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Analysis of environmental factors affecting the incidence of testicular cancer, with particular emphasis on testicular germ cell tumors (TGCTs). Literature review

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Abstract:
Introduction: Testicular cancer is the most common malignancy among men in the 20-44 age group. Most of the incidence is testicular germ cell tumor. In recent years there has been a steady increase in the incidence of this cancer. For this reason, we analyzed available articles on environmental risk factors that may influence the incidence of increased testicular malignancies

Material and methods: Review of the specialized literature in the field of urology and articles available on PubMed, searching by the keywords “testicular cancer,” “testicular cancer risk factors,” “germ cell tumor,” “tgct‘’

Aim of the study: The purpose of the study is to review the available literature and research papers regarding risk factors for malignant tumors of the testis.

Summary: In recent years, there has been an increase in the incidence of testicular cancer, especially among men aged 20-44 years. The vast majority of it is germ cell tumors (TGCT). This article discusses the influence of environmental factors on the development of testicular cancer, with particular emphasis on the induction of TGCT. Studies indicate an association between exposure to trichloroethylene and other solvents and the risk of TGCT induction. The role of exposure to pesticides (especially fungicides), organic chlorine compounds, and viruses was also indicated to increase the risk of developing TGCTs,. The association of neoplasia with marijuana and tobacco use has also been studied, but needs further research. There is a need for continued research regarding heavy metals, infertility and factors related to pregnancy and the perinatal period. It is necessary to know the mechanisms that induce the process of carcinogenesis in the testis, which will enable the use of prevention and prophylaxis.

Keywords:
“testicular cancer”, “germ cell tumor”, “testicular germ cell tumor”,”TGCT”, “testicular cancer risk factors”, “testicular cancer environmental risk factors”, “testis”, “pesticides”, “solvents”

Introduction

The incidence of testicular cancer has been on the rise in recent years. This is a very worrying trend due to the group of patients this condition affects, as testicular cancers are the most common malignant tumors in the group of men aged 20-44 [1,5,6] According to Polish data from the Krajowy Rejestr Nowotworów report for 2021, testicular cancers accounted for 27% of incidence and 10% of deaths in the population of young men [1]. The number of cases of malignant tumors of the testis in Poland in absolute numbers as of 2021 was 1303 men, in 2020 - 1156, while in 1990 only 416 cases were reported [1,2,3]. Histopathologically, germ cell tumors, i.e. tumors originating from germ cells, are responsible for 90% of testicular tumors. Currently in force is the division of tumors according to the WHO, the so-called WHO “Blue Book” (Urinary and Male Genital Tumours WHO Classification of Tumours, 5th Edition, Volume 8). We distinguish noninvasive germ cell neoplasia, which includes germ cell neoplasia in situ, seminomas, a group of non-seminomas (embryonal carcinoma, yolk sac tumor, choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor, teratoma (postpubertal type and with somatic-type malignancy), mixed germ cell tumors, germ cell tumors of unknown type [4]. The classifications also distinguished GCTs unrealised to germ cell neoplasia in situ [4]. The remaining testicular tumors are stromal tumors (sex cord- stromal tumors of the testis), but they represent a minority (about 10%) [5] .Given the increasing trend in incidence, we reviewed papers examining the influence of environmental factors on the incidence of testicular tumors with an emphasis on germ cell tumors due to their predominance [5,6].

Exposure to solvents

A multicenter prospective case-control study (Project TESTIS) was conducted on a population of men born in France with a histopathologically confirmed diagnosis of testicular germ cell tumor (TGCT). The patient population was isolated by affiliated sperm banks in France (French network- CECOS), to which the sick men reported before treatment. Control groups were not allowed to have a medical history of testicular cancer and cryptorchidism, so as not to disrupt the results. Exposure information was collected from the men and by trained interviewers from their mothers or close relatives. Blood samples were also taken from some of the men. Data were collected on the entire employment history of the patient and his parents (up to the child's 17th birthday), and an in-depth analysis was made of exposure factors and exposure - its duration and severity, detailing groups of substances (pesticides, plasticizers, solvents, welding fumes and heavy metals). Asking about domestic exposure (domestic) focused on pesticides used in gardening, pet treatment, insecticides and fungicides used, and for lice treatment. Environmental exposure included collecting data on residence, household and school addresses. Mothers were asked about their residence history for the year before conception until their son reached age 17. In addition, information was collected on smoking, maternal and son drug use, and the patient's physical activity [7].

Project TESTIS study group is also used to assess other exposures, which will be discussed later in the article [8, 9, 12, 28]. Based on the collected group, a study was conducted to evaluate the effect of occupational exposure to solvents on the development of TGCT [8, 9]. Solvent exposure was assessed according to the occupational exposure matrix (JEM), by which the participants' work period was evaluated for exposure to various solvents Probability of exposure, intensity and frequency of exposure were assessed. The second method of exposure assessment was JEM+SQ+EA, which was a combination of JEM assessment with SQ (self-reported questionnaire) and EA (expert assessment). By using this assessment, the risk of incorrect exposure assessment was minimized. A Cumulative Exposure Score (CES) was calculated for each person, summing the periods of work with exposure to the solvent in question. Participants were categorized as “never exposed,” “low exposed” and “high exposed.” The use of JEM+SQ+EA in a retrospective exposure analysis seems to have a positive effect on the reliability of exposure assessment [9].

It was noted that trichloroethylene exposure is positively associated with the risk of TGCT (OR 1.80, 95% CI 1.12-2.90), especially for high exposure (OR 2.23, 95% CI 1.19-4.18). Exposure to trichloroethylene likely influences the development of TGCT among those exposed. For ketones and esters, a positive association was also found (OR 1.63, 95% CI 1.16-2.30), especially in the low exposure category (OR 1.74, 95% CI 1.10-2.74). For fuel and petroleum solvents, low exposure was associated with an OR of 1.48 (95% CI 1.06-2.07) [9]. Analyzing only exposure with JEM (without SQ and EA), there were no results to associate occupational exposure with the development of TGCT. It was noted that mothers exposed to fuel petroleum based solvents in the 1970s had a higher risk of developing TGCT in their sons, a slight increase in the risk of developing nonseminoma in sons whose fathers were highly exposed to trichloroethylene [8] . However, further studies are needed to better understand the mechanism [8, 9]. The Danish NORD-TEST study evaluated the effect of parents' occupational exposure to organic solvents on the occurrence of TGCT in sons. The study included 8112 cases of TGCT (seminoma and nonseminoma) and 26264 controls.

There was a significant increase in TGCT risk associated with maternal exposure to a group of aromatic hydrocarbon solvents (ARHC) (OR=1.53) and toluene exposure (OR=1.67). There was no evidence of an association between paternal exposure and TGCT, except for exposure to perchloroethylene in Finland (OR=2.42) [10]. A study evaluating the impact of parental occupational exposure to solvents and heavy metals-NORD-TEST Denmark-was also conducted. The study group consisted of men born in Denmark and diagnosed between the ages of 14 and 49 between 1981 and 2014. The analysis was conducted separately for mothers' and fathers' occupational exposures and employment data were collected from the databases of the Danish Pension Fund (ATP). Occupational exposure was assessed using the NOCCA-JEM matrix. It included 24 chemical agents (ie, solvents, heavy metals, combustion products, animal- and wood dusts, asbestos, crystalline silica and formaldehyde, among others). No statistically significant associations were observed between maternal or paternal exposure to solvents and heavy metals and the risk of TGCT in their sons (OR values for different parental exposures were close to 1.0) [11].

Exposure to pesticides

The effect of pesticides on the development of TGCT is one of the best studied environmental factors that has been of interest to researchers for many years [12, 13].

A study was conducted on a group of 570 TGCT cases and two control groups (as part of Project TESTIS). The data were categorized taking into account direct or indirect use by other household members, and were divided by frequency of pesticide use-never, less than once a month, daily. Analyses were also carried out taking into account, among other things, place of birth (urban or rural), time of year when the first trimester of pregnancy occurred. It was confirmed that prenatal and early childhood exposure to pesticides (particularly those used in gardening and as pesticides) could increase the risk of developing TGCT. Fungicide use was associated with an increased risk of TGCT, especially for nonseminoma. The risk of developing TGCT overall increased by 73% (OR = 1.73), and for the nonseminoma subtype the risk increased by 144% (OR = 2.44). The use of fungicides or insecticides in wood treatment (OR = 2.35) and the use of insecticides on pets such as dogs and cats (OR = 1.95) were also associated with a higher risk of nonseminoma. There was no statistically significant association between the domestic use of pesticides such as insecticides and herbicides and the risk of TGCT. The risk was higher for men whose mothers used pesticides personally or in their homes. Exposure to pesticides was more significant for those born in rural areas, which may be explained by the use of pesticides in agriculture. The use of pesticides did not increase the incidence of seminoma [12].

A large international study conducted in Denmark, Finland, Norway and Sweden evaluating parental occupational exposure to pesticides during the prenatal period on the development of TGCT in sons was the NORD-TEST population-based registry clinical-control study. It was conducted on 9569 cases and 32,028 controls. It found no association between both mothers' and fathers' exposure and their sons' risk of TGCT, with an OR (odds ratio) of 0.83 (95% CI 0.56-1.23) for mothers and 1.03 (95% CI 0.92-1.14) for fathers, respectively. Individual analyses for fungicides, insecticides and herbicides also showed no association with TGCT risk [13].

Marijuana and tobacco

The correlation between marijuana consumption and the incidence of testicular cancer has been an area of interest for researchers since the 1990s. Unfortunately, we do not have a large number of reliable studies to draw clear and strong conclusions. Based on the available meta-analyses, we can conclude that marijuana use did not significantly increase the risk of developing seminoma. A significant increase in the risk of developing non-seminoma cancers was noted [14, 15].

It has been shown that there is no clear association between ever using marijuana and the risk of TGCTs suggesting insufficient evidence that occasional marijuana use has a significant effect on the development of this type of cancer (OR = 1.19, 95% CI 0.72-1.95), an increase in risk with current marijuana use, which increased the risk of developing TGCTs by 62% (OR = 1.62, 95% CI 1.13-2.31), suggesting a significant increase in the risk of developing this cancer [14]. Regular marijuana use (regular was defined as consumption at least once a week) was also shown to nearly double the risk of developing TGCT (OR = 1.92, 95% CI 1.35-2.72). Marijuana use for at least 10 years was also associated with a higher risk (OR = 1.50, 95% CI 1.08-2.09) [14].The association between smoking and TGCT risk based on available studies was estimated at 1.18 (95% CI 1.05-1.33), indicating a moderate increase in the risk of developing TGCT [15]. Studies and meta-analyses analyzing the association between maternal smoking and the incidence of testicular cancer in sons have emerged[16, 17]. The results of two meta-analyses indicate that there is no clear association between maternal smoking, both during pregnancy and after the child's birth, and the risk of developing testicular cancer in sons [16,17]. Both the effects of marijuana and tobacco use require further study [14,15,16,17].

Viral infections

Most studies and systematic reviews have shown some effect of viral infections on the risk of developing testicular cancer [18,19].

A particularly strong correlation has been shown for HIV and EBV infections. Testicular cancer is the third most common AIDS-related malignancy, and the risk of developing this cancer is independent of treatment with HAART therapy [18].

The studies analyzed indicate an effect of HIV infection on the development of seminoma, while no effect on the occurrence of nonseminoma has been proven. The relationship of EBV and CMV viruses on the occurrence of testicular cancer is inconclusive and requires further study. HPV infection did not show an association with testicular cancer in the studies analyzed, and the same was true for parvovirus B19 [18,19].

Further studies are needed to better understand the mechanism by which viral infections affect the process of carcinogenesis in testicular cells [18, 19].

Organic chlorine compounds

Studies evaluating the effects of organic chlorine compounds on the development of TGCT have been conducted, providing evidence of an association between blood levels of p,p′-DDE, oxychlordane and trans-nonachlor and the risk of TGCT, especially of the seminoma type [20]. PCB1 levels (especially group 1, which have potential estrogen-like effects) have been shown to be associated with the risk of developing TGCT, both in seminomas and nonseminomas [21, 22].

PCBs are likely to interfere with estrogen and androgen endocrine pathways, which can induce the development of TGCT particularly during embryonic development [21]. The results of this study indicate that further research is sensible, especially for PCBs [20 ,21, 22].

Male infertility

One of the semen parameters that may correlate with reduced pregnancy rates is increased sperm DNA fragmentation [23,24] and reduced ability of sperm to bind to hyaluronic acid (HBA test) [23]. The Polish study evaluated the degree of sperm chromatin fragmentation and HBA in two groups- in men from infertile couples and in patients awaiting orchidectomy and oncological treatment after a diagnosis of TGCT. Semen was evaluated by basic analysis according to the WHO standard,additionally DNA fragmentation was measured by SCDA (Sperm Chromatin Dispersion Assay) and sperm maturity was assessed by HBA test. DNA fragmentation was expressed as the DNA Fragmentation Index (DFI)-a value below 30% was considered normal, while in the HBA binding test, the result was expressed as the percentage of motile sperm that bound to HA-values above 80% were considered normal. The study showed that 96% of patients with TGCT and 76% of men from infertile couples had abnormal DFI and/or HBA results. It should be noted that the study included men with TGCT prior to cancer treatment. The high percentage of patients with reduced HBA indicates that the cancer process impairs sperm maturation. These results suggest that despite cryopreservation of semen prior to oncologic treatment for patients with TGCT, these sperm may have limited fertilization capacity [23]. In a meta-analysis evaluating the effects of various factors on sperm DNA fragmentation, it was confirmed that testicular tumors increase fragmentation [24]. A published meta-analysis examining the association between vasectomy and the incidence of testicular cancer found no statistically significant association. However, the data are not very strong and further studies are required [25].

Personal care products

A study was conducted to see if personal care products used by mothers during pregnancy and lactation affect the development of TGCT. Mothers were asked about their use of products such as brightener, face cream, body lotion, deodorant or antiperspirant and sunscreen. They found that using face cream more than once a week was associated with a significantly increased risk of sons developing TGCT (OR: 1.42, 95% CI: 1.08-1.86, p-trend: 0.01) compared to no cream use at all. None of the other products tested were associated with TGCT risk. The researchers explain this by the presence of estrogen-like endocrine-disrupting chemicals (EDCs) in creams (such as phthalates and parabens), which enter a woman's blood through the skin and then through the placenta to the fetus. However, the topic of the impact of substances in cosmetic products requires further research and analysis of the impact of specific substances [26].

Heavy metals

In addition to the impact of parents' occupational exposure to solvents, the previously mentioned NORD-TEST Denmark study examined their exposure to heavy metals. Only an increased risk of testicular cancer was observed in sons whose fathers were exposed to chromium and toluene (OR 1.50; 95% CI 1.01-2.24), most of whom worked in woodworking [11].

The NORD-TEST study evaluated the association between prenatal parental exposure to woodworking occupations and the risk of TGCT in the offspring. However, the study did not provide evidence of an association between prenatal parental exposure to woodworking occupations and the risk of TGCT in sons [27].
In France, a study was conducted on the association between fathers' occupational exposure to heavy metals and welding fumes and the risk of developing TGCTs in sons. The study was part of the aforementioned project- TESTIS. Exposure to heavy metals and welding fumes was assessed using the INTEROCC-JEM matrix. Based on occupational codes and exposure levels, risks were estimated. A distinction was made between not exposed, low exposure, and high exposure. After analyzing the data, no statistically significant associations were found between fathers' occupational exposure to heavy metals and welding fumes and their sons' risk of TGCT [28].

Per- and Poly-fluoroalkyl Substances (PFAS)

In a meta-analysis examining the effects of PFASs- particularly perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS)-on tumorigenesis in the kidney, liver and testes,it was found that high levels of PFAS exposure may increase the risk of testicular cancer (RR = 2.22, 95% CI = 1.12-4.39; p = 0.057). This association, however, was not as strong as the association with kidney cancer [29].

Birth weight

A meta-analysis examining the association between birth weight and later onset of testicular cancer noted that men weighing less than 2,500 grams at birth had a higher risk of developing testicular cancer in later life compared to those of normal birth weight (2,500- 4,000 grams was considered normal birth weight) (OR = 1.18, 95% CI: 1.01-1.38). Low birth weight was a risk factor especially for seminomas (OR = 1.44; 95% CI 1.11-1.88). A similar trend was observed for men with birth weights above 4,000 g (OR = 1.12; 95% CI 1.02-1.22). However, the data for high birth weight are not as strong as those for low birth weight [30].

Hyperemesis gravidarum (HG)

HG is a condition affecting pregnant women, characterized by severe nausea and vomiting, which can lead to maternal malnutrition. In the context of testicular cancer, a meta-analysis conducted showed that HG was significantly associated with a higher risk of testicular cancer in sons (OR = 1.60; CI = 1.07-2.39). The association of HG with testicular cancer requires continued research [31].

Conclusion

In this article, we have highlighted valuable scientific studies on environmental factors that may influence the development of testicular cancer. Although there are multicenter and reliable studies, the topic is still not completely explored. The large number of patients of reproductive age makes testicular cancer a significant public health issue. One major challenge is the limited understanding of the mechanisms of carcinogenesis in the testes. Future investigations should focus on understanding how environmental factors actually play a role in cancer development.

Conducting studies that provide statistically significant correlations is difficult due to the difficulty in collecting a representative cohort of patients. Assembling an appropriate cohort of patients for the results to be statistically significant is challenging and requires careful patient selection, including the excluding of patients with other known risk factors, for example, genetic factors.In addition to conducting further research to improve our knowledge of risk factors, we should think about increasing the detection of cancer, especially in the early stages, to allow for a complete cure.

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Author's contribution:
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Software: Michał Szyc
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Investigation: Michał Szyc, Anita Ptak
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