Families of men with fertility problems show distinct patterns of increased risk for several types of cancer

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For the first time researchers have identified patterns of risk for several different types of cancer in men with fertility problems and their

families.

The study, which is in *Human Reproduction*, found that families of men who have very few or no sperm in their semen have a higher risk of developing cancer, including developing cancer at younger ages, compared to families of fertile men.

The risk and the type of cancer varied greatly depending on whether the men had low numbers of sperm (oligozoospermic) or none (azoospermic), with several cancers identified in distinct clusters of families.

The researchers, led by Dr. Joemy Ramsay, assistant professor at the University of Utah, Salt Lake City, U.S., hope their findings will improve their understanding of the biological mechanisms involved in both cancer and infertility. This would enable doctors to make more accurate predictions of risk of cancer for men with fertility problems and their families, and to improve the counseling that could be offered to them.

Previous research has shown that male infertility is linked to an increased risk of cancer in the men and their families, but the results have been inconsistent. Increased risks and the types of cancer varied considerably between family groups and depending on whether the men were oligozoospermic or azoospermic.

"In this study, we wanted to describe the extent to which patterns of cancer risk vary between families of subfertile men, and whether this risk is seen in all families or is driven by a small subset of families, akin to the way mutations in the BRCA gene increase the risk of breast cancer in families that carry this mutation," said Dr. Ramsay.

"By identifying families with similar patterns of cancer, we may be able

to discover factors that are involved in both infertility and cancer."

Dr. Ramsay and colleagues took results from semen analyses carried out between 1996 and 2017 from 786 men attending fertility clinics in Utah, and they matched them with information from 5,674 fertile men in the general population who had at least one child to ensure they were fertile. Among the men with fertility problems, 426 were azoospermic and 360 were severely oligozoospermic (with less than 1.5 million sperm per milliliter of semen).

The researchers collected information on first, second and third degree relatives using the Utah Population Database. Cancer diagnoses were identified from the Utah Cancer Registry.

"We simultaneously assessed the risk for multiple types of cancer within each family and then we performed a cluster analysis to find groups of families with similar patterns of risk for multiple cancers," said Dr. Ramsay. "This is the first study to describe these multicancer patterns in families of subfertile men."

When the researchers looked at all families of azoospermic men, they saw a significantly increased risk of five cancers: bone and joint cancer (156% increased risk), soft tissue cancers such as sarcomas (56% increased risk), cancers of the womb (27% increased risk), Hodgkin Lymphomas (60% increased risk), and thyroid cancers (54% increased risk).

Families of the severely oligozoospermic men had a significantly increased risk of three cancers: colon cancer (16% increased risk), bone and joint (143% increased risk), and testicular cancer (134% increased risk). The researchers also found a 61% decreased risk of esophageal cancer (cancer of the gullet).

The researchers found the risk of cancer and the types of cancer varied greatly among the families of men with fertility problems, both by type of subfertility and also within subfertility type. This could explain the inconsistent associations between subfertility and cancer in previous studies. For example, the study found an increased risk of testicular cancer in only a third of the clusters of families of oligozoospermic men, but the increased risk ranged from four- to 24-fold depending on family cluster.

Among the families of azoospermic men, the researchers identified 13 clusters of families. One cluster, which included the majority of the families, had a risk of cancer that was similar to that in the general population. However, the remaining 12 clusters all had increased risks of developing at least one type of cancer. Among the families of oligozoospermic men, there were 12 distinct clusters and all of them had an increased risk for at least one type of cancer.

"Our study identified several unique patterns of cancer risk in families of men with poor fertility. When family members share cancer risk patterns, it suggests that they have genetic, environmental, or health behaviors in common. Genetic and environmental exposures can also act together to increase cancer risk," said Dr. Ramsay.

"By identifying which groups of families have similar cancer risk patterns we can improve our understanding of the biological mechanisms of both cancer and infertility. It will help us to assess the risk of cancer for families and provide improved patient counseling."

The researchers have carried out genetic sequencing studies to look for specific genetic mutations that may be driving the associations between subfertility and cancer seen in this study.

Strengths of the study include the use of data from population registries

for family structure, cancer diagnosis and subfertility.

Limitations include lack of semen measures for the fertile men, lack of information on other health conditions, lifestyle risk factors, such as smoking and body mass index, and exposure to environmental risk factors among the subfertile men; and, finally, that the men with fertility problems in this study were all seen at a fertility clinic and, therefore, represent a subset of the overall population of subfertile men who had the socioeconomic means to be evaluated by a doctor.

More information: Joemy Ramsay et al, Describing patterns of familial cancer risk in subfertile men using population pedigree data, *Human Reproduction* (2023). DOI: 10.1093/humrep/dead270

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