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

Ross E. Anderson*, Heidi A. Hanson, William T. Lowrance, Jeffrey Redshaw, Siam Oottamasathien, Anthony Schaeffer, Erica Johnstone, Kenneth I. Aston, Douglas T. Carrell, Patrick Cartwright, Ken R. Smith, and James M. Hotaling

Division of Urology, Department of Surgery (REA, WTL, JR, SO, AS, KIA, DTC, PC, JMH) and Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology (EJ, DTC), Department of Family and Preventive Medicine and Population Sciences (HAH) and Department of Family and Consumer Studies and Population Sciences (KRS), Huntsman Cancer Institute and Department of Human Genetics, School of Medicine (KIA, DTC), University of Utah, Salt Lake City, Utah

Abstract

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).

*Correspondence and requests for reprints: Division of Urology, Department of Surgery, University of Utah School of Medicine, 30 North 1900 East, Room 3B420, Salt Lake City, Utah 84132 (telephone: 801-213-2700; FAX: 801-585-2891; r.anderson@hsc.utah.edu).

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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.

Keywords

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 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 relatives of men with male factor infertility and men with normal semen parameters case-case analyses were also completed, in which relatives of men with abnormal semen parameters were compared to relatives of men with normal semen parameters.

All relatives of men who underwent SA and their fertile population controls were included in analyses. For example, for families containing brothers with semen analyses each man was included as a separate index case and the risk among relatives of each case was calculated separately. This approach has been shown to lead to unbiased estimates of risk.¹⁸ We used the Huber-White sandwich estimator of variance for clustered data corrected for the nonindependence of observations within families.¹⁹ Relatives of fertile men not presenting in a fertility clinic served as the reference group in all analyses except as noted.

Time was measured as years at risk. All models controlled for gender when the cancer was not gender specific, and birth year. Death date and the last known date of residing in Utah were used as the date of right censoring. Analyses were performed for all cancers combined and then for the most common subtypes of childhood cancer seen in our population, including ALL, brain cancer, Hodgkin lymphoma and bone/joint cancers.

RESULTS

Our subfertile cohort of 10,511 men had a total of 32,151 siblings and 152,015 cousins, while control men had a total of 31,740 siblings and 175,738 cousins who were included in the final analysis. There were no significant differences in average followup between the siblings and cousins of subfertile men and controls (224.9 vs 225.3 and 219.1 vs 218.3 months, respectively).

A total of 170 childhood cancers were identified in siblings and 958 were identified in cousins. A total of 95 childhood cancers were diagnosed in the siblings of men who underwent SA compared to 75 in the control group. The 3 most common cancers diagnosed in siblings were ALL in 37, brain cancer in 35 and Hodgkin lymphoma in 15. There were no differences in the number of cancers diagnosed in family members based on gender.

A total of 517 childhood cancers were diagnosed in the cousins of men who underwent SA compared to 441 in the control group. The 3 most common cancers diagnosed in cousins were ALL in 180, brain cancer in 156 and bone/joint cancers in 73.

Any-Site Cancer

The siblings of men with an oligozoospermic concentration were at nearly twofold increased risk for any-site cancer compared to the siblings of controls (HR 2.09, 95% CI 1.18–3.69, fig. 2). The siblings of men with an oligozoospermic count were also at an associated increased risk of any-site cancer compared to the siblings of controls (HR 1.90, 95% CI

1.03–3.48, fig. 3). All other semen parameters did not demonstrate a significant change in risk for any-site cancer in the siblings of men who underwent SA compared to fertile control siblings.

Acute Lymphoblastic Leukemia

For the siblings of men with an oligozoospermic concentration there was a threefold increased risk of ALL compared to the siblings of controls (HR 3.07, 95% CI 1.11–8.46, table 3). The siblings of men with azoospermia or a normozoospermic concentration were not at increased risk (fig. 2). All other semen parameters did not demonstrate a significant change in the risk of ALL in the siblings of men who underwent SA.

Brain Cancer

Brain cancer was the second most common childhood cancer in our cohort in siblings and cousins. The quality of semen parameters did not demonstrate a significant difference in childhood cancer risk for the siblings or cousins of men who underwent SA compared to fertile control family members.

Cousins

There was no significant difference in cancer risk (any-site or site specific) between the cousins of men who underwent SA and their respective controls based on semen parameters.

DISCUSSION

Using the SHARE semen analysis database, we identified an association between semen quality and childhood cancers in the family members of men with an oligozoospermic concentration and count. This suggests an inherent link between infertility and cancer risk. While other studies have shown the complexity of the infertility and health phenotype, to our knowledge this is the first study to investigate whether the quality of semen parameters in a man is associated with a childhood cancer risk in their family members.

The association between infertility and leukemia in the offspring has been identified in several large European population database studies. One of the larger studies used the Medical Birth Registry of Norway.²⁰ That study showed that, although the overall cancer risk was no different, if a couple used ART, their offspring was at increased risk for leukemia. The French ESCALE Study (Étude Sur les Cancers et les Leucémies de l'Enfant) demonstrated an increased risk of ALL in the offspring of mothers who used ovulation induction but not in vitro fertilization or artificial insemination compared to fertile control children.⁴ Maternal factors, such as hormonal adjuncts during conception, specific ART therapies and subfertility, are all associated with leukemia risk in offspring.

We found an increased risk of leukemia in the siblings of men with an oligozoospermic concentration. This emphasizes the importance of understanding the impact of subfertility on the somatic health of their family members. Further, it poses the question of whether the linkage seen in these studies is, in fact, a result of familial genetic or environmental factors that predispose family members to cancer and infertility.

Our finding of an increased risk of leukemia in first-degree relatives is suggestive of a shared genetic insult or an environmental exposure that affects both fertility and leukemia risk. A meta-analysis of exposure and associated risks of leukemia demonstrated that occupational and household product exposure increased the relative risk of childhood leukemia.²¹ A shared environmental exposure at the household level is a possible explanation for the association of a higher cancer risk in the siblings of oligozoospermic men.

To further complicate this story, male infertility results from rare variants in 3,500 genes required for spermatogenesis and it is often a result of de novo mutations.^{22–24} This heterogeneity in male factor infertility results in the inability to identify a cause of infertility in 22% of cases.²⁵ There is now evidence that parental health and exposures can influence the health of an offspring through epigenetic changes.^{26,27}

Since the childhood cancer risk was increased in the siblings of oligozoospermic men, epigenetic changes in 1 parent or both parents is another possible mechanism. Similar to our prior work, we found this elevated cancer risk in oligozoospermic but not azoospermic men and their family members.¹⁷ A possible explanation for this is that the aberrant stem cells found in both these groups could theoretically represent a somatic stem cell dysregulation leading to cancer. However, the genetics underlying this are so disordered in the azoospermic group that they are nonfunctional and not associated with familial cancer risk.

There also may be a common mechanism between known molecular contributors to infertility, like DNA mismatch repair, and cancers such as ALL.²⁸ Future studies investigating the health of the offspring of subfertile parents should not ignore the role of the father, and the broader genetic and environmental components that may lead to these observed associations.

Despite the interesting findings of this study, it is not without limitations.

1) We used a fertile population control group of men and their associated siblings/cousins to attempt to minimize the inherent shortcomings of this retrospective cohort study. 2) We did not have SA data on our fertile controls. 3) We did not have medical comorbidity indexes or smoking status for the men who underwent SA. In Utah the age adjusted rate of cancer at all sites in children younger than 15 years is similar to the rate in the United States (15.6 vs 16/100,000 person-years).²⁹ We were unable to control for subject location in the state and environmental exposure is a potential confounder for this study but we plan to investigate this in future studies. Our database did not subcategorize each infertile male by infertility diagnosis, for example Klinefelter syndrome. This did not impact our goal of understanding how semen parameters influenced familial cancer risk but in future studies we will investigate associations of specific diagnoses and familial cancer risks. 4) This study only involved Utah residents and the state has less ethnic and racial diversity than other regions. 5) We do not know the proportion of female partners with diagnosed infertility. 6) There is a possible selection bias based on socioeconomic status because this cohort of men had the means to be evaluated as an individual or couple seeking infertility evaluation. It is important to note that, because childhood cancer is a rare event and our study was subject to

these limitations, more research is needed to make a definitive causal statement about the observed associations.

The risk of leukemia associated with subfertility may be due to a genetic predisposition to infertility or to shared familial exposure. It may not be due to ART itself. This study has helped identify families with both an increased cancer risk and infertility. In the future we need to focus on identifying a common mechanism that impacts spermatogonial and hematopoietic stem cells. We also plan to investigate environmental factors that affect male infertility and cancer risk using residential proximity to known sites of pollution.

CONCLUSIONS

Oligozoospermia was associated with an increased risk of childhood cancer and ALL in the siblings of subfertile men who underwent SA compared to fertile controls. This suggests a shared genetic/epigenetic insult or an environmental exposure that merits further investigation.

Acknowledgments

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Abbreviations and Acronyms

ALL	acute lymphoblastic leukemia
ART	assisted reproductive technology
SA	semen analysis
UPDB	Utah Population Database

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Figure 1.

Figure 2. Semen concentration and risk of any site cancer and ALL in siblings of men who underwent semen analysis compared to fertile controls.

Figure 3.
Semen count and risk of any site cancer and ALL in siblings of men.

Table 1

Cohort demographics

Semen Analysis	No. Pts	Mean $\pm$ SD (range)	
+ Sibling:			
Birth yr	10,511	1977.06 $\pm$ 6.18	(1951–1992)
Death yr	59	2009.24 $\pm$ 3.11	(2000–2013)
Last yr known alive	10,511	2012.62 $\pm$ 1.93	(1997–2015)
1st Yr semen analysis collected	10,511	2007.02 $\pm$ 4.36	(1996–2014)
No. semen analyses	10,511	1.24 $\pm$ 0.63	(1–10)
Age at semen analysis	10,511	29.96 $\pm$ 4.77	(21–55)
+ 1st Cousin:			
Birth yr	10,300	1976.41 $\pm$ 6.86	(1941–1992)
Death yr	61	2009.26 $\pm$ 3.28	(2000–2013)
Last yr known alive	10,300	2012.59 $\pm$ 1.98	(1996–2015)
1st Yr semen analysis collected	10,300	2006.77 $\pm$ 4.49	(1996–2014)
No. semen analyses	10,300	1.23 $\pm$ 0.61	(1–10)
Age at semen analysis	10,300	30.36 $\pm$ 5.25	(21–67)

Table 2

Semen parameters of men with semen analysis

	No. Pts (%)
Concentration:	
Azoospermia	436 (4.15)
Oligozoospermia	1,088 (10.35)
Normozoospermia	5,452 (51.87)
Hyperzoospermia	3,535 (33.63)
Count:	
Azoospermia	436 (4.15)
Oligozoospermia	1,042 (9.91)
Normozoospermia	7,923 (75.38)
Hyperzoospermia	1,110 (10.56)
Motility:	
Azoospermia	436 (4.15)
Quartile 1 (0–49)	2,370 (22.55)
Quartile 2 (50–59)	2,110 (20.07)
Quartile 3 (60–69)	2,340 (22.26)
Quartile 4 (70–100)	3,255 (30.97)
Vitality:	
Azoospermia	185 (3.87)
Quartile 1 (0–45)	1,094 (22.87)
Quartile 2 (46–55)	1,023 (21.39)
Quartile 3 (56–64.4)	1,259 (26.32)
Quartile 4 (64.5–94)	1,222 (25.55)
Morphology:	
Azoospermia	185 (4.05)
Quartile 1	952 (20.82)
Quartile 2	1,143 (25.00)
Quartile 3	1,184 (25.90)
Quartile 4	1,108 (24.23)
Total motile count:	
Azoospermia	185 (3.87)
Quartile 1	1,179 (24.65)
Quartile 2	1,068 (22.33)
Quartile 3	1,131 (23.65)
Quartile 4	1,220 (25.51)

Table 3

Semen parameters and childhood cancer risk in siblings

Model vs Fertile Controls	Sibling Childhood Ca HR (95% CI)		
	All Site	Acute Lymphoblastic Lymphoma	Brain
Concentration:			
Azoospermia	1.37 (0.50–3.74)	1.66 (0.22–12.77)	1.84 (0.24–14.24)
Oligozoospermia	2.09 (1.18–3.69)	3.07 (1.11–8.46)	1.29 (0.29–5.83)
Normozoospermia	1.15 (0.78–1.68)	1.14 (0.51–2.53)	1.40 (0.62–3.16)
Hyperzoospermia	1.15 (0.74–1.78)	1.27 (0.52–3.10)	1.49 (0.59–3.78)
Count:			
Azoospermia	1.37 (0.50–3.74)	1.66 (0.22–12.78)	1.84 (0.24–14.23)
Oligozoospermia	1.90 (1.03–3.48)	2.54 (0.85–7.61)	2.07 (0.57–7.43)
Normozoospermia	1.20 (0.85–1.69)	1.19 (0.58–2.44)	1.44 (0.68–3.04)
Hyperzoospermia	0.99 (0.47–2.07)	1.73 (0.50–6.01)	0.65 (0.08–5.07)
Motility:			
Azoospermia	1.36 (0.50–3.74)	1.66 (0.22–12.77)	1.84 (0.24–14.22)
Quartile 1 (0–49)	0.95 (0.54–1.68)	1.10 (0.36–3.32)	0.64 (0.14–2.81)
Quartile 2 (50–59)	1.33 (0.81–2.19)	1.24 (0.40–3.82)	2.20 (0.83–5.83)
Quartile 3 (60–69)	1.68 (1.08–2.61)	1.62 (0.64–4.12)	2.58 (1.07–6.26)
Quartile 4 (70–100)	1.11 (0.71–1.74)	1.49 (0.62–3.60)	0.78 (0.25–2.42)