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Is Vasectomy a Risk Factor for Prostate Cancer?

Harry A. Guess

Recently, several case–control studies have suggested that vasectomy may predispose to prostate cancer. Other studies have found no increase in risk. All of these studies have a number of limitations. Taken together, these studies do not provide convincing evidence that vasectomy increases the risk of prostate cancer. However, in view of the high prevalence of prostate cancer and the growing worldwide importance of vasectomy as a form of contraception, further epidemiological research is warranted. After briefly commenting on the experimental studies we will examine the epidemiological studies in more detail. This will be done by first summarising the designs and main findings of the most relevant published studies and then discussing methodological issues relating to the studies taken as a whole. Finally, we will present conclusions and offer recommendations for future research.
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EXPERIMENTAL STUDIES

ANIMAL STUDIES of vasectomy have shown considerable variability between species, making it difficult to extrapolate these findings to humans [1]. While an excess of spontaneous liver tumours following vasectomy has been clearly demonstrated in one strain of mice [2], it would be premature to draw any conclusions about human prostate cancer risk from this. Various types of anti-sperm antibodies have been demonstrated serologically in a high proportion of men following vasectomy [3]. Morphological changes in the human testis following vasectomy have been well documented [4], however, the authors argued convincingly that the fibrotic changes appeared to result from the mechanical obstruction produced by vasectomy rather than

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from any autoimmune effects. While prostate secretory function has been found to be decreased following vasectomy [5], prostate volume does not appear to be affected. A study in 56 pairs of men using transrectal ultrasonography [6] found no influence of vasectomy on either total prostrate volume or volume of the peripheral zone, where most prostate cancers originate [7]. In human clinical studies there is conflicting evidence on whether vasectomy affects plasma testosterone levels [8–10]. It appears that even if there is an increase, the amount of the increase is small and levels are generally within the normal range [10].

In summary, animal studies and human clinical studies show that vasectomy has a variety of immunological, morphological and hormonal effects and that there is a high degree of variability between species in the types of effects that occur. None of this information provides a clear biological basis for hypothesising that vasectomy may increase prostrate cancer risk in man.

EPIDEMIOLOGICAL STUDIES OF VASECTOMY AND PROSTATE CANCER

Rosenberg *et al.* [11] reported an association between vasectomy and prostate cancer discovered while examining multiple comparisons in an ongoing hospital-based case–control surveillance study. In this study 220 men age 40–69 with prostate cancer diagnosed within the past year and with no concurrent or prior cancer were compared with 571 non-cancer controls admitted for trauma or appendicitis and with 960 cancer controls admitted for cancer of the colon, rectum, bladder or pancreas. With non-cancer controls the adjusted odds ratio was 5.3 [95% confidence interval (CI): 2.7–10] and with cancer controls the adjusted odds ratio was 3.5 (95% CI: 2.1–6.0) (Table 2). There was no tendency for the relative risk to increase as the interval since vasectomy increased. The relative risk was somewhat higher in men whose prostate cancer was localised, suggesting the possibility of increased medical surveillance among men with a history of vasectomy. However, a statistically significant elevation in relative risk remained when analysis was confined to cases with extensive disease.

Mettlin *et al.* [12] conducted a hospital-based case–control study to test the hypothesis generated by the study of Rosenberg *et al.* [11]. Information on both cases and controls came from a questionnaire administered since 1982 to all patients admitted to the Roswell Park Memorial Institute. The questionnaire asks each man whether he has had a vasectomy and, if so, at what age. The cases consisted of the 614 men aged 50 and older who were diagnosed with prostate cancer and who did not report a vasectomy within 5 years of their prostate cancer diagnosis. The controls consisted of 2588 men diagnosed with cancer at a site outside the genitourinary system and meeting the same exclusions on age and recent vasectomy history as the cases. The adjusted odds ratio for a vasectomy more than 5 years prior to cancer diagnosis was 1.7 (95% CI: 1.1–2.6) (Table 3). There was a statistically significant trend towards increasing relative risk with increasing interval since vasectomy ($P = 0.04$). Among men whose vasectomy was 13–18 years earlier, the relative risk was 2.2 (95% CI: 1.0–4.6).

In a letter to the editor commenting on the above studies, Spitz *et al.* [13] reported data on 343 prostate cancer cases and 360 age-matched other-cancer controls from a hospital-based

Table 1. *Summary of findings on vasectomy and prostate cancer*

Reference	Study type	Study size	Results
Rosenberg [11]	Case–control hospital based non-cancer and cancer controls	220 cases, 960 cancer controls, 571 non-cancer controls	RR = 5.3 (95%CI: 2.1–10.0) (non-cancer controls) RR = 3.5 (95%CI: 2.1–6.0) cancer controls
Mettlin [12]	Case–control hospital-based cancer controls	614 cases 2588 controls	RR = 1.7 (95%CI: 1.1–2.6) RR = 2.2 (95%CI: 1.0–4.6) (13–18 years postvasectomy)
Spitz [13] Newell [14]	Case–control hospital-based cancer controls	343 cases 360 controls	RR = 1.6 (95%CI: 1.1–2.3) RR = 2.2 (95%CI: 1.1–4.3) (≥ 27 years postvasectomy)
Honda [15]	Case–control population based neighbourhood controls telephone intervals	216 matched case–control pairs	RR = 1.4 (95%CI: 0.9–2.3) RR = 2.2 (95%CI: 1.0–4.8) (20–29 years postvasectomy) RR = 4.4 (95%CI: 0.9–21) (30+ years postvasectomy)
Sidney [16, 17]	Cohort	5119 vasectomised men each matched to 3 non-vasectomised men	RR = 1.0 (95%CI: 0.7–1.6)
Ross [19]	Case–control population based	110 matched case–control pairs	RR = 0.5 (95%CI: 0.2–1.4)*
Massey (personal communication, cited in [21])	Cohort	10 500 matched pairs, 8 years of follow-up	"Slight deficit" of prostate cancer in men with vasectomy

RR, Relative risk.

* This confidence interval has been calculated from the data in [19]; it does not appear in [19].

Table 2. Case–control study of Rosenberg et al. [11]

	Prostate cancer cases			Cancer controls			Non-cancer controls		
		With vasectomy			With vasectomy			With vasectomy	
Age	Total	No.	%	Total	No.	%	Total	No.	%
40–49	9	4	44.4	126	12	9.5	258	22	8.5
50–59	44	9	20.5	358	18	5.0	182	8	4.4
60–69	167	9	5.4	476	12	2.5	131	2	1.5
Total	220	22	10.0	960	42	3.3*	571	32	2.4*
Odds ratio					3.5			5.3	
95% confidence interval					2.1–6.0			2.7–10	

* Standardised to age distribution of cases.

case–control study conducted at the M.D. Anderson Cancer Center. This extended an earlier analysis published by Newell *et al.* [14]. The adjusted odds ratio was 1.6 (95% CI: 1.1–2.3). For men whose interval since vasectomy was in the higher tertile (≥ 27 years) the odds ratio was 2.2 (95% CI: 1.1–4.3). Repeating the analyses using the cancer control criteria of Rosenberg *et al.* [11] the odds ratio was 2.2 (95% CI: 1.1–4.5) and with the cancer control criteria of Mettlin *et al.* [12] the odds ratio was 1.4 (95% CI: 0.9–2.1).

Honda *et al.* [15] conducted a population-based case–control study in which 216 prostate cancer cases in white men aged 60 years and under with no history of cancer were pair-matched to neighbourhood controls whose age was within 5 years of the case's age. The pair-matched odds ratio for vasectomy in married men was 1.4 (95% CI: 0.9–2.3). There was a positive association between the number of years since the vasectomy and prostate cancer risk (one-sided $P = 0.01$). For men with vasectomy 20–29 years earlier the odds ratio was 2.2 (95% CI: 1.0–4.8) and for men with vasectomy 30 or more years earlier the odds ratio was 4.4 (95% CI: 0.9–21.0). Only 55% of the eligible cases in this study were interviewed and the interviews were conducted by telephone. The interviewed cases tended to have less advanced prostate cancer at diagnosis. This study found a statistically significant positive association between prostate cancer and each of the following variables: cigarette smoking, father or brother with prostate cancer, a history of prostatitis and a history of enlarged prostate.

Sidney *et al.* [16, 17] examined the relationship between vasectomy and prostate cancer in a cohort study of members of the Northern California Kaiser Permanente Medical Care Program who underwent multiphasic health checkups including questionnaires that asked men about vasectomy history. The reason for this study was stated by Sidney [16] to have been the finding of an increased risk of prostate cancer of marginal statistical significance in an earlier study of this population that had addressed heart disease and a variety of other illnesses but had not specifically addressed prostate cancer [18]. Sidney *et al.* [17] cited the result from data in the original study (that did not appear in the publication) as a relative risk of 2.1 with a 95% CI of 0.8–5.5 ($P = 0.13$). For the initial prostate cancer study [16] each of 5332 men with a history of vasectomy was compared with three unvasectomised men matched for age, race, marital status and date and location of the examination. In the second report [17] 213 of the matched sets were excluded because of history of hospitalisation for any of the following in any members of the matched sets prior to the multiphasic health check-up: prostate cancer, bladder cancer, benign prostatic hypertrophy, or surgery for other prostatic disorders. This left 5119 matched sets for analysis. The relative risk of prostate cancer among the vasectomised men was 1.0 (95% CI 0.7–1.6). The relative risk was approximately one, regardless of length of interval since vasectomy.

Table 3. Case–control study of Mettlin et al. [12]

	Prostate cancer cases			Cancer controls		
		With vasectomy			With vasectomy	
Age	Total	No.	%	Total	No.	%
50–57	52	6	11.5	569	62	10.9
58–62	84	10	11.9	521	35	6.7
63–67	138	7	5.1	570	14	2.5
68–72	148	4	2.7	437	9	2.1
≥ 73	192	4	2.0	491	3	0.6
Total	614	31	5.0	2588	123	3.1*
Odds ratio					1.7	
95% confidence interval					1.1–2.6	

* Standardised to age distribution of cases.

Ross *et al.* [19] reported results from a case–control study conducted in a Los Angeles retirement community. He found a matched odds ratio of 0.5 (95% CI: 0.2–1.4) for prostate cancer among vasectomised men in a case–control study of 110 matched pairs examining a number of possible risk factors. (The confidence interval was not reported in this article; it is calculated from the tabular data in the article.)

Massey *et al.* [20] reported results from a large cohort study identified through clinic and physician records of men who had received a vasectomy for contraceptive purposes in Minneapolis, Rochester Minnesota, Los Angeles and Eureka California. The study included 10 590 vasectomised men and an equal number of pair-matched controls. The median length of follow-up after vasectomy was 7.9 years. The authors studied 54 diseases of special interest (not including prostate cancer) and found that except for epididymitis-orchitis the incidence of diseases in the men with vasectomies was similar to or lower than for their paired controls. Although no information on prostate cancer was presented in this publication, Perlman [21] cited a personnal communication from Massey that there was a slight deficit of prostate cancer after 8 years among vasectomised men in 10 500 matched pairs of vasectomised/non-vasectomised men from this study, which is known as the Health Status of American Men Study.

Goldacre *et al* [22] reported a cohort study to examine subsequent hospitalisations among all 1764 men age 25–49 in Scotland who were coded in the medical records as having a vasectomy between 1968 and 1974. The median postoperative follow-up was 4.4 years. While no hospital diagnosis of prostate cancer were recorded in 8028 person-years of follow-up in this cohort, the young age and short duration of follow-up provide too little power to make this study of much value in addressing the magnitude of excess prostate cancer risk reported in the more recent studies.

Walker *et al.* [23] conducted a cohort study of 6092 men whose vasectomies were identified through pathology records. The study was conducted through record linkage in the Puget Sound Group Health Cooperative (GHC) in Seattle, Washington. The incidence of subsequent hospitalisations in this group was compared within 5-year age strata to that in the remainder of the men in the GHC. The authors found no increase in first-time hospital discharges for all malignant neoplasms. Prostate cancer was not specifically addressed.

REVIEW OF EPIDEMIOLOGICAL STUDIES

Bias due to screening for strong associations

As Rosenberg *et al.* [11] noted, they discovered a statistical association between vasectomy and prostate cancer unexpectedly while systematically screening large numbers of disease-exposure relationships in an ongoing hospital-based care–control surveillance study. The selection process itself has a tendency to yield upwardly biased relative risks, because selecting for unusually strong associations also selects for high values of measurement error. Neither the confidence intervals nor the relative risks in this study can be interpreted in a conventional way. Not only do findings emerging from such a process appear to be more highly statistically significant than they actually are—and hence less likely to be due to change—but also they appear stronger than they actually are—and hence less likely to be due to bias or confounding. It is, therefore, not surprising that the relative risks calculated by Rosenberg *et al.* [11] are larger than those found in other studies.

Potential for bias in hospital-based case–control studies

Three of the six published epidemiological studies that specifically addressed vasectomy as a risk factor for prostate cancer have been hospital-based case–control studies [11–13]. The similarity in design makes these studies liable to similar kinds of systematic error (bias) and is a weakness in the body of epidemiologic evidence linking vasectomy and prostate cancer. In addition, it may be argued that absence of bias in hospital-based case–control studies can be particularly difficult to verify. To explain this it is necessary to examine the concept of a case–control study more closely.

The cases in any case–control study may be regarded as consisting of the totality of cases arising from a hypothetical population that includes the cases and all those people who would have been counted as cases if they had developed the disease under study. When the cases are from a hospital the latter group may be thought of as the "catchment population" of the hospital for the disease and the time period under study. The distinguishing feature of a hospital-based case–control study is that not only the cases but also the controls are drawn from patients admitted to the hospital. The controls should be chosen to be representative, with respect to exposure and confounders, of those who would have been counted as cases if they had developed the disease under study [24].

It is this latter requirement that often poses difficulties [25]. For example, if trauma cases at a given hospital typically come from a catchment population with a low vasectomy rate while prostate cancer cases typically come from a catchment population with a high vasectomy rate, then a trauma patient at this hospital would not be as likely to have had a vasectomy as would a randomly chosen person who would have been included as a case if he had developed prostate cancer. Under such circumstances trauma patients would not be appropriate controls. Even with a detailed knowledge of referral patterns of a hospital it may be impossible to know whether such a bias is operating in the selection of controls.

Spitz *et al.* [13] reported case–control comparisons for vasectomy and prostate cancer using the same cases and two different definitions of other cancer controls. Relative risks of 1.4 and 2.2 were found using the cancer control definitions of Mettlin *et al* [12] and Rosenberg *et al* [11], respectively. This wide variation in point estimates with the same choice of cases and differing definitions of controls illustrates how differing definitions of controls can affect risk estimates.

Perlman *et al.* [21] noted that the percentage of controls in the study by Rosenberg *et al.* [11] who were exposed was far fewer than what would be expected in the general northeastern U.S.A. population of comparably aged white men. Rosenberg *et al.* [26] responded that the comparison with general population rates was problematic since vasectomy rates vary considerably not only by age but also by locality, education and religion. The many factors affecting vasectomy rates make it especially difficult to determine whether the choice of controls could have resulted in incorrect estimates of exposure and hence could have led to bias, in either direction, in the estimates of relative risks. Both Perlman's analysis and Rosenberg's response illustrate the complexity of assessing the potential for bias in hospital-based case–control studies of vasectomy and prostate cancer.

Surveillance bias

Until about 20 years ago, prostatectomies performed for benign prostatic hyperplasia commonly included bilateral vasectomies. The latter procedure was performed because it was then believed to help prevent post-operative epididymitis [27]. Men who have had subtotal prostatectomies for benign prostatic hyperplasia remain at risk for prostate cancer [28] and might be under more urological surveillance for prostate cancer than men without urologic problems. In the study by Sidney *et al.* [17] men with benign prostatic hypertrophy or with prostate surgery were excluded from the cohort study so this form of bias should not occur, with the other studies it is less clear.

Bias due to misclassification

Patients who had a subtotal prostatectomy 20 or more years ago might not have been informed about whether their operation included a vasectomy. Since patients were typically told that a common effect of transurethral prostatectomy was for ejaculation to flow back into the bladder instead of outward (retrograde ejaculation or "dry ejaculation"), many surgeons did not consider it necessary to further inform them as to whether their prostatectomy had included a vasectomy. It is also possible that a patient whose prostatectomy did not include a vasectomy might think that it did because of their failure to have normal ejaculations. A vasectomy performed as part of a prostatectomy would probably not have been coded as a separate procedure. In some hospitals, it is possible that even the operative records of the prostatectomy might not reliably have recorded whether or

not the procedure included a vasectomy (Dr Michael Lieber, Department of Urology, Mayo Clinic, Personal Communication, 24 August 1991).

Mettlin *et al.* [12] called attention to a study comparing self-reported histories of circumcision with examinations by physicians who were blinded to the results of the patient reports and who were instructed to record on the basis of their examination whether or not the men were circumcised [29]. About 25% of the 192 men in the study reported circumcision when examination showed they were not and about 10% reported a negative history of circumcision when examination showed that they had been circumcised. These results make it at least plausible that an appreciable amount of misclassification may be expected in self-reported vasectomy histories. In the study by Mettlin *et al.* [12] a true odds ratio of 1.0 could have could be falsely elevated to the reported level of 1.7 with less than 6% differential misclassification [30]. Since all of the studies conducted to date relied on self-reported vasectomy histories, misclassification bias in either direction appears highly possible.

The telephone interview method of Honda *et al.* [15] has been criticised [31, 32] as having the potential for bias due to misclassification by under-reporting of exposure among controls. In a study of vasectomy and testicular cancer [33] where the information was obtained by telephone interview, the overall relative risk of 1.5 was found to be due entirely to a relative risk of 8.7 among Catholic men. The authors concluded that there was likely to have been under-reporting of vasectomy among Catholic controls.

CONCLUSIONS

The experimental and epidemiological studies published to date do not provide convincing evidence that vasectomy predisposes to human prostate cancer. The epidemiological study which has provoked the current increased interest in this topic [11] was one in which the finding emerged unexpectedly through a systematic process of screening many exposure-disease associations. As discussed above, such a process yields risk estimates that are biased upward by an unknown amount. All of the six published studies which specifically addressed vasectomy and prostate cancer appear to have relied upon self-reports of vasectomy. Bias due to misclassification is quite plausible and could have substantially affected results—in either direction—in several of the studies. Bias due to control selection in hospital-based case–control studies is difficult to exclude entirely, as illustrated by the results of Spitz [13] who produced two very different point estimates of relative risk with the same set of prostate cancer cases and the definitions of other-cancer controls used by Mettlin (relative risk = 1.4) and Rosenberg (relative risk = 2.2).

While these studies do not provide answers, they clearly suggest the need for further epidemiological research. Because vasectomy is so widely practiced and prostate cancer is a common disease in many countries, even a small increase in risk of prostate cancer in countries where both vasectomy and prostate cancer are common could have important effects on public health. However, in many countries, neither the descriptive epidemiology of vasectomy nor that of prostate cancer has been sufficiently characterised to support a recommendation for a more definitive analytical epidemiological study to evaluate vasectomy as a potential risk factor for prostate cancer. Such descriptive information is needed to assess feasibility and to assist in planning analytical studies in countries where such studies appear warranted, when balanced against other public health needs. In planning future analytical epidemiological studies particular attention should be given to addressing the types of methodological issues identified above.

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Possible Biological Mechanisms for a Relationship Between Vasectomy and Prostatic Cancer

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INTRODUCTION

THERE IS no obvious logical biological mechanism for a relationship between vasectomy and prostatic cancer. There are four categories of physiological alterations after vasectomy which theoretically could increase the incidence or accelerate the growth of prostate cancer. They are (1) a change in endocrine status; (2) an alteration in systemic or local immunity; (3) a variation in exposure of the prostate to cancer enhancing growth factors and/or inhibitors of these factors; and (4) a decrease in undefined factors which inhibit malignant growth or enhance growth of non-malignant prostatic tissue. These theoretically possible relationships will be discussed in the order listed above. It is well documented that vasectomy does cause alterations in the testis, particularly in spermatogenesis, both in experimental animals [1–10] and men [11–14]. In addition, changes occur in the epididymis [15–17]. Vasectomy also results in immunological effects particularly the generation of antisperm antibodies in the majority of individuals in many species including man [18–22]. Prospective carefully conducted epidemiological studies (too extensive to review here) have not documented any increases in immunological disease states or atherosclerosis in men after vasectomy. Indeed, the prospective studies designed to investigate possible relationships between vasectomy and any disease states have all shown no correlation between vasectomy and disease. However, recent retrospective analyses have suggested a relationship between vasectomy and testis cancer [23, 24] as well as prostate cancer [25, 26].

THE ENDOCRINE HYPOTHESIS

There is extensive literature on the endocrinological effects of vasectomy in experimental animals and man. The majority of studies in man have shown no change in endocrine parameters after vasectomy [27–36]. Several studies in rats suggested that vasectomy might decrease serum testosterone levels [7, 37, 38]. However, the validity of these animal investigations has been questioned because of the possibility that the observed alterations were due to injury to testicular blood supply during the vasectomy. A few studies in man have suggested an increase in circulating androgen levels after vasectomy. Purvis *et al.* [39] found an elevation in plasma oestrogen and dihydrotestosterone but not leuteinising hormone (LH) or testosterone after vasectomy. Smith *et al.* [40] found an increase in LH and testosterone and a decrease in oestradiol levels after vasectomy. It should be emphasised that although the alterations were statistically significant all values were in the normal range. The same group [41] found an obliteration of the annual rhythm of testosterone and LH after vasectomy. In summary, the majority of evidence suggests that vasectomy does not cause significant alterations in endocrine function in man; however, there is some evidence of small increases in circulating androgen levels and one study showed a decrease in circulating oestradiol concentration. If these latter investigations are correct, one could postulate that the observed shifts in endocrine parameters favour the development of prostate cancer.

THE IMMUNOLOGICAL HYPOTHESIS

As stated above, there is no doubt that vasectomy has immunological consequences in many individuals. The most obvious of these is the generation of antisperm antibodies. It is possible, but unlikely that these antibodies by an as yet undetermined mechanism accelerate the development of prostatic cancer. It is also possible that vasectomy by eliminating the flow of testicular and epididymal fluids to the prostate decreases local immune factors, for example lymphocyte activated killer cells (LAK cells), which prevent the initiation of growth of prostate cancer. It has been recently demonstrated that LAK cells can inhibit the growth of prostate cancer in rats [42]. In summary, there is no hard evidence for a relationship between vasectomy and prostate cancer which is immunologically generated; however there are theoretically possible mechanisms such as those discussed above.

THE GROWTH FACTOR-INHIBITOR HYPOTHESIS

Recent studies from two laboratories indicate that androgen independent human prostate cancer cell lines proliferate by secreting growth factors, such as epidermal growth factor and transforming growth factor alpha, which work via receptor mediated autocrine mechanisms [43, 44] to enhance tumour cell growth. Indeed, suramin a new antineoplastic agent which works by inhibiting the binding of growth factors to cancer cells has been promoted as a possible agent for the treatment of

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