Male Infertility and Testicular Cancer – Points of Common Causality

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Abstract
Testicular cancer and male infertility are male reproductive health problems that have increased in frequency in the past few decades. Our article examines the relationship between these two disease states, focusing particularly on those causal mechanisms that link the two. Genetic mechanisms, including mutations in the SRY and p53 genes, as well as persistent oxidative stress, have been associated with both of these diseases. Endocrine-disrupting chemicals have also been implicated in the aetiology of both infertility and testicular cancer. The shared aetiology of these two disease states is strongly indicative of a link between male infertility and testicular cancer. While future research will undoubtedly strengthen the relationship between them, the current knowledge on this subject makes a persuasive case for careful consideration of this link when clinicians are making treatment decisions for patients with infertility or testicular cancer.

Keywords
Male infertility, testicular cancer, endocrine disruption, testicular dysgenesis, SRY gene mutation, p53 gene mutation, oxidative stress

In recent years, male reproductive health has declined markedly in developed countries. Semen quality has decreased and, consequently, the number of infertile males has increased. Additionally, there has been a six-fold increase in the incidence of testicular cancer. Recent studies have found the infertile population to be at increased risk of developing gonadal tumours, suggesting that there is a possible association between these two health problems.

This article explores the link between male infertility and testicular cancer by presenting information on the genetic and environmental basis of this linkage. The evidence presented in this article strongly suggests that there is a causal relationship between male infertility and testicular cancer. It is our hope that clinicians will be able to use this evidence to guide their treatment decisions when caring for patients diagnosed with infertility or testicular cancer.

Current Risk Factors for Testicular Cancer
Although many potential risk factors for germ cell tumours have been proposed, few of the claims have been substantiated. Thus far, only cryptorchidism, contralateral testicular germ cell tumour and familial history of testicular cancer have proved to be sound predictors of testicular cancer risk. A meta-analysis of 20 case-control studies conducted by Dieckmann found the relative risk of testicular germ cell tumours in individuals with a history of undescended testes to be five times greater than that of men without such a history. Men with a familial history of testicular cancer are three to 10 times more likely to develop it themselves, perhaps by inheriting a susceptibility gene on the X chromosome.

Additionally, patients with unilateral testicular germ cell tumours possess a much greater risk of developing a contralateral germ cell tumour.

Incidence and Known Causes of Male Infertility
Infertility affects roughly 15% of couples. Most cases are considered idiopathic. Both non-genetic and genetic factors contribute by influencing physiological processes related to spermatogenesis. Genetic abnormalities are associated with approximately 15–30% of male infertility cases. Structural defects are responsible for a small proportion of all male infertility cases.

Association of Male Infertility and Testicular Cancer
Some studies have looked retrospectively at the pre-cancer fertility capacity of men who later developed testicular cancer. For example, it has been shown that men who develop testicular cancer have fewer children than age-matched men who do not develop testicular cancer. A study by Petersen and Skakkebaek analysed the semen quality of men diagnosed with unilateral testicular cancer. This group reported that the quality of semen collected from these men was much poorer than would typically be expected for a man possessing one functional testis. Carcinoma in situ (CIS), a pre-cancerous cellular condition, is also seen more frequently in the testicular biopsies of men evaluated for sub-fertility or infertility. This would strongly suggest that men with fertility problems, even those who go undiagnosed with sub-fertility, are at an increased risk of developing testicular cancer.
Recent research has supported the existence of this increased risk, although the exact impact infertility or subfertility has on a man’s risk of developing testicular cancer is still disputed. A study by Jacobson reported the increased risk of testicular cancer in men with fertility problems to be 1.6 times that of men with normal semen parameters. A more recent study by Raman estimated the incidence of testicular cancer in infertile men to be 20 times greater than that of men with proven fertility (i.e. biological children). Perhaps one reason for the discrepancies in these values is the multiple mechanisms that could potentially link male infertility and testicular cancer. Multiple genetic causes, as well as environmental variables, have been implicated to play a role as causal links between these two disease states.

**Genetic Causes**
Both male infertility and testicular cancer have been associated with the SRY gene, DNA repair genes and tumour suppressor gene mutations. Mutations in the SRY gene have been linked to gonadal tumour formation and infertility. Alterations of the SRY gene are most commonly associated with complete gonadal dysgenesis. Patients with these alterations can present with phenotypes ranging from streak gonads such as those seen in Turner syndrome to genital ambiguity. One meta-analysis noted gonadal tumour formation in 52.5% of patients with SRY abnormalities.

Supraphysiological levels of reactive oxygen species (ROS) in the semen lead to oxidative damage to the sperm, which may manifest as DNA breakage, cross-linkage and mutations. Recent studies have shown that infertile men have high ROS levels in the seminal fluid. In addition to causing DNA damage, ROS also results in the production of highly mutagenic compounds that can further increase an individual’s susceptibility to tumour formation. Chronic oxidative damage is indicative of a deficiency in DNA repair mechanisms. In addition, mutations in these repair genes can result in deletions or expansions of small repeat DNA sequences, leading to unstable components that have been noted in many forms of cancer. Furthermore, these mutations and expansions of DNA repeat sequences can manifest as male infertility.

Cases of male infertility and cancer formation have also been attributed to deficiencies in tumour suppressor genes, particularly p53. The gene plays a crucial role in tumour prevention and stress response pathways. It also helps to co-ordinate a variety of cellular responses from cell cycle arrest and apoptosis to the maintenance of genomic stability. This gene also has an important role in spermatogenesis – specifically during the prophase of meiosis within primary spermatocytes. Mutations result in chromosomal and genomic instability, increasing the chance that -null cells will become malignant and gain additional mutations. This genomic instability would also compromise the sperm’s ability to fertilise an egg. It has also been reported that p53 has a role in the upregulation of certain antioxidant genes. A knockout of this gene would thus leave the cell without an important defence against ROS. Therefore, at high ROS levels, such as those seen in infertile patients, the cell would be susceptible to an even greater amount of oxidative stress and subsequent DNA damage.

**Environmental Causes**
Researchers are currently focusing on endocrine-disrupting chemicals or xenoestrogens as a possible mediating factor linking testicular cancer and male infertility. These are antiandrogenic agents that mimic oestrogens.

Phthalates, gums and paints are antiandrogenic chemicals that are ubiquitous in human life. They have been used as plasticisers in polyvinyl chloride (PVC) products and are constituents of many infant toys, storage containers and medical devices. While experts recommend that daily exposure be limited to 2mg, with nearly 18 billion pounds of phthalates being produced per year, many individuals have occupational or medical exposures greatly in excess of these guidelines.

These agents are believed to lead to an increase in oestrogen levels in the blood. This inhibits the hypothalamic-pituitary-gonadal axis, resulting in decreased production of follicle-stimulating hormone (FSH) and, subsequently, a fixing of the Sertoli cell number or prevention of the production of additional Sertoli cells.

In most mammals, Sertoli cell replication occurs only during foetal and post-natal life. The Sertoli cell number thus becomes fixed at a particular stage of development. However, in humans the Sertoli cell number increases significantly between late foetal and pre-pubertal life and also increases further during puberty. Hence, the window for adverse effect on Sertoli cells in humans is longer than that known for other mammalian species. Thus, after exposure to environmental hormones, xenoestrogens or environmental endocrine disruptors, these chemicals accumulate in the body, and their effects are biomagnified over a period of time.

Intact and competent Sertoli cells are required for optimal spermatogenesis and spermiogenesis. Therefore, when these cells function improperly, hypospermatogenesis and infertility can occur. Additionally, the malfunctioning of Sertoli cells leads to the arrest of many gonocytes at an early stage of maturation. These arrested gonocytes are thought to be the forerunners to CIS (see Figure 1). Fifty per cent or more of those diagnosed with CIS will develop invasive testicular cancer within five years. Additionally, as a
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consequence of decreased testosterone levels, there will also be a diminished number of Sertoli cells, thereby compounding the problems associated with their malfunction.

The resulting elevation in maternal and foetal oestrogens associated with exposure to endocrine-disrupting chemicals also inhibits FSH secretion, lowers levels of anti-Müllerian hormone (AMH) and decreases expression of the SRY gene. This may result in abnormal sexual differentiation leading to cryptorchidism and hypospadias as well as hypospermatogenesis.24 It also eventually may lead to testicular cancer through a process known as hormonal carcinogenesis.20–22 These four illnesses – cryptorchidism, hypospadias, hypospermatogenesis and testicular cancer – are considered hallmark components of testicular dysgenesis syndrome (TDS).

Evidence from Human Retrospective Studies

Human retrospective studies have provided considerable evidence supporting the theory that endocrine-disrupting chemicals play a role in the induction of male reproductive health disorders. One potent source of synthetic oestrogen exposure is pesticides, which are known to possess oestrogenic, antiandrogenic and aromatase-inhibiting effects in vivo. It has been shown that maternal exposure to pesticides during pregnancy is associated with an increased risk of cryptorchidism in male infants.23 A separate study also found that women who worked in greenhouses while pregnant gave birth to sons with significant reproductive health impairment, particularly cryptorchidism.24

Studies investigating the different hormone levels in males with testicular cancer or infertility have been helpful in further elucidating the pathway leading to these reproductive health issues. Testosterone levels have been reported to be lower in infertile men than in men with proven fertility. Infertile men also tend to have a lower testosterone/luteinising hormone (LH) ratio and higher serum LH levels.25 Higher levels of LH and FSH, in addition to low serum testosterone levels, have also been documented in men with CIS and testicular cancer.26

Taken together, these hormonal changes are indicative of compensated Leydig cell failure. The pituitary gland releases luteinising hormone to stimulate the Leydig cells to produce testosterone. When Leydig cells fail to properly receive or interpret this signal, the pituitary secretes more LH to compensate, resulting in high levels of LH and low levels of testosterone in the blood. The decreased androgen production that accompanies Leydig cell malfunction has recently been shown to have a dramatic effect on the number of Sertoli cells in the perinatal period. Faulty nurse cells will be less capable of nurturing germ cells into mature spermatozoa, leading to poor semen quality in adulthood and also to germ cell maturation arrest, increasing the likelihood of developing CIS and testicular cancer (see Figure 1).25,26

Clinical Recommendations

The increased risk of testicular cancer associated with male infertility speaks strongly for the importance of incorporating testicular cancer screening into the routine care of infertile men. Whereas the only definitive way to determine whether testicular cancer is present is to perform a testicular biopsy, this test is invasive and may not be a practical way to screen a large population of infertile males. Scrotal ultrasonography can detect the presence of tissue irregularities that might be indicative of testicular cancer or CIS. Perhaps the easiest way to provide testicular cancer screening to those suffering from male infertility is to teach them how to perform self-examinations. This would allow the patient to detect palpable changes in the testicular tissue that might precede testicular cancer.

Conclusion

In summary, male infertility and testicular cancer are linked as a result of common genetic and environmental causes. In the future, the identification of the detailed causal mechanisms resulting in these health problems will enhance the ability of physicians to make responsible clinical decisions for the management of patients with infertility or testicular cancer. However, currently the link between these two disease states is strong enough to warrant serious consideration by clinicians. This information should be communicated to affected patients when discussing their treatment options.

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