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Clinical Research Article

Azoospermia/Oligozoospermia and Prostate Cancer Are Increased in Families of Women With Primary Ovarian Insufficiency

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Abstract

Background: Nonobstructive azoospermia (NOA) and primary ovarian insufficiency (POI) have common genetics that may also predispose patients to cancer risk.

Objectives: We hypothesized that NOA or severe oligozoospermia and the risk of male cancers would be higher in families of women with POI.

Methods: Women with POI were identified using International Classification of Disease codes in electronic medical records (1995-2021) from 2 major healthcare systems in Utah and reviewed for accuracy. Using genealogy information in the Utah Population Database, women with POI (n = 392) and their relatives were included if there were at least 3 generations of ancestors available. Men with NOA or severe oligozoospermia (≤5 million/mL) from the Subfertility Health and Assisted Reproduction and the Environment Study were identified in these families and risk was calculated in relatives compared to population rates. The relative risk of prostate and testicular cancer was examined using the Utah Cancer Registry.

Results: There was an increased risk of NOA/severe oligozoospermia in relatives of women with POI among first- (relative risk 2.8 [95% confidence interval 1.1, 6.7]; $P = .03$), second- (3.1 [1.1, 6.7]; $P = .02$), and third-degree relatives (1.8 [1.1, 3.1]; $P = .03$). In these families with POI and NOA/oligozoospermia (n = 21), prostate cancer risk was higher in first- (3.5 [1.1, 8.1]; $P = .016$) and second-degree relatives (3.1 [1.9, 4.8]; $P = .000008$).

Conclusion: The data demonstrate excess familial clustering of severe spermatogenic impairment compared to matched population rates, along with higher prostate cancer risk in relatives of women with POI. These findings support a common genetic contribution to POI, spermatogenic impairment, and prostate cancer.

Key Words: meiosis, heritability, infertility, genetics, prostate cancer, menopause

Primary ovarian insufficiency (POI) results from the loss of oocytes before the age of 40 years. Chromosomal abnormalities, *FMR1* premutations, and autoimmune disease are the most common etiologies [1]. Next-generation sequencing can identify a potential genetic cause in 18% to 43% of the remaining women with POI [2-5]. While these genetic causes are highly heterogeneous, they can be categorized into definable gene sets [2].

There are 2 causal gene sets that are shared by women with POI and men with nonobstructive azoospermia (NOA) [6]. These include genes important for gonadal development and those important for prophase of meiosis I, particularly for completing homologous recombination [6]. Since our original manuscript outlining 10 meiosis I genes causing both POI and NOA [6], the number of genes continues to grow through the study of single consanguineous families and members of different families [7-12].

We previously demonstrated that POI is familial using the Utah Population Database (UPDB), a population-based genealogy database that is linked to electronic medical records [13]. Conservatively, 6.3% of women with POI had a first-, second-, or third-degree relative with POI. Taking into account the shared genetic risk between POI and NOA [6], it is possible that considering NOA in these families could increase the proportion of familial cases. We therefore searched for cases of NOA in our 3-generation families with POI.

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In addition to risk for POI and NOA, genes involved in homologous recombination and meiosis may also predispose to cancer risk [6]. We have evidence that women with POI have an increased risk for breast cancer and that family members have an increased risk of breast, prostate, and colon cancer [14]. A case-control study of azoospermic men also demonstrated an approximately 2-fold increase in cancer risk compared with controls [15]. We therefore hypothesized that families with women who carried a diagnosis of POI and men with NOA would also have an increased prostate and testicular cancer risk and tested that hypothesis in our 3-generation families.

Methods

Subjects

Women ≤40 years with POI were identified using the electronic medical records from 1995 to 2021 at the University of Utah Health Science Center and Intermountain Healthcare, as described previously [13]. Together, these 2 healthcare systems serve approximately 85% of all residents in the state of Utah [16]. Briefly, cases of POI were initially identified using International Classification of Disease (ICD)-9 (256.3, 256.31, 256.39) and ICD-10 codes (E28.3, E28.31, E28.39, E28.310, E28.319), electronic medical records text indicating POI diagnoses, and/or consistent lab values (elevated FSH > 20 IU/L or anti-Müllerian hormone <0.08 ng/mL in a woman under the age of 40 years at the time of the laboratory draw). We excluded patients who had medication, ICD, or current procedural terminology codes indicating hysterectomy, oophorectomy, endometriosis with pelvic surgery, pelvic radiation, or chemotherapy before the diagnosis of POI and those with rheumatologic disorders treated with cyclophosphamide [13]. We also excluded ICD codes indicating Turner syndrome (ICD-9 758.6 and ICD-10 Q96). Following list generation, the charts of all probable cases were individually reviewed by a medical or reproductive endocrinologist (C.K.W. or L.E.V.) for appropriate inclusion.

Men with NOA or severe oligozoospermia (≤5 million/mL) were identified from the Subfertility Health and Assisted Reproduction and the Environment (SHARE) study. We excluded men who had a previous history of radiation or chemotherapy, were using high-dose androgens, or had current prostatitis that would be expected to alter spermatogenesis. SHARE includes data from men undergoing a semen analysis for fertility treatment at the University of Utah and Intermountain Healthcare between 1996 and 2017 (n = 26 146) [17]. Semen analyses were performed following the fourth (1999) or fifth (2010) edition of the World Health Organization manual for examination and processing of human semen at the time of sample collection. The SHARE database represents a highly inclusive and well-validated male infertility cohort based on the scope of inclusion and the diagnosis based on semen analyses [17].

Pedigree Creation

The UPDB is a unique database that links genealogy information dating back to the 1800s to medical record information and other demographic data sources [16]. In total, over 11 million individuals are represented in the UPBD, and approximately 2.2 million of those individuals have at least 3 generations of genealogical data available. This database allows for powerful linkage of multigenerational cohorts and identification of similar disease states among families. To use the UPDB, medical record numbers for women with POI were converted to UPDB identification numbers by an independent oversight group. The UPDB IDs were then linked to genealogy information contained within the UPDB. For this multigenerational study, all subjects included in the final analysis were required to have at least 3 generations of genealogy information available (proband, both parents, and all 4 grandparents). Three generations of data make it more likely that complete family and medical data is available for any woman.

The same oversight group identified men with NOA or severe oligozoospermia who were part of the SHARE cohort [17]. A flag identified the presence of any of these men in the POI pedigrees (Fig. 1).

Cancer diagnoses were found in all male family members using an existing linkage between the UPDB and the Utah Cancer Registry. For the male family members, National Cancer Institute Surveillance Epidemiology and End Result registry codes for prostate (28010) and testicular (28020) cancers were identified for each subject (Fig. 1).

Ethics

The University of Utah and Intermountain Healthcare Institutional Review Boards and the Resource for Genetic and Epidemiologic Research, overseers of UPDB data, approved this study.

Calculation of Relative Risk

We estimated the relative risk of NOA or severe oligozoospermia in first-, second-, and third-degree relatives. Relative risk (RR) was estimated as the ratio of the observed number of cases of NOA/oligozoospermia for a specific relative type (eg, first-degree relatives) compared to the expected number of NOA/oligozoospermia cases based on population rates. We calculated population rates of NOA/oligozoospermia for each 5-year birth cohort represented by NOA/oligozoospermia cases and

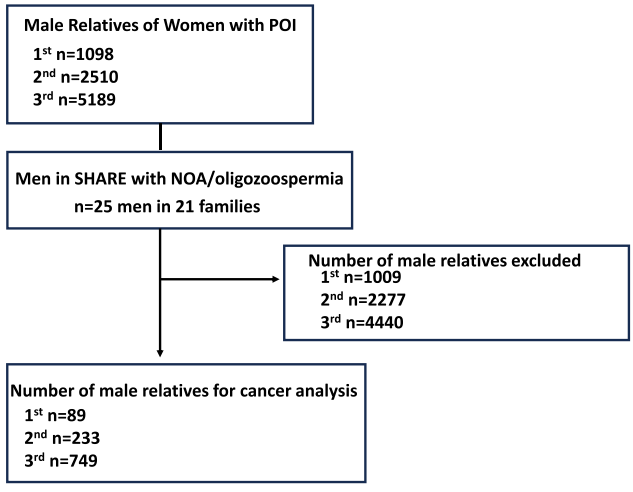

Figure 1. STROBE diagram for included male relatives. There were 25 men among the relatives of women with POI who had NOA or oligozoospermia, as identified in the Subfertility Health and Assisted Reproduction and the Environment Study database [17]. These men were found among 21 families centered on at least 1 woman with POI. The relatives in these families are included in the cancer analysis.

Abbreviations: NOA, nonobstructive azoospermia; POI, primary ovarian insufficiency.

birthplace (Utah or outside of Utah) within the University of Utah Health Sciences and Intermountain Healthcare. The rate was defined by the total number of NOA/oligozoospermia cases within a cohort divided by the total cohort size. The number of expected cases was calculated as the sum of each cohort-specific NOA/oligozoospermia risk for each individual in a set of relatives of a specific type (eg, first-degree relatives). The population rate would be conservative if NOA/oligozoospermia cases in the population were not captured by the SHARE cohort. Approximate 95% confidence intervals and exact hypothesis tests of the null hypothesis (RR = 1.0) were constructed assuming that the number of NOA/oligozoospermia cases found among the relatives follows a Poisson distribution. Of note, first-degree relatives are defined as fathers, brothers, and sons of cases. Second-degree relatives include grandfathers, uncles, nephews, half-brothers, and grandsons. Third-degree relatives include great-grandfathers, great-grandsons, and first cousins.

In addition, we examined the RR for prostate and testicular cancer among relatives of women with POI and a male relative with NOA/oligozoospermia. RR was estimated as the ratio of the observed number of cancer cases for a specific relative type compared to the expected number of cancer cases for the specific relative type based on population rates, as previously. A Bonferroni correction was used to account for multiple testing with 2 cancers assessed ($P < .025$).

Results

We identified a cohort of 392 women with POI from the University of Utah and Intermountain Healthcare who also had at least 3 generations of genealogical data available in the UPDB [13]. These 392 individuals diagnosed with POI had 1098 male and 1041 female first-degree relatives, 2510 male and 2842 female second-degree relatives, and 5189 male and 5877 female third-degree relatives with healthcare data at either the University of Utah or Intermountain Healthcare. Twenty-one families of women with POI had at least 1 male family member with NOA or severe oligozoospermia (Fig. 1). These families are a subset of the families identified previously [14].

There were 25 men with NOA/oligozoospermia found in these families. Twenty-three of the men had 1 relative with POI, while 2 of these 25 men were relatives to 2 women with POI. We observed an excess number of men with NOA/oligozoospermia among relatives of women with POI compared with population rates (Table 1). Specifically, we demonstrated an increased RR for NOA/oligozoospermia in first-, second-, and third-degree relatives.

In families of women with POI and a male member with NOA/oligozoospermia (Fig. 1), there was an increase in prostate cancer risk in first- and second-degree relatives (Table 2). The median age at diagnosis of prostate cancer was 71 years (first quartile 65 years, third quartile 76 years) and the minimum age was 47 years with ≤10 persons diagnosed at 55 years or younger. There were no cases of prostate cancer in the 25 men with NOA/oligozoospermia. There were no cases of testicular cancer in first- or second-degree relatives.

Discussion

Men with NOA or severe oligozoospermia were more likely to be found in families of women with POI than in control families. In addition, the first- and second-degree male members of these families with POI and NOA/oligozoospermia had an increased risk for prostate cancer. These findings support a common genetic and/or environmental relationship between POI and NOA and the potential link to prostate cancer risk.

The genetics of POI and NOA converge in meiosis I genes, particularly genes important for homologous recombination

Table 1. Increased risk of male nonobstructive azoospermia or severe oligozoospermia (≤5 million/mL) in first-, second-, and third-degree male relatives of women with POI

Relationship	Total male relative number	Observed	Expected	Relative risk (95% confidence intervals)	*P*-value
First degree	1098	≤10	1.75	2.85 (1.12-6.65)	.033
Second degree	2510	≤10	1.95	3.08 (1.13-6.71)	.015
Third degree	5189	14	7.69	1.82 (1.10-3.06)	.030

Based on Utah Population Database regulations for oversight by the Utah Resource for Genetic and Epidemiologic Research, observed counts ≤ 10 were not listed to protect the identity of the patients.
Abbreviation: POI, primary ovarian insufficiency.

Table 2. Increased risk of prostate cancer among first- and second-degree relatives in 21 families of women with POI and a male relative who had nonobstructive azoospermia or severe oligozoospermia (≤5 million/mL).

Relationship	Total male relative number	Cancer type	Observed	Expected	Relative risk (95% confidence intervals)	*P*-value
First degree	89	Prostate	≤10	1.44	3.48 (1.13-8.13)	.016
Second degree	233	Prostate	21	6.71	3.13 (1.94-4.78)	.000008
Third degree	749	Prostate Testicular	25 ≤10	17.16 1.01	1.46 (0.94-2.15) 1.98 (0.24-7.16)	.068 .27

Based on Utah Population Database regulations for oversight by the Utah Resource for Genetic and Epidemiologic Research, observed counts ≤10 were not listed to protect the identity of the patients. Bonferroni multiple testing correction $P < .025$.
Abbreviation: POI, primary ovarian insufficiency.

[6]. Meiosis I is arrested at the diplotene stage of prophase in oocytes at birth and occurs in spermatocytes in the testes [18, 19]. Mutations in genes that regulate the process of homologous recombination will therefore result in a loss of early growing oocytes or spermatocytes at the checkpoints due to failure of precise recombination [20]. The loss of oocytes may occur before puberty in the case of recessive loss of function, resulting in the absence of pubertal development because the oocyte is required for follicle formation and estradiol production. Because the Leydig cells do not depend on the presence of spermatocytes to make testosterone, men with recessive mutations in genes of homologous recombination will have apparently normal puberty and may not be identified until attempting pregnancy [21]. Therefore, the convergence of male and female infertility may not be recognized in families, even in severe cases. It is still expected that these families have the same causal variants for POI in females and NOA in males.

There was some evidence for specific causes of POI and NOA in our cohort based on a review of the women in the family with POI. Two pairs each of POI subjects had karyotype abnormalities including an X chromosome translocation and autosome inversion, which could also explain the NOA in their male relatives. Small deletions of the X chromosome have been demonstrated in both NOA and POI [22, 23]. The specific breakpoint of the autosome inversion would need to be sequenced to determine if there is a potential causal gene in the region of the break. In a third family, there was a history of autoimmune polyglandular syndrome type 2 in the women with POI. Polyglandular syndrome type 1 and type 2 may be the cause of male hypogonadism in a familial case related to autoimmune gonadal dysfunction [24]. Finally, 1 woman with POI had completed whole genome sequencing [14] and had 2 pathogenic variants: 1 in Fanconi anemia complementation group A (*FANCA*; p.Val372AlafsTer42) and 1 in *RECQL4* (p.Arg758Ter). Both have been associated with POI in a heterozygous [25] or recessive state [26], and *FANCA* has been associated with NOA in the homozygous state [27]. For the remaining 17 subjects, additional recruitment and gene sequencing will be needed to identify a candidate gene. We will also need to examine possible epigenetic changes associated with our disorders.

Prostate cancer is the most common cancer in men, with complex genetics encompassing both rare and common gene variants. While our families are a subset of those we identified previously [14], the RR for prostate cancer is significantly higher in first- (RR 3.48 [95% confidence interval 1.13, 8.13] vs 1.64 [1.18, 2.23]) and second-degree relatives (3.13 [1.94, 4.78] vs 1.54 [1.32, 1.79]) compared to the cancer analyses for all POI cases. The higher risk could be related to shared genetics. The shared genes associated with meiosis I homologous recombination, such as the Fanconi family of genes, are rare causes of prostate cancer risk but are more likely to be involved in prostate cancer in these families with POI and NOA [27-29]. For example, heterozygous rare variants in *BRCA2* have been demonstrated to increase prostate cancer risk [30, 31]. Compound heterozygous variants cause POI and primary amenorrhea, while heterozygous rare variants cause POI at later ages [2, 29]. Although *BRCA2* remains a strong candidate for NOA, recessive *BRCA2* variants have not yet been identified, and heterozygous variants might not be detected without quantitative semen analyses as haploinsufficiency may only decrease sperm number [27]. An increased risk of prostate cancer for carriers of mutations in *FANCA* and *RECQL4,* found in a woman with POI in our cohort, has been reported [31, 32]. Taken together, the genetics of POI, NOA, and prostate cancer in these families are likely to overlap. In addition, environmental factors, such as pesticides or smoking, could also be involved as it is possible that these families live in similar regions across the state or have similar lifestyles.

The risk of prostate cancer, particularly early-onset prostate cancer, has generally been found to be higher when examined in younger men being treated for infertility [33-35]. In 1 study, the incidence of prostate cancer was increased by 60% in men who conceived through in vitro fertilization/intracytoplasmic sperm injection, which was performed solely for men with NOA/oligozoospermia [36]. The current study does not look directly at infertility among family members who had increased prostate cancer risk, but there was no prostate cancer in the subjects with NOA/oligozoospermia. Prostate cancer was diagnosed under age 55 years in less than 10 men, suggesting that young age at diagnosis was not typical in these families.

There are several limitations to our study. We do not have genetics or epigenetics on all of these families to make more definitive conclusions about a potentially shared cause. We started with families of women with POI. We may have missed affected subjects with NOA in families with POI because we are limited by presentation to a physician and participation in the SHARE study, which is a highly inclusive and well-validated male infertility cohort based on the scope of inclusion within 2 healthcare systems that serve 85% of the state, and the diagnosis based on semen analyses [17]. We may also miss men with NOA in the Utah population, resulting in an overestimate of the relationship between POI and NOA in our population. Finally, we are limited by a largely northern European population, although 10.4% of these women had Hispanic ethnicity, which may not have generalizable results for other races and ethnicities. Regardless, our cohort is unique in its genealogic depth and connection to medical information, providing an important new perspective from which to examine our hypotheses.

Regarding the cancer analysis, there are additional limitations. The number of testicular cases is small, and we may miss a significant relationship based on the limited power. Nevertheless, we previously did not see an increased RR of testicular cancer in all male relatives of women with POI despite larger numbers [14]. We do note that prostate cancer was increased in all relative groups in women with POI, including third-degree relatives, when we did not restrict families to those with both POI and NOA/oligozoospermia, potentially demonstrating the results of using larger numbers [14]. We may have missed cancer cases if they were diagnosed outside of the state of Utah. Finally, it is not clear if there is greater use of androgen treatment in these male relatives compared to others in the population, which could accelerate the growth of prostate cancer in families of women with POI. However, as discussed previously, hormonal puberty may proceed normally in these patients, making testosterone unnecessary in many with NOA [21].

Familial cases of POI and NOA/severe oligozoospermia have the potential to uncover shared genetic inheritance. They further suggest shared risk for POI, NOA, and prostate cancer. These data suggest that family history during infertility evaluations should be directed at both male and female relatives to discern infertility and cancer risk in these families.

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Disclosures

J.H. reports the following disclosures: consulting fees/equity: Carrot Fertility, Turtle Health (ended in 2023); equity: InductionBio; leadership position/equity/consulting fees: Paterna Bioscienes (in vitro spermatogenesis startup). None of these are related to the current work. No other authors have anything to declare.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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