Increased Risk of Cancer in Infertile Men: Analysis of U.S. Claims Data

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Abbreviations and Acronyms

HL = Hodgkin lymphoma

NHL = nonHodgkin lymphoma

SEER = Surveillance, Epidemiology, and End Results

SIR = standardized incidence rate

Accepted for publication November 10, 2014.

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† Financial interest and/or other relationship with Sandstone Diagnostics and Reprovantage.

‡ Nothing to disclose.

§ Financial interest and/or other relationship with the American Hospital Association, Kaiser Permanente and National Institute for Health Care Management.

For another article on a related topic see page 1709.

Editor's Note: This article is the fifth of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1732 and 1733.

Purpose: Aberrations in reproductive fitness may be a harbinger of medical diseases in men. Data suggest a higher risk of testicular cancer in infertile men. However, the relationship between infertility and other cancers remains uncertain.

Materials and Methods: We analyzed subjects from the Truven Health MarketScan® claims database from 2001 to 2009. Infertile men were identified through diagnosis and treatment codes. Comparison groups were created of men who underwent vasectomy and a control cohort of men who were not infertile and had not undergone vasectomy. The incidence of cancer was compared to national U.S. estimates. Infertile men were also compared to men who underwent vasectomy and the control cohort using a Cox regression model.

Results: A total of 76,083 infertile men were identified with an average age of 35.1 years. Overall 112,655 men who underwent vasectomy and 760,830 control men were assembled. Compared to age adjusted national averages, infertile, vasectomy and control subjects in the study cohorts had higher rates of all cancers and many individual cancers. In time to event analysis, infertile men had a higher risk of cancer than those who underwent vasectomy or controls. Infertile men had a higher risk of testis cancer, nonHodgkin lymphoma and all cancers than the vasectomy and control groups.

Conclusions: Consistent with prior reports, we identified an increased risk of testicular cancer in infertile men. The current data also suggest that infertile men are at an increased risk of all cancers in the years after infertility evaluation. Future research should focus on confirming these associations and elucidating pathways between infertility and cancer.

Key Words: infertility, male; fertility; neoplasms

Aberrations in reproductive fitness may be a harbinger of medical diseases in men. Recent studies suggest that male infertility is associated with an increased risk of cancer in the years after an infertility evaluation. To date, most studies support an increased risk of testis cancer in subfertile men. Using paternity as a surrogate for fertility, a case control study demonstrated a higher risk of testis cancer in men with fewer offspring.[1] This group later confirmed these findings in a cohort of infertile men by showing that men with impaired semen quality had a higher subsequent risk of testis

0022-5347/15/1935-1596/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.11.080
Vol. 193, 1596-1601, May 2015
Printed in U.S.A.

cancer (SIR 1.6, 95% CI 1.3–1.9).[2] Walsh et al examined a cohort of infertile couples in California and found that men with male factor infertility (as defined by a treating provider) had an increased risk of testis cancer (SIR 2.8, 95% CI 1.5–4.8).[3]

While infertile men are thought to be at higher risk for testis cancer, the risks of other malignancies are less certain. Walsh et al also found that men with male factor infertility were at higher risk for high grade prostate cancer, although overall prostate cancer risk was unaltered.[4] In contrast, a case control study demonstrated that infertile men had a lower risk of prostate cancer.[5] Thomas et al identified a trend associating male factor infertility with breast cancer in a questionnaire based case control study.[6] As azoospermia, the most severe form of male factor infertility, would involve the highest risk of adverse health outcomes, we examined cancer incidence in men with azoospermia and found that azoospermic men had an increased risk of all cancers (SIR 2.9, 95% CI 1.4–5.4).[7]

Investigators have hypothesized that genetic, hormonal, environmental, lifestyle or in utero factors could explain a link between a man's fertility and cancer risk.[8,9] As approximately 10% of the male human genome is involved in reproduction, it is not unlikely that other health conditions may be linked to impaired fertility.[10,11] However, the relationship between fertility and cancer is difficult to track given the low incidence of cancer in reproductive age men and the difficulty in following reproductive outcomes without centralized registries.

Since many private insurance organizations cover infertility testing, we used a large database of health insurance claims to examine outcomes in men with male infertility. Given the biological plausibility of this association, the conflicting data in the literature and the relevance to millions of men impacted by infertility, we investigated whether a diagnosis of male factor infertility was associated with subsequent cancer risk.

MATERIALS AND METHODS

Patients

We analyzed subjects in the Truven Health MarketScan Commercial Claims and Encounters database. This database provides information from adjudicated and paid insurance claims filed for the care of privately insured individuals with employment based insurance through a participating employer. MarketScan provides claims data on 77 million covered lives since 1996. This study used data from 2001 through 2009. The number of individuals represented in the database varies over time and the more recent years of the data contain more than 30 million covered lives.

We focused on a cohort of likely infertile men, identified by outpatient claims with an infertility diagnosis code (ICD-9 606.x, V26.21) or by the presence on any claim of a procedure code (CPT) for fertility testing or semen analysis/semen preparation (89300, 89310, 89320, 89321, 89322, 89325, 89329, 89330, 89331). We recorded the first date of a relevant diagnosis or procedure code as the index date. Given the variation in infertility coding and reimbursement practices in the U.S., we attempted to be as broad as possible with our definition.

As cancer diagnosis and treatment can lead to additional cancers, men with any claim with a diagnosis code for cancer before the index date or within 1 year after the index date were excluded from study. Subjects were required to be enrolled in a plan covered by the database for at least 1 year before and for more than 1 year after the index date. Subjects were also required to be between 18 and 50 years old on the index date.

A comparison group of men age 18 to 50 with claims containing a procedure code for vasectomy (CPT 55250 or 55450) was assembled, as this group should include few or no infertile men.[12] Men in this group were assigned an index date as the earliest date of a claim with a vasectomy procedure code, and were required to be enrolled in a plan covered by the database for at least 1 year before and 1 year after the index date. In addition, a control group of men not in either of the 2 previously described cohorts was assembled. We selected 10 men for each man in the infertile cohort, matched by age and followup time.

For each man the number of outpatient visits after the index date was ascertained based on the presence of claims with CPT codes indicating new and followup office visits, consultations or preventive medicine encounters. Medical comorbidities were determined based on ICD-9 codes on any claim, and included hypertension (401-405), obesity (278.0), smoking (305.1, V1582) and diabetes (250-250.93).

Outcome Ascertainment

Cancer diagnoses were identified using diagnosis codes on inpatient and outpatient claims. Diagnosis codes identifying cancer were aligned to SEER definitions. We identified men with claims diagnoses indicating the presence of any invasive cancer (ICD-9 140-209 excluding skin squamous cell, skin basal cell and noninvasive cancers), and identified men with codes indicating the presence of specific cancers such as upper respiratory (140.x-149.x, 160.x, 161.x), stomach (151.x), colorectal (153.x, 154.0, 154.1, 154.8), liver and gallbladder (155.x and 156.x), pancreas (157.x), lung (162.x), melanoma (172.x), breast (175.x), prostate (185.x), testis (186.x), bladder (188.x), kidney (189.0, 189.1), brain and nervous system (191.x, 192.x), thyroid (193.x), nonHodgkin lymphoma (200.x, 202.x), Hodgkin lymphoma (201.x), leukemia (204.x, 205.x, 206.x, 207.x, 208.x) and esophageal (150.x).

Statistical Analysis

Men accrued at-risk time beginning 1 year after their index dates until cancer diagnosis or December 31 of the final year of enrollment in a health plan in the MarketScan database. The first year was excluded from analysis since a cancer diagnosis in this period was an exclusion criterion.

We compared cancer incidence rates in our cohorts with cancer incidence in the general U.S. population using