# Cancer risk in first- and second-degree relatives of men with poor semen quality

Ross E. Anderson, M.D., M.C.R.,[a] Heidi A. Hanson, Ph.D., M.S.,[c] Darshan P. Patel, M.D.,[a] Erica Johnstone, M.D.,[b] Kenneth I. Aston, Ph.D., H.C.L.D.,[a] Douglas T. Carrell, Ph.D., H.C.L.D.,[a,d] William T. Lowrance, M.D., M.P.H.,[a] Ken R. Smith, Ph.D.,[e] and James M. Hotaling, M.D., M.S.[a]

[a] Division of Urology, Department of Surgery, University of Utah; [b] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Utah; [c] Department of Family and Preventive Medicine and Population Sciences, Huntsman Cancer Institute, University of Utah; [d] Department of Human Genetics, University of Utah School of Medicine; and [e] Department of Family and Consumer Studies and Population Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah

**Objective:** To further characterize the association of male infertility with health risks by evaluating semen quality and cancer risk in family members.
**Design:** Retrospective, cohort study.
**Setting:** Not applicable.
**Patient(s):** A total of 12,889 men undergoing SA and 12,889 fertile control subjects that had first-degree relative (FDR) data (n = 130,689) and 8,032 men with SA and 8,032 fertile control subjects with complete second-degree relative (SDR) data (n = 247,204) were identified through the UPDB. An equal number of fertile population control subjects were matched.
**Interventions:** None.
**Main Outcome Measure(s):** Adult all-site, testicular, thyroid, breast, prostate, melanoma, bladder, ovarian, and kidney cancer diagnoses in FDRs and SDRs.
**Result(s):** The FDRs of men with SA had a 52% increased risk of testicular cancer compared with the FDRs of fertile population control subjects. There was no significant difference in testicular cancer risk for the SDRs based on any of the semen parameters. The FDRs and SDRs of azoospermic men had a significantly increased risk of thyroid cancer compared with fertile population control subjects.
**Conclusion(s):** These data suggest a link between male infertility and selected cancer risk in relatives. This highlights the possibilities of shared biologic mechanisms between the two diseases, exposure to environmental factors, and an increased level of genetic and/or epigenetic burden in subfertile men and their relatives that may be associated with risk of cancer. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
**Key Words:** Epidemiology, infertility, testicular cancer, semen analysis, andrology

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Each year, more than 700,000 men in the United States are estimated to pursue evaluation of male-factor infertility (1). Male subfertility is argued to be a biomarker for overall male somatic health (2, 3). It has been linked to increased risk for testicular, prostate, colon cancer, reduced lifespan, and possibly cardiovascular disease and metabolic syndrome (4–8). Epidemiologic studies have demonstrated the association between infertility and testicular cancer, with the increased risk of developing testicular cancer estimated to be 30%–90% (6, 9). Similarly, infertile men have 2.6 times the risk of high-grade prostate cancer, yet little is known of the cancer risk for an infertile man's family members (7).

Eisenberg et al. used a medical claims database to compare cancer risk in male infertility patients, men with prior vasectomy, and healthy control subjects and demonstrated an increased cancer risk of genitourinary cancer, particularly testis cancer, in the infertile men (10). However, the study was limited by claims-level analysis and could not examine the association of specific semen quality parameters and cancer risk.

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Reprint requests: Ross E. Anderson, M.D., M.C.R., Division of Urology, Department of Surgery, University of Utah School of Medicine, 30 North 1900 East, Rm #3B420, Salt Lake City, Utah 84132 (E-mail: r.anderson@hsc.utah.edu).

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Testis cancer, much like male infertility, may be the result of genetic, epigenetic, and environmental insults. However, unlike male infertility, testis cancer has a well known and documented risk of heritability. If a man has a brother with testicular cancer, his relative risk of testicular cancer is 8–12 times greater than the general population's, and the relative risk is 2–4 times higher if a man has a father with testicular cancer history (11–13). We hypothesized that the association between infertility and testis cancer might also share a familial component, wherein the genetic risk factors that predispose a man to infertility may also confer additive risk of testicular cancer. Therefore, we sought to determine a familial association between male infertility and cancer risk, with the use of the multigenerational Utah Population Database (UPDB), which is linked to the Utah and Idaho Cancer Registries, as well as the University of Utah UU and Intermountain Health Care (IHC) semen analysis (SA) databases. Our primary objective was to characterize the male infertility phenotype based on cancer risk in the first-degree (FDRs) and second-degree (SDRs) relatives of men who underwent SA. Also, we evaluated if specific semen quality defects were associated with an increased cancer risk in family members.

## MATERIALS AND METHODS

### Data

This study used the data compiled by the Subfertility Health and Assisted Reproduction (SHARE) study that has been linked to the UPDB. The SHARE database is composed of men who underwent SA at the UU Andrology Clinic from 1996 to 2011 and at IHC from 2002 to 2011. The UPDB is a health data repository that collects and integrates data about residents of Utah, a state in the intermountain west with a population of 2.8 million people. The database includes biodemographic, health, economic, cancer, and genetic data by linking various sources, including medical records from the two largest health care systems in the state, state driver licenses, and birth, marriage, and death certificate data. It also houses extensive pedigree data from the mid-19th century, which allows researchers to study health outcomes across multiple generations. Many epidemiologic studies have used the complex pedigrees of the UPDB to identify and understand familial diseases (14–17). This integration of data combines biospecimen data with a population resource that contains medical, genealogic, and administrative data to create a unique and comprehensive database for the evaluation of fertility and familial cancer history.

### Measures

We evaluated the association of familial cancers and infertility based on the following semen parameters: sperm count (millions [M]), sperm concentration (M/mL), sperm motility (percentage of sperm with forward motility), total motile count (M), sperm head morphology, and vitality. Total motile count, sperm head morphology, and vitality data were available only from the UU database. SAs were performed and processed based on the 2010 World Health Organization guidelines (18). If a man had more than one SA on record, we used the mean value for each semen parameter. A sperm concentration of 0 M/mL was categorized as azoospermia, <15 M/mL as oligozoospermia, 15–178 M/mL as normozoospermia, and >178 M/mL as hyperzoospermia (based on the 90th percentile of data). Total sperm count was categorized as follows: 0 M as azoospermia, <39 M as oligozoospermia, 39–579 M as normozoospermia, and >579 M as hyperzoospermia (based on the 90th percentile). Sperm motility and vitality cut points were made based on quartiles and were as follows: azoospermia, >0–49%, 50%–59%, 60%–69%, and 70%–100%. Total motile count and sperm head morphology were all categorized based on empirically derived quartiles (Q1–Q4).

Cancer diagnoses were obtained from the UPDB with the use of linked data from the Utah and Idaho Cancer Registries and Utah death certificates. The Utah Cancer Registry (UCR) is a National Cancer Institute Surveillance Epidemiology and End Result (SEER) registry and has collected information on all cancer diagnoses from 1966 to 2012 for Utah residents. Before 1966, individuals with cancer were identified with the use of cause of death information listed on the Utah state death certificates, which have been linked to the UPDB from 1905 to the present. This study was approved by the Institutional Review Boards of the UU and IHC by the Utah Resource for Genetic and Epidemiologic Research (www.research.utah.edu/rge/; no. IRB_00069711).

### Study Design

We performed a retrospective cohort analysis of cancer risk in FDRs and SDRs of men who underwent SA as part of an infertility work-up at the UU Andrology Clinic from 1996 to 2011, or had SA performed by Intermountain Health Care from 2002 to 2011. Together, these two tertiary medical centers' andrology labs have captured ~90% of all SAs performed in Utah since 2004.

We identified 26,147 men with SAs performed during our study period. This cohort included all men evaluated from these two assisted reproductive technology centers, and therefore both fertile men, infertile men, and men with infertile female partners were included. Men presented for male-factor infertility workup or as part of a couple's evaluation for infertility. We excluded 1,424 men who did not link to another record in UPDB, 434 with inadequate follow-up, and 449 with cancer before SA. There were 10,910 men without complete pedigree information on their parents, and therefore a total of 12,889 men were available with FDR information. This cohort of men was used to study the cancers diagnosed in FDRs. Another 4,857 men did not have full pedigree information available on their grandparents, which left 8,032 men with complete SDR information available for analysis.

Fertile population control subjects were selected randomly without replacement from the UPDB. Men seen at the IHC or UU clinics were excluded from the pool of potential control subjects. Control subjects were required to be residents of the state of Utah with adequate follow-up