



Why is the rate of testicular cancer increasing?

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In this issue Dr. Hannah Weir and colleagues (page 201) evaluate trends in the incidence of testicular germ cell cancer in Ontario over the last 30 years.¹ They report that the rate has increased about 60% overall, consistent with a 2% annual increase, and that the increase has been greatest in the youngest group (age 15 to 29).

Their finding is not surprising. Over the last couple of years the media have publicized an increase in the incidence of testicular cancer and a decline in the average sperm count. An increased incidence of testicular cancer has been reported worldwide; in northern Europe the incidence has increased by 3 to 4 times.

This epidemiologic evidence has been accompanied by provocative reports of a reduction in testicular size and spermatogenesis rate in several countries. A Finnish study comparing testicles from autopsies performed between 1981 and 1991 reported an 11% reduction in testis weight and a 27% to 56% reduction in the incidence of spermatogenesis.² A French group reported similar findings.³

There has also been an increase in reports of genital abnormalities, including hypospadias, cryptorchidism and gonadal intersex abnormalities.^{4,5} The increased incidence of germ cell cancers among men with testicular atrophy, testicular dysgenesis, cryptorchidism and infertility suggests a common etiologic relation between germ cell cancers and these genital abnormalities. It is a reasonable hypothesis that toxins acting during the early fetal development of the gonads are involved in the reduction in testicular size and spermatogenesis rate and the increase in the incidence of testicular germ cell cancer. This hypothesis is further supported by evidence of a fetal origin of carcinoma *in situ* of the testis, an established precursor of testicular germ cell cancer.

Most ultrasound and tumour markers, such as α -feto-protein and β -human chorionic gonadotropin, have increased our ability to detect subclinical disease. It is possible that some tumours are removed before they are rejected immunologically or undergo involution and disappear. Currently, however, almost all patients diagnosed with localized testis cancer present with a palpable testicular mass. These masses, if left untreated, progress rapidly. Thus, the impact of overdiagnosis is at best minor and insufficient to explain the sustained worldwide increase in incidence.

The concept that estrogen-mimicking chemicals act as hormonal disrupters transplacentally to interfere with gonadal development in utero is based in part on reports of gonadal abnormalities occurring after exposure to diethylstilbestrol (DES) in utero.⁶⁻⁸ The increased incidence of testis cancer after DES exposure has been disputed on the basis of case-control studies failing to show a relation.⁹⁻¹⁴ This lack of correlation may be due to the small number of fetuses exposed to DES during the critical period (weeks 7 to 10), thus decreasing statistical power.

A recent finding supporting the relation between estrogenic exposure in utero and testicular cancer is the observation that dizygotic twins, whose maternal estrogen levels are higher than those of monozygotic twins, have a higher incidence of testicular cancer.¹⁵ The same relation was found in female twins with respect to the incidence of breast cancer, another estrogen-associated disease.¹⁵ Other factors associated with variations in intrauterine hormone levels, including birth order, increased bleeding during pregnancy and excessive nausea during pregnancy, have been associated with an increased risk of testicular cancer.¹⁶

More evidence supporting the contribution of a uterine hormonal factor are data from a population-based study comparing the risk of testicular cancer in fathers and brothers of patients with the disease.¹⁷ Fathers of more than 2000 Danish children with testicular cancer had rates of testicular cancer that were twice as high as expected from general population data. Brothers of 702 of these cases had rates that were 12 times higher than expected.

Which environmental agents are the likely culprits? A number of microcontaminants have hormone-disrupting properties, either with estrogenic or antiandrogenic activity. The list includes DDT, PCBs, nonylphenol, bisphenola and vinclozolin.

Finally, several reports have suggested a relation between testicular germ cell cancer and a sedentary lifestyle (i.e., increased testicular temperatures), focusing on the role of heat as a toxic insult.¹⁸

Epidemiologic trends support the concept that testicular cancer, undescended testis, hypospadias and impaired spermatogenesis are related biologically. A substantial amount of evidence indicates that environmental pollutants with estrogenic or antiandrogenic activity result in hormonal disruption and are responsible for the steadily



increasing incidence of testicular cancer. This hypothesis is also supported by wildlife studies. For example, small genitalia and decreased semen quality have been reported in Florida alligators¹⁹ and American panthers.²⁰

What consequence these findings should have on public policy with respect to environmental contamination is unclear. A more precise understanding of the effect of these chemicals on the developing testis would allow an informed and rational approach to this contentious subject.

A number of outstanding epidemiological issues remain. Why is the incidence of testicular cancer highest among young adults, with little risk among older men, even though spermatogenesis is a lifelong process? Why are there pronounced geographical and racial differences in the incidence? What is the explanation for the birth cohort effect? Why is testicular cancer more common in men with abnormally developed gonads? More research is needed to answer these questions.

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