

# Pretreatment Semen Parameters in Men With Cancer

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## Abbreviations and Acronyms

GI = gastrointestinal

NCRMN = National Cooperative Reproductive Medicine Network

NHL = nonHodgkin's lymphoma

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**Purpose:** Whether the presence or specific type of cancer significantly affects semen quality is controversial. We evaluated the semen parameters and associated malignancies of men with cancer who cryopreserved sperm at our institution before undergoing therapy.

**Materials and Methods:** We reviewed the database from our cryopreservation laboratory during a 5-year period. Office charts of 409 of 1,409 patients were available for review. Age at banking, semen volume, sperm density, percent motile sperm and type of cancer were recorded. Semen parameters were compared to values for fertile and subfertile men established by the National Cooperative Reproductive Medicine Network as well as from a large local pre-vasectomy cohort to consider geographic variations.

**Results:** A total of 717 semen samples from 409 men included 45% with testicular cancer, 10% with Hodgkin's lymphoma, 7% with nonHodgkin's lymphoma, 6% with sarcoma, 6% with prostate cancer, 5% with leukemia, 3% with gastrointestinal cancer and 2% with central nervous system tumors. Of these men 16% had unspecified or other rare malignancies. Mean patient age was 29.9 years (range 11.9 to 87.7), mean semen volume was 2.8 ml (range 0.1 to 15.0), mean sperm density was  $47.4 \times 10^6/\text{ml}$  (range 0.1 to 320) and mean sperm motility was 50.0% (range 1% to 90%). For men with testicular cancer sperm density and motility were in the intermediate range. Parameters for men with all other malignancies were in the fertile range for density and intermediate range for motility.

**Conclusions:** Men with most types of cancer have pretreatment semen parameters in the fertile range for density and in the intermediate range for motility. However, men with testicular cancer statistically have lower semen quality compared to those with other malignancies. These findings further highlight the importance of pretreatment fertility preservation in this patient population before undergoing gonadotoxic treatments.

**Key Words:** semen, cryopreservation, neoplasms, spermatozoa, infertility

GONADOTOXICITY and testicular dysfunction are well-known side effects of cancer therapies since chemotherapy, radiotherapy and surgery can all affect fertility potential.<sup>1-6</sup> However, whether men with cancer have impaired testicular function even before

undergoing these treatments is controversial.

Because men of reproductive age with cancer are encouraged to cryopreserve sperm before undergoing treatment, pretreatment semen analyses of these men are readily avail-

able.<sup>7</sup> However, published results of large studies are conflicting.<sup>8–15</sup> Some suggest that cancer adversely affects semen quality,<sup>8,9,15</sup> while others have found no differences between semen analyses of men with and without cancer.<sup>11</sup> Additionally, some studies suggest that the type of malignancy impacts semen quality<sup>12,13,15</sup> whereas others do not.<sup>10,14</sup>

To further address the question of whether the presence and/or specific type of cancer significantly affects semen quality, we reviewed the semen analyses and associated malignancies of men with cancer who cryopreserved sperm at our institution before undergoing cancer therapy.

## MATERIALS AND METHODS

We reviewed the database from our cryopreservation laboratory from January 2000 to September 2005. Institutional review board approval was obtained. Office charts of all patients in the database were reviewed. Men with cancer who cryopreserved sperm before undergoing treatment were included in the data analysis. Exclusion criteria were absence of cancer or any previous cancer therapy including chemotherapy, radiotherapy or surgery. Men with azoospermia were not included in this study since they had no sperm to cryopreserve and, therefore, were not recorded in the database.

Age at banking, number of samples banked, semen volume, sperm concentration, percent motile sperm, forward progression and type of cancer were recorded. Semen parameters were compared to values for fertile and subfertile men established by the NCRMN<sup>16</sup> and to published data from a large local pre-vasectomy cohort<sup>17</sup> to address geographic variations in semen quality.

Semen samples were collected by masturbation and were analyzed by WHO guidelines after 30 minutes of liquefaction at 37C. Sperm concentrations and percent motile sperm were determined by manually counting and calculating the average of 3 high powered fields.

Statistical methodology consisted of descriptive statistics (mean, range, frequency distribution), as well as Stu-

dent's unpaired t tests and ANOVA analysis. All statistical analyses were performed using Microsoft Excel Statistical Software 2003, setting the statistical significance level at  $p < 0.05$ .

## RESULTS

The sperm cryopreservation database contained 2,680 samples from 1,409 men. Of these 1,409 men 409 met inclusion criteria and had office charts available for review. These 409 men with cancer banked 717 samples (mean 1.8, range 1 to 6) before undergoing therapy.

Of the men 45% had testicular cancer and the remainder had various hematological and soft tissue malignancies (fig. 1). Patients whose cancer incidence was less than 1% of the total were grouped collectively as other types of cancers, and included thyroid (6), melanoma (4), osteoblastoma (1), bladder (1), lung (1), nasopharyngeal (1), liver (1), plasmacytoma (1), shoulder teratoma (1) and primitive neuroectodermal tumor (1). The unknown category refers to men who reported having cancer but did not specify the cancer type.

The data for all patients are presented in the table. Overall for all men with cancer who cryopreserved before therapy mean age was 29.9 years (range 11.9 to 87.7), mean semen volume was 2.8 ml (range 0.1 to 15), mean sperm density was  $47.4 \times 10^6/\text{ml}$  (range 0.1 to 320) and mean sperm motility was 50% (range 1 to 90).

For men with testicular cancer mean age was 28.4 years (range 14.8 to 54.4), mean semen volume was 2.8 ml (range 0.2 to 15), mean density was  $32.9 \times 10^6/\text{ml}$  (range 0.2 to 308.5) and mean motility was 48.5% (range 1 to 85). Mean sperm density and motility for these patients with testicular cancer fell in the intermediate range as determined by the

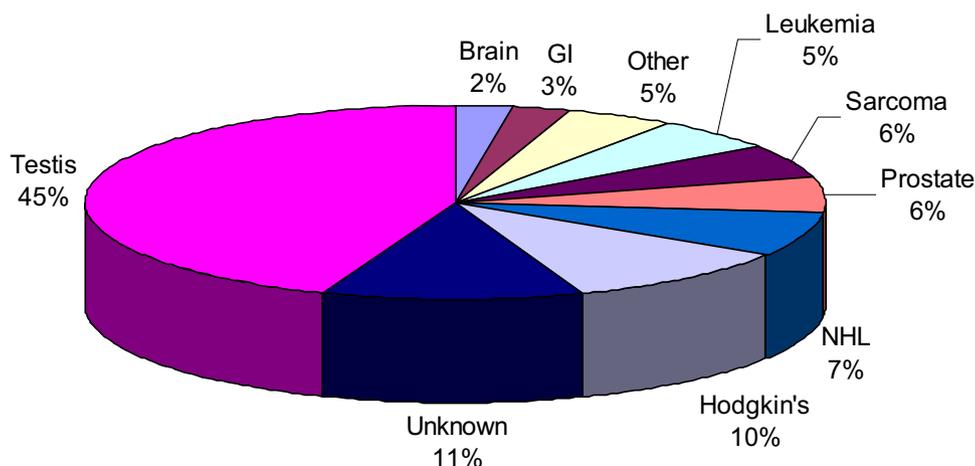


Figure 1. Men with cancer who banked sperm before treatment

	No. (%)		Mean (range)					
	Pts	Samples	Pt Age at Cryopreservation	Semen Vol (ml)	Sperm Density (10 <sup>6</sup> /ml)	Sperm Motility (%)	Forward Progression	Total Motile Sperm (million)
All	409	717	29.9 (11.9–87.7)	2.8 (0.1–15)	47.4 (0.1–320)	50.0 (1–90)	2.4 (1.0–3.5)	76.1 (0.01–672)
Testis	179 (45)	351 (49)	28.4 (14.8–54.4)	2.8 (0.2–15)	32.9 (1.0–308.5)*	48.5 (1–85)*	2.5 (1.0–3.5)	49.4 (0.01–634.8)*
Hodgkin's	43 (10)	72 (10)	27.8 (14.7–87.7)	3.0 (0.6–8.5)	60.6 (1.5–153.5)	57.0 (25–90)	2.5 (1.5–3.0)	125.0 (6.5–463.3)
NHL	31 (7)	51 (7)	28.9 (16.0–48.6)	2.6 (0.8–8.0)	70.1 (6.5–247)	55.6 (25–70)	2.6 (1.5–3.0)	101.2 (10.5–555.8)
Prostate	24 (6)	44 (6)	51.6 (38.7–65.8)*	2.8 (0.4–5.5)	83.5 (0.4–308)	50.2 (25–90)	2.3 (1.0–3.0)	123.8 (5–463.3)
Leukemia	22 (5)	30 (4)	28.6 (14.8–54.4)	3.0 (1.0–8.0)	68.0 (13.5–320)	49.7 (20–70)	2.4 (1.5–3.0)	122.5 (5.4–672)
Sarcoma	24 (6)	40 (6)	23.8 (15.8–45.5)	3.1 (0.9–4.5)	63.7 (1.0–250)	56.0 (2.0–80)	2.4 (1.5–3.0)	128.0 (0.04–657)
GI	11 (3)	19 (3)	34.5 (25.6–39.9)	2.3 (1.0–4.5)	92.6 (1.0–222)	53.2 (15–70)	2.5 (2.0–3.0)	127.0 (0.375–375)
Brain	10 (2)	18 (2)	33.2 (19.3–44.7)	3.3 (1.2–9.0)	53.6 (1.5–129)	50.0 (20–60)	2.4 (2.0–3.0)	113.9 (0.9–485)
Other	18 (5)	22 (3)	30.1 (11.9–42.1)	3.0 (0.1–9.5)	49.7 (1.3–170)	49.5 (1.0–75)	2.5 (1.0–3.5)	65.7 (0.03–319)
Unknown	47 (11)	70 (10)	28.7 (14.8–56.3)	2.8 (0.4–10.5)	42.3 (2.0–163)	51.0 (25–75)	2.4 (2.0–3.0)	68.0 (0.4–374)

\* p <0.05 vs all other cancers excluding other and unknown.

NCRMN study (13.5 to 48.0 × 10<sup>6</sup>/ml and 32% to 63%, respectively).<sup>16</sup>

In contrast, parameters for men with all other known malignancies were in the fertile range for density (greater than 48.0 × 10<sup>6</sup>/ml) and in the intermediate range for motility. Additionally, 45% of men with testicular cancer were in the subfertile range, which was defined as a sperm density less than 13.5 million,<sup>16</sup> compared to 16% of men with all other known cancers and 10% of men before undergoing vasectomy (fig. 2).<sup>17</sup>

Overall men with testicular cancer had sperm concentrations that were significantly lower than those with other malignancies. Using WHO criteria 52% of men with testicular cancer were oligospermic compared to 12% to 30% of men with other cancers (figs. 3 and 4).<sup>18</sup>

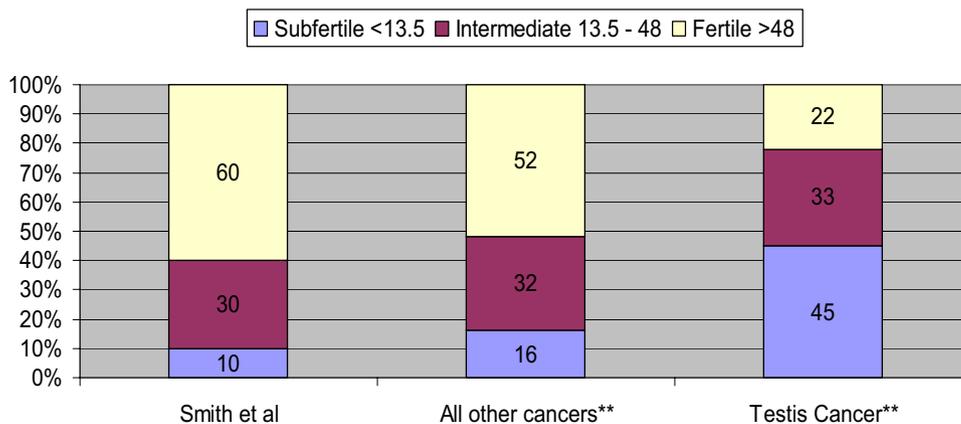
**DISCUSSION**

To our knowledge this analysis represents the largest United States series addressing semen quality in

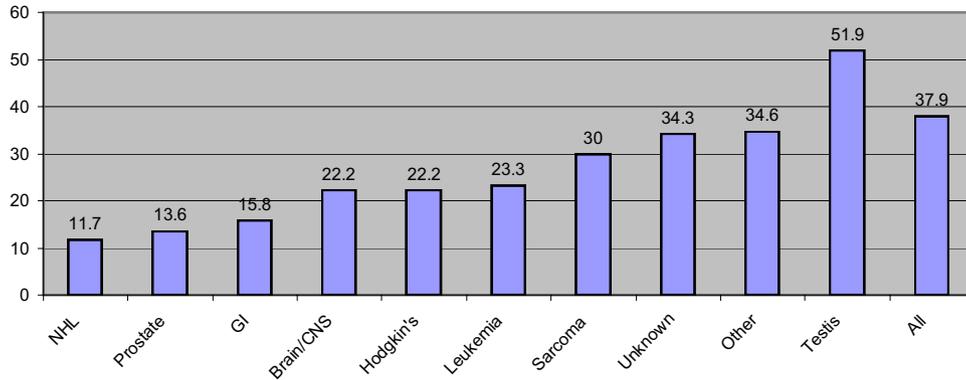
men with cancer. We found that men with testicular cancer as a group had a lower sperm concentration and lower sperm motility than men with other types of cancer.

A number of studies report that cancer adversely affects semen quality. Colpi et al reviewed the Italian experience with sperm cryopreservation by men with cancer.<sup>8</sup> They reported normal semen parameters according to WHO criteria in only 40% of men with lymphoma, 37% with testicular cancer and 37% with other tumors. Likewise Lass et al reported that 50% of men with cancer who cryopreserved at their institution had fewer than 10 million motile sperm per ejaculate.<sup>15</sup> Finally Hallak et al demonstrated that men with testicular cancer had semen parameters that were inferior to those of normal controls.<sup>9</sup>

In contrast a recent North American report found semen analyses to be similar in men with and those without cancer. Rofeim and Gilbert compared semen parameters of 214 men with a variety of cancers to



**Figure 2.** Fertility ranges based on sperm density (NCRMN values) for men with cancer and historical controls. Double asterisks indicate current study.



**Figure 3.** Percentage of oligospermic (WHO 1999) samples by cancer. CNS, central nervous system

22 men without cancer and found no significant differences between the groups.<sup>11</sup>

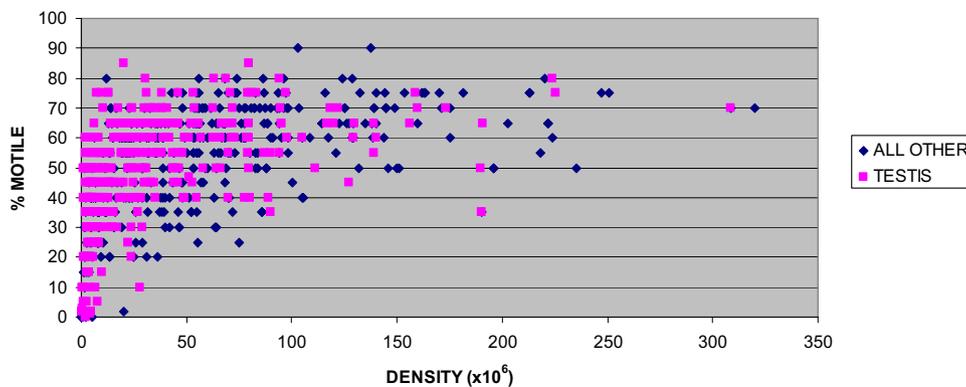
Some studies suggest that the type of malignancy impacts semen quality. A large Italian study of 776 men with cancer demonstrated that sperm density was significantly reduced in men with testicular cancer but that sperm quality did not vary significantly among men with other malignancies.<sup>12</sup> Similarly a British study of 314 patients with cancer found that men with testicular cancer had the lowest pretreatment sperm concentrations compared to those with other malignant neoplasms.<sup>13</sup> Lass et al also found that men with testicular tumors had significantly lower sperm quality compared to those with hematological or other malignancies.<sup>15</sup>

However, there is also evidence to suggest that the type of malignancy does not impact semen quality. Meseguer et al reviewed semen parameters of 184 Spanish men who banked sperm before cancer treatment and found no significant differences in total sperm counts among men with different malignancies.<sup>10</sup> Likewise Chung et al found that sperm counts and motility did not differ by type of cancer in 97 patients who froze sperm at their institution before the initiation of cancer therapy.<sup>14</sup>

The causes of poor semen quality in patients with cancer are not well understood and multiple factors are likely involved. Some of these factors include preexisting defects in germ cells, local tumor effects, endocrine disturbances, and autoimmune and systemic effects of cancer.<sup>19</sup> A detailed discussion of these factors is beyond the scope of this article.

Some limitations of this study deserve discussion. Patients who cryopreserved sperm at our institution were primarily referred by oncologists or treating institutions. Thus, for them to bank sperm their oncologists not only needed to know about the availability of a regional cryopreservation laboratory but they also had to be willing to discuss this issue with the patient and his family. Additionally, patients themselves must be physically capable of producing a sample (or samples) and not be completely debilitated by disease. An increased referral network could alter our regional data, as could data from patients who were too incapacitated to produce semen samples or who needed to start emergency treatment for their condition without time permitting them to cryopreserve sperm.

A number of office charts lacked information regarding pertinent medical histories and physical ex-



**Figure 4.** Pretreatment semen analyses of men with cancer

aminations. Since patients were typically referred only to bank sperm they were not always seen by a physician. Thus, it was not always possible to determine which patients had additional risk factors for male infertility—ie did patients have varicoceles or histories of undescended testes, infections, trauma, etc? Further knowledge of patient history could alter our data. For example, a history of undescended testes is a risk factor for male infertility and testicular carcinoma.<sup>20</sup>

Men with azoospermia were not included in this study. Ragni et al reported that 11.6% of men who wished to cryopreserve sperm at their institution were azoospermic.<sup>12</sup> This ranged from 3.9% of men with nonHodgkin's lymphoma up to 15.3% of men with testicular tumors. In a smaller study Lass et al reported that 10.5% of untreated men were azoospermic including 9.6% with testicular tumors, 13.3% with leukemia or lymphoma and 3.7% of men with other malignancies.<sup>15</sup> However, omitting patients with azoospermia probably did not significantly alter our findings for 2 reasons. Adding more men with azoospermia men to our study group would further support our primary finding that men with cancer, particularly testis cancer, have semen

parameters that are inferior to those of men without cancer. In addition, in the era of in vitro fertilization/ intracytoplasmic sperm injection even men with severe oligospermia were able to bank sperm at our laboratory and their data were included in our analysis. Thus, although important to consider, the fact that men with azoospermia men were omitted from analysis should not have a significant bearing on the outcomes and conclusions of this study.

## CONCLUSIONS

Our cohort of men with testicular cancer had inferior semen parameters compared to men with other malignancies and men without cancer. Since testis tumors can affect spermatogenesis in the ipsilateral as well as the contralateral testis, these data reflect intrinsic testicular failure and the frequent secondary effect of abnormal hormonal status seen in this population. This information adds to the body of literature about the fertility status of men with cancer and it further highlights the importance of fertility preservation in this patient population at risk for impaired testicular function even before undergoing gonadotoxic treatments.

## REFERENCES

1. Giwercman A and Petersen PM: Cancer and male infertility. *Baillieres Best Pract Res Clin Endocrinol Metab* 2000; **14**: 453.
2. Jacobsen KD, Olsen DR, Fossa KM and Fossa SD: External beam abdominal radiotherapy in patients with seminoma stage I: field type, testicular dose, and spermatogenesis. *Int J Radiat Oncol Biol Phys* 1997; **38**: 95.
3. Carson SA, Gentry WL, Smith AL and Buster JE: Feasibility of semen collection and cryopreservation during chemotherapy. *Hum Reprod* 1991; **6**: 992.
4. Meirow D and Schenker JG: Cancer and male infertility. *Hum Reprod* 1995; **10**: 2017.
5. Naysmith TE, Blake DA, Harvey VJ and Johnson NP: Do men undergoing sterilizing cancer treatments have a fertile future? *Hum Reprod* 1998; **13**: 3250.
6. Sheinfeld, J, McKiernan J and Bosl GJ: Surgery of testicular tumors. In: *Campbell's Urology*, 8th ed. Edited by P Walsh, AB Retik, ED Vaughan and AJ Wein. Philadelphia: WB Saunders Co 2002; p 2926.
7. Shin D, Lo KC and Lipshultz LI: Treatment options for the infertile male with cancer. *J Natl Cancer Inst Monogr* 2005; **34**: 48.
8. Colpi GM, Colpi EM, Castiglioni F and Grugnetti C: Semen cryopreservation from oncological patients: the Italian experience. *Eur J Obstet Gynecol Reprod Biol* 2004; **113**: S12.
9. Hallak J, Kolettis PN, Sekhon VS, Thomas AJ Jr and Agarwal A: Sperm cryopreservation in patients with testicular cancer. *Urology* 1999; **54**: 894.
10. Meseguer M, Molina N, Garcia-Velasco JA, Remohi J, Pellicer A and Garrido N: Sperm cryopreservation in oncological patients: a 14-year follow-up study. *Fertil Steril* 2006; **85**: 640.
11. Rofeim O and Gilbert BR: Normal semen parameters in cancer patients presenting for cryopreservation before gonadotoxic therapy. *Fertil Steril* 2004; **82**: 505.
12. Ragni G, Somigliana E, Restelli L, Salvi R, Arnoldi M and Paffoni A: Sperm banking and rate of assisted reproduction treatment: insights from a 15-year cryopreservation program for male cancer patients. *Cancer* 2003; **97**: 1624.
13. Bahadur G, Ozturk O, Muneer A, Wafa R, Ashraf A and Jaman N: Semen quality before and after gonadotoxic treatment. *Hum Reprod* 2005; **20**: 774.
14. Chung K, Irani J, Knee G, Efymow B, Blasco L and Patrizio P: Sperm cryopreservation for male patients with cancer: an epidemiological analysis at the University of Pennsylvania. *Eur J Obstet Gynecol Reprod Biol* 2004; **113**: S7.
15. Lass A, Akagbosu F, Abusheikha N, Hassounah M, Blayney M, Avery S et al: A programme of semen cryopreservation for patients with malignant disease in a tertiary infertility centre: lessons from 8 years' experience. *Hum Reprod* 1998; **13**: 3256.
16. Guzik DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C et al: Sperm morphology, motility, and concentration in fertile and infertile men. *N Engl J Med* 2001; **345**: 1388.
17. Smith KD, Stultz DR, Jackson JR and Steinberger E: Evaluation of sperm counts and total sperm counts in 2543 men requesting vasectomy. *Andrologia* 1978; **10**: 362.
18. WHO Laboratory Manual for the Examination of Human Semen and Semen-Cervical Mucus Interaction, 4th ed. Cambridge: Cambridge University Press 1999.
19. Agarwal A and Allamaneni SS: Disruption of spermatogenesis by the cancer disease process. *J Natl Cancer Inst Monogr* 2005; **34**: 9.
20. Lee PA: Fertility after cryptorchidism: epidemiology and other outcome studies. *Urology* 2005; **66**: 427.