



# Risk in Perspective

## Testicular Cancer: What's Going On?

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***"A sustained and geographically widespread trend toward increasing appearance of a cancer announces an increasing public health problem and challenges us to identify an explanation."***

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Testicular cancer is increasingly in the news and in the minds of epidemiologists as they struggle to account for increasing trends around the world. While this cancer is not one of the most common to afflict the human population, it is by no means rare—of every 1000 males, between 2 to 4 can be expected to develop testicular cancer sometime during life, with many cases appearing in young adulthood. Testicular cancers account for about 1% of all newly diagnosed neoplasms in males. Since testicular cancers often appear particularly early in life (in young adulthood rather than in late middle age or later as with most cancers), men dying from this disease lose a particularly large number of years of life (36, on average).

The incidence of testicular cancer (that is, the rate of diagnosis of new cases) seems to have undergone a progressive increase over the last three decades. In the United States, the estimated incidence increased 2.2% per year from 1950 to 1992. Danish scientists have documented similar increases in some Scandinavian countries and in Britain. Rates vary from country to country; for instance, Denmark has a particularly high rate, while nearby Finland has a rate that is lower than that of most developed nations. Participants at a recent European workshop noted that increases of some magnitude appear to be occurring in all nations for which a reliable tumor registry exists.

Fortunately, over the past decades, our ability to successfully treat testicular cancer has improved markedly. The rate of testicular cancer deaths is actually decreasing in the U.S. at about 3% per year even as incidence rises. In the early 1950's the survival rate 5 years from diagnosis was only 57%, but by the late 1980's it had increased to over

95%, mainly as a result of advances in chemotherapy. As with many cancers, success in treatment improves markedly for tumors that are discovered in early stages.

In this issue of RISK IN PERSPECTIVE, we examine current understanding of testicular cancer causes, including the prospects for identifying preventable environmental factors that may underlie the trends of the last 30 years.

### WHAT MAY BE CAUSING THE CHANGE?

A sustained and geographically widespread trend toward increasing appearance of a cancer announces an increasing public health problem and challenges us to identify an explanation. The rapid, progressive, and widespread change raises the possibility that some changing aspect of our environment may be responsible.

As with some other cancers, there is evidence that a fraction of testicular cancers have a substantial hereditary cause. This evidence includes the early onset of these tumors, the observed higher risk in men with affected family members (and in men whose mothers have had breast cancer), the higher rate of bilateral tumors (i.e., in both testicles) in men with a family history, and the observation of certain genetic anomalies in some patients. To date, however, there has been no identification of a "testicular cancer gene" that is responsible for this apparent hereditary influence. In any case, genetic predisposition seems to account for only a fraction of cases.

There are some clear ethnic differences in testicular cancer rates. White men have the highest rates, both in the U.S. and internationally. Black men have recorded lower overall incidences, and Asian and Hispanic men have intermediate rates. Interestingly,

the lower rates in Blacks seem to be holding steady; it is the increasing rates in White men that account for the trends. Moreover, this increase seems to be happening mostly in the younger age groups, with rates in older men remaining relatively unchanged over time.

Some occupations have been reported to have somewhat higher than average rates of testicular cancer, including workers in health-related occupations, manufacturing, aircraft production or maintenance, crude petroleum and natural gas industries, farmers, leather dyers and tanners, miners, food and beverage workers, workers in filling stations, and workers in "sedentary" occupations. No single agent or group of agents has been identified among these occupations, although heavy metals and dimethylformamide have been suggested. A few studies point to other potential risk factors, including exposure to the mumps virus, injury to the scrotum, high social class, and vasectomy. These factors are not considered well established, and the magnitudes of their effects on risk (if any) do not appear to be large. In any case, they do not readily explain the trends over time.

### CRYPTORCHIDISM AND TESTICULAR CANCER

The single factor that carries highest risk of testicular cancer (and indeed, the only risk influence that is considered confirmed) is cryptorchidism. Cryptorchidism is the technical name for the failure of one or both testicles to descend before birth into the scrotum from their place of formation in the abdomen (a condition which is typically fairly easy to correct surgically). The incidence of undescended testes at birth is under 3% in the general population, while 10 to 12% of patients with testicular cancer have a history of this condition. A history of cryptorchidism increases the probability of developing testicular cancer as an adult by a factor of 3.5 to 5 times.

There is evidence that the incidence of cryptorchidism has been increasing since the 1940's, perhaps explaining the trends in testicular cancer. This begs the question, however, of why cryptorchidism rates have increased, and the data on this phenomenon are less clear than they are for cancer. It also remains unclear why undescended testicles and testicular cancer are associated. On the one hand, the abnormal position of

the testicle during development may be the cause of the increased risk of eventual testicular cancer. This hypothesis is supported by the fact that surgical correction of the maldescent seems to mitigate the risk. On the other hand, the failure to descend and the cancer risk may be common manifestations of some underlying abnormality of the testicle, presumably arising during the period of fetal development. In either case, the focus shifts to explaining the causes of the increased incidence of cryptorchidism in the last decades.

Testicular descent is under the control of hormones. Animal experiments show that, during critical periods of fetal development, excesses of estrogens or insufficient androgens can lead to abnormalities of the genitourinary tract. It has been hypothesized that estrogen-mimicking chemicals in the environment may prompt such effects, and may underlie trends in testicular cancer, cryptorchidism, as well as sperm count and other reproductive effects. To date, however, experimental evidence of actions on testicular descent or testicular cancer, particularly at the low doses expected from environmental exposure, has not been developed. Whether moderate-to-low changes in hormone levels that humans might experience can have any such effects is unclear; some indicators of moderately increased estrogen levels for the fetus (first births, maternal nausea during pregnancy) showed small effects on testicular cancer risk in some studies. On the other hand, the drug diethylstilbestrol (which is a powerful mimic of the body's own estrogen that was given to many pregnant women in the 1950's and 1960's and has been shown to cause a number of reproductive abnormalities in their offspring) appears to have no pronounced effect on testicular cancer in males exposed during their fetal development.

In sum, the causes of the changing rates of testicular cancer are not clear at present. The widespread and progressive changes over the course of a few decades suggest that environmental factors may be involved, yet the lack of increase in all ethnic groups suggests variation in susceptibility or exposure. Effects on hormonal control of development are biologically plausible, but there is little positive experimental evidence that such effects are actually responsible. This will continue to be a public health topic of concern and of important research focus.

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### FURTHER READING:

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