

Male Infertility and Subsequent Risk of Cancer Development

Michael Lao MD, Stanton C. Honig MD

Michael Lao MD, is a resident at The University of Connecticut Health Center, Division of Urology, Farmington, CT. Correspondence may be directed to Lao@uchc.edu. Stanton C. Honig MD is the Director of Men's Health in the Department of Urology, Yale School of Medicine, in New Haven CT. Correspondence may be directed to stanton.honig@yale.edu.

Abstract

Infertility occurs in 15% of the population; and 30–50% of the time, the problem is due to a male factor. There is active research attempting to elucidate how male factor infertility fits into the picture of overall men's health. Research in the past has established that a thorough male fertility evaluation can uncover various medical pathologies. There is now growing evidence that suggests male infertility is a potential harbinger for subsequent cancer development. In this review of pertinent articles, the current evidence regarding fertility and development of genitourinary and other cancers will be discussed, in particular, testicular and prostate cancer. In addition, various etiologic factors that explain the pathophysiology of infertility and progression to cancer will also be reviewed. It is possible that male factor infertility is a surrogate marker for subsequent cancer development.

Keywords: infertility, cancer, prostate, testes, oncology

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Introduction

Infertility is the failure to conceive after one year of regular unprotected intercourse. Roughly 15% of couples will experience problems with fertility, and 30–50% of the time the problem it is due to a male factor.^{1,2} Active research is now trying to uncover how infertility fits into the picture of men's health. By obtaining a comprehensive male fertility evaluation, Honig et al discovered that medical pathologies can be uncovered, some of which had potentially life-threatening consequences.³ Their retrospective analysis of 1,236 male infertility patients found 13 men (1.1%) with significant medical pathology. Half of these were testicular cancer identified through abnormal semen parameters.

Couples presenting to fertility clinics are often evaluated with the primary focus on the female. Treatment is often directed towards assisted reproductive technologies (ART) without a full male evaluation. An infertility evaluation is frequently centered on the female because of more female involvement in pregnancy and advances in ART that make it possible to achieve pregnancy without a male evaluation. Since significant medical pathology can be identified during a male work up, there has been an increased trend towards this evaluation. Kolettis and associates found that, through a male evaluation, certain pathologies such as cystic fibrosis and urological cancers can be uncovered.⁴ Sigman similarly discovered that an endocrine evaluation can lead to the discovery of many treatable endocrine disorders.⁵

New data suggests a possible link between male factor infertility and the subsequent development of genitourinary malignancies, particularly of the testes and prostate. Previous data focused on identification of significant medical pathology at the time of the evaluation. But what about the relationship between male infertility and the subsequent development of cancers? This paper focuses on the evidence-based data evaluating this question. A search was conducted via PubMed with keywords such as 'infertility, cancer, prostate, and testes.' Articles included in our review were of the most relevant in the field of male infertility and cancer risk. Most articles were recent papers from 2008 and onward. Key landmark papers before 2008 were included if it contributed to the discussion. All relevant information for each study is presented in Table 1.

Infertility and Testis Cancer in a Danish Cohort

Incidence of male infertility has been found to be increasing during the past couple of decades in some studies.^{6,7} Noticing also an increasing incidence of testis cancer by others, researchers have evaluated the possibility of an association between male infertility and development of cancer. Testis cancer is the most common cancer among young men in industrialized countries.⁸ Several investigators have already made strides in uncovering the potential that male infertility might be a harbinger for developing cancers of testicular and prostate origin.^{9–14} Men with testis cancer often have abnormal semen parameters, but this association has not been studied prospectively. Prior studies have used paternity or offspring number as opposed to direct analysis of semen characteristics. There is no best measure of true male fertility potential but semen characteristics remove the partner variable from the equation. Prior studies used surrogate markers for fertility, as opposed to direct analysis of semen characteristics.

Surrogate markers, such as paternity or offspring number, cannot reliably predict fertility. These measures do not consider whether someone had few offspring because they desire only one child or because they have a true underlying fertility problem. Jacobsen et al were one of the first investigators to study semen characteristics and their risk of testis cancer development.¹ They performed a retrospective cohort study of men who presented to infertility clinics and had semen analysis performed in Copenhagen between 1963 and 1995. These men were then linked to the Danish Cancer Registry from 1943–1995. Patient demographics were obtained from various other population registers. The authors excluded men who had cancer before their semen evaluation and only used the first set of semen analyses. Expected number of cancer cases was obtained by multiplying years at risk with primary cancer rates in the Danish population. For data analysis, the authors used standardized incidence ratios (SIRs) and 95% confidence intervals (CIs). The main outcome measured was the SIR of testis cancer in this cohort, compared to the total population of Danish men.

Table 1: Study characteristics

	Study type	Cancer	Number	Variable	SIR (95% CI)
Jacobsen et al (2000)	Retrospective cohort	Testis	32,442		
	Mean age: Not given			All infertility patients	1.6 (1.3-1.9)
				Semen Concentration	
				0-20x10 ⁶ /ml	2.3 (1.6-3.2)
				>20x10 ⁶ /ml	1.1 (0.8-1.5)
				Motility	
				Poor motility	2.5 (1.0-5.2)
				Good motility	1.6 (1.1-2.1)
				Proportion abnormal	
				>75%	3.0 (0.8-7.6)
0-75%	1.3 (1.0-1.7)				
Walsh et al (2009)	Retrospective cohort	Testis	19,106	All infertility patients	1.3 (0.9-1.9)
				Male factory infertility	2.8 (1.5-4.8)
				No male factory infertility	1.1 (0.6-1.7)
Walsh et al (2010)	Retrospective cohort	Prostate	19,106	All Prostate cancer	
				Male factor infertility	1.3 (1.0-1.7)
				No Male factor infertility	0.7 (0.6-0.9)
				Low grade prostate cancer (Gleason 5-7)	
				Male factor infertility	1.2 (0.8-1.6)
				No Male factor infertility	0.7 (0.6-1.0)
				High grade prostate cancer (Gleason 8-10)	
				Male factor infertility	2.0 (1.2-3.0)
No Male factor infertility	0.8 (0.5-1.3)				
Swerdlow et al (2005)	Retrospective cohort (All Klinefelter syndrome)	All types (selected)	3,518		
		Lung		1.4 (1.0-1.9)	
		Breast		19.2 (5.2-49.2)	
		Prostate		0.2 (0.02-0.7)	
		NHL		2.0 (0.8-3.9)	
Eisenberg et al (2013)	Retrospective cohort	All types	2,238	All infertile men	1.7 (1.2-2.5)
				Azoospermic (451)	2.9 (1.4-5.4)
				Non-azoospermic (1,787)	1.4 (0.9-2.2)
				<50 year old azoospermic (419)	3.7 (1.7-7.0)

SIR: Standardized incidence ratio
 CI: Confidence interval
 NHL: Non-Hodgkins Lymphoma

Jacobsen et al collected information from a large Danish cohort of 32,442 men. In this group, semen analysis showed 29,177 men had some sperm, 2,675 were azoospermic, and 590 men had no data regarding semen characteristics. Jacobsen found that men who presented as a couple for infertility were more likely to develop testis cancer than those of the general Danish male population (SIR 1.6; 95% CI 1.3–1.9). Within the cohort, there were 89 cases of testis cancer, with seminomas being the most common (50 patients). The highest risk for developing cancer was in the first two years after semen analysis, with an SIR of 1.8 (95% CI 1.1–2.7). SIR for developing cancer was highest when stratifying men by measures of semen quality, such as low semen concentration, poor semen motility, and higher number of abnormal sperm morphology. Men with lower sperm concentrations (0–20 x 10⁶ ml) had higher risk of testis cancer (SIR 2.3; 95% CI 1.6–3.2) than those with higher sperm concentrations (>20 x 10⁶ ml) (SIR 1.1; 95% CI 0.8–1.5). Azoospermic men who had no children before analysis had a higher risk of testis cancer (SIR 3.5) when compared to azoospermic men who had children in the past (SIR 2.0). Predictably, the risk of testis cancer was increased as the patient had an increasing number of subfertility measures—up to SIR 9.3 if there were three subfertility measures present (low concentration, poor motility, and abnormal morphology).

This study supports the idea of a possible common etiologic factor for low semen quality and risk of testis cancer. This is a robust level 2b retrospective cohort study of prognosis with a large sample size. This study eliminated some of the flaws in prior studies by using actual measurable semen parameters in which we can make comparisons. A potential weakness of the study is the fact that the overall analysis included some fully fertile men in which only the female partner was infertile. The authors claim the observed risk of testis cancer would undoubtedly become even higher if these men were excluded. Another weakness is that the study only recorded the first cancer of any origin, potentially missing urologic cancers that developed later in life. As will be discussed later, the authors raised the suggestion that testis cancer has origins in fetal life.^{15,16}

Infertility and Testis Cancer in an American Cohort

As the association between male infertility and cancer was receiving greater attention, Walsh et al hypothesized similarly

in a US-based cohort.⁶ It was unclear if results from European cohorts could be applied to the US population, because testis cancer has nearly twice the incidence in some Scandinavian countries.^{6,7} The other existing US-based studies have given conflicting results and are weakened by a limited number of patients, study design flaws, and usage of surrogate markers for infertility in lieu of a formal infertility evaluation.

Information on couples evaluated for infertility between 1967 and 1998 were obtained from 15 California infertility centers. The males in the couple were linked to the California Cancer Registry, which holds information on all cases of histologically confirmed cancers. Incidence of testis cancer in this cohort was compared with an age-matched sample of men from the general California population, using the Surveillance Epidemiology and End Results Program (SEER). Men diagnosed as having cancer before infertility evaluation, and if cancer was diagnosed within one year after infertility evaluation, were excluded. This was done primarily because the investigators were uncertain if the cancer itself or subsequent treatments were responsible for the infertility. Couples not actively trying to conceive were also excluded. Data were presented as SIR and 95% CI. Using the Cox proportional hazards, a regression model risk for testis cancer in men with and without male factor infertility was calculated.

This was a large multi-institutional cohort of 51,461 couples seeking treatment at infertility clinics in California. Since care was primarily focused on the female, only 42,274 men with identifying information were used, and complete demographics were found for only 22,562 of these men, which comprised the final cohort. Using this US-based cohort, presence or absence of male factor infertility was known for 19,106 men. Of these, 4,549 had male factor infertility as defined by the combination of physician decision and World Health Organization (WHO) criteria. There were 14,557 men without male factor infertility and the remainder had no data recorded. Baseline characteristics of men with and without male factor infertility were overall similar. There were a larger proportion of men with male factor infertility that developed testis cancer, compared with those without male factor infertility (0.3% and 0.1%, respectively). A total of 34 cases of testis cancer occurred at least one year after beginning infertility evaluations with 5.6 years as the mean time from evaluation to cancer diagnosis. When comparing the 34 cases to the expected 25 cases of testis

cancer, it was found that males as part of an infertile couple were 1.3 times more likely to develop testis cancer, regardless of male fertility status (SIR 1.3; 95% CI 0.9–1.9). Of the men with male factor infertility, 13 cases of testis cancer were observed, when only 5 were expected (SIR 2.8; 95% CI 1.5–4.8). Interestingly, men without male factor infertility had no significant evidence of increased cancer risk when compared to general California population (SIR 1.1; 95% CI 0.6–1.7). Using Cox proportional hazards regression models, and controlling for age, duration of infertility treatment, and location of infertility treatment center, men with infertility had 2.8 times the risk of developing testis cancer, compared to those without male factor infertility (HR 2.8; 95% CI 1.3–6.0).

This large level 2b study suggests male factor infertility may be a risk factor for developing testis cancer. Despite differences in incidences of cancer between the US and Danish populations, Walsh et al were able to find support for Jacobsen's study with a similar risk of developing testis cancer in males with infertility. One weakness of this study is that, unlike the Jacobsen cohort, there were no data on sperm characteristics, so we cannot say with complete certainty which factors strongly contributes to cancer development. Another potential weakness is that the recording of infertility evaluations started accruing before cancer registry began collecting information. The potential for cancers to be missed because they developed before inception of cancer registry remains. Thus cancers that were diagnosed before the registry existed were never accounted for, and these patients might have been falsely labeled as never developing cancer. This would decrease the number of cancers identified and the risk of cancer might be even higher than what was found in this cohort. High socioeconomic status is a known risk factor for testis cancer, and this status may also be the reason why individuals seek an infertility evaluation in the first place, thereby increasing the odds of diagnosing a cancer.¹⁷ But it is also important to consider that it is unlikely that being exposed to infertility care increases one's odds of being diagnosed with a testis cancer. The idea that male infertility treatment was the cause of subsequent cancers is unlikely, because oftentimes the male component is bypassed in the infertility evaluation of the couple. A more plausible idea is that there is a common exposure underlying both infertility and testis cancer. One theory proposed by the authors suggests that some forms of male infertility can be associated with defects of DNA repair, which is also associated with tumorigenesis.^{18–21} Skakkebaek

et al. proposed this testicular dysgenesis syndrome. This takes the biologic approach one step further by incorporating adverse environmental influences into the equation to support a new concept that infertility and cancer might be originating from a single underlying entity.²¹ These theories are unproven and the authors call for more research to further elucidate an underlying mechanism.

Infertility and Prostate Cancer

Working on the hypothesis that male infertility may be a risk factor for developing cancers, Walsh investigated infertility and its possible link to prostate cancer.²² Prostate cancer is the most commonly diagnosed cancer in men. The most common risk factors include age, family history, and race, but the cause still remains poorly understood.²³ It has been reported that fatherhood status may be a potential risk factor for prostate cancer, but various studies looking into this have been inconclusive.^{24,25} Some studies have shown that men without offspring were less likely to be diagnosed with prostate cancer, compared to men with offspring. The study also found that, among men with children, cancer risk was highest among those with fewest children, and that risk decreased with each additional child.²⁴ On the other hand, other studies show no association between prostate cancer and fecundity.^{26,27} The major flaw with these reports was the usage of surrogate markers for infertility in absence of a thorough fertility evaluation. These studies are hard to interpret because these patients can be childless due to lack of opportunity, choice, female infertility or true male factor infertility. Walsh used the same cohort of men presenting for infertility evaluation as in the prior study and studied the risk of prostate cancer.⁶ Using similar methods as the previous article, they used an age-and geography-matched sample of men from the general California population to determine risk of prostate cancer in men with and without male factor infertility. Male factor infertility was defined based on 1999 WHO semen guidelines and was coded by the treating clinician as a dichotomous variable (yes/no).

A total of 168 cases of prostate cancer that occurred at least one year after infertility evaluation were identified. Most of them were adenocarcinomas (97%, 163 patients). Most cohort members had a Gleason score of ≤ 7 (Gleason 5–7) (defined as low-grade prostate cancer) being the most common. The remainder of individuals was classified as high-grade prostate cancer (Gleason 8–10). Median time from infertility evaluation

to cancer diagnosis was 11 years. There were 185 expected cases of prostate cancer, but only 168 were identified in this study. This seems to suggest that men evaluated for infertility were not at an increased risk of cancer, compared to the general population, (SIR 0.9; 95% CI 0.8–1.1). Men with male factor infertility had a particularly elevated risk for high-grade prostate cancer. Men with male factor infertility had an SIR of 1.3 (95% CI 1.0–1.7) for all-grade prostate cancers, SIR 1.2 for low-grade cancer (95% CI 0.8–1.6), and SIR 2.0 (95% CI 1.2–3.0) for high-grade prostate cancer. In men without male factor infertility, there was a lower risk of developing any grade prostate cancer. Using Cox proportional hazards regression analysis, men with male factor infertility were found to be 2.8 times more likely to develop any prostate cancer, compared to those without male factor infertility (HR 2.8; 95% CI 2.0–4.0). If controlling for age, duration of infertility treatment, and infertility treatment facility, men with male factor infertility were 1.8 times more likely to develop prostate cancer, compared to those without male factor infertility (95% CI 1.2–2.5). If stratifying by grade of cancer, men with male factor were 1.6 times (95% CI 1.0–2.4) more likely to be diagnosed with prostate cancer with Gleason score 5–7 cancer, and 2.6 times (95% CI 1.4–4.8) more likely to be diagnosed with prostate cancer with Gleason score 8–10 cancer. Age was found to be the strongest independent predictor of developing prostate cancer, with each additional year increasing the risk of developing cancer by 10%.

This study proposes that male infertility is an early identifiable risk factor for the subsequent development of high-grade prostate cancer and suggests a link between infertility and development of a second genitourinary cancer. The authors of this paper recognized some possible biases and confounders. Those seeking evaluation for infertility might have a higher likelihood of prostate cancer diagnosis due to greater chances of seeking medical care and improved access to care.²⁸ Men with male factor infertility will thus have a higher likelihood of urological evaluation and subsequent prostate cancer screening. In addition, this study did not break down the groups into individual Gleason scores. Many who currently treat prostate cancer would argue that this breakdown does not address clinically significant versus clinically insignificant prostate cancers. The results here are consistent with findings of Jorgensen et al that found decreased prostate cancer risk with increasing paternity.²⁴ In this study the results show that

those who are sub-fertile or demonstrate decreasing paternity have an increased risk of prostate cancer. The difference between these studies is that the Jorgensen study was not able to account for the patient's pregnancy intent, while patients in this cohort were being evaluated for infertility and actively attempting to conceive. Walsh et al. explain the results on the basis of a common exposure underlying both male infertility and prostate cancer. The Jerusalem Perinatal Study of men who had stillborn offspring and who had decreased paternity were found to have increased risk of developing prostate cancer.²⁹

Other studies have shown that the Y-chromosome may be implicated in both male infertility and prostate cancer. Certain micro-deletions and differential expression of Y chromosome genes may play a role in the development of infertility and prostate cancer.³⁰ Among all who developed prostate cancer, those with the fewest sons had the highest risk of disease-specific mortality. Another common exposure might be in the form of DNA repair defects. These repair defects have been shown to be associated with male infertility. Faulty DNA repair has been implicated in tumorigenesis, especially prostate cancer.^{20,31} The authors call for further research into the biological pathways that may link male infertility and prostate cancer.

Infertility and General Oncological Development

A study by Swerdlow et al further supported the idea of an association between infertility and cancer development.³¹ This study in particular looked at cancer incidence and mortality in men with Klinefelter syndrome. Men with this syndrome typically have one extra X-chromosome and exhibit an array of endocrine abnormalities.³² Hypogonadism is a predominant feature in these patients, with other physical, hormonal, and developmental abnormalities. Case reports have suggested that men with this disorder have increased risk of certain cancers, but the lack of large cohort studies has limited the data regarding cancer risk in these individuals. As seen in prior studies and case reports, Klinefelter patients have elevated risk of breast cancers, teratoma, and other cancers.^{33–35} The need for a larger cohort was evident in order to better understand cancer incidence and mortality from a larger group of men with Klinefelter syndrome.

The investigators collected data from 27 cytogenetic labs in

Great Britain on patients with Klinefelter syndrome, from a population of more than 50 million over a period of 44 years. Individuals were excluded if they had a pre-existing cancer. Beginning with 4,806 patients with Klinefelter syndrome, a cohort of 3,518 men remained after various exclusion criteria, such as insufficient patient information and those who had Down syndrome. These patients were then linked to various population registers to collect demographic data. This cohort of 3,518 cytogenetically diagnosed men with Klinefelter had their cancer incidence and mortality compared against men in a national register using SIRs.

Most of these patients were of the 47,XXY karyotype and most were diagnosed between the ages of 15 and 44 years. After accounting for deaths, emigration, and loss to follow up, 2,970 cohort members were followed to the end of the study period. SIR for all cancers was 0.9 (95% CI 0.7–1.1), which is not statistically significantly increased, compared with the general population. But when broken down by individual cancer, men with Klinefelter syndrome had higher incidence for lung (SIR 1.4; 95% CI 1.0–1.9), breast cancer (SIR 19.2; 95% CI 5.2–49.2), and non-Hodgkin lymphoma (SIR 2.0; 95% CI 0.8–3.9); however these men exhibited lower incidence for prostate cancer (SIR 0.2; 95% CI 0.02–0.7).

This study showed that men with Klinefelter had higher incidence of some malignancies like breast, lung, and non-Hodgkin's lymphoma but decreased incidence of prostate cancer. Klinefelter men have substantially decreased androgen levels and increased estradiol levels up to twice that of normal men. This may explain why breast cancer risk among men with Klinefelter is so high. Klinefelter patients have significantly decreased levels of androgens, which have been shown to have a negative influence on fertility. Limitations to this study include that the authors did not include all cases of Klinefelter, only those identified via cytogenetic registers. The prevalence at birth is 1 in 1,000 male births, giving us an expected 350 cases born each year, but in this study, only about 100 cases of Klinefelter syndrome per year were diagnosed, thus only a minority of cases reached cytogenetic diagnosis.

Risk of Cancer in Azoospermic Men

Azoospermia occurs in 15% of infertile men and about 1% of all men in the United States. Azoospermia can further be divided into non-obstructive azoospermia and obstructive

azoospermia, with the former being most common. As noted, idiopathic non-obstructive azoospermia is thought to arise from defects of spermatogenesis, suggesting a genetic basis for disease. Defects of DNA repair and gene alterations have been shown to occur in high frequency in these azoospermic men.¹⁸⁻²¹ Similar defects are now thought to contribute to cancer development. Is there an elevated risk of developing cancer in these azoospermic men? All prior studies reviewed in this paper did not isolate and study patients based on their azoospermic status. In light of these questions, Eisenberg et al examined whether men with azoospermia have an elevated risk of cancers.³⁶

This was a cohort study of men presenting for an infertility evaluation in Texas between 1989 and 2009. From this group, azoospermic men were linked to the state cancer registry to measure cancer incidence in the years following an infertility evaluation. There were 22,089 patients identified with semen data from 1989 to 2009. However, the cancer registry only collected data from 1995 to 2009, so a significant portion of patient data were not used because of this truncation. After excluding patients due to patient migration, history of vasectomy, evaluation for reasons other than infertility, and cancer diagnosis within 6 months of initial semen analysis, only 2,238 men composed the final cohort. Once again the authors used SIRs and analysis was performed on the entire cohort and as a subgroup of men with or without azoospermia. There were 451 men (20%) in this cohort evaluated for infertility and identified as having azoospermia, while the remaining 1,787 men did not have azoospermia. Mean age at infertility evaluation was 35.7 years, and no significant differences were seen among the two groups. Common etiologies of non-obstructive azoospermia include idiopathic, Y-chromosome deletion, abnormal karyotype, and varicocele, while common etiologies of obstructive azoospermia include congenital absence of vas deferens and prior vasectomy. The results show that infertile men had a 70% higher risk of cancer than the general Texas population. There was 29 cases of cancer observed when they expected only 16.7 cases in infertile men (SIR 1.7; 95% CI 1.2–2.5). When stratifying by azoospermic status, these men had an almost 300% higher risk of cancer than the general Texas population (SIR 2.9; 95% CI 1.4–5.4). Infertile men without azoospermia had a trend towards higher rate of cancer (SIR 1.4; 95% CI 0.9–2.2). Using Cox regression analysis, they showed that azoospermic men had a 2.2 higher

risk of cancer than non-azoospermic men. On subgroup analysis, the authors looked at men aged under 50 years, when most reproductive efforts occur. Young azoospermic men had higher risk of cancer, (SIR 3.7; 95% CI 1.7–7.0). While young non-azoospermic men had a trend towards higher risk (SIR 1.6; 95% CI 0.9–2.5). Various cancers were recorded, ranging from brain, central nervous system, prostate, testicular, melanoma, lung, and thyroid. Of the 29 patients who developed cancer, 7 were prostate cancers and 2 were testicular cancers. This study was unique in that it demonstrated that not only urologic cancers are more frequently seen in patients with infertility, but non-urologic cancers can also be present. The most common cancers were prostate, testicular, and central nervous system malignancies. Some proposed mechanisms will be discussed later in the review. Some limitations do exist in this study. Similar to prior papers, only the first cancer diagnosis was included, thus possibly missing future cancers. There were also a significant amount of exclusions implemented limiting the cohort size. However, this would affect data equally for both azoospermic and non-azoospermic patients. Some patients were falsely labeled as azoospermic, when in fact they had a history of vasectomy, a fault the authors did acknowledge. Detection bias can also play a role in this study, possibly contributing to greater medical care in those seeking fertility evaluation. Although relative risk of cancer development between azoospermic and non-azoospermic men is significant, the absolute risk of developing cancer is still very low.

Possible Mechanisms of Cancer Development

In a subsequent review by Walsh, various mechanisms behind infertility and cancer were discussed.³⁷ It is now widely believed that male reproductive failure may precede testis and prostate cancer. Male infertility as an early indicator for the development of future urologic cancers needs to be further explored. Future research should also focus on the exact mechanisms and pathways that lead us from infertility to oncologic development. Ongoing studies have shown the Y-chromosome to be involved in both prostate cancer and fertility because it contains specific genes involved in the development of genitourinary cancers and spermatogenesis.^{29,38} Y-chromosome micro-deletions are an uncommon, but known, genetic cause of male infertility.³⁹ Theoretically, a Y-chromosome locus might be responsible for failure to father male offspring and for developing prostate cancer.^{29,38–45} Harlap et al. found that absence of male offspring resulted in a 40%

increased risk for prostate cancer (RR 1.4, 95% CI 1.04–1.91).²⁹ Other studies have found no such association.^{46,47}

Multiple other proposed mechanisms underlie impaired male reproductive health and the development of prostate cancer. Androgen production and sensitivity has been implicated as a common etiologic factor for both infertility and prostate cancer because of its influence on testicular and prostatic tissues. The testicular dysgenesis syndrome is interesting in that it encompasses environmental factors, genetics, hormones, and infertility to the development of cancers.²¹ This theory posits that exposure to toxins and underlying genetic predispositions are responsible for developing disorders like cryptorchidism, hypospadias, and infertility. As a result of abnormal gonadal function, androgen sensitive organs like the prostate may not receive adequate signals during development; this abnormal development is believed to predispose people to an increased risk of developing future cancer of the prostate.^{48,49} Variations in number of CAG repeats in genes that code for androgen receptors have been described in association with both male infertility and prostate cancer. Long stretches of CAG repeats may be associated with derangement of sperm production; however, these data have not been reproducible.^{50–53}

Epigenetics is a method by which environmental exposures such as gonadotoxins and drugs can influence fertility and cancer risk. Epigenetic processes such as DNA methylation and histone deacetylation have been shown to suppress gene expression and have detrimental influences on spermatogenesis. Rajender et al found that epigenetic changes are associated with poor semen quality and similar changes have been seen in the development of prostate cancer.^{54,55} Methoxychlor and vinclozolin are examples of chemical compounds that have been shown through epigenetic modification to cause defects of spermatogenesis and poor prostate health.⁵⁶ Of significant interest are the environmental toxins that mimic the effect of estrogens such as phytoestrogens and xenoestrogens. Exposure to these endocrine disruptors can cause reproductive toxicity, manifesting as cryptorchidism, hypospadias, decreased semen quality, and impaired fertility.⁵⁷ The prostate gland is very hormonally sensitive; there is increasing evidence that endocrine disruptors might impact prostate cancer risk through interference with estrogen signaling and altered estrogen levels. During development, there is increased sensitivity of these compounds in the prostate, making them vulnerable to such disruptors.^{58,59}

Conclusion

Great advances have been made in elucidating the pathways that may connect male reproductive health and future risk of genitourinary cancers. As we further evaluate the connection between infertility and cancer risk, we can better serve our patients by identifying these risk factors. Although the data are presently evolving, it is possible that male factor infertility is a surrogate marker for subsequent development of testicular and prostate cancer. There seems to be certain genetic pathways that may be able to link male infertility and subsequent cancer risk. At present, only Grade C evidence based on level 2b quality studies exists to answer these questions. Better-defined longitudinal studies following male factor infertility patients will better answer this question.

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