Male Infertility and Prostate Cancer Risk: A Nested Case-Control Study

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Conflict of Interest

None of the authors have any financial interests, affiliations, or relationships that are relevant to any part of the present study.

Abstract

The pathogenesis of prostate cancer is unclear, although experimental evidence implicates androgens as playing an important role. Infertile men frequently suffer from some degree of hypogonadism and may hence be hypothesized to be at lower risk of developing prostate cancer than fertile men. To test this hypothesis, we conducted a case-control study nested within **"**the Malmö Diet and Cancer Study" cohort in Sweden, inviting 661 prostate cancer cases, and 661 age-matched controls to participate.

Of the 975 (74%) respondents, we excluded 84 childless men with unknown fertility status. Thus, 891 men were included, providing 445 prostate cancer cases and 446 controls. Of these, 841 (94%) men were biological fathers and 50 (6%) men were infertile. Logistic regression showed that the infertile men were at significantly lower risk of being diagnosed with prostate cancer than the fertile men (odds ratio, 0.45; 95% confidence interval, 0.25-0.83). Conditional and unconditional multivariate models, adjusting for socioeconomic, anthropometric, and health-status-related factors, provided similar estimates.

We conclude that enduring male infertility is associated with a reduced prostate cancer risk, thus corroborating the theory that normal testicular function, and hence most probably sufficient steroidogenesis, is an important contributing factor to the later development of this malignancy.

Keywords: Androgens; Case–control studies; Hypogonadism; Infertility, male; Prostatic neoplasms

Introduction

The pathogenesis of prostate cancer is not fully understood, although experimental evidence implicates androgens as playing an important role. For example, laboratory experiments show that androgens are involved in cell growth and proliferation in prostate cancer cell lines [1;2], that androgens act as promoters for prostate carcinogenesis [3;4], and that androgen deprivation in animal models prevents prostate cancer development [5].

Epidemiological studies have to date provided no evidence for a relationship between elevated androgen concentrations in the circulation and excess prostate cancer risk [6]. This finding is consistent with the proposed androgen saturation model, which posits the existence of a certain threshold level of maximal androgenic stimulation, above which there is no further increase in risk of prostatic carcinogenesis [7]. However, a level of androgenic stimulation below this threshold would, consequently, entail a reduced risk of prostate cancer. Consonant with this hypothesis is the finding of only two cases of non-fatal prostate cancer in an epidemiological study of 3,518 men with Klinefelter syndrome [8], for whom congenital hypogonadism is a typical feature.

Infertile men frequently present with hypogonadism and some degree of testicular dysfunction [9;10], which in many cases is believed to be of fetal origin [9;11]. Therefore, fertility status in reproductive age, and hence testicular function, may function as a better estimator of the degree of long-term androgenic stimulation of prostatic tissue than an assessment of circulating androgen concentrations later in life, at which time the malignancy may already have developed.

Since retrospective clinical information about reproductive dysfunction in youth is often unavailable, involuntary childlessness may instead be used as a proxy indicator for subnormal fertility. Such an approach has been used in two large, national cancer registry-based studies, which reported that childless men had a significantly lower risk of being diagnosed with

prostate cancer than men who had fathered a child [12;13]. Although these studies provide evidence for an association between childlessness and prostate cancer risk, they did not exclude cases of childlessness attributable to personal choice, lack of opportunity, or female-factor infertility and did not adjust for any factors other than age [12;13] and marital status [13].

We hypothesize that men with enduring infertility, being more prone to suffer from testicular dysfunction and hence, hypogonadism, are at lower risk of developing prostate cancer later in life than are men with normal fertility. To test this hypothesis, we assessed the association between prostate cancer and involuntary childlessness attributable to male infertility, in a nested case-control study.

Materials and Methods

Study population

Between 1991 and 1996, all persons born between 1923 and 1945 who were living in the city of Malmö, Sweden, were invited to participate in the prospective "Malmö Diet and Cancer Study" (MDCS) [14]. The only exclusion criteria were insufficient Swedish language skills or mental incapacity. Baseline data were acquired by a self-administered questionnaire and physical examination, and a blood sample was obtained by venipuncture. The questionnaire provided information regarding educational attainment, occupation, physical activity, social network, use of tobacco and alcohol, health, medical history, medication, and disease in close relatives. Anthropometric data, including height, weight, and body fat proportion (measured using an impedance method), were registered. Body mass index (BMI) at baseline was calculated from height and weight and was estimated at 20 years of age using the self-reported weight at that age. The study recruited 12,121 men, resulting in a capture rate of approximately 38% of the target male population.

Ascertainment of prostate cancer cases and selection of controls

Using data from the Swedish National Cancer Registry, we identified all 661 prevalent cases of prostate cancer in the MDCS cohort who were still alive as of 31st December 2006, and who were registered as still participating. For each index case, one living control without diagnosed prostate cancer at the end of follow-up was randomly selected from the MDCS cohort, matching for sex, age (± 90 days), and the date of enrollment in the cohort (± 90 days).

Collection of fertility-related data

The 1,322 selected men were sent invitations to participate and surveys with fertility-related questions in 2007. They were asked whether they had ever tried to beget a child, how many biological children they had (living and deceased), if they had ever been diagnosed with a disease or other abnormalities that may have affected their fertility status, and whether they had ever undergone a clinical assessment for involuntary childlessness, and if so, what were the results. Written informed consent was obtained from all participants along with the returned surveys. The study was approved by the Regional Ethical Review Board in Lund, Sweden.

Assessment of tumor stage and grade

Tumor stage at diagnosis, assessed by digital rectal examination, was obtained from patient records at the Department of Urology at Malmö University Hospital. Histopathological tumor grading was performed by any of three senior, National Board-certified pathologists at the Department of Pathology at Malmö University Hospital, using specimens from the initial, diagnostic prostate biopsies.

Definition of male infertility

Infertility is defined, in epidemiological terms, as the inability to conceive after a 12-month period of unprotected intercourse. Infertility can be attributed to male factors, female factors, or a combination thereof. The present study used a narrower definition of male infertility in that only men with an enduring (life-long) history of involuntary childlessness were categorized as infertile, excluding those cases where a previous medical evaluation of the couple had revealed exclusively female-factor infertility. Childless men who reported having contributed to a pregnancy were thus classified as fertile, as were childless men with only deceased offspring.

Statistical analysis

The background characteristics of the prostate cancer cases and controls were compared using the *t* test for continuous variables and the χ^2 test for categorical variables. Likewise, the characteristics of the infertile and fertile men with prostate cancer were compared using the *t* test for continuous variables and Fisher's exact test for categorical variables. We analyzed the data using both conditional binary logistic regression on available matched pairs and age-adjusted unconditional binary logistic regression on all available subjects to calculate odds ratios (OR) and the associated 95% confidence intervals (CI). The principal analysis was an evaluation of the association between male fertility status, treated as a binary variable representing infertility or fertility, and diagnosis of prostate cancer. The fertile men constituted the referent group in all analyses. To screen other potential explanatory variables for subsequent multivariate analysis, we tested a number of socioeconomic, anthropometric, and health-status-related factors as covariates in the principal model by stepwise inclusion and exclusion. The factors were eliminated if they did not change the estimate of the principal model by >15%. This elimination method gave similar results to excluding covariates using a backward stepwise approach. To further assess the association between male infertility and prostate cancer, we fitted three multivariate models including terms for height, weight, waist circumference, educational level, marital status, smoking status, country of birth, and history of urogenital infection (epididymitis, prostatitis, urinary tract infection caused by intestinal bacteria, or infection with *Chlamydia trachomatis* or *Neisseria gonorrhoeae*). These variables were included because they either emerged as significant explanatory variables in the analysis described above (urogenital infection) or had been reported to be associated with prostate cancer risk in previous studies [15-19].

Fisher's exact test was used to assess whether the prostate cancers occurring in the groups of infertile and fertile men differed with respect to tumor grade or stage. The statistical analysis

was conducted using SPSS version 17 (SPSS Inc., Chicago, IL, USA). A two-sided $p < 0.05$ was considered to indicate statistical significance.

Results

Of the 1,322 eligible participants, 975 (74%) men responded with a completed survey. Respondents and non-respondents were of similar age, with the mean age and standard deviation (SD) being 74.3 years (SD ± 5.7), and 75.4 years (SD ± 6.0), respectively. The proportion of married men among respondents, 77%, was slightly higher than the 69% among non-respondents, while the proportion of foreign born men was 7 and 14%, respectively. Figure 1 details the flow of participants through the study.

Since we aimed to evaluate the association between male-factor infertility and prostate cancer, we excluded the 77 men stating that they had never tried to beget a child and accordingly had unknown fertility status. Of the remaining 898 men, we further excluded seven individuals in childless relationships where a medical evaluation of the couple had revealed only female-factor infertility, and the childlessness therefore most likely was a consequence of the partner's infertility. Thus, 891 (67%) men were included for analysis, providing 445 (50%) prostate cancer cases and 446 (50%) controls. Table 1 displays the background characteristics of the subjects with and without diagnosed prostate cancer. Compared with controls, the cases had significantly more children, a higher proportion had a history of urogenital infection, and fewer had previously undergone a clinical assessment due to infertility.

Table 2 displays a comparison of the background characteristics of the prostate cancer cases according to fertility status. Compared with the fertile men, the infertile men had a significantly larger waist circumference at baseline, were heavier at 20 years of age, had a higher BMI at 20 years of age, and were more likely to have undergone a clinical evaluation due to infertility. Table 3 presents the stage and grade of the prostate cancers occurring among the infertile men compared with the tumors occurring among the fertile men. There were no significant differences between the two groups of men with respect to tumor characteristics.

Table 4 shows the ORs with 95% CI of the association between male infertility and prostate cancer. The odds of prostate cancer diagnosis were significantly lower for the infertile men, compared with the fertile men; in the principal, age-adjusted unconditional model, using all available subjects, the OR was 0.45 (95% CI: 0.25-0.83), and in the conditional model, using the 308 matched pairs, the OR was 0.36 (95% CI: 0.17-0.77). None of the other factors significantly changed the estimates, although having a history of urogenital infection, was independently associated with prostate cancer risk, with the unconditional model giving an OR of 1.54 (95% CI: 1.12-2.11), and the conditional model an OR of 1.48 (95% CI: 1.00-2.19). The multivariate models rendered results that were very similar to those obtained in the principal analyses.

Discussion

In this nested case-control study, we found that the odds of being diagnosed with prostate cancer were approximately halved for men with enduring infertility in relation to men with proven fertility. This association was unaffected by adjustment for a number of socioeconomic, anthropometric, and health-status-related factors. However, in agreement with some previous reports [17], having a history of epididymitis, prostatitis, urinary tract infection, or a sexually transmissible infection independently increased the odds of prostate cancer diagnosis.

Our main finding is confirmatory of the national cancer registry-based studies [12;13]. The Swedish study, including 48,850 prostate cancer cases, reported an OR for prostate cancer diagnosis of 0.83 for childless men, compared with men with two or more children [12]. The Danish study, including 3,400 prostate cancer cases, reported a rate ratio for prostate cancer diagnosis of 0.84 for childless men compared with fathers of at least one child [13]. In contrast, a meta-analysis of 18 epidemiological studies on the association between fecundity and prostate cancer found no significant association [17].

While previous studies have focused on the association between childlessness and prostate cancer risk, the aim of the present study was to evaluate the association of, specifically, male-factor infertility with prostate cancer risk. Therefore, we excluded all cases of childlessness attributable to personal choice or lack of opportunity. We endeavored to exclude all cases of female-factor-dependent childlessness to ensure that the remaining cases of childlessness were attributable, at least in part, to male-factor infertility. However, previous medical evaluations of the childless couples had revealed female-factor infertility with no demonstrable male factor among only 7/57 (12%), a smaller proportion than expected [20]. Hence, it is highly probable that the group of 50 childless men classified as being infertile also included some cases where the infecundity was instead caused by an undiagnosed female

factor. This misclassification should, however, cause bias toward the null. Similarly, it is likely that there were some undiagnosed cases of prostate cancer among the controls (which were not screened), again resulting in a misclassification with bias toward the null.

Another limitation of our study was the exclusion of deceased men, potentially causing an inclusion bias regarding the grade and stage of prostate cancer, since mortality is higher in men with more aggressive or advanced disease. However, we found no evidence of significant differences in tumor parameters between the infertile and fertile participants. Moreover, our results are consistent with the national cancer registry-based studies, which included all nationally reported cases of prostate cancer [12;13]. Reporting to the Swedish National Cancer Registry is mandatory, and the completeness of registration has been found to be approximately 99% [21]. Since these studies included entire birth cohorts, the lower odds of prostate cancer diagnosis for the childless men cannot have been an artifactual result caused by a higher prostate cancer-specific mortality relative to the men who were fathers. Hence, the aforementioned findings support the interpretation that such an inclusion bias is not the main explanation for the reduction in odds of prostate cancer diagnosis among the infertile men in the present study.

A possible limitation concerning the conception of our study is the inference of subnormal testicular function in the group of infertile men. This premise is based on the findings of previous studies, which showed that men with idiopathic infertility had significantly lower concentrations of serum testosterone, higher LH, higher estrogen, lower testosterone-to-LH ratios and higher estrogen-to-testosterone ratios than men with proven fertility [9]. Similarly, men with non-obstructive azoospermia or severe oligozoospermia were reported to have significantly lower concentrations of serum testosterone, higher estradiol, lower serum testosterone-to-estradiol ratios, and higher FSH than age-matched fertile controls [10].

Androgen concentrations in the baseline MDCS blood samples were not assessed, because we deemed that they would not provide accurate appraisals of gonadal function in youth for the following reasons. Malignant tumors of the prostate may be assumed to arise over a period of several decades, suggesting that androgenic exposure during early adulthood may be of greater importance for carcinogenesis than the androgenic exposure during the 5-8 decades of life, which was the age of the men at enrollment in MDCS. Moreover, the association between androgenicity and prostate cancer risk may be distorted by the existence of undiagnosed prostate cancer cases at baseline, via a possible effect of the disease itself on androgen concentrations [22-24]. Furthermore, a single assessment of circulating androgen concentrations cannot correctly determine total androgenicity, since it is a function of the entire androgen signaling pathway from the hypothalamus to the testis and back, involving not only the androgen itself, but also its receptor and co-factors [25;26]. A further complicating matter is the poor correlation between androgen concentrations in the circulation and in the prostate [27-29]. Consequently, enduring infertility, and hence hypogonadism, can be held to be a better long-term indicator of reduced androgenic stimulation of the prostate than an assessment of circulating androgen concentrations in late adulthood.

We found a significantly stronger (inverse) association between prostate cancer and male infertility than between prostate cancer and any of the other analyzed factors. Moreover, apart from for age and heredity, the association appears to be stronger than the associations reported for other prostate cancer risk modifying factors in other studies, thus corroborating the hypothesis that endocrine factors play an important role in the development of prostate cancer. However, caution should be exercised in interpreting the magnitude of the OR in terms of relative risk since the present study used a prevalent case-control design. Additionally, the external validity of our study may be limited, since the absolute risks of male-factor infertility and prostate cancer in the MDCS cohort from which the study

participants were selected may differ from the corresponding risks in the background population. However, the OR should be less sensitive to any biases that may have inadvertently been introduced. A strength of our study was that we were able to analyze the potential influence of a large number of socioeconomic, biometric, and health-status-related factors that in some epidemiological studies have been reported to be associated with prostate cancer risk [15-19].

The results of our study support the hypothesis that chronic testicular dysfunction is protective against the later development of prostate cancer, comparable to the situation for men with Klinefelter syndrome [8]. We suggest that this protective effect may be a result of the frequently associated hypogonadism [9;10], resulting in a reduction in the level of androgenic stimulation to below the proposed androgen saturation threshold [7]. In “the Prostate Cancer Prevention Trial” (PCPT), men treated with the 5α-reductase inhibitor finasteride, which prevents the conversion of testosterone to 5α-dihydrotestosterone, exhibited a 25% reduction in the overall rate of prostate cancer diagnosis [30]. Similarly, in “the Reduction by Dutasteride of Prostate Cancer Events study” (REDUCE), men treated with dutasteride, also a 5α-reductase inhibitor, exhibited a 23% overall relative risk reduction for prostate cancer [31]. Thus, the results from PCPT and REDUCE appear to support the hypothesis of an androgen saturation effect on the overall risk of prostate cancer development.

In conclusion, this study provides further evidence that enduring male infertility is associated with a significantly lower risk of prostate cancer diagnosis, suggesting that adequate testicular function, and hence most probably sufficient steroidogenesis, is an important contributing factor to the later development of the malignancy.

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Figure Legends

Fig. 1 Selection of cases and controls for inclusion in the study. Men stating that they had never tried to beget a child and who hence had unknown fertility status were excluded. Childless men who were in relationships where a clinical evaluation had revealed solely female-factor infertility were also excluded.

Table 1 Characteristics of prostate cancer cases and controls

	Cases (n = 445)	Controls (n = 446)	p-value[a]
Age (years)	74.3 ± 5.7	74.3 ± 5.7	0.97
Number of biological children (n)	2.1 ± 1.0	1.9 ± 1.0	0.01
Body mass index at baseline (kg/m^2)	26.0 ± 3.1	26.2 ± 3.3	0.46
Waist circumference at baseline (cm)	93.4 ± 9.0	93.2 ± 9.6	0.70
Body fat at baseline, proportion by weight (%)	20.6 ± 4.5	20.4 ± 4.4	0.38
Self-reported weight at 20 years of age (kg)	68.5 ± 8.0	68.5 ± 8.0	0.94
Estimated body mass index at 20 years of age (kg/m^2)	22.0 ± 2.2	22.1 ± 2.1	0.51
Country of birth			
Native born	402 (90)	399 (89)	
Foreign born	28 (6)	33 (7)	0.80
Unknown	15 (3)	14 (3)	
Highest education level			
≥12 years	168 (38)	162 (36)	
<12 years	261 (59)	269 (60)	0.88
Unknown	16 (4)	15 (3)	
Marital status at baseline			
Married	355 (80)	355 (80)	
Divorced	48 (11)	52 (12)	
Widower	18 (4)	18 (4)	0.98
Single or never married	9 (2)	7 (2)	
Unknown	15 (3)	14 (3)	
Smoking status at baseline			
Regular smoker	65 (15)	81 (18)	
Non-smoker or sporadic smoker	365 (82)	351 (79)	0.36
Unknown	15 (3)	14 (3)	
Previous investigation due to infertility			
Performed	29 (7)	51 (11)	
Not performed	399 (90)	378 (85)	0.04
Unknown	17 (4)	17 (4)	
History of urogenital infection[b]			
Positive history	117 (26)	84 (19)	0.008
No history	328 (74)	362 (81)	

Data given as mean ± standard deviation or number (percent).

[a]Two-sided t test for continuous variables and χ^2 for categorical variables.

[b]Epididymitis, prostatitis, urinary tract infection caused by intestinal bacteria, or infection with *Chlamydia trachomatis* or *Neisseria gonorrhoeae.*

Table 2 Comparison of characteristics of prostate cancer cases according to fertility status

	Infertile men (n = 16)	Fertile men (n = 429)	p-value[a]
Age (years)	76.0 ± 5.5	74.2 ± 5.7	0.22
Age at diagnosis of prostate cancer (years)	67.6 ± 6.4	67.6 ± 5.7	0.97
Number of biological children (n)	0	2.2 ± 1.0	<0.001
Body mass index at baseline (kg/m^2)	27.3 ± 4.1	26.0 ± 3.1	0.10
Waist circumference at baseline (cm)	98.0 ± 10.4	93.3 ± 8.9	0.04
Body fat at baseline, proportion by weight (%)	21.3 ± 5.8	20.6 ± 4.5	0.55
Self-reported weight at 20 years of age (kg)	74.2 ± 11.6	68.4 ± 7.8	0.01
Estimated body mass index at 20 years of age (kg/m^2)	23.6 ± 3.1	21.9 ± 2.2	0.01
Country of birth			
Native born	14 (88%)	388 (90%)	
Foreign born	1 (6%)	27 (6%)	0.59
Unknown	1 (6%)	14 (3%)	
Highest education level			
≥12 years	5 (31%)	163 (38%)	
<12 years	10 (63%)	251 (59%)	0.54
Unknown	1 (6%)	15 (3%)	
Marital status at baseline			
Married	13 (81%)	342 (80%)	
Divorced	1 (6%)	47 (11%)	
Widower	1 (6%)	17 (4%)	0.69
Single or never married	0 (0%)	9 (2%)	
Unknown	1 (6%)	14 (3%)	
Smoking status at baseline			
Regular smoker	3 (19%)	62 (14%)	
Non-smoker or sporadic smoker	12 (75%)	353 (82%)	0.34
Unknown	1 (6%)	14 (3%)	
Previous investigation due to infertility			
Performed	5 (31%)	24 (6%)	
Not performed	7 (44%)	392 (91%)	<0.001
Unknown	4 (25%)	13 (3%)	
History of urogenital infection[b]			
Positive history	2 (13%)	115 (27%)	0.26
No history	14 (88%)	314 (73%)	

Data given as mean ± standard deviation or number (percent).

[a]Two-sided *t* test for continuous variables and Fisher's exact test for categorical variables.

[b]Epididymitis, prostatitis, urinary tract infection caused by intestinal bacteria, or infection with *Chlamydia trachomatis* or *Neisseria gonorrhoeae.*

Table 3 Stage and grade of prostate cancers according to fertility status

	Infertile men (*n* = 16) *n* (%)	Fertile men (*n* = 429) *n* (%)	*p*-value[a]
Tumor stage			
T1	7 (44)	179 (42)	
T2	5 (31)	167 (39)	
T3	3 (19)	70 (16)	0.58
T4	0 (0)	1 (0)	
Unknown	1 (6)	12 (3)	
Gleason score			
<7	7 (44)	229 (53)	
7	3 (19)	96 (22)	0.41
>7	2 (13)	24 (6)	
Unknown	4 (25)	80 (19)	

[a]Fisher's exact test.

Table 4 Association between male infertility and prostate cancer, a case-control study nested in the Malmö Diet and Cancer Study

Factors[a]	Unconditional analyses[b]		Conditional analyses[c]	
	No. of cases/controls	OR (95% CI)	No. of cases/controls	OR (95% CI)
Male infertility and age only	445/446	0.45 (0.25-0.83)	NA	NA
Date of enrollment in MDCS	445/446	0.45 (0.24-0.83)	308/308	0.36 (0.17-0.77)
Marital status at baseline	430/432	0.45 (0.24-0.86)	286/286	0.30 (0.13-0.73)
Level of highest educational attainment	429/431	0.48 (0.25-0.90)	285/285	0.32 (0.14-0.76)
Occupational category	429/431	0.40 (0.21-0.78)	286/286	0.31 (0.13-0.72)
Country of birth (native or foreign born)	430/432	0.46 (0.25-0.87)	286/286	0.32 (0.14-0.75)
Smoking status at baseline	408/406	0.47 (0.24-0.90)	251/251	0.28 (0.11-0.77)
Swedish moist oral tobacco (“snus”) use at baseline	430/432	0.47 (0.25-0.88)	286/286	0.32 (0.14-0.74)
Alcohol consumption (mL/last 30 days)	430/431	0.49 (0.26-0.92)	285/285	0.34 (0.14-0.80)
Height at baseline (cm)	445/446	0.45 (0.24-0.83)	308/308	0.36 (0.17-0.77)
Weight at baseline (kg)	445/446	0.45 (0.25-0.83)	308/308	0.36 (0.17-0.78)
Body mass index at baseline (kg/m^2)	445/446	0.46 (0.25-0.84)	308/308	0.37 (0.17-0.80)
Waist circumference at baseline (cm)	445/446	0.45 (0.24-0.82)	308/308	0.37 (0.17-0.78)
Body fat at baseline, proportion by weight (%)	442/446	0.42 (0.23-0.78)	306/306	0.32 (0.14-0.71)
Self-reported weight at 20 years of age (kg)	366/354	0.39 (0.19-0.78)	224/224	0.16 (0.05-0.55)
Estimated body mass index at 20 years of age (kg/m^2)	366/354	0.40 (0.20-0.81)	224/224	0.16 (0.05-0.55)
Hypertension at baseline	389/377	0.40 (0.20-0.80)	244/244	0.20 (0.07-0.58)
History of atherosclerotic disease[d]	393/381	0.43 (0.22-0.85)	247/247	0.20 (0.07-0.58)
History of urogenital infection[e]	445/446	0.44 (0.24-0.81)	308/308	0.36 (0.17-0.76)
History of varicocoele	440/443	0.47 (0.26-0.87)	301/301	0.41 (0.19-0.88)
History of cryptorchidism	439/443	0.44 (0.23-0.82)	300/300	0.39 (0.18-0.85)
Multivariate model 1[f]	445/446	0.44 (0.24-0.81)	308/308	0.36 (0.17-0.77)
Multivariate model 2[g]	445/446	0.43 (0.23-0.80)	308/308	0.37 (0.17-0.79)
Multivariate model 3[h]	407/405	0.42 (0.21-0.83)	250/250	0.27 (0.10-0.75)

OR odds ratio; *CI* confidence interval; *MDCS* the “Malmö Diet and Cancer Study”.

[a]Factors tested by stepwise inclusion and exclusion as covariates in the principal model. Referent categories for categorical variables: marital status: married, level of highest educational attainment: university degree, occupational category: manual laborer, country of birth: native born, smoking status: not current smoker, and “snus” use: not current user. For diseases and abnormalities, the referent category was negative history.

[b]All analyses are age-adjusted.

[c]Case-control pairs matched for age (±90 days), and date of enrollment in MDCS (±90 days).

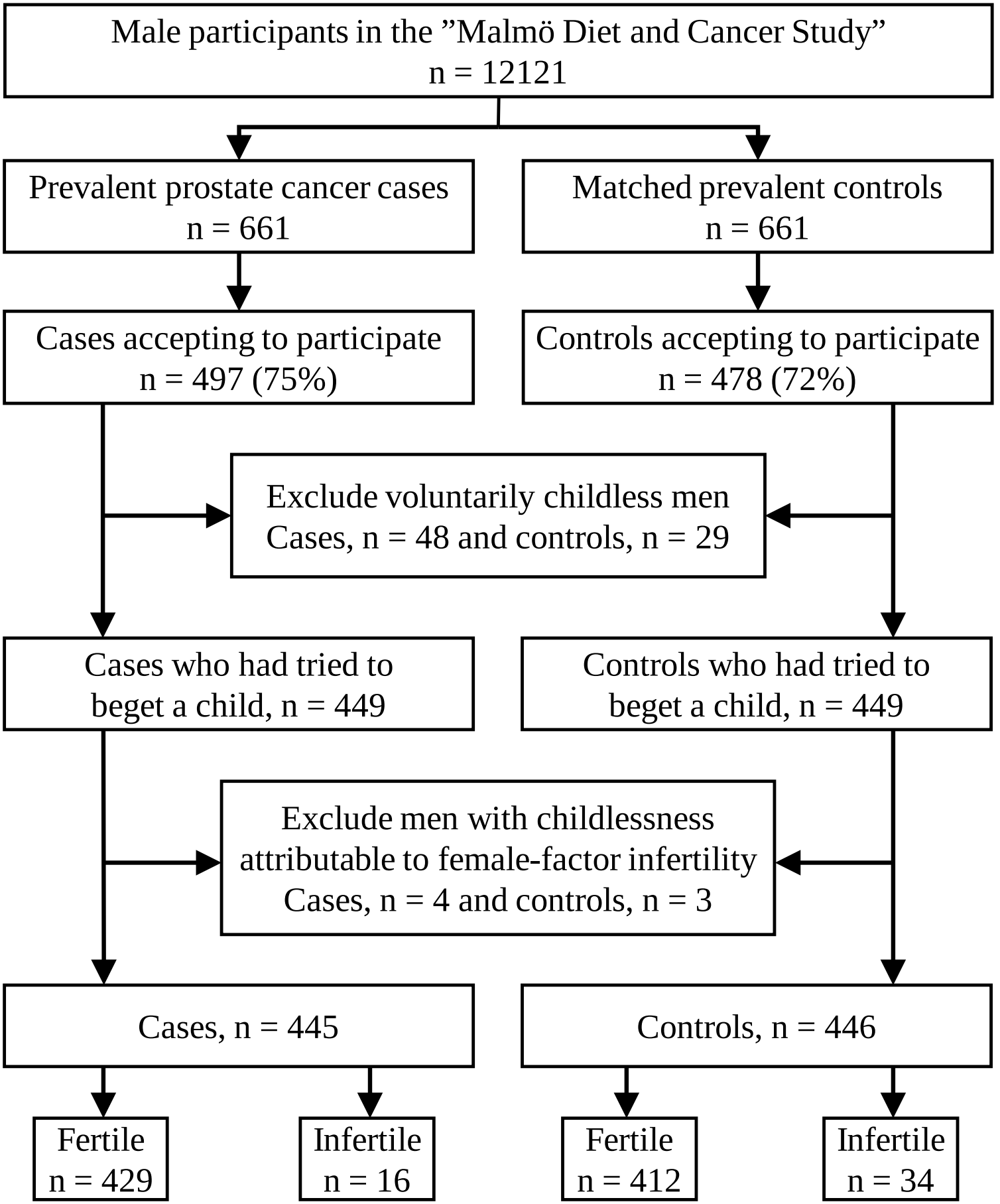
[d]Cardiac infarction, stroke, intermittent claudication, or hypertension.

[e]Epididymitis, prostatitis, urinary tract infection caused by intestinal bacteria, or infection with *Chlamydia trachomatis* or *Neisseria gonorrhoeae.*

[f]Adjusted for age (continuous) and previous history (negative/positive) of urogenital infections (as [e]).

[g]Adjusted for covariates in multivariate model 1, plus height (continuous), weight (continuous), and waist circumference (continuous).

[h]Adjusted for covariates in multivariate model 2, plus level of highest educational attainment (university degree/higher education [>1year]/secondary school/junior secondary school/primary school/did not complete primary school), marital status (married/single/divorced/widower), smoking status (not current smoker/current smoker), and country of birth (native born/foreign born).


Male participants in the ”Malmö Diet and Cancer Study”
n = 12121
Prevalent prostate cancer cases
n = 661
Matched prevalent controls
n = 661
Cases accepting to participate
n = 497 (75%)
Controls accepting to participate
n = 478 (72%)
Exclude voluntarily childless men
Cases, n = 48 and controls, n = 29
Cases who had tried to
beget a child, n = 449
Controls who had tried to
beget a child, n = 449
Exclude men with childlessness
attributable to female-factor infertility
Cases, n = 4 and controls, n = 3
Cases, n = 445
Controls, n = 446
Fertile
n = 429
Infertile
n = 16
Fertile
n = 412
Infertile
n = 34