*Radiol Oncol* 1998; 32(2): 201–5.

*review*

# The cause of testicular cancer

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*The cause of testicular cancer, like of most other cancers, is unknown, but the groups of men with higher incidence of this type of cancer are being investigated. Familial patterns of testicular cancer are reported, as well as the influence of oncogenes, particular predisposition factors of congenital anomalies of the urogenital tract, starting with the failure of the testis descent (cryptorhism). Since the incidence of cryptorhism is growing in the world, this could prove to be the main cause of the higher incidence of testicular cancer.*
*The atrophy of the germinal epithelium is also ascribed a special role in the incidence of testicular cancer. The impact of the oestrogen from environment, possibly affecting the spermatogenesis and probably causing higher incidence of congenital anomalies of the urogenital tract, has been lately intensively studied as well.*
*Social factors may prove significant, too, while physical trauma has not been determined as the cause of testicular cancer, and it could only be considered as one of the potential co-causes of the cancer.*

*Key words: testicular neoplasm, etiology*

## Introduction

Since the incidence of testicular cancer has been growing both in the World,[1,2] and in Slovenia,[3] the possible causes of this disease have been the subject of many studies. The real cause of the testicular cancer has remained unknown, but the groups of men with higher incidence are being studied.

## Genetic causes

Familial testicular cancer has been debated as a potential and possibly independent risk factor.[4] Familial patterns of testicular cancer can be related to a groups of patients with higher incidence of congenital anomalies, as well as to patients with tumours in the counter-lateral testis[5] and to Down's syndrome. Such families have been reported as displaying a 6 to 10 times higher incidence of testicular cancer. The most frequent chromosomal anomalies have been looked for, those which cause malignant alteration in testicles.[6]

An international study of 100 families with a familial form of testicular cancer, carried out under the auspices of the UK Imperial Cancer Research Fund, has revealed considerable genetic heterogeneity. There is no evidence of a single genomic region accounting for the occurrence of testicular cancer, but rather of several such regions.[7] Some sole

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cytogenetic abnormalities have nevertheless been found in patients with nonseminomatous tumours.[8]

The most frequent chromosomal anomalies related to malignant alterations in testicles are still being looked for,[6,9] and in particular there are looking for oncogenes. The most frequent oncogenes detected in testicular tumours and related to oncogenesis are K-ras2, PDGFA and N-myc oncogenes.

## Predisposition factors of congenital anomalies of urogenital tract

The incidence of testicular cancer is higher in patients with the anomalies of the urogenital tract, especially the failure of testis descent (cryptorhism), but also ingvinal hernia, hydrocele and hypospadias. As much as 10% of testicular neoplasm are associated with cryptorhism, in spite of the orchriopexy.[10,11] The risk factor for testicular tumours is 40 times higher with the failure of testis descent. The risk is a little lower if the operation of the cryptorhism is performed before the age of six. The risk of cancer is also high in the contralateral descended testis.[12]

Since the incidence of cryptorhism is growing in the World, this could prove to be the main cause of the higher incidence of testicular cancer.[13,14]

Patients who have had one testicular tumour are more likely to develop a contralateral tumour.[15,16] The incidence of carcinoma in situ of the contralateral testis in patients who have had one testicular tumour is about 5%, and about 50% of patients with carcinoma in situ develop invasive malignancy within 5 years.[17]

## The atrophy of testis

In to the above mentioned factors, the atrophy of the germinal epithelium is supposed to be significant as well, most frequent in the pathogenesis of tumours.[18] The reports that the atrophy, as a complication after vasectomy, is a risk factor for testicular tumours, also speak in favour of this theory.[19] When a tumour is diagnosed in a testis, higher levels of FSH would represent a risk factor for a secondary tumour.[19] The incidence of testicular cancer is also higher with fertility disorders, which are closely linked with atrophy of testis.[5]

Contrary to that, Giwercman and others[20] report that the risk of carcinoma in situ of testis is not higher in moderately oligozoospermic men. Bilateral testicular biopsies were performed in 207 men of infertile couples. No carcinoma in situ were detected in any of them. Although the authors believe that there is substantial evidence of a fetal origin of carcinoma in situ, patients in whom the biopsy revealed no carcinoma should also be closely monitored. The results presented namely refer to moderately oligozoospremic men only.

## Hormonal factors

The peak incidence of testicular cancer in young men suggests that gestational development and events during early infancy and puberty are important in the pathogenesis of the disease. There are two potentially significant events: the transformation of fetal germ cells into carcinoma in situ cells and later conversion of carcinoma in situ cells into fully invasive cancer. Several hypotheses suggest an endocrinological background of testicular neoplasia.[21]

Since the inhibin B, which is considerably higher in the first year of life, could not be traced in boys with anorhism, this hormone could prove to be especially significant for the occurrence of testicular cancer. After puberty, relatively higher levels of oestrogen and androgen receptors could be relevant for the etiology of testicular cancer.[13]

Estrogens probably play an important role in the etiopathogenesis of testicular cancer. This was the conclusion of the study by Nakazuma,[22] which revealed that the serum levels of estradiol and hCG were significantly above normal values both in systemic and spermatic veins of patients with nonseminoma germ cell tumours. Higher levels of estrogens in the serum could, on the other hand, be the consequence of the tumour and not its cause, as the production of hCG is the consequence of the growth of the germ cell tumours.[23]

The oestrogen in the environment are considered to be the most important cause of the low quality of sperm in the last 20 years,[24] and they are also blamed for a higher incidence of innate malformations and possibly for the incidence of testicular cancer.

Women, who were on estrogen diethylstilbestrol during pregnancy, have been studied. Since the drug has estrogenic effect, it was presumed a possible cause of testicular cancer. But a detailed review of the effect of the in-utero exposure to diethylstilbestrol showed only an adverse effect on the reproductive tract in male progeny.[25] Tests on animals showed that while prenatal estrogen exposure does induce more severe and earlier testicular abnormalities, manifesting themselves as regressive changes in the germinal epithelium and Sertoli's cells, atrophied seminiferous tubules and dysplasia of the rete testis epithelium, the presence of neoplasm has never been confirmed.[26]

The impact of diethylstilbestol, taken by pregnant women, on the incidence of vaginal cancer in their daughters has been confirmed, and the estrogens from the environment are likely responsible for a higher incidence of breast cancer. The hypothesis of these estrogens promoting testicular cancer is still viable,[27,28] and the development of serum markers determining the exposure of an individual to estrogens in the environment is very important.[29] The investigation into the impact of estrogens on the incidence of testicular cancer is very insensitive. Oestrogen has been related to the lower quality of sperm and to the higher incidence of hypogonadism and cryptorhism.[27,28,30]

Since estrogens are related to the genesis of other types of cancer, over 2200 mothers of the boys who developed testicular cancer, were studied in Denmark. The study revealed no higher incidence of breast cancer, of endometric or of ovarian cancer in them, so that these women did not represent a higher risk group of oestrogen related cancers.[31] Indirectly, this could mean that estrogens may not play a role as important as was thought in the genesis of testicular cancer. Such a conclusion would be premature, however, since countries with a higher incidence of breast cancer (which is likely estrogen related cancer) also report a higher incidence of testicular cancer, and it would suggest some relation between the two.

## Social factors

The incidence of testicular cancer is higher in men of higher social status.[1] We detected a relatively high percentage (40.2%) of patients with college or university education.[10] A better social status may be related to more frequent diaper changes and consequently higher temperature in the genital area during the first months of life. The influence of temperature on the incidence of testicular cancer has not been studied enough.

## The impact of trauma

The impact of trauma on the development of testicular cancer has not been cleared. Most probably, trauma does not raise the incidence of testicular cancer. The fact that a larger number of patients mention trauma in their

anamnesis can be ascribed to the acute attention paid to a blows received in the genital area. Patients may discover at that point tissue hardening or swellings.[10,32]

Despite the above, certain sports (cycling and horse riding) could cause injuries related to the development of testicular cancer.[33] It is possible that any type of injury could act as an additional conducive factor to the already existing cause. Swerdlow reports an increased incidence of testicular cancer when biopsy was performed in addition to orchidopexy.[34]

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