0.45-1.63)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

Male breast cancer cases have higher crude odds ratio of finasteride use compared to controls, although this difference is not significant (OR=1.30; 95%CI, 0.89-1.91) (Table 2.3). When adjusting for confounders, the odds ratio decrease to 1.20 (0.81-1.77). For cumulative finasteride use the odds ratio is highest for medium users (4-6 packs) although none of the odds ratios are significant.

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Table 2.4. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer excluding dutasteride users before index date. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	967	41,800	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	38	1,258	1.18 (0.84-1.65)	1.09 (0.77-1.53)
Non-user (<2 packs of 98 5 mg pills)	977	42,004	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	9	290	1.24 (0.64-2.42)	1.14 (0.58-2.23)
Cumulative use medium (4-6 packs)	7	200	1.35 (0.63-2.88)	1.24 (0.58-2.65)
Cumulative use high (7+ packs)	12	564	0.79 (0.44-1.41)	0.72 (0.40-1.29)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

When including data from Sweden, the odds ratios of finasteride use and breast cancer decrease (Table 2.4) compared to the results of only Denmark and Finland (Table 2.3). The conclusion is therefore the same with no association between finasteride use and breast cancer risk.

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Secondary analysis 1

Table 2.5. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Stratified by age.

Age	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
<65 years	Non-user (<2 redemptions)	267	12,603	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	4	114	1.64 (0.59-4.55)	1.69 (0.59-4.82)
	Non-user (<2 packs of 98 5 mg pills)	269	12,626	NA	NA
	Cumulative use low (2-3 packs)	0	39	NA	NA
	Cumulative use medium (4-6 packs)	0	16	NA	NA
	Cumulative use high (7+ packs)	<3	36	NA	NA
≥65 years	Non-user (<2 redemptions)	387	16,543	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	26	883	1.18 (0.78-1.78)	1.08 (0.71-1.64)
	Non-user (<2 packs)	394	16,723	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	6	173	1.43 (0.63-3.25)	1.28 (0.56-2.93)
	Cumulative use medium (4-6 packs)	5	128	1.52 (0.61-3.74)	1.38 (0.56-3.41)
	Cumulative use high (7+ packs)	8	402	0.76 (0.37-1.56)	0.70 (0.34-1.44)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

NA, no risk estimate since model did not converge.

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Among males below age 65 years, the association between finasteride use and breast cancer risk is insignificantly increase (OR=1.69; 95%CI, 0.59-4.82) (Table 2.5). Among males 65 years and above, the results are increased especially among medium cumulative use (OR=1.38; 95%CI, 0.56-3.41), but none of the risk estimates are significant.

Table 2.6. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Stratified by age.

Age	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
<65 years	Non-user (<2 redemptions)	392	18,562	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	5	143	1.64 (0.66-4.07)	1.73 (0.67-4.44)
	Non-user (<2 packs of 98 5 mg pills)	394	18,586	NA	NA
	Cumulative use low (2-3 packs)	0	49	NA	NA
	Cumulative use medium (4-6 packs)	<3	21	NA	NA
	Cumulative use high (7+ packs)	<3	49	NA	NA
≥65 years	Non-user (<2 redemptions)	579	23,631	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	33	1213	1.05 (0.73-1.50)	0.96 (0.66-1.39)
	Non-user (<2 packs)	587	23,821	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	9	259	1.35 (0.69-2.65)	1.23 (0.62-2.41)
	Cumulative use medium (4-6 packs)	6	200	1.12 (0.49-2.53)	1.03 (0.45-2.34)
	Cumulative use high (7+ packs)	10	564	0.65 (0.35-1.24)	0.60 (0.31-1.13)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences.

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Conditional logistic regression.
NA, no risk estimate since model did not converge.

When including Sweden, the odds ratios for the age-stratified results decrease (Table 2.6) compared to the results including only Denmark and Finland (Table 2.5). Among men aged 65 years and above, the adjusted odds ratios of finasteride use (OR=0.96; 0.66-1.39) and for high cumulative use (OR=0.60; 0.31-1.13) are below unity, but none of the risk estimates are significant.

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Secondary analysis 2

Table 2.7. Number of finasteride users and non-users and breast cancer cases within the benign prostatic hyperplasia cohort. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

	Finasteride users	Finasteride non-users	Breast cancer cases	Controls
Denmark	234	2,027	66	2,195
Finland	217	745	26	936
Sweden	222	1,229	42	1,409

In the benign prostatic hyperplasia cohort, the number of finasteride users is 234, 217 and 222 in Denmark, Finland and Sweden, respectively (Table 2.7). The number of breast cancer cases is 66, 26 and 42 in the same countries.

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Table 2.8. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Analysis within the benign prostatic hyperplasia cohort.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	77	2,695	1.00 (ref)	NA
User (2+ redemptions)	15	436	1.40 (0.74-2.63)	NA
Non-user (<2 packs of 98 5 mg pills)	79	2,796	1.00 (ref)	NA
Cumulative use low (2-3 packs)	<3	88	0.95 (0.20-4.51)	NA
Cumulative use medium (4-6 packs)	5	67	4.64 (1.46-14.80)	NA
Cumulative use high (7+ packs)	6	180	1.49 (0.56-3.93)	NA

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

NA, no risk estimate since model did not converge.

In the benign prostatic hyperplasia cohort, the crude association between finasteride use and breast cancer risk is insignificantly increased (OR=1.40; 95%CI, 0.74-2.63) (Table 2.8) and among medium cumulative use, the association is significant (OR=4.64; 95%CI, 1.46-14.80). In the adjusted models, the risk estimates cannot be reported since the models do not converge.

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Table 2.9. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Analysis within the benign prostatic hyperplasia cohort.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	116	3,885	1.00 (ref)	NA
User (2+ redemptions)	18	655	1.01 (0.58-1.77)	NA
Non-user (<2 packs of 98 5 mg pills)	118	3,990	1.00 (ref)	NA
Cumulative use low (2-3 packs)	4	142	1.32 (0.42-4.16)	NA
Cumulative use medium (4-6 packs)	5	112	2.15 (0.77-6.01)	NA
Cumulative use high (7+ packs)	7	296	0.82 (0.36-1.91)	NA

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

NA, no risk estimate since model did not converge.

When including Sweden in the analysis of the benign prostatic hyperplasia cohort, the odds ratio decreases in the crude models and there is no association between finasteride use and breast cancer (Table 2.9). In the adjusted models, the risk estimates could not be reported since the models do not converge.

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Secondary analysis 3

Table 2.10. Number of finasteride users among alpha-blocker non-users and alpha-blocker users among finasteride non-users in substudy 2. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

	Alpha-blocker non-users		Finasteride non-users	
	Finasteride users	**Finasteride non-users**	**Alpha-blocker users**	**Alpha-blocker non-users**
Denmark	284 (1.5%)	18,153 (98.5%)	1,497 (7.6%)	18,153 (92.4%)
Finland	202 (2.1%)	9,231 (97.9%)	919 (9.1%)	9,231 (90.9%)
Sweden	175 (1.4%)	12,736 (98.6%)	628 (4.7%)	12,736 (95.3%)

Among alpha-blocker non-users, the number of finasteride users is 284, 202 and 175 in Denmark, Finland and Sweden (Table 2.10). Among finasteride non-users, the number of alpha-blocker users is 1497, 919 and 628 in the same countries.

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Table 2.11. Association between finasteride use (use versus non-use) among alpha-blocker non-users and alpha-blocker use among finasteride non-users and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014.

	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Finasteride use among alpha-blocker non-users				
Non-user (<2 redemptions)	597	26,787	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	13	473	1.12 (0.63-1.97)	1.09 (0.61-1.94)
Alpha-blocker use among Finasteride non-users				
Non-user (<2 redemptions)	597	26,787	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	57	2,359	1.00 (0.75-1.33)	0.93 (0.69-1.25)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

Both in the crude and adjusted models, finasteride use are not associated with breast cancer among alpha-blocker non-users (Table 2.11). Among finasteride non-users, alpha-blocker use is not associated with breast cancer.

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Table 2.12. Association between finasteride use (use versus non-use) among alpha-blocker non-users and alpha-blocker use among finasteride non-users and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Finasteride use among alpha-blocker non-users				
Non-user (<2 redemptions)	891	39,229	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	16	645	0.97 (0.58-1.62)	0.94 (0.56-1.57)
Alpha-blocker use among Finasteride non-users				
Non-user (<2 redemptions)	891	39,229	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	80	2,964	1.10 (0.87-1.41)	1.04 (0.81-1.34)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

When including Sweden, no association between finasteride use among alpha-blocker non-users and breast cancer is observed (Table 2.12). Alpha-blocker use is not associated with breast cancer among finasteride non-users.

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Secondary analysis 4

Table 2.13. Association between finasteride or dutasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014.

Finasteride or dutasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	650	28,957	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	34	1,186	1.17 (0.81-1.67)	1.07 (0.74-1.56)
Non-user (<2 packs of 98 pills) (3)	659	29,200	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	7	250	1.19 (0.56-2.55)	1.09 (0.51-2.34)
Cumulative use medium (4-6 packs)	6	166	1.43 (0.63-3.26)	1.31 (0.57-3.00)
Cumulative use high (7+ packs)	12	527	0.88 (0.49-1.59)	0.81 (0.44-1.47)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

(3) Finasteride use is included as number of 5 mg pills and dutasteride use is included as number of 0.5 mg pills. The cumulative use is defined as number of packs with 5 mg finasteride pills and 0.5 mg dutasteride pills.

In the analysis including finasteride and dutasteride use combined, there is slightly increased odds ratio for medium cumulative use (OR=1.31; 95%CI, 0.57-3.00), but no estimates are significant (Table 2.13).

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Table 2.14. Association between finasteride or dutasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

Finasteride or dutasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	967	41,945	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	42	1,604	1.02 (0.74-1.41)	0.95 (0.68-1.32)
Non-user (<2 packs of 98 pills) (3)	977	42,213	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	10	361	1.12 (0.59-2.11)	1.03 (0.54-1.95)
Cumulative use medium (4-6 packs)	8	254	1.20 (0.59-2.45)	1.11 (0.54-2.27)
Cumulative use high (7+ packs)	14	721	0.72 (0.42-1.25)	0.66 (0.38-1.15)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

(3) Finasteride use is included as number of 5 mg pills and dutasteride use is included as number of 0.5 mg pills. The cumulative use is defined as number of packs with 5 mg finasteride pills and 0.5 mg dutasteride pills.

When including Sweden, the odds ratios decrease with no association between finasteride and dutasteride use combined and breast cancer (Table 2.14).

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Table 2.15. Association between finasteride use (years of use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-users (<2 redemptions)	654	29,146	1.00 (ref)	1.00 (ref)
1-3 years	27	752	1.47 (0.98-2.19)	1.36 (0.91-2.05)
4-5 years	<3	124	0.64 (0.16-2.63)	0.59 (0.14-2.42)
6+ years	<3	121	0.33 (0.05-2.35)	0.31 (0.04-2.24)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

In the analysis of years of finasteride use, there is increased odds ratio of breast cancer among short-term use (OR=1.36; 95%CI, 0.91-2.05) although this association is not significant (Table 2.15). There is no long-term use association.

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Table 2.16. Association between finasteride use (years of use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-users (<2 redemptions)	971	42,193	1.00 (ref)	1.00 (ref)
1-3 years	33	1,047	1.24 (0.86-1.77)	1.16 (0.80-1.67)
4-5 years	4	168	0.92 (0.34-2.50)	0.84 (0.31-2.30)
6+ years	<3	141	0.27 (0.04-1.96)	0.26 (0.04-1.85)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

When including Sweden, the odds ratios decrease meaning that there is no association between years of finasteride use and breast cancer (Table 2.16).

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Table 2.17. Association between finasteride use (years since first finasteride use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-users (0 redemptions)	644	28,907	1.00 (ref)	1.00 (ref)
<1 year	8	153	2.25 (1.10-4.61)	2.17 (1.06-4.47)
1-2 years	13	289	1.96 (1.11-3.45)	1.81 (1.02-3.21)
3-4 years	9	236	1.57 (0.79-3.11)	1.46 (0.73-2.89)
5+ years	10	558	0.72 (0.38-1.36)	0.66 (0.34-1.26)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

In the analysis of years since first finasteride use, there is increased risk among persons with short time since first finasteride use, e.g. 1-2 years since first finasteride prescription is associated with odds ratio of 1.81 (95%CI, 1.02-3.21) in the adjusted analysis (Table 2.17). Long time since first prescription is not associated with breast cancer.

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Table 2.18. Association between finasteride use (years since first finasteride use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-users (0 redemptions)	958	41,872	1.00 (ref)	1.00 (ref)
<1 year	10	258	1.57 (0.83-2.96)	1.50 (0.79-2.85)
1-2 years	19	454	1.71 (1.07-2.73)	1.59 (0.99-2.56)
3-4 years	11	338	1.29 (0.70-2.37)	1.20 (0.65-2.22)
5+ years	11	627	0.69 (0.37-1.26)	0.64 (0.34-1.18)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

When including Sweden, the risk estimates decrease compared to the analysis with Denmark and Finland and all odds ratio estimates are insignificant in the adjusted model (Table 2.18).

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Table 2.19. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Only include 5 mg finasteride as finasteride users.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	654	29,144	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	30	996	1.23 (0.84-1.80)	1.14 (0.77-1.68)
Non-user (<2 packs of 98 5 mg pills)	663	29,347	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	6	211	1.19 (0.52-2.70)	1.09 (0.48-2.49)
Cumulative use medium (4-6 packs)	5	144	1.38 (0.56-3.39)	1.27 (0.51-3.13)
Cumulative use high (7+ packs)	10	438	0.88 (0.46-1.68)	0.82 (0.43-1.57)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

In the analysis only including 5 mg finasteride use as exposure, there is a slightly increased odds ratio of breast cancer especially among medium cumulative use (Table 2.19). None of the odds ratios are significant.

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Table 2.20. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Only include 5 mg finasteride as finasteride users.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	971	42,189	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	38	1,353	1.10 (0.79-1.54)	1.03 (0.73-1.45)
Non-user (<2 packs of 98 5 mg pills)	981	42,403	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	9	306	1.17 (0.60-2.29)	1.09 (0.55-2.13)
Cumulative use medium (4-6 packs)	7	220	1.21 (0.57-2.59)	1.13 (0.53-2.41)
Cumulative use high (7+ packs)	12	613	0.73 (0.41-1.32)	0.68 (0.38-1.22)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

When including Sweden, all odds ratios decreased and none of the odds ratios are significant (Table 2.20).

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Table 2.21. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Include persons who only redeemed one prescription as exposed.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (0 redemptions)	644	28,907	1.00 (ref)	1.00 (ref)
User (1+ redemptions)	40	1,236	1.35 (0.97-1.89)	1.26 (0.89-1.78)
Non-user (<1 packs of 98 5 mg pills)	652	29,119	1.00 (ref)	1.00 (ref)
Cumulative use low (1-3 packs)	17	442	1.63 (1.00-2.68)	1.53 (0.93-2.52)
Cumulative use medium (4-6 packs)	5	144	1.40 (0.57-3.44)	1.30 (0.53-3.21)
Cumulative use high (7+ packs)	10	438	0.90 (0.47-1.71)	0.84 (0.44-1.60)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

In the analysis including persons with only one finasteride prescription as exposed, the odds ratios increase compared to the primary analysis including persons with two prescriptions as exposed (Table 2.3). Especially low cumulative use increase markedly (OR=1.53; 95%CI, 0.93-2.52) (Table 2.21). None of the risk estimates are significant.

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Table 2.22. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Include persons who only redeemed one prescription as exposed.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (0 redemptions)	958	41,872	1.00 (ref)	1.00 (ref)
User (1+ redemptions)	51	1,677	1.22 (0.91-1.64)	1.14 (0.84-1.55)
Non-user (<1 packs of 98 5 mg pills)	966	42,101	1.00 (ref)	1.00 (ref)
Cumulative use low (1-3 packs)	24	614	1.59 (1.05-2.40)	1.49 (0.98-2.27)
Cumulative use medium (4-6 packs)	7	221	1.23 (0.57-2.62)	1.15 (0.54-2.46)
Cumulative use high (7+ packs)	12	613	0.75 (0.42-1.34)	0.70 (0.39-1.25)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

When including Sweden, the risk estimates decrease although the odds ratio for low cumulative finasteride use is still insignificantly increased (OR=1.49; 95%CI, 0.98-2.27).

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Table 2.23. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1997/1999 to 2013/2014. Change the requirement for new user by excluding Finasteride users with first redemption of finasteride within the first 2 years of follow-up.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	650	29,097	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	21	742	1.13 (0.72-1.78)	1.05 (0.66-1.66)
Non-user (<2 packs of 98 5 mg pills)	657	29,233	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	<3	161	0.51 (0.13-2.07)	0.47 (0.11-1.90)
Cumulative use medium (4-6 packs)	4	113	1.38 (0.50-3.77)	1.28 (0.47-3.51)
Cumulative use high (7+ packs)	8	332	0.91 (0.44-1.87)	0.84 (0.41-1.74)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

When changing the requirement for new user the risk estimates decrease especially for low cumulative finasteride use (OR=0.47; 95%CI, 0.11-1.90). None of the odds ratios are significant.

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Table 2.24. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1997), Finland (1999) and Sweden (2007) to 2013/2014. Change the requirement for new user by excluding finasteride users with first redemption of Finasteride within the first 2 years of follow-up.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	967	42,130	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	27	1,004	1.03 (0.69-1.54)	0.97 (0.65-1.45)
Non-user (<2 packs of 98 5 mg pills)	974	42,275	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	4	233	0.67 (0.25-1.82)	0.63 (0.23-1.70)
Cumulative use medium (4-6 packs)	6	177	1.27 (0.56-2.88)	1.18 (0.52-2.70)
Cumulative use high (7+ packs)	10	449	0.82 (0.43-1.56)	0.76 (0.40-1.46)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

When including Sweden the risk estimates are closer to no association (Table 2.24). No odds ratios are significant.

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Table 2.25. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Analysis stratified diagnosis of gynecomastia.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with diagnosis of gynecomastia	Non-user (<2 redemptions)	32	98	NA	NA
	User (2+ redemptions)	0	3	NA	NA
	Non-user (<2 packs of 98 5 mg pills)	32	99	NA	NA
	Cumulative use low (2-3 packs)	0	<3	NA	NA
	Cumulative use medium (4-6 packs)	0	0	NA	NA
	Cumulative use high (7+ packs)	0	<3	NA	NA
Among men without diagnosis of gynecomastia	Non-user (<2 redemptions)	622	29,048	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	30	994	1.28 (0.87-1.88)	1.19 (0.80-1.76)
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	Non-user (<2 packs)	631	29,250	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	6	211	1.25 (0.55-2.83)	1.15 (0.50-2.62)
	Cumulative use medium (4-6 packs)	5	144	1.43 (0.58-3.53)	1.33 (0.54-3.29)
	Cumulative use high (7+ packs)	10	437	0.92 (0.48-1.75)	0.85 (0.45-1.63)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

NA, no risk estimate since model did not converge.

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In the analysis stratified by diagnosis of gynecomastia, the number of men with gynecomastia is too low to estimate the association between finasteride use and breast cancer (Table 2.25). Among men without a diagnosis of gynecomastia, the results are similar to the main results (Table 2.3).

Table 2.26. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Analysis stratified diagnosis of gynaecomastia.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with diagnosis of gynecomastia	Non-user (<2 redemptions)	50	122	NA	NA
	User (2+ redemptions)	0	6	NA	NA
	Non-user (<2 packs of 98 5 mg pills)	50	123	NA	NA
	Cumulative use low (2-3 packs)	0	<3	NA	NA
	Cumulative use medium (4-6 packs)	0	0	NA	NA
	Cumulative use high (7+ packs)	0	3	NA	NA
Among men without diagnosis of gynecomastia	Non-user (<2 redemptions)	921	42,071	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	38	1,350	1.16 (0.83-1.62)	1.09 (0.77-1.54)
	Non-user (<2 packs)	931	42,284	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	9	306	1.24 (0.63-2.42)	1.16 (0.59-2.28)
	Cumulative use medium (4-6 packs)	7	221	1.26 (0.59-2.69)	1.18 (0.55-2.54)
	Cumulative use high (7+ packs)	12	610	0.77 (0.43-1.39)	0.72 (0.40-1.30)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

NA, no risk estimate since model did not converge.

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When including Sweden, the results are similar to Table 2.25 with no estimates among men with a diagnosis of gynecomastia and results are similar to the main analysis for men without a diagnosis of gynecomastia (Table 2.26).

Table 2.27. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Analysis stratified by use of drugs or exposed to environmental agents that cause or may cause gynecomastia.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with use of drugs or exposed to environmental agents	Non-user (<2 redemptions)	41	1,687	NA	NA
	User (2+ redemptions)	0	75	NA	NA
	Non-user (<2 packs of 98 5 mg pills)	41	1,704	NA	NA
	Cumulative use low (2-3 packs)	0	16	NA	NA
	Cumulative use medium (4-6 packs)	0	14	NA	NA
	Cumulative use high (7+ packs)	0	28	NA	NA
Among men without use of drugs or not exposed to environmental agents	Non-user (<2 redemptions)	613	27,459	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	30	922	1.32 (0.90-1.94)	1.21 (0.82-1.79)
	Non-user (<2 packs)	622	27,645	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	6	196	1.29 (0.57-2.93)	1.17 (0.51-2.67)
	Cumulative use medium (4-6 packs)	5	130	1.54 (0.63-3.81)	1.40 (0.56-3.46)
	Cumulative use high (7+ packs)	10	410	0.93 (0.49-1.78)	0.86 (0.45-1.64)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

NA, no risk estimate since model did not converge.

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In the analysis stratified by use of drugs or exposed to environmental agents that may cause gynecomastia, the number of men exposed is too low to estimate the association between finasteride use and breast cancer (Table 2.27). Among men without a diagnosis of gynecomastia, the results are similar to the main results (Table 2.3).

Table 2.28. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Analysis stratified by use of drugs or exposed to environmental agents that cause or may cause gynecomastia.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among use of drugs or exposed to environmental agents	Non-user (<2 redemptions)	52	2,021	NA	NA
	User (2+ redemptions)	<3	91	NA	NA
	Non-user (<2 packs of 98 5 mg pills)	52	2,039	NA	NA
	Cumulative use low (2-3 packs)	<3	19	NA	NA
	Cumulative use medium (4-6 packs)	0	17	NA	NA
	Cumulative use high (7+ packs)	0	37	NA	NA
Among men without use of drugs or not exposed to environmental agents	Non-user (<2 redemptions)	919	40,172	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	37	1,265	1.13 (0.80-1.60)	1.04 (0.73-1.48)
	Non-user (<2 packs)	929	40,368	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	8	289	1.08 (0.53-2.20)	0.99 (0.49-2.02)
	Cumulative use medium (4-6 packs)	7	204	1.30 (0.61-2.77)	1.19 (0.55-2.55)
	Cumulative use high (7+ packs)	12	576	0.77 (0.43-1.39)	0.71 (0.39-1.27)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

NA, no risk estimate since model did not converge.

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When including Sweden, the results are similar to Table 2.27 with no estimates among men exposed to drugs or agents that may cause gynecomastia and results are similar to the main analysis for men without a diagnosis of gynecomastia (Table 2.28).

Table 2.29. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Analysis stratified by number of prescriptions.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with low number of prescriptions	Non-user (<2 redemptions)	318	15,050	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	5	149	1.84 (0.72-4.67)	1.68 (0.65-4.34)
	Non-user (<2 packs of 98 5 mg pills)	321	15,098	NA	NA
	Cumulative use low (2-3 packs)	<3	45	NA	NA
	Cumulative use medium (4-6 packs)	0	23	NA	NA
	Cumulative use high (7+ packs)	<3	33	NA	NA
Among men with high number of prescriptions	Non-user (<2 redemptions)	336	14,096	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	25	848	1.22 (0.79-1.86)	1.13 (0.73-1.74)
	Non-user (<2 packs)	342	14,251	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	5	167	1.21 (0.49-3.01)	1.12 (0.45-2.79)
	Cumulative use medium (4-6 packs)	5	121	1.51 (0.61-3.74)	1.35 (0.54-3.37)
	Cumulative use high (7+ packs)	9	405	0.93 (0.47-1.86)	0.87 (0.44-1.74)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences.

Confidential

Conditional logistic regression.

NA, no risk estimate since model did not converge.

In the analysis stratified by number of prescriptions, the number of finasteride users among men with low number of prescriptions is too low to estimate the association between cumulative finasteride use and breast cancer, while the association between finasteride use showed increased odds ratio (OR=1.68; 95%CI, 0.65-4.34) which is not significant (Table 2.29). Among men with high number of prescriptions the results are similar to the main results (Table 2.3).

Table 2.30. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Analysis stratified by number of prescriptions.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with low number of prescriptions	Non-user (<2 redemptions)	477	21,803	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	6	169	1.70 (0.72-4.00)	1.64 (0.69-3.92)
	Non-user (<2 packs of 98 5 mg pills)	481	21,853	NA	NA
	Cumulative use low (2-3 packs)	<3	51	NA	NA
	Cumulative use medium (4-6 packs)	0	28	NA	NA
	Cumulative use high (7+ packs)	<3	40	NA	NA
Among men with high number of prescriptions	Non-user (<2 redemptions)	494	20,390	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	32	1,187	1.08 (0.74-1.57)	0.99 (0.68-1.45)
	Non-user (<2 packs)	500	20,554	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	8	257	1.28 (0.62-2.62)	1.18 (0.57-2.43)
	Cumulative use medium (4-6 packs)	7	193	1.34 (0.62-2.89)	1.21 (0.56-2.61)

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	Cumulative use high (7+ packs)	11	573	0.76 (0.41-1.41)	0.69 (0.37-1.29)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

NA, no risk estimate since model did not converge.

When including Sweden, the results decrease slightly with increased odds ratio among men with low number of prescriptions (OR=1.64; 95%CI, 0.69-3.92), but all estimates are insignificant (Table 2.30).

Table 2.31. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Analysis stratified by number of surgeries.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with low number of surgeries	Non-user (<2 redemptions)	334	19,047	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	14	398	1.98 (1.11-3.50)	1.96 (1.10-3.48)
	Non-user (<2 packs of 98 5 mg pills)	341	19,127	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	<3	92	1.35 (0.32-5.66)	1.32 (0.31-5.56)
	Cumulative use medium (4-6 packs)	<3	57	0.85 (0.11-6.41)	0.83 (0.11-6.26)
	Cumulative use high (7+ packs)	4	169	1.22 (0.43-3.41)	1.22 (0.43-3.41)
Among men with high number of surgeries	Non-user (<2 redemptions)	320	10,099	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	16	599	0.76 (0.45-1.28)	0.74 (0.44-1.26)
	Non-user (<2 packs)	322	10,222	1.00 (ref)	1.00 (ref)

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	Cumulative use low (2-3 packs)	4	120	0.87 (0.31-2.41)	0.82 (0.29-2.31)
	Cumulative use medium (4-6 packs)	4	87	1.38 (0.49-3.89)	1.32 (0.46-3.76)
	Cumulative use high (7+ packs)	6	269	0.70 (0.30-1.61)	0.69 (0.30-1.60)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

Among men with low number of surgeries, there is significantly increased odds ratio of breast cancer among finasteride users (OR=1.96; 95%CI, 1.10-3.48), while no clear pattern is observed for cumulative use (Table 2.31). Among men with high number of surgeries, no clear pattern is observed for association between finasteride use and breast cancer.

Table 2.32. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Analysis stratified by number of surgeries.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with low number of surgeries	Non-user (<2 redemptions)	470	26,371	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	15	457	1.91 (1.10-3.31)	1.88 (1.08-3.28)
	Non-user (<2 packs of 98 5 mg pills)	478	26,452	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	<3	110	1.21 (0.29-5.03)	1.18 (0.28-4.93)
	Cumulative use medium (4-6 packs)	<3	73	0.71 (0.10-5.35)	0.71 (0.09-5.29)
	Cumulative use high (7+ packs)	4	193	1.10 (0.39-3.07)	1.08 (0.39-3.02)

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Among men with high number of surgeries	Non-user (<2 redemptions)	501	15,822	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	23	899	0.74 (0.48-1.14)	0.73 (0.47-1.13)
	Non-user (<2 packs)	503	15,955	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	7	198	0.99 (0.46-2.15)	0.97 (0.44-2.11)
	Cumulative use medium (4-6 packs)	6	148	1.18 (0.51-2.72)	1.17 (0.50-2.71)
	Cumulative use high (7+ packs)	8	420	0.57 (0.28-1.17)	0.57 (0.27-1.17)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

When including Sweden, the odds ratio decreased but is still significantly increased among finasteride users with low number of surgeries (OR=1.88; 95%CI, 1.08-3.28). No clear pattern is observed among men with high number of surgeries.

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Table 2.33. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Analysis stratified number of hospital contacts.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with low number of hospital contacts	Non-user (<2 redemptions)	283	16,519	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	9	284	1.69 (0.84-3.41)	1.70 (0.84-3.44)
	Non-user (<2 packs of 98 5 mg pills)	286	16,583	NA	NA
	Cumulative use low (2-3 packs)	<3	67	NA	NA
	Cumulative use medium (4-6 packs)	0	38	NA	NA
	Cumulative use high (7+ packs)	4	115	NA	NA
Among men with high number of hospital contacts	Non-user (<2 redemptions)	371	12,627	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	21	713	1.02 (0.64-1.62)	0.97 (0.61-1.55)
	Non-user (<2 packs)	377	12,766	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	4	145	0.92 (0.34-2.53)	0.85 (0.31-2.34)
	Cumulative use medium (4-6 packs)	5	106	1.68 (0.67-4.19)	1.56 (0.62-3.93)
	Cumulative use high (7+ packs)	6	323	0.64 (0.28-1.47)	0.61 (0.26-1.40)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

NA, no risk estimate since model did not converge.

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Among men with low number of hospital contacts, an increased odds ratio is observed among finasteride users although insignificant (OR=1.70; 95%CI, 0.84-3.44). Among men with high number of hospital contacts, no clear pattern is observed (Table 2.33).

Table 2.34. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Analysis stratified number of hospital contacts.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with low number of hospital contacts	Non-user (<2 redemptions)	416	23,369	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	10	347	1.57 (0.81-3.05)	1.57 (0.81-3.07)
	Non-user (<2 packs of 98 5 mg pills)	420	23,434	NA	NA
	Cumulative use low (2-3 packs)	<3	87	NA	NA
	Cumulative use medium (4-6 packs)	0	48	NA	NA
	Cumulative use high (7+ packs)	4	147	NA	NA
Among men with high number of hospital contacts	Non-user (<2 redemptions)	555	18,824	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	28	1,009	0.93 (0.62-1.38)	0.89 (0.59-1.34)
	Non-user (<2 packs)	561	18,973	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	7	221	1.04 (0.48-2.24)	0.99 (0.46-2.13)
	Cumulative use medium (4-6 packs)	7	173	1.37 (0.64-2.96)	1.31 (0.60-2.84)
	Cumulative use high (7+ packs)	8	466	0.56 (0.27-1.15)	0.54 (0.26-1.11)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences.

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Conditional logistic regression.

NA, no risk estimate since model did not converge.

When including Sweden, the risk estimates decrease slightly and none of the risk estimates are significant (Table 2.34).

Table 2.35. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Analysis stratified by diagnosis of urinary retention.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with urinary retention	Non-user (<2 redemptions)	27	852	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	5	99	2.54 (0.61-10.50)	1.35 (0.27-6.69)
	Non-user (<2 packs of 98 5 mg pills)	29	881	NA	NA
	Cumulative use low (2-3 packs)	0	17	NA	NA
	Cumulative use medium (4-6 packs)	<3	19	NA	NA
	Cumulative use high (7+ packs)	<3	34	NA	NA
Among men without urinary retention	Non-user (<2 redemptions)	627	28,294	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	25	898	1.14 (0.75-1.73)	1.09 (0.71-1.67)
	Non-user (<2 packs)	634	28,468	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	6	195	1.33 (0.59-3.01)	1.26 (0.55-2.87)
	Cumulative use medium (4-6 packs)	4	125	1.25 (0.46-3.39)	1.18 (0.43-3.22)
	Cumulative use high (7+ packs)	8	404	0.76 (0.37-1.56)	0.72 (0.35-1.49)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences.

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Conditional logistic regression.
NA, no risk estimate since model did not converge.

Among men with urinary retention, an increased odds ratio is observed for finasteride use but the risk estimate is insignificant (Table 2.35). The association between cumulative finasteride use cannot be estimated since the model does not converge. Among men without urinary retention slightly increased odds ratios are observed but none of the estimates are significant.

Table 2.36. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Analysis stratified by diagnosis of urinary retention.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with urinary retention	Non-user (<2 redemptions)	40	1,279	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	5	163	1.19 (0.34-4.23)	1.02 (0.27-3.87)
	Non-user (<2 packs of 98 5 mg pills)	42	1,311	NA	NA
	Cumulative use low (2-3 packs)	0	38	NA	NA
	Cumulative use medium (4-6 packs)	<3	32	NA	NA
	Cumulative use high (7+ packs)	<3	61	NA	NA
Among men without urinary retention	Non-user (<2 redemptions)	931	40,914	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	33	1,193	1.10 (0.76-1.57)	1.04 (0.72-1.51)
	Non-user (<2 packs)	939	41,096	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	9	270	1.37 (0.70-2.67)	1.29 (0.66-2.54)
	Cumulative use medium (4-6 packs)	6	189	1.19 (0.52-2.70)	1.12 (0.49-2.54)
	Cumulative use high (7+ packs)	10	552	0.68 (0.36-1.29)	0.64 (0.34-1.22)

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(1) Matched for age and country. Conditional logistic regression.
(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

When including Sweden, the risk estimates decrease showing no significant association between finasteride use and breast cancer among men with and without urinary retention (Table 2.36).

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Table 2.37. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Analysis stratified cancer stage at diagnosis.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Localized cancer at diagnosis	Non-user (<2 redemptions)	257	11,648	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	15	372	1.73 (1.00-2.99)	1.57 (0.90-2.75)
	Non-user (<2 packs of 98 5 mg pills)	260	11,726	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	4	75	2.26 (0.81-6.30)	2.02 (0.72-5.69)
	Cumulative use medium (4-6 packs)	<3	62	0.72 (0.10-5.21)	0.65 (0.09-4.77)
	Cumulative use high (7+ packs)	7	157	1.86 (0.84-4.11)	1.68 (0.76-3.73)
Regional or metastatic cancer at diagnosis	Non-user (<2 redemptions)	332	14,691	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	13	527	0.97 (0.54-1.72)	1.01 (0.56-1.81)
	Non-user (<2 packs)	337	14,795	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	<3	114	0.73 (0.18-2.99)	0.74 (0.18-3.05)
	Cumulative use medium (4-6 packs)	4	69	2.06 (0.74-5.76)	2.15 (0.77-6.02)
	Cumulative use high (7+ packs)	<3	240	0.30 (0.07-1.24)	0.31 (0.08-1.29)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

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Among men with localized cancer at diagnosis, finasteride use is associated with breast cancer although the risk estimate is not significant in the adjusted model (OR=1.57; 95%CI, 0.90-2.75) (Table 2.37). Cumulative finasteride use is not associated with breast cancer. Among men with regional or metastatic cancer at diagnosis, no association is observed between finasteride use and breast cancer.

Table 2.38. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Analysis stratified cancer stage at diagnosis.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Localized cancer at diagnosis	Non-user (<2 redemptions)	440	19,080	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	19	617	1.21 (0.75-1.95)	1.05 (0.64-1.72)
	Non-user (<2 packs of 98 5 mg pills)	443	19,166	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	6	132	1.78 (0.78-4.08)	1.54 (0.67-3.56)
	Cumulative use medium (4-6 packs)	<3	112	0.71 (0.18-2.90)	0.63 (0.15-2.57)
	Cumulative use high (7+ packs)	8	287	1.06 (0.52-2.19)	0.90 (0.44-1.88)
Regional or metastatic cancer at diagnosis	Non-user (<2 redemptions)	429	18,764	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	17	634	1.04 (0.63-1.73)	1.13 (0.67-1.89)
	Non-user (<2 packs)	435	18,870	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	3	148	0.82 (0.26-2.58)	0.87 (0.27-2.76)
	Cumulative use medium (4-6 packs)	5	96	1.87 (0.75-4.66)	2.00 (0.80-5.02)
	Cumulative use high (7+ packs)	3	284	0.39 (0.12-1.22)	0.41 (0.13-1.32)

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(1) Matched for age and country. Conditional logistic regression.
(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

When including Sweden, the risk estimates decreased slightly showing no clear association between finasteride use and breast cancer for local and regional and metastatic cancer (Table 2.38).

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Table 2.38.extra.1. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Analysis stratified by diagnosis of benign breast disease.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with benign breast disease	Non-user (<2 redemptions)	11	54	NA	NA
	User (2+ redemptions)	<3	5	NA	NA
	Non-user (<2 packs of 98 5 mg pills)	12	55	NA	NA
	Cumulative use low (2-3 packs)	0	<3	NA	NA
	Cumulative use medium (4-6 packs)	0	0	NA	NA
	Cumulative use high (7+ packs)	0	3	NA	NA
Among men without benign breast disease	Non-user (<2 redemptions)	643	29,092	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	29	992	1.22 (0.83-1.80)	1.13 (0.76-1.68)
	Non-user (<2 packs)	651	29,294	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	6	211	1.20 (0.53-2.71)	1.10 (0.48-2.50)
	Cumulative use medium (4-6 packs)	5	144	1.39 (0.57-3.43)	1.28 (0.52-3.17)
	Cumulative use high (7+ packs)	10	435	0.93 (0.49-1.76)	0.86 (0.45-1.64)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

NA, no risk estimate since model did not converge.

In the analysis stratified by diagnosis of benign breast disease, the number of men with benign breast disease is too low to estimate the association between finasteride use and breast cancer (Table 2.38.extra.1). Among men without a diagnosis of benign breast disease, the results are slightly lower than the main results (Table 2.3).

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Table 2.38.extra.2. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Analysis stratified by diagnosis of benign breast disease.

	Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with benign breast disease	Non-user (<2 redemptions)	14	58	NA	NA
	User (2+ redemptions)	<3	5	NA	NA
	Non-user (<2 packs of 98 5 mg pills)	15	59	NA	NA
	Cumulative use low (2-3 packs)	0	<3	NA	NA
	Cumulative use medium (4-6 packs)	0	0	NA	NA
	Cumulative use high (7+ packs)	0	3	NA	NA
Among men without benign breast disease	Non-user (<2 redemptions)	957	42,135	1.00 (ref)	1.00 (ref)
	User (2+ redemptions)	37	1,351	1.10 (0.78-1.54)	1.02 (0.72-1.44)
	Non-user (<2 packs)	966	42,348	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	9	307	1.18 (0.60-2.30)	1.09 (0.56-2.14)
	Cumulative use medium (4-6 packs)	7	221	1.22 (0.57-2.61)	1.13 (0.53-2.43)
	Cumulative use high (7+ packs)	12	610	0.76 (0.42-1.36)	0.70 (0.39-1.26)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Conditional logistic regression.

NA, no risk estimate since model did not converge.

When including Sweden, the model could not estimate the association between finasteride use and breast cancer among men with benign breast disease (Table 2.38.extra.2). Among men without benign breast disease, the association is similar to the main analysis (Table 2.4).

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Table 2.39. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Latency analysis inferring 1 year of lag time between finasteride use and breast cancer.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	659	29,277	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	25	866	1.16 (0.77-1.77)	1.07 (0.70-1.64)
Non-user (<2 packs of 98 5 mg pills)	664	29,464	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	9	175	2.14 (1.09-4.22)	1.97 (0.99-3.91)
Cumulative use medium (4-6 packs)	5	132	1.47 (0.60-3.62)	1.35 (0.55-3.34)
Cumulative use high (7+ packs)	6	372	0.62 (0.27-1.41)	0.58 (0.25-1.32)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Confounders aare included as the main analysis without any lagging. Conditional logistic regression.

In the analysis inferring 1 year lag time between finasteride use and breast cancer, the association decrease compared to the main analysis (OR=1.07; 95%CI, 0.70-1.64) (Table 2.39). For cumulative finasteride use the risk estimate is highest for low cumulative intake (OR=1.97; 95%CI, 0.99-3.91), but is lower for higher cumulative intake.

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Table 2.40. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1995/1997 to 2013/2014. Latency analysis inferring 2 years of lag time between finasteride use and breast cancer.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	666	29,403	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	18	740	0.95 (0.58-1.55)	0.87 (0.53-1.43)
Non-user (<2 packs of 98 5 mg pills)	670	29,564	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	6	156	1.54 (0.67-3.51)	1.40 (0.61-3.20)
Cumulative use medium (4-6 packs)	4	111	1.34 (0.49-3.70)	1.23 (0.44-3.41)
Cumulative use high (7+ packs)	4	312	0.49 (0.18-1.32)	0.45 (0.17-1.23)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Confounders are included as the main analysis without any lagging. Conditional logistic regression.

In the analysis inferring 2 years lag time between finasteride use and breast cancer, the odds ratios decrease further and show no clear association between finasteride use and breast cancer (Table 2.40).

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Table 2.41. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Latency analysis inferring 1 year of lag time between finasteride use and breast cancer.

Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	977	42,398	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	32	1,151	1.09 (0.75-1.57)	1.01 (0.69-1.47)
Non-user (<2 packs of 98 5 mg pills)	982	42,597	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	13	248	2.09 (1.19-3.68)	1.94 (1.10-3.44)
Cumulative use medium (4-6 packs)	6	207	1.10 (0.48-2.48)	1.01 (0.44-2.30)
Cumulative use high (7+ packs)	8	497	0.60 (0.30-1.23)	0.56 (0.28-1.15)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Confounders are included as the main analysis without any lagging. Conditional logistic regression.

When including Sweden, the risk estimates decrease only showing increased odds ratio among low cumulative finasteride use (Table 2.41).

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Table 2.42. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1997) and Sweden (2005) to 2013/2014. Latency analysis inferring 2 years of lag time between finasteride use and breast cancer.

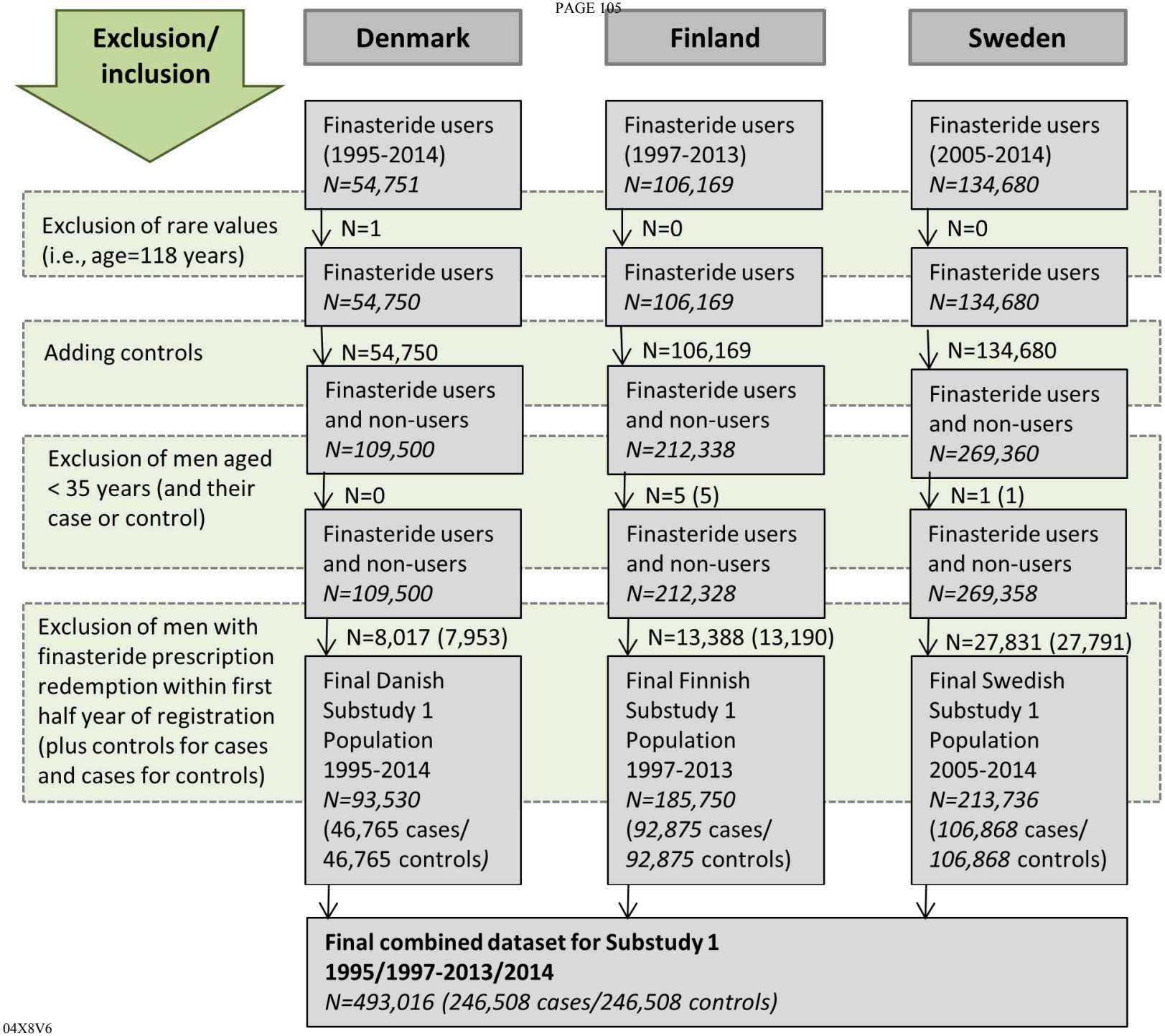
Finasteride use	Cases	Controls	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 redemptions)	987	42,604	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	22	945	0.89 (0.58-1.38)	0.82 (0.53-1.28)
Non-user (<2 packs of 98 5 mg pills)	991	42,777	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	8	215	1.45 (0.71-2.97)	1.34 (0.65-2.74)
Cumulative use medium (4-6 packs)	4	170	0.87 (0.32-2.36)	0.81 (0.29-2.20)
Cumulative use high (7+ packs)	6	387	0.58 (0.26-1.31)	0.54 (0.24-1.22)

(1) Matched for age and country. Conditional logistic regression.

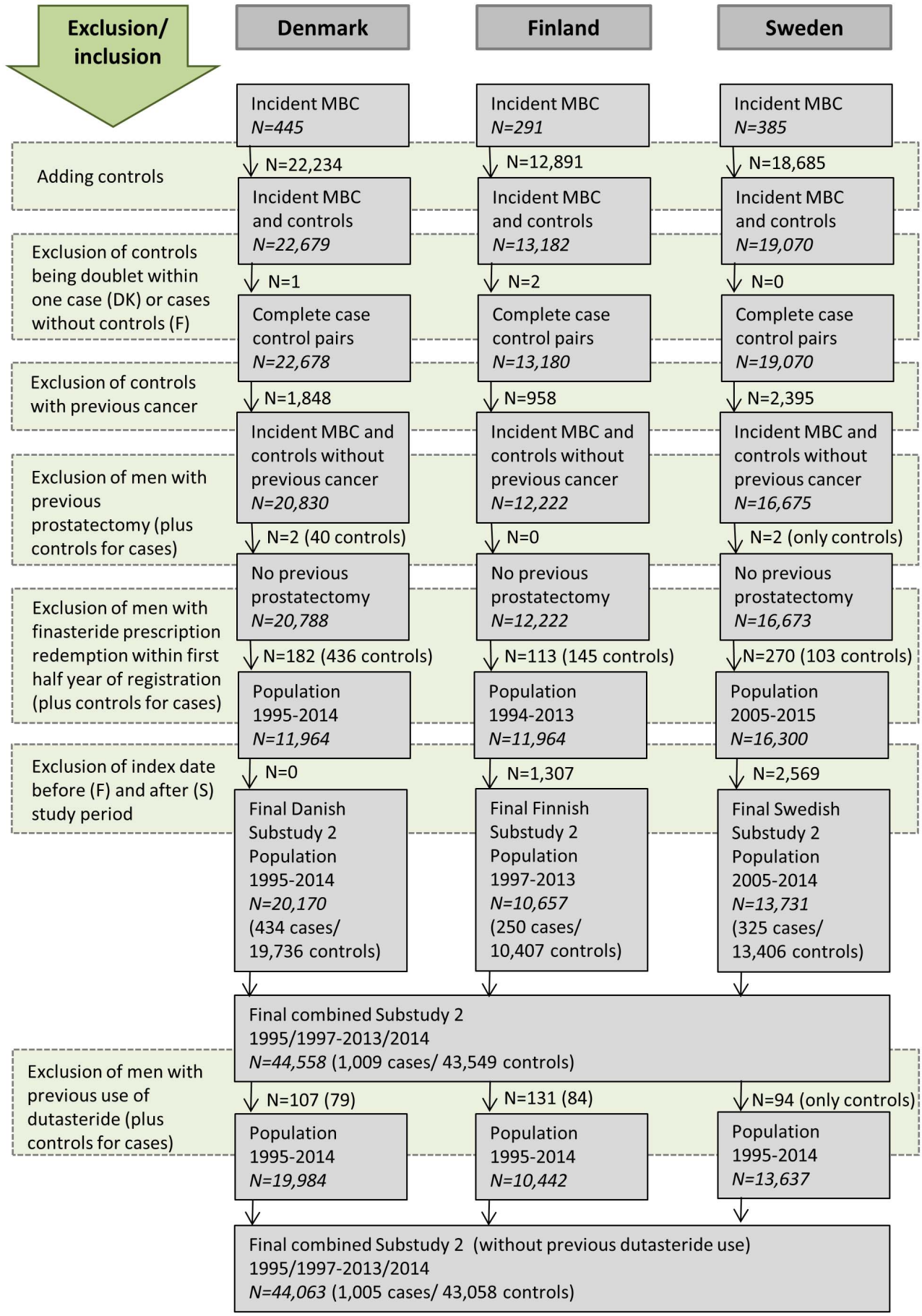
(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, educational level, testicular disorders and urban/rural differences. Confounders are included as the main analysis without any lagging. Conditional logistic regression.

When including Sweden and inferring 2 years lag, there is no association between finasteride use and breast cancer (Table 2.42).

ANNEX 1D FLOWCHART SUBSTUDY1


Exclusion/ inclusion
Denmark
Finland
Sweden
Finasteride users (1995-2014) N=54,751
Finasteride users (1997-2013) N=106,169
Finasteride users (2005-2014) N=134,680
Exclusion of rare values (i.e., age=118 years)
N=1
N=0
N=0
Finasteride users N=54,750
Finasteride users N=106,169
Finasteride users N=134,680
Adding controls
N=54,750
N=106,169
N=134,680
Finasteride users and non-users N=109,500
Finasteride users and non-users N=212,338
Finasteride users and non-users N=269,360
Exclusion of men aged < 35 years (and their case or control)
N=0
N=5 (5)
N=1 (1)
Finasteride users and non-users N=109,500
Finasteride users and non-users N=212,328
Finasteride users and non-users N=269,358
Exclusion of men with finasteride prescription redemption within first half year of registration (plus controls for cases and cases for controls)
N=8,017 (7,953)
N=13,388 (13,190)
N=27,831 (27,791)
Final Danish Substudy 1 Population 1995-2014 N=93,530 (46,765 cases/ 46,765 controls)
Final Finnish Substudy 1 Population 1997-2013 N=185,750 (92,875 cases/ 92,875 controls)
Final Swedish Substudy 1 Population 2005-2014 N=213,736 (106,868 cases/ 106,868 controls)
Final combined dataset for Substudy 1 1995/1997-2013/2014 N=493,016 (246,508 cases/246,508 controls)

ANNEX 1E FLOWCHART SUBSTUDY2



MBC = male breast cancer; DK = Denmark, F = Finland, S = Sweden

04X8V6

ANNEX 1F PROTOCOL AMENDMENT DATED ON 10-FEB-2015

February 10, 2015

To: EP02003.021 Registry owners/IRBs

RE: Finasteride Nordic Registry Study (EP02003.021) - Administrative Change Letter

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This memo serves to notify registry owners that the timelines for the Finasteride Nordic Registry Study have been adjusted. In addition, after discussion with experts and after ensuring available specifications/coding of the variables from the different country registries, the tables on potential confounding factors, factors potentially associated with surveillance bias and registers included in this study had to be amended. These changes are minor and listed below:

- The study period has been extended from 2012 to 2013 throughout the protocol; data for 2013 will be requested (if available).
- Abstract page 3 and throughout Section 9: As the DAG has been performed, the wording in the protocol regarding the DAG has been updated to reflect. In addition, the results of the DAG have been added and the Statistical Analysis Plan (SAP) is referred to for further details.
- Abstract page 4 and Page 8, Section 9.1.3. Substudy 2: Combining the use of finasteride and dutasteride (i.e. use of any 5alpha-reductase inhibitors) has been included as a supplementary analysis and the Statistical Analysis Plan (SAP) is referred to for further details.
- Page 5, Section 6: Milestones: The timeline for this study has been taken out of protocol and added as standalone document 11 in Annex 1.
- Page 11-14, Table 2: Information on potential confounding factors: This table had to be amended to account for the exclusion of 4 variables (BRAC1 and BRAC2 gene mutations; Never having had children; Charlson's comorbidity index; Number of prescriptions) and inclusion of 2 new variables (Dietary intake of animal fat; History of bone fractures).
- Page 15, Table 3: Information on factors potentially associated with surveillance bias included in the study and data sources: This table had to be amended to account for the exclusion of 2 variables (Number of visits to general practitioner, prior benign prostatic hyperplasia therapy) and inclusion of 2 new variables (Number of prescriptions; Number of admissions).
- Page 16-17, Table 4: Registers included in this study: The names and dates of the national registers have been update and the national health service registers have been removed.
- Page 24-25, Section 11: More detail has been added to this section in compliance with the template.
- EnCePP checklist is included in Annex 2

Thank you for your attention in this matter.

ANNEX 1G PROTOCOL AMENDMENT DATED ON JAN 2018

January 2018

To: EP02003.021 Registry owners/IRBs

RE: Finasteride Nordic Registry Study (EP02003.021) - Administrative Change Letter

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This amendment concerns the previously submitted study protocol regarding Finasteride Nordic Registry Study (EU procedure SE/H/158/01/FU/02), that was approved in May 2015. The major change is the exclusion of Norway data from the study. As per protocol, the data from four Nordic countries (i.e. Sweden, Denmark, Finland and Norway) was planned for inclusion in the analysis. However, due to changes to the privacy legislations in various European countries, there have been significant challenges and delays in obtaining and linking data from registers to obtain the dataset needed to conduct the study.

As of October 2017, an academic research organization (Applied Economics and Health Research, ApEHR), which has been contracted to conduct the study on behalf of MSD, was able to secure the data from Sweden, Denmark and Finland but not from Norway. The data from Norway has to be collected from a variety of registers separately and then sent to a coordinating unit for data linkage. The Norwegian prescription register does not allow linkage to other registers. Despite multiple efforts to obtain these data, including attempts through a third party, the Nordman collaboration, there is no clear timeline for data delivery. As a consequence, it is not possible to obtain these data in a timely manner to fulfil our commitment, and to deliver the final study report in the second quarter 2018.

In order to avoid further delays in completing this post-authorization safety study, MSD, in agreement with ApEHR, decided to proceed with the data analysis collected from Sweden, Denmark and Finland, and to exclude data from Norway. This decision was also based on the fact that Norway contributes the least number of person-year exposure to finasteride (59605/1365088=4.4% person-years), and the least number of male breast-cancer cases (101/902=11.2%), per Stage 1 study [Ref. 5.4: 04TKBN], compared to the other three countries included in the study. The lack of data from Norway has a minor impact on the power of the study: the final analysis has 80% power to detect a minimum Odds Ratio (OR) of 1.65 in the absence of Norwegian Data, and 1.51 if data from Norway were available and could be included.

In addition to the exclusion of Norway data from the study, minor amendments to the protocol are also made and listed below:

Amendment	Date of change	Reference to the protocol	Deviation Description	Required Action	Justifications
1	Dec 20 2017	9.1.3. Substudy 2	Finland: The controls are matched to the cases both on time, age and municipality. The municipality matching is a deviation from protocol.	The investigators have pair id included in the conditional logistic regression analysis.	This deviation was due to the error by Statistics Finland. This change in sampling of controls will in a few instances result in a lower number of controls since the investigators match closely on age and municipality. Since the investigators have sampled up to 50 controls per case this change will have minor influence on the power of the study.
2	Dec 20, 2017	9.7. Data analysis, and Table 3	Finland: Both substudy 1 and 2. Numbers of prescriptions for the surveillance bias analysis are collected for the whole study period instead of the last 10 years, i.e. from 1994 onwards. This influences tables 1.21 and 1.22 on how surveillance bias influences finasteride use and table 2.29 and 2.30 on how surveillance bias may influence the association between finasteride use and breast cancer.	None.	This is the way prescriptions have been collected in Finland. This change may result in slightly more redemptions in Finland for persons sampled by the end of the study period. The investigators deem this as a minor deviation.
3	Dec 20, 2017	9.7. Data analysis	Finland: Only data on Finasteride 5mg are available and only available since 1997	The investigators analyze the data available.	The low dose of finasteride used for treating male baldness will not be included for Finnish men. This is a minor deviation since the majority of cases and controls will be older men who will not be treated for baldness, which means that the investigators will have most of the exposure in Finland.
4	Dec 20, 2017	9.7. Data analysis, and Table 2	Sweden: Urbanization is provided by municipality and not by residential location.	The investigators harmonize data across the three countries.	The investigators harmonize data across the three countries and will include this information as a binary measure of urban area versus rural area, which means that the relative measure of urban versus rural will be nation-specific. The influence will therefore be minimal.
5	Dec 20, 2017	9.7. Data analysis, and Table 2	Sweden: Data on dietary factors is not available in substudy 1a.	Sweden will not be included in these analyses.	The analysis of influence of dietary factors will only be studied among Finnish and Danish men. The investigators do not anticipate that the associations between dietary factors and finasteride are different

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Amendment	Date of change	Reference to the protocol	Deviation Description	Required Action	Justifications
					between the three countries.
6	Dec 20, 2017	9.7. Data analysis, and Table 2	Substudy 1a - survey study: In Finland, only information on vegetables intake is available in 2011 (and no information on fruit intake).	Change definition of variable.	The investigators have changed the variable to vegetable intake for Denmark and Finland (Sweden do not have dietary factors, see Amendment 5) at all time points instead of a combined variable for vegetable and fruit intake. The focus will therefore be on one dimension of healthy eating.
7	Dec 20, 2017	9.7. Data analysis, and Table 3	Number of hospitalizations as a measure of surveillance bias. The investigators will include number of contacts to hospitals instead of number of hospitalizations. This will influence tables 1.21, 1.22, 2.33 and 2.34. Contact includes both in hospital, outpatient and emergency room visits.	The investigators include number of contacts to hospitals and not number of hospitalizations.	The number of contacts to hospitals is more relevant measure of surveillance bias instead of number of hospitalizations since surveillance of medical doctors will happen at each contact.
8	Dec 20, 2017	9.7. Data analysis	In the protocol, it is stated that it should be considered to use propensity score for confounder adjustment in substudy 2. In the analysis, the investigators have decided to not to use propensity scores in the adjustments in substudy 2.	None.	This is a precision improvement of the protocol. In the development of the analysis strategy from the protocol to the outline in the statistical analysis plan, the investigators have reconsidered the use of Propensity Score Matching (PSM) in relation to the case-control design in sub study 2. Using PSM in case-control studies may introduce bias since the investigators sample cases and controls conditional on the outcome, which may introduce collider bias. Furthermore, the number of confounding factors in substudy 2 is not large which makes it less relevant to combine the confounding factors into one propensity score. The investigators have therefore decided not to use PSM in substudy 2.

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Amendment	Date of change	Reference to the protocol	Deviation Description	Required Action	Justifications
9	Dec 20, 2017	9.7. Data analysis	The variables living as a single man and living in urban area should have been collected one year before index date and the variable occupation exposure should have been collected two years before baseline. Since the register data is not collected at the same time points in all countries these variables have been changed to the most recent information available.	The investigators will include the most recent information available.	For the census data from Finland, the investigators have information every 5th year, meaning that the investigators will not be able to construct single man and living in urban area one year before. Since information on these variables is collected at different time points in the three countries, the investigators have changed the variables to collect the most recent information before index date.
10	Dec 20, 2017	9.7. Data analysis, and Table 2	Table 1.1. Men who have had night-shift work are not included as occupational exposure.	Occupational codes for these specific occupations were not possible to identify. Occupational codes excluded.	It was not possible based on register information to identify occupations that were characterized as night-shift work. This information should only have been included in substudy 1 to describe finasteride users and was not a confounding factor in substudy 2. This omission should have a minor influence on the study results.
11	Dec 20, 2017	9.7. Data analysis	Table 1.10. Change the table which originally should have investigated use of finasteride among alpha blocker users and vice versa to investigate alpha-blockers use stratified by finasteride use. (The study question is whether alpha-blocker use is before finasteride use).	This means that the left-hand side of the table should be to investigate alpha-blocker use among finasteride users while on the right hand side the investigators will investigate alpha-blocker use among finasteride non-users.	This is a precision improvement of the protocol. The reason for changing this analysis is that the focus of the present study is on finasteride use and not alpha blocker use in general and the investigators have therefore not sampled alpha blocker users.
12	Dec 20, 2017	9.7. Data analysis	Tables 1.11 and 1.12. Exclusion of these tables of how descriptive factors are associated with finasteride use among persons without alpha-blockers and with alpha-blocker use among finasteride non-users.	Exclusion of table 1.11 and 1.12	The question was raised from tables 1.10-1.12 was to investigate the use and co-use of alpha-blockers and finasteride in the Nordic countries. The study of the association between covariates and alpha-blockers among finasteride non-users, and finasteride users among alpha-blocker non-users is not relevant for the present study. The investigators have therefore not applied for data on a cohort of

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Amendment	Date of change	Reference to the protocol	Deviation Description	Required Action	Justifications
					alpha-blocker users and non-users.
13	Dec 20, 2017	9.7. Data analysis	Table 1.21-1.32 (supplementary analysis 8 of the influence of surveillance bias) will be changed to one table (now numbered table 1.21 and 1.22) on the association between the surveillance bias variables and finasteride use. The investigators will also include benign breast disease as a surveillance bias variable.	Change of table 1.21-1.32.	Supplementary analyses concerning surveillance bias will be changed to the association between the surveillance variables and finasteride use. The investigators will also include benign breast disease as a surveillance bias variable. The analysis was stated in the protocol, but the tables were not listed in the table shells.
14	Dec 20, 2017	9.7. Data analysis	Table 1.33-1.34 (analysis of association between covariates and finasteride users among breast cancer cases) will be excluded.	Exclusion of table 1.33 and 1.34.	The tables are excluded since the investigators do not have breast cancer information in substudy 1.
15	Dec 20, 2017	9.7. Data analysis	Concerning substudy 1a, the number of finasteride users and non-users in the survey data is too small to study cumulative finasteride use. Tables: 1A.1-1A.4 will therefore only include finasteride use versus non-use.	Restrict the analysis to the binary outcome.	This is a minor change since the investigators are primarily interested in investigating the association between self-reported factors and finasteride use and not on cumulative use of finasteride.
16	Dec 20, 2017	9.7. Data analysis	Finland: Survey data. Instead of looking 5 years back from index date the investigators look 10 years back. This will influence tables: 1a.1-1a.4.	Changed period for inclusion of survey data information.	The investigators only have survey data from 2000 and 2011, and all the persons included between 2006-2010 would not be included with the 5-year interval. This has minor influence since the investigators expect that life style factors will be relatively constant in the specific age span for the present study.

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Amendment	Date of change	Reference to the protocol	Deviation Description	Required Action	Justifications
17	Dec 20, 2017	9.7. Data analysis	Finland. Survey data. The investigators have received grams of meat per day, which is not compatible with variable of interest (daily intake of animal fat).	Exclusion of variable.	The investigators do not include meat intake in Finland. Since the investigators have no dietary data from Sweden, the analysis of meat intake and finasteride use will only be based on Danish data. This is a limitation which minimizes the generalizability of the result of meat intake and finasteride use. Since substudy 1A is primarily a descriptive study, this modification will have a minor impact.
18	Dec 20, 2017	9.7. Data analysis	Substudy 1: Omit Supplementary analysis 9 (analysis of lag 1 and lag 2 on the association between covariates and finasteride use).	Omit analysis.	The analysis does not add information to answer the substudy 1 aim because an analysis of whether a confounder measured longer away in time is stronger or weaker associated with finasteride use is not relevant for substudy 1 research question.
19	Dec 20, 2017	9.7. Data analysis	Substudy 1A. The investigators suggest only to do the analyses in substudy 1A for all three countries combined instead of Finland and Denmark separately.	Omit table 1A.3.	The sample size in substudy 1A is not large. The analysis is meaningful when data for all the three countries are combined.

Thank you for your attention in this matter.

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[Ref. 5.4: 04TKBN] Meijer, M., Thygesen, L. C., Green, A., Emneus, M., Brasso, K., Iversen, P., Pukkala, E., Bolin, K., Stavem, K. and Ersbøll, A. K. (2017), Finasteride treatment and male breast cancer: a register-based cohort study in four Nordic countries. Cancer Med. doi:10.1002/cam4.1273

ANNEX 1H SAP

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

Statistical Analysis Plan

Version 1: 30 January 2015

INVESTIGATOR

PPD

- PPD
- PPD

PPD

- PPD
- PPD
- PPD

National scientific coordinators

- Denmark: PPD
- Finland: PPD
- Norway: TBD
- Sweden: PPD

Expert group

- PPD Denmark
- PPD Denmark

Additional experts will be included as the project starts

Table of Contents

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List of Abbreviations

ATC	Anatomical Therapeutic Chemical Classification System
DAG	Directional acyclic graph
EU	The European Union
FDA	US Food and Drug Administration
ICD	International Classification of Diseases
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
OR	Odds ratio

List of Definitions

Male breast cancer	*A primary male breast cancer case will be defined as one that is recorded in the cancer registers, as per ICD-7 (170) and ICD-10-CM (C50).*
Finasteride use	*Finasteride use as per ATC-codes G04CB01,D11AX10 and G04CB04 in Finland from 1994–1996 in the prescription registers will be defined both as a binary variable (at least two prescriptions of finasteride versus less than two prescriptions) and a cumulative variable (2–3 packs of 98 pills, 4–6 packs, or 7+ packs of finasteride versus less than two packs of finasteride).*
Dutasteride use	*Dutasteride use is a as per ATC-code G04CB02 (at least two prescriptions of dutasteride). Dutasteride is a drug within the same drug class as finasteride.*
Potential confounders	*Potential confounders are defined as factors based on the literature and/or expert knowledge which are candidates to confound the association between finasteride use and male breast cancer.*
Confounder	*A confounder is a variable other than the main variables under study (finasteride use and male breast cancer) that is assumed to confound of the association between finasteride use and male breast cancer. Confounders will be identified from the directional acyclic graph (DAG) performed prior to the study including all potential confounders.*
Covering period for registered information	*The registers' covering period is defined as the period where information from the national patient registers, the cancer registers, the civil registration systems and the prescriptions registers for each country is available. The covering period for registered information is 1995–2013 for Denmark, 1994–2013 for Finland, 2008–2013 for Norway, and 2005–2013 for Sweden.*

1 Statistical Analysis Plan

Study objectives

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

1. Describe finasteride users (two and more prescriptions of finasteride) compared to non-users (less than two prescriptions of finasteride) with respect to potential confounding factors (substudy 1).
2. Analyze the effect of finasteride use on male breast cancer incidence while taking account of confounding factors decided in a directional acyclic graph (DAG) (substudy 2).

The hypotheses are:

1. There is a systematic difference between finasteride users and non-users (less than two prescriptions of finasteride) 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, therefore the model adjusted for confounding factors will have a lower odds ratio.

The reason for defining finasteride users as persons with two or more prescriptions of finasteride is because these persons with repeated purchases of finasteride are more likely to also have used most of the drugs compared to persons with only one prescription.

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 prescription, cancer incidence, contacts to primary health care, the secondary and tertiary hospital system, the civil registration system, and registers on occupational group. The registers include information from different time periods (see Table 1 below). The covering period refers to the period where information is available from the four central registers in this study: the central registration systems, the cancer registers, the prescriptions registers and the national patient registers. The covering period is 1995–2013 for Denmark, 1994–2013 for Finland, 2008–2013 for Norway, and 2005–2013 for Sweden. Linkage between the registers is possible due to the unique individual identification numbers (Gissler and Haukka, 2004; Thygesen et al, 2011). We will also include national health surveys conducted in each of the countries several times during follow-up.

Table 1: Registers included in the study

Country	Register	Registration period
Denmark	Prescription register	1995–2013
	Cancer register	1943–2013
	National patient register	1977–2013 (outpatient contacts since 1995)
	Civil registration system	1968–2013
	Register-based labor force statistics (RAS statistics)	1980–2013

Table 1: Registers included in the study

Country	Register	Registration period
	National Health Surveys	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 labor force statistics (AaNAV)	2000 (2007) – 2013
	National Health Surveys	1994–2003
Sweden	Prescription register	2005–2013
	Cancer register	1958–2013
	Patient register	1987–2013
	Civil registration system (Register over total population)	1968–2013
	Register on labor 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 et al, 2011; Pukkala, 2011). The national patient registers include diagnostic and treatment information for patients treated at the secondary and tertiary hospital level (Lynge et al, 2011; Pukkala, 2011). Clinical experts have been consulted on how to include this information. The codes will be described in the data control template. Information on date of birth, immigration, emigration, and death will be 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 et al, 2011; Pukkala et al, 2009).

We will also include information from population surveys conducted in Denmark (Christensen et al, 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 (further described in the "study population" section below).

Data management

The handling of data includes seven steps.

1. All national scientific coordinators will apply to 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 (less than two prescriptions of finasteride).
   - Study population consisting of all 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 registers described in the section "Data sources". All national scientific coordinators will produce a data control report describing the checks performed and describing how the final dataset should be constructed from the registers received including suggestions for modifications and exclusions. A template for data control will be provided. 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. The national specific coordinators should send the original data together with the data control report that describes data and suggestion on how to handle missing values and invalid codes to the Danish specific coordinator who is responsible for cleaning the data. Please also read section 1.1.3 of this document for further elaboration of how the handling of missing data will be done. Data control includes:
   a. Information on known misclassification of each variable, e.g. underreporting, low sensitivity or specificity, categorization with obvious invalid values
   b. Check for legal values for each categorical variable. Check for reasonable distribution of variables. Include advice on how to handle odd observations.
   c. Check for reasonable minimum, maximum and central tendency (median, mean) for each continuous variable. Checks for outliers must be performed by e.g. explorative plots such as box-whiskers plot. Include advice on how to handle odd observations.
   d. Check of chronological relation between date variables: At least date of birth before all other dates and date of death after all dates, but also reasonable relation of dates of diagnoses and prescriptions. Odd patterns should be described and include solutions for handling such observations.
   e. Check of missing information on variables and advice on how to handle such observations (e.g. delete observations with missing information, put missing observations into a specific category, etc.).
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 by the national scientific coordinators 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 "Study objective") using SAS version 9.3 will be performed by the Danish scientific coordinator. Please also see section 1.1.

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: In Denmark, we excluded 307 prescriptions among 737,124 prescriptions with no date of birth. In Sweden, Norway and Finland we didn't have to exclude any persons because of inconsistencies between dates. If the same pattern is observed in this study we will also remove persons with inconsistencies as we believe this is a negligible proportion that is too small to influence the results.

Study population

The two substudies consist of two study populations:

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). We defined users as persons with at least two subsequent prescriptions to be more certain that they were actually exposed. 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 2005–2013 in Sweden. During the analysis phase we will also compare users with a higher consumption of finasteride with users with lower consumption and non-users (less than two prescriptions of finasteride). 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 the analysis for differences in age.

In substudy 1A we will include all finasteride users (substudy 1 data) who previously have participated in a survey. The information required on life-style factors for substudy 1A is collected only through these surveys. Each finasteride user will be compared to sampled non-users (less than two prescriptions of finasteride) who previously have participated in a survey. We will include the most recent information with respect to finasteride use on life-style factors.

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 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 odds ratio (OR) in section 1.3).

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 (both as one group and 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
- 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).

Variables

ICD8, ICD9 and ICD10 codes have been used in different time periods in the four Nordic countries (Engholm et al, 2010) (see Table 2 below).

Table 2: Overview of the when ICD7, ICD8, ICD9 and ICD10 codes were used in each of the Nordic countries.

	ICD7	ICD8	ICD9	ICD10
Denmark	1958-1968	1969–1993	ICD9 never used in Denmark	1994–present
Finland	1952-1968	1969–1986	1987–1995	1996–present
Norway	1958-1968	1969–1985	1986–1995	1996–present
Sweden	1960-1968	1969–1986	1987–1996	1997–present

A primary breast cancer case will be defined as one that is recorded in the cancer registers, *as per ICD-7 (170) and 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).

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. For both substudies finasteride use will be defined both as a binary variable (at least two prescriptions of finasteride versus less than two prescriptions) and a

cumulative variable (2–3 packs of 98 pills, 4–6 packs, or 7+ packs of finasteride versus less than two packs of finasteride).

In substudy 1, the dependent variable is both redemption of two or more finasteride prescriptions and the comparison group of males with less than two prescriptions sampled from the population and 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 3. 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 redemption of two or more finasteride prescriptions and the comparison group of males with less than two prescriptions sampled from the population and 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 3, but in the analysis only variables in the selected minimum sufficient confounder set in the DAG will be included (described in more detail in the DAG document). Furthermore, variables that may be associated with surveillance bias will be studied (Table 4).

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 3, 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 4 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. Furthermore, side effects of finasteride use are breast tenderness, gynaacomastia, etc, which could lead to more careful surveillance of finasteride users. The analyses in substudy 2 will be stratified on each of the factors to detect whether an increased OR could be explained by surveillance bias (also termed detection bias). Another appropriate approach for addressing potential detection bias would have been to compare cases at different levels of each variable in table 4 regarding cancer stage at diagnosis. However, the validity on cancer stage variable in the registers is low and this approach is therefore not feasible (Jensen 2002).

Table 3: Information on potential confounding factors that will be included in substudy 1 and may be included in substudy 2 depending on the final DAG developed

Confounding factors	Explanation	Data source (also see Table 1)	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 might be associated with higher detection of breast cancer	National Patient Registers. Included the following breast complains if codes are available and reliable in the register: breast pain, nipple pain and nipple tenderness.	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 from nation-wide registers and self-reported height and weight from nation-wide surveys	National Patient Registers including the following disorders: Obesity. Furthermore self-reported height and weight from nation-wide surveys	Any diagnosis before finasteride use or self-reported BMI before finasteride use. Obesity is defined as BMI $\geq$ 30	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, toxic liver disease with fibrosis and cirrhosis, liver fibrosis and cirrhosis, and if codes are available and reliable in the registers we will additionally include liver disorders that can be associated with changes in androgen/estrogen due to reduced metabolism of estrogens, alterations of sex hormone-binding globulin synthesis/free hormone levels.	Any diagnosis before finasteride use	Any diagnosis before breast cancer index date

Table 3: Information on potential confounding factors that will be included in substudy 1 and may be included in substudy 2 depending on the final DAG developed

Confounding factors	Explanation	Data source (also see Table 1)	Substudy 1 (1)	Substudy 2 (2)
- 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 have this syndrome and may therefore not be relevant in the present study	National Patient Registers	Any diagnosis before finasteride use	Any diagnosis before breast cancer index date
- 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 labor force Finland: Censuses Norway: Censuses Sweden: Register-based labor force behavior; place of work; employer etc. (source: LISA)	Labor market affiliation in any of these occupations two calendar years before finasteride use	Labor market affiliation in any of these occupations two calendar years before breast cancer index date
Family exposures				

Table 3: Information on potential confounding factors that will be included in substudy 1 and may be included in substudy 2 depending on the final DAG developed

Confounding factors	Explanation	Data source (also see Table 1)	Substudy 1 (1)	Substudy 2 (2)
- 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
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 within last 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 within last five years before finasteride use	Self-reported information will not be included
- Dietary intake of vegetables and fruit	Vegetable and fruit intake is a preventive factor for breast cancer	Nation-wide surveys	Intake within last five years before finasteride use	Self-reported information will not be included
Dietary intake of	Animal fat is a risk factor for breast cancer	Nation-wide surveys	Intake within last five years before finasteride	Self-reported information will not be

Table 3: Information on potential confounding factors that will be included in substudy 1 and may be included in substudy 2 depending on the final DAG developed

Confounding factors	Explanation	Data source (also see Table 1)	Substudy 1 (1)	Substudy 2 (2)
animal fat			use	included
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 labor force Finland: Censuses Norway: Census 2001 Sweden: Register-based labor 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	Living as a single man is associated with Finasteride use	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	Any diagnosis before finasteride use	Any diagnosis 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) (Brinton et al, 2014)	National patient registers	Any diagnosis before finasteride use	Any diagnosis 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 4: 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 1)	Substudy 2
- Benign breast disease	One side-effect of finasteride use is gyneaecomastia. Gyneaecomastia is part of the benign breast disease variable described elsewhere. Gyneaecomastia and benign breast disease might be associated with higher detection of breast cancer	National Patient Registers	Any diagnosis before breast cancer index date
- Use of drugs or exposure to environmental agents that cause or may 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

The categorization of variables is shown in Table 5. For some variables (e.g. number of prescriptions redeemed, number of admissions and data of birth) we cannot decide *a priori* whether to include the variables continuously or categorically. We will test the assumption of linearity by including, in the outcome model, the variable both continuously and categorically and evaluate the significance of the categorical variable for significance indicating violation of the linearity assumption.

Table 5: Categorization of variables

Variables	Time period in relation to index date (finasteride use or breast cancer diagnosis)	Coding
Finasteride use (dichotomous)	As long as possible	0: 0–1 prescription 1: two or more prescriptions
Finasteride use (cumulative use)	As long as possible	1: 0–1 packs of 98 pills 2: 2–3 packs 3: 4–6 packs 4: 7+ packs
Testicular abnormalities/disorders	As long as possible	0: no diagnosis registered 1: yes
Benign breast disease	As long as possible	0: no diagnosis registered 1: yes
Obesity	As long as possible	0: no diagnosis registered and BMI<30 from self-report 1: yes or BMI≥30
Liver cirrhosis	As long as possible	0: no diagnosis registered 1: yes
Klinefelter's syndrome	As long as possible	0: no diagnosis registered 1: yes
Estrogen therapy	10 years before first finasteride prescription/cancer index date	0: 0–1 prescription 1: two or more prescriptions
Occupational exposure	Two calendar years before first finasteride prescription/cancer index date	0: have not worked in any of perfume industry, high-temperature environments and night-shift work 1: have worked in the perfume industry, in high-temperature environments or night-shift work
Family history of breast cancer	As long as possible	0: no parents/siblings with cancer diagnosis 1: one or more parent(s)/sibling(s) with cancer diagnosis
Radiation exposure	As long as possible	0: no diagnosis registered 1: yes
Alcohol intake	Five years before finasteride use	0: <21 units/week 1: ≥21 units/week
Physical inactivity	Five years before finasteride	1:sedentary

Table 5: Categorization of variables

Variables	Time period in relation to index date (finasteride use or breast cancer diagnosis)	Coding
	use	2:light physical activity (<4hours/week) 3:moderate/high physical activity (≥4hours/week)
Dietary intake of fruit and vegetables	Five years before finasteride use	0: consuming fruit and/or vegetables less than daily 1: consuming fruit and/or vegetables daily
Dietary intake of animal fat	Five years before finasteride use	0: consuming animal fat less than daily 1: consuming animal fat daily
Socioeconomic position (years of education)	The year before first finasteride prescription/cancer index date	The categorization of socio-economic position will be based on inputs from the national coordinators and official classifications. The official ISCED classification will probably be used for classification of educational level.
Living as a single	The year before first finasteride prescription/cancer index date	0: not living alone (married or unmarried) 1: living as a single man
Urban/rural differences	The year before first finasteride prescription/cancer index date	Based on inputs from the national coordinators, the official definitions of urban and rural areas from each statistical office will be used
Diabetes	10 years before first finasteride prescription/cancer index date	0: no diagnosis registered 1: yes
History of bone fracture	10 years before first finasteride prescription/cancer index date	0: no diagnosis registered 1: yes
Use of drugs or exposure to environmental agents that cause or may cause gynaecomastia	As long as possible	0: 0–1 prescription 1: two or more prescriptions
Number of prescriptions redeemed	10 years before first finasteride prescription/cancer index date	Continuous or binary (the median and below and above the median)
Number of surgeries	As long as possible	Continuous or binary (the median and below and above the median)
Number of admissions	10 years before cancer index date	Continuous or binary (the median and below and above the median)
Urinary retention	As long as possible	0: no diagnosis registered 1: yes

Table 5: Categorization of variables

Variables	Time period in relation to index date (finasteride use or breast cancer diagnosis)	Coding
Cancer stage	No, cancer stage of the index cancer	1: Localized 2: Regional 3: Metastatic
Date of birth	---	Continuous or categorical in five year age groups in substudy 1. Age not included in substudy 2 as we match on age

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; it has been shown that the validity and completeness of the Danish Cancer Registry is high (Gjerstorff, 2011) and that the registration of incident breast cancer tumors had a very high completeness in the Danish Cancer Registry (Jensen, 2002). This validity study does only include female breast cancer and shows that the completeness of the cancer diagnosis registration in the Danish Cancer Registry was 100 % compared to the medical records of the study cohort (Jensen, 2002). The completeness and validity of the Swedish Cancer Registry is high, as only 1.4% of the of the cancer cases reported in the national patient register were not found in the Swedish Cancer Registry; however, this percentage was higher for male breast cancer (i.e. 25% for persons aged 0-69 years and 31% for persons 70 years or older, but these numbers relied on very few cases) (Barlow 2009). Studies of the Norwegian Cancer Register have shown that the data were accurate and close-to-complete, as 94 % of the cases registers in the national patient register were registered with the same diagnosis in the Norwegian Cancer Register (Larsen 2009; Bakken 2014). The completeness and validity of the Finnish Cancer Registry has been evaluated as very high (Pukkala, 2011). The Danish National Prescription Registry has data of high quality including detailed information on dispensed drugs and as the register covers all prescription dispensed in Danish pharmacies, loss to follow-up is unlikely for individuals with permanent residence in Denmark (Kildemoes, 2011). The completeness of the Norwegian and Swedish prescription registers is characterized as good (Furu 2008; Wettermark 2007). Completeness of registration in the Norwegian prescription register is ensured by law and quality checks are carried out monthly and half-yearly to identify possible errors or inconsistencies (Furu 2008). The patient identity data are only missing for approximately 0.3 % of all items in the Swedish prescription register (Wettermark 2007). The Finnish prescription register has been described in detail and considered as excellent (Klaukka 2001). The Norwegian Patient Register had relatively good agreement with the Norwegian Cancer Register, as mentioned above (Bakken 2012) and the completeness and accuracy of the Finnish Patient Register has been evaluated as varying from satisfactory to very good for common diagnoses with positive predictive values ranging from 75%–99% (Sund 2012). The validity of the Swedish Patient Register is high for many, but not all diagnoses. The positive predictive values

of most diagnoses in the Swedish Patient Register compared to medical records ranged from 85–95% (Ludvigsson 2011).

The statistical analyses will be performed on servers at Statistics Denmark. The statistical programs will be stored at the servers at Statistics Denmark and will be attached as a stand-alone document to the final study report.

The programming (data management and statistical analyses) will be performed 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. If any inconsistencies are found, the programming will be reviewed until complete agreement.

1.1 Statistical Methods

The data analyses are comprised of analyses from substudy 1 (including 1A) and substudy 2. Prior to the data analyses, a directional acyclic graph (DAG) of the association between finasteride use and male breast cancer including potential confounders was derived. A set of table shells of how all of the analyses results will be presented can be found in a separate document.

Directional acyclic graph

The Danish national investigators and the clinical expert group have derived the DAG, using a previously developed methodology (Greenland et al., 1999). This development highlights factors associated with finasteride use, factors that are a consequence of finasteride use, and factors associated with male breast cancer risk. The DAG clarifies whether the factors listed in Table 3 are or may be classified as confounders, colliders, or intermediate variables. This clarification decides which confounders will be included in substudy 2. All factors associated with finasteride use or male breast cancer will be included in the descriptive substudy 1. Please refer to the description in the DAG document. 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.

Substudy 1

In substudy 1, persons with at least two subsequent prescriptions of finasteride and persons with less than two prescriptions of finasteride and persons with different levels of cumulative finasteride use, i.e. 0–1 packs, 2–3 packs, 4–6 packs, and 7+ packs (one pack is equivalent to 98 pills, 5 mg per pill) are compared with respect to potential confounding factors described in Table 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 (less than two prescriptions of finasteride) using density sampling (Rothman et al, 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 (i.e. date of inclusion or date of second finasteride prescription) and information on confounding factors will be extracted for the period before the index date (see Table 3 for the time frame before index date). Using this sampling scheme the odds ratio (OR) 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 et al, 2008). For the cumulative use analysis, three logistic regression models will be performed: Men with 2-3 packs will be compared with the non-users (0-1 packs), men with 4-6 packs will be compared with non-users and men with 7+ packs will be compared to non-users. This means that a man with 7 or more packs of finasteride will be included in all three analyses compared with the same non-users and the groups will therefore not be mutually exclusive. Information on confounders will be obtained for the time when the man fulfills finasteride use (2, 4 and 7 packs of finasteride use). For confounders with more than two categories, the OR estimated can be interpreted as incidence rate ratios for each category compared to a reference group. Two groups of analyses will be performed: Univariable analyses including each potential confounder one at a time and adjusted analyses including each potential confounder one at a time adjusted for age, country and calendar time. Several supplementary analyses will be performed including use of 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 1.1.2.

The matching criteria of substudy 1 are:

- Country
- Follow-up time (density sampling)

Substudy 1A

In substudy 1A finasteride users will be compared with non-users (less than two prescriptions of finasteride) in a logistic regression model with respect to self-reported life-style factors as obesity, alcohol intake, and physical inactivity – these analyses are also listed in Table 3. In this study, we link national surveys including self-reported information on these potential confounders with finasteride users and non-users on an individual level, defined by use of a binary and a cumulative measure of finasteride use (substudy 1 data). This means that individual level data is available on both life-style factors and finasteride use.

Substudy 2

In substudy 2, the effect of finasteride use versus non-use (less than two prescriptions of finasteride) and cumulative finasteride use on male breast cancer is analyzed taking account of the confounding factors selected by the previously developed DAG. 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 1.3). This substudy will also utilize a new user design by excluding as cases and as controls finasteride or

dutasteride users with the first redemption within the first 6 months of registration. Conditional logistic regression will be performed to take account of the country- and age-matching. 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 5 alpha reductase inhibitor), 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, cumulative use analysis and stratified on factors associated with surveillance bias and latency. In the cumulative use analysis the groups will be mutually exclusive. The supplementary analyses are further described in section 1.1.2.

The matching criteria of substudy 2 are:

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

1.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. descriptive statistics, odds ratios, incidence rates, test/retest reliability)

For both substudies finasteride use will be defined as a binary variable (at least two prescriptions of finasteride versus less than two prescriptions) and 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 both a long follow-up time including only Denmark and Finland (1995/1994–2013) and a follow-up period including the available data from all four countries (Denmark (1995–2013), Finland (1994–2013), Norway (2008–2013), and Sweden (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 Table 6a and Table 6b: A (long follow-up in Denmark and Finland and binary finasteride use); B (long follow-up in Denmark and Finland 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 (less than two prescriptions of finasteride) and between cumulative finasteride use. OR estimates and 95% confidence intervals will be calculated. The main analyses will include these two definitions of finasteride use among long follow-up data from Denmark (1995–2013) and Finland (1994–2013) and all available data including all four countries (Denmark, Finland, Norway (2008–2013) and Sweden (2005–2013)), i.e. analyses A-D (Table 6a).

In substudy 1A, the same main analyses as in substudy 1 will be done, i.e. we will include dependent variables as a binary variable and as a cumulative variable in Denmark and Finland and 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 both finasteride use versus non-use and cumulative finasteride use and including confounding factors in the analysis. We will

include confounding factors established by the DAG developed before substudy 1. 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. We will include confounders with the categorization presented in Table 5. Conditional logistic regression will be performed to take account of the country- and age-matching. OR estimates and 95% confidence intervals will be calculated. The analyses will be performed with long follow-up data from Denmark (1995–2013) and Finland (1994–2013) and including all available follow-up time (Denmark, Finland, Norway (2008–2013) and Sweden (2005–2013) as described above (i.e. analyses A–D).

1.1.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. odds ratios for finasteride use, incidence rates of finasteride use)

The secondary objective of the study is to examine the robustness of the study findings by performing supplementary analyses for each substudy. The supplementary analyses performed for substudy 1 (please also see Table 6a) to further elaborate the associations between potential confounders and finasteride use are:

1. Age-stratified analysis (below 65 years of age and 65 years and older)
2. Analysis within the benign prostatic hyperplasia cohort (see below)
3. Analysis comparing alpha-blockers users with finasteride users as outcome (see below)
4. Analyze years of finasteride use as dependent variable (1–3, 4–5 and 6+ years)
5. Analyze 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. Change the requirement for new user by excluding finasteride users with first redemption of finasteride within the first 2 years of follow-up
8. Stratify the analysis by each variable associated with surveillance bias
9. Latency analyses by inferring 1 and 2 years of lag time between confounding factors and finasteride use
10. Analysis of self-reported life-style factors (substudy 1A)

Moreover, 11 supplementary analyses will be performed for substudy 2 (please also see Table 6b) to further elaborate the associations between finasteride use and breast cancer. All analyses will be confounder adjusted.

1. Age-stratified analysis (below 65 years of age and 65 years and older)
2. Analysis within the benign prostatic hyperplasia cohort (see below)
3. Analysis comparing alpha-blockers use with finasteride use as exposure (see below)
4. Analysis of combined finasteride and dutasteride use (i.e. use of any 5 alpha reductase inhibitor)

5. Use years of finasteride use as exposure (1–3, 4–5 and 6+ years)

6. Use 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 each variable associated with surveillance bias
11. Perform latency analyses by inferring 1 and 2 years of lag time between exposure and confounders and breast cancer

The supplementary analysis number 2 in both substudy 1 and substudy 2 will be performed within a cohort of men with diagnosis or treatment for benign prostatic disease termed the benign prostatic hyperplasia (BPH) cohort.

The supplementary analysis number 3 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 odds ratios of finasteride and alpha-blockers on male breast cancer are comparable in these two analyses, this may support the hypothesis that unmeasured confounding by indication is present, while if the odds ratio 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 between the Nordic countries and because of lack of power when excluding persons exposed to both finasteride or alpha-blockers or to none of those drugs.

Table 6a: 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 (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 4)												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. The letters and numbers of types of analyses refer to the analyses described in sections 1.1.1 and 1.1.2.

Table 6b: Overview of the data analysis - 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 (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								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 4)														X	
Latency	Latency analyses															X

Abbreviations: DK, Denmark; F, Finland; N, Norway; S, Sweden. The letters and numbers of types of analyses refer to the analyses described in sections 1.1.1 and 1.1.2.

1.1.3 Missing data

For register-based variables normally no registration is often interpreted as the person does not have the disease or use the drug, e.g. no registration of finasteride use is interpreted as the person has not used finasteride or no registration of benign breast disease is interpreted as the person have not been diagnosed. The reimbursement system and hospital system of the Nordic countries support this interpretation.

For a few of the included register-based variables (in Table 3 it is the following variables: socio-economic position, cancer stage (among breast cancer cases), family history of breast cancer, occupational information and living as a single man, urban/rural differences) all included persons should have information. We expect that a small minority will have missing information on these variables. We will include the input from each national scientific coordinators from the data management report (see section 1) to decide how to handle missing values for each variable.

For the supplementary analysis of life-style and self-reported variables in substudy 1A more missing values will be evident. The major part of missing will be due to non-response while a smaller proportion will be due to item missingness of the specific questions. One way to account for the potential non-response bias in surveys is to perform a weighted analysis using inverse predicted probabilities of response status as the weight function based on socioeconomic position, age and sex making the participants representative for the invited population sample. This will be done if these weights are available. Otherwise we will perform substudy 1A among persons without missing values on these variables (complete-case analysis).

1.2 Bias

A limitation of the study is the comparison of users with non-users (less than two prescriptions of finasteride), where the observed association between male breast cancer and finasteride use may be influenced by confounding by indication since finasteride users may have more comorbidities. Comparing patients on finasteride to patients on alpha blockers might not be fully successful in addressing the issues around this bias.

Furthermore, finasteride users may have more contacts with medical staff. E.g. diabetes is associated with BPH and thereby with finasteride use and is associated with breast cancer. This could result in a spuriously higher incidence of breast cancer among finasteride users than among a random sample of males (due to surveillance bias). Number of admissions is used as a surrogate for the potential of occurrence of this bias.

Another appropriate approach for addressing potential detection bias would have been to compare cases at different levels of each variable in table 4 regarding cancer stage at diagnosis. However, the validity on cancer stage variable in the registers is low and this approach is therefore not feasible (Jensen 2002).

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. As such, the study results might be subject to the effect of some residual confounding.

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 1993, but the limitation is important to consider for Norway and Sweden.

Survey data included in substudy 1A may be limited due to non-response bias as those not participating in the surveys may differ from the survey participants. This may introduce selection bias in the estimation of the association between life-style factors and finasteride use, e.g. smokers may be underrepresented.

1.2.1 Methods to Minimize Bias

In the analysis, we try to assess confounding by indication and surveillance bias by adjusting for comorbidities, by performing analysis of the separate effects of alpha-blockers and finasteride, and by performing the analysis within the benign prostatic hyperplasia cohort. However, it is conceivable that accurately determining, and adjusting for, the impact of confounding by indication and surveillance bias, which is related to the use of drug and the diagnosis of cancer, may not be fully achieved. This is because channeling bias stemming from the different adverse events profiles of alpha blocker vs. finasteride can influence the type of patients that are prescribed one of the two drugs. Additionally, physician may be more likely to examine finasteride patients' breasts because they are aware of the association between finasteride and benign breast disorders. Further, alpha blockers are not associated with surveillance bias even when given for patients with the same indication as finasteride. So, comparing patients on the two drugs will not address this limitation in the study.

Regarding confounding, we think that underestimation of the prevalence of confounders measured in a clinical setting, e.g. diagnoses of diseases, may be related with finasteride use in that the contact with doctor may be more likely to have a condition diagnosed and be more likely to receive finasteride. This bias may mimic differential misclassification resulting in stronger observed associations for substudy 1. For the non-clinical confounders, e.g. employment status, 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. Therefore, the study results might be subject to the effect of some residual confounding. However, whether this underestimation will result in an over- or underestimation of the association between finasteride use and breast cancer cannot be predicted (substudy 2).

We will evaluate the influence of truncation bias 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 and performing analyses only including Denmark and Finland where truncation bias will be smaller.

One way to account for the potential non-response bias in surveys is to perform a weighted analysis using inverse predicted probabilities of response status as the weight function based on socioeconomic position, age and sex making the participants representative for the invited population sample. This was done for the Danish survey.

1.2.2 Limitations

In addition to other limitations and sources of bias listed earlier in this SAP and in the protocol, we have other limitations to consider. A 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.

The study is done in four Nordic countries and the pattern of finasteride use, incidence of male breast cancer and the association between finasteride use and male breast cancer may not be generalizable to other parts of the world.

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. E.g. the response rate of the Danish surveys is between 60-70 percent and the response rates of the Finnish surveys varies between 57 and 96 percent. This could introduce selection bias in the estimation.

When identifying patients who have redeemed prescriptions on alpha-blocker use, we are not able to get information on the indication of alpha-blockers meaning that some of these patients might have BPH while others do not, which might bias the result of this supplementary analysis against finasteride. Further, alpha blockers are not associated with surveillance bias even when given for patients with the same indication as finasteride. So, comparing patients on the two drugs will not address this limitation in the study.

1.3 Sample Size and Power Calculations

Substudy 1 includes all finasteride users and a random sample of country-matched non-users (less than two prescriptions of finasteride). 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 2008–2009, 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 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 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:

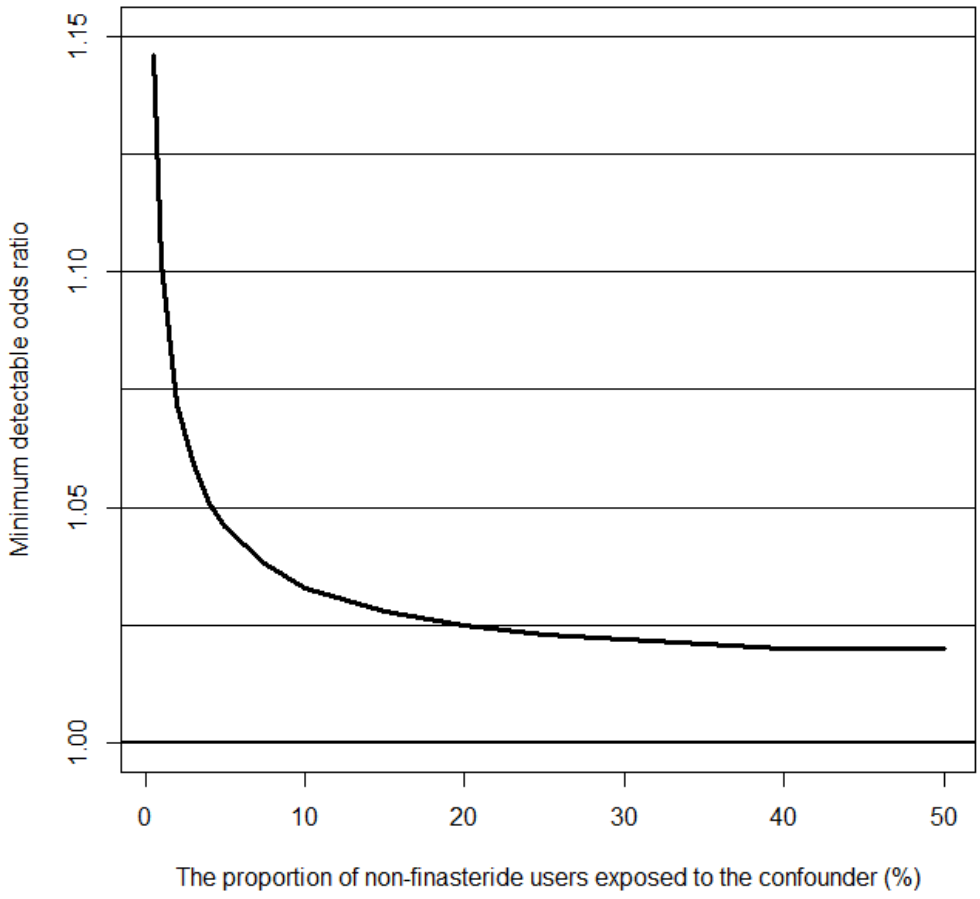
- Power = 90%
- Alpha = 5%
- Two-sided test
- 214,000 finasteride users (two and more prescriptions of finasteride)
- 214,000 non-users (less than two prescriptions of finasteride)

If we vary the proportion of non-finasteride users exposed to the confounder we can estimate the minimum detectable OR (Table 7 and figure 1).

Table 7: 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

Figure 1: Minimal detectable odds ratio by proportion of exposed among finasteride non-users in substudy1.



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 an OR 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 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 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 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 phase of the study (Stage 1 Study report, unpublished). In that phase, 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 finasteride use (2+ prescriptions) versus less than two prescriptions and cumulative finasteride use (0–1 packs of 98 pills of 5 mg, 2–3 packs, 4–6 packs, and 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 0.05, 0.1 and 0.2

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 8). 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 8: Minimal detectable OR for substudy 2

Correlation of exposure between pairs	The proportion of exposed controls	Case:control ratio			
		1:10 controls	1:25 controls	1:50 controls	1:500 controls
0.05	0.3%	3.23	3.11	3.08	3.04
	0.5%	2.65	2.57	2.54	2.52
	1%	2.11	2.07	2.05	2.03
	1.5%	1.89	1.86	1.84	1.83
	2%	1.77	1.73	1.72	1.71
	3%	1.62	1.60	1.59	1.58
	4%	1.53	1.51	1.51	1.50
0.1	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
0.2	0.3%	3.50	3.30	3.25	3.20
	0.5%	2.80	2.68	2.64	2.61
	1%	2.20	2.13	2.10	2.08
	1.5%	1.95	1.90	1.88	1.86
	2%	1.81	1.77	1.75	1.74
	3%	1.65	1.62	1.61	1.60
	4%	1.56	1.54	1.53	1.52

Figure 2a: Minimal detectable odds ratio (z-axis) by probability of exposure among controls (x-axis) and number of controls per case (y-axis) in substudy 2 with correlation of exposure between pairs in the case-control set at 0.1

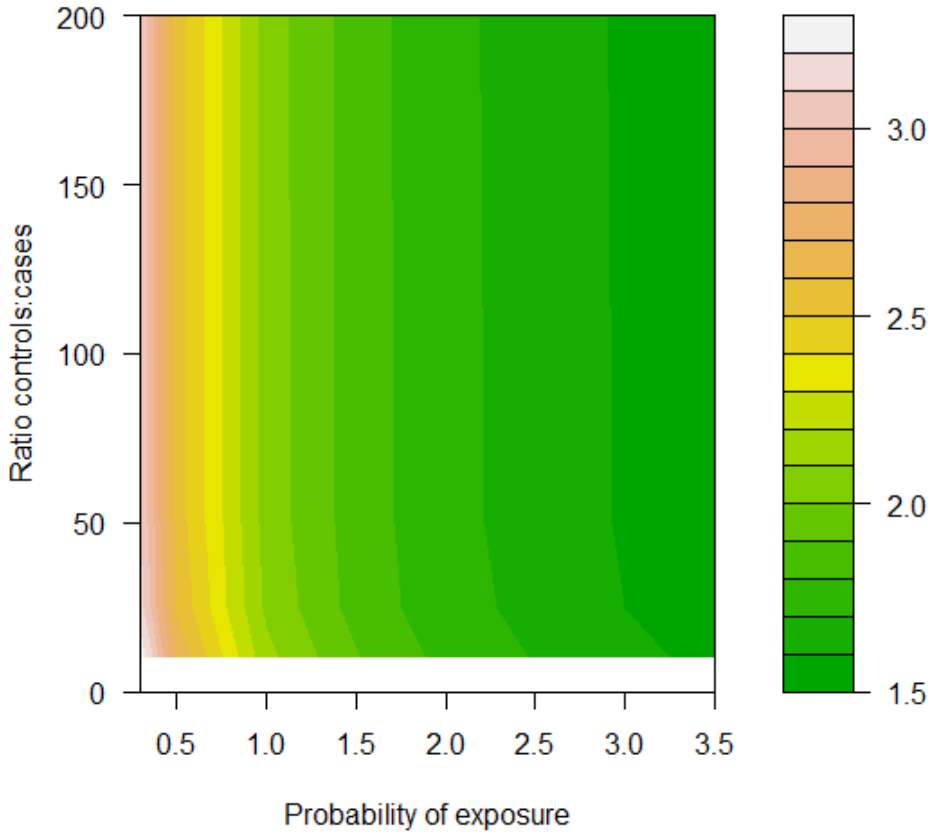
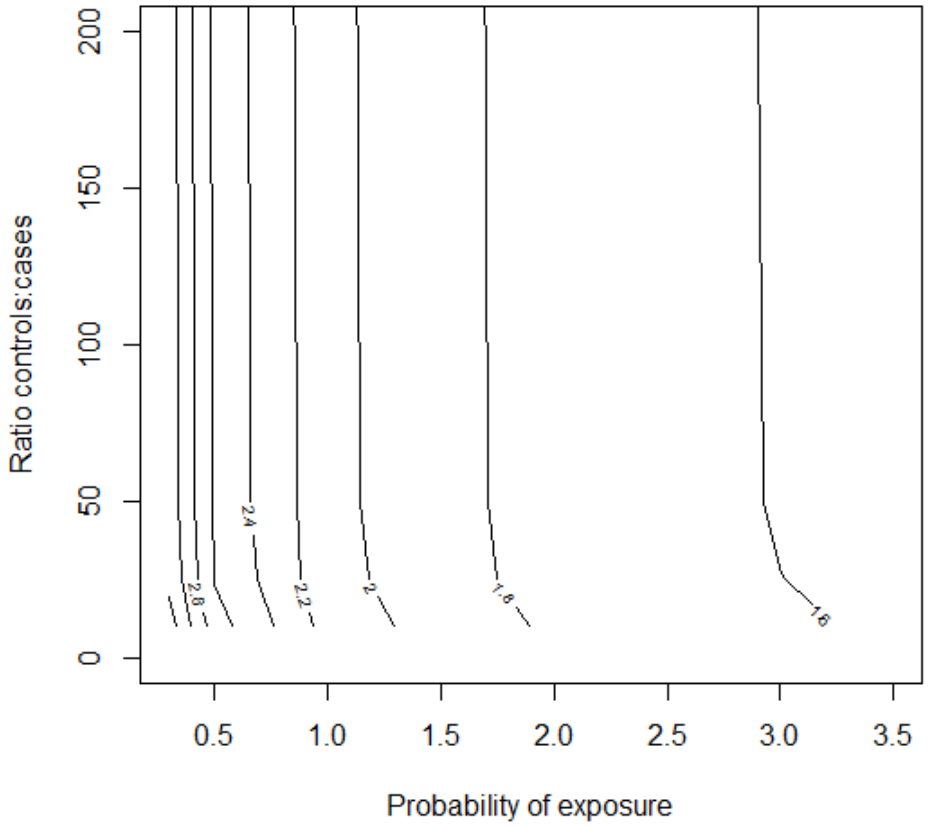


Figure 2b: Minimal detectable odds ratio (z-axis) by probability of exposure among controls (x-axis) and number of controls per case (y-axis) in substudy 2 with correlation of exposure between pairs in the case-control set at 0.1



Figures 2a and 2b show the minimal detectable odds ratio by probability of exposure and number of controls per case, e.g. for an exposure with prevalence of 1% and 50 controls per case, we will be able to detect a odds ratio of 2.06. Table 8 and Figure 2 support 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. Even though the previous study reported an increased incidence rate of 1.44 (95% CI, 1.11-1.88) (Stage 1 Study report, unpublished), the hypothesis of the present study is whether the point estimate moves strongly towards the null when comparing the adjusted model with the age- and country-adjusted model that generated the 1.44 estimate. This is mirrored in the second hypothesis of the study (see section 1).

2 Administrative and Regulatory details

Study registration and posting of study results will be done in compliance with the current regulations and are the obligation of Merck, as Sponsor of this study. Merck has the responsibility of submitting any information about the study and its results to the required results databases, i.e. clintrials.gov or ENCePP.

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4 Appendices

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5 Attachments

- Table shells
- DAG for the study on finasteride use and male breast cancer

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

Table Shells

Version 1: 23 January 2015

INVESTIGATOR

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National scientific coordinators

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- Finland: PPD
- Norway: TBD
- Sweden: PPD

Expert group

- PPD Denmark
- PPD Denmark

Additional experts will be included as the project starts

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Background tables

Table 0.1. Descriptive analysis of the Nordic populations by country, age and sex by 1st January 2010

	Denmark	Finland	Norway	Sweden
Population size	n	n	n	n
Men, *n (%)*	n (%)	n (%)	n (%)	n (%)
Age, *n (%)*				
- 0-34	n (%)	n (%)	n (%)	n (%)
- 35-64	n (%)	n (%)	n (%)	n (%)
- 65+	n (%)	n (%)	n (%)	n (%)

Table 0.2. Descriptive analysis of breast cancer incidence in the male Nordic population by country and calendar time

	Denmark	Finland	Norway	Sweden
Number of cases, *n*	n	n	n	n
Incidence rate per 100,000 person-years	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)
Incidence rate by age per 100,000 person-years				
- 0-34	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)
- 35-64	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)
- 65+	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)
Incidence rate by calendar time per 100,000 person-years				
- 1994-1998	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)
- 2000-2004	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)
- 2005-2009	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)
- 2010-2013	IR (95%CI)	IR (95%CI)	IR (95%CI)	IR (95%CI)

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Substudy 1

Objective: Describe finasteride users compared to non-users with respect to potential confounding factors

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Table 1.1. Descriptive analysis of male finasteride users (both finasteride use versus non-use and cumulative finasteride use versus non-use) with respect to potential confounding factors. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Numbers (%) if nothing else is stated

Potential confounding factors	**Finasteride users**				**Finasteride non-users**
	User	**Cumulative use**			
	2+ packs	**2-3 packs**	**4-6 packs**	**7+ packs**	**<2 packs**
Age, *mean (standard deviation)*	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Increased estrogen and decreased androgen levels					
- Testicular-abnormalities / disorders	n (%)	n (%)	n (%)	n (%)	n (%)
- Benign breast disease	n (%)	n (%)	n (%)	n (%)	n (%)
- Obesity	n (%)	n (%)	n (%)	n (%)	n (%)
- Liver cirrhosis	n (%)	n (%)	n (%)	n (%)	n (%)
- Klinefelter's syndrome	n (%)	n (%)	n (%)	n (%)	n (%)
- Estrogen therapy	n (%)	n (%)	n (%)	n (%)	n (%)
- Occupational exposures two years before index date (1)	n (%)	n (%)	n (%)	n (%)	n (%)
Family exposures					
- Family history of breast cancer	n (%)	n (%)	n (%)	n (%)	n (%)
Ionizing radiation and cancer treatment					
- Radiation exposure (2)	n (%)	n (%)	n (%)	n (%)	n (%)
Socio-economic differences					
- Socio-economic position					
- Low (<9 years of education)	n (%)	n (%)	n (%)	n (%)	n (%)
- Medium (10-12 years of education)	n (%)	n (%)	n (%)	n (%)	n (%)
- High (>12 years of education)	n (%)	n (%)	n (%)	n (%)	n (%)
- Living as a single man year before	n (%)	n (%)	n (%)	n (%)	n (%)
- Never having had children	n (%)	n (%)	n (%)	n (%)	n (%)
- Living in urban area one year before	n (%)	n (%)	n (%)	n (%)	n (%)

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Table 1.1. Descriptive analysis of male finasteride users (both finasteride use versus non-use and cumulative finasteride use versus non-use) with respect to potential confounding factors. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Numbers (%) if nothing else is stated

Potential confounding factors	**Finasteride users**				**Finasteride non-users**
	User	**Cumulative use**			
	2+ packs	**2-3 packs**	**4-6 packs**	**7+ packs**	**<2 packs**
Other factors					
- Charlson's comorbidity index 10 years before					
- Low (score=0)	n (%)	n (%)	n (%)	n (%)	n (%)
- Medium (score=1-2)	n (%)	n (%)	n (%)	n (%)	n (%)
- High (score=3+)	n (%)	n (%)	n (%)	n (%)	n (%)
- Number of prescriptions , *mean (standard deviation)*	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
- Diabetes	n (%)	n (%)	n (%)	n (%)	n (%)
- History of bone fractures	n (%)	n (%)	n (%)	n (%)	n (%)

(1) Having worked in perfume industry, high-temperature environment or had night-shift work.

(2) Including men treated with radiotherapy for pulmonary tuberculosis.

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Table 1.2. Descriptive analysis of male finasteride users (finasteride use versus non-use and cumulative finasteride use versus non-use) with respect to potential confounding factors. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Numbers (%) if nothing else is stated

Potential confounding factors	**Finasteride users**				**Finasteride non-users**
	User	**Cumulative use**			
	2+ packs	**2-3 packs**	**4-6 packs**	**7+ packs**	**<2 packs**
Age, *mean (standard deviation)*	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Increased estrogen and decreased androgen levels					
- Testicular-abnormalities / disorders	n (%)	n (%)	n (%)	n (%)	n (%)
- Benign breast disease	n (%)	n (%)	n (%)	n (%)	n (%)
- Obesity	n (%)	n (%)	n (%)	n (%)	n (%)
- Liver cirrhosis	n (%)	n (%)	n (%)	n (%)	n (%)
- Klinefelter's syndrome	n (%)	n (%)	n (%)	n (%)	n (%)
- Estrogen therapy	n (%)	n (%)	n (%)	n (%)	n (%)
- Occupational exposures two years before index date (1)	n (%)	n (%)	n (%)	n (%)	n (%)
Family exposures					
- Family history of breast cancer	n (%)	n (%)	n (%)	n (%)	n (%)
Ionizing radiation and cancer treatment					
- Radiation exposure (2)	n (%)	n (%)	n (%)	n (%)	n (%)
Socio-economic differences					
- Socio-economic position					
- Low (<9 years of education)	n (%)	n (%)	n (%)	n (%)	n (%)
- Medium (10-12 years of education)	n (%)	n (%)	n (%)	n (%)	n (%)

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Table 1.2. Descriptive analysis of male finasteride users (finasteride use versus non-use and cumulative finasteride use versus non-use) with respect to potential confounding factors. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Numbers (%) if nothing else is stated

Potential confounding factors	**Finasteride users**				**Finasteride non-users**
	User	**Cumulative use**			
	2+ packs	**2-3 packs**	**4-6 packs**	**7+ packs**	**<2 packs**
- High (>12 years of education)	n (%)	n (%)	n (%)	n (%)	n (%)
- Living as a single man year before	n (%)	n (%)	n (%)	n (%)	n (%)
- Never having had children	n (%)	n (%)	n (%)	n (%)	n (%)
- Living in urban area one year before	n (%)	n (%)	n (%)	n (%)	n (%)
Other factors					
- Charlson's comorbidity index 10 years before					
- Low (score=0)	n (%)	n (%)	n (%)	n (%)	n (%)
- Medium (score=1-2)	n (%)	n (%)	n (%)	n (%)	n (%)
- High (score=3+)	n (%)	n (%)	n (%)	n (%)	n (%)
- Number of prescriptions , *mean (standard deviation)*	n (%)	n (%)	n (%)	n (%)	n (%)
- Diabetes	n (%)	n (%)	n (%)	n (%)	n (%)
- History of bone fractures	n (%)	n (%)	n (%)	n (%)	n (%)

(1) Having worked in perfume industry, high-temperature environment or had night-shift work.

(2) Including men treated with radiotherapy for pulmonary tuberculosis.

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Table 1.3. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013.

	Age-, year- and country-adjusted				Adjusted (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Benign breast disease	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Obesity	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Liver cirrhosis	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Klinefelter's syndrome	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Estrogen therapy	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Occupational exposures (2)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Family exposures								
- Family history of breast cancer	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Ionizing radiation and cancer treatment								
- Radiation exposure (3)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Socio-economic differences								
- Socio-economic position								
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- High (>12 years of education)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Living as a single man year before	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Living in urban area one year before	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Other factors								
- Diabetes	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- History of bone fractures	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)

(1) Model mutually adjusted for all included variables.

(2) Having worked in perfume industry, high-temperature environment or had night-shift work.

(3) Including men treated with radiotherapy for pulmonary tuberculosis.

Confidential

Table 1.4. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

	Age-, year- and country-adjusted				Adjusted (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Benign breast disease	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Obesity	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Liver cirrhosis	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Klinefelter's syndrome	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Estrogen therapy	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Occupational exposures (2)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Family exposures								
- Family history of breast cancer	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Ionizing radiation and cancer treatment								
- Radiation exposure (3)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Socio-economic differences								
- Socio-economic position								
- Low (<9 years of education)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Medium (10-12 years of education)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- High (>12 years of education)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Living as a single man year before	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Living in urban area one year before	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Other factors								
- Diabetes	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- History of bone fractures	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)

Confidential

(1) Model mutually adjusted for all included variables.
(2) Having worked in perfume industry, high-temperature environment or had night-shift work.
(3) Including men treated with radiotherapy for pulmonary tuberculosis.

Confidential

Supplementary analysis 1

Table 1.5. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1994/1995 to 2013. Analysis stratified by age.

	Below age 65 years (1)				65 years and older (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…								

(1) Model mutually adjusted for all included variables.

Table 1.6. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis stratified by age.

	Below age 65 years (1)				65 years and older (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders								
Etc…								

(1) Model mutually adjusted for all included variables.

Confidential

Supplementary analysis 2

Table 1.7. Number of finasteride users and non-users within the benign prostatic hyperplasia cohort. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

	Finasteride users	Finasteride non-users
Denmark	n	n
Finland	n	n
Norway	n	n
Sweden	n	n

Table 1.8. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Analysis nested within the benign prostatic hyperplasia cohort.

	Below age 65 years (1)				65 years and older (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…								

(1) Model mutually adjusted for all included variables.

Table 1.9. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis nested within the benign prostatic hyperplasia cohort

	Below age 65 years (1)				65 years and older (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders								
Etc…								

Confidential

(1) Model mutually adjusted for all included variables.

Confidential

Supplementary analysis 3

Table 1.10. Number of finasteride users among alpha-blocker non-users and alpha-blocker users among finasteride non-users. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

	Alpha-blocker non-users		Finasteride non-users	
	Finasteride users	Finasteride non-users	Alpha-blocker users	Alpha-blocker non-users
Denmark	n	n	n	n
Finland	n	n	n	n
Norway	n	n	n	n
Sweden	n	n	n	n

Table 1.11. Association between potential confounding factors and finasteride use among alpha-blocker non-users and alpha-blocker use among finasteride non-users (use versus non-use). Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013.

	Finasteride use among alpha-blocker non-users	Alpha-blocker use among finasteride non-users
Increased estrogen and decreased androgen levels		
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)
Etc…		

(1) Model mutually adjusted for all included variables.

Table 1.12. Association between potential confounding factors and finasteride use among alpha-blocker non-users and alpha-blocker use among finasteride non-users (use versus non-use). Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

	Finasteride use among alpha-blocker non-users	Alpha-blocker use among finasteride non-users
Increased estrogen and decreased androgen levels		
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)
Etc…		

Confidential

(1) Model mutually adjusted for all included variables.

Supplementary analysis 4

Table 1.13. Association between potential confounding factors and finasteride use (years of finasteride use). Denmark and Finland from 1994/1995 to 2013.

	Years of finasteride use		
	1-3 years	4-5 years	6+ years
Increased estrogen and decreased androgen levels			
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…			

(1) Model mutually adjusted for all included variables.

Table 1.14. Association between potential confounding factors and finasteride use (years of finasteride use). Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

	Years of finasteride use		
	1-3 years	4-5 years	6+ years
Increased estrogen and decreased androgen levels			
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…			

(1) Model mutually adjusted for all included variables.

Confidential

Supplementary analysis 5

Table 1.15. Association between potential confounding factors and finasteride use (years since first finasteride use). Denmark and Finland from 1994/1995 to 2013.

	Years since first finasteride use			
	<1 year	**1-2 years**	**3-4 years**	**5+ years**
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…				

(1) Model mutually adjusted for all included variables.

Table 1.16. Association between potential confounding factors and finasteride use (years since first finasteride use). Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

	Years since first finasteride use			
	<1 year	**1-2 years**	**3-4 years**	**5+ years**
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…				

(1) Model mutually adjusted for all included variables.

Confidential

Supplementary analysis 6

Table 1.17. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1994/1995 to 2013. Only included 5 mg finasteride as finasteride users.

	Finasteride use			
	2+ packs	**2-3 packs**	**4-6 packs**	**7+ packs**
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…				

(1) Model mutually adjusted for all included variables.

Table 1.18. Table 1.16. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Only included 5 mg finasteride as finasteride users.

	Finasteride use			
	2+ packs	**2-3 packs**	**4-6 packs**	**7+ packs**
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…				

(1) Model mutually adjusted for all included variables.

Confidential

Supplementary analysis 7

Table 1.19. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1994/1995 to 2013. Changed the requirement for new users by excluding finasteride users with first redemption of finasteride within the first 2 years of follow-up.

	Finasteride use			
	2+ packs	**2-3 packs**	**4-6 packs**	**7+ packs**
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…				

(1) Model mutually adjusted for all included variables.

Table 1.20. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Changed the requirement for new users by excluding finasteride users with first redemption of finasteride within the first 2 years of follow-up.

	Finasteride use			
	2+ packs	**2-3 packs**	**4-6 packs**	**7+ packs**
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…				

(1) Model mutually adjusted for all included variables.

Confidential

Supplementary analysis 8

Table 1.21. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1994/1995 to 2013. Analysis among men with diagnosis of gynaecomastia

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Table 1.22. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis among men without diagnosis of gynaecomastia.

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders								
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Confidential

Table 1.23. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1994/1995 to 2013. Analysis among users of drugs or exposed to environmental agents that cause or may cause gynaecomastia.

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Table 1.24. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis among non-users of drugs or non-exposed to environmental agents that cause or may cause gynaecomastia.

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders								
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Confidential

Table 1.25. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1994/1995 to 2013. Analysis among men with low number of prescriptions (the median and below number of drugs prescribed)

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Table 1.26. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis among men with high number of prescriptions (above the median number of drugs prescribed).

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders								
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Confidential

Table 1.27. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1994/1995 to 2013. Analysis among men with low number of surgeries (the median and below number of surgeries).

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Table 1.28. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis among men with high number of surgeries (above the median number of surgeries).

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders								
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Confidential

Table 1.29. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1994/1995 to 2013. Analysis among men with low number of admissions (the median and below number of admissions).

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Table 1.30. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis among men with high number of admissions (the median and below number of admissions).

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders								
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Confidential

Table 1.31. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1994/1995 to 2013. Analysis among men with urinary retention.

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Table 1.32. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis among men without urinary retention.

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders								
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Confidential

Table 1.33. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1994/1995 to 2013. Analysis among men with localized breast cancer at diagnosis.

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Table 1.34. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis among men with regional or metastatic breast cancer at diagnosis.

	Having variable associated with surv bias (1)				Not having variable associated with surv bias (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels								
- Testicular-abnormalities / disorders								
Etc…								

(1) Model mutually adjusted for all included variables.

surv = surveillance

Confidential

Supplementary analysis 9

Table 1.35. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1994/1995 to 2013. Latency analysis inferring 1 year of lag time between potential confounding factors and finasteride use.

	Finasteride use			
	2+ packs	**2-3 packs**	**4-6 packs**	**7+ packs**
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…				

(1) Model mutually adjusted for all included variables.

Table 1.36. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark and Finland from 1994/1995 to 2013. Latency analysis inferring 2 years of lag time between potential confounding factors and finasteride use.

	Finasteride use			
	2+ packs	**2-3 packs**	**4-6 packs**	**7+ packs**
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Etc…				

(1) Model mutually adjusted for all included variables.

Confidential

Table 1.37. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Latency analysis inferring 1 year of lag time between potential confounding factors and finasteride use.

	Finasteride use			
	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders				
Etc…				

(1) Model mutually adjusted for all included variables.

Table 1.38. Association between potential confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Latency analysis inferring 2 years of lag time between potential confounding factors and finasteride use.

	Finasteride use			
	2+ packs	2-3 packs	4-6 packs	7+ packs
Increased estrogen and decreased androgen levels				
- Testicular-abnormalities / disorders				
Etc…				

(1) Model mutually adjusted for all included variables.

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Supplementary analysis 10 (substudy 1A)

Objective: Same objective as substudy 1 but including self-reported lifestyle factors.

Table 1A.1. Descriptive analysis of male finasteride users (both finasteride use versus non-use and cumulative finasteride use versus non-use) with respect to self-reported potential confounding factors measured up to five years before finasteride use from surveys. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Numbers (%).

	Finasteride users (1)				Finasteride
	2+ packs	2-3 packs	4-6 packs	7+ packs	non-users
- Obesity (BMI)					
- ≤ 30	n (%)	n (%)	n (%)	n (%)	n (%)
- > 30	n (%)	n (%)	n (%)	n (%)	n (%)
- Alcohol intake (drinks/week)					
- ≤ 21	n (%)	n (%)	n (%)	n (%)	n (%)
- > 21	n (%)	n (%)	n (%)	n (%)	n (%)
- Physical activity					
- sedentary	n (%)	n (%)	n (%)	n (%)	n (%)
- light physical activity (<4 hours/week)	n (%)	n (%)	n (%)	n (%)	n (%)
- moderate/high physical activity (≥4 hours/week)	n (%)	n (%)	n (%)	n (%)	n (%)
- Dietary intake of fruit and vegetables					
- less than daily	n (%)	n (%)	n (%)	n (%)	n (%)
- fruit and/or vegetables daily	n (%)	n (%)	n (%)	n (%)	n (%)
- Dietary intake of animal fat					
- less than daily	n (%)	n (%)	n (%)	n (%)	n (%)
- animal fat daily	n (%)	n (%)	n (%)	n (%)	n (%)

(1) Finasteride users: Redeemed at least two prescriptions of finasteride. Non-users men who have redeemed less than two prescriptions

Confidential

Table 1A.2. Descriptive analysis of male finasteride users (both finasteride use versus non-use and cumulative finasteride use versus non-users with respect to self-reported potential confounding factors measured up to five years before finasteride use from surveys. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Numbers (%).

	Finasteride users (1)				Finasteride
	2+ packs	2-3 packs	4-6 packs	7+ packs	non-users
- Obesity (BMI)					
- ≤ 30	n (%)	n (%)	n (%)	n (%)	n (%)
- > 30	n (%)	n (%)	n (%)	n (%)	n (%)
- Alcohol intake (drinks/week)					
- ≤ 21	n (%)	n (%)	n (%)	n (%)	n (%)
- > 21	n (%)	n (%)	n (%)	n (%)	n (%)
- Physical activity					
- sedentary	n (%)	n (%)	n (%)	n (%)	n (%)
- light physical activity (<4 hours/week)	n (%)	n (%)	n (%)	n (%)	n (%)
- moderate/high physical activity (≥4 hours/week)	n (%)	n (%)	n (%)	n (%)	n (%)
- Dietary intake of fruit and vegetables					
- less than daily	n (%)	n (%)	n (%)	n (%)	n (%)
- fruit and/or vegetables daily	n (%)	n (%)	n (%)	n (%)	n (%)
- Dietary intake of animal fat					
- less than daily	n (%)	n (%)	n (%)	n (%)	n (%)
- animal fat daily	n (%)	n (%)	n (%)	n (%)	n (%)

(1) Finasteride users: Redeemed at least two prescriptions of finasteride. Non-users men who have redeemed less than two prescriptions

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Table 1A.3. Association between potential self-reported confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013.

	Age-, year- and country-adjusted				Adjusted (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
- Obesity (BMI)								
- ≤ 30	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- > 30	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Alcohol intake (drinks/week)								
- ≤ 21	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- > 21	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Physical activity								
- sedentary	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- light physical activity (<4 hours/week)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- moderate/high physical activity (≥4 hours/week)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Dietary intake of fruit and vegetables								
- less than daily	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- fruit and/or vegetables daily	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Dietary intake of animal fat								
- less than daily	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- animal fat daily	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)

(1) Model mutually adjusted for all self-reported variables and all register-based variables (see Table 1.1).

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Table 1A.4. Association between potential self-reported confounding factors and finasteride use (both use versus non-use and cumulative use versus non-use). Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

	Age-, year- and country-adjusted				Adjusted (1)			
	2+ packs	2-3 packs	4-6 packs	7+ packs	2+ packs	2-3 packs	4-6 packs	7+ packs
- Obesity (BMI)								
- ≤ 30	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- > 30	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Alcohol intake (drinks/week)								
- ≤ 21	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- > 21	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- Physical activity								
- sedentary	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- light physical activity (<4 hours/week)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- moderate/high physical activity (≥4 hours/week)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Dietary intake of fruit and vegetables								
- less than daily	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- fruit and/or vegetables daily	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
- Dietary intake of animal fat								
- less than daily	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
- animal fat daily	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)

(1) Model mutually adjusted for all self-reported variables and all register-based variables (see Table 1.1).

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Substudy 2

Objective: Analyze the effect of finasteride use on male breast cancer incidence while taking account of confounding factors decided in a directional acyclic graph (DAG).

Confidential

Table 2.1. Descriptive analysis of male breast cancer cases and controls with respect to potential confounding factors. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Numbers (%) if nothing else is stated

	Breast cancer cases	Controls
Finasteride use		
Non-user (<2 packs)	n (%)	n (%)
User (2+ packs)	n (%)	n (%)
Cumulative use low (2-3 packs)	n (%)	n (%)
Cumulative use medium (4-6 packs)	n (%)	n (%)
Cumulative use high (7+ packs)	n (%)	n (%)
Age, *mean (standard deviation)*	Mean (SD)	Mean (SD)
Benign prostatic hyperplasia	n (%)	n (%)
Estrogen therapy	n (%)	n (%)
Exogenous testosterone	n (%)	n (%)
Klinefelter's syndrome	n (%)	n (%)
Socioeconomic position	n (%)	n (%)
Testicular disorders	n (%)	n (%)
Urban	n (%)	n (%)

Confidential

Table 2.2. Descriptive analysis of male breast cancer cases and controls with respect to potential confounding factors. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Numbers (%) if nothing else is stated

	Breast cancer cases	Controls
Finasteride use		
Non-user (<2 packs)	n (%)	n (%)
User (2+ packs)	n (%)	n (%)
Cumulative use low (2-3 packs)	n (%)	n (%)
Cumulative use medium (4-6 packs)	n (%)	n (%)
Cumulative use high (7+ packs)	n (%)	n (%)
Age, *mean (standard deviation)*	Mean (SD)	Mean (SD)
Benign prostatic hyperplasia	n (%)	n (%)
Estrogen therapy	n (%)	n (%)
Exogenous testosterone	n (%)	n (%)
Klinefelter's syndrome	n (%)	n (%)
Socioeconomic position	n (%)	n (%)
Testicular disorders	n (%)	n (%)
Urban	n (%)	n (%)

Confidential

Table 2.3. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

Confidential

Table 2.4. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Secondary analysis 1

Table 2.5. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Stratified by age.

Age	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
<65 years	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
≥65 years	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.6. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Stratified by age.

Age	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
<65 years	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
≥65 years	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Secondary analysis 2

Table 2.7. Number of finasteride users and non-users and breast cancer cases within the benign prostatic hyperplasia cohort. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

	Finasteride users	Finasteride non-users	Breast cancer cases	Controls
Denmark	n	n	n	n
Finland	n	n	n	n
Norway	n	n	n	n
Sweden	n	n	n	n

Table 2.8. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Analysis within the benign prostatic hyperplasia cohort.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.9. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis within the benign prostatic hyperplasia cohort.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Secondary analysis 3

Table 2.10. Number of finasteride users among alpha-blocker non-users and alpha-blocker users among finasteride non-users in substudy 2. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

	Alpha-blocker non-users		Finasteride non-users	
	Finasteride users	Finasteride non-users	Alpha-blocker users	Alpha-blocker non-users
Denmark	n	n	n	n
Finland	n	n	n	n
Norway	n	n	n	n
Sweden	n	n	n	n

Table 2.11. Association between finasteride use (use versus non-use) among alpha-blocker non-users and alpha-blocker use among finasteride non-users and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013.

	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Finasteride use among alpha-blocker non-users	n / n	n / n	1.00 (ref)	1.00 (ref)
Non-user (<2 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
User (2+ packs)				
	n / n	n / n	1.00 (ref)	1.00 (ref)
Alpha-blocker use among Finasteride non-users	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.12. Association between finasteride use (use versus non-use) among alpha-blocker non-users and alpha-blocker use among finasteride non-users and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Finasteride use among alpha-blocker non-users	n / n	n / n	1.00 (ref)	1.00 (ref)
Non-user (<2 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
User (2+ packs)				
	n / n	n / n	1.00 (ref)	1.00 (ref)
Alpha-blocker use among Finasteride non-users	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

Confidential

Secondary analysis 4

Table 2.13. Association between finasteride or dutasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013.

Finasteride or dutasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

Confidential

Table 2.14. Association between finasteride or dutasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

Finasteride or dutasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

Confidential

Secondary analysis 5

Table 2.15. Association between finasteride use (years of use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-users (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
1-3 years	n / n	n / n	OR (95%CI)	OR (95%CI)
4-5 years	n / n	n / n	OR (95%CI)	OR (95%CI)
6+ years	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

Table 2.16. Association between finasteride use (years of use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-users (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
1-3 years	n / n	n / n	OR (95%CI)	OR (95%CI)
4-5 years	n / n	n / n	OR (95%CI)	OR (95%CI)
6+ years	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.17. Association between finasteride use (years since first finasteride use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-users (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
<1 year	n / n	n / n	OR (95%CI)	OR (95%CI)
1-2 years	n / n	n / n	OR (95%CI)	OR (95%CI)
3-4 years	n / n	n / n	OR (95%CI)	OR (95%CI)
5+ years	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

Table 2.18. Association between finasteride use (years since first finasteride use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-users (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
<1 year	n / n	n / n	OR (95%CI)	OR (95%CI)
1-2 years	n / n	n / n	OR (95%CI)	OR (95%CI)
3-4 years	n / n	n / n	OR (95%CI)	OR (95%CI)
5+ years	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.19. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Only include 5 mg finasteride as finasteride users.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

Table 2.20. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Only include 5 mg finasteride as finasteride users.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

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Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.21. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Include persons who only redeem one prescription as exposed.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.22. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Include persons who only redeem one prescription as exposed.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.23. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Change the requirement for new user by excluding Finasteride users with first redemption of Finasteride within the first 2 years of follow-up.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.24. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Change the requirement for new user by excluding Finasteride users with first redemption of Finasteride within the first 2 years of follow-up.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.25. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Analysis stratified diagnosis of gynaecomastia.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with diagnosis of gynaecomastia	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Among men without diagnosis of gynaecomastia	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.26. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis stratified diagnosis of gynaecomastia.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with diagnosis of gynaecomastia	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Among men without diagnosis of gynaecomastia	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.27. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Analysis stratified by use of drugs or exposed to environmental agents that cause or may cause gynaecomastia.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among use of drugs or exposed to environmental agents	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Among men without use of drugs or not exposed to environmental agents	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.28. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis stratified by use of drugs or exposed to environmental agents that cause or may cause gynaecomastia.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among use of drugs or exposed to environmental agents	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Among men without use of drugs or not exposed to environmental agents	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.29. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Analysis stratified by number of prescriptions.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with low number of prescriptions	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Among men with high number of prescriptions	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.30. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis stratified by number of prescriptions.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with low number of prescriptions	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Among men with high number of prescriptions	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.31. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Analysis stratified by number of surgeries.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with low number of surgeries	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Among men with high number of surgeries	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.32. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis stratified by number of surgeries.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with low number of surgeries	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Among men with high number of surgeries	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.33. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Analysis stratified number of admissions.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with low number of admissions	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Among men with high number of admissions	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.34. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis stratified number of admissions.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with low number of admissions	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Among men with high number of admissions	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.35. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Analysis stratified by diagnosis of urinary retention.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with urinary retention	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Among men without urinary retention	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.36. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis stratified by diagnosis of urinary retention.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Among men with urinary retention	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Among men without urinary retention	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.37. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Analysis stratified cancer stage at diagnosis.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Localized cancer at diagnosis	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Regional or metastatic cancer at diagnosis	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.38. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Analysis stratified cancer stage at diagnosis.

	Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Localized cancer at diagnosis	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Regional or metastatic cancer at diagnosis	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
	Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
	Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Secondary analysis 11

Table 2.39. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Latency analysis inferring 1 year of lag time between finasteride use and breast cancer.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.40. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark and Finland from 1994/1995 to 2013. Latency analysis inferring 2 years of lag time between finasteride use and breast cancer.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.41. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Latency analysis inferring 1 year of lag time between finasteride use and breast cancer.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

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Table 2.42. Association between finasteride use (both use versus non-use and cumulative use versus non-use) and male breast cancer. Males aged 35 years and above in Denmark (1995), Finland (1994), Norway (2004) and Sweden (2005) to 2013. Latency analysis inferring 2 years of lag time between finasteride use and breast cancer.

Finasteride use	Cases exposed / unexposed	Controls exposed / unexposed	Crude odds ratio (95%CI) (1)	Adjusted odds ratio (95%CI) (2)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
User (2+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Non-user (<2 packs)	n / n	n / n	1.00 (ref)	1.00 (ref)
Cumulative use low (2-3 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use medium (4-6 packs)	n / n	n / n	OR (95%CI)	OR (95%CI)
Cumulative use high (7+ packs)	n / n	n / n	OR (95%CI)	OR (95%CI)

(1) Matched for age and country. Conditional logistic regression.

(2) Matched for age and country and adjusted for benign prostatic hyperplasia, estrogen therapy, exogenous testosterone, Klinefelter's syndrome, socioeconomic position, testicular disorders and urban/rural differences. Conditional logistic regression.

23 January 2015

DAG for the study on finasteride use and male breast cancer

Conclusions drawn on associations between finasteride use, male breast cancer and potential confounders from the DAG workshop 18 June 2014

The purpose of the DAG Workshop was to choose which confounding factors that should be included and adjusted for. This was done by going through a table with all proposed potential confounders. Here the conclusion for each arrow will be stated, while the discussion of each variable can be found in the minutes from the DAG workshop.

Variable type	Variable name	Conclusion
Exposure	Finansteride use	Finasteride use increase risk of benign breast disease and change in estrogen / androgen ratio. It may also increase risk of MBC (main hypothesis for the study).
Outcome	Male breast cancer (MBC)	We have included no variables that are affected by MBC, which is not the topic of this study.
Potential confounders	**Testicular disorders**	Testicular disorders may be negatively associated with finasteride use and MBC. Testicular disorders may increase use of exogenous testosterone. There are concerns of the quality of data for this variable since the large time span from the diagnosis of testicular disorders and the use of finasteride or diagnosis of MBC. There will be substantial underreporting in the registers.
	Exogenous testosterone	Exogenous testosterone and Klinefelter syndrome were discussed at this point and later on. The conclusion was that testicular disorders may increase use of exogenous testosterone (also noted above) and exogenous testosterone may be associated with lower finasteride use and lower risk of MBC. Furthermore, exogenous testosterone was associated with increased risk of bone fractures.
	Benign breast diseases	Benign breast diseases may increase risk of MBC.
	Anti androgens	Anti-androgens increase risk of benign breast disease.
	Benign prostatic hyperplasia (BPH)	BPH increase risk of benign breast disease and increase use of anti-androgens (even though this is rare). Later on it was noted that BPH also had a direct effect on MBC. Finally, BPH increase risk of finasteride use. It was proposed that BPH should be 'surgery for BPH' and not diagnosis of BPH. NOTE: At a later TC it was agreed that we use the broader definition 'diagnosis or surgery for BPH'.
	Obesity	We included two 'change in estrogen / androgen ratio' – pre is before the onset of BPH and post is after use of finasteride. Obesity increase estrogen and therefore also the ratio, which then moves on to influence BPH etc. Change in estrogen / androgen ratio may increase risk of

		MBC. We have also added that obesity increase risk of diabetes.
	Occupational exposure	Occupational exposures may increase risk of MBC and some industries are also associated with physical activity or inactivity.
	Liver cirrhosis	Liver cirrhosis may change estrogen/androgen ratio. We have put no other arrows pointing out of liver cirrhosis.
	Klinefelter's syndrome	May decrease use of finasteride and decrease risk of MBC.
	Estrogen therapy	May increase use of finasteride and increase risk of MBC. May also increase risk of benign breast disease.
	BRCA and Family history	BRCA and family history increase risk of MBC.
	Radiation	Radiation increase risk of MBC.
	Dietary factors (vegetables/fruit and animal fat) and lifestyle factors (physical inactivity, smoking and alcohol)	Dietary factors (low vegetables/fruit and high animal fat) may increase risk of obesity. Animal fat may increase risk of MBC. Physical inactivity may increase estrogen/androgen ratio. Smoking may decrease risk of obesity, may decrease estrogen/androgen ratio and decrease physical activity. Alcohol intake may increase risk of obesity, increase risk of liver cirrhosis and increase risk of MBC.
	Marital status/Single man	Marital status / living as a single man lower fruit/vegetable intake and increase animal fat intake, increase risk of physical inactivity, increase smoking and increase alcohol intake.
	SEP – socioeconomic position	SEP increases vegetable/fruit intake, decreases animal fat intake, increases physical activity and decreases smoking. SEP increases finasteride use.
	Never had children	This factor is not included in the DAG.
	Urban/rural differences	Living in an urban area is associated with higher intake of vegetables/fruit, lower intake of animal fat, higher physical activity, lower smoking and higher alcohol intake. Incidence of MBC is higher in urban areas.
	Comorbidity	Not include a general comorbidity index in the DAG. Include bone fractures (no arrows point away from bone fractures) and diabetes (increases risk of MBC) in the DAG.

Input from the reviewing process (eSCR and internal Merck review) December 2014

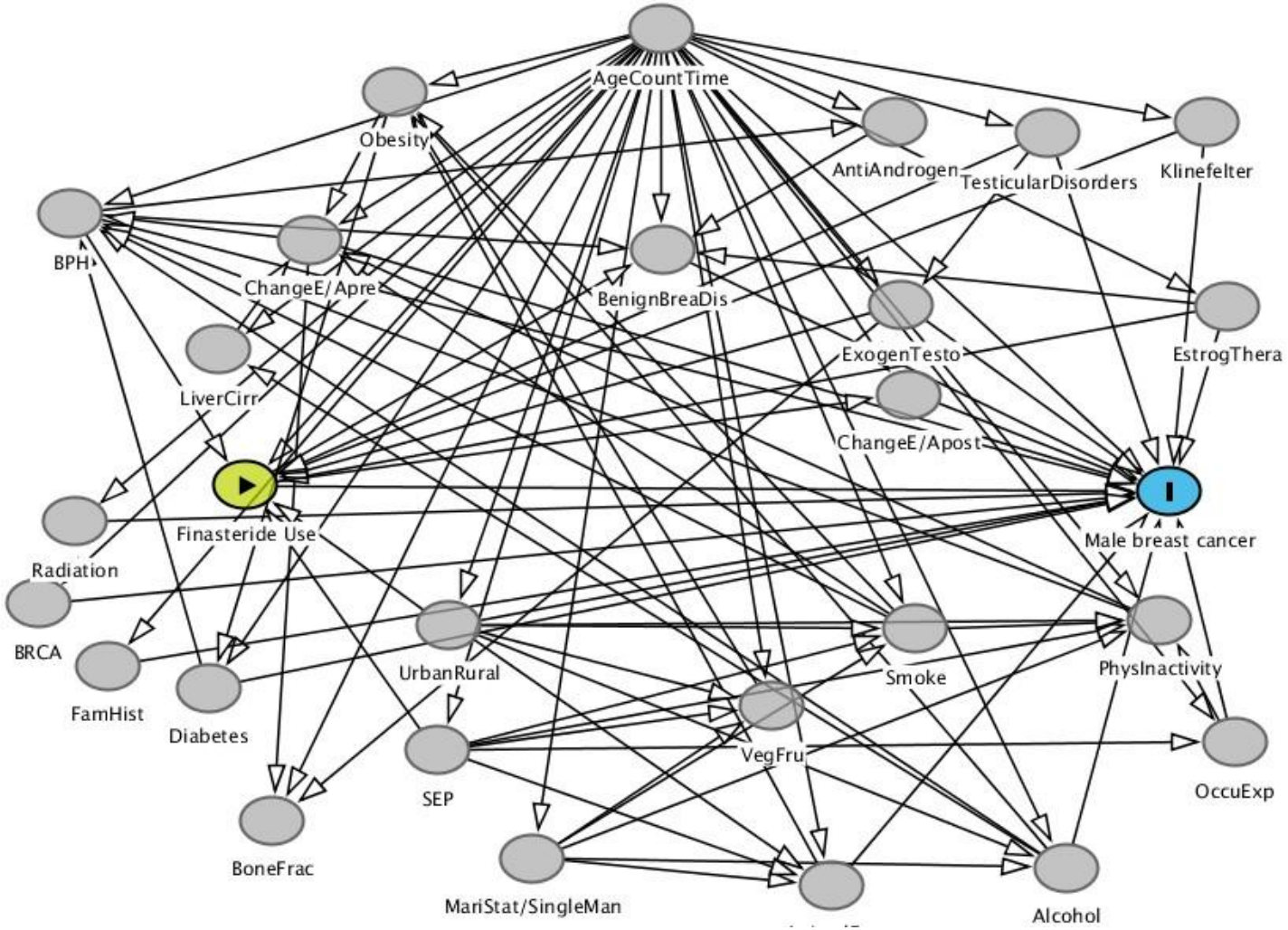
During the review further inputs were put forward. These inputs and effects on the DAG are presented in the following table.

Variable type	Variable name	Effect on DAG
Potential confounders	Age	Age is suggested as a confounder. It is already included in the study as a matching criteria, but we have added arrows from age to all other factors in the DAG. We think it is hard to have the arrows go the other way.
	Country	It has been put forward for some of the variables (e.g. finasteride use and male breast cancer incidence), but there may be country specific differences for many of the variables in the DAG. We have added arrows from country to all variables. We think don't think the arrows go the other way.
	Time	Calendar time may be associated with all factors in the DAG. We have added arrows from time to all variables.
	Smoke	Increases risk of BPH
	Alcohol	Increases risk of BPH
	Physinactivity	Increases risk of BPH
	Diabetes	Increases risk of BPH

Because age, country and time have the same arrows, e.g. from the factors to all other variables, we include all three factors into one node. This is only done to reduce the number of arrows in the DAG. Furthermore we don't think there will be arrows between the three factors.

The conclusions from the DAG workshop and the inputs from the review process ended with a DAG (Figure 1).

Figure 1. DAG for the association between finasteride use and male breast cancer



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Directed acyclic graph (DAG)

The development of a DAG highlights factors associated with finasteride use, factors that are a consequence of finasteride use, and factors associated with male breast cancer risk. The DAG will pinpoint which variables should be included in the analysis of the association between Finasteride use and male breast cancer (substudy 2) 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 finateride 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 used the software DAGitty version 2.1 (www.dagitty.net) to identify 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.

DAGitty uses the method developed by Pearl (2000) and Shier & Platt (2008). Although other articles have described the DAG approach to confounding (e.g. Greenland et al 1999), these articles demonstrate relatively simple DAGs. However, many problems require complicated DAGs and little has been published on how to assess whether a particular subset of covariates potentially reduces or increases bias in this context. The authors have developed a pragmatic and simpler approach.

It suffices to restrict our attention to the part of the model that consists of exposure, outcome, and their ancestors for identifying sufficient adjustment sets. A minimal sufficient adjustment set is a sufficient adjustment set of which no proper subset is itself sufficient.

DAGitty uses a 6-step method developed by Pearl (Pearl 2000) and further described by Schrier & Platt (Schrier 2008). The method ends up with minimum sufficient sets that make it possible to estimate the total effect of exposure (finasteride use) on outcome (male breast cancer). Table 1 shows the five minimum sufficient sets possible for the DAG developed (Figure 1).

Sufficient sets

In Table 1 the minimum sufficient sets in the DAG (Figure 1) are listed.

Table 1. Minimum sufficient sets for the DAG developed (Figure 1)

		Minimum sufficient set				
Variable names	**Acronym**	1	2	3	4	5
Age, country and time	AgeCountTime	X	X	X	X	X
Alcohol intake	Alcohol	X	X	X		
Intake of animal fat	AnimalFat	X	X	X	X	
Benign prostatic hyperplasia	BPH	X	X	X	X	X
Change estrogen/androgen before (1)	ChangeE/Apre	X				
Diabetes	Diabetes	X				
Estrogen therapy	EstrogThera	X	X	X	X	X
Exogenous testosterone	ExogenTesto	X	X	X	X	X
Klinefelter's syndrome	Klinefelter	X	X	X	X	X
Socioeconomic position	SEP					X
Liver cirrhosis	LiverCirr					
Marital status / living as a single man	MariStat/SingleMan				X	
Obesity	Obesity		X			
Occupational exposure	OccuExp	X	X	X	X	
Physical inactivity	PhysInactivity		X	X	X	
Smoking	Smoke		X	X	X	
Testicular disorders	TesticularDisorders	X	X	X	X	X
Urban / rural	UrbanRural	X	X	X	X	X
Intake of vegetable and fruits	VegFru			X	X	

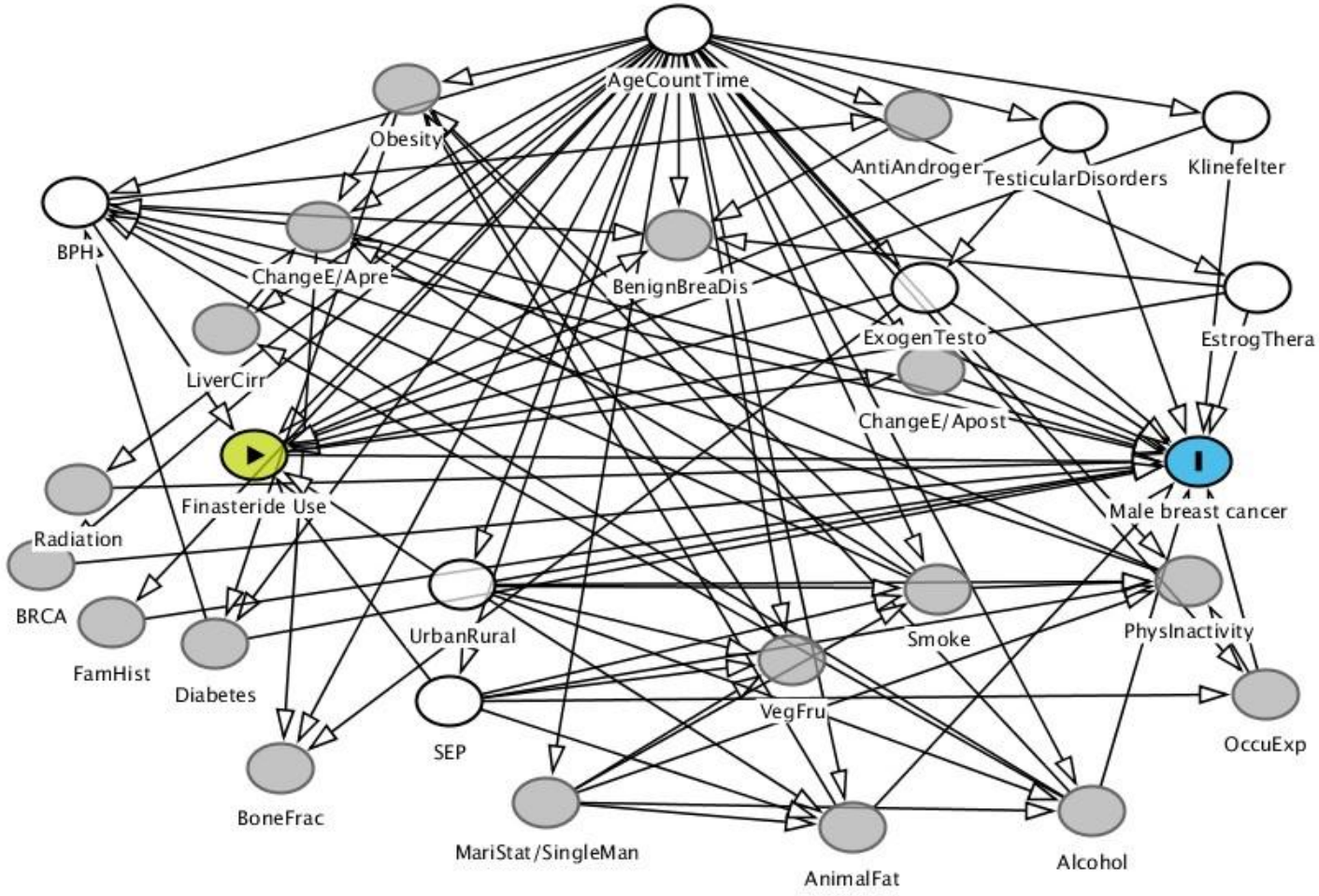
Grey background, variables not measured (self-reported lifestyle factors).

(1) Change in the estrogen / androgen ratio before finasteride use.

Minimum sufficient sets 1-4 include self-reported life-style factors, which will not be possible to include in substudy 2 (case-control study of finasteride use and male breast cancer) due to the low incidence rate of male breast cancer and thereby very few cases also participating in surveys on lifestyle factors.

Minimum sufficient set 5 includes variables, which could be measured in nation-wide registers. This sufficient set is the variables suggested to be included in substudy 2. Below we discuss the completeness and validity of each of these variables in registers. Figure 2 is the DAG highlighting adjustment for minimum sufficient set 5.

Figure 2. Final DAG including adjustment set 5 (bold circles)



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Sufficient set proposed for adjustment

The sufficient set 7 includes adjustment for seven variables:

- AgeCountTime: Age, country and time
- BPH: Benign prostatic hyperplasia
- EstrogThera: Estrogen therapy
- ExogenTesto: Exogenous testosterone
- Klinefelter: Klinefelter's syndrome
- SEP: Socioeconomic position
- TesticularDisorders: Testicular disorders
- UrbanRural: Urban/rural differences

Completeness and validity of variables in the minimum sufficient set

Even though we have a set of variables sufficient to adjust for confounding it is important to evaluate the completeness and validity of these variables in the relevant registers.

Age

Information on age has high validity due to the complete registration of date of birth of all residents in the Nordic countries.

Country

Information on country has high validity due to the complete registration of all residents in all four countries.

Time

Information on date of birth, immigration, emigration and death have high validity due to the complete registration of all residents in the Nordic countries. Therefore it is possible to know exactly who is at risk at a given point in time during follow-up.

Benign prostatic hyperplasia (BPH)

Information on BPH will be based on diagnoses or surgical treatment of benign prostatic hyperplasia from the national patient registers. By including both surgical procedures and discharge diagnoses in the definition, the definition will most likely be sufficient. If anything, it will overestimate the true prevalence of BPH due to misclassification of diagnosis.

Estrogen therapy

Estrogen therapy is based on prescriptions of relevant drugs. The prescription registers are deemed complete and valid for dispensed drugs in all four Nordic countries (Kildemoes 2011; Furu 2008; Wettermark 2007; Klaukka 2001).

Exogenous testosterone

Exogenous testosterone is based on prescriptions of relevant drugs deemed complete and valid for dispensed drugs.

Klinefelter's syndrome

Klinefelter's syndrome will be based on diagnoses from national patient registers. The diagnosis of Klinefelter's syndrome is valid when based on the patient register.

Socioeconomic position

Socioeconomic position will be based on years of education. This information is deemed to be of high completeness and validity (Jensen 2011).

Testicular disorders

Testicular disorders will be based on diagnoses from national patient registers. This diagnosis is likely the most difficult of the variables to validate. Some testicular disorders and cryptochism are probably valid, but may include some less specific diagnoses. However, these are likely few.

Urban/rural differences

Information on urban and rural differences is based on the definitions of the national statistical offices. The information is based on dwelling registers deemed to have high completeness and validity (Thygesen 2011).

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