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Vasectomy: potential links to an increased risk of aggressive prostate cancer?

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Summary

Several studies have found associations between aggressive prostate cancer and having a vasectomy. However, findings from two very recent meta-analyses have found that this is not the case. Therefore, the data is mixed. Herein, we detail the controversy between vasectomy and prostate cancer risk, particularly aggressive prostate cancer, by shedding some light on the molecular pathways, potential risk factors, and suggested links for those considering vasectomy and medical professionals who perform it. We conclude by supporting the American Urological Association's position that, while patients should be informed of potential risks of vasectomy, there is no established link between prostate cancer and choosing to have a vasectomy.

Keywords

prostate; cancer; vasectomy; risk; epidemiology

Vasectomy is the foremost utilized non-diagnostic operation performed by urologists in the United States.[1] Technically, this involves cutting the vas and often removing a small piece of the vas to prevent recannulation. The net result is that sperm and other testicular by-products do not make it to the prostate and are not part of the ejaculate, therefore making vasectomy extremely effective birth control. While side effects can occur (sperm granuloma and chronic pain in the testes known as orchalgia), traditionally, vasectomy has been thought to be devoid of other long-term sequelae. However, some studies suggest that vasectomy may be linked with greater prostate cancer (PC) risk, specifically aggressive PC.[2–4] Herein, we briefly review these data, discuss the potential molecular mechanisms that could link vasectomy with PC risk, and provide some clinical insight that may explain the observed associations. Finally, we conclude with advice regarding how to discuss this risk with patients considering vasectomy.

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PC is the most common solid cancer in men with over 220,000 new cases each year and the second leading cause of cancer death in men with over 27,000 deaths each year.[5] Given this high prevalence, any condition that can even modestly increase risk, could lead to a large number of excess cases. While historically, age, race, and family history were considered the only risk factors for PC[6–8], more recent studies have suggested additional risk factors such as epigenetic changes[9], inflammation and prostate tissue damage[10], smoking[11], sexually transmitted infections[12,13], and obesity.[14] Relevant to this review, several studies have also suggested a link between vasectomy and increased PC risk. [2–4]

Prior to reviewing the literature on vasectomy and PC risk, we first will review potential molecular mechanisms that have been postulated to explain the increased PC risk seen in some studies. While the exact biological mechanisms and molecular pathways through which vasectomy may influence PC risk are unclear, possible explanations have included anatomical changes in the testis[15], epididymis[16], and vas, including changes in the secretions of vas proteins.[17] Interestingly, a study found that insulin growth factor (IGF)-1 and IGF binding protein-3 (IGF-BP3) levels in the seminal plasma were significantly lower after vasectomy.[18] While IGF-1 has been significantly associated with increased PC risk in humans[19], IGF-BP3 has been associated with lower risk of PC.[20] As such, the net result of lower IGF-1 and IGF-BP3 on PC risk is hard to assess. Moreover, it has been found that vasectomized men have decreased expression of semen TGF β -1 and TGF β -3 relative to non-vasectomized men.[21] Given that TGF β has an inhibitory effect on PC tumor growth[22,23], lower TGF β levels could contribute to higher PC risk. Furthermore, it has been suggested that changes in semen protein behavior (both up and downregulation)[21] may influence PC proliferation. Interestingly, the increased proliferation effect was modeled in rats in a study which examined the effects of vasectomy on the prostate. Like the human study, they found that vasectomy increased cell proliferation in the prostate post-vasectomy. [24] More studies in both animals and humans are required to better understand these findings.

Given the potential plausibility that vasectomy may link with PC risk, it is noteworthy that indeed, some studies have found a link between vasectomy and increased PC risk. In their 1998 systematic review of five cohort and nine case-control studies, Bernal-Delgado et al reported a 23% increased risk of PC among men who reported having a vasectomy.[25] In two independent retrospective and prospective studies, Giovannucci et al found that, in almost 25,000 men combined, vasectomy increased PC risk by 56–66%.[3,26] More recently, however, a study from the Health Professionals Follow-up Study (HPFS) examined nearly 50,000 men, over 6,000 of which were diagnosed with PC, with a 24-year follow-up timeframe and found that of the 25% of the men in their cohort who had had a vasectomy, there was a 10% increased risk of developing PC in general, but a 22% increased risk of developing high-grade PC.[4] Among these studies, one interesting observation is the consistent decreasing magnitude of the increased risk of PC after vasectomy over time, potentially related to the increased PSA testing over time, which has leveled the field in terms of PC detection.

While the above studies certainly suggest a link between vasectomy and PC risk, this does not imply vasectomy causes PC. Rather, an association is a place to start looking and suggests that something is linking vasectomy and PC – whether it is the vasectomy itself (casual), the greater screening that occurs among men who undergo vasectomy (detection bias), or some other shared factor between vasectomy and PC (explained by a confounder). Indeed, much of the association between vasectomy and PC risk in these prior studies is presumed to relate to both screening bias (i.e. vasectomies are performed by urologists and urologists are more likely to screen for PC) and detection bias (PC is detected almost solely through screening; due to the fact that men who have a vasectomy require more medical attention and thus are screened more frequently allowing more cancers to be caught: more PSA screening → more biopsies).[27] Importantly, a recent study tried to address this and concluded that this could not account for the positive association between vasectomy and aggressive PC risk.[4] Specifically, the authors adjusted for ongoing PSA testing and analyzed men who were highly screened between 1996 and 2010, which in theory should account for screening differences between men who did and did not have a vasectomy, and while vasectomy was no longer linked with overall PC risk ($p=0.41$), it remained linked with increased risk of higher grade PC including Gleason 7 and 8–10 PC (22–28% increased risk).

While this study certainly supports a link between vasectomy and PC risk, it is noteworthy that multiple studies found no link between vasectomy and PC risk.[28–30] Given this controversy, a recent meta-analysis examined this issue. Using data published up through 2014 (including the results from Siddiqui et al), Liu et al examined results from nine cohort studies, with data from over 1.1 million men (ages 20–75) of which 7,539 were diagnosed with PC, and found no significant differences in PC risk among men who did or did not have a vasectomy ($p=0.48$).[31] Moreover, in subgroups defined by time since vasectomy, geographic location, follow-up time, and year of publication, there remained no significant associations between vasectomy and PC risk within any strata. Additionally, in a leave-one-out analysis, there again, remained no significant associations between vasectomy and PC risk regardless of which paper was excluded, suggesting the results of the meta-analysis were not driven by a single-study. Finally, another meta-analysis also published in 2015 came to identical conclusions regarding the lack of significant association between vasectomy and PC risk.[32]

Given the lack of clear molecular explanations, the overall modest positive associations even in the positive studies, and the negative meta-analyses, it is difficult to accept that a true association exists between vasectomy and PC risk. While it is hoped that in time and with more studies we will have stronger evidence for or against such an association, the strongest evidence to date points to no link between vasectomy and PC risk. As such, given the clear benefits of vasectomy and the at best unclear risks, men should not be dissuaded against vasectomy due to concerns about PC. On the contrary, given the strength of the meta-analysis finding no linkage, we would advise that doctors not discuss with their patients concerns about PC. This approach is in keeping with the recommendations of the American Urological Association.[1] In our practice, we do not advise patients about these potential risks.

So, what's the take home message? The best evidence to date suggests no link between vasectomy and PC risk, though, we cannot indisputably rule out a very weak effect. However, if in an analysis of over 1,000,000 men was unable to find a significant effect, how clinically relevant could it be?

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