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Urologic Conditions Associated with Malignancy

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Abstract

Introduction: Recent advances in cancer research have highlighted the role of genetics in the malignancy. Genetic dysregulation of core cellular functions similarly influences benign conditions. These common genetic factors have led researchers to identify an association between certain urologic conditions and malignancy. The objective of this review is to evaluate the literature linking benign urologic conditions including male infertility, Peyronie's disease, cryptorchidism, and hypospadias, to malignancy.

Methods: A search of PubMed was performed using the following search terms and their combinations: male infertility, female infertility, cancer, malignancy, mortality, male urologic conditions, azoospermia, Peyronie's disease, cryptorchidism, hypospadias, and genetics. Studies were assessed for quality and included or excluded based on study design and relevance to the topic of urologic conditions and malignancy.

Results: A total of 52 studies were evaluated, of which 38 were included. Associations between male infertility and testicular cancer, prostate cancer, and other cancers including melanoma, bladder cancer, and thyroid cancer were examined. Several genetic alterations were found to be common in the pathogenesis of both male infertility and carcinogenesis. Associations between female infertility and breast, ovarian, and endometrial cancer are also assessed, as are the relationships between Peyronie's disease, cryptorchidism, and hypospadias and malignancy.

Conclusions: Recent work has identified associations between a number of malignancies and benign urologic conditions including male infertility, Peyronie's disease, cryptorchidism, and hypospadias. Molecular and genetic mechanisms have been proposed, but no definitive causal relationships have been identified to date. Future work will continue to better define the links between malignancy and benign urologic conditions and ultimately facilitate risk stratification, screening, and treatment of affected men.

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Keywords

Male infertility; testicular cancer; prostate cancer; Peyronie's disease; cryptorchidism; hypospadias

Introduction

Cancer affects approximately 36.9% of men and women during their lifespan, and recent advancements in cancer research have continued to support the strong influence of genetics as a key factor in the development of malignancy [1]. Genetic dysregulation in the setting of malignancy often impacts core cellular functions that lead to dysfunctional cell differentiation and growth. These functions, when abnormal, may also lead to benign disease such as heart disease, inflammatory bowel disease, male infertility, and other urologic conditions [1–4]. It is likely that the same genetic defects that predispose to malignancy may influence the development and progression of at least some of these benign conditions. In fact, recent genetic studies have revealed several common genetic factors between benign and malignant urologic conditions, including infertility, Peyronie's disease (PD), cryptorchidism, and hypospadias [1, 5, 6].

Infertility affects up to 15% of couples, with a male factor solely responsible in approximately 20% of infertile couples and contributory in another 30%–40% of couples [7]. Recent work has linked a number of urologic conditions, including male infertility, to increased cancer risk [8, 9]. Studies have identified genetic factors that may predispose to the development of malignancy in the setting of male factor infertility, PD, cryptorchidism, hypospadias, and benign prostatic hyperplasia (BPH) [1, 4, 10–13]. A large number of cancer-associated genes have been identified that are involved in regulatory processes of cell growth and differentiation and thus affect both benign and malignant processes. Examples include oncogenes that promote progression of cell growth such as the androgen receptor (AR), rearranged during transfection (RET), and thyroid stimulating hormone receptor (TSHR) genes, as well as tumor suppressor genes such as Wilms tumor 1 (WT1), cyclin-dependent kinase inhibitor 2A (CDKN2A), retinoblastoma (RB1), and SMAD Family Member 4 (SMAD4) [1]. The AR is involved in androgen insensitivity syndrome, WT1 is critical in the process of male sex determination, RB1 and RET are vital in the maintenance of undifferentiated spermatogonial stem cells, and SMAD4 is partly responsible for the regulation of Sertoli and Leydig cells in the testes [1]. Disruptions in the functions of these genes can result in benign disease such as infertility, as well as dysregulated cell growth and possibly consequent malignancy.

Recent work has identified male factor infertility as a biomarker for testis and prostate cancer [14, 15]. Male infertility has been linked to other cancers including melanoma, bladder cancer, thyroid cancer, Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), and leukemia, as well as increased cancer risk in family members [8, 9]. Investigations into genetic bases and epigenetic influences has also shown a connection between male infertility and cancer [1, 16]. Several other urologic conditions have also recently been linked to cancer including PD, cryptorchidism, and hypospadias. While most

of these relationships are based on clinical associations, related genetic factors that contribute to each of these conditions provide a potential bridge between these conditions. Understanding these associations in the context of continued advancements in research will ultimately assist urologic oncologists with risk stratification, screening, and treatment of affected men. In this review, we provide a narrative of urologic conditions associated with cancer, and highlight mechanistic aspects of these conditions that may help explain the relationship between these conditions and malignancy.

Methods

A search of the PubMed database was performed using the following search terms and their combinations: male infertility, female infertility, cancer, malignancy, mortality, male urologic conditions, azoospermia, Peyronie's Disease, cryptorchidism, hypospadias, and genetics. Studies were included if they were systematic reviews, published abstracts, or hypothesis-driven studies including randomized controlled trials, case-control studies, or cohort studies with at least 100 subjects. Inclusion criteria additionally included the requirement of addressing male or female infertility, benign urologic conditions, or genetics and epigenetics in the context of urology. Studies were excluded if they were not written in English or did not meet the above inclusion criteria. A total of 56 studies were evaluated and 38 included in the review.

Male Infertility and Cancer

The first study linking male infertility and general health was published in 1994 [17]. Honig, Lipshultz, and Jarow examined a cohort of 1,236 men presenting for infertility evaluation at 2 institutions and observed that these men had a higher frequency of medical pathology – testicular tumors, brain tumors, spinal cord tumors, ejaculatory dysfunction due to mesonephric duct anomalies, and Klinefelter's syndrome – compared to the general population. Kolettis and Sabanegh found similar results when examining a cohort of 536 men, further supporting a role for male infertility as a marker for general health [18]. The authors found significant medical pathology – cystic fibrosis mutations, testis cancer, prostate cancer, diabetes mellitus, and hypothyroidism – in 33 out of their 536 patients (6%).

Recent studies have built upon this connection and identified a relationship between male infertility and cancer, which to date remains the strongest association between urologic disease and malignancy. While the associations between testicular and prostate cancer have been the most extensively studied, other cancers including melanoma, bladder and thyroid cancer, Hodgkin's and non-Hodgkin's lymphomas, and leukemias also occur at higher rates in infertile compared to fertile men (Table 1).

Testicular Cancer

Testicular cancer is a relatively uncommon cancer overall, constituting 1–2% of all tumors in men, though it is the most common solid malignancy in males 15–34 years old [19]. Although the incidence of testicular cancer has increased over the last several years, the mortality rate has continued to decrease as a result of advances in chemotherapy and

multidisciplinary management regimens [20]. In fact, testicular cancer is mostly curable with a 5-year survival rate for all stages of testis cancer of 96.6% [21].

Among infertile men, rates of testicular cancer are higher than in fertile men. Hanson et al. performed a retrospective cohort study evaluating semen analyses and observed that oligozoospermic men had an increased risk of testicular cancer compared with fertile control subjects with a hazard ratio (HR) of 10.3 (95% CI 4.1–26.2) [Table 1] [22]. Møller and Skakkebaek used paternity status as a surrogate for fertility and observed that men who had fathered a child or initiated a pregnancy had a significantly decreased risk of developing testicular cancer with an odds ratio (OR) of 0.63 (95% CI 0.47–0.85) [23]. Walsh et al. obtained data from 15 California infertility centers and linked these data to the California Cancer Registry, ultimately examining a cohort of 22,562 men (4,549 with male factor infertility, 14,557 with no male factor infertility, and 3,456 with unknown male fertility status) [14]. The authors found that men seeking infertility treatment had an increased risk of developing testicular cancer with a standardized incidence ratio (SIR) of 1.3 (95% CI 0.9–1.9). An even higher risk of testicular cancer (SIR of 2.8, 95% CI 1.5–4.8) was identified in men with known male factor infertility. In a related study, Eisenberg et al. analyzed the Truven Health Analytics MarketScan® database and compared cancer risk in 76,083 infertile men to 760,830 controls, finding that infertile men had a higher risk of testicular cancer (HR of 1.99 (95% CI 1.47–2.70)) [9].

Proposed mechanisms that could potentially explain the link between male infertility and the development of testicular cancer include genetic alterations in the sex-determining region of the Y chromosome (SRY) gene, which is essential for testicular development (Figure 1) (Table 2) [24]. Specifically, SRY gene expression during the fifth to seventh week of gestation promotes differentiation of the primary gonad into a primitive testis [25]. In the absence of SRY, an ovary develops. Consequently, mutations in SRY are thought to cause both gonadal dysgenesis and tumor development [24]. The tumor suppressor gene p53 is believed to be involved in these processes as well. [26]. Important in tumor prevention and genomic stability, p53 is vital for meiosis within primary spermatocytes. Mutations may lead to chromosomal and genetic instability that increase the probability of cancer cell development [26, 27]. Structural chromosomal defects such as amplification of the 12p region, specifically isochromosome (i(12p)) formation, have been linked to invasive testicular germ cell cancer (TGCC) and impaired spermatogenesis [26, 28]. Copy number increases in the 17q region have also been associated with TGCCs: gain of the proximal region 17q11-q21 with nonseminomas and gain of the distal region 17q24-qter common to all TGCCs [29]. These increases in DNA copy number likely demonstrate the common mechanism of gene overexpression and consequent promotion of neoplastic and malignant cell behavior. Ultimately, a relationship between infertility and subsequent development of testicular cancer presents an opportunity for improved clinical outcomes. As the relationship between infertility and testicular cancer becomes more clearly defined, and we understand the causal molecular and genetic factors that result in these conditions, early risk stratification based on genetic and clinical data, with subsequent early detection or prevention will become feasible. This route of preventative care may result in cost savings as potential testicular malignancy is discovered and acted on earlier or before it occurs at all [30].

Prostate Cancer

Prostate cancer is the most common malignancy in men, with an estimated 161,000 cases in the United States in 2017 [31]. Established risk factors include age, ethnicity, and family history, but recent studies have found that male infertility is also a risk factor [32]. Jørgensen et al. used fatherhood as a surrogate for male fertility and demonstrated a decreasing prostate cancer risk among fathers with an increasing number of children [33]. Walsh et al. used the previously described cohort of 15 California fertility centers with patients linked to the California Cancer Registry and observed a higher risk of developing high-grade prostate cancer (SIR of 2.0, 95% CI 1.2–3.0) in these men [15]. Notably, men evaluated for infertility but who were not necessarily infertile were not found to be at increased risk of prostate cancer (SIR of 0.9, 95% CI 0.8–1.1). Eisenberg et al. utilized the Truven Health Analytics MarketScan® database and compared cancer risk in 76,083 infertile men compared with 760,830 controls, finding that infertile men had a higher risk of prostate cancer compared to controls (HR of 1.78 (95% CI 1.41–2.25)) [9].

While Jørgensen et al. found that fathering children decreased prostate cancer risk, Walsh et al. and Eisenberg et al. used more direct assessments of infertility to find an association between infertility and prostate cancer risk. A number of mechanisms have been proposed to explain this linkage, including CAG repeats in the AR, prostasomes, and DNA mismatch repair [34]. Mosaad et al. found a negative correlation between AR CAG repeat length and sperm count, suggesting that longer stretches of AR CAG repeats may be associated with dysfunctional sperm production via decreased AR function [35]. Neto et al. found an increased prostate cancer risk in subjects with shorter CAG repeat lengths, hypothesizing that the shorter CAG repeat lengths are associated with higher transcriptional activity and consequently are linked with higher prostate cancer risk [36]. Prostasomes, small vesicles produced by the epithelial cells of the prostate acini, transfer proteins to sperm to modulate motility and function and aid in protection of the sperm within the female reproductive system [37]. Notably, the same properties that help prostasomes promote sperm function may also increase the risk of prostate cancer. One hypothesis is that the phosphorylation of proteins found on the prostasome surface may also be responsible for the phosphorylation and dephosphorylation of proteins critical to cell proliferation and malignant transformation pathways. The DNA mismatch repair gene PMS1 homolog 2 (PMS2) has been linked to infertility and increased risk for prostate cancer. Impaired mismatch repair function allows mutations to accumulate that disrupt normal cellular processes and lead to genomic instability and consequent spermatogenic failure and cancer development [38, 39].

Other Cancers

While previous work identified relationships between male infertility and testis and prostate cancer, other malignancies may also be linked to male infertility. In the same study used to identify links to testicular and prostate cancer, Eisenberg et al. found significantly increased risks of melanoma (HR 1.37, 95% CI 1.06–1.77), bladder cancer (HR 2.29, 95% CI 1.49–3.50), thyroid cancer (HR 1.52, 95% CI 1.01–2.30), Hodgkin's lymphoma (HR 1.67, 95% CI 1.04–2.67), non-Hodgkin's lymphoma (1.76, 95% CI 1.39–2.23), and leukemia (HR 1.82, 95% CI 1.29–2.59) in infertile men compared to controls [9]. In the same retrospective cohort study that linked oligozoospermia to testicular cancer, Hanson et al. found that

hyperzoospermic men – men with sperm concentrations and counts in the 90th percentiles of the distribution – had double the risk of melanoma compared to normozoospermic men (HR 2.7, 95% CI 1.4–5.3) [22]

The above associations remain to be confirmed and underlying mechanisms more clearly elucidated to determine how these conditions are associated. Current proposed mechanisms are similar to those identified in testicular and prostate cancer and include defects in DNA mismatch repair genes and epigenetic modifications such as the aforementioned PMS2 gene, a mismatch repair gene which leads to infertility characterized by meiotic arrest and cancer due to mutation accumulation and genomic instability [40]. One proposed epigenetic modification gene is HIWI, a gene found on chromosome 12, expressed in germline cells, and believed to regulate stem cell self-renewal, gametogenesis, and RNA interference [40]. The gene is essential to the asymmetric division of germline stem cells and the production and maintenance of daughter stem cells. The HIWI locus (12q24.33) displays a genetic linkage to the development of TGCC and thus it is believed that HIWI can predispose to both male infertility and malignancy.

Additionally, male factor infertility is associated with increased familial cancer risk. A 2016 study by Anderson et al. found that first-degree relatives of men who received a semen analysis for infertility evaluation had a 52% increased risk of testicular cancer when compared with the first-degree relatives of fertile control men [41]. A second study by Anderson et al. in 2017 demonstrated that the siblings and cousins of subfertile men had a twofold increased risk of childhood cancer and threefold increased risk of acute lymphoblastic leukemia compared to the siblings of fertile control men [42].

Proposed Mechanisms

While no molecular mechanisms have causally linked male infertility to any associated malignancies, it is likely that there are numerous genes that regulate male fertility that, when altered, could result in increased risk for one or more malignancies. More than 1,500 genes are thought to contribute to spermatogenesis, and defects in one or more of these may facilitate the cellular growth and proliferation that results in malignancy [8]. For example, mutational defects in DNA repair affect meiosis and mitosis and consequently the processes of both spermatogenesis and carcinogenesis, especially as oxidative stress-related DNA fragmentation is more frequent in subfertile men and can lead to decreased sperm motility and fertilization ability [1, 43–45]. Epigenetic modifications – DNA hypermethylation, imprinting, and histone modification – may also modify the relationship between infertility and cancer [16]. For example, methylation at promoters in the cancer genome has been identified in the RASSF1A (Ras-association domain family 1, isoform A) gene as well as in tumor suppressor genes and DNA repair genes such as MutL homolog 1 (MLH1), cyclin-dependent kinase inhibitor 2A and 2B (CDKN2A and CDKN2B), O-6-methylguanine-DNA methyltransferase (MGMT), glutathione S-transferase pi 1 (GSTP1), Werner syndrome ATP-dependent helicase (WRN), and breast cancer 1 (BRCA1) [46]. The histone methyltransferase EHMT2, which results in male infertility when ablated, can also function to epigenetically silence tumor suppressor genes via methylation of H3K9.

Lifestyle considerations may also predispose to both infertility and cancer. Obesity and smoking both negatively impact fertility, and both have strong data linking them to malignancy and mortality. Environmental exposures may also play a role in both infertility and cancer, as cytotoxic drugs and radiation can both damage the germinal epithelium. Environmental toxins such as phthalates, which can induce testicular dysgenesis *in utero*, have also been identified [40]. One study found that infants born to mothers taking exogenous hormones during pregnancy were more likely to develop testicular cancer (OR 4.9, 95% CI 1.7–13.9), suggesting an influence of hormone exposure [47].

Female Infertility and Cancer

Recently, female infertility has also been linked to malignancy. A recent literature review by Hanson et al. examined 26 studies and evaluated the relationship between female infertility and other comorbidities, including malignancy [48]. Results were conflicting for breast cancer, with seven studies showing no significant difference or contradictory evidence for an increased risk of breast cancer development in infertile women. In addition to these seven studies, one other study showed a lower risk of breast cancer in infertile women while another showed an increased risk of breast cancer in the setting of infertility [49–56]. The data for ovarian cancer are similarly controversial: only one of nine studies showed a clear increase in ovarian cancer risk in women with an infertility-associated diagnosis [57]. An association between infertility in women and endometrial cancer shows a more promising link. Four out of five studies found significant increases in endometrial cancer risk among infertility subgroups [49–51, 58]. The one study that did not identify an increased risk did not compare infertile and fertile women, but rather infertile women who underwent assisted reproduction and those who did not, ultimately finding a statistically insignificant result [56].

Other Urologic Conditions Linked to Cancer

Several other male urologic conditions have been associated with cancer, including PD, cryptorchidism, and hypospadias (Table 3).

Peyronie's Disease

Peyronie's disease is a progressive fibrosing condition of the penis defined by the formation of fibrous plaque within the tunica albuginea that can lead to penile curvature, shortening, narrowing, and pain [59]. The incidence of PD, which can be inherited in autosomal dominant fashion, is estimated at approximately 22.4 per 100,000 men [60, 61].

Recent studies have found an association between PD and benign disease. Pastuszak et al. utilized a Cox regression model adjusting for age, smoking, obesity, health care visits per year, urology visits per year, and years of follow-up on a cohort of 8,728 men with PD; 204,147 men with erectile dysfunction (ED); and 87,280 controls [59]. The authors found that compared to age-matched controls without ED or PD, men with PD had increased risks of developing benign prostatic hyperplasia (HR 3.37, 95% CI 3.21–3.53), prostatitis (HR 2.61, 95% CI 2.39–2.85), lower urinary tract symptoms (HR 2.58, 95% CI 2.39–2.85) and keloids (HR 1.56, 95% CI 1.16–2.11). Interestingly, all of these conditions are linked by the

common pathogenic pathway of abnormal myofibroblast activity. Thus, an intrinsic defect in myofibroblast activity could predispose to all of these conditions. Men with PD in this cohort also had a lower risk of hypertension (HR 0.76, 95% CI 0.72–0.81), hyperlipidemia (HR 0.78, 95% CI 0.73–0.82), diabetes mellitus (HR 0.68, 95% CI 0.60–0.77), renal disease (HR 0.76, 95% CI 0.59–0.97), and liver disease (HR 0.82, 95% CI 0.70–0.96) compared to men with ED and healthy controls.

Recent work has also linked PD and cancer. Pastuszak et al. analyzed data from the Truven Health Analytics MarketScan® claims database from 2007–2013 and identified 48,423 men with PD and 484,230 controls [5]. Men with PD had an increased risk of developing stomach cancer (HR 1.43, 95% CI 1.06–1.14), testis cancer (HR 1.39, 95% CI 1.05–1.84), and melanoma (HR 1.19, 95% CI 1.02–1.38). Genetic abnormalities contributory to PD such as duplication of chromosomes 7 and 8, Y chromosome deletions, and structural alterations such as reciprocal translocations of 46XY,t(11;12)(q11,p11), 46XY,t(1;5)(q25;q11), and inversion of 46XY,inv(7)(p22q36) may overlap with the Y chromosome abnormalities associated with cancer [4]. Similarly, a study showing blunted p53 response following irradiation of PD plaque-derived fibroblast cultures compared to normal tunica albuginea fibroblast cultures may reflect a mechanism similar to the dysfunctional p53 tumor suppressor function in cancer [62].

Cryptorchidism

Cryptorchidism is the most common congenital abnormality of the genitourinary tract with a rate of approximately 7% among male infants [63]. Schnack et al. assessed the risk of TGCC in patients with a history of cryptorchidism [6]. The authors evaluated 5,441 patients with TGCC and found that men born with cryptorchidism had an increased risk of developing TGCC with a relative risk (RR) of 3.71 (95% CI 3.29–4.19). This association is mostly believed to be the result of several insults, including genetic and environmental factors, that lead to a primary abnormality within the genitourinary system and subsequent irregular embryological and fetal development. For example, genetic susceptibility studies that identified increased risk ratios for twins, brothers, and offspring of affected fathers support a genetic contribution, while links to environmental factors such as early maternal exposure to diethylstilbestrol have also been identified [64, 65]. These studies, however, did not provide any specific genes that may influence these relationships.

Hypospadias

Hypospadias is also a common congenital anomaly, occurring in approximately 1 of 125 male live births [66]. Similar to their work on cryptorchidism, Schnack et al. also examined the association between hypospadias and TGCC in the same cohort of 5,441 patients with TGCC. The authors found that, similar to men with a history of cryptorchidism, men with a history of hypospadias had an increased risk of developing TGCC (RR 2.13, 95% CI 1.29–3.61) [6]. Factors ranging from genetics to environmental influences such as exposure to estrogenic or antiandrogenic chemicals *in utero* are thought to impact the development of hypospadias and subsequently TGCC.

Conclusion

Recent studies have identified relationships between malignancy and numerous urologic conditions including male infertility, PD, cryptorchidism, and hypospadias. While no definitive causal molecular or genetic mechanisms linking these conditions have been identified, it is likely that these conditions are linked via such mechanisms, and are likely further influenced by environment and lifestyle. Additional work to better define the molecular links between malignancy and benign urologic conditions is needed in order both better understand these relationships, as well as to facilitate risk stratification, screening, and treatment of affected men. As research continues to examine the relationships between these conditions and malignancies as well as their etiologies, a clearer picture on the best management strategy will undoubtedly be defined.

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Male Infertility & Cancer Development

Figure 1.
Male infertility and cancer development.

Table 1.**Male infertility and associated malignancies**

Cancer	Study	N	Findings
<i>Testicular cancer</i>	Hanson et al. [22]	20,433	Men with oligozoospermia demonstrate an increased risk of testicular cancer compared to fertile control subjects (HR = 10.3, 95% CI 4.1–26.2)
	Møller and Skakkebaek [23]	1,234	Men who had fathered a child or impregnated a women had a significantly decreased risk of developing testicular (OR = 0.63, 95% CI 0.47–0.85)
	Walsh et al. [14]	22,562	Men seeking infertility treatment had an increased risk of developing testicular cancer (SIR = 1.3, 95% CI 0.9–1.9) An even higher risk (SIR = 2.8, 95% CI 1.5–4.8) was identified in those with known male factor infertility
	Eisenberg et al. [9]	836,913	Infertile men had a higher risk of testicular cancer compared to controls (HR of 1.99 (95% CI 1.47–2.70))
<i>Prostate cancer</i>	Jørgensen et al. [33]	3,400	Childless fathers had a 16% reduced risk of prostate cancer compared with fathers with multiple children A significant trend of decreasing prostate cancer risk among fathers was found with increasing number of children.
	Walsh et al. [15]	168	Men with male factor infertility had a higher risk of developing high-grade prostate cancer (SIR of 2.0, 95% CI 1.2–3.0). Notably, men evaluated for infertility but not necessarily with male factors were not found to have a higher risk of prostate cancer (SIR of 0.9, 95% CI 0.8–1.1)
	Eisenberg et al. [9]	836,913	Infertile men had a higher risk of developing prostate cancer compared to controls (HR = 1.78, 95% CI 1.41–2.25)
<i>Other cancers</i>	Eisenberg et al. [9]	836,913	Significantly increased risks of melanoma (HR 1.37, 95% CI 1.06–1.77), bladder cancer (HR 2.29, 95% CI 1.49–3.50), thyroid cancer (HR 1.52, 95% CI 1.01–2.30), HL (HR 1.67, 95% CI 1.04–2.67), NHL (HR 1.76, 95% CI 1.39–2.23), and leukemia (HR 1.82, 95% CI 1.29–2.59) compared to controls
	Hanson et al. [22]	20,433	Hyperzoospermic men (sperm concentration and counts in the 90 th percentiles of the distribution) had double the risk of melanoma compared to normozoospermic men (HR 2.7, 95% CI 1.4–5.3)

Table 2.

Genes and their roles in carcinogenesis and male infertility.

Gene	Role in Carcinogenesis	Role in Male Infertility	Common Factors
<i>AR</i>	Shorter CAG repeat lengths are associated with higher AR transcriptional activity and consequent higher cancer risk	Longer stretches of AR CAG repeats may be associated with dysfunctional sperm production via decreased AR function	CAG repeat length associated with AR transcriptional activity
<i>PMS2</i>	Impaired DNA mismatch repair allows for accumulation of mutations and genomic instability, subsequent cancer development	Accumulation of mutations and genomic instability causes spermatogenetic failure	Mismatch repair disruption causes genomic instability
<i>HIWI</i>	Expressed in germ-line cells and governs stem cell self-renewal, gametogenesis, and RNA interference. HIWI locus 12q24.33 displays a genetic link to development of TGCC	Essential in division of germ-line stem cells and gametogenesis and thus can lead to male infertility	Gene critical in stem cell self-renewal and gametogenesis
<i>SRY</i>	Promotes differentiation of the primary gonad into a primitive testis, but when altered can cause gonadal dysgenesis and tumor development	Absence of SRY leads to formation of an ovary. Additionally, mutation of SRY leads to gonadal dysgenesis.	Gonadal dysgenesis
<i>p53</i>	Tumor suppressor gene that when mutated, leads to chromosomal and genetic instability and consequent cancer cell development	Vital for meiosis within primary spermatocytes	p53 important in meiosis and chromosomal and genetic stability

Table 3.

Other urologic conditions linked to cancer

Urologic condition	Study	N	Findings
<i>Peyronie's disease</i>	Pastuszek et al. [59]	300,155	Men with PD had increased risks of developing benign prostatic hyperplasia (HR 3.37, 95% CI 3.21–3.53), prostatitis (HR 2.61, 95% CI 2.392.85), lower urinary tract symptoms (HR 2.58, 95% CI 2.39–2.85) and keloids (HR 1.56, 95% CI 1.16–2.11) Men with PD had a lower risk of being diagnosed with hypertension (HR 0.76, 95% CI 0.72–0.81), hyperlipidemia (HR 0.78, 95% CI 0.73–0.82), diabetes mellitus (HR 0.68, 95% CI 0.60–0.77), renal disease (HR 0.76, 95% CI 0.590.97), and liver disease (HR 0.82, 95% CI 0.70–0.96) compared to men with ED and healthy controls.
	Pastuszek et al. [5]	532,653	Compared to controls, men with PD had an increased risk of developing stomach cancer (HR 1.43, 95% CI 1.06–1.14), testis cancer (HR 1.39, 95% CI 1.05–1.84), and melanoma (HR 1.19, 95% CI 1.02–1.38)
<i>Cryptorchidism</i>	Schnack et al. [6]	5,441	Men with a history of cryptorchidism have an increased risk of developing TGCC (RR = 3.71, 95% CI 3.29–4.19)
<i>Hypospadias</i>	Schnack et al. [6]	5,441	Men with a history of hypospadias demonstrated an increased risk of developing TGCC (RR = 2.13, 95% CI 1.29–3.61)