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Genitourinary cancer patients have worse baseline semen parameters than healthy sperm bankers

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ABSTRACT

Background: While the spermatotoxic properties of cancer treatments such as chemotherapy and radiation therapy are widely recognized, the effect of malignancy itself on male fertility is not clearly understood.

Objectives: To determine whether malignancy is associated with diminished semen quality prior to spermatotoxic treatment among sperm bankers.

Materials and Methods: Retrospective database review of de-identified records was obtained for all episodes of sperm banking performed at a cryobank from January 2004 to May 2017 for one of the following reasons: 'future use' (e.g., military deployment and gender reassignment); infertility; benign disease; and malignancy, further categorized as testicular, other genitourinary (GU), solid non-GU, hematologic, or unspecified. Dependent variables of interest were ejaculatory volume, sperm concentration, % motility, and total motile sperm count (TMSC), as well as post-thaw TMSC.

Results: A total of 1558 patients met the inclusion criteria. Multivariable regression analysis on log-transformed data controlling for age demonstrated decreased ejaculatory volume and sperm concentration, % motility, and TMSC in the infertility group as compared to the 'future use' group ($p < 0.001$). Testicular cancer was associated with decreased sperm concentration, TMSC, and post-thaw TMSC ($p < 0.001$); other GU malignancy was associated with decreased ejaculatory volume ($p < 0.001$). Benign disease, solid non-GU malignancy, hematologic malignancy, and unspecified malignancy were not associated with decreased parameters.

Discussion: In addition to sperm bankers with known fertility issues, sperm bankers with testicular and other GU malignancy had worse baseline semen parameters as compared to individuals pursuing banking for future use. These findings can inform patient counseling and consent prior to sperm banking and disease treatment.

Conclusion: Individuals with testicular and other GU malignancy who banked spermatozoa before undergoing spermatotoxic therapy demonstrated worse baseline semen parameters as compared to individuals banking spermatozoa for non-medical reasons.

INTRODUCTION

While the spermatotoxic potential of cancer treatments such as chemotherapy and radiation therapy is well recognized, the effect of malignancy itself on male fertility prior to oncologic treatment is less clearly understood. It has been suggested that as many as two-thirds of cancer patients have impaired fertility at baseline (van Casteren *et al.*, 2010), but studies have reported heterogeneous findings as to whether and how specific types of malignancy are linked to diminished semen parameters (Auger *et al.*, 2016; Caponecchia *et al.*, 2016; Paoli *et al.*, 2016; DiNofia *et al.*, 2017; MacKenna *et al.*, 2017). This study investigated whether sperm bankers with various forms of malignancy demonstrated worse baseline semen parameters as compared to individuals with non-oncologic indications for banking.

MATERIAL AND METHODS

With IRB approval, de-identified records were obtained for all episodes of sperm banking performed at a large full-service cryogenic laboratory from January 2004 to May 2017. Encounters were included in the study if they had been attributed one of the following reasons for sperm banking: 'future use' (e.g., military deployment, at-risk travel, occupational hazard, gender reassignment, or prior to vasectomy); known infertility; benign disease (e.g., aplastic anemia, systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis); and malignancy.

Malignancy was further categorized as testicular, other genitourinary (GU), solid non-GU, hematologic, or unspecified. Sperm bankers with exposure to chemotherapy or pelvic radiation prior to banking were excluded. For any sperm banker with multiple specimens, the average of each semen parameter across encounters was used.

All patients were instructed to abstain from ejaculation for three days prior to sample collection. Fresh ejaculate was liquefied in a 37 °C incubator for 20 minutes before performing manual semen analysis. An equal volume of either TEST-yolk buffer (Irvine Scientific, Irvine, CA) or Sperm Maintenance Medium (Irvine Scientific, Irvine, CA) was added in dropwise fashion to each specimen. Specimens were cryopreserved in sterile plastic cryovials in liquid nitrogen vapor, followed by plunging and storage in the liquid phase. A post-thaw test vial was held at room temperature for seven minutes, then incubated at 37°C for 14–15 min before post-thaw analysis was performed in accordance with WHO 4th or 5th edition guidelines, based on year of sample production (World Health Organization, 2010).

Dependent variables of interest included ejaculatory volume, sperm concentration, % motility, and total motile sperm count (TMSC; defined as ejaculatory volume × sperm concentration × % motility), as well as post-thaw TMSC on a test thaw sample. Mann–Whitney *U*-test and multivariable regression analysis of log-transformed data controlling for age were performed, with the 'future use' group serving as reference for other groups. Additional regressions were performed with only significant variables included and adjusted for interaction with age where relevant. Analyses were performed using Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, Version 24) software.

RESULTS

A total of 1558 patients met the inclusion criteria (Table 1). In total, there were 822 patients with malignancy: 284 with testicular cancer, 98 with other GU malignancy, 180 with solid non-GU malignancy, 197 with hematologic malignancy, and 63 with other malignancy. There were 287 patients cryopreserving sperm for future use, 380 patients with infertility, and 69 patients with benign disease.

On Mann–Whitney *U*-test (Table 2A), all measured semen parameters were significantly decreased for the infertility group as compared to the 'future use' group ($p \leq 0.003$). All forms of malignancy were associated with lower TMSC. In addition, testicular cancer was associated with decreased concentration ($p < 0.001$) and lower post-thaw TMSC ($p < 0.001$). Other GU malignancy and solid non-GU malignancy were associated with lower ejaculatory volume ($p < 0.001$ and $p = 0.044$, respectively) and decreased % motility ($p < 0.001$ for both); hematologic malignancy, with decreased concentration ($p = 0.027$), % motility ($p < 0.001$), and post-thaw TMSC ($p = 0.012$); and unspecified malignancy, with decreased % motility ($p = 0.015$) and post-thaw TMSC ($p = 0.022$). Benign disease was associated with worse % motility ($p = 0.002$) and lower TMSC ($p = 0.013$).

On multivariable regression analysis of log-transformed data controlling for age (Table 2B), ejaculatory volume, sperm concentration, % motility, and TMSC remained significantly decreased for the infertility group as compared to the 'future use' group ($p < 0.001$). For every year of age, log % motility decreased by 0.2% ($p = 0.024$); within the infertility group, every year of age reduced log % motility by an incremental 1.3% ($p < 0.001$). Testicular malignancy was associated with decreased sperm concentration ($p < 0.001$), TMSC ($p < 0.001$), and post-thaw TMSC ($p < 0.001$). Other GU malignancy was associated with decreased ejaculatory volume ($p < 0.001$). Benign disease, solid non-GU malignancy, hematologic malignancy, and unspecified malignancy were not associated with any variables.

Table 1 Mean age by sperm banking diagnosis

Group (*N*)	Mean (SD) age in years	*p*-value[a]
Future use (287)	31.7 (10.0)	–
Benign disease (69)	30.4 (8.6)	$p = 0.251$
Infertility (380)	40.7 (8.4)	$\mathbf{p < 0.001}$
Testicular (284)	27.9 (6.3)	$\mathbf{p < 0.001}$
Other GU (98)	49.1 (8.8)	$\mathbf{p < 0.001}$
Solid non-GU (180)	30.9 (8.5)	$p = 0.427$
Heme (197)	27.9 (7.2)	$\mathbf{p < 0.001}$
Unspecified (63)	32.6 (11.9)	$p = 0.979$

[a]Reference group: patients banking spermatozoa for "future use".

DISCUSSION

This retrospective study examined baseline semen parameters for a large sample of sperm bankers who were banking spermatozoa for a wide variety of reasons. As compared to men banking spermatozoa for 'future use', with no other strict medical indication for banking, men with testicular and other GU malignancy demonstrated worse baseline semen quality. Infertility as a reason for banking was negatively associated with semen quality, as would be expected given the known diagnosis of infertility. Benign disease was not associated with any of the measured parameters.

The question of whether malignancy itself is negatively associated with semen quality has been investigated at length in the past. To date, however, there is no clear consensus; controversy remains over whether the type of malignancy affects semen quality (Williams *et al.*, 2009) and even over whether men with cancer have worse semen parameters as compared to men without cancer (Degl'Innocenti *et al.*, 2013; Williams, 2013). Some studies have linked testicular cancer and lymphoproliferative disorders to worse sperm concentration (Caponecchia *et al.*, 2016), total sperm count (Bizet *et al.*, 2012), and post-thaw motile count (Hotaling *et al.*, 2013). van Casteren *et al.* (2010) found that nearly two-thirds of men referred for sperm cryopreservation prior to chemotherapy and radiotherapy had abnormal semen parameters; men with testicular cancer had significantly lower sperm concentration as compared to men with other types of malignancy. Ragni *et al.* (2003) also reported worse sperm quality among men with testicular cancer as compared to men with other malignancies. Auger *et al.* (2016) reported that only roughly one-third of leukemia patients and less than two-thirds of patients with testicular cancer, sarcomas, or brain tumors were normozoospermic.

In contrast, Meseguer *et al.* (2006) found no difference in total sperm count, and Chung *et al.* (2004) found no difference in sperm count or motility, when comparing across malignancy types. Meanwhile, Degl'Innocenti *et al.* (2013) reported no

Table 2 Semen parameters by sperm banking diagnosis[a]

Median (1st, 3rd quartile)	Future use (*N* = 287)	Benign disease (*N* = 69)	Infertility (*N* = 380)	Malignancy				
				Testicular (*N* = 284)	Other GU (*N* = 98)	Solid non-GU (*N* = 180)	Heme (*N* = 197)	Unspecified (*N* = 63)
(A) Univariate analysis (Mann–Whitney *U* test)								
Volume (cc)	3.5 (2.7, 5.0)	3.5 (1.7, 5.3) (*p* = 0.336)	**1.1 (0.5, 3.0) (*p* < 0.001)**	3.5 (2.5, 4.75) (*p* = 0.449)	**2.8 (1.8, 4.0) (*p* < 0.001)**	**3.1 (2.0, 5.0) (*p* = 0.044)**	3.5 (2.3, 4.5) (*p* = 0.077)	3.3 (2.4, 4.0) (*p* = 0.063)
Concentration (million/mL)	65.0 (38.6, 94.0)	57.2 (27.5, 86.3) (*p* = 0.119)	**2.3 (0.4, 52.0) (*p* < 0.001)**	**28.3 (9.8, 54.0) (*p* < 0.001)**	68.0 (41.5, 104.4) (*p* = 0.409)	66.8 (26.8, 100.1) (*p* = 0.742)	**54.0 (25.7, 95.0) (*p* = 0.027)**	49.5 (14.9, 92.6) (*p* = 0.067)
Motility (%)	65.0 (54.0, 73.0)	**59.0 (44.0, 67.0) (*p* = 0.002)**	**53.3 (29.0, 70.0) (*p* < 0.001)**	63.0 (50.0, 72.6) (*p* = 0.096)	**56.5 (45.0, 65.8) (*p* < 0.001)**	**60.5 (46.8, 70.0) (*p* < 0.001)**	**55.5 (41.0, 66.0) (*p* < 0.001)**	**53.5 (44.2, 73.5) (*p* = 0.015)**
TMSC[b] (million)	156.8 (79.8, 239.7)	**107.5 (33.9, 211.0) (*p* = 0.013)**	**65.6 (1.1, 157.7) (*p* < 0.001)**	**63.0 (25.7, 131.5) (*p* < 0.001)**	**105.9 (44.0, 197.5) (*p* = 0.001)**	**116.6 (38.8, 224.2) (*p* = 0.002)**	**98.0 (34.5, 200.9) (*p* < 0.001)**	**106.0 (20.2, 185.1) (*p* = 0.002)**
Post-thaw TMSC (million)	8.2 (3.2, 15.0)	7.1 (2.9, 13.1) (*p* = 0.412)	**6.0 (2.5, 11.1) (*p* = 0.003)**	**3.3 (1.1, 7.4) (*p* < 0.001)**	7.5 (3.1, 12.9) (*p* = 0.342)	7.9 (2.3, 14.3) (*p* = 0.319)	**6.2 (1.6, 14.3) (*p* = 0.012)**	**5.0 (1.7, 11.7) (*p* = 0.022)**

	Beta (standard error)		
	Infertility	Testicular malignancy	Other GU malignancy
(B) Multivariable regression analysis[c]			
Log volume (cc)	−0.43 (0.03) *p* < 0.001	–	−0.11 (0.03) *p* < 0.001
Log concentration (million/mL)	−0.92 (0.04) *p* < 0.001	−0.27 (0.05) *p* < 0.001	–
Log motility (%)	0.375 (0.10) *p* < 0.001	–	–
Log TMSC (million)[b]	−.52 (0.06) *p* < 0.001	−0.23 (0.05) *p* < 0.001	–
Log post-thaw TMSC (million)	–	−0.267 (0.04) *p* < 0.001	–

[a]Reference group: patients banking spermatozoa for 'future use'. [b]TMSC, total motile sperm count. [c]Only statistically significant values shown.

difference in basal semen quality or post-thaw motility recovery among men with hematologic or other cancers, as compared to men with non-cancer pathologies.

Given the persistent lack of consensus, the question of whether and how malignancy affects basal semen quality warrants further consideration. Our study represents a contribution to this ongoing area of investigation. Its robust sample size is a unique strength of the study; our analysis included 1558 patients, which to our knowledge constitutes one of the largest study populations reported. Moreover, it involved participants across several categories of disease, both malignant and non-malignant, as well as participants banking spermatozoa for non-medical reasons. This enabled comparisons across malignancy types, as well as between men with cancer and men without cancer.

Another unique strength of our analysis is the inclusion of a control group consisting of men banking for 'future use', rather than for medical reasons. This is in distinction to other studies, such as Williams *et al.*, which did not include a non-cancer control group, or Degl'Innocenti *et al.*, which used men with non-cancer pathologies, such as spinal cord injuries, as a control group (Williams *et al.*, 2009; Degl'Innocenti *et al.*, 2013). Men who are cryopreserving spermatozoa for non-medical reasons, such as military deployment, provide a better proxy for 'normal' parameters than men who are cryopreserving spermatozoa due to a medical pathology. Our finding that individuals banking spermatozoa for an infertility-related concern demonstrated worse semen quality than 'future use' individuals supports the internal consistency of our analysis.

The etiology for impaired semen quality among sperm bankers with malignancy is unknown. Hypothesized mechanisms include autoimmune, endocrine, and stress-induced effects of cancer, as well as testicular dysgenesis among men with testicular cancer (Williams *et al.*, 2009; Katz *et al.*, 2013; Hamano *et al.*, 2017). While it is beyond the scope of this study to propose mechanisms for the observed differences in semen quality, it is feasible that some or all of these factors may be involved. It is also possible that the physical, psychological, and emotional strain of coping with a cancer diagnosis—and in many cases, the time pressure of imminent treatment with chemotherapy or radiation therapy—makes it harder for men with cancer to produce adequate specimens for sperm banking as compared to men banking for non-medical reasons. A limitation of the cryogenic facility database is that it does not routinely capture information on the constitutional status or psychological state of men at the time of sperm banking, so it is not possible to assess the potential effect of these factors on sperm quality.

Patients with benign disease were excluded from the study if they had undergone chemotherapy, such as methotrexate for psoriatic arthritis or cyclophosphamide for systemic lupus erythematosus or Wegener's granulomatosis. The patients included in the study, in other words, were those who banked spermatozoa prior to initiation of chemotherapy. It is possible that these

patients sustained other potentially spermatotoxic treatments for their conditions that were not captured in the database, but this is unlikely given that relevant prior treatments are recorded routinely at the time of banking. Moreover, additional exclusions would likely only further reinforce the study finding that benign disease was not associated with worse semen parameters.

An additional limitation of our study is the absence of demographic information about the sperm bankers aside from age, as dictated by the protocol at the cryogenic facility regarding what information is collected about sperm bankers. It is possible that certain behaviors, such as smoking, or patient characteristics, such as obesity, may predispose individuals to both malignancy and compromised fertility; such potential associations cannot be assessed within this study.

As rates of survival among young male cancer patients improve, family planning and fertility preservation for patients with malignancy have become increasingly important. Counseling these patients on their risk of future infertility, and on their options for fertility preservation, is considered standard of care but continues to be an area of needed improvement (Hotaling *et al.*, 2013; Williams, 2013; Hamano *et al.*, 2017). For instance, only a small percentage of men diagnosed with cancer choose to bank spermatozoa, with reported rates ranging from less than 5% to approximately 25%; this deficiency has been attributed in part to inadequate patient education and awareness (Chung *et al.*, 2004; Polland & Berookhim, 2016; Hamano *et al.*, 2017).

Our study found that sperm bankers with certain types of malignancy had lower total motile sperm counts as compared to individuals banking for non-medical indications. These findings further support the need for thorough counseling on the risks of infertility for patients with malignancy who are of reproductive age. Simply informing patients of the fertility risks of cancer treatment and the option for cryopreservation is not sufficient. If their malignancy is associated with worse baseline semen parameters, these individuals may be at risk of compromised fertility even prior to spermatotoxic treatments such as radiation and chemotherapy and should be counseled on this possibility as well.

Our findings have other logistical implications. Patients with malignancies that are associated with diminished post-thaw motile sperm count may benefit from preserving more vials at the time of initial sperm banking. In our study, testicular cancer was associated with decreased post-thaw motile count; this is consistent with the finding reported by Hotaling *et al.* (2013). Anticipating this possibility can allow providers to counsel patients in order to help them prepare appropriately for future fertility needs.

As young male cancer survivorship increases, it is increasingly important to understand the nuances of fertility preservation in this population. The option for future family building, if desired, may provide emotional and psychological comfort for cancer patients as they undergo potentially spermatotoxic treatments (Schover *et al.*, 1999; Saito *et al.*, 2005; Schover, 2009). The results reported here can help to guide planning prior to the initiation of cancer treatment. In addition to offering sperm cryopreservation, it is essential to counsel these patients thoroughly on their risk of infertility, both pre-existing and related to cancer treatments, so that their fertility-preservation decisions are as informed as possible.

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REFERENCES

Auger J, Sermondade N & Eustache F. (2016) Semen quality of 4480 young cancer and systemic disease patients: baseline data and clinical considerations. *Basic Clin Androl* 26, 3.

Bizet P, Saias-Magnan J, Jouve E, Grillo JM, Karsenty G, Metzler-Guillemain C & Perrin J. (2012) Sperm cryopreservation before cancer treatment: a 15-year monocentric experience. *Reprod Biomed Online* 24, 321–330.

Caponecchia L, Cimino G, Sacchetto R, Fiori C, Sebastianelli A, Salacone P, Marcucci I, Tomassini S & Rago R. (2016) Do malignant diseases affect semen quality? Sperm parameters of men with cancers. *Andrologia* 48, 333–340.

van Casteren NJ, Boellaard WP, Romijn JC & Dohle GR. (2010) Gonadal dysfunction in male cancer patients before cytotoxic treatment. *Int J Androl* 33, 73–79.

Chung K, Irani J, Knee G, Efymow B, Blasco L & Patrizio P. (2004) Sperm cryopreservation for male patients with cancer: an epidemiological analysis at the University of Pennsylvania. *Eur J Obstet Gynecol Reprod Biol* 113(Suppl 1), S7–S11.

Degl'Innocenti S, Filimberti E, Magini A, Krausz C, Lombardi G, Fino MG, Rastrelli G, Maggi M & Baldi E. (2013) Semen cryopreservation for men banking for oligospermia, cancers, and other pathologies: prediction of post-thaw outcome using basal semen quality. *Fertil Steril* 100, 1555–1563 e1-3.

DiNofia AM, Wang X, Yannekis G, Ogle S, Hobbie WL, Carlson CA & Ginsberg JP. (2017) Analysis of semen parameters in a young cohort of cancer patients. *Pediatr Blood Cancer* 64, 381–386.

Hamano I, Hatakeyama S & Ohyama C. (2017) Fertility preservation of patients with testicular cancer. *Reprod Med Biol* 16, 240–251.

Hotaling JM, Lopushnyan NA, Davenport M, Christensen H, Pagel ER, Muller CH & Walsh TJ. (2013) Raw and test-thaw semen parameters after cryopreservation among men with newly diagnosed cancer. *Fertil Steril* 99, 464–469.

Katz DJ, Kolon TF, Feldman DR & Mulhall JP. (2013) Fertility preservation strategies for male patients with cancer. *Nat Rev Urol* 10, 463–472.

MacKenna A, Crosby J, Huidobro C, Correa E & Duque G. (2017) Semen quality before cryopreservation and after thawing in 543 patients with testicular cancer. *JBRA Assist Reprod* 21, 31–34.

Meseguer M, Molina N, Garcia-Velasco JA, Remohi J, Pellicer A & Garrido N. (2006) Sperm cryopreservation in oncological patients: a 14-year follow-up study. *Fertil Steril* 85, 640–645.

Paoli D, Rizzo F, Fiore G, Pallotti F, Pulsoni A, Annechini G, Lombardo F, Lenzi A & Gandini L. (2016) Spermatogenesis in Hodgkin's lymphoma patients: a retrospective study of semen quality before and after different chemotherapy regimens. *Hum Reprod* 31, 263–272.

Polland A & Berookhim BM. (2016) Fertility concerns in men with genitourinary malignancies: treatment dilemmas, fertility options, and medicolegal considerations. *Urol Oncol* 34, 399–406.

Ragni G, Somigliana E, Restelli L, Salvi R, Arnoldi M & Paffoni A. (2003) Sperm banking and rate of assisted reproduction treatment: insights from a 15-year cryopreservation program for male cancer patients. *Cancer* 97, 1624–1629.

Saito K, Suzuki K, Iwasaki A, Yumura Y & Kubota Y. (2005) Sperm cryopreservation before cancer chemotherapy helps in the emotional battle against cancer. *Cancer* 104, 521–524.

Schover LR. (2009) Patient attitudes toward fertility preservation. *Pediatr Blood Cancer* 53, 281–284.

Schover LR, Rybicki LA, Martin BA & Bringelsen KA. (1999) Having children after cancer. A pilot survey of survivors' attitudes and experiences. *Cancer* 86, 697–709.

Williams DHt. (2013) Fertility preservation in the male with cancer. *Curr Urol Rep* 14, 315–326.

Williams DHt, Karpman E, Sander JC, Spiess PE, Pisters LL & Lipshultz LI. (2009) Pretreatment semen parameters in men with cancer. *J Urol* 181, 736–740.

World Health Organization. *WHO Laboratory Manual for the Examination and Processing of Human Semen*. Geneva, Switzerland: WHO, 2010.