Childhood Cancer Risk in the Siblings and Cousins of Men with Poor Semen Quality

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Abbreviations and Acronyms

ALL = acute lymphoblastic leukemia

ART = assisted reproductive technology

SA = semen analysis

UPDB = Utah Population Database

Accepted for publication September 21, 2016.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by Grant 1K12HD085852-01 (HAH).

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Purpose: Poor semen quality is associated with reduced somatic health and increased cancer risk. Infertility and cancer are increasingly being linked by epidemiologists and basic scientists. We sought to identify semen parameters associated with an increased childhood cancer risk in the family members of subfertile men.

Materials and Methods: We performed a retrospective cohort study in men from the SHARE (Subfertility Heath and Assisted Reproduction) study who underwent semen analysis between 1994 and 2011. We used fertile population controls from the Utah Population Data Base. Our primary outcome was the risk of any childhood (18 years or younger) cancer in the siblings and cousins of men who underwent semen analysis compared to fertile, age matched controls. Cox proportional hazard regression models were used to test the association between semen quality and childhood cancer incidence.

Results: We selected 10,511 men with complete semen analysis and an equal number of fertile controls. These men had a total of 63,891 siblings and 327,753 cousins. A total of 170 and 958 childhood cancers were identified in siblings and cousins, respectively. The 3 most common cancers diagnosed in siblings were acute lymphoblastic leukemia in 37, brain cancer in 35 and Hodgkin lymphoma in 15. Oligozoospermia was associated with a twofold increased risk of any childhood cancer and a threefold increased risk of acute lymphoblastic leukemia in the siblings of subfertile men compared to fertile controls (HR 2.09, 95% CI 1.18–3.69 vs HR 3.07, 95% CI 1.11–8.46).

Conclusions: Siblings of men with oligozoospermia are at increased risk for any-site cancer and acute lymphoblastic leukemia. This suggests a shared genetic/epigenetic insult or an environmental exposure that merits further investigation.

Key Words: testis, oligospermia, siblings, neoplasms, precursor cell lymphoblastic leukemia-lymphoma

Cancer is the second most common cause of childhood death after trauma and leukemia is the most common subtype of the estimated 10,380 new cases each year.[1] There is mounting evidence that a link exists between infertility and leukemia. A Danish population study showed that if a

0022-5347/17/1973-0898/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2016.09.110
Vol. 197, 898-905, March 2017
Printed in U.S.A.

woman was evaluated for infertility, there was a significantly increased risk of leukemia developing in the offspring in childhood (HR 1.30, 95% CI 1.06−1.60).[2] This increased risk was postulated to stem from drugs used for ovulation induction, such as clomiphene citrate, but male factors have not been investigated.[3,4] Less is known about the association of male factor infertility and the risks of associated cancers in the offspring or family members.

Male factor infertility is extremely common with a self-reported 7.5% of American men having undergone SA at an assisted reproduction center.[5] Of American couples 15% report infertility and 1.5% of children are born through ART.[6] Defining the phenotype of male factor infertility is an active area of research and several studies demonstrated associations with an increased risk of cancers, obesity and poor overall health.[7−11]

With a known increased risk of cancers in men undergoing SA, we sought to identify semen parameters associated with an increased childhood cancer risk in the family members of subfertile men. Our goal was to explore the association between male infertility and childhood cancer risk in family members using the multigenerational UPDB. Understanding the familial risk of cancer in subfertile men will help elucidate biological and environmental mechanisms leading to infertility in men and the health of their family members.

Our primary objective was to characterize the male infertility phenotype based on childhood cancer risk in the siblings and cousins of men who underwent SA. We hypothesized that poor quality semen parameters are associated with an increased childhood cancer risk in the family members of men who undergo SA.

METHODS

Data

We used data compiled in the SHARE study, which combines medical, genealogical and administrative data with biospecimen data to create a unique resource for the evaluation of fertility and familial cancer history. This was then coupled to UPDB, a health data repository with more than 8 million individuals and 22 million records. Multiple epidemiological studies have used the complex pedigrees of the UPDB to identify and understand familial diseases.[12−15]

Cancer diagnoses were obtained from UPDB using linked data from the Utah Cancer Registry and Utah death certificates. This registry is a NCI (National Cancer Institute) SEER (Surveillance, Epidemiology and End Result) registry that has collected information on all cancer diagnoses from 1966 to 2012 for Utah residents. The study was approved by the University of Utah institutional review boards (www.research.utah.edu/rge/) No. IRB_00069711.

Study Design

We performed a retrospective cohort analysis of childhood cancer risk in siblings and cousins of men who underwent SA at the University of Utah Andrology Clinic from 1996 to 2011 and at the Intermountain® Healthcare Sunquest™ system from 2002 to 2011. Together these 2 andrology laboratories have captured approximately 90% of all semen analyses performed in Utah since 2004.

We identified 26,147 men in whom SA was performed during our study period. This cohort included all men evaluated at these 2 assisted reproductive technology centers. Thus, fertile men, infertile men and men with infertile female partners were included. Men presented for male factor infertility workup or as part of the evaluation for infertility of a couple. The sample of men with SA consisted of 12,889 men with complete information on first-degree relatives. Figure 1 lists inclusion and exclusion criteria.

Fertile population controls were selected randomly without replacement from UPDB. Men evaluated at either infertility clinic were excluded from the pool of potential controls. Controls were required to be residents of Utah with adequate followup or familial data in UPDB. They were matched by age and birth year at a matching ratio of 1:1. We used birth certificate data to define fertile as having at least 1 naturally conceived child. We did not have SA data on the controls. These men did not have a cancer diagnosis at the time of SA in the matched subfertile male.

Siblings and cousins of men with SA and the respective relatives of the matched controls were selected from UPDB. This provided a total of 63,891 siblings and 327,753 cousins born after 1966. We chose to only look at the siblings and cousins of men who underwent semen analyses because the Utah Cancer Registry was founded in 1966 and we would not have had adequate followup for older family members. A total of 10,511 men with SA had at least 1 sibling and 10,300 had at least 1 cousin born after 1966. Tables 1 and 2 show descriptive statistics for these men. Childhood cancer was defined as a cancer diagnosis at age 18 years or less.

SAs were performed and processed based on the 2010 WHO guidelines.[16] When men underwent more than 1 SA, the mean of each semen parameter was used for our study. Details regarding the subcategorization of semen parameters in this data set were previously published.[17]

Statistical Methods

Cox regression models were used to test the association between semen quality and childhood cancer incidence in siblings and cousins of men with SA and matched controls. The risk in relatives of men who underwent SA compared to relatives of controls was determined independently for each relation type (sibling and cousin). Analyses were done to compare any-site and site specific cancer risk separately in siblings and cousins of men seen at a fertility clinic to those in fertile population controls. We then investigated the association by semen parameter in separate models. To determine the risk of cancer in