RESEARCH COMMUNICATION

Is it Reporting Bias Doubled the Risk of Prostate Cancer in Vasectomised Men in Mumbai, India?

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Abstract

Background: Vasectomy is a common method of family planning in India and worldwide. The objective of the present study was to assess the association of vasectomy with prostate cancer in a low risk population of a developing country. A population based case control study was conducted in Mumbai, India, for this purpose. Methods: Included in this study were microscopically proved cases of prostate cancer diagnosed during 1998 to 2000 and registered by Bombay Population Based Cancer Registry (n=594). The controls were healthy men belonging to the resident general population of Mumbai, India. Two controls for each case matched by age and place of residence were selected as the comparison group. Data on vasectomy and potential confounding factors were obtained by structured face to face interviews. After exclusions, 390 cases and 780 controls were available for final analysis and confounding was controlled by multiple logistic regression. Results: Overall 14.9% of cases and 10.0% of controls had undergone vasectomy. Compared with no vasectomy the OR with ever having undergone vasectomy was 1.9 (95% CI: 1.3-2.9), after controlling for age and other possible confounding factors. The risk for those who had had a vasectomy before the age of 45 years was 2.1 fold (95% CI: 1.2-3.9) and for those who underwent the procedure at a later age was 1.8 fold (95% CI: 1.1-2.9). The linear trend for an increase in risk with a decrease in age at vasectomy was statistically significant (p for trend= 0.01). The risk for those who completed 25 years or more time since undergoing vasectomy was 3.8 fold (95% CI: 1.9-7.6) and for those who completed less than 25 years it was 1.2 fold (95% CI: 0.7-2.1). The linear trend for an increase in risk with an increase in time since vasectomy was highly significant (p for trend = 0.001). Conclusion: There are major public health and birth control implications on vasectomy increases the risk for prostate cancer. It is likely, however, that biases identified in this study result in high estimates of risk and the true risk due to vasectomy is substantially less than the estimated one. Due to the several limitations and possibilities for reporting biases in this study, the evidence for the estimates of the higher odds ratio for prostate cancer in vasectomised men may not be a strong one. In view of the importance of vasectomy for fertility control, further studies with good design and conduct (the information on vasectomy need to be collected with better reliability) are required to clarify the issue of vasectomy associations with prostate cancer.

Key Words: vasectomy - prostate cancer - case control - reporting bias

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Introduction

Vasectomy is the safest method for male sterilization (Schwingl and Guess 2000). 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 (Population Information Program 1992). In India, vasectomy has been practiced since the 1950s following ongoing promotion by the National Family Planning Programme (Populationa Research Centre (PRC) Punjab University, Chandigarh and International Institute for Population Sciences (IIPS) 1995, Thakore and Patel 1972, Choudhuri 1975). It is estimated that 13 million Indian men have had a vasectomy and that 7% of all married couples in the reproductive age group use vasectomy as a method of contraception. The majority of these men underwent the procedure by the late 1970s and now are entering the age range of greatest prostate cancer risk (Tripathy et al. 1994).

The possibility of a relationship between vasectomy and prostate cancer was initially raised with the publication of two retrospective epidemiology studies by Rosenberg and Metlin et al in 1990 (Rosenberg et al. 1990, Mettlin et al. 1990). After these two articles were published, a panel of experts gathered at the World Health Organisation in Geneva to discuss the hypothesis that men who had a vasectomy have an increased risk of prostate cancer. The unanimous

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consensus of this group was that the available data did not suggest a link but that additional research should be conducted. In 1993, Giovannucci et al (1993b) published a retrospective analysis of the possible relationship between vasectomy and prostate cancer which raised significant concern in the scientific community and the media. The editorial published in the same issue of the Journal of the American Medical Association pointed out the problems in the study of Giovannucci et al, emphasizing that they were not at all conclusive and again suggested that additional research was needed (Howards and Peterson 1993).

Indeed, many recent studies showed no increased risk (Zhu et al. 1996, Deantoni et al. 1997, Bernaldelgado et al. 1998), and have failed to find a link between vasectomy and prostate cancer. Scientists have been unable to identify a biologically plausible reason for vasectomy to increase a man's cancer risk. The idea that there is an association between vasectomy and any true increase in prostate cancer risk has only weak scientific support. 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 (Sandlow and Kreder 1996).

Several studies looking at a possible connection between vasectomy and prostate cancer are currently under way. The largest of these studies is the NCIs Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which began in 1992. The PLCO Trial is evaluating screening procedures for prostate cancer and will prospectively examine potential risk factors, including vasectomy, associated with prostate cancer. The PLCO is a long-term study; results are expected by 2015 (Meister et al. 2002).

As vasectomy is a common method of family planning in India and worldwide, its health consequences in general and any risk for development of prostate cancer in particular, needs to be studied. With this aim, a population based case control study for prostate cancer has been conducted in Mumbai, India.

Materials and Methods

This study was conducted at Bombay Population Based Cancer Registry (PBCR), located at Mumbai, India. The Bombay PBCR is one of the oldest (established in 1963) and biggest cancer registries in the world and it functions as a unit of the Indian Cancer Society at Mumbai with the aim of obtaining reliable morbidity and mortality data on cancer, from a precisely defined urban population (Greater Mumbai) (12 million inhabitants).

This study was planned and conducted as a matched case-control study. The cases were all prostate cancer patients registered by the Bombay PBCR during the period, 1st January 1998 to 31st December 2000. Only cases who had a microscopic proof of diagnosis were included in the study. Two controls were elected for each case to ensure enough power for the study. The controls were elected from the neighborhood of each case aiming at a maximum age difference of +-5 years between the case-control pair/triplet. Controls who had a past history of urological disease or had undergone surgery for benign prostatic hyperplasia (BPH) of the prostate have been excluded from the study. These questions were raised before conducting an interview and only eligible controls were interviewed.

During the period 1998 to 2000, a total of 766 prostate cancer cases were registered by the Bombay PBCR. Out of these, 172 (22.5%) cases that were not having any microscopic proof of diagnosis were excluded from this study. An attempt had been made to interview all the 594 (77.5%) cases with microscopic proof of diagnosis and their respective age matched controls.

Keeping the objective of this study as the guidelines, a questionnaire was prepared for data collection. The questionnaire consisted of the following sections,

1. Identification particulars
2. Socio-demographic parameters
3. History of vasectomy
4. General dietary patterns
5. Tobacco and alcohol habits

The questions were constructed by an expert committee that consisted of clinicians and epidemiologists.

One trained male social investigator was appointed to collect the exposure history of the cases and controls. An appeal letter signed by the principal investigator of our organization was provided in order for a permission to interview the cases and controls. The interview has been carried out for all eligible cases and respective controls from 1st November, 1999 to 30th October 2001. After interviewing a case, all efforts were made to interview simultaneously two controls. For those cases having a single control or no controls, a second and third visit was made within a week time in order to find out respective controls. To collect the exposure history of cases who already died before an interview has been made by interviewing the nearest relative of the patient, that is, either wife or son or male sibling. Over 95% of the proxy respondents were either wife or son or male sibling and 5% were others.

Although all efforts have been made to interview all the 594 microscopically proved cases and respective age matched controls, two controls for each case, only 390 cases (65.7%) and 780 controls were available to be included in the study for final analysis. The reasons for excluding the remaining 204 cases (34.3%) were due to migration, door closed, not willing to give personal details, too old / died and proxy respondents were not available or not cooperative to complete the interview, no eligible controls were available in the neighborhoods, controls were not willing to give personal details etc. Among the 390 cases included in the final analysis, 142 cases were estimated to have the time of death before the time of interview. Therefore the information was received by proxy respondents. In another 14 cases the interview was known to be based on proxy respondents mainly because of advanced disease and severe condition of the patient. The information for a total of 156 (40.0%) cases was therefore known to be collected by interviewing

proxy respondents. For the remaining 234 (60.0%) cases, information was reported by self. For all the 780 controls included in the final analysis, information was reported by self. Masking of the investigator for data collection could not be ensured although the objectives/hypothesis of the study was not made known to him.

For some of the cases, it was not possible to find the proper age matched controls residing in the neighborhood of the respective cases due to less number of old age men in the general population of Mumbai. More than 60% of the age matched case-control triplets included in the study for final analysis had an age difference of more than +-5 years between the case-control pairs or triplets, mainly because the neighborhood controls were younger than the cases. Hence a failure in age matching occurred.

The data collected by the social investigator was compiled and quality checks were carried out. Due to failure in age matching, unconditional logistic regression method was used for risk estimates. The details of the methods were taken from Breslow and Day (1980).

The multiple logistic regression method was employed to estimate the adjusted odds ratios for vasectomy, age at vasectomy and time since vasectomy with 95% CI. Since the etiology of prostate cancer is largely unknown, the adjusted odds ratios for vasectomy, age at vasectomy and time since vasectomy were obtained by adjusting with age and other probable confounding characteristics under study. The analysis was conducted using the Stata statistical software (version 7.0).

Results

The distribution of the cases and controls by age-group and other characteristics are presented in table 1. There was a significant difference of 6.8 years between the mean age of the cases (71.2) and controls (64.4) and so the controls were younger than the cases.

The adjusted odds ratios for vasectomy, age at vasectomy and time since vasectomy were estimated by adjusting with age and other probable confounding characteristics under study.

14.9% of the cases reported vasectomy compared to 10.0% of the controls. The risk of getting prostate cancer for men who reported a vasectomy was 1.9 fold compared to those who did not and was statistically significant (adjusted OR , table 2).

Age at vasectomy was grouped into two groups and it was observed that a higher proportion of cases (6.4%) had undergone vasectomy before the age of 45 years compared to that of the control group (4.2%). The risk for those who had a vasectomy before the age of 45 years was 2.1 fold and those who had it at a later age was 1.8 fold compared to those who did not had a vasectomy (adjusted OR, table 2). The linear trend for an increase in risk with a decrease in age at vasectomy was statistically significant (p for trend = 0.01).

A higher proportion of cases (9.2%) completed 25 years or more time since vasectomy compared to that of the control group (1.7%). The risk for those who completed 25 years or more time since vasectomy was 3.8 fold compared to those who did not had a vasectomy (adjusted OR, table 2). The linear trend for an increase in risk with an increase in time since vasectomy was highly significant (p for trend = 0.001).

Table 1. Distribution of Cases (n=390) and Controls (n=780) by Age Group,socio demographic, dietary and lifestyle characteristics under study

Characteristic	Cases N (%)	Controls N (%)
Age group		
<55	16 (4.1)	58 (7.4)
55–64	63 (16.2)	305 (39.1)
65–74	163 (41.8)	338 (43.3)
75–84	108 (27.7)	71 (9.1)
85+	40 (10.3)	8 (1.0)
Mean	71.2	64.4
Age at marriage		
<=19	82 (21.0)	200 (25.6)
20–24	244 (62.6)	541 (69.4)
25+	64 (16.4)	39 (5.0)
Mean	21.2	20.4
Fruits and vegetables (kg per week)		
< 2	84 (21.5)	75 (9.6)
2–3	103 (26.4)	247 (31.7)
>3	203 (52.1)	458 (58.7)
Fish (kg per week)		
No	154 (39.5)	248 (31.8)
<1	100 (25.6)	239 (30.6)
1+	136 (34.9)	293 (37.6)
Meat (kg per week)		
No	109 (27.9)	183 (23.5)
<1	119 (30.5)	274 (35.1)
1+	162 (41.5)	323 (41.4)
Coffee (cups per week)		
<2	260 (66.7)	473 (60.6)
2+	130 (33.3)	307 (39.4)
Tea (cups per week)		
1–2	26 (6.7)	32 (4.1)
3–6	240 (61.5)	549 (70.4)
7+	124 (31.8)	199 (25.5)
Oil/Fat (kg per month)		
<1	69 (17.7)	138 (17.7)
1–2	291 (74.6)	617 (79.1)
>2	30 (7.7)	25 (3.2)
Tobacco smoking		
No	94 (24.1)	148 (19.0)
Yes	296 (75.9)	632 (81.0)
Tobacco chewing		
No	339 (86.9)	669 (85.8)
Yes	51 (13.1)	111 (14.2)
Alcohol drinking		
No	113 (29.0)	111 (14.2)
Yes	277 (71.0)	669 (85.8)

Table 2. Univariate and Adjusted Odds Ratios for Vasectomy, Age at Vasectomy and Time Since Vasectomy by Unconditional Logistic Regression Method for (n=390) Cases and (n=780) Controls

Characteristic	Cases N (%)	Controls N (%)	Univariate OR (95% CI)	Adjusted* OR (95% CI)	p trend
Vasectomy					
No	332 (85.1)	702 (90.0)	1.0	1.0	
Yes	58 (14.9)	78 (10.0)	1.6 (1.1-2.3)	1.9(1.3-2.9)	
Age at vasectomy					
<45	25 (6.4)	33 (4.2)	1.6 (1.0-2.7)	2.1 (1.2-3.9)	
45+	33 (8.5)	45 (5.8)	1.6 (1.0-2.5)	1.8 (1.1-2.9)	0.01
Time since vasectomy					
<25	22 (5.6)	65 (8.3)	0.7 (0.4-1.2)	1.2 (0.7-2.1)	
25+	36 (9.2)	13 (1.7)	5.9 (3.1-11.2)	3.8 (1.9-7.6)	0.001

* the adjusted odds ratios were obtained by adjusting with age and other probable confounding characteristics under study

Discussion

The present study suggested that vasectomy is a risk factor for prostate cancer. The risk was higher in those who had it at an earlier age and the risk increased as the time since vasectomy increased. There was a significant trend of increasing risk with increasing time since vasectomy and also with an earlier age at vasectomy. These findings were consistent with many of the earlier studies (Honda et al. 1988, Mettlin et al. 1990, Rosenberg et al. 1990, Spitz et al. 1991, Hayes et al. 1993, Giovannucci et al. 1993a, Giovannucci et al. 1993b, Hsing et al. 1994) and also with the earlier pilot hospital based case control study conducted in India (Platz et al. 1997). In the pilot study the risk of prostate cancer associated with vasectomy appeared to be higher among men who underwent vasectomy at least two decades prior to cancer diagnosis or who were at least 40 years old at vasectomy (Platz et al. 1997).

There had been concern over a positive association between vasectomy and prostate cancer since the late 1980' s when Honda et al. (1988) first reported findings from their population based case control study. This relation remains controversial with some studies reporting a positive (Mettlin et al. 1990, Rosenberg et al. 1990, Spitz et al. 1991, Hayes et al. 1993, Giovannucci et al. 1993a, Giovannucci et al. 1993b, Hsing et al. 1994, Lesko et al 1996) and others no association (Rosenberg et al. 1994, John et al. 1995, Sidney et al. 1991, Zhu et al. 1996, Strayer 2002, Lynge 2002, Cox et al. 2002). Several other 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 (Mettlin et al. 1990, Rosenberg et al. 1990, Giovannucci et al. 1993a, Giovannucci et al. 1993b, Hsing et al. 1994). In a recent meta-analysis (Dennis et al. 2002) examining vasectomy status, age at vasectomy, and time since vasectomy the pooled relative risk estimate for those who had had a vasectomy compared with those who did not was 1.37 (95% CI 1.15-1.62) based on five cohort studies and 17 case-control studies. The relative risk estimate varied by study design with the lowest risk for population based case control studies. In a case control study conducted 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 the results (Hsing et al. 1994). A systematic review of the literature was published by Bernal-Delgado et al (1998), which documented the lack of a significant relationship between vasectomy and prostate cancer. Only 3 of the 14 studies determined vasectomy status by methods other than self-report (Bernal-Delgado et al. 1998). None of these reported an association and this shows the bias about the collection of information. Interestingly, 11 of the 14 studies evaluated in this review reported the existence of an excess risk. In 6 of these studies, the association was statistically significant but Bernal-Delgado et al (1998) demonstrated the existence of numerous methodological problems especially in the studies that showed the greatest increase in risk. A review of the literature by DerSimonian et al (1993) also found the evidence to be conflicting with several methodological errors.

A number of mechanisms have been proposed to explain how vasectomy may increase the risk of prostate cancer (Howards 1993). A recent report of John et al states that the ratio of dihydrrotestosterone-to-testestorone was higher and the serum concentration of sex hormone binding globulin was lower in men who underwent vasectomy versus those who did not (John et al. 1995), most previous studies have failed to determine a relationship between vasectomy and circulating androgens (Richards et al. 1981).

Two main criticisms of those studies purporting a positive association are that detection bias or confounding might have produced a spurious association between vasectomy and prostate cancer (Chacko et al. 2002). For example, detection bias might have arisen if those who underwent vasectomy were more likely to have repeated medical contact with greater opportunity for screening, and thus, detection of asymptomatic prostate cancer. In our study detection bias is unlikely. Cases and controls were drawn from a population in India were screening for prostate cancer was not customary and most cases were symptomatic at diagnosis. Confounding might have gone unnoticed because the

majority of the positive studies published to date have been conducted in the US where those dietary and lifestyle factors that potentially confound the relation between vasectomy and prostate cancer may be operating similarly in each study. We controlled for confounding in our analysis by including age, marital history, tobacco and alcohol habits, dietary habits, etc. Residual confounding by these factors cannot be entirely ruled out, however.

Since 204 cases (34.3%) among the 594 eligible cases were dropped due to several reasons as mentioned earlier, there may be a possibility for selection bias. Any differences in the exposure history between the cases included and dropped may result in biased and inconsistent estimates. Yet, for the controls, since we have used population based controls, the bias in the selection of controls might have minimized.

However, several limitations should be considered for the estimated high risk of prostate cancer in vasectomized men. It may be due to any unmeasured confounding because the etiology of prostate cancer is largely unknown. It is impossible, therefore, to assure that true risk factors for prostate cancer are equally distributed between men who had undergone vasectomy and men who had not. The Nurses' Health Study (Giovannucci et al. 1992) indicated that men who underwent vasectomy had a lower total mortality than men who did not. Men who underwent vasectomy in that study must, therefore, have different characteristics from men who did not. It is entirely possible that some of these characteristics increases the risk of prostate cancer. Regarding confounding factors, it of course remains true that we know little about the actual etiology of prostate cancer.

Potential information bias from proxy respondents is a concern in this study. The results from additional analysis restricted to direct respondents yielded an adjusted insignificant (the statistical insignificance can be due to the decrease in sample size) odds ratio of 1.4, indicating a substantial reduction in risk for vasectomy compared with the results for vasectomy (OR 1.9, 95% CI 1.3-2.9) by including proxy respondents.

Reporting bias may account for the difference in estimates of risk based on information for vasectomy reported by self and by a proxy. It is important to note that for 40% of the cases who were dead or in advanced conditions, the information is reported by proxies and since vasectomy is a sort of operation and the cases were seriously hospitalised, the proxies might have tended to answer positive for vasectomy. This might have caused over reporting of vasectomy for cases. The controls were all younger and healthy persons and because vasectomy was self reported, there is possibility for under reporting since vasectomy is a very personal and in fact humiliating a man' s personality to express in front of family members and relatives. The dose response relationship on age at vasectomy and time since vasectomy may also be due to some psychosocial background, the crudest family planning policy occurred in the youth of these men. It may also have been especially embarrassing to have vasectomy at a young age.

The impact of any reduction in popularity of vasectomy attributable to concerns regarding prostate cancer is most likely to be felt in developing countries, particularly in several countries in Asia and Africa where maternal and infant mortality rates are high and vasectomy programs are just beginning to grow. If vasectomy is a risk factor for prostate cancer, people need to know and informed choices need to be made. By contrast, if associations are spurious but believed to be real, the popularity of a highly effective contraceptive will be reduced, opportunities to reduce unintended pregnancy will be lost, and maternal and infant mortality and morbidity will increase. The evidence for the estimates of the higher odds ratio for prostate cancer in vasectomised men may not be a strong one due to the biases discussed above. In view of the importance of vasectomy for fertility control, further studies with good design and conduct (the information on vasectomy need to be collected with better reliability) are required to clarify the issue of the association of vasectomy with prostate cancer.

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