Vasectomy and risk of prostate cancer: population based matched cohort study

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ABSTRACT

OBJECTIVE
To determine the association between vasectomy and prostate cancer, adjusting for measures of health seeking behaviour.

DESIGN
Population based matched cohort study.

SETTING
Multiple validated healthcare databases in Ontario, Canada, 1994-2012.

PARTICIPANTS
326,607 men aged 20 to 65 who had undergone vasectomy were identified through physician billing codes and matched 1:1 on age (within two years), year of cohort entry, comorbidity score, and geographical region to men who did not undergo a vasectomy.

MAIN OUTCOMES MEASURES
The primary outcome was incident prostate cancer. Secondary outcomes were prostate cancer related grade, stage, and mortality.

RESULTS
3462 incident cases of prostate cancer were identified after a median follow-up of 10.9 years: 1843 (53.2%) in the vasectomy group and 1619 (46.8%) in the non-vasectomy group. In unadjusted analysis, vasectomy was associated with a slightly increased risk of incident prostate cancer (hazard ratio 1.13, 95% confidence interval 1.05 to 1.20). After adjustment for measures of health seeking behaviour, however, no association remained (adjusted hazard ratio 1.02, 95% confidence interval 0.95 to 1.09). Moreover, no association was found between vasectomy and high grade prostate cancer (adjusted odds ratio 1.05, 95% confidence interval 0.67 to 1.66), advanced stage prostate cancer (adjusted odds ratio 1.04, 0.81 to 1.34), or mortality (adjusted hazard ratio 1.06, 0.60 to 1.85).

CONCLUSION
The findings do not support an independent association between vasectomy and prostate cancer.

Introduction
Vasectomy is a minor outpatient procedure with few short term complications.1-2 It is effective in most men and one of the most reliable and cost effective long term methods of contraception.3-4 An estimated 33 million women worldwide rely on their partner’s vasectomy for contraception.5

Several studies have explored the possible association between vasectomy and prostate cancer, with conflicting results.6-30 Potential biological mechanisms supporting an association between vasectomy and incident prostate cancer include increases in androgen levels, which are hypothesised to increase the risk of prostate cancer,11 and impaired secretory function of the prostate, which might prolong exposure of the prostate to carcinogenic factors.11 Although some studies have shown an increase in serum dihydrotestosterone and testosterone after vasectomy,32-34 others have found no statistically significant change in androgen levels.35-36 Similarly, findings on the association between frequency of ejaculation and risk of prostate cancer are conflicting.37-38 Thus the possible biological relation, if any, between vasectomy and prostate cancer remains unclear.

Many of the studies that found an association between vasectomy and prostate cancer were limited by sample size and the potential for selection, recall, and detection biases. Given the frequency of vasectomy, even a small increased risk of prostate cancer would constitute a major public health problem. We examined the association between vasectomy and prostate cancer in a large population based cohort, adjusting for health seeking behaviours that might have biased other studies examining this association.

Methods
Setting and data sources
We conducted a population based matched cohort study of residents in Ontario, Canada. With a population of about 14 million in 2016,9 Ontario is Canada’s most populous province, and residents have universal access to physician services and hospital care. We used the Ontario health insurance plan database to identify physician claims for vasectomy. The Ontario Cancer Registry10 was used to identify patients with incident prostate...
cancer (international classification of diseases, ninth and 10th revisions (ICD-9: 185 and ICD-10: C61, respectively), characteristics of their tumour, and date and cause of death, where applicable. It is a validated, population based tumour registry maintained by Cancer Care Ontario and is estimated to be more than 95% complete.\textsuperscript{50-51} We obtained data on admissions to hospitals from the Canadian Institute for health information discharge abstract database,\textsuperscript{62} national ambulatory care reporting system, and same day surgery database, which contain detailed clinical information on admissions to hospitals and emergency departments and outpatient surgical procedures in Ontario. We obtained basic personal data from the registered persons database, a registry of all Ontario residents eligible for health insurance. These databases were linked in an anonymous fashion using encrypted health card numbers, and are routinely used to study the long term consequences of medical care.\textsuperscript{43,45} Details of the databases used and their validity have been described elsewhere.\textsuperscript{46}

Study participants
We identified all men aged 20 to 65 who underwent a vasectomy between 1 April 1994 and 31 December 2012. We excluded those with a diagnosis of prostate cancer before vasectomy, those who underwent a vasovasostomy (vasectomy reversal) at any time before the censoring date, and those who underwent other procedures on the same day that were inconsistent with receipt of a vasectomy for the purpose of contraception—for example, vasectomy performed on the same day as prostatectomy or vesiculectomy (removal of seminal vesicles). The date of vasectomy served as the index date.

For each man who underwent vasectomy, we selected one man who did not, matching on age (within two years), comorbidity score (defined using the Johns Hopkins adjusted clinical groups case mix system),\textsuperscript{47} geographical area (defined by the first three digits of the postal code), and index date. The Johns Hopkins adjusted clinical case mix system was designed to predict healthcare use and considers the duration, severity, and intensity of service use related to both inpatient and outpatient claims, details of which have been provided elsewhere.\textsuperscript{48} To assign a score to each patient for this study, we used data from Ontario health insurance plan, the Canadian Institute for Health Information, and the national ambulatory care reporting system. We randomly assigned an index date within one year of the vasectomy date of the corresponding matched participant to account for temporal changes in prostate cancer screening and diagnosis over time. Because men not undergoing a vasectomy might be infertile, and infertility might be related to risk of prostate cancer,\textsuperscript{49} we also excluded those with a diagnosis of infertility from the cohort of non-vasectomised men.

Outcome assessment
The primary outcome was incident prostate cancer, defined as the first recorded date of prostate cancer diagnosis in the Ontario Cancer Registry. Secondary outcomes included prostate cancer related grade, stage, and mortality. We categorised prostate cancer grade as low (Gleason score 2-6), intermediate (Gleason score 7), or high (Gleason score 8-10), and prostate cancer stage as either localised (stage T1c) or advanced (stage T3+, N+, or M+).

We followed participants until their date of last contact with health services, death, or the end of the study period, whichever occurred first. For the analysis of mortality, we followed patients until 31 December 2012, the last date for which cancer specific mortality data were available. For all other outcomes, we followed patients until 31 March 2014.

Covariates
To deal with the possibility of healthy user bias, we obtained data on the number of admissions to hospitals and the number of visits to general practitioners, specialists, urologists, and emergency departments. For each of these, we identified the number of interactions in the year preceding the index date and between the index date and end of follow-up. To account for survival bias, whereby those who survive longer are likely to have a higher number of interactions with healthcare services, we standardised interactions with healthcare services to duration of follow-up by dividing the number of interactions by follow-up time.

To adjust for potential detection bias, we obtained data on the number of colonoscopies, faecal occult blood tests, and cholesterol tests. We chose these tests as they are insured under the universal healthcare system in Ontario and therefore the data were available within the databases used for this study, whereas testing for prostate specific antigen is not. We assumed that patients undergoing these prevention tests would also be likely to undergo testing for prostate specific antigen. Indeed, the association between prostate and colorectal cancer screening has been shown among men in Alberta, another province in Canada with universal healthcare.\textsuperscript{50} We similarly divided these tests into subcategories according to whether they occurred before or after the index date.

We also collected data on socioeconomic status to control for potential confounding, as such status relates to receipt of both vasectomy and cancer screening.\textsuperscript{51,52} Finally, an association between sexually transmitted infections and risk of prostate cancer has been reported;\textsuperscript{53} although results of testing for sexually transmitted infections are not available in administrative data, we also evaluated the number of these tests performed during the study period.

Statistical analysis
For each outcome we evaluated the standardised difference according to vasectomy or non-vasectomy group. We adjusted models based on covariates that were considered to be meaningfully different between the groups (standardised difference >0.10). As the numbers of prostate cancer specific deaths were limited, a decision was made a priori to evaluate differences between groups on age at diagnosis of prostate cancer, rural status, fifth of income, and comorbidity score only.

We obtained cumulative probability estimates for incident prostate cancer using the Kaplan-Meier method. To
estimate the association between vasectomy and risk of incident prostate cancer and mortality, we conducted time-to-event analyses using population averaged Cox proportional hazard regression. For prostate cancer grade and stage, we used logistic regression models.

We performed a tracer analysis by examining the outcome of incident non-Hodgkin's lymphoma, in a fashion identical to the analysis of incident prostate cancer. As there is no reason to anticipate an association between vasectomy and non-Hodgkin's lymphoma, we reasoned that a positive association in this analysis would suggest that any observed association between vasectomy and risk of prostate cancer might reflect residual confounding.

All statistical analyses were performed using SAS (version 9.3; SAS Institute, Cary, NC). We considered a two sided P value of 0.05 to be statistically significant.

Sensitivity analysis
To further evaluate the potential for confounding on the association between vasectomy and risk of prostate cancer, we performed three additional analyses in which we included only income fifth, interactions with health services before index date, or interactions with health services after index date. The last two models only included variables found to be meaningfully different between the groups (standardised difference >0.10).

Patient involvement
No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. No plans have been made to disseminate the results of the research to study participants; however, results will be disseminated to the relevant patient community.

Results
Over the 18 year study period, 395,836 men underwent vasectomy. Of these, 326,607 (82.5%) were matched to an equal number of men who did not undergo vasectomy. Unmatched cases tended to be younger and have higher comorbidity scores than matched cases. Table 1 shows the characteristics of the cohort. The median follow-up was 10.9 years (interquartile range 6.3-15.4).

Incident prostate cancer
Overall, 3462 incident cases of prostate cancer were identified: 1843 (53.2%) in the vasectomy group and

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Table 1 | Cohort characteristics. Values are means (standard deviations) unless stated otherwise

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Vasectomy group (n=326,607)</th>
<th>Non-vasectomy group (n=326,607)</th>
<th>Standardised difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at index date (years)</td>
<td>37.3 (6.15)</td>
<td>37.3 (6.24)</td>
<td>—</td>
</tr>
<tr>
<td>Comorbidity score (No (%)):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>191,967 (58.8)</td>
<td>191,967 (58.8)</td>
<td>—</td>
</tr>
<tr>
<td>5-9</td>
<td>126,974 (38.9)</td>
<td>126,974 (38.9)</td>
<td>—</td>
</tr>
<tr>
<td>10-14</td>
<td>7611 (2.3)</td>
<td>7611 (2.3)</td>
<td>—</td>
</tr>
<tr>
<td>15-19</td>
<td>55 (0.0)</td>
<td>55 (0.0)</td>
<td>—</td>
</tr>
<tr>
<td>Rural (No (%))</td>
<td>47,398 (14.5)</td>
<td>48,291 (14.8)</td>
<td>—</td>
</tr>
<tr>
<td>Income fifth (No (%)):</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>1 (lowest)</td>
<td>40,772 (12.5)</td>
<td>55,500 (17.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>56,209 (17.2)</td>
<td>61,775 (18.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>69,943 (21.4)</td>
<td>68,555 (21.0)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>80,908 (24.8)</td>
<td>74,270 (22.7)</td>
<td></td>
</tr>
<tr>
<td>5 (highest)</td>
<td>78,775 (24.3)</td>
<td>66,507 (20.4)</td>
<td></td>
</tr>
<tr>
<td>Health service used in year before index date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visits to general practitioners</td>
<td>2.91 (3.11)</td>
<td>2.87 (4.28)</td>
<td>0.01</td>
</tr>
<tr>
<td>Visits to specialists</td>
<td>1.23 (2.32)</td>
<td>0.93 (3.08)</td>
<td>0.11</td>
</tr>
<tr>
<td>Visits to urologists</td>
<td>0.54 (0.59)</td>
<td>0.05 (0.37)</td>
<td>1.00</td>
</tr>
<tr>
<td>Admissions to hospitals</td>
<td>0.02 (0.14)</td>
<td>0.03 (0.21)</td>
<td>0.08</td>
</tr>
<tr>
<td>Visits to emergency departments</td>
<td>0.17 (0.56)</td>
<td>0.24 (0.73)</td>
<td>0.11</td>
</tr>
<tr>
<td>Colonoscopies</td>
<td>0.01 (0.11)</td>
<td>0.01 (0.11)</td>
<td>0.01</td>
</tr>
<tr>
<td>Faecal occult blood tests</td>
<td>0.01 (0.13)</td>
<td>0.01 (0.11)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sexually transmitted infection tests</td>
<td>0.01 (0.16)</td>
<td>0.01 (0.16)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cholesterol tests</td>
<td>0.29 (0.55)</td>
<td>0.25 (0.57)</td>
<td>0.06</td>
</tr>
<tr>
<td>Health service used between index date and end of follow-up (per year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visits to general practitioners</td>
<td>2.34 (2.62)</td>
<td>2.86 (4.07)</td>
<td>0.15</td>
</tr>
<tr>
<td>Visits to specialists</td>
<td>0.96 (1.92)</td>
<td>1.10 (2.45)</td>
<td>0.06</td>
</tr>
<tr>
<td>Visits to urologists</td>
<td>0.08 (0.28)</td>
<td>0.06 (0.41)</td>
<td>0.06</td>
</tr>
<tr>
<td>Admissions to hospitals</td>
<td>0.03 (0.25)</td>
<td>0.04 (0.36)</td>
<td>0.04</td>
</tr>
<tr>
<td>Visits to emergency departments</td>
<td>0.29 (0.49)</td>
<td>0.35 (0.94)</td>
<td>0.08</td>
</tr>
<tr>
<td>Colonoscopies</td>
<td>0.02 (0.06)</td>
<td>0.02 (0.06)</td>
<td>0.05</td>
</tr>
<tr>
<td>Faecal occult blood tests</td>
<td>0.03 (0.08)</td>
<td>0.03 (0.08)</td>
<td>0.0</td>
</tr>
<tr>
<td>Sexually transmitted infection tests</td>
<td>0.01 (0.05)</td>
<td>0.01 (0.09)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cholesterol tests</td>
<td>0.30 (0.36)</td>
<td>0.33 (0.42)</td>
<td>0.09</td>
</tr>
</tbody>
</table>
1619 (46.8%) in the non-vasectomy group. Figure 1 shows the cumulative probability of incident prostate cancer, stratified by vasectomy status. In the unadjusted analysis, vasectomy was associated with a modest but statistically significant increased risk of incident prostate cancer (hazard ratio 1.13, 95% confidence interval 1.05 to 1.20). Variables found to be meaningfully different between the groups and included in the multivariable model were income fifth; visits to specialists, urologists, and emergency departments in the year before the index date; and visits to general practitioners between the index date and end of follow-up. After adjustment for these variables, the association between vasectomy and incident prostate cancer was no longer discernible (table 2, adjusted hazard ratio 1.02, 95% confidence interval 0.95 to 1.09).

Sensitivity analyses were conducted excluding men aged less than 50 and less than 60 at their last follow-up. No association was found between vasectomy and incident prostate cancer after restricting analyses to men with follow-up at least to age 50 (adjusted hazard ratio 1.06, 0.98 to 1.15) or at least to age 60 (1.06, 0.91 to 1.23).

![Cumulative probability of incident prostate cancer by vasectomy status](image)

**Fig 1** Cumulative probability of incident prostate cancer by vasectomy status

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td><strong>Adjusted</strong>*</td>
</tr>
<tr>
<td>No vasectomy</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>1.13 (1.05 to 1.20)</td>
</tr>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Age at index date</td>
<td>1.19 (1.18 to 1.19)</td>
</tr>
<tr>
<td><strong>Comorbidity score:</strong></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>5-9</td>
<td>1.51 (1.41 to 1.62)</td>
</tr>
<tr>
<td>10-14</td>
<td>2.36 (1.99 to 2.80)</td>
</tr>
<tr>
<td>15-19</td>
<td>0.001 (0.001 to 0.002)</td>
</tr>
<tr>
<td><strong>Rural status:</strong></td>
<td></td>
</tr>
<tr>
<td>Not rural</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Rural</td>
<td>0.75 (0.68 to 0.83)</td>
</tr>
<tr>
<td><strong>Income fifth:</strong></td>
<td></td>
</tr>
<tr>
<td>1 (lowest)</td>
<td>0.53 (0.47 to 0.59)</td>
</tr>
<tr>
<td>2</td>
<td>0.55 (0.50 to 0.61)</td>
</tr>
<tr>
<td>3</td>
<td>0.62 (0.56 to 0.68)</td>
</tr>
<tr>
<td>4</td>
<td>0.69 (0.64 to 0.76)</td>
</tr>
<tr>
<td>5 (highest)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td><strong>Health service used in year before index date</strong></td>
<td></td>
</tr>
<tr>
<td>Visits to general practitioners</td>
<td>1.02 (1.02 to 1.03)</td>
</tr>
<tr>
<td>Visits to specialists</td>
<td>1.02 (1.02 to 1.02)</td>
</tr>
<tr>
<td>Visits to urologists</td>
<td>1.23 (1.19 to 1.28)</td>
</tr>
<tr>
<td>Admissions to hospitals</td>
<td>0.89 (0.73 to 1.09)</td>
</tr>
<tr>
<td>Visits to emergency departments</td>
<td>0.92 (0.84 to 0.99)</td>
</tr>
<tr>
<td>Colonoscopies</td>
<td>2.29 (1.92 to 2.72)</td>
</tr>
<tr>
<td>Faecal occult blood tests</td>
<td>2.10 (1.78 to 2.47)</td>
</tr>
<tr>
<td>Sexually transmitted infection tests</td>
<td>1.00 (0.81 to 1.22)</td>
</tr>
<tr>
<td>Cholesterol tests</td>
<td>1.48 (1.43 to 1.53)</td>
</tr>
<tr>
<td><strong>Health service used between index date and end of follow-up</strong></td>
<td></td>
</tr>
<tr>
<td>Visits to general practitioners</td>
<td>1.04 (1.04 to 1.05)</td>
</tr>
<tr>
<td>Visits to specialists</td>
<td>1.04 (1.03 to 1.04)</td>
</tr>
<tr>
<td>Visits to urologists</td>
<td>1.31 (1.25 to 1.37)</td>
</tr>
<tr>
<td>Admissions to hospitals</td>
<td>1.14 (1.10 to 1.18)</td>
</tr>
<tr>
<td>Visits to emergency departments</td>
<td>0.63 (0.55 to 0.73)</td>
</tr>
<tr>
<td>Colonoscopies</td>
<td>21.6 (11.3 to 41.0)</td>
</tr>
<tr>
<td>Faecal occult blood tests</td>
<td>18.9 (14.2 to 25.1)</td>
</tr>
<tr>
<td>Sexually transmitted infection tests</td>
<td>1.18 (0.78 to 1.77)</td>
</tr>
<tr>
<td>Cholesterol tests</td>
<td>2.07 (1.84 to 2.32)</td>
</tr>
</tbody>
</table>

*Multivariable model included variables found to be meaningfully different between groups (standardised difference >0.10).
Prostate cancer grade and stage
Cancer grade was available for 1364 (39.4%) men with a diagnosis of prostate cancer: low grade in 540 (39.6%), intermediate in 704 (51.6%), and high in 120 (8.8%) (see supplementary table S1). Compared with low grade prostate cancer, vasectomy was not associated with an increased risk of intermediate or high grade cancer in any analyses (table 3).

Cancer stage was available for 1790 (51.7%) men with a diagnosis of prostate cancer: the cancer was localised in 1408 (78.7%) and advanced at the time of diagnosis in 382 (21.3%) (see supplementary table S2). Vasectomy was not associated with advanced stage at diagnosis in any analyses (table 3).

Prostate cancer specific mortality
Overall, 50 patients died from prostate cancer (see supplementary table S3). Vasectomy was not associated with prostate cancer specific mortality (table 3).

Incident non-Hodgkin’s lymphoma
In the tracer analysis, we identified 1100 cases of incident non-Hodgkin’s lymphoma: 533 (48.4%) in the vasectomy group and 567 (51.6%) in the non-vasectomy group. Vasectomy was not statistically significantly associated with incident non-Hodgkin’s lymphoma (table 3).

Sensitivity analysis
The association between vasectomy and risk of prostate cancer was no longer evident when including interactions with health services before index date (see supplementary table S4).

Discussion
In this population based study spanning nearly 20 years, we observed no statistically significant association between vasectomy and prostate cancer related risk, grade, stage, or mortality. Our findings have important implications for patients, clinicians, guidelines, policy makers, and family planning support groups.

Previous studies of the association between vasectomy and prostate cancer have produced conflicting results.6,7 Most of these studies included fewer than 100 men with prostate cancer among those undergoing vasectomy and had limited follow-up. Furthermore, concerns have been raised about bias, unmeasured confounding, and chance in relation to the small increased risk found by others.5,4 Recently published meta-analyses of these studies found that vasectomy was not associated with risk of prostate cancer,6,7 and guidelines from the American Urological Association in 2012 recommended that clinicians do not need to routinely discuss prostate cancer during preoperative counselling of men considering vasectomy.55

A large prospective cohort study published in 2014, however, found that history of vasectomy was associated with a 10% increased risk of prostate cancer overall and a roughly 20% increased risk of high grade and lethal disease.30 This study received much media attention,56 might have caused anxiety among men who were planning or had already undergone a vasectomy, and even prompted a formal response from the American Urological Association.57 The study relied on data from the Health Professionals Follow-up Study, and the history of vasectomy was obtained through questionnaires and might therefore have been prone to selection and recall bias. Additional concerns raised by the American Urological Association included inconsistencies with previous reports on the same cohort of men, and residual confounding.57 After considering all the evidence to date, the association reaffirmed its 2012 guideline recommendations against routine discussion of prostate cancer during preoperative counselling of men considering vasectomy.57 Our results strengthen the current evidence and support these recommendations.

Inappropriately decreasing the use of vasectomy as a form of contraception because of concerns related to prostate cancer would be a disservice to both men and women. Compared with its female counterpart, tubal ligation, vasectomy is more cost effective, with average healthcare costs of £50 compared with £1000 for the female procedure.54

Table 3 | Association between vasectomy and prostate cancer related grade, stage, and mortality and incident non-Hodgkin’s lymphoma. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Vasectomy group</th>
<th>Non-vasectomy group</th>
<th>Hazard ratio or odds ratio (vasectomy v non-vasectomy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer grade (n=1364):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>296 (60.3)</td>
<td>244 (38.7)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>378 (51.5)</td>
<td>326 (51.8)</td>
<td>0.96 (0.76 to 1.20)</td>
</tr>
<tr>
<td>High</td>
<td>60 (8.2)</td>
<td>60 (9.5)</td>
<td>0.82 (0.56 to 1.22)</td>
</tr>
<tr>
<td>Prostate cancer stage (n=1790):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localised</td>
<td>767 (78.7)</td>
<td>661 (78.6)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Advanced</td>
<td>202 (21.3)</td>
<td>180 (21.4)</td>
<td>0.99 (0.79 to 1.24)</td>
</tr>
<tr>
<td>Cancer specific mortality</td>
<td>26 (0.1)</td>
<td>24 (0.1)</td>
<td>1.01 (0.58 to 1.75)</td>
</tr>
<tr>
<td>Incident non-Hodgkin’s lymphoma</td>
<td>533 (39.2)</td>
<td>567 (42.4)</td>
<td>0.93 (0.83 to 1.05)</td>
</tr>
</tbody>
</table>

*Adjusted for socioeconomic status, number of visits to specialists and urologists in year before index date, and number of visits to general practitioners and admissions to hospitals between index date and end of follow-up.
†Adjusted for socioeconomic status, number of visits to specialists and urologists in year before index date, and number of visits to general practitioners and faecal occult blood tests between index date and end of follow-up.
‡Adjusted for income fifth, number of visits to specialists, urologists, and emergency departments in year before index date, and number of visits to general practitioners between index date and end of follow-up.
costs about one third of those for tubal ligation. Further-
more, compared with vasectomy, tubal ligation is 20
times more likely to have associated major complica-
tions, such as haemorrhage, infection, ectopic pregnancy,
and injury to adjacent organs. Although procedure related
mortality is rare, tubal ligation is about 12 times more
likely to be associated with death compared with vasec-
tomy. These differences are particularly important in
developing countries, where risks associated with steril-
sation procedures might be even greater.

Strengths and limitations of this study
Our study has several strengths. Firstly, we used a popu-
lation based approach and therefore included men of all
ethnicities, socioeconomic status, and with comorbid-
ties, thereby minimising selection bias. Furthermore,
because healthcare is publically administered in Ontario,
all patients had universal access to healthcare services
and cancer related screening. Secondly, we relied on vali-
dated, comprehensive databases, whereas most stud-
ies on this topic have relied on interviews and questionnaires. Thirdly, we were able to minimise detect-
tion bias by controlling for various kinds of interactions
with healthcare services throughout the study period.
Indeed, our sensitivity analysis suggests that the unad-
justed analysis showing a positive association between
vasectomy and risk of prostate cancer might have been
driven by interactions with health services in the year
before the index date. This suggests that those undergo-
ing a vasectomy are more likely to undergo screening for
prostate cancer before undergoing the procedure itself, as
has been shown previously. Accordingly, this baseline
screening might have led to risk adjusted monitoring of
patients in the vasectomy group, resulting in increased
detection of prostate cancer. Finally, the results of our pre-
specified tracer analysis evaluating incident non-Hod-
gkin’s lymphoma, a cancer unrelated to the urinary tract
or androgen levels and where no association with vasec-
tomy would be expected, further support our findings.

Some limitations of our study merit emphasis. Firstly,
although administrative data provide the advantage of
studying large populations, these databases are not
designed for clinical research, and some degree of out-
come misclassification is likely. The databases used in
this study, however, have been independently validated
for cancer related outcomes. Secondly, we were unable to account for possible differences in testing for
prostate specific antigen between groups; our results,
however, suggest that the use of surrogate cancer
screening tests might have accounted for this, as shown
by the strong associations between colorectal cancer
screening tests and incident prostate cancer. Thirdly,
data on prostate cancer grade and stage were incom-
plete. Fourthly, certain risk factors for prostate cancer,
such as family history, ethnicity, dietary factors, use of
5α-reductase inhibitors, and ejaculatory frequency
cannot be obtained through administrative data.
However, there is no reason to anticipate that these
would be differentially distributed across groups.
Finally, longer follow-up would have permitted ascer-
tainment of more cases of prostate cancer. This limita-
tion applies to both the vasectomy group and the non-vasectomy group and we attempted to mitigate this
limitation by performing sensitivity analyses of those
with follow-up at least to age 50 and 60, and found sim-
ilar associations to those of our primary analysis.
Despite these limitations, our study is the largest to
evaluate the association between vasectomy and prostate cancer and found no statistically significant
association between vasectomy and prostate cancer
related risk, grade, stage, or mortality.

Conclusion
The findings of this study show that vasectomy does not
seem to be independently associated with prostate
cancer. These results support the use of vasectomy as a
safe method of contraception in men.

Contributors: MN, RJH, EMM, QL, MMM, CCE, GSK, KAJ, and DJN
conceived and designed the study. QL acquired the data. MN, RJH,
EMM, QL, MMM, CCE, GSK, KAJ, and DJN analysed and interpreted
the data. MN drafted the manuscript. MN, RJH, EMM, QL, MMM, CCE,
GSK, KAJ, and DJN revised the manuscript for important intellectual
content. MN and QL carried out the statistical analyses, had full access to all
of the data in the study, and act as guarantors for the integrity of the
data and the accuracy of the data analysis.

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Transparency: The lead authors (MN and QL) affirm that the
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study being reported; that no important aspects of the study have
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(and, if relevant, registered) have been explained.

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