

# **Testicular Cancer: Peer-Reviewed Analysis**

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## **Testicular Cancer**

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Testicular cancer is the most common cancer in young men (ages 15-45). In the testes, cancer of the germ cells (immature sperm) is by far the most frequent, though cancer of the testosterone-producing Leydig cells can also occur. Fortunately, treatment for testicular cancer has markedly improved over the past several decades, and the disease is frequently curable with combinations of surgery, chemotherapy, and radiation. As a result, mortality from testicular cancer has declined, but the incidence of new cases has steadily increased in many countries since the 1940's.

## **Epidemiology**

In the United States, the incidence of testicular cancer dramatically increased by nearly 300% between the late 1930s and late 1970s. Over the past 25 years, incidence has continued to increase at about 2.2% annually for white men, while remaining nearly constant for black men.<sup>1 2</sup> The rate of increase has been even sharper in some countries, including the United Kingdom and Denmark, where testicular cancer incidence is the highest in the world.<sup>3</sup>

Low and relatively constant incidence rates of testicular cancer are seen not only in black men in the United States but also in Africans, Asians, and, South Americans. Rates among Japanese and Chinese migrants to the US, however, are higher than among those living in Asia, suggesting that environmental as well as genetically-determined ethnic factors are involved in the origins of this cancer.<sup>4</sup>

## **Causes of Testicular Cancer**

The cause(s) of testicular cancer are not well understood, but the age distribution of the disease, twin studies, studies of the uterine environment during fetal development, laboratory animal studies, and identification of risk factors provide important clues.

## **Genetic Inheritance**

The familial relative risk of testicular cancer is higher than in many cancers. Brothers of men with testicular cancer have an approximately 8 fold increased risk of developing the disease.<sup>5</sup> Two studies conclude that 25-33% of testicular cancer cases result from genetic predisposition.<sup>6 7</sup> However, these studies must be interpreted with caution because shared environmental factors as well as genetic inheritance may influence the outcome of studies of cancer incidence in families.

## **Environmental Factors**

The fetal and childhood environment is a particularly important determinant of testicular cancer risk. Fetal environmental factors include maternal hormone levels and chemicals that cross the placenta, directly exposing the fetus during critical periods of development. An analysis of a large Swedish database of cancer in families concludes that childhood and non-shared environmental factors together account for about 75% of testicular cancer cases.<sup>8</sup>

It is important to consider the well-documented increased rate of testicular cancer in the context of other apparent changes in male reproductive health. It is the changing pattern of several diseases or conditions that provides clues to their origins and the most convincing evidence of the importance of the fetal environment. Along with the increases in testicular cancer, many studies suggest that male fertility and sperm counts are declining in some parts of the world and the incidence of cryptorchidism (undescended testes) and hypospadias (an abnormality of the penis in which the opening is on the underside of the shaft rather than at the tip) is increasing.<sup>9 10</sup>

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## **The Hormonal Environment**

Considerable recent interest has focused on the role of hormonal factors in the development of testicular cancer. A large amount of research in laboratory animals and humans points to the importance of the period of fetal development in determining the subsequent risk of developing testicular cancer. This research can be summarized as follows:

Development of the male reproductive tract is under the control of hormones during fetal development. Of course, testosterone from the fetal testes plays an important role, but estrogen and pituitary hormones, among others, are also critical.<sup>12 13 14</sup>

Animal studies show that fetal exposure to estrogen or estrogenic chemicals can cause not only reduced sperm counts, cryptorchidism, and hypospadias, but also fundamental changes in the germ cells (immature sperm) that persist after birth and that may be precursors to cancerous changes in those cells.<sup>15 16 17</sup>

Animal studies also show that fetal exposure to anti-androgens, which block the action of testosterone or impair its synthesis, also cause similar abnormalities of male reproductive tract development. Anti-androgens for which this has been shown include the pesticides vinclozolin, procymidone, DDE, which is the metabolite of DDT, and some phthalates, which are plasticizers used in many different consumer products and which are almost universally present in the blood and urine of human populations.<sup>18 19 20</sup>

Human studies also indicate that the risk of testicular cancer sharply increases with abnormalities of testis development, including non-descent into the scrotum and low sperm counts associated with infertility.<sup>21 22</sup> Numerous studies report an increased risk of testicular cancer in an undescended testis of 2-9 fold.<sup>23</sup> In a male with only one undescended testis, the excess cancer risk in the testis that has normally descended into the scrotum during development is not as large, but some studies find that the risk in that testis is also somewhat elevated.<sup>24</sup>

In humans, evidence that estrogenic exposures in the developing fetus play a role in increasing testicular cancer risk is inconclusive. Testicular cancer risks in male offspring are highest in first pregnancies, when estrogen levels are higher than in subsequent pregnancies.<sup>25 26</sup> Some evidence points to maternal estrogen exposure as increasing the risk of testicular cancer in their sons. In one study, the risk was increased 5 fold if a woman had used prescription hormones, prescription medications for conditions associated with threatened miscarriage, injections or pills to determine pregnancy, or oral contraceptives around the time of conception.<sup>27</sup> However, studies of sons born to mothers who took the synthetic estrogen, diethylstilbestrol (DES), during pregnancy show mixed results with some showing no significantly increased risk of testicular cancer.<sup>28</sup> The research on DES sons is complicated because testicular cancer remains relatively uncommon even though its incidence is increasing, and because gaps in record keeping often make it difficult to know with certainty whether or not a man with testicular cancer was actually exposed to DES during fetal development. To get around this latter limitation a 16-year prospective study followed over 3000 men whose prenatal DES exposure status was known.<sup>29</sup> The investigators reported that men who had been exposed to DES during fetal development had a 3 fold higher risk of developing testicular cancer, although even in this study, the number of participants and cases was small enough that the increased risk was not statistically significant. Nonetheless, the results support the hypothesis that fetal exposures to abnormal levels of estrogen increase the risk of subsequently developing testicular cancer. It is worth noting, however, that DES was not used in Denmark where testicular cancer risk is the highest in the world, so DES alone cannot explain the trends.

Other hormones, including testosterone and pituitary hormones also are likely to play a role, and environmental factors that alter their normal levels may also alter testicular cancer risk. Some investigators suggest that the marked difference in testicular cancer risk between blacks and whites can be explained by differences in hormone exposures during fetal development. In a study of 20 black women and 20 white women during their first pregnancies, testosterone levels in black women were 48% higher than those in white women in the early weeks of pregnancy.<sup>30</sup> Estrogen levels were only slightly higher in black women. It may be that the relative excess of testosterone exposure in black males during fetal development explains the lower testicular cancer risk in black men.

Pituitary hormones may also play a role. In boys with Down's syndrome, testicular cancer risk is elevated despite lower overall cancer risk when compared to the rest of the population.<sup>31</sup> In mothers who give birth to a boy with Down's syndrome, and in boys with Down's syndrome, pituitary hormones (follicle stimulating hormone and luteinizing hormone) are elevated.<sup>32 33</sup> Boys with Down's syndrome also have an increased risk of undescended testes.

Taken together these threads of evidence suggest that the fetal hormonal environment plays an important role in determining subsequent risk of developing testicular cancer. Elevated exposures to estrogen or estrogenic agents, decreased exposure to testosterone, and increased levels of pituitary hormones may all participate in increasing the risk. Maternal exposures to hormonally active agents such as birth control pills, some pesticides, phthalate plasticizers, and other industrial chemicals used in consumer products may alter the fetal hormonal environment and male reproductive tract development, including the testes. However, except for DES, there is no evidence in humans that abnormal male development has actually occurred as a result of

these exposures. Nevertheless, it is important to keep in mind that health effects that only become apparent decades after the exposure of concern make this an extremely difficult link to study and indirect evidence, along with a changing pattern of disease, may be the best evidence that will ever be available in human populations.

### **Other Risk Factors**

In addition to evaluation of the fetal environment, a number of studies have tried to identify other testicular cancer risk factors. Contradictory or inconsistent findings for inguinal hernia, a history of mumps virus infection of the testis, and trauma as risk factors have been reported.<sup>34 35 36</sup> A large study in Great Britain found early onset of puberty and lack of exercise to be risk factors for testicular cancer.<sup>37</sup> Occupational exposures have also been investigated as possible causes of testicular cancer. In some studies, men who served in the military are at increased risk of testicular cancer.<sup>38 39</sup> Viet Nam veterans and military dogs used in Viet Nam were reported at an increased risk of testicular cancer.<sup>40 41</sup> Small increased risks for testicular cancer have also been reported in some studies of farmers, but not in others, and a 2.5 fold increased risk was reported in a study of licensed pesticide applicators.<sup>42 43</sup> In one study, occupational exposure to magnetic fields was also reported to increase the risk of testicular cancer up to four fold.<sup>44</sup>

### **Summary**

The incidence of testicular cancer has sharply and steadily increased in many countries, including the United States, over the past 50 years. Genetic inheritance probably explains about 25% of cases and the rest are largely influenced by environmental factors not well understood. However, most investigators conclude that hormonal factors appear to play a role during fetal development in shaping subsequent testicular cancer risk. Estrogen, testosterone, pituitary hormones, and others play important roles in development of the male reproductive tract. Alterations in these hormone levels or exposure to exogenous agents with hormonal activity (endocrine disruptors) are likely to alter testicular development and testicular cancer risk. Evidence from animal and human studies implicate increased exposure to estrogen, estrogenic agents, or anti-androgens during fetal development. After birth, inconclusive evidence suggests that some pesticides and strong electromagnetic fields also increase testicular cancer risks.

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