

Disruption of Spermatogenesis by the Cancer Disease Process

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In the past, cancer survivors tended to be most concerned about disease recurrence and treatment side effects. As survival rates have increased, however, patients are now also concerned about quality-of-life issues such as preserving fertility potential. It is well known that cancer treatment adversely affects male fertility via direct effects on the testis and/or through the endocrine glands. Evidence also suggests that the disease process itself may affect a man's fertility by influencing spermatogenesis. However, the causes of poor semen quality in cancer patients are not well understood. Multiple factors are likely involved, including preexisting defects in germ cells, systemic effects of cancer, and endocrine and immunological disturbances. This paper will summarize available evidence on different factors involved in impaired spermatogenesis in patients with various cancers with emphasis on testicular cancer and Hodgkin lymphoma. Cryopreservation of spermatozoa is a simple and practical approach available to all patients with cancer who wish to preserve their fertilizing potential before cancer therapy. [J Natl Cancer Inst Monogr 2005;34:9–12]

CANCER IN GENERAL

Cancer is one of the leading causes of death in the United States. The American Cancer Society estimates that almost 1.4 million new cancer cases will be diagnosed in 2004 (1). During the last two decades, major advances in the treatment of malignant tumors have significantly improved survival, especially in adolescent cancers. Even though survival rates vary greatly by cancer type and stage at diagnosis, the 5-year relative survival rate is 63% for all cancers combined. Estimates from the National Cancer Institute indicate that as of January 2000, almost 10 million Americans were living with a history of cancer (1). However, many young men with cancer have been affected by temporary or permanent infertility—a major quality-of-life issue.

CANCER AND FERTILITY

Testicular cancer and Hodgkin disease are among the most common malignant diseases affecting young men of reproductive age. Infertility is a major concern for men with cancer who are undergoing chemotherapy, radiation therapy, or surgery because most of these regimens cause sterility. Several studies have reported that semen quality is poor in patients with cancer, indicating that some cancer patients have decreased fertility potential even before starting treatment (2–8). A recent study on semen quality in 205 adolescent male patients with cancer found that semen parameters were lower in the cancer patients than in healthy control subjects (count [$\times 10^6$]: 50.63 versus 84.51; motility [%]: 45.05 vs. 68.45, and volume [mL]: 1.59 vs. 2.96) (8). It is vital to determine a patient's pretreatment fertility potential so that we can understand how the cancer disease and its treatment

will affect his fertility and advise him on how he can best preserve his fertility before undergoing treatment (9,10). When the cancer process itself is the cause of the patient's decreased fertility potential, spermatogenesis may improve after cure of the disease process (11).

TESTICULAR CANCER

Testicular cancer is the most common malignancy in young men of reproductive age. The association between testicular cancer and abnormalities of spermatogenesis is well known (3,5,6,12–15). A recent study found that sperm count was statistically significantly lower in 83 patients with testicular germ cell cancer (TGCC; $15 \times 10^6/\text{mL}$ versus $48 \times 10^6/\text{mL}$) than in healthy men (6). However, the exact mechanism responsible for the decreased semen quality in testicular cancer patients is not well established (6). It appears that there are multiple mechanisms involved in this association, and these mechanisms may differ between patients (16). One study reported that 66% (79/120) of the patients achieved paternity within 1 year before diagnosis of TGCC, compared with 43% (38/88) after treatment (17).

PREEXISTING SPERMATOGENESIS DEFECTS

Bilateral undescended testis is associated with increased risk of testicular malignancy. Spermatogenesis defects have been observed in patients with this condition (18). Thus, it is possible that a preexisting defect in germ cells leads to both cancer and defective spermatogenesis. A genetic abnormality or exposure to abnormal hormonal levels in utero results in germ cell defects. Reports of spermatogenesis defects in the contralateral testis in patients with cancer support this line of reasoning (3).

One study found that patients with testicular cancer had a high incidence of carcinoma in situ changes in the contralateral testis (8.7%). In the same study, signs of testicular dysgenesis were observed in 25.2% of contralateral testicular biopsies in 218 patients with TGCC (15). The authors reported abnormal or absent spermatogenesis in 48.6% of these patients. However, this theory may not apply to all patients with cancer because other studies have reported previous fertility in patients with testicular cancer (19) and improvement in semen parameters after cancer treatment (11).

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LOCAL EFFECTS BY TUMOR

Local effects of the tumor itself can cause impaired spermatogenesis. This conclusion is based on the observation that the number of spermatogenesis defects in testicular tissue is highest in the tissue closest to the tumor (20). However, when orchietomy specimens with benign lesions were examined, uniform spermatogenesis was observed (14). This finding may rule out mass effect as a cause of impaired spermatogenesis, but malignant tumors are fast growing. These findings can be explained by paracrine action of the secretory substances of the tumor (hormones, cytokines).

AUTOIMMUNE CAUSES

Testicular cancers disrupt the blood–testis barrier. This barrier prevents autoantibodies forming against sperm. Antisperm antibodies develop as a result of the disruption of the blood–testis barrier by cancer, which may play a role in poor semen analysis results. Using the immunofluorescent technique, Foster et al. (21) found antisperm antibodies in 21% of cancer patients. Another study found antisperm antibodies in 73% of patients with testicular cancer, compared with 8% in healthy control subjects (22).

ENDOCRINE FACTORS

Spermatogenesis is a complex process that is well controlled by the hypothalamic–pituitary–gonadal axis. Various hormones not only control when spermatogenesis begins but also help ensure that spermatozoa develop normally. Any imbalance in the hormonal status of the body and seminiferous tubules could lead to disturbances in the process of spermatogenesis. Cancer may alter balance of hormones and thus impair spermatogenesis in two ways: first, the general systemic effects of cancer may lead to the over- or undersecretion of hormones by the endocrine glands, and second, tumor tissue may secrete its own set of hormones such as β -human chorionic gonadotrophin (β -hCG) and α -fetoprotein (AFP), which can affect the process of spermatogenesis.

In one study, β -hCG levels were elevated in 58%–70% of patients with TGCC but not in any of the healthy control subjects (3,6). The authors of that study also reported significantly decreased levels of luteinizing hormone and inhibin B and elevated levels of follicle-stimulating hormone in their patients (6). Morrish et al. (23) proposed a paracrine–endocrine mechanism for impaired spermatogenesis in which β -hCG produced by cancer cells elevates intratesticular levels of estradiol.

Using multiregression analysis, Hansen et al. (13) found that elevated serum AFP levels were significantly correlated with decreased sperm count in addition to a history of cryptorchidism and a seminomatous tumor. These authors also found elevated follicle-stimulating hormone levels in 33% of 97 patients with testicular cancer and elevated luteinizing hormone levels in 14% of patients without β -hCG in their serum.

SYSTEMIC EFFECTS OF CANCER

Cancer in general evokes a systemic response in the body. Cytokines such as interleukins, tumor necrosis factors, and other substances secreted by tumor tissue and body defense cells may

mediate this systemic response. This theory can explain why semen parameters can improve after testicular cancer treatment (24). Stress associated with cancer diagnosis itself can impair the semen quality through disturbances in hormone levels (4).

Finally, it should be noted that in testicular cancer patients, semen parameters, especially sperm count, may be affected by orchietomy on the side of cancer. However, the presence of spermatogenesis defects in ipsilateral (20) and also in contralateral testis (15) may rule out the possibility that the presence of solitary testis is the cause of impaired semen parameters in these patients. The effect of a single testis on sperm quality in patients with cancer may be more accurately examined by evaluating the functional properties of the sperm rather than just sperm count.

HODGKIN LYMPHOMA

Pretreatment impairment of spermatogenesis has been well studied in patients with Hodgkin disease (2,7,25–29). The effect of treatment on spermatogenesis is more severe in Hodgkin disease patients treated with alkylating chemotherapy agents (mechlorethamine, vincristine, procarbazine and prednisone regimen) compared with nonalkylating agents (adriamycin, bleomycin, vinblastine, dacarbazine regimen). Viviani et al. (27) studied testicular dysfunction in 92 patients with Hodgkin disease and reported semen abnormalities in 67% of the patients. The authors found no correlation between semen abnormalities and disease stage or systemic symptoms. Levels of follicle-stimulating hormone, luteinizing hormone, testosterone, and prolactin in this group of patients were comparable to levels in healthy donors. Some studies have correlated the stage of the disease with abnormal semen (7). Other studies have found a correlation between semen quality and systemic effects of Hodgkin disease such as fever (25).

A recent study of patients with Hodgkin disease found that 47% had an abnormal semen analysis (28). In that study, semen quality was significantly correlated with the hemoglobin rate but not with disease stage or fever. A different study consisting of 158 patients with Hodgkin disease reported that elevated levels of erythrocyte sedimentation rate and advanced disease stage were prognostic factors for severe fertility damage (7).

Redman et al. (26) postulated that the immunological process associated with cancer induces spermatogenesis disorder. They detected sperm agglutinins in 31% of patients with Hodgkin disease but in no healthy control subjects. Helper and suppressor T lymphocytes may play a role in normal spermatogenesis (30). Systemic disturbances in the balance between subpopulations of T lymphocytes occur in patients with Hodgkin disease, and it is hypothesized that these disturbances could be a cause of dyspermia in these patients (30).

OTHER CANCERS

Leukemia is one of the common malignancies that affects children and those of reproductive age. Although the effect of leukemia treatment on fertility is well known, few studies have analyzed the pretreatment semen quality in patients with this disease. Hallak et al. (31) found that pretreatment semen quality was poor in patients with acute and chronic leukemia. Specifically, the median motile sperm count (19.5×10^6 versus 129.6×10^6 ; $P = .0001$) and motility (45% versus 64%; $P < .05$) were lower in patients with leukemia than in healthy donors. In recent years,

there has been increased referral by oncologists for semen cryopreservation in patients with leukemia before bone marrow transplantation to preserve fertility.

Patients with cancers other than testicular cancer, Hodgkin disease, and leukemia may also experience subfertility as a result of impaired spermatogenesis (8), although adequate studies are not available to confirm or refute this theory. In one study, total motile sperm count was significantly lower in patients with carcinoma ($46.9 \times 10^6/\text{mL}$) and sarcoma ($66.3 \times 10^6/\text{mL}$) compared with a group of healthy semen donors ($129.6 \times 10^6/\text{mL}$) (32). Hallak et al. (33) reported poor sperm count and motility in patients with various cancers including central nervous system tumors. Poor semen quality in these patients may be a result of endocrine disturbances at central levels, systemic consequences of cancer, or both.

MUTAGENIC POTENTIAL OF PRETREATMENT SEMEN

There are concerns that men with cancer who initiate a pregnancy either before or after treatment may have children who are at an increased risk for congenital anomalies. However, Hansen et al. (34) studied the rate of congenital abnormalities in children born to fathers with cancer before treatment and observed a congenital malformation rate of 3.8%, which is comparable to the general population. Redman et al. (26) found no congenital abnormalities in three children who were born using cryopreserved semen from patients with Hodgkin disease. Moreover, Spermon et al. (17) reported a 4% rate of congenital malformations in children born before ($n = 194$) or after ($n = 81$) treatment of testicular cancer, compared with 2.2% in the general population. Thus, cancer patients should be informed that, currently, there is no available evidence for increased incidence of congenital abnormalities in children.

MODALITIES TO PRESERVE FERTILITY BEFORE CANCER TREATMENT

Cryopreservation is a well-established process that is used for various indications in reproductive medicine. Cryopreservation of semen is a practical way to preserve fertility in men with cancer. The process affects sperm from cancer patients and healthy donors in a similar fashion (35). A study found that the percentage change in semen parameters did not differ between patients with testicular cancer ($n = 157$) and healthy donors ($n = 50$) (5). The cancer patients did have a statistically significantly lower prefreeze and postthaw motile sperm count ($P = .0001$) and motility ($P = .0001$) than the donors. However, the availability of in vitro fertilization and intracytoplasmic sperm injection can enable patients with low postthaw spermatozoa to father their own biological children. In a study from our lab, cryopreserved spermatozoa of cancer patients that were used in assisted-reproduction techniques resulted in a 52% (15/29) pregnancy rate (36).

Referral for sperm cryopreservation is gradually increasing, although the percentage of patients who use their cryopreserved semen to initiate a pregnancy is low. One study found that 56 of 342 patients disposed of their cryopreserved semen because the patient died, his fertility improved, or he had no plans for children (37). Yet another study reported that of 686 patients with various cancers who cryopreserved their sperm, 36 used the semen for assisted reproduction and 124 patients discarded it (38).

Even so, we believe that all male cancer patients should be counseled about this option (36).

Alternative approaches that are available include testicular tissue cryopreservation (39) and germ cell (spermatogonia) transplantation (40). Research into germ cell transplantation is developing rapidly and provides a promising hope to preserve fertility in cancer patients.

CONCLUSION

In spite of numerous studies reporting impaired semen quality in patients with cancer, we still do not understand the exact mechanisms of fertility impairment. A wide variability in semen quality is observed in patients with decreased fertility before treatment. This can be explained only by a multifactorial etiology of impaired spermatogenesis. The multiple factors may include preexisting defects in germ cells, systemic effects of cancer, effects of humoral factors secreted by cancer cells, alterations in the hypothalamic-pituitary-gonadal axis, the immunological process, and stress associated with diagnosis of cancer. Previous studies have generally used semen parameters as an end point to assess the effect of cancer disease process on spermatogenesis. However, a comparison of the sperm-fertilizing capacity between cancer patients and fertile controls before cancer treatment may provide clearer understanding of this subject.

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