Vasectomy and Risk of Prostate Cancer

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Vasectomy is the safest method of surgical sterilization. It has become an increasingly common procedure in many countries since the early 1970s. Worldwide about 42 to 60 million couples rely on vasectomy for contraception. Concerns about the safety of vasectomy arose following reports in 1990 of an increased risk of prostate cancer from 2 hospital-based data systems analyzed using case-control methods. The analysis of a further set of cases and controls from 1 of these hospital-based surveillance systems found no significant association, suggesting that the earlier finding was due to chance. Reviews of these and other early studies concluded that vasectomy was probably not a risk factor for prostate cancer. Moreover, a biological explanation of any association seemed unlikely. In 1993, however, 2 large cohort studies showed a significantly increased risk, particularly 20 or more years after vasectomy (when the relative risk [RR] was 1.9 compared to men of European descent). Although the evidence was inconsistent, sufficient concern arose for many urologists to screen vasectomized men early for prostate cancer and to discourage vasectomy in men with a strong family history of prostate cancer.

In view of the widespread use of vasectomy and the relatively common occurrence of prostate cancer, any association of vasectomy with prostate cancer would be of great importance. A recent Australian study found a higher rate of prostate cancer among men who had a vasectomy vs those who had not had a vasectomy.

Context Vasectomy is a common method of contraception, but concern exists about a reported association with risk of prostate cancer.

Objective To examine whether vasectomy increases risk of prostate cancer.

Design, Setting, and Participants National population-based case-control study of 923 new cases of prostate cancer among men aged 40 to 74 years from the New Zealand Cancer Registry who were on the general electoral roll. Controls (n=1224) were randomly selected from the general electoral roll, with frequency matching to cases in 5-year age groups. Cases (3-15 months after diagnosis) and controls were interviewed by telephone between January 1997 and November 1999.

Main Outcome Measures Relative risk (RR) of prostate cancer for men who had had a vasectomy vs those who had not.

Results There was no association between prostate cancer and vasectomy (RR, 0.92; 95% confidence interval [CI], 0.75-1.14) nor with time since vasectomy (RR, 0.92; 95% CI, 0.68-1.23 for ≥25 years since vasectomy). Adjustment for social class, geographic region, religious affiliation, and a family history of prostate cancer did not affect these RRs.

Conclusions Vasectomy does not increase the risk of prostate cancer, even after 25 years or more.

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METHODS

The source population of cases comprised all New Zealand men newly diagnosed with prostate cancer. To maximize the response rate and avoid confounding by ethnicity, the study was restricted to men of European descent. In New Zealand, Maori people choose whether to be on the general electoral roll or a separate Maori electoral roll. To be eligible for inclusion in this national population-based study, case and control subjects had to be listed on the general electoral roll, have a traceable telephone number, have been married, and be aged 40 to 74 years. Approval for the study team to approach the patients was sought from each patient’s consultant and general practitioner. Consultants were also asked for the clinical TNM stage at diagnosis. Approval for the study was given by all regional ethics committees in New Zealand, and men were invited to give consent for interview.

Cases

The National Cancer Registry forwarded histology reports of prostate cancer for all men diagnosed between April 1, 1996, and December 31, 1998. There were 3186 men aged 40 to 74 years with prostate cancer reported.

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during this time. The reports were reviewed by 2 authors (M.J.S. and B.C.), and 31 men without confirmed adenocarcinoma of the prostate, or with cancer found incidentally at cystoprostatectomy for bladder cancer, were excluded. Because a project in the Auckland area was being completed at the beginning of this study, 446 men aged 40 to 74 years, diagnosed before April 1, 1997, and living in the Auckland region, were excluded. Control subjects living in this area were approached only after April 1, 1997. Because we were notified of more prostate cancer cases than expected, during the last 6 months of the study a random selection of approximately 50% of prostate cancer cases (stage T2 or higher) was included, giving a total of 2132 potentially eligible men with prostate cancer of all stages.

Electoral roll listings (Maori or general electoral roll) were found for 2027 of the 2118 men (96%) sought (14 were excluded due to death). Telephone numbers were found for 1862 of the 1883 men (99%) on the general electoral roll for whom numbers were sought. The rest (144) were either on the Maori roll, dead, reported too late, known to have stage T1 cancers before the telephone number was sought, or were excluded because the consultant (medical specialist, usually a urologist) did not participate. One consultant replied to requests for staging information only after the study commenced. Altogether the TNM stage was known for 1545 men but unknown for 538 men. Initially the design of the study did not include men with stage T1 prostate cancer. However, it was later decided to include a random sample of about 200 men with stage T1 prostate cancer, diagnosed between July 1, 1996, and November 30, 1997. All other T1 cases (344) were excluded, leaving 1210 men with prostate cancer of all stages.

Cases had to be interviewed between 3 and 15 months after diagnosis. Cases were interviewed by telephone from January 1997 to November 1999. Due to delays beyond 15 months after diagnosis, 89 men were excluded, and an additional 39 were excluded because they had never been married. The outcome for the 1082 potentially eligible cases is shown in Table 1.

The pathological specimens of a random sample of 100 cases were independently reviewed by one of the authors (B.D.), and all 100 original diagnoses were confirmed.

### Controls

Electoral registration is compulsory for all people 18 years or older in New Zealand, and the information is available in electronic form for research purposes. About 95% of adults are listed on the electoral roll. Control subjects were randomly selected from the general electoral roll and frequency matched in 5-year age groups with the cases of prostate cancer; 1819 men in all. Telephone numbers were found for 1689 of these men (93%), to whom a letter seeking participation in a study of health problems was sent. If no response was received, consent for interview was sought by telephone and an interview date arranged.

All control subjects were interviewed between January 1997 and November 1999. The 24 men selected as controls who had a previous diagnosis of prostate cancer were excluded, as were the 83 men who had never been married. The outcome for the remaining 1582 control subjects is shown in Table 1.

#### Data Collection

Information was collected using identical methods for cases and controls. Interviews were conducted by telephone, took about 30 minutes, and sought information about previous illnesses, vasectomy, smoking and alcohol consumption, prostate-specific antigen (PSA) testing and digital rectal examination (DRE), previous urological symptoms and operations, any family history of cancer, and sociodemographic characteristics. All interviews were conducted by 3 trained interviewers. Validation of the history of vasectomy for a sample of 103 men was attempted. Due to the length of time elapsed since vasectomy, only 49 records were located. For those that were traced, all self-reports of vasectomy were confirmed.

Interviewers did not know whether they were interviewing a case or a control until partway through the telephone interview, after information about vasectomy had been collected. The study hypothesis was not disclosed to subjects.

#### Definition of Terms

A positive family history of prostate cancer was defined as having a brother or father reported to have prostate cancer. A New Zealand scale based on occupation was used to assign 6 levels of social class from the longest-held occupation. Due to the small numbers in the lowest 2 categories, these were combined to create 5 levels of social class for analysis. The regional boundaries of 4 recent health purchasing authorities defined geographic regions of similar population size from the north to the south of the country.

Self-reported average weekly consumption of beer, wine, and spirits was combined using estimated alcohol contents of 3.5%, 12.5%, and 37.5%, respectively. For liqueurs and fortified wine, estimates of alcoholic content of 40% and 18%, respectively, were used. Total weekly alcohol consumption over the previous 5 years was categorized into quartiles with cut points of 52, 129, and

<table>
<thead>
<tr>
<th>Table 1. Potentially Eligible Cases and Controls</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total potentially eligible men</td>
<td>1082</td>
<td>1582</td>
</tr>
<tr>
<td>Not interviewed</td>
<td>125</td>
<td>321</td>
</tr>
<tr>
<td>Died before interview completed</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>Doctor refused</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Subject refused</td>
<td>39</td>
<td>196</td>
</tr>
<tr>
<td>Too ill</td>
<td>34</td>
<td>22</td>
</tr>
<tr>
<td>Not traced or living overseas</td>
<td>3</td>
<td>41</td>
</tr>
<tr>
<td>Language difficulties</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Interviewed</td>
<td>957</td>
<td>1261</td>
</tr>
<tr>
<td>Excluded after interview (ineligible)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Interviewed and eligible</td>
<td>953</td>
<td>1280</td>
</tr>
</tbody>
</table>

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250 mL per week. Cigarette smoking was defined as smoking more than 1 cigarette a day for more than a year.

Statistical Analyses
Most respondents (97%) were of European descent, and the analysis was confined to the 923 cases and 1224 controls in this ethnic group. For each control a reference date was calculated by subtracting 340 days (11.2 months) from the date of interview to correspond with the mean time between diagnosis and interview among the cases. After interview, 1 control was excluded because he was younger than 40 years on his reference date.

Standard methods for analysis of case-control studies were used. Relative risks were estimated by calculating odds ratios using logistic regression. SPSS version 6.1 (SPSS Inc, Chicago, Ill) was used for all analyses. Adjustment for age was made by using age as a continuous variable in the regression models.

RESULTS
The mean ages for cases and controls were 66.3 years and 65.1 years, respectively. The age-adjusted RRs for selected characteristics of case and control subjects are shown in Table 2. Men who reported having a father or brother with a diagnosis of prostate cancer had an increased risk of prostate cancer (RR, 2.63; 95% confidence interval [CI], 1.88-3.68). Inclusion of uncles with a diagnosis of prostate cancer to define a positive family history did not appreciably alter the estimated RR.

The RR of prostate cancer did not differ significantly among men of different religious affiliation or geographic region of residence (data not shown). A small but statistically insignificant elevation in RR was present for men of social classes 3 and 4 relative to the highest social class, 1, but no significant heterogeneity in risk of prostate cancer by social class was observed. There was no association with a history of sexually transmitted disease. A history of smoking (current smokers and ex-smokers), consumption of alcohol in the past 5 years (each quartile compared with nondrinkers), and number of children were not related to risk of prostate cancer (data not shown).

Self-report of a PSA test at least 18 months before interview was more common among cases (RR, 1.36; 95% CI, 1.08-1.71) and most pronounced for stage T1 and T2 cases (Table 3). Controls were significantly less likely than cases to know whether they had had a PSA test (RR, 0.56; 95% CI, 0.43-0.72). Cases were significantly less likely to have had a DRE at least 18 months prior to interview than controls (RR, 0.79; 95% CI, 0.66-0.94), an effect confined to stage T3 and T4 cases. Cases were significantly less likely to know whether they had had a DRE (RR, 2.45; 95% CI, 1.21-4.94), an effect confined to stage T1 and T2 cases.

The age-adjusted RRs of prostate cancer from vasectomy overall and for selected subgroups are shown in Table 4. For both cases and controls, the mean age at vasectomy was 41.3 years. The prevalence of vasectomy in controls, adjusted to the age distribution of New Zealand European men aged 40 to 74 years, was 44%. A history of vasectomy was less common among cases than controls, although this was not statistically significant (RR, 0.92; 95% CI, 0.75-1.14). Adjustment for social class, geographic region, religious affiliation, and a family history of prostate cancer had little effect on the RR of prostate cancer from vasectomy (RR, 0.92; 95% CI, 0.74-1.13).

Similar proportions of cases (9%) and controls (10%) had a vasectomy 25 years or more previously, representing 38% of all men with a vasectomy. The RR of pros-
tate cancer was not elevated for men whose vasectomy was at least 25 years previous (RR, 0.92; 95% CI, 0.68-1.23). Also, no trend in RR with years since vasectomy was apparent. Adjustment for social class, geographic region, religious affiliation, and a family history of prostate cancer did not appreciably alter the estimates of RR for each period since vasectomy. The RR of prostate cancer after vasectomy was not increased for any age at vasectomy. There was also no statistically significant variation in RR by age at diagnosis. For the few men aged 40 to 49 years at diagnosis, an increased RR of prostate cancer after vasectomy was observed, but this was not statistically significant. The RR of prostate cancer from vasectomy was not appreciably different among men with or without a family history of prostate cancer.

When the case series comprised only men with stage T1 prostate cancer, vasectomy was again less common among men with prostate cancer, although not significantly so (RR, 0.87; 95% CI, 0.61-1.25). When only stage T4 cases were included, the RR was reduced further (RR, 0.53; 95% CI, 0.20-1.41) but was still not significant. The RR was highest for stage T2 cases (RR, 1.02; 95% CI, 0.80-1.32). Adjustment for a family history of prostate cancer, and reporting at least 1 PSA test or at least 1 DRE 18 months or longer before interview, made no appreciable difference to the results obtained for each stage.

When the analysis was confined to stage T1 cases, no elevation in the RR of prostate cancer 25 years or more after vasectomy was found (RR, 0.82; 95% CI, 0.48-1.40). Similarly, no elevation in RR 25 years or more after vasectomy was found among those with cancer at stage T2 or higher (RR, 0.94; 95% CI, 0.69-1.29).
COMMENT

This large national population-based case-control study provides strong evidence that vasectomy does not increase the risk of prostate cancer. No elevation in risk was found 25 years or more after vasectomy, even though 38% of men with vasectomy were in this group. Adjustment for a family history of prostate cancer or other possible explanatory variables did not affect these results.

Although many men are diagnosed and treated for prostate cancer as outpatients, the cases for this study came from the entire population through statutory notification of cancers by all pathology laboratories. Response rates for both cases and controls were high, minimizing the possible effects of selection bias. Pathological review of a sample of diagnostic specimens confirmed the diagnosis of prostate cancer.

Possible interviewer bias was avoided by collecting information about vasectomy before interviewers were aware of the case or control status of each subject. Vasectomy status was obtained by self-report, and validation of vasectomy proved difficult, but in the small sample in which validation was sought and was possible, all reports of vasectomy were confirmed. Unlike many exposures measured in epidemiologic investigations, few men are in any doubt about whether they have undergone vasectomy; where vasectomy history has been confirmed, self-report of age at vasectomy is highly correlated with physician-reported age.16

More frequent contact with urologists among men with previous vasectomy, particularly in the United States, might have produced detection bias in some studies. In New Zealand, vasectomy was initially performed by urologists, but soon many family doctors offered this service. Therefore, any detection bias from close surveillance by urologists is unlikely. Also, annual medical checks have not been a major feature of the New Zealand health care service.

Detection bias does not appear to have affected the relationship between vasectomy and prostate cancer in our study, as risk was not altered by adjustment for a prior PSA test or DRE. Furthermore, no association between prostate cancer and vasectomy was found for any stage of disease, suggesting that misclassification of stage of disease at diagnosis was unlikely to have influenced the results.

The variation in RRs for different stages of prostate cancer associated with a PSA test or DRE at least 18 months before interview is consistent with the presentation of men with prostate cancer. For example, men with more advanced cancer are less likely to have a DRE before their date of diagnosis. Men whose cancer was diagnosed through investigation for persistent or rising PSA levels would be more likely to have stage T1 or T2 cancer. Some diagnoses of stage T1 cancer are incidental findings from transurethral resection of the prostate for urological symptoms. Detection of prostate cancer through PSA testing and the possible inclusion of postsurgical staging information could lead to detection bias among stage T1 and T2 cases.

What are possible confounders of the association between prostate cancer and vasectomy? Intercountry variation in prostate cancer incidence and mortality, time trends, and the general absence of a social class gradient do not support a sexually transmitted disease etiology for prostate cancer. However, a recent nested case-control study that found an association with positive human papillomavirus (HPV)-16 and HPV-18 serology has rekindled interest in this hypothesis.17 If vasectomy were associated with increased numbers of partners and a sexually transmitted infection were a risk factor for prostate cancer, this would be a potential confounder of the association between vasectomy and prostate cancer. While no association between a history of a sexually transmitted disease and prostate cancer was found in our study, the low prevalence of previous sexually transmitted disease suggests that considerable underreporting occurred.

We did not collect dietary information. In a previous study reporting an association of prostate cancer with vasectomy, there was little confounding by dietary factors; associations between prostate cancer and dietary nutrients (including some vegetable fats and antioxidants) appear weak.18,23 While selenium intake may affect the risk of prostate cancer,22 confounding of any association with vasectomy seems unlikely. Alcohol consumption23 and cigarette smoking24 have not been consistently associated with an increased risk of prostate cancer, which was confirmed in our study. We also examined religious affiliation and geographic variation because these factors could be associated with both the use of vasectomy and the incidence of prostate cancer. In fact, they were found not to be confounders in our study.

Three studies found no association between serum testosterone, dihydrotestosterone, their ratio, or 3α, 17β androstanediol glucuronide and the risk of prostate cancer.25,26 However, serum levels may not reflect differences in prostatic concentrations of these hormones. Because no major causative factor for prostate cancer has been determined, there is potential for confounding by some unknown factor to influence associations with vasectomy. Hence, small elevated RRs obtained from case-control or cohort studies require cautious interpretation.

Several studies have reported an association between vasectomy and prostate cancer, with RRs as high as 6.7 in 1 case-control study and 1.9 in some cohort studies.3,4,9,10,26 Most case-control studies reporting an association have used hospital-based cases and controls, which may be more susceptible to selection bias than population-based studies. In a case-control study in China, the RR varied from 2.0 to 6.7, depending on the control series used in the analysis, indicating the degree to which selection bias may influence results.28 Our results are consistent with several recent studies that have not found a significant association between vasectomy and prostate cancer.29-34 In particular, several cohort studies using record linkage have not found any increased risk of prostate cancer among men with vasec-
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5. A systematic review of 9 case-control and 5 cohort studies reported wide variation in estimated RRs, which were sensitive to differences in the study population, study design, presence of detection bias, and inadequate control selection. Also, publication bias was likely. The low prevalence of vasectomy among control subjects in some studies raises the possibility of bias in the collection of vasectomy information from cases and controls. If prostate cancer takes some time to develop after exposure to a causative agent, an elevation in the RR within a short time after the operation is likely to be due to detection bias or some form of misclassification of disease or exposure.

Another possible explanation for the inconsistency in the results is that, in areas of relatively low vasectomy prevalence, men seeking vasectomy may be more likely to possess other factors that increase their risk of prostate cancer, whereas in areas of high vasectomy prevalence such as New Zealand, this effect would be diluted by the addition of many men with vasectomy without such characteristics. However, in a study that covered several geographic areas of the United States with more than 2-fold variation in vasectomy prevalence, an elevated risk of prostate cancer from vasectomy was found in regions with both high and low prevalence of vasectomy.

The high prevalence of vasectomy and the large size of our case-control study provided a 99% statistical power to detect an RR of 1.5 or higher at the 5% level of significance. There was 80% statistical power to detect such a risk after 25 years or more had elapsed since vasectomy. That no association between prostate cancer and vasectomy was found, even 25 years or more after vasectomy, strongly suggests that there is no increased risk of prostate cancer after this procedure.

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Acquisition of data: Cox, Sneyd.
Analysis and interpretation of data: Cox, Sneyd, Paul, Delahunt, Skegg.
Drafting of the manuscript: Cox, Sneyd.
Critical revision of the manuscript for important intellectual content: Cox, Sneyd, Paul, Delahunt, Skegg.

Statistical expertise: Cox.
Obtained funding: Cox, Skegg.
Administrative, technical, or material support: Cox, Sneyd, Delahunt.
Study supervision: Cox, Paul, Skegg.
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