Aetiological factors of the testicular cancer myths and reality

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Abstract

Testicular cancer constitutes a rather rare malignant neoplasia which primarily affects younger males. The introduction of platinum in the armory of chemotherapeutic agents over the last 40 years, has led to exceptionally high rates in total cancer survivorship. At approximately the same period, the incidence of the disease has doubled. The aetiological correlations of factors are few so far, and thus, no accepted theory explaining the phenomenon has been established.

The present study was realized by searching for published epidemiological studies on the Internet.

KEY WORDS:
cancer, testicles, epidemiology
INTRODUCTION

Testicular cancer accounts for 1-1.5% of the total number of neoplasias developing in men and for 5% of the total urological tumors with 3-10 new cases per 100,000 of male population per annum in the West world. During the 70s and the 80s, an incidence increase was recorded, especially in Northern Europe countries, whereas the majority of industrially developed countries in Europe, North America and Oceania present a clear tendency in incidence increase. The incidence of testicular cancer has doubled over the last 40 years, yet, it remains a rather uncommon disease and its incidence ranges from 1/100,000 in Asians, Africans and Afro-Americans to 9.2/100,000 in Denmark. The age composition in patients with testicular cancer is clearly differentiated from that of other malignant neoplasias, with the majority of patients being within the age range of 25-35. A second but clearly smaller extreme value in the distribution of such neoplasias appears after the age of 80. Regarding the correlation between race and testicular cancer incidence, the white race evidently presents an increased incidence compared to the rest races. The countries mainly exhibiting an increase in frequency in the disease development are the so-called “West world countries” like Canada, USA, UK and Scandinavia. The mortality rates are generally low, with a 5-year survivorship increasing from 63% to more than 90% over the last 30 years. Health scientists usually etiologically associate a number of factors with testicular cancer such as the white race, ectopic testis, gonadal dysgenesis, family history etc. However, a thorough review of the literature reveals fewer than anticipated factors with established aetiological correlation. The present review aims not only to indicate the aetiological factors but also to make the readership think of the reasons the malignant testicular neoplasias incidence rate to double over the last decades.

REPORTED AETIOLOGICAL FACTORS

Cryptorchism: The first reports on the correlation between cryptorchism and testicular cancer trace back to the 19th century. Even though the aetiological correlation has not been documented, based on repeated studies, the factor statistically associated with testicular cancer is cryptorchism. Cryptorchism increases the risk of developing testicular cancer by 2 to 4 times; certain studies report the risk of developing testicular cancer in patients with cryptorchism as 5-fold or 10-fold. Over the last 40 years, Danish epidemiological data report an increase in the impact of cryptorchism. Nonetheless, it is impressive that between the neighboring countries Denmark and Finland, significant differences have been found in relation to the sperm quality as well as the incidence of cryptorchism. Between the countries in question, there are also differences regarding the incidence of the testicular cancer.

Carcinoma in situ (Cis): This specific correlation was first described in the 1970s. In essence, Cis constitutes the precursor histological lesion from which seminomatous and/or non-seminomatous testicular tumors will emerge. Exceptions are the infantile seminoma and
sperm cell seminoma. 50% of the patients diagnosed with Cis, will develop invasive cancer within the next 5 years.9

**Factors related to pregnancy and perinatal factors:** regarding the correlation of birth weight and testicular cancer development, other studies conclude in a positive correlation and others in an unclear correlation11,12. An increase potential of developing cancer by 50% was observed on premature newborns (born at least 2 weeks earlier than expected), whereas over-mature newborns exhibited limited possibilities of developing cancer10. Based on the above, it was presumed that the positive correlation between premature birth and testicular cancer development is precipitated by the increase exposure to intrauterine oestrogens11.

With respect to children of females smoking during pregnancy, most studies conclude that there is an evident correlation between the risk of developing cancer and smoking during pregnancy11. Interestingly, there is a positive correlation between metachronous lung cancer in females smoking during pregnancy and testicular cancer in their male children. The carcinogenic effect of smoking hereto, is supported by its anti-oestrogenic effect13.

**Hormones:** Based on the fact that a) intrauterine exposure of the male fetus to increased concentration of oestrogens predisposes for testicular cancer development and b) assuming that the intrauterine concentration of oestrogens is increased on first deliveries compared to the subsequent ones for the same mother, it is advocated that first-born males exhibit increased probabilities to develop testicular cancer compared to the next male children. This assumption seems to be supported by a study on males born in Sweden prior to 196014.

Diethylstilbestrol, a hormone prescribed from 1940 until the 1970s to pregnant females for the avoidance of complications during gestation - later withdrawn due to its documented correlation with the manifestation of clear cell vaginal cancer in the female children of pregnant women on the hormone during gestation- is supposed to proportionally relate to the development of testicular carcinogenesis. However, there is no evidence. In any case, the administration of hormones (any type), seems to condition for developing testicular cancer.11

**Factors related to the individual himself**

**Age:** In general terms, cancer is a disease of the elder adults and testicular cancer is the exception that proves the rule. The age distribution of neoplasia is evident, primarily peaking in ages 25-35 and with a distinct smaller peaking after the age of 80. The manifestation of certain cases soon after puberty, led to the presumption that the flood of genital hormones in puberty forces the survivorship and dominance of the cancerous cells15.

**Race:** Testicular cancer cases have a certain increased incidence rate on the white race compared to the other races16. The aetiology is not yet detected albeit the indications of hormonal involvement.
Androgens: A study associating the development of baldness to testicular cancer found that males with extended baldness exhibited a 20% reduced probability of being affected. Biologically, males with increased androgen values in serum, develop baldness at an earlier age. Consequently, the androgens seem to have a protective role.

Age of puberty onset: Even though this factor is purely subjective and extremely difficult to define, it is possible that late puberty onset in men acts protectively against developing testicular cancer.

Body Mass Index (BMI): Data on BMI and testicular cancer association are quite confusing. The risk of malignant neoplasia development is reported as increased in both patients with high and low BMI. At times, the evidence of any correlation is not obtained. The situation is clearer regarding testicular cancer and height; the majority of investigators conclude in a positive correlation between height and cancer. The conceivable aetiology has been attributed to nutritional as well as to hormonal factors (the latter mainly associated with Insulin-like growth factor-IGF).

Working environment: Despite the positive association between certain professions and testicular cancer development, the study field on the specific factor is endless. DiMethylFormamide (DMF) has been identified as a carcinogenic factor in tanners and aircraft maintenance workers. Other potential carcinogenic factors include: fertilizers, exposure to emissions and smoke and chemical agents used in pesticides. An increased incidence rate of the disease has also been observed in individuals that used to reside in areas with increased water pollution from nitrogens.

Reproductive ability: As “subfertility” we define the “failure to conceive after a year of regular unprotected sexual intercourse with the same partner”. Subfertile males bear the increased risk of growing testicular cancer. Nevertheless, whether subfertility constitutes a risk factor for the development of testicular cancer or whether cancer and subfertility share aetiology, is a matter that requires authentication.

It is of great interest that after World War II, according to the epidemiological data, male subfertility rates decline, whilst at the same period, testicular cancer incidence progressively increases. A data meta-analysis of 61 investigations revealed that during the period 1938 to 1990, a substantive decrease in sperm volume as well as in sperm count is observed. A number of logical assumptions explain this fact: intrauterine exposure to diethylstilbestrol, exposure to environmental chemicals which invade and disturb the endocrine glands function, change in eating habits subsequent to the increase of high standard of living and the dominance of sedentary life. These factors suggest that the hormonal balance in males is determining in the avoidance of testicular carcinogenesis.

Sperm duct ligation or transaction: Around the end of the 1980s, sperm duct ligation or transaction was considered as a predisposing factor for developing testicular cancer. In many countries, the said technique constitutes the most commonly known contraception method.
While investigating the credibility of the aforementioned hypothesis, no significant statistical correlation was found.

**Conditions possibly correlated to testicular neoplasms**

*Unilateral testicular neoplasms*: Men with unilateral testicular neoplasm bear increased probabilities of developing testicular cancer on the other testis as well.

*Inguinal hernia*: Inguinal hernias diagnosed prior to the age of 15, seem to be associated with unilateral testicular neoplasms.

A great number of infectious and non-infectious factors have been evaluated with regard to their possible correlation to malignant testicular neoplasms. These include: sexually transmitted diseases (STD), hydrocele, infectious mononucleosis (IM), neonatal jaundice (NJ) and parotitis-induced orchitis. In relation to the latter factor, albeit the evident view to the contrary, no positive correlation has been established.

**Other factors**:  
*Smoking*: Testicular cancer is a disease mainly affecting younger ages when the patients either have not started smoking yet or they have not been exposed to the harmful tobacco products for a long term.  
*Electromagnetic Radiation (EMR)*: The electromagnetic waves have literally invaded our everyday lives over the last 30 years the least. Conducted studies on the association between the electromagnetic fields in non-working environments and the likelihood of developing malignant testicular neoplasias are practically unsubstantial. The single study (which discusses the effect of the electromagnetic waves produced by electric blankets on the possibility of developing malignant testicular neoplasms) does not deliver a positive correlation.

*Mechanical trauma*: Scrotal trauma used to be considered as a predisposing factor for developing testicular tumors. Nowadays, the trauma in question is no longer considered to cause de novo cancer but rather either to increase the mitotic activity in the affected testis or to urge the individual to pay more attention in an area where a malignant disorder was previously concomitant.

*Testicular temperature*: Despite the established view to the contrary, no well-documented correlation between the increased testicular temperature and testicular cancer was found.

**Factors associated with lifestyle**

*Socio-financial status*: Increased socio-financial status is reported as a predisposing factor for testicular carcinogenesis. Education, a widely common index of socio-financial status, has been inculpated as a predisposing factor for developing testicular cancer.
Physical fitness: There are no reliable studies correlating a person’s physical fitness to testicular neoplasms.

Eating habits: The association of eating habits with tumorigenesis increasingly gains the way\textsuperscript{37}. Testicular cancer\textsuperscript{38}, as well as a number of hormone-dependent cancers like mammary cancer, prostatic cancer, ovarian cancer, colorectal cancer, have been correlated with the increased intake of fat acids. The introduction of increased intake of dairy products since the 1940s and the 1950s coincides with the synchronous increase in malignant testicular carcinogenesis\textsuperscript{39}. Given that the aforementioned products present increased content in female hormones such as oestrogens and progesterone, it was presumed that the female hormones in the dairy products trigger the development of testicular tumors. The intake of vegetable oestrogens through diet does not seem to take part in tumorigenesis\textsuperscript{40}. The low intake of fruits and vegetables and the increased consumption of meat\textsuperscript{41} are associated with the possibility of growing testicular tumors.

Urban residency: It has not been scientifically documented that living in a city constitutes a predisposing factor for developing testicular cancer\textsuperscript{42}.

Familial correlation – genetic predisposition:

The increased familial incidence rate of testicular cancer\textsuperscript{43,44} guides us to hypothesize the existence of a genome predisposing the development of the disease. Isochromosome 12i(12p) appears in 80% of malignant testicular neoplasias. This is the change most commonly met in cancers of this type\textsuperscript{45}. Chromosomes 7, 8, 12, 21, X additions and chromosomes 11, 13, 18 deletions are frequently observed\textsuperscript{46}. A recently guilty gene is Xq27\textsuperscript{47} which is found in 33% of testicular cancer cases\textsuperscript{48}.

Testicular germ cell tumors (TGCT) in adolescents and adults are responsible for 1.5-2% of all germ cell tumors in adults. The relative risk (RR) for developing TGCT is 3.8x for fathers, 8.3x for brothers and 3.9x for sons-carriers; this shows that the genetic predisposition constitutes an important predisposing factor for developing testicular cancer\textsuperscript{49}. The onset of the disease at an early age, the bilateral existence of tumor sites and the increased aggression of the disease suggest familial predisposition\textsuperscript{50}. Investigations into the correlation between genetic predisposition and probability of developing adult testicular cancer\textsuperscript{51}, found a positive correlation at 25%. In general terms, the changes concerning chromosomal alterations between familial/bilateral and sporadic TGCT are insignificant\textsuperscript{52}. Nevertheless, the Testicular Cancer Linkage Consortium (TCLC) has determined an area which is responsible for both the development of testicular cancer and cryptorchism in Xq27. Generally, the view of the genetic predisposition in the development of testicular tumors is underlying, however, the existence of solitary alteration responsible for the totality of malignancies should rather be excluded.
**Transgenders**

Individuals with 46XY, 45X/46XY gonadal dysgenesis, manifest extremely increased probabilities in developing testicular cancer; some investigators claim it accounts for 10-50%.

**CONCLUSION**

Testicular cancer is a rare type of cancer which primarily affects white men and constitutes the most common malignant neoplasma in males aged 15-34. Over the last 40 years, the total survivorship rate has impressively increased reaching almost 90% nowadays. Few of the factors reported as aetiological are scientifically documented. Most of them remain to be elucidated. The change in eating habits as well as the environmental changes with the addition of chemicals and the increase of exposure to EMR after the World War II coincides with the increase in male subfertility as well as the increase of testicular cancer incidence rate. Perhaps, it is this particular point that investigators should pay more attention to in the future.

Περίληψη

Ο καρκίνος του όρχεως αποτελεί ένα μάλλον σπάνιο κακόηθες νεόπλασμα το οποίο προσβάλλει κυρίως τις νεότερες ηλικίες. Η είσοδος της πλατίνας στη χημειοθεραπευτική φαρέτρα κατά τα τελευταία 40 έτη έχει οδηγήσει σε εξαιρετικά υψηλά ποσοστά συνολικής επιβίωσης. Κατά το ίδιο περίπτωμα κρονικό διάστημα η επίπτωση της νόσου έχει διπλασιαστεί. Οι παράγοντες με αιτιολογική συσχέτιση είναι έως τώρα ελάχιστοι με αποτέλεσμα να μην έχει διατυπωθεί κάποια αποδεκτή θεωρεία για την εξήγηση του φαινομένου. Η παραπάνω εργασία πραγματοποιήθηκε κατόπιν αναζητήσεως δημοσιευμένων επιδημιολογικών μελετών μέσω του διαδικτύου.

Λέξεις ευρετηριασμού

καρκίνος, όρχεις, επιδημιολογία

**References**


