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The effect of vasectomy reversal on prostate cancer risk: International meta-analysis of 684,660 men with vasectomies.

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Running Head: No effect from vasectomy reversal on prostate cancer risk

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Abstract

Purpose: Evidence on the effect of vasectomy on prostate cancer is conflicting, with the issue of detection bias a key criticism. We examine the effect of vasectomy reversal on prostate cancer risk in a cohort of vasectomised men; evidence of a protective effect would be consistent with a harmful effect of vasectomy on prostate cancer risk, while nullifying the issue of detection bias.

Methods: Data were sourced from five population-level linked health databases located in Australia, Canada and the United Kingdom. Cox proportional hazards regression analysis compared the risk of prostate cancer in those with vasectomy reversal (n=9,754) to those with a vasectomy but no reversal (n=684,660); data from each jurisdiction were combined in a meta-analysis.

Results: The combined analysis showed no protective effect of vasectomy reversal on incidence of prostate cancer when compared to those who had vasectomy alone (HR, 95%CI: 0.92, 0.70-1.21).

Conclusion: These results align with previous studies that found no evidence of a link between vasectomy and prostate cancer.

Introduction

The effect of vasectomy on the risk of prostate cancer has been widely researched since the early 1990s when two studies reported an elevated risk of prostate cancer in vasectomised men [1-3]. A large number of additional studies followed, with conflicting results [4-8]. Conclusions drawn from meta-analysis and systematic reviews have also been inconsistent, with findings indicating either no effect of vasectomy on prostate cancer [9-11] or a small effect [12-14].

Studies on this issue have invariably compared observational data on the risk of developing prostate cancer between individuals who have elected to have a vasectomy, and those who have not, with attempts made to control for confounding factors. One key criticism levelled at many of the studies which have found an effect is the issue of detection bias. Prostate cancer is unique in that the vast majority of cases are not clinically significant, and may go undetected during an individual's lifetime. Prostate cancer is also highly prevalent, with a study of autopsy results suggesting the prevalence of invasive prostate cancer in men over 50 to be around 25% [15]. Given this, any factor that increases the intensity of examinations for prostate cancer will likely result in an increased diagnosis of prostate cancer [3]. Individuals who elect to have a vasectomy may have a higher level of engagement with medical surveillance, resulting in specious increases in rates of prostate cancer. For example, several studies have found that men undergoing a vasectomy are more likely to be screened for prostate cancer prior to vasectomy [5,16], with ongoing monitoring likely to occur after vasectomy.

Several potential biological mechanisms have been suggested through which vasectomy may influence prostate cancer risk[17]. These include known alterations in seminal fluid composition and hormone levels in vasectomised men which could favour the development of malignancy; the production of sperm antibodies in vasectomised men; a reduction in local immune factors which occurs in vasectomised men; and the promotion of growth factors which favour the

development and progression of prostate cancer [17]. The evidence that any one of these specific mechanisms increases prostate cancer risk is currently limited[12].

If vasectomy increases the risk of prostate cancer by one of the above mechanisms, then individuals who have their vasectomy reversed might find their risk of prostate cancer subsequently lower as compared to those who remain with a vasectomy, at least to the extent that the mechanisms and their putative carcinogenic effects are remediable. Comparing vasectomised men with those who have had their vasectomy reversed provides an alternative way to investigate the risk of vasectomy on prostate cancer. This approach helps reduce the risk of detection bias, as all individuals will have originally undergone a vasectomy, and so have a similar likelihood of prostate cancer screening based on health system engagement [18].

In this study we evaluate whether vasectomy reversal offers protection against prostate cancer risk in vasectomised men. A finding of such a protective effect would be consistent with a harmful effect of vasectomy on the risk of prostate cancer. Due to the relatively small numbers of vasectomy reversals, our analysis was conducted on data from five population-level, linked health record databases located in Australia (the states of Western Australia and New South Wales), Canada (the province of Ontario), Wales and Scotland, with results pooled in a meta-analysis.

Methods

Data for this study were sourced from five regional record linkage centres: the Western Australian Data Linkage Branch, the Centre for Health Record Linkage in New South Wales, Australia; the Institute for Clinical Evaluative Sciences in Ontario, Canada; the Information Services Division, Scotland, and the SAIL databank in Wales. Each regional centre had linked

together hospital separations, mortality and cancer registration data from their respective regions at an individual level. De-identified linked data extractions took place at each centre.

Data were extracted for all individuals with a vasectomy procedure. All teams worked from a common dataset creation protocol, though specific extraction codes depended on the coding system applied in each jurisdiction. Individuals needed to be aged 20 or over at time of vasectomy and to have no diagnosis of prostate cancer prior to vasectomy to be included in the study. Teams were instructed to use data from all years available, and to follow-up individuals for as long as their datasets allowed; there was no minimum follow-up time for inclusion in the study. For each individual in the study, extracted data included presence of vasectomy reversal, age at time of vasectomy/vasectomy reversal, date of vasectomy/vasectomy reversal, date of death (if deceased) and date of first diagnosis of prostate cancer (if diagnosed with prostate cancer, determined by entry in cancer registry datasets). Cox proportional hazards regression was performed comparing the vasectomised men with and without a vasectomy reversal, with time until prostate cancer diagnosis as the outcome, and data censored at the end of the available study period or earlier death of the individual. Vasectomy reversal was included as a time-dependent exposure within the model. The analysis was stratified by age at vasectomy/vasectomy reversal categorised into five-year groups to control for potential confounding by age. Analysis on each dataset was performed locally by researchers in each jurisdiction. Each participating institution prepared local ethics and data linkage applications to access the data in their region. Counts of vasectomy and vasectomy reversal cases, along with hazard ratio and confidence intervals for the age-adjusted effect of vasectomy reversal on prostate cancer in vasectomised men, were then pooled in a random effects meta-analysis.

Results

Data were received from Australia (the states of Western Australia and New South Wales), Canada (the province of Ontario), Wales and Scotland. In total, there were 9,754 men with vasectomy reversals, and 684,660 men with a vasectomy. Table 1 shows the breakdown of the study population by region.

The age-adjusted hazard ratio for each region, along with the combined hazard ratio, are shown in Figure 1. In Wales the vasectomy reversal cohort (comprising only 88 individuals) experienced no cases of prostate cancer; as such hazard ratios could not be estimated for this region. The combined analysis showed no concrete evidence of a protective effect of vasectomy reversal on incidence of prostate cancer when compared to those who had a vasectomy with no reversal (Hazard ratio, 95% confidence interval: 0.92, 0.70-1.21). There was no evidence of heterogeneity of results (I^2=0.1%, p=0.391).

Discussion

This study found no obvious protective effect of vasectomy reversal on prostate cancer in vasectomised men. As such, the results align with previous studies which found little or no evidence of a link between vasectomy and prostate cancer.

Our study had several advantages over many of the previous studies. By comparing vasectomised men with men who had a vasectomy reversal, we have avoided issues of detection bias, which has been levelled at previous studies. The use of validated health record databases avoids many issues that occur with self-reporting. The inclusion of over 600,000 vasectomised men from three continents makes it arguably the largest study of the issue to date.

The limitations of our study include the restricted number of confounders used within the prescribed analysis (five year age bands only). It is possible differences existed between those with and without vasectomy reversal that may have affected prostate cancer risk. Potential

factors include the extent of screening for prostate cancer (for instance number of urology visits, testing for prostate specific antigen), level of engagement with the healthcare system (for instance frequency of GP visits) as well as a range of risk factors for prostate cancer (such as ethnicity, family history and diet). This information is not present in the administrative data used in this study. We have attempted to control for detection bias by comparing only men who have had a vasectomy, who will likely have similar levels of health engagement and prostate cancer screening. The vasectomies in this study occurred in hospital settings and thus were likely conducted by urologists, although Ontario data also included vasectomies conducted in primary care settings.

Despite the lengthy follow up time of our study, peak incidence of prostate cancer diagnosis occurs late in life, beyond the follow up period for the majority of individuals in our study; longer follow up times would provide greater certainty in our findings. The validity of our study relies on the assumption that, if vasectomy increases the risk of prostate cancer, then this increased risk is remediated to a measurable extent by reversal of the vasectomy. The proposed biological mechanisms are amenable to this view [18], however, it is possible that some alternative mechanism may increase the risk of prostate cancer following vasectomy, regardless of subsequent vasectomy reversal. Men planning to undergo vasectomy reversal may have received additional screening for prostate cancer, leading to those with prostate cancer or suspicion of prostate cancer potentially being denied vasectomy reversal. This would result in a healthier reversal cohort, and could have potentially biased our results towards the finding of a protective effect of vasectomy reversal. Not all vasectomies and vasectomy reversals have been captured. Vasectomies that occurred in primary care settings rather than in hospital were not captured in this study, with the exception of Ontario. In Wales and Scotland, vasectomy and vasectomy reversals that occur outside the public health system are not recorded

in administrative collections. In Ontario, Scotland and Wales, vasectomy reversals are typically not available under the public system to individuals who simply wish to have more children, but only for specific medical reasons. As such, we can expect some individuals in the Wales and Scotland vasectomy cohorts to have had a private vasectomy reversal which is not captured in our data, potentially biasing our results towards the null. However, such bias is likely to be very small, given the rarity of vasectomy reversals in comparison to vasectomies.

The absence of recording of private vasectomy reversals is the likely cause of the particularly low numbers in Wales. The exclusion of Welsh data from our pooled results due to the lack of prostate cancer outcomes in vasectomy reversal cases has the potential to bias our results upwards; however given that Welsh data represents less than 1% of our total vasectomy reversal cases, any such bias would be very minimal.

Previously published results suggest any effect size (if an effect exists) is likely to be small. Indeed, the most recent systematic review and meta-analysis found a statistically significant effect size of just 1.05, with the authors suggesting that this is unlikely to be causal[12]. This result falls within the confidence intervals of the present study, and such an effect cannot be ruled out. However, the most parsimonious explanation for our results is that there is no increased prostate cancer risk in vasectomised men and this accords with evidence from a number of high quality studies [5,7,8] and several meta-analyses [9-11].

The difficulty of removing all possible confounders, and the apparent small effect size (if any), means that the existence of an effect of vasectomy on prostate cancer would be difficult to establish conclusively through observational epidemiology. Further exploration of this issue should focus on alternate research designs and modalities wherever possible. Studies that further explore potential biological mechanisms for the proposed link would be valuable contributions.

Based on the results of this study and in line with previous findings, no concrete causal link between prostate cancer and vasectomy has been established. Current guidelines, which do not require discussion of prostate cancer risk for those seeking a vasectomy [19], appear appropriate.

Tables:

Table 1: Data collections included as part of the meta-analysis

Region	Ontario	Scotland	Wales	New South Wales	Western Australia
Number of vasectomies	374,519	159,089	37,133	58,503	55,416
Number of reversals	3,984	2,227	88	2,440	1,015
Population	11.6 million	5.2 million	3.0 million	6.8 million	1.6 million
Years of data	1992-2015	1981-2016	1998-2015	2001-2014	1972-2009
Median age:					
At Vasectomy	36	35	37	39	36
At Reversal	38	37	38	42	37
Median follow up:					
Vasectomy only cohort	14 years	21 years	12 years	7 years	15 years
Reversal cohort	17 years	19 years	15 years	7 years	18 years
Median time between vasectomy and reversal	6 years	7 years	6 years	4 years	5 years

Figure Legends:

Figure 1: Age-standardised hazard ratios comparing time to prostate cancer diagnosis between vasectomy and vasectomy reversal cohorts.

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Appendix A: Data sources and codes used

Western Australia:

Vasectomy and vasectomy reversal procedures were identified in the Western Australian Hospital Morbidity Data Collection, which contains individual level data on all separations in public and private hospitals in Western Australia. Vasectomies which occur in a (private) primary care setting, rather than within the hospital system are not found within this dataset. However, as this dataset includes private hospitals, all vasectomy reversals will be found within this dataset. Vasectomy reversal and vasectomy were identified by hospital separation records with a procedure code as vasectomy reversal (ICD-9-CM 63.8X; ACHI; 37619-00, 37619-01, 37616-00, 37616-01; ICPM 5-634, 5-637) or vasectomy (ICD-9-CM: 63.7X, ACHI: 37623-02, 37623-03; ICPM 5-636, 5-981).

Prostate cancer diagnosis was identified as an entry in the Western Australian Cancer Registry (ICD-10: C61). Mortality data was made available from the mortality registry of Western Australia for each individual in the study.

New South Wales:

Vasectomy and vasectomy reversal procedures were identified in the Admitted Patient Data Collection, which contains individual level data on all public and private hospital separations for the state of New South Wales, Australia. Any vasectomies occurring outside of the hospital system (i.e. in primary care) are not recorded in this dataset. As this dataset includes private hospitals, all vasectomy reversals are expected to be found within the dataset.

Vasectomies and vasectomy reversals were identified by hospital separation records with a procedure code of vasectomy (ACHI: 37623-02, 37623-03) and vasectomy reversal (ACHI; 37619-00, 37619-01, 37616-00, 37616-01).

Prostate cancer diagnosis was identified by an entry in the NSW Cancer Registry (ICD-10: C61). Death was identified through the NSW mortality registry.

Wales:

Vasectomy and vasectomy reversal procedures were identified in the Patient Episode Database for Wales, containing individual level data on all hospital admissions at hospitals belonging to the National Health Service (NHS). Vasectomy and vasectomy reversals occurring in private hospitals and vasectomies occurring in community settings are not captured in these datasets. Vasectomy reversals for non-medical reasons are not provided by the NHS.

Vasectomy and vasectomy reversals were identified by hospital admissions records with a procedure code as vasectomy (OPCS: N17) or vasectomy reversal (OPCS: N18). Prostate cancer diagnosis was identified as a record in the Welsh Cancer Intelligence &

Surveillance Unit (WCISU) dataset, which is the National Cancer Registry for Wales, with a diagnosis code of prostate cancer (ICD-10: C61). Mortality data was identified from the Office of National Statistics Annual District Death Extract.

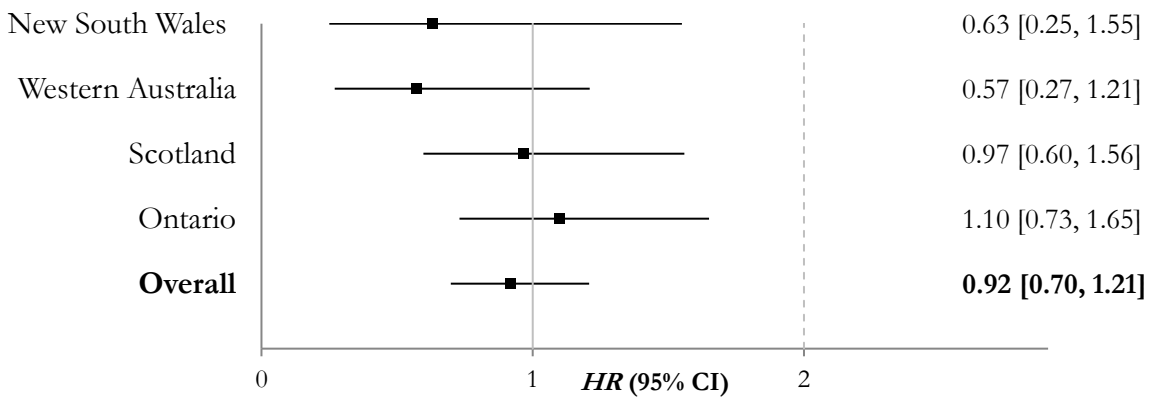
Scotland:

The General/Acute and Inpatient Day Case dataset (SMR01) was used to identify vasectomy and vasectomy reversal procedures that occurred in National Health Service hospitals in Scotland. Vasectomies can also occur in private hospitals, and outside of hospital, including in sexual and reproductive health clinics and GP surgeries; the SMR01 dataset does not capture this. Vasectomy reversals for non-medical reasons are funded under the National Health Service on a case by case basis. Cases and controls were identified by hospital admission records with a procedure code as vasectomy reversal (OPCS3: 652, OPCS4: N18) or vasectomy (OPCS3: 651, OPCS4 N17). The Cancer Registrations Database (SMR06) was used to identify prostate cancer diagnosis (ICD-10: C61). Mortality data was accessed from the Death Registrations database provided by the Registrar General.

Ontario:

Vasectomy and vasectomy reversal procedures were identified using the Discharge Abstract Database, containing individual level data on all inpatient hospitalisations, and the Ontario Health Insurance Plan (OHIP) database, containing claims made by health care providers for insured services (i.e. including vasectomies occurring outside of the hospital setting). Vasectomy reversal is not covered under OHIP other than for medical reasons, however privately funded vasectomy reversals are recorded in the Discharge Abstract Database.

Vasectomy was identified from hospital records containing a procedure code for vasectomy (ICD-9: 756; ICD-10: 1QN51) or from the OHIP database (fee code S626, without E545). Reversal was identified similarly; a procedure code in hospital records (ICD-9=757; ICD-10; IQN82, IQN80) or from OHIP claims (codes S623, S625). Prostate cancer diagnosis was identified using the Ontario Cancer Registry (ICD-10: C61), while mortality data was sourced from the Vital Statistics Mortality Dataset.


New South Wales
Western Australia
Scotland
Ontario
Overall
0.63 [0.25, 1.55]
0.57 [0.27, 1.21]
0.97 [0.60, 1.56]
1.10 [0.73, 1.65]
0.92 [0.70, 1.21]
0
1
2
HR (95% CI)