Supplementary Online Content

Bhindi B, Wallis CJD, Nayan M, et al. The association between vasectomy and prostate cancer: a systematic review and meta-analysis. *JAMA Intern Med.* Published online July 17, 2017. doi:10.1001/jamainternmed.2017.2791

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Literature Search Strategy

All searches were run on March 21, 2017; no restrictions on language or publication date; controlled vocabulary and keywords were used for vasectomy and prostate cancer.

Ovid MEDLINE(R) 1946 to Present and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily

1. vasectomy/ or (vasectom* or postvasectom* or deferentectom* or (vas adj3 (ligat* or occlusion* or occlud*)) or vasoligat* or vasocclu* or (spermatic adj2 cord adj2 resect*)).tw.
2. ductus deferens/su or (ductus adj3 deferens adj3 (ligat* or occlu* or surg* or procedur*)).tw.
3. exp prostatic neoplasms/ or (prostat* adj5 (neoplas* or cancer* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour or mass or metastat*)).tw.
4. (1 or 2) and 3

Embase 1988 to 2017 Week 12

1. vasectomy/ or (vasectom* or postvasectom* or deferentectom* or (vas adj3 (ligat* or occlusion* or occlud*)) or vasoligat* or vasocclu* or (spermatic adj2 cord adj2 resect*)).tw.
2. vas deferens/su or (ductus adj3 deferens adj3 (ligat* or occlu* or surg* or procedur*)).tw.
3. exp prostatic cancer/ or (prostat* adj5 (neoplas* or cancer* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour or mass or metastat*)).tw.
4. (1 or 2) and 3

Web of Science

1. #4 AND #3
2. ts=(prostat* NEAR/5 (neoplas* or cancer* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour or mass or metastat*))
3. #2 OR #1
4. ts=(ductus NEAR/3 deferens NEAR/3 (ligat* or occlu* or surg* or procedur*))
5. ts=(vasectom* or postvasectom* or deferentectom* or (vas NEAR/3 (ligat* or occlusion* or occlud*)) or vasoligat* or vasocclu* or (spermatic NEAR/3 cord NEAR/3 resect*))

Scopus

((TITLE-ABS-KEY (vasectom* OR postvasectom* OR deferentectom* OR (vas W/3 (ligat* OR occlusion* OR occlud*)) OR vasoligat* OR vasocclu* OR (spermatic W/3 cord W/3 resect*))) OR (TITLE-ABS-KEY (ductus W/3 deferens W/3 (ligat* OR occlu* OR surg* OR procedur*)))) AND (TITLE-ABS-KEY (prostat* W/5 (neoplas* OR cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour OR mass OR metastat*)))

eAppendix 2. Exclusion Following Full Text Review

First Author	Journal	Year	Reason for exclusion
No author	CA – A Cancer Journal	2000	Not original research (editorial/letter)
Adshead	Medicine Today	2004	Not original research (review article)
Aiken	Pan American J…	2014	Not original research (editorial/letter)
Alcaraz	European J of Cont…	1996	Not original research (review article)
Allen	Nursing Standard	1993	Not original research (editorial/letter)
Anonymous	Lancet	1991	Not original research (editorial/letter)
Anonymous	Nursing Standard	1992	Not original research (editorial/letter)
Anonymous	Amer Fam Physician	1993	Not original research (editorial/letter)
Anonymous	Consumer Report Hea..	1994	Not original research (editorial/letter)
Anonymous	Contracept Tech Update	1998	Not original research (editorial/letter)
Bowersox	J Nat Canc Inst	1993a	Not original research (editorial/letter)
Bowersox	J Nat Canc Inst	1993b	Not original research (editorial/letter)
Broadbent	Evidence-based Practice	2012	Not original research (editorial/letter)
Camila Fernadez	Revista Chilena de…	2015	Not original research (editorial/letter)
Chacko	J Urol	2002	Duplication of study cohort (abstract; full article included in our analysis– Chacko 2002)
Choo	Lancet	1993	Not original research (editorial/letter)
Chung	Epi & Infection	2013	Effect estimate not provided and unable to calculate from provided data. Unable to get in touch with corresponding author.
Colditz	Am J Epi	1991	Duplication of study cohort (abstract; full articles included in our analysis: Giovannucci 1993a and Siddiqui 2014)
Crozier	J Clin Epi	1993	Not original research (review article)
Diconsiglio	Fam Plan World	1993	Not original research (editorial/letter)
Djerassi	Nature	1994	Not original research (editorial/letter)
Galletly	Eur J Cancer Care	1998	Not original research (review article)
Giovannucci	J Am Med Assoc	1993b	Duplication of study cohort (updated report included in our analysis: Siddiqui 2014)
Giovannucci	J Am Med Assoc	1993c	Not original research (editorial/letter)
Giovannucci	N Engl J Med	1992	Did not evaluate outcome of interest
Hayes	J Nat Cancer Inst	1995	Not original research (editorial/letter)
Hayes	Brit J Cancer	2000	Did not evaluate exposure of interest

Hodgson	Aging Male	2009	Not original research (review article)
Holman	BJU International	2000	Did not evaluate outcome of interest
Howards	West J Med	1994	Not original research (editorial/letter)
James	J Biosocial Science	1994	Not original research (review article)
Keetch	J Urol	1995	Did not evaluate exposure-outcome association of interest (looks at risk of prostate cancer in father/brother/uncle as a function of vasectomy in proband)
Lesko	Am J Epi	1997	Duplication of study cohort (abstract; full article included in our analysis: Lesko 1999)
Lesko	J Urol	1999	Duplication of study cohort (erratum published; most updated version was used: Lesko 1999)
Lightfoot	Ann Epi	2000	Duplication of study cohort (abstract; full article included in our analysis: Lightfoot 2004)
Littlejohns	Cancer Epi	2016	Did not evaluate outcome of interest
Mahon	J Urol Nursing	1993	Not original research (review article)
Melchior	Deutsche Med Wochen	2002	Not original research (editorial/letter)
Moller	Brit Med J	1994	Duplication of study cohort (updated report included in our analysis: Lynge 2002)
Nguyen-V..	Lancet	1993	Not original research (editorial/letter)
Nienhuis	Brit Med J	1992	Duplication of study cohort (updated report included in our analysis: Goldacre 2005)
Olsen	Ugeskrift for Laeger	1993	Not original research (editorial/letter)
Peterson	Am J Epi	1992	Did not evaluate outcome of interest
Preston	J Urol	2013	Duplication of study cohort (Siddiqui 2014); reported on different main exposure
Puhan	Praxis	2003	Not original research (review article)
Rees	Practitioner	2014	Not original research (editorial/letter)
Rider	J Urol	2015	Duplication of study cohort (Siddiqui 2014); reported on different main exposure
Rosenberg	Am J Epi	1989	Duplication of study cohort (abstract; full article included in our analysis: Rosenberg 1994)
Rosenberg	Am J Epi	1990	Duplication of study cohort (updated report included in our analysis: Rosenberg 1994)
Sarkar	Int Med J	1999	Not original research (review article)
Schroder	Neder Tijd voor Genees	1993	Not original research (review article)
Sidney	J Urol	1987	Duplication of study cohort (updated report included in our analysis: Hiatt 1994)

Sidney	Cancer Cause & Control	1991	Duplication of study cohort (updated report included in our analysis: Hiatt 1994)
Skegg	New Zeal Med J	1993	Not original research (editorial/letter)
Skeeg	Eur J Cancer	1993	Not original research (review article)
Spence	Am J Epi	2012	Did not evaluate exposure of interest
Stollerman	Hospital Practice	1993	Not original research (editorial/letter)
Strayer	J Fam Practice	2002	Not original research (editorial/letter)
Sutcliffe	Canc Epi Biomark Prev	2006	Duplication of study cohort (Siddiqui 2014); reported on different main exposure
Van Leeuwen	J Urol	2010	Duplication of study cohort (abstract; full article included in our analysis: Van Leeuwen 2011)
Walsh	Fert & Steril	2012	Effect estimate not provided and unable to calculate from provided data. Contacted corresponding author, raw data is no longer available to calculate necessary effect estimate.
Wise	Brit Med J	2014	Not original research (editorial/letter)

eAppendix 3. Pooled Estimates of Studies Reporting Unadjusted Effect Estimates

Among cohort studies reporting unadjusted measures of effect, we found no significant increased risk among all studies (4 studies; RR=1.02; 95%CI 0.81-1.30; p=0.16; I^2=42%), and small statistically significant associations in the single study utilizing a time-to-event analysis (HR=1.13; 95%CI 1.05-1.20; p=0.0005) and two studies deemed at low risk of bias (RR=1.12; 95% 1.05-1.20; p=0.0005; I^2=0%)(**Supplemental Figure 1**).

The meta-analysis of case-control studies reporting unadjusted odds ratios for a statistically significant association between vasectomy and PCa (31 studies; OR=1.16; 95%CI 1.02-1.32; p=0.02; I^2 = 66%). However, there was no longer a significant association when restricting to studies with a low risk of bias (7 studies; OR=0.98; 95%CI 0.84-1.15; p=0.11; I^2=42%)(**Supplemental Figure 1**).

Although similar in direction, the association between vasectomy and PCa did not reach statistical significance among cross-sectional studies reporting unadjusted measures of effect (4 studies; OR=1.49; 95%CI 0.56-3.96; p=0.43; I^2 = 99%)(**Supplemental Figure 1**).

eAppendix 4. Calculation of Estimates for Absolute Risk Increase, Number Needed to Harm, and Population-Attributable Fraction

For this estimation, the effect estimate from cohort studies deemed at low risk of bias was used (RR 1.05; 95%CI 1.02-1.09).

Absolute lifetime risk (AR) of prostate cancer: 12.9%[1]

Probability of having a vasectomy (p_v): 10%[2,3]

Calculation absolute lifetime risk of PCa among men who do not and do get a vasectomy:

$$\begin{aligned} AR_{[PCa\text{-}overall]} &= AR_{[PCa\text{-}no\text{-}vasectomy]} * (1 - p_v) + AR_{[PCa\text{-}vasectomy]} * p_y \\ &= AR_{[PCa\text{-}no\text{-}vasectomy]} * (1 - p_v) + RR_{[vasectomy]} * AR_{[PCa\text{-}no\text{-}vasectomy]} * p_y \\ &= AR_{[PCa\text{-}no\text{-}vasectomy]} * ((1 - p_v) + RR_{[vasectomy]} * p_y) \end{aligned}$$

$$\begin{aligned} AR_{[PCa\text{-}no\text{-}vasectomy]} &= AR_{[PCa\text{-}overall]} / ((1 - p_v) + RR_{[vasectomy]} * p_y) \\ &= AR_{[PCa\text{-}overall]} / (1 + p_y * (RR_{[vasectomy]} - 1)) \\ &= 0.129 / (1 + 0.10 * (1.05 - 1)) \\ &= 0.128 \end{aligned}$$

$$AR_{[PCa\text{-}vasectomy]} = RR_{[vasectomy]} * AR_{[PCa\text{-}no\text{-}vasectomy]} = 0.135$$

Of note, due to the low magnitude of the $RR_{[vasectomy]}$, the probability of getting a vasectomy has a very small influence in this calculated estimate, and therefore variation in the probability of having a vasectomy is of little importance here.

Calculation of absolute risk increase (ARI) and number needed to harm (NNH):

$$\begin{aligned} ARI &= AR_{[PCa\text{-}no\text{-}vasectomy]} - AR_{[PCa\text{-}no\text{-}vasectomy]} \\ &= 0.006 \text{ (95\%CI 0.003-0.012)} \\ &= \mathbf{0.6\% \text{ (95\%CI 0.3-1.2)}} \end{aligned}$$

$$\begin{aligned} NNH &= 1 / ARR \\ &= \mathbf{156} \end{aligned}$$

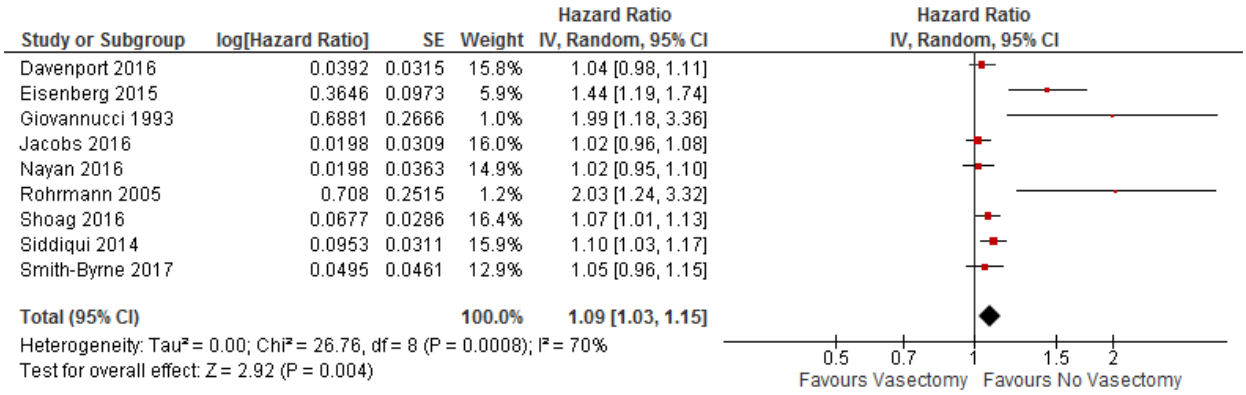
Calculation of Population Attributable Fraction (PAF):

$$\begin{aligned} PAF &= p_v (RR_{[vasectomy]} - 1) / (p_v (RR_{[vasectomy]} - 1) + 1) \\ &= (0.10 * (1.05 - 1)) / (0.10 * (1.05 - 1) + 1) \\ &= 0.005 \text{ (95\%CI 0.002-0.009)} \\ &= \mathbf{0.5\% \text{ (95\%CI 0.2-0.9)}} \end{aligned}$$

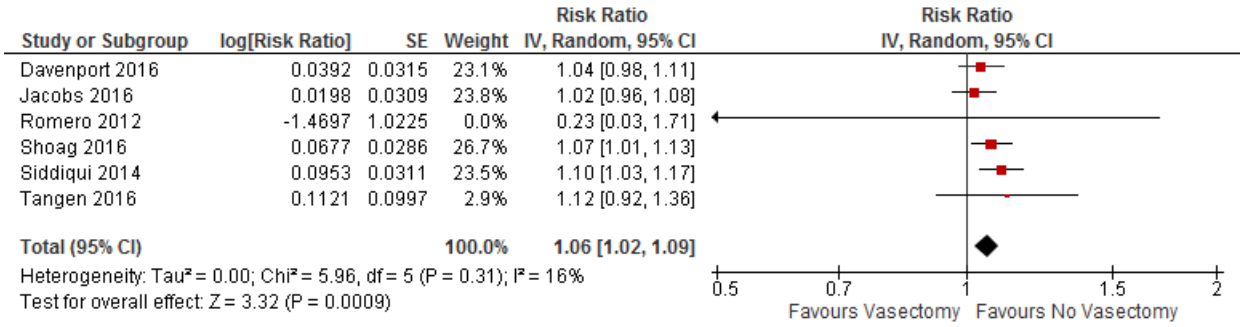
eAppendix 5. Discussion of Hill's Criteria of Causation

The criterion of temporality is the only one of the nine that is satisfied. Meanwhile, the criteria of strength and consistency of the association have not been satisfied, based on our analysis. Similarly, based on our review, a biological gradient has not been consistently demonstrated when considering time since vasectomy. One cannot argue for specificity, since vasectomy has been also previously been reported as associated with testicular cancer, cardiovascular disease, and dementia, all of which have been discredited.[4] Also, the case for biologic plausibility is tenuous. While hormonal imbalances,[5] immunologic effects,[6] cell proliferative changes[7] have been suggested to play a role, the data are limited and the exact mechanisms remain speculative.[4,8] Finally, to our knowledge there are no analogies, assessments of coherence, or experimental evidence to support the argument for an association between vasectomy and PCa. Thus, the argument for causality is not compelling given the amount of time and resource that has been dedicated to this research question over the past three decades.

eFigure 1. Forest Plots for Meta-Analyses of the Adjusted Estimates for the Association Between Vasectomy and Any Prostate Cancer for Cohort Studies Reporting on Time-to-Event Analyses



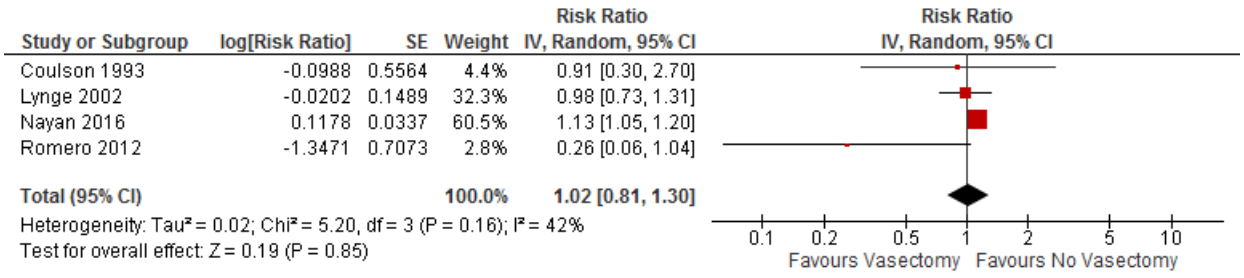
eFigure 2. Meta-Analysis of Cohort Studies That Accounted for PSA Testing



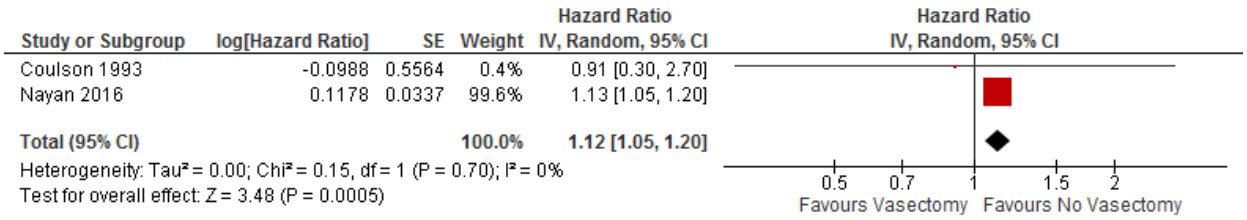
Abbreviations: SE = standard error; IV = inverse variance; CI = confidence interval

eFigure 3. Forest Plots for Meta-Analyses of Unadjusted Estimates for the Association Between Vasectomy and Any Prostate Cancer by Study Design and Risk of Bias

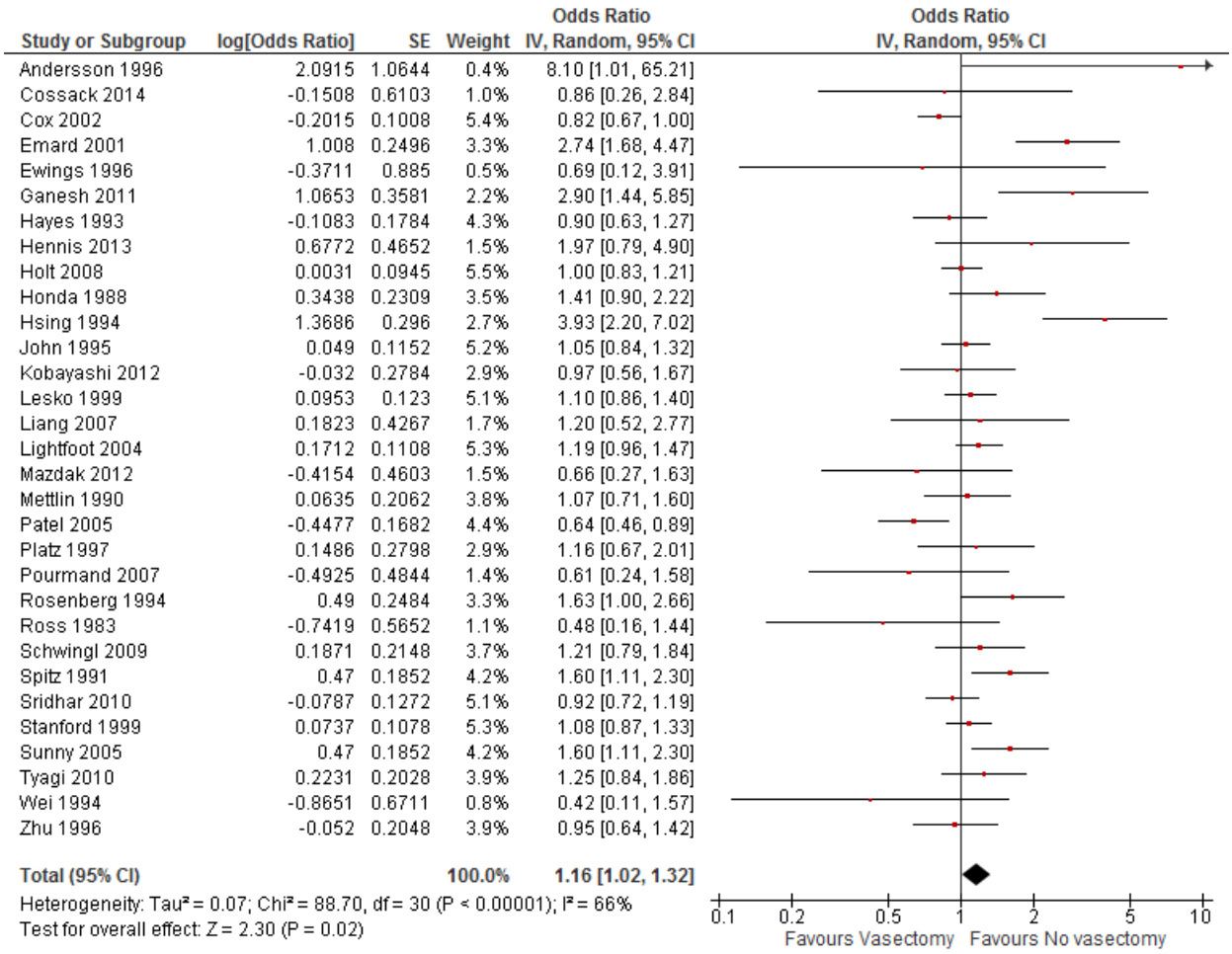
Supplementary Figure 3a: All cohort studies



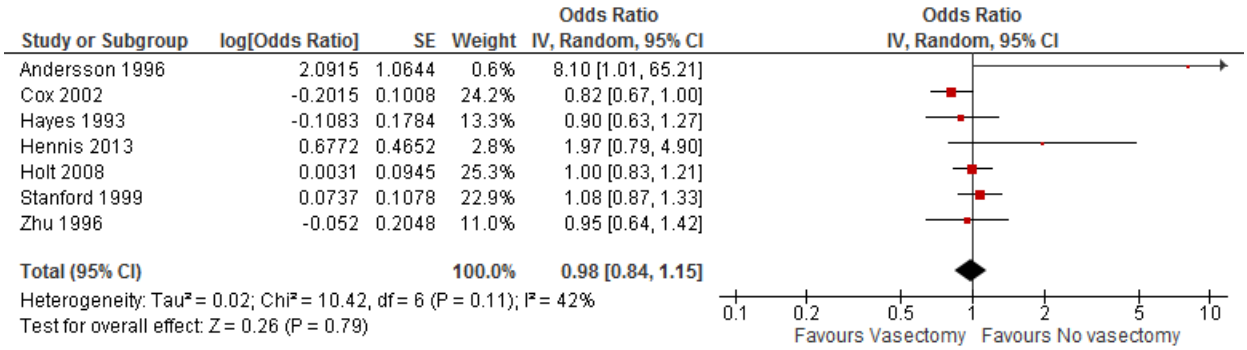
Supplementary Figure 3b: Cohort studies, low risk of bias



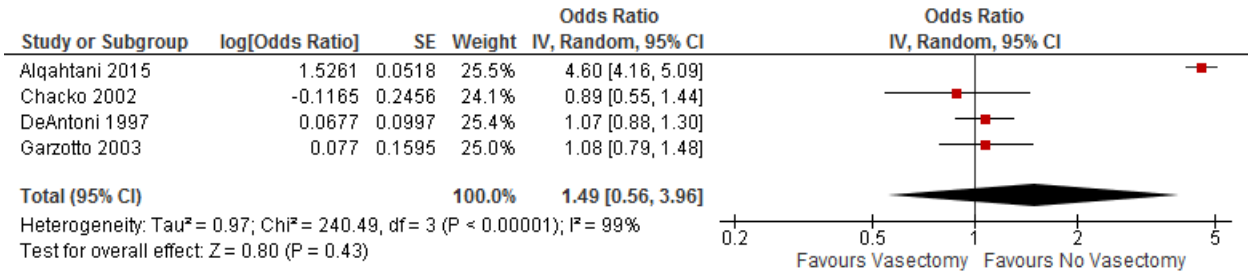
Supplementary Figure 3c: All case-control studies



Supplementary Figure 3d: Case-control studies, low risk of bias



Supplementary Figure 3e: Cross-sectional studies

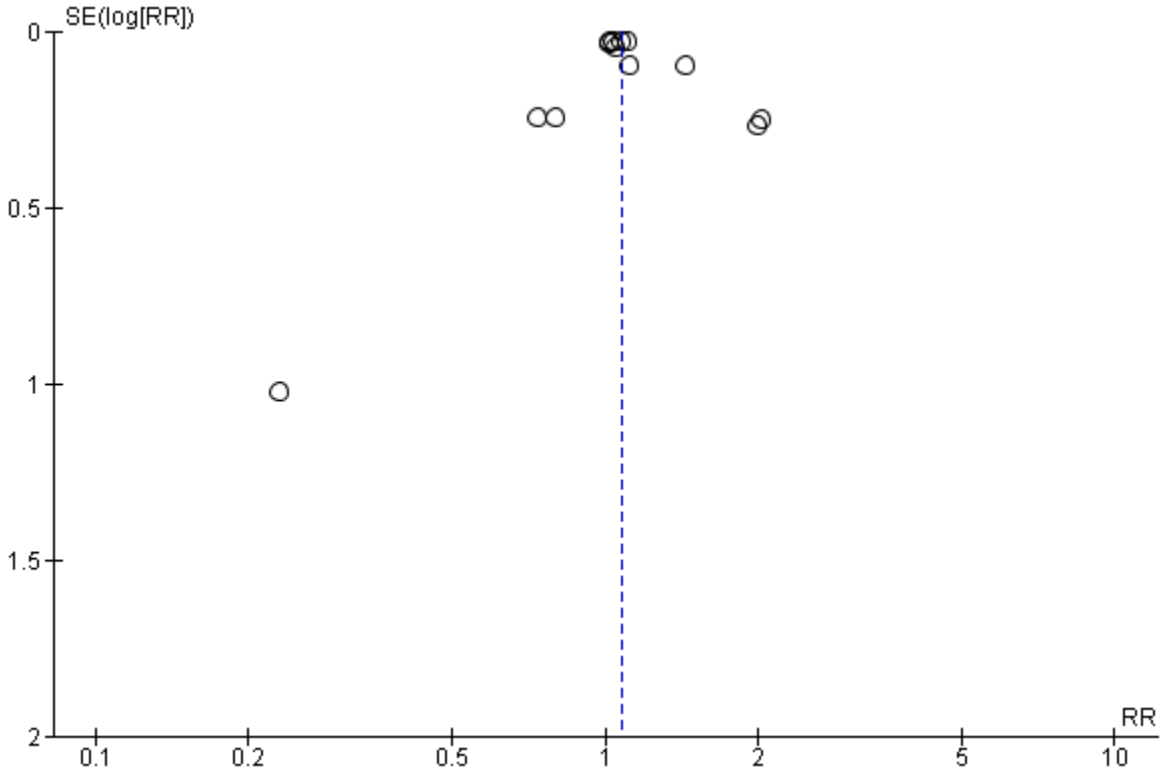


Legend: Plots are shown for (a) all cohort studies, (b) cohort studies deemed as low risk of bias, (c) for all case-control studies, (d) for case-control studies deemed as low risk of bias, and (e) for all cross-sectional studies.

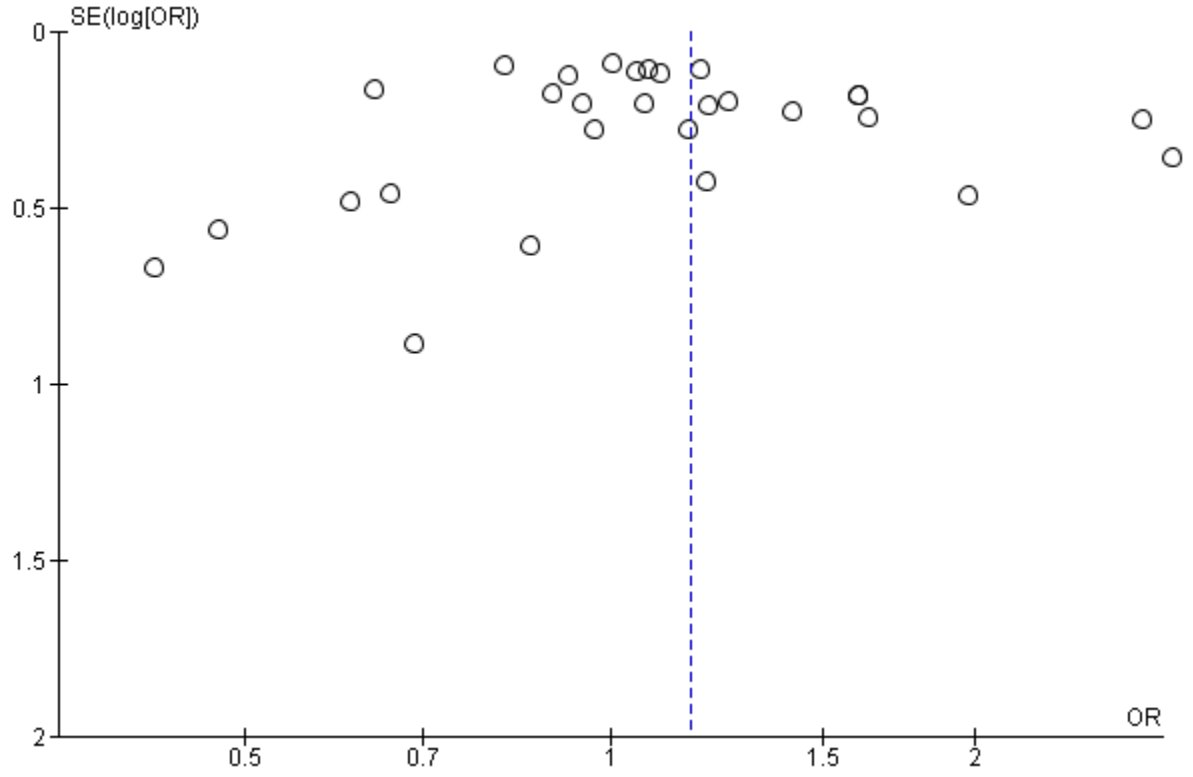
Abbreviations: SE = standard error; IV = inverse variance; CI = confidence interval

eFigure 4. Funnel Plots

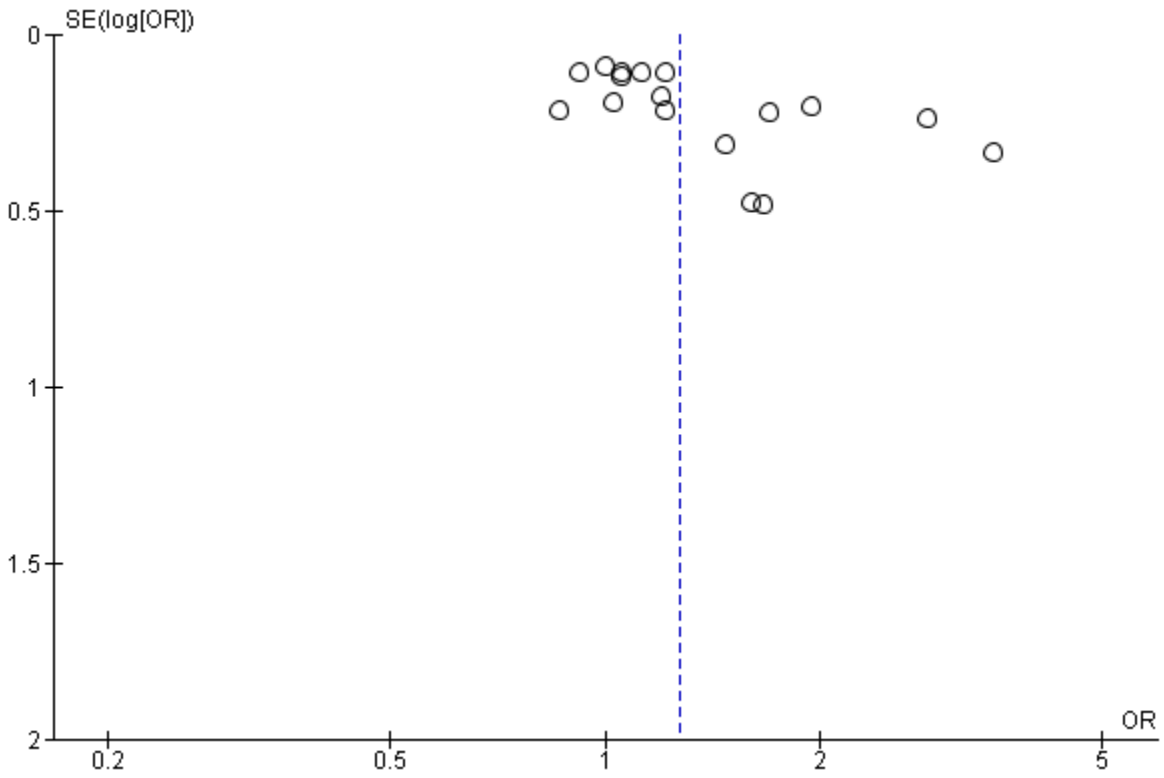
Supplementary Figure 4a: All cohort studies reporting adjusted measure of effect.



Supplementary Figure 4b: All case-control studies reporting unadjusted measure of effect.



Supplementary Figure 4c: All case-control studies reporting adjusted measure of effect.



Legend: Funnel plots of (a) cohort studies reporting adjusted measures of effect, (b) case-control studies reporting unadjusted measures of effect, and (c) case-control studies reporting adjusted measures of effect.

eTable 1. Risk Adjustment for Each Included Study

Cohort studies	
Author (year)	**Risk adjustment**
Coulson (1993)	Vasectomy control group was matched on age, race, marital status, and neighbourhood; no regression adjustment
Davenport (2016)	Not reported
Eisenberg (2015)	Adjusted for age, year of evaluation, comorbidity, follow-up time
Giovannucci (1993)	Age-adjusted Then further adjusted for smoking, alcohol intake, educational level, body-mass index, geographical residence in separate models (but these estimates were not reported)
Goldacre (2005)	Age-adjusted
Hiatt (1994)	Adjusted for age, race, marital status, education
Jacobs (2016)	CPS-II (lethal Pca): Adjusted for age, race, education, BMI, smoking. CPS-II-N: Adjusted for age, race, education, BMI, smoking, history of PSA testing
Lynge (2002)	Standardized by age and year of diagnosis
Nayan (2016)	Matched on: age, co-morbidity, geographical area, index date Incident Pca: Further adjusted for income level, visit to specialists, visits to urologists, emergency room visits, GP visits HG and Adv Pca: Further adjusted for socioeconomic status, visits to specialists and urologists, visits to GPs, emergency room visits, admissions to hospital Prostate cancer mortality: Further adjusted for income level
Rohrmann (2005)	Adjusted for age. Authors additionally considered adjusting for body-mass index, smoking history, history of brother or father with prostate cancer, alcohol consumption, intake of processed meat, intake of tomatoes or tomato juice, use of Vitamin E - but none of these appeared to be confounders and therefore only age-adjusted

	estimates were provided
Romero (2012)	Multivariable analysis performed, however it is not stated what was adjusted for
Shoag (2016)	Stratified by age at vasectomy and study arm (i.e. screening vs. usual care) Adjusted for baseline demographics, including history of prior PSA screening and DRE
Siddiqui (2014)	Adjusted for age, race, height, BMI, vigorous physical activity, smoking, diabetes, family history of Pca, multivitamin use, use of Vitamin E supplements, history of PSA testing
Byrne (2017)	Stratification by age at recruitment and recruitment center; Adjusted for body-mass index, smoking status, marital status, educational attainment, alcohol consumption, physical activity, protein for dairy sources
Tangen (2016)	Adjusted for age, ethnicity, family history, baseline PSA level
Van Leeuwen (2011)	Adjusted for age, Charlson comorbidity score, family history of Pca, IPSS, DRE, serum PSA, prostate volume, TRUS findings
Case control studies	
Author (Year)	**Risk adjustment**
Andersson (1996)	Age
Lesko (1999)	Age-matched Further adjusted for race, religion, level of education, FMHx of Pca, dietary fat intake, BMI, alcohol use, tobacco use, coffee use, urological symptoms, number of MD visits in past 2 years
Cossack (2014)	None
Cox (2002)	Age-adjusted. Further adjusted for social class, geographical region, religious affiliation, family history of PCa did not alter estimates (but this adjusted estimate were not reported).

Emard (2001)	None
Ewings (1996)	Controls were age-matched. Further age-adjustment was performed, but estimates did not change and therefore unadjusted age-matched ORs were reported
Ganesh (2011)	Adjusted for age, education, and religion
Hayes (1993)	Adjusted for age, race
Hennis (2013)	Matched on age (by 5 year age groups) Adjusted for age, marital status, religion, lifetime occupation, family history of PCa, waist-hip ratio
Holt (2008)	Adjusted for age, race, first-degree family history of prostate cancer, screening history of PSA/DRE in last 5 years
Honda (1988)	Age and neighborhood matched Stated that adjustment for cigarette smoking, demographic variables, marital factors, fertility factors, sexual history factors did not substantially alter associations, but adjusted estimates were not reported.
Hsing (1994)	Adjusted for marital status, socioeconomic index, alcohol use, BPH, prostatitis
John (1995)	Matched and adjusted for region of residence, age, race/ethnicity
Kobayashi (2012)	*None (study evaluating diff exposure. Vasectomy OR calculated)
Liang (2007)	Matched for age, sex, race, resident location Not further risk-adjusted
Lightfoot (2004)	Age-adjusted estimate provided. This was a study of Pca risk factors. They did not include in final multivariable model since not retained upon stepwise selection
Mazdak (2012)	None
Mettlin (1990)	Age-adjusted
Nair-Shalliker (2016)	Age-adjusted

Patel (2005)	Adjusted for age, race, education, family history of prostate cancer in first degree relative
Platz (1997)	Age-adjusted MV1: Adjusted for age, smoking MV2: Adjusted for age, smoking, alcohol drinking, employment status, marital status, education, religion, languages spoken, residence, rural area, previous residence, monthly family income
Pourmand (2007)	None
Rosenberg (1994)	Adjusted for age, years of education, marital status, number of hospitalizations, cigarette smoking, interview year, geographical area
Ross (1983)	Matched on birth-date No risk adjustment otherwise
Schwingl (2009)	Matched on age and residence in the primary catchment area of hospital Potential confounding variables were included in models if they changed OR estimate by >5%. However, it is not stated which variables were included in final model.
Spitz (1991)	Age matched, otherwise no multivariable adjustment
Sridhar (2010)	None
Stanford (1999)	Adjusted for age, race, family history of prostate cancer, number of PSA tests within 5y before reference date
Sunny (2005)	Age-matched Adjusted for age and "other probable confounding characteristics" (exact variable not specified)
Tyagi (2010)	Age-matched Not further risk-adjusted
Wei (1994)	Matched on age, sex, race, day of admission
Weinmann (2010)	Matched on age, race, health plan, and length of health plan membership

Zhu (1996)	Matched on year of birth, Group Health Cooperative Membership, length of Group Health Cooperative enrolment, source of primary medical care Adjusted for year of birth, Group Health Cooperative membership, length of Group Health Cooperative enrolment, source of primary medical care, family history of prostate cancer
Cross-sectional studies	
Author (year)	**Risk adjustment**
Alqahtani (2015)	None
Chacko (2002)	None
DeAntoni (1997)	None
Garzotto (2003)	None

eTable 2. Newcastle-Ottawa Scale for Risk of Bias Assessment of Studies Included in the Meta-Analysis

Studies	Selection				Comparability	Outcome			Overall
	Representativeness of exposed cohort	Selection of non-exposed	Ascertainment of exposure	Outcome not present at start		Assessment of outcome	Adequate follow-up length	Adequacy of follow-up	
Cohort studies									
Coulson (1993)	1	1	1	1	1	1	1	1	8
Davenport (2016)	1	1	0	1	0	0	0	0	3
Eisenberg (2015)	1	1	1	1	1	1	0	0	6
Giovannucci (1993)	1	1	0	1	1	0	1	1	6
Goldacre (2005)	1	1	1	1	1	1	1	1	8
Hiatt (1994)	1	1	0	1	1	1	0	1	6
Jacobs (2016)	1	1	0	1	2	1	1	1	8
Lynge (2002)	1	0	1	1	0	1	1	1	6
Nayan (2016)	1	1	1	1	2	1	1	1	9
Rohrmann (2005)	1	1	0	1	1	1	1	0	6
Romero (2012)	1	1	0	1	0	1	0	0	4
Shoag (2016)	1	1	0	1	2	1	1	1	8
Siddiqui (2014)	1	1	0	1	2	1	1	1	8
Smith-Byrne (2017)	1	1	0	1	1	1	1	1	7
Tangen (2016)	1	1	0	1	1	1	1	1	7
Van Leeuwen (2011)	1	1	0	1	2	1	1	1	8
Cross-sectional studies									
Alqahtani (2015)	0	1	0	1	0	1	0	0	3
Chacko (2002)	0	1	0	1	0	1	0	0	3
DeAntoni (1997)	1	1	0	1	0	1	0	0	4
Garzotto (2003)	0	1	0	1	0	1	0	0	3

	Selection					Exposure			
	Case definition	Representativeness of cases	Selection of controls	Control definition	Comparability	Ascertainment of exposure	Comparable ascertainment method	Non-response rate	Overall
Case-control studies									
Andersson (1996)	1	1	1	1	1	1	1	1	8
Cossack (2014)	0	0	1	0	0	0	1	0	2
Cox (2002)	1	1	1	1	1	1	1	1	8
Emard (2001)	1	1	0	0	0	1	1	0	4
Ewings (1996)	1	1	0	0	1	0	1	1	5
Ganesh (2011)	1	0	0	1	1	0	1	0	4
Hayes (1993)	1	1	1	1	1	0	1	1	7
Hennis (2013)	1	1	1	0	1	1	1	1	7
Holt (2008)	1	1	1	0	2	0	1	1	7
Honda (1988)	1	0	1	0	1	0	1	0	4
Hsing (1994)	1	0	1	0	1	0	0	0	3
John (1995)	1	1	1	0	1	0	1	1	6
Kobayashi (2012)	1	0	0	1	0	1	1	0	4
Lesko (1999)	1	0	1	1	1	1	1	0	6
Liang (2007)	1	0	0	0	1	0	1	0	3
Lightfoot (2004)	1	1	1	0	1	0	1	0	5
Mazdak (2012)	1	0	0	1	0	0	0	0	2
Mettlin (1990)	0	1	0	0	1	0	1	0	3
Nair-Shalliker (2016)	0	1	1	0	1	0	1	0	4
Patel (2005)	1	1	1	0	1	0	1	1	6
Platz (1997)	1	1	0	0	1	0	1	1	5
Pourmand (2007)	1	0	0	1	0	0	1	1	4
Rosenberg (1994)	1	1	0	1	1	0	1	1	6
Ross (1983)	0	0	1	1	1	0	1	0	4
Schwingl (2009)	1	0	0	0	1	0	1	0	3
Spitz (1991)	1	0	0	0	1	0	1	0	3
Sridhar (2010)	1	1	0	1	0	0	1	0	4
Stanford (1999)	1	1	1	1	2	1	1	1	9
Sunny (2005)	1	0	1	1	1	0	1	0	5
Tyagi (2010)	1	0	1	0	1	0	1	0	4

Wei (1994)	1	0	0	0	1	0	1	0	3
Weinmann (2010)	0	1	0	1	1	0	0	0	3
Zhu (1996)	1	1	0	1	1	1	1	1	7

eTable 3. Pooled Adjusted Estimates for Association Between Vasectomy and Prostate Cancer, Excluding Abstracts

Analysis	**Pooled effect estimate**
All cohort studies	aRR=1.10; 95% CI 1.01-1.19; p=0.02; I^2=69%
Time-to-event analyses	aHR=1.12; 95% CI 1.03-1.22; p=0.009; I^2=77%
Low risk-of-bias studies	aHR=1.05; 95% CI 1.01-1.09; p=0.02; I^2=20%

eTable 4. Studies Reporting on the Impact Time Since Vasectomy on the Association Between Vasectomy and Prostate Cancer

Study (year)	Time since vasectomy					
	<5 years	**5–9 years**	**10–14 years**	**15–19 years**	**20–29 years**	**≥30 years**
Cohort design						
Giovannucci (1993)	HR=1.11 (95%CI 0.46-2.70)		HR=1.26 (95%CI 0.75-2.10)		HR=1.89 (95%CI 1.14-3.14)	
Goldacre (2005)	RR=0.77 (95%CI 0.02-4.29)	RR=0.37 (95%CI 0.01-2.06)	RR=0.69 (95%CI 0.34-1.24)		RR=0.93 (95%CI 0.40-1.85)	
Lynge (2002)	SIR=0.95 (95%CI 0.31-2.21)	SIR=1.24 (95%CI 0.71-2.01)	SIR=1.12 (95%CI 0.69-1.72)	SIR=0.40 (95%CI 0.11-1.02)		
Rohrmann (2005)	HR=2.21 (95%CI 0.92-5.34)				HR=2.03 (95%CI 1.19-3.47)	
Siddiqui (2014)	<23yrs: HR=1.12 (1.01-1.25)				≥23yrs: HR=1.10 (1.02-1.17)	
Smith-Byrne (2017)	NR (test for heterogeneity by time since vasectomy: p=0.9)[a]					
Case-control design						
Lesko (1999)	OR=1.1 (95%CI 0.5-2.4)			OR=1.7 (95%CI 0.7-3.8)	OR=4.3 (95%CI 1.7-11.0)	
Cox (2002)	OR=0.76 (95%CI 0.46-1.26)			OR=1.16 (95%CI 0.76-1.78)	20-24yrs: OR=0.92 (95%CI 0.66-1.30) ≥25yrs: OR=0.92 (95%CI 0.68-1.23)	

Emard (2001)	1-2y: OR=2.1 (95%CI 0.5-9.5) 3-4y: OR=4.8 (95%CI 0.5-10.6)	5-6y: OR=0.5 (95%CI 0.1-5.0) 7-8y: OR=0.9 (95%CI 0.3-3.0) 9-10y: OR=2.3 (95%CI 1.0-6.1) 11-12y: OR=1.5 (95%CI 0.8-3.5) 13-14y: OR=2.9 (95%CI 1.5-5.5)		OR=3.2 (95%CI 1.4-7.5)		
Hayes (1993)	NR	OR=1.2 (95%CI 0.5-2.9)	OR=1.0 (95%CI 0.6-1.6)		OR=1.5 (95%CI 0.8-2.7)	
Holt (2008)	OR=1.1 (95%CI 0.7-1.6)			OR=1.6 (95%CI 1.0-2.7)	20-24yrs: OR=1.1 (95%CI 0.7-1.7) 25-29yrs: OR=1.1 (95%CI 0.8-1.6)	30-34yrs: OR=0.9 (95%CI 0.6-1.2) □35yrs: OR=0.7 (95%CI 0.5-1.1)
Honda (1988)	RR=0.7 (95%CI 0.3-1.9)	RR=1.0 (95%CI 0.5-2.0)			RR=2.2 (95%CI 1.0-4.8)	RR=4.4 (95%CI 0.9-21.0)
John (1995)	OR=1.3 (95%CI 0.82-2.0)				OR=0.97 (95%CI 0.66-1.4)	OR=1.0 (95%CI 0.71-1.4)
Mettlin (1990)	Tertile I (5-12yrs)[b]:	Tertile II (13-	Tertile III (□19yrs)[b]:			

	RR=1.2 (95%CI 0.5-2.8)		18yrs)[b]: RR=2.2 (95%CI 1.0-4.6)		RR=1.5 (95%CI 0.7-3.4)	
Platz (1997)	OR=1.25 (95%CI 0.35-4.40)				OR=1.56 (95%CI 0.79-3.08)	
Rosenberg (1994)	no PCa cases		RR=2.1 (95%CI 0.5-8.6)	RR=1.4 (95%CI 0.5-4.2)		
Schwingl (2009)	NR		OR=0.75 (95%CI 0.21-2.74)		OR=1.21 (95%CI 0.65-2.25)	OR=1.39 (95%CI 0.74-2.62)
Spitz (1991)	Not reported for <27yrs				□27yrs: RR=2.2 (95%CI 1.1-4.3)[c]	
Stanford (1999)	OR=0.68 (95%CI 0.2-1.9)	OR=0.68 (95%CI 0.3-1.5)	OR=0.94 (95%CI 0.5-1.6)	OR=1.11 (95%CI 0.7-1.7)	20-24y: OR=1.11 (95%CI 0.8-1.6) 25-29y: OR=1.42 (95%CI 0.9-2.2)	OR=1.23 (95%CI 0.7-2.1)
Sunny (2005)	OR=1.2 (95%CI 0.7-2.1)					OR=3.8 (95%CI 1.9-7.6)
Zhu (1996)	OR=0.99 (95%CI 0.51-1.95)				OR=0.84 (95%CI 0.51-1.38)	
Cross-sectional design						
DeAntoni (1997)	OR=0.76 (95%CI 0.31-1.84)		OR=1.613 (95%CI 0.832-3.127)		OR=1.025 (0.580-1.809)	

Effect estimates stratified by time since vasectomy are shown. The width of each cell represents the range of time since vasectomy for each given estimate, based on how it lines up with column headings. Exceptions are indicated in the table.

[a] Effect estimates were not reported by subcategories of time since vasectomy, and only interaction testing was reported.

[b] Time since vasectomy was categorized into tertiles.

[c] Only highest tertile reported. It was stated that there was no evidence of a trend.

Abbreviations: NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; CI = confidence interval

eTable 5. Studies Reporting on the Impact of Age at Vasectomy on the Association Between Vasectomy and Prostate Cancer

Study (year)	**Age at vasectomy**					
	<30	**30-34**	**35-39**	**40-44**	**45-49**	**□50**
Cohort design						
Lynge (2002)	SIR=14.26 (95%CI 1.73-51.57)	SIR=0.84 (95%CI 0.31-1.82)		SIR=0.80 (95%CI 0.48-1.25)		50-59y.o.: SIR=1.06 (95%CI 0.56-1.81) □60y.o.: SIR=1.65 (95%CI 0.61-3.60)
Rohrmann (2005)	HR=1.77 (95%CI 0.93-3.37)			HR=2.63 (95%CI 1.40-4.94)		
Siddiqui (2014)	<38y.o.: HR=1.14 (95%CI 1.04-1.24)			□38y.o.: 1.08 (95%CI 1.00-1.16)		
Smith-Byrne (2017)	<38y.o.: HR=1.18 (95%CI 1.03-1.35)			□38y.o.: HR=0.99 (95%CI 0.89-1.09)		
	p-interaction=0.04					
Cross-sectional design						
Lesko (1999)	OR=2.7 (95%CI 1.3-5.4)		OR=1.6 (95%CI 0.7-3.5)	OR=0.9 (95%CI 0.3-2.9)		
Cox (2002)	OR=1.23 (95%CI 0.76-2.01)		OR=0.81 (95%CI 0.56-1.17)	OR=0.78 (95%CI 0.50-1.20)	OR=0.78 (95%CI 0.50-1.20)	OR=0.76 (95%CI 0.45-1.30)

Hayes (1993)	25-34y.o.: OR=2.0 (95%CI 1.0-4.0)		OR=1.0 (95%CI 0.6-1.3)	OR=1.0 (95%CI 0.5-1.8)	
Holt (2008)	OR=1.0 (95%CI 0.8-1.2)	OR=0.8 (95%CI 0.6-1.2)	OR=0.9 (95%CI 0.7-1.3)	OR=1.3 (95%CI 0.9-1.7)	
John (1995)	OR=0.95 (95%CI 0.68-1.3)			OR=1.2 (95%CI 0.85-1.6)	
Platz (1997)	OR=0.77 (95%CI 0.26-2.33)			OR=2.10 (95%CI 1.02-4.31)	
Rosenberg (1994)	RR=3.4 (95%CI 0.8-14)			RR=1.2 (95%CI 0.4-3.3)	RR=1.8 (95%CI 0.3-11)
Schwingl (2009)	OR=1.25 (95%CI 0.57-2.73)		OR=1.48 (95%CI 0.80-2.73)	OR=0.89 (95%CI 0.42-1.92)	
Stanford (1999)	OR=1.15 (95%CI 0.7-1.8)	OR=1.30 (95%CI 0.9-1.9)	OR=1.07 (95%CI 0.7-1.6)	OR=0.96 (95%CI 0.7-1.4)	
Sunny (2005)	OR=2.1 (95%CI 1.2-3.9)			OR=1.8 (95%CI 1.1-2.9)	
Zhu (1996)	OR=0.95 (95%CI 0.52-1.72)		OR=0.83 (95%CI 0.49-1.39)		

Effect estimates stratified by age at vasectomy are shown. The width of each cell represents the range of age at vasectomy for each given estimate, based on how it lines up with column headings. Exceptions are indicated in the table.

Abbreviations: NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; CI = confidence interval; y.o.=years old.

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