Male infertility: a biomarker of individual and familial cancer risk

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Associations between male infertility and cancer are gaining clinical attention. Relationships between infertility and cancer have traditionally been studied in women, but recent work has focused on the male component of reproduction. Infertile men are at an elevated risk to develop various malignancies later in life, primarily genitourinary malignancies such as testicular and prostate cancer. Rates of testicular and high-grade prostate cancer in infertile men appear to be at least double the risk in the general population. The link between infertility and malignancy highlights the importance of thorough evaluation and long-term follow up—beyond a simple semen analysis. A detailed urologic evaluation, possibly including scrotal ultrasound, may be beneficial to screen infertile men for testicular cancer. Publications have also demonstrated that male infertility can be a biomarker for cancer risk in first- and second-degree relatives. Testicular cancer risk in first-degree relatives of infertile men is 52% higher than the risk in relatives of fertile control men, and male infertility has been associated with a two- to threefold elevation in risk of childhood cancer in the siblings of infertile men. Links between infertility and malignancy are multifactorial, and exact mechanistic explanations are still not fully understood. Although more studies are needed to assess levels of risk and create screening recommendations in this population, understanding the relationship between male infertility and malignancy is crucial to provide comprehensive counseling for infertile men and their families. (Fertil Steril® 2018;109:6–19. ©2017 by American Society for Reproductive Medicine.)

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Male-factor infertility is extremely common. In the United States, ~15% of couples report infertility, and a male component is thought to be a contributing factor in up to 50% of infertility cases (1). Approximately 7.5% of American men have undergone semen analysis at an assisted reproduction center as part of a fertility evaluation, and each year nearly 700,000 men pursue an evaluation for male-factor infertility in the United States (2, 3). There is a growing body of literature demonstrating that both male and female infertility may be associated with long-term health consequences, including an elevated risk of malignancy (4–7). Historically, research has focused on the overall health of the female partner during an infertility evaluation. Strong correlations have been documented between female infertility and certain types of cancer, but comparatively less is known about the risk of malignancy in infertile men (6, 8).

One of the challenges that researchers face when evaluating associations between male infertility and malignancy risk is the severe lack of centralized data related to male infertility. Large-scale databases, such as the Society for Assisted Reproductive Technology (SART) clinical summary report and the National ART [assisted reproductive technology] Surveillance System (NASS) published by the Centers for Disease Control and Prevention (CDC), are not specifically designed to include important information about male-factor infertility. In addition, cancer databases, such as the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, have a wealth of information regarding malignancy, but this information is not tied to infertility. Evaluating both individual and familial health risks associated with a diagnosis of male infertility becomes logistically difficult when data are scarce. Databases such as the National Survey of Family Growth (NSFG) and the Reproductive Medicine Network do collect some data regarding male infertility, but those databases were originally designed for women, making their application to male-factor infertility less than ideal. The Andrology Research Consortium database was built for the purpose of collecting data about male-factor infertility, but currently there are relatively limited data available from that source. Large population-level databases such as the Truven Health Marketscan and the Utah

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Population Database have proven to be useful in performing retrospective cohort studies looking at male infertility, but similarly to most other databases, they were not specifically designed to collect data related to male infertility. Using existing databases to determine an exact cause for infertility is also relatively more difficult in men than in women, and in the setting of idiopathic male-factor infertility, identifying causal relationships between infertility and health comorbidities can be problematic (9).

Until recently, publications within the medical literature have placed less emphasis on the male component of reproduction and possible associations between male infertility and malignancy (10). Although it is understood that treatment for cancer may negatively affect one's fertility, it is becoming increasingly clear that male-factor infertility may play an important role in the overall health status of men, and that men with infertility may be at an increased risk to develop incident testicular cancer, prostate cancer, non-Hodgkin lymphoma, leukemia, melanoma, and other types of malignancy (7, 11, 12). In addition, recent work has proposed that male infertility may be not only a biomarker of the overall health status of the infertile patient but also a marker of the health status and malignancy risk for family members (3, 13, 14). Molecular, environmental, and genetic factors linking male infertility to malignancy have been suggested, and there are increasing data to support specific mechanisms that predispose men to both infertility and malignancy. The hypothesis that male infertility may be a harbinger of certain types of malignancy, such as testicular cancer, is gaining clinical acceptance (15). In the following review, no Institutional Review Board approval was necessary.

CANCER RISK AMONG INFERTILE MEN

Testis Cancer

One of the most well documented associations between male infertility and malignancy is seen with testicular cancer. In some ways, this is not surprising, given that spermatogenesis and testicular tumors are both some of the highest-throughput processes in the human body in the benign and malignant states, respectively. Both infertility and testicular cancer are often diagnosed at a relatively young age, with the average age at testicular cancer diagnosis being 33 years. For the general male population in the United States, the lifetime risk of testicular cancer is about 1 in 263 (16). The vast majority of testicular cancers are of germ cell origin (~98%) (17). Although testicular cancer represents only 1% of malignancies in men, it is the most common cancer diagnosed in young men aged 15–34 years (17, 18). The overall prevalence of testicular cancer in the United States is 4.84 per 100,000 men and 1 in 100,000 for black men (19). Globally, the incidence of testicular cancer appears to be increasing, although mortality related to this malignancy has declined in Western countries in recent decades (17). Owing to successful treatments, a man's lifetime risk of dying from testicular cancer is low, ~1 in 5,000 (16).

Various explanations have been proposed for the link between male infertility and testicular cancer because there appears to be a strong epidemiologic and biologic connection between these two disease processes (18). Consistently, significant elevations in rates of testicular cancer are seen among men with infertility and poor semen quality. Multiple studies have evaluated specific rates of testicular cancer among infertile male populations (Table 1). Specific elevations in testicular cancer risk vary depending on the publication, from a twofold elevation in risk seen in a large study of United States claims data to >20 times higher risk in a retrospective cohort study of 3,847 infertile men who were compared with a baseline healthy population (5, 7, 20–24). A large retrospective cohort study from the Utah Population Database of 20,433 men undergoing semen analysis demonstrated elevated risk of testicular cancer in men with oligozoospermia based on concentration (hazard ratio [HR] 11.9) and sperm count (HR 10.3). Men in the lowest quartile of motility, viability, morphology, or total motile count were also found to have higher risk of testicular cancer (20). One large study evaluating 2,179 healthy, young military recruits found no cases of testicular cancer with the use of scrotal ultrasound for screening, whereas pooled data from infertile men who underwent similar scrotal ultrasound screening showed a testicular cancer incidence of ~0.5% (18, 25). The finding of scrotal masses in the infertile male population is not uncommon, and although most of these masses are benign and can be safely followed with surveillance, the recommendation for routine use of scrotal ultrasound in men with infertility is worth considering owing to the relatively frequent finding of malignancy at the time of an infertility consultation (25–27). Compared with physical examination, ultrasound appears to be a superior means to detect testicular abnormalities. In a study by Pierik et al., 67% of ultrasound findings were not evident on palpation, and only one out of seven testicular tumors were identified by physical exam alone (25). At this time, there is insufficient evidence to advocate the routine use of scrotal ultrasound in all infertile men, although ultrasound could be beneficial if future evidence supports its cost effectiveness.

The connection between male infertility and testicular cancer is likely multifactorial, with a combination of hormonal, genetic, in utero, and environmental factors contributing to the development of testicular cancer in the infertile population (17). Figure 1 details possible mechanistic links between male infertility and testicular cancer. High estrogen levels in utero may contribute to the development of this malignancy. Hormonal disruptions during embryologic development may disrupt normal modulation of primordial germ cells as well as mesenchymal and Sertoli cell differentiation, leading to later problems related to steroidogenesis and spermatogenesis (e.g., testicular dysgenesis syndrome) (18, 28, 29). Abnormalities in these pathways may result in a predisposition to both infertility and testicular cancer.

Testicular abnormalities such as cryptorchidism are a known risk factor for the development of testicular malignancy, with relative risk elevations ranging from four to nine (23). Cryptorchidism is also strongly associated with infertility and is one of the most common etiologies for azoospermia in adults (30). The prevalence of cryptorchidism in full-term male infants is ~1%–3% but has been reported to