Male infertility: a biomarker of individual and familial cancer risk

Brent M. Hanson, M.D.,[a] Michael L. Eisenberg, M.D.,[b] and James M. Hotaling, M.D., M.S., F.E.C.S.M.[c]

[a] Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, Utah; [b] Male Reproductive Medicine and Surgery Program, Departments of Urology and Obstetrics and Gynecology, Stanford University, Stanford, California; and [c] Center for Reconstructive Urology and Men's Health, Department of Surgery–Urology, University of Utah, Salt Lake City, Utah

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.)
Key Words: Male infertility, cancer, malignancy, familial risk

Discuss: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/22369-24937

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

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

TABLE 1

Publications evaluating male infertility and testicular cancer.

First author	Title	Year	Country	Study participants (n)	Study design	Infertility definition	Main findings
Henderson	Risk factors for cancer of the testis in young men	1979	United States	131 case subjects; 131 control subjects	Case-control	Fatherhood status of married men (no children)	Elevated risk of testicular cancer in married men who had never had children compared to married men who had children (OR 1.38)
Swerdlow	Testis cancer: postnatal hormonal factors, sexual behavior, and fertility	1989	United Kingdom	259 case subjects; 489 control subjects	Case-control	>1 year of unprotected intercourse without pregnancy	Elevated risk of testicular cancer in men who had gone >1 year of unprotected intercourse without pregnancy compared with men who achieved pregnancy in <1 year of unprotected intercourse (OR 1.76, 95% CI 1.08–2.86)
Bettocchi	A review of testicular intratubular germ cell neoplasia in infertile men	1994	United Kingdom	2,739 infertile men undergoing testicular biopsy	Retrospective cohort	Azoospermia or severe oligospermia	Unilateral intratubular germ cell neoplasia found in 0.6% of infertile men undergoing testicular biopsy
United Kingdom Testicular Cancer Study Group	Etiology of testicular cancer: association with congenital abnormalities, age at puberty, infertility, and exercise	1994	United Kingdom	794 case subjects; 794 control subjects	Case-control	Primary care provider documentation of diagnosis of infertility	Elevated risk of testicular cancer in men with undescended testis (OR 3.82, 95% CI 2.24–6.52); men with self-reported difficulties conceiving had a nonsignificant elevated risk of testicular germ cell tumors (OR 2.66, 95% CI 0.94–7.54)
Moller	Risk of testicular cancer in subfertile men	1999	Denmark	514 case subjects; 720 control subjects	Case-control	Classification of fertility as low, normal, or high based on number of children before testicular cancer diagnosis compared with control group	Reduced risk of testicular cancer associated with paternity (OR 0.63, 95% CI 0.47–0.85)
Jacobsen	Fertility and offspring sex ratio of men who develop testicular	2000	Denmark	3530 case subjects; 488,957 control subjects	Case-control	Standardized fertility ratio (ratio of	Men who developed testicular cancer had reduced fertility

Hanson. Male infertility and cancer risk. Fertil Steril 2017.

TABLE 1

Continued.

First author	Title	Year	Country	Study participants (n)	Study design	Infertility definition	Main findings
	cancer: record linkage study					observed to expected live births)	before cancer diagnosis (standardized fertility rate ratio 0.93, 95% CI 0.89–0.97); reduction in fertility more pronounced in men with nonseminoma
Jacobsen	Risk of testicular cancer in men with abnormal semen characteristics	2000	Denmark	32,442 men who underwent semen analysis	Retrospective cohort	Men with abnormal semen analysis	Elevated risk of testicular cancer with low semen concentration (SIR 2.3), poor motility (SIR 2.5), and high proportion of abnormal morphology (SIR 3.0)
Doria-Rose	Subfertility and the risk of testicular germ cell tumors	2005	United States	329 case subjects; 672 control subjects	Case-control	Telephone interview self-reported infertility, number of children >2 years before testicular cancer diagnosis	Testicular cancer risk was decreased among men who had children (age-adjusted OR 0.76, 95% CI 0.54–1.06); prior diagnosis of infertility associated with increased risk of testicular cancer (OR 2.40, 95% CI 1.00–5.77)
Raman	Increased incidence of testicular cancer in men presenting with infertility and abnormal semen analysis	2005	United States	3,847 men with infertility and abnormal semen analysis	Retrospective cohort	Abnormal semen analysis based on WHO criteria	SIR of testicular cancer 22.9 (95% CI 22.4–23.5) comparing infertile group to control population
Walsh	Increased risk of testicular germ cell cancer among infertile men	2009	United States	22,562 male partners of infertile couples	Retrospective cohort	Abnormal semen analysis based on WHO criteria	Men seeking infertility treatment had increased risk of testicular cancer (SIR 1.3, 95% CI 0.9–1.9); infertile men three times more likely to develop testicular cancer compared with fertile men (HR 2.8, 95% CI 1.3–6.0).

Hanson. Male infertility and cancer risk. Fertil Steril 2017.

TABLE 1

Continued.

First author	Title	Year	Country	Study participants (n)	Study design	Infertility definition	Main findings
Eisenberg	Increased risk of cancer in infertile men: analysis of US claims data	2015	United States	76,083 infertile men; 112,655 men who underwent vasectomy; 760,830 control men	Retrospective cohort	Outpatient claim with male infertility diagnosis code	49% higher risk of all cancers in infertile men and twofold higher risk of testicular cancer
Hanson	Subfertility increases risk of testicular cancer: evidence from population-based semen samples	2016	United States	20,433 men who underwent semen analysis; 20,433 fertile control men	Retrospective cohort	Oligozoospermia on semen analysis	Men undergoing semen analysis had increased risk of testicular cancer (HR 3.3)l increased risk of testicular cancer in men with oligozoospermia based on concentration (HR 11.9) and sperm count (HR 10.3); men in lowest quartile of motility (HR 4.1), viability (HR 6.6), morphology (HR 4.2), or total motile count (HR 6.9) had higher risk of testicular cancer

Note: CI = confidence interval; HR = hazard ratio; OR = odds ratio; SIR = standardized incidence ratio; WHO = World Health Organization.

Hanson. Male infertility and cancer risk. Fertil Steril 2017.

FIGURE 1

Potential mechanisms between male infertility and testicular cancer.

Hanson. Male infertility and cancer risk. Fertil Steril 2017.
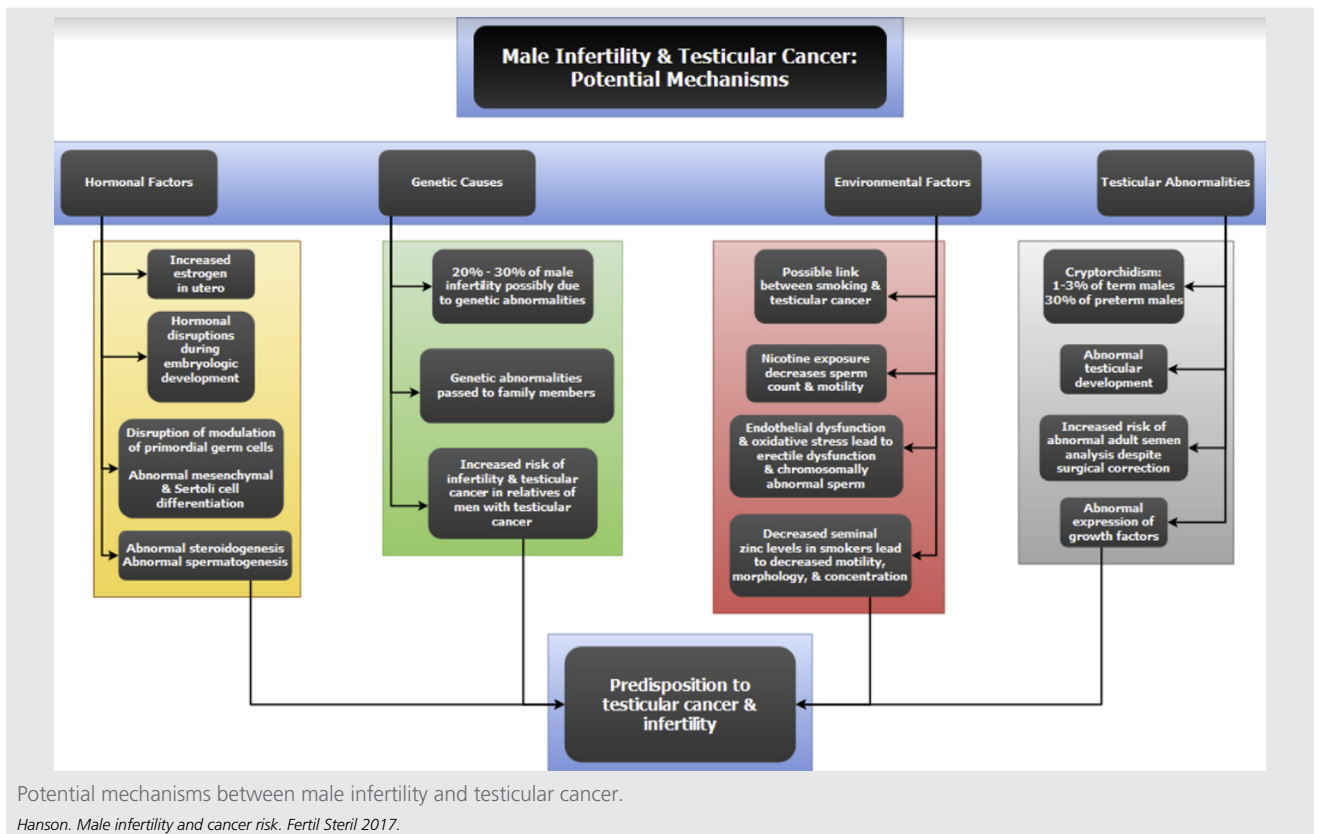
be as high as 30% in premature male infants (31). Despite improvements in fertility outcomes for adult men who have undergone surgical correction of cryptorchidism as infants, subfertility as an adult remains a concern. After surgery, ∼80% of adult men with a history of bilateral cryptorchidism and 30% of men with a history of unilateral cryptorchidism have abnormal sperm counts (32). Abnormal testicular development and dysregulation of expression of growth factors seen in cryptorchid males may contribute to both subsequent infertility as well as testicular cancer risk (33).

From 20% to 30% of male infertility is thought to be caused by genetic defects, and some of these genetic changes may also play a role in the development of testicular cancer. The possibility of an underlying genetic component to the link between male infertility and testicular cancer is highlighted by epidemiologic studies suggesting that the brothers of men with testicular cancer may also have decreased fertility and be at an elevated risk of developing testicular cancer (18, 34). Several unknown moderate risk genes may explain some of the inherited susceptibility seen with testicular cancer and may also have a detrimental impact on male fertility (35).

Environmental factors, such as smoking, may predispose men to both infertility and testicular cancer. Smoking has been proposed in certain studies as a risk factor for testicular cancer, and men who smoke have been shown to have higher rates of erectile dysfunction, elevations in chromosomally abnormal sperm, and decreased sperm concentration,

motility, and morphology (36–38). Interestingly, in a study from Canada both former and current smokers appeared to be at an elevated risk of developing testicular cancer, suggesting that the effect of smoking cessation on decreasing the subsequent development of testicular cancer may be minimal (39). However, not all publications support the connection between tobacco use and testicular cancer. A recent Italian study reported no apparent association between alcohol or tobacco use during adolescence (ages 13–19 years) and later diagnoses of testicular cancer (40). Maternal smoking during pregnancy may lead to elevated rates of cryptorchidism in male offspring, which is a known risk factor for the future development of testicular cancer. Male offspring who were exposed to tobacco in utero may also suffer from impaired semen quality in adulthood, although the influence on fecundability is less clear (41). Although smoking and other environmental or occupational exposures may have a negative health impact with detrimental effects on fertility, the relationships between tobacco use, environmental exposures, and testicular cancer are not entirely clear from a mechanistic standpoint.

Prostate Cancer

A significant amount of recent data is also available regarding associations between male infertility and prostate cancer, although the relationship between infertility and

TABLE 2

Publications evaluating male infertility and prostate cancer.

First author	Title	Year	Country	Study participants (n)	Study design	Infertility definition	Main findings
Jorgensen	Fatherhood status and prostate cancer risk	2008	Denmark	All Danish men born 1935–1988, using the Civil Registration System (3400 developed prostate cancer during 1968–2003)	Retrospective cohort	Childless status	Childless men were found to be at a 16% reduced risk of prostate cancer compared with fathers (RR 0.84, 95% CI 0.73–0.95)
Ruhayel	Male infertility and prostate cancer risk: a nested case-control study	2010	Sweden	445 prostate cancer case subjects; 446 control subjects	Case-control	Involuntary childlessness based on self-reported questionnaire	Infertile men had a lower risk of prostate cancer than fertile men (OR 0.45, 95% CI 0.25–0.83)
Walsh	Increased risk of high-grade prostate cancer among infertile men	2010	United States	22,562 men who were evaluated for infertility	Retrospective cohort	Abnormal semen analysis based on WHO criteria	Men evaluated for infertility but with normal semen analysis did not have an increased risk of cancer (SIR 0.9, 95% CI 0.8–1.1). Infertile men had an elevated risk of high–grade prostate cancer (SIR, 2.0; 95% CI, 1.2–3.0). On multivariate analyses, men with male factor infertility were 2.6 times more likely to be diagnosed with high-grade prostate cancer (HR 2.6, 95% CI 1.4–4.8).
Eisenberg	Fatherhood and incident prostate cancer in a prospective US cohort	2011	United States	161,823 men aged 50–71 y without a cancer diagnosis at baseline; 8,134 cases of prostate cancer during follow-up	Prospective cohort	Fatherhood status based on self-reported questionnaire	There was no relationship between fatherhood and incident prostate cancer (HR 0.94, 95% CI 0.86–1.02)
Wiren	Fatherhood status and risk of prostate cancer: nationwide, population-based case-control study	2013	Sweden	117,328 prostate cancer patients	Case-control	Fatherhood status based on data from a nationwide statistics register	Childless men had a 17% decreased risk of prostate cancer compared with fathers (OR 0.83, 95% CI 0.82–0.84)
Eisenberg	Increased risk of cancer in infertile men: analysis of US claims data	2015	United States	76,083 infertile men 112,655 men who underwent vasectomy; 760,830 control men	Retrospective cohort	Outpatient claim with male infertility diagnosis code	Infertile men had an elevated risk of developing prostate cancer (SIR 2.83, 95% CI 2.26–3.49)

Hanson. Male infertility and cancer risk. Fertil Steril 2017.

TABLE 2

Continued.

First author	Title	Year	Country	Study participants (n)	Study design	Infertility definition	Main findings
Hanson	Subfertility increases risk of testicular cancer: evidence from population-based semen samples	2016	United States	20,433 men who underwent semen analysis; 20,433 fertile control men	Retrospective cohort	Oligozoospermia on semen analysis	There was no significant relationship between infertility and prostate cancer risk for this population, likely owing to the relatively short follow-up time and young age at baseline
Mao	Reduced risk of prostate cancer in childless men compared with fathers	2016	China	Review and analysis of 11 publications	Systematic review and meta-analysis	Childless status	There was a significantly reduced risk of prostate cancer associated with being childless (OR 0.91, 95% CI 0.87–0.96).

Note: CI = confidence interval; HR = hazard ratio; OR = odds ratio; RR = relative risk; SIR = standardized incidence ratio; WHO = World Health Organization.

Hanson. Male infertility and cancer risk. Fertil Steril 2017.

prostate cancer is less clear than with testicular cancer (Table 2). One of the earliest publications evaluating the relationship between infertility and prostate cancer was a study from 2010 which evaluated 22,562 men in California who had undergone fertility testing at one of 15 infertility centers. Data from these men were linked to the California Cancer Registry and demonstrated that men who were diagnosed with male-factor infertility were not at an overall increased risk of developing prostate cancer (standardized incidence ratio [SIR] 0.9, 95% confidence interval [CI] 0.8–1.1), but a subset analysis did reveal an increased risk of developing high-grade prostate cancer among infertile men (SIR 2.0, 95% CI 1.2–3.0) compared with age-matched control men (42). A separate study evaluating 76,083 infertile men with the use of United States claims data demonstrated an elevated risk of prostate cancer related to male infertility (HR 1.78, 95% CI 1.41–2.25) in some but not all analyses (7). In contrast, a retrospective cohort study from 2016 evaluating 20,433 men who underwent semen analysis did not find an association between male infertility and prostate cancer (HR 0.90, 95% CI 0.54–1.52) although this could be explained by relatively short follow-up time and young average age of study participants (20). In addition, a nested case-control study in Sweden reported a lower odds of prostate cancer in men with a history of male infertility (43). Importantly, in studies demonstrating an association between infertility and prostate cancer, there appears to be a significant chronologic separation between a diagnosis of infertility and a diagnosis of prostate cancer. A diagnosis of infertility in a man's fourth decade of life appears to confer an elevated risk of prostate cancer in his sixth decade (44).

Several studies using large databases have used fatherhood status as a proxy for male infertility and evaluated the relationship between fatherhood and a subsequent prostate cancer diagnosis (5, 45–47). A large meta-analysis from 2016 provided a summary of 11 publications that examined prostate cancer risk based on fatherhood status. Overall, a pooled analysis suggested a decreased risk of prostate cancer in childless men (odds ratio [OR] 0.91, 95% CI 0.87–0.96) (48). The authors hypothesized that childless men may lie at a lower androgen state and thus would be at lower risk for prostate cancer. It should be noted that fatherhood status is an imperfect marker of infertility, making it difficult to directly apply conclusions from these publications to the infertile population.

Mechanisms linking prostate cancer to male infertility remain largely hypothetic, and, given the somewhat conflicting nature of current data, identifying a causal relationship between these two disease processes remains a challenge. Theories involving environmental modulators, genetic influences, and hormonal function that have been proposed to explain associations between infertility and testicular cancer have been extrapolated to prostate cancer as well (44). With abnormal gonadal function, the prostate may receive aberrant signals during key phases of development which could result in an elevated risk of malignancy. In addition, variations in CAG repeats in the gene encoding the androgen receptor or problems with DNA mismatch repair may have implications for both male infertility and prostate cancer (44).

TABLE 3

Publications evaluating male infertility and other types of cancer.

First author	Title	Year	Country	Study participants (n)	Study design	Infertility definition	Main findings
Jacobsen	Risk of testicular cancer in men with abnormal semen characteristics	2000	Denmark	32,442 men who underwent semen analysis	Retrospective cohort	Men with abnormal semen analysis	No significant elevation in risk of overall malignancy for men undergoing semen analysis (SIR 1.1, 95% CI 1.0–1.2); elevation in cancers of the peritoneum and digestive organs in this cohort (SIR 3.7, 95% CI 1.3–8.0), as well as testicular cancer (SIR 1.6, 95% CI 1.3–1.9).
Eisenberg	Increased risk of cancer among azoospermic men	2013	United States	2,238 men evaluated for infertility, of whom 451 had azoospermia	Retrospective cohort	Men with azoospermia on semen analysis	Infertile men had a higher risk of cancer (SIR 1.7, 95% CI 1.2–2.5); azoospermic men also had an elevated risk of cancer (SIR 2.9, 95% CI 1.4–5.4); infertile men without azoospermia had a nonsignificant trend toward higher cancer rates (SIR 1.4, 95% CI 0.9–2.2)
Eisenberg	Increased risk of cancer in infertile men: analysis of US claims data	2015	United States	76,083 infertile men; 112,655 men who underwent vasectomy; 760,830 control men	Retrospective cohort	Outpatient claim with male infertility diagnosis code	Infertile men had an elevated risk of all cancers compared with control men (SIR 1.80, 95% CI 1.66–1.95); also an elevated risk of melanoma (SIR 2.07, 95% CI 1.60–2.62), bladder cancer (SIR 2.92, 95% CI 1.92–4.24), brain and CNS malignancies (SIR 1.78, 95% CI 1.13–2.67), thyroid cancer (SIR 1.66, 95% CI 1.09–2.41), Hodgkin lymphoma (SIR 2.12, 95% CI 1.31–3.24), non-Hodgkin lymphoma (SIR 3.18, 95% CI 2.53–3.93), and leukemia (SIR 2.82, 95% CI 2.00–3.85)

Hanson. Male infertility and cancer risk. Fertil Steril 2017.

TABLE 3

Continued.

First author	Title	Year	Country	Study design	Study participants (n)	Infertility definition	Main findings
Hanson	Subfertility increases risk of testicular cancer: evidence from population-based semen samples	2016	United States	Retrospective cohort	20,433 men who underwent semen analysis; 20,433 fertile control men	Oligozoospermia on semen analysis	Men with sperm concentration and count in the 90th percentile had increased risk of melanoma (HR for concentration 2.1; HR for count 2.7).

Note: CI = confidence interval; CNS = central nervous system; HR = hazard ratio; SIR = standardized incidence ratio.

Hanson. Male infertility and cancer risk. Fertil Steril 2017.

Other Cancers

Compared with testicular cancer and prostate cancer, much less is known about the associations between male infertility and other types of cancer (Table 3). Until a few years ago, research in this area was nonexistent, so trends are only beginning to emerge that link male infertility to malignancies outside of the genitourinary tract. Using a large United States insurance claims dataset, Eisenberg et al. examined 76,083 infertile men and demonstrated that infertile men have an elevated risk of melanoma (SIR 2.07, 95% CI 1.60–2.62), bladder cancer (SIR 2.92, 95% CI 1.92–4.24), thyroid cancer (SIR 1.66, 95% CI 1.09–2.41), Hodgkin lymphoma (SIR 2.12, 95% CI 1.31–3.24), non-Hodgkin lymphoma (SIR 3.18, 95% CI 2.53–3.93), and leukemia (SIR 2.82, 95% CI 2.00–3.85). However, the risks of several malignancies were also elevated for the control groups. With the use of internal comparisons, the group concluded that men with male infertility had higher risks of testis cancer, non-Hodgkin lymphoma, and all cancers. In the same study, infertile men had a 49% higher overall cancer risk compared with control men [7]. A similar study performed in Texas demonstrated that in a population of 22,089 men who underwent semen analysis, azoospermic men had a significantly elevated risk of any cancer diagnosis (SIR 2.9, 95% CI 1.4–5.4). There was also a nonsignificant trend toward higher rates of cancer in nonazoospermic men who had been diagnosed with male-factor infertility (SIR 1.4, 95% CI 0.9–2.2) [49].

Interestingly, a Utah study of 20,433 men undergoing semen analysis demonstrated a doubling of the risk of melanoma in men within the highest quartile of total motile sperm count (HR 2.0, 95% CI 1.0–3.87), which would contradict the proposed association between melanoma and poor semen parameters. That population database study also demonstrated a trend toward increased risk of any cancer with decreasing sperm motility (HR 1.19, 95% CI 1.1–1.4), but no elevated risk of malignancy was noted related to changes in morphology, viability, or total motile counts [20].

Aside from testicular cancer and prostate cancer, reported associations between male infertility and other types of cancer are relatively scarce. Other groups have failed to identify any non–germ cell tumors among infertile men [21]. There is a paucity of literature linking male infertility to many types of cancer, and a causal relationship between infertility and cancer remains uncertain [7]. However, common biologic mechanisms may underlie many associations between subfertility and cancer risk. Because a significant percentage of the male genome is involved with reproduction, genetic abnormalities may lead to adverse reproductive health as well as future malignancies [50]. Fetal exposures or environmental factors, such as tobacco smoking, may also predispose men to subfertility and can lead to elevated risk of various malignancies, such as lung cancer and bladder cancer, in the future [51]. Although the association between testicular cancer and male infertility has been well studied, associations between infertility and other types of cancer continue to emerge. Studies to confirm these associations and describe possible causal pathways are crucial going forward.
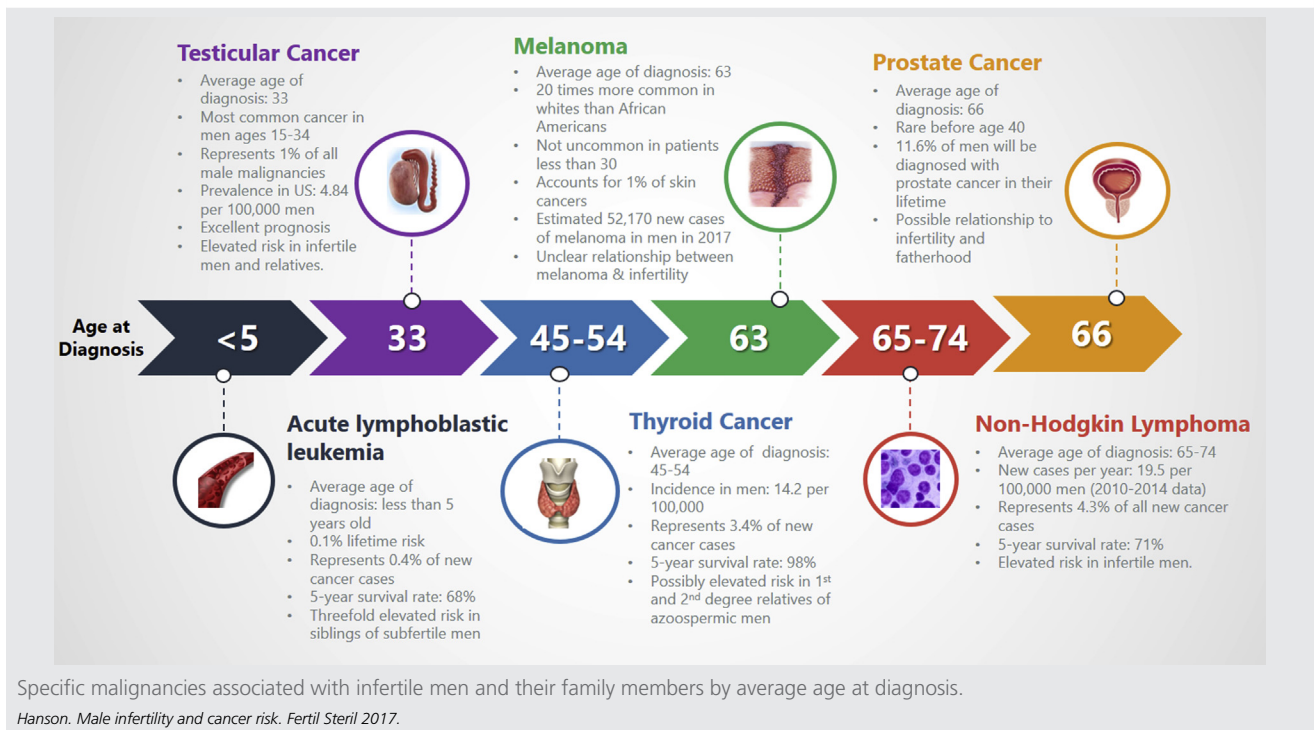
TABLE 4

Publications evaluating male infertility and risk to family members.

First author	Title	Year	Country	Study participants (n)	Study design	Infertile population	Main findings
Anderson	Cancer risk in 1st- and 2nd-degree relatives of men with poor semen quality	2016	United States	12,889 men undergoing semen analysis; 12,889 fertile control men	Retrospective cohort	Men undergoing semen analysis, azoospermic men	1st-degree relatives of men undergoing semen analysis had a 52% increased risk of testicular cancer compared with 1st-degree relatives of fertile control men; no significant difference in testicular cancer risk for 2nd-degree relatives; 1st- and 2nd-degree relatives of azoospermic men had significantly increased risk of thyroid cancer compared with relatives of fertile control men
Anderson	Childhood cancer risk in the siblings and cousins of men with poor semen quality	2017	United States	10,511 men with complete semen analysis; 10,511 fertile control men; 63,891 siblings; 327,753 cousins	Retrospective cohort	Men undergoing semen analysis, oligozoospermic men	Oligozoospermia associated with twofold increased risk of any childhood cancer and threefold increased risk of acute lymphoblastic leukemia in siblings of subfertile men compared with fertile control men (HR 2.09 [95% CI 1.18–3.69] vs. HR 3.07 [95% CI 1.11–8.46])
Hanson	Risk of childhood mortality in family members of men with poor semen quality	2017	United States	12,889 men who underwent semen analysis with familial data in the Utah Population Database	Retrospective cohort	Men undergoing semen analysis, stratified by semen parameters	No association between semen quality and risk for childhood cancer mortality in 1st- or 2nd-degree relatives (1st-degree relatives: HR 0.98, 95% CI 0.62–1.54; 2nd-degree relatives: HR 1.12, 95% CI 0.83–1.50)

Note: CI = confidence interval; HR = hazard ratio.

Hanson. Male infertility and cancer risk. Fertil Steril 2017.

FIGURE 2

Testicular Cancer
- Average age of diagnosis: 33
- Most common cancer in men ages 15-34
- Represents 1% of all male malignancies
- Prevalence in US: 4.84 per 100,000 men
- Excellent prognosis
- Elevated risk in infertile men and relatives.

Melanoma
- Average age of diagnosis: 63
- 20 times more common in whites than African Americans
- Not uncommon in patients less than 30
- Accounts for 1% of skin cancers
- Estimated 52,170 new cases of melanoma in men in 2017
- Unclear relationship between melanoma & infertility

Prostate Cancer
- Average age of diagnosis: 66
- Rare before age 40
- 11.6% of men will be diagnosed with prostate cancer in their lifetime
- Possible relationship to infertility and fatherhood

Age at Diagnosis: <5 | 33 | 45-54 | 63 | 65-74 | 66

Acute lymphoblastic leukemia
- Average age of diagnosis: less than 5 years old
- 0.1% lifetime risk
- Represents 0.4% of new cancer cases
- 5-year survival rate: 68%
- Threefold elevated risk in siblings of subfertile men

Thyroid Cancer
- Average age of diagnosis: 45-54
- Incidence in men: 14.2 per 100,000
- Represents 3.4% of new cancer cases
- 5-year survival rate: 98%
- Possibly elevated risk in 1st and 2nd degree relatives of azoospermic men

Non-Hodgkin Lymphoma
- Average age of diagnosis: 65-74
- New cases per year: 19.5 per 100,000 men (2010-2014 data)
- Represents 4.3% of all new cancer cases
- 5-year survival rate: 71%
- Elevated risk in infertile men.

Specific malignancies associated with infertile men and their family members by average age at diagnosis.

Hanson. Male infertility and cancer risk. Fertil Steril 2017.

FAMILIAL CANCER RISK

An infertility diagnosis in a man appears to carry health consequences for that individual, but data increasingly demonstrate that infertility may also be a biomarker of health for the infertile man's family members (Table 4). A study published in 2016 evaluated 12,889 men who underwent semen analysis and 12,889 fertile control men. That study evaluated the risks of a generalized diagnosis of any cancer as well as specific cancer risks for testicular cancer, thyroid cancer, breast cancer, prostate cancer, melanoma, bladder cancer, ovarian cancer, and kidney cancer were evaluated among first- and second-degree relatives. It demonstrated that the first-degree relatives of men who underwent semen analysis for an infertility evaluation had a 52% increased risk of testicular cancer compared with first-degree relatives of fertile control men. Second-degree relatives did not appear to have an elevated testicular cancer risk. In addition, first- and second-degree relatives of azoospermic men were found to have a significantly increased risk of thyroid cancer compared with fertile control men (3).

Another study evaluating the siblings and cousins of 10,511 men in Utah who underwent complete semen analysis demonstrated a twofold increased risk of any childhood cancer (HR 2.09, 95% CI 1.18–3.69) and a threefold increased risk of acute lymphoblastic leukemia (HR 3.07, 95% CI 1.11–8.46) in the siblings of subfertile men compared with fertile control men. That study found that the three most common types of cancer diagnosed in the siblings of men with abnormal semen parameters were acute lymphoblastic leukemia, brain cancer, and Hodgkin lymphoma (13). Aside from those studies, data evaluating the risk of malignancy in family members of infertile men are essentially absent. Overall, very few studies have evaluated the risk of malignancy in the family members of infertile men. Shared genetics or environmental exposures provide plausible mechanisms. Given the trend toward elevated risk of various malignancies in first- and second-degree relatives of infertile men in the existing data, this appears to be an area of particular importance for future research.

DISCUSSION

Male infertility is heterogeneous, complex, and often multifactorial. The exact cause of male infertility is frequently unknown, with 40%–50% of male-factor infertility cases classified as idiopathic or unexplained (52). Similarly, associations between infertile men, their family members, and incident cancer are poorly understood. To date, specific causal mechanisms relating infertility to malignancy are lacking. Nevertheless, strong evidence is emerging to support the idea that men with infertility are at an increased risk of developing various malignancies. Figure 2 highlights the specific malignancies associated with infertile men and their family members. A more thorough understanding of the impact of genetics and epigenetics on infertility will likely elucidate mechanistic pathways that connect infertility to cancer.

More than 1,500 genes are thought to contribute to spermatogenesis alone, so it is plausible that defects in any of these genes may also be tied to the development of cancers of the reproductive system as well as other organ systems (3, 53, 54). Genetic defects resulting in male infertility and cancer may also provide an explanation for elevated risks of cancer seen in the family members of infertile men (34, 35). Furthermore, DNA mismatch repair defects also

represent a promising new avenue of investigation that could potentially link the mechanisms of male infertility and oncogenesis (55–57).

Specific cancer risks may be related to underlying genetic, epigenetic, environmental, and hormonal causes of male infertility. As these associations become clear, it will be important to determine if there are subsets of infertile men who are predisposed to particular malignancies. In addition, clarifying the chronologic separation between the time of an infertility diagnosis and the presence of specific malignancies will allow for more thorough counseling of infertile patients. Associations between infertility and malignancy have important implications for overall health, and having an understanding of these associated disease processes is paramount to comprehensive care in the infertile population.

CONCLUSION

The strongest and most studied relationship between male infertility and malignancy is that with testicular cancer, in both infertile men themselves and their relatives (5, 7, 20–24). There appears to be a direct relationship between male infertility and the development of high-grade prostate cancer, although data do not consistently support that association and studies of fatherhood seem to suggest that being childless may decrease a man's risk of developing prostate cancer (5, 7, 20, 42, 44–48). Relatively less is known about the risk of subfertile men developing other types of cancer, although elevations in rates of melanoma, bladder cancer, thyroid cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, and leukemia have been noted (7). Further research regarding cancer risk in the family members of infertile men is necessary to better understand the implications of a male infertility diagnosis (3, 13, 14).

REFERENCES

1. American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril 2015;103:18–25.
2. Anderson JE, Farr SL, Jamieson DJ. Infertility services reported by men in the United States: national survey data. Fertil Steril 2009;91:2466–70.
3. Anderson RE, Hanson HA, Patel DP, Johnstone E, Aston KI, Carrell DT, et al. Cancer risk in first- and second-degree relatives of men with poor semen quality. Fertil Steril 2016;106:731–8.
4. Salonia A, Matloob R, Gallina A. Are infertile men less healthy than fertile men? Results of a prospective case-control survey. Eur Urol 2009;56:1025.
5. Rogers MJ, Walsh TJ. Male infertility and risk of cancer. Semin Reprod Med 2017;35:298–303.
6. Hanson B, Johnstone E, Dorais J, Silver B, Peterson CM, Hotaling J. Female infertility, infertility-associated diagnoses, and comorbidities: a review. J Assist Reprod Genet 2017;34:167–77.
7. Eisenberg ML, Li S, Brooks JD, Cullen MR, Baker LC. Increased risk of cancer in infertile men: analysis of U.S. claims data. J Urol 2015;193:1596–601.
8. Kroener L, Dumesic D, Al-Safi Z. Use of fertility medications and cancer risk: a review and update. Curr Opin Obstet Gynecol 2017;29:195–201.
9. Jarow J, Sigman M, Kolettis PN, Lipschultz LR, McClure RD, Nangia AK, et al. The optimal evaluation of the infertile male: American Urological Association best practice statement. 2011. Available at: www.auanet.org/documents//education/clinical-guidance/Male-Infertility-d.pdf. Accessed August 19, 2017.
10. Petok W. Infertility counseling (or the lack thereof) of the forgotten male partner. Fertil Steril 2015;104:260–6.
11. Brinton LA, Westhoff CL, Scoccia B, Lamb EJ, Althuis MD, Mabie JE, et al. Causes of infertility as predictors of subsequent cancer risk. Epidemiology 2005;16:500–7.
12. Kort JD, Eisenberg ML, Millheiser LS, Westphal LM. Fertility issues in cancer survivorship. CA Cancer J Clin 2014;64:118–34.
13. Anderson RE, Hanson HA, Lowrance WT, Redshaw J, Oottamasathien S, Schaeffer A, et al. Childhood cancer risk in the siblings and cousins of men with poor semen quality. J Urol 2017;197:898–905.
14. Hanson HA, Mayer EN, Anderson RE, Aston KI, Carrell DT, Berger J, et al. Risk of childhood mortality in family members of men with poor sperm quality. Hum Reprod 2017;32:239–47.
15. Tvrda E, Agarwal A, Alkuhaimi N. Male reproductive cancer and infertility: a mutual relationship. Int J Mol Sci 2015;16:7230–60.
16. American Cancer Society. What are the key statistics about testicular cancer? 2017. Available at: https://www.cancer.org/cancer/testicular-cancer/about/key-statistics.html. Accessed August 2, 2017.
17. Shanmugalingam T, Soultati A, Chowdhury S, Rudman S, van Hemelrijck M. Global incidence and outcome of testicular cancer. Clin Epidemiol 2013;5: 417–27.
18. Paduch D. Testicular cancer and male infertility. Curr Opin Urol 2006;16: 419–27.
19. McGlynn KA, Devesa SS, Sigurdson AJ. Trends in the incidence of testicular germ cell tumors in the United States. Cancer 2003;97:63–70.
20. Hanson HA, Anderson RE, Aston KI, Carrell DT, Smith KR, Hotaling JM. Subfertility increases risk of testicular cancer: evidence from population-based semen samples. Fertil Steril 2016;105:322–8.
21. Jacobsen R, Bostofte E, Engholm G, Hansen J, Olsen JH, Skakkebaek NE, et al. Risk of testicular cancer in men with abnormal semen characteristics: cohort study. BMJ 2000;321:789–92.
22. Raman JD, Nobert CF, Goldstein M. Increased incidence of testicular cancer in men presenting with infertility and abnormal semen analysis. J Urol 2005; 174:1819–22.
23. Venn A, Healy D, McLachlan R. Cancer risks associated with the diagnosis of infertility. Best Pract Res Clin Obstet Gynaecol 2003;17:343–67.
24. Walsh TJ, Croughan MS, Schembri M, Chan JM, Turek PJ. Increased risk of testicular germ cell cancer among infertile men. Arch Intern Med 2009;169: 351–6.
25. Pierik FH, Dohle GR, van Muiswinkel JM. Is routine scrotal ultrasound advantageous in infertile men? J Urol 1999;162:1618–20.
26. Behre HM, Kliesch S, Schadel F, Nieschlag E. Clinical relevance of scrotal and transrectal ultrasonography in andrological patients. Int J Androl 1995;18: 27–31.
27. Bieniek JM, Juvet T, Margolis M, Grober ED, Lo KC, Jarvi KA. Prevalence and management of incidental small testicular masses discovered on ultrasonographic evaluation of male infertility. J Urol 5 August 2017, doi: 10.1016/j.juro.2017.08.004. [ePub ahead of print.].
28. Skakkebaek NE, Rajpert-DeMeyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod 2001;16:972–8.
29. Skakkebaek NE, Rajpert-DeMeyts E, Buck-Louis GM, Toppari J, Andersson AM, Eisenberg ML, et al. Male reproductive disorders and fertility trends: influences of environment and genetic susceptibility. Physiol Rev 2016;96:55–97.
30. Hadziselimovic F, Herzog B. The importance of both and early orchidopexy and germ cell maturation. Lancet 2001;358:1156–7.
31. Kolon F. Cryptorchidism: diagnosis, treatment and long-term prognosis. Urol Clin North Am 2004;31:469–80.
32. Cortes D. Infertility despite surgery for cryptorchidism in childhood can be classified by patients with normal or elevated follicle-stimulating hormone and identified at orchidopexy. BJU Int 2003;91:670–4.
33. Ferguson L, Agoulnik A. Testicular cancer and cryptorchidism. Front Endocrinol 2013;4:32.
34. Richiardi L, Akre O, Montgomery SM. Fecundity and twinning rates as measures of fertility before diagnosis of germ-cell testicular cancer. J Natl Cancer Inst 2004;96:145–7.
35. Richiardi L, Pettersson A, Akre O. Genetic and environmental risk factors for testicular cancer. Int J Androl 2007;30:230–40.

36. Eisenberg ML, Li S, Cullen MR, Baker LC. Increased risk of incident medical conditions in infertile men: analysis of United States claims data. Fertil Steril 2016;105:629–36.

37. Pasqualotto FF, Lucon AM, Sobreiro BP. Effects of medical therapy, alcohol, smoking, and endocrine disruptors on male infertility. Rev Hosp Clin Fac Med Sao Paulo 2004;49:375–82.

38. Liu RZ, Gao JC, Zhang HG, Wang RX, Zhang ZH, Liu XY. Seminal plasma zinc level may be associated with the effect of cigarette smoking on sperm parameters. J Int Med Res 2010;38:923.

39. Srivastava A, Kreiger N. Cigarette smoking and testicular cancer. Cancer Epidemiol Biomarkers Prev 2004;13:49–54.

40. Moirano G, Zugna D, Grasso C, Mirabelli D, Lista P, Ciuffreda L, et al. Postnatal risk factors for testicular cancer: the EPSAM case-control study. Int J Cancer 2017;141:1803-10., Published online 2017;141:1803-10..

41. Hakonsen LB, Ernst A, Ramlau-Hansen CH. Maternal cigarette smoking during pregnancy and reproductive health in children: a review of epidemiological studies. Asian J Androl 2014;16:39–49.

42. Walsh TJ, Schembri M, Turek PJ, Chan JM, Carroll PR, Smith JF, et al. Increased risk of high-grade prostate cancer among infertile men. Cancer 2010;116:2140–7.

43. Ruhayel Y, Giwercman A, Ulmert D, Rylander L, Bjartell A, Manjer J, et al. Male infertility and prostate cancer risk: a nested case-control study. Cancer Causes Control 2010;21:1635–43.

44. Walsh T. Male reproductive health and prostate cancer risk. Curr Opin Urol 2011;21:506–13.

45. Jorgensen KT, Pedersen BV, Johansen C, Frisch M. Fatherhood status and prostate cancer risk. Cancer 2008;112:919–23.

46. Wiren SM, Drevin Li, Carlsson SV. Fatherhood status and risk of prostate cancer: nationwide, population-based case-control study. Int J Cancer 2013; 133:937–43.

47. Eisenberg ML, Park Y, Brinton LA, Hollenbeck AR, Schatzkin A. Fatherhood and incident prostate cancer in a prospective US cohort. Int J Epidemiol 2011;40:480–7.

48. Mao Y, Xu X, Zheng X, Xie L. Reduced risk of prostate cancer in childless men as compared to fathers: a systematic review and meta-analysis. Sci Rep 2016;6:19210.

49. Eisenberg ML, Betts P, Herder D, Lamb DJ, Lipshultz LI. Increased risk of cancer among azoospermic men. Fertil Steril 2013;100:681–5.

50. Hotaling JM, Carrell DT. Clinical genetic testing for male factor infertility: current applications and future directions. Andrology 2014;2:339.

51. Skeldon SC, Goldenberg L. Bladder cancer: a portal into men's health. Urol Oncol 2015;33:40–4.

52. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility. Philadelphia: Lippincott Williams & Wilkins; 2011.

53. Schultz N, Hamra FK, Garbers DL. A multitude of genes expressed solely in meiotic or postmeiotic spermatogenic cells offers a myriad of contraceptive targets. Proc Natl Acad Sci U S A 2003;100:12201–6.

54. Aston KI, Conrad DF. A review of genome-wide approaches to study the genetic basis for spermatogenic defects. Spermatogenesis 2012;927:397–410.

55. Ji G, Long Y, Zhou Y, Huang C, Gu A, Want X. Common variants in mismatch repair genes associated with increased risk of sperm DNA damage and male infertility. BMC Med 2012;10:49.

56. Wei K, Clark AB, Wong E, Kane MF, Mazur DJ, Parris T, et al. Inactivation of exonuclease 1 in mice results in DNA mismatch repair defects, increased cancer susceptibility, and male and female sterility. Genes Dev 2003;17:603–14.

57. Terribas E, Bonache S, Garcia-Arevalo M, Sanchez J, Franco E, Bassas L, et al. Changes in the expression profile of the meiosis-involved mismatch repair genes in impaired human spermatogenesis. J Androl 2010;31:346–57.