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Review

Investigating Genetic and Environmental Factors in Testicular Cancer's Development: A Review Study

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HIGHLIGHTS

- The attention is paid to environmental chemicals and heat exposure, their function in cancer development, and recent advances at the molecular level have been studied.
- Physical risk factors like exposure to ionizing radiation, UV radiation, and electrical work, exposure to heat stress increased risk of TC.
- Genetic mutation in the SLC16A5 gene strongly associated with cisplatin-induced toxicity.

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ABSTRACT

Testicular cancer (TC) is among the specific clinical problems of our time. Current therapy is highly effective, confirming 5-year disease-free survival in approximately 95% of ill people. TC is a prevalent type of cancer diagnosed in males between 14 and 44 ages, with an incidence of less than 1 in 9.9 cases per 100,000 men nationwide, but the total number of TC. Increase worldwide. In addition, the danger of expanding cancer in people with cancer during 15 years after diagnosis is 2%. These complicated and different conditions must be found in the clinical evidence base. Genetic, environmental, and hormonal elements are related to developing diseases and disorders in response to treatment and danger of relapse. This research discusses current topics that explain the relative contribution of the problems mentioned above to TC development. Additionally, we pay attention to environmental chemicals and heat exposure, their function in cancer development, and recent advances at the molecular level have been studied.

Keywords: Endocrine Disorders; Susceptibility Genes; Sexual Development Disorders; Environmental Factor

Introduction

With approximately 1% of recently diagnosed cancers in men, TC is a regular tumor in males aged 14 to 44 years, regarded to be of working/reproductive age. Before the years between 1970 and 1979, the death rate of TC because of metastatic degenerative disease was so high that the only treatment with a risk of recurrence was retroperitoneal lymph node dissection with or without radiotherapy. Later, "rules of the game" were changed by the development of influential chemotherapy. Indeed, A five-year survival of over 95% is achieved by an existing multidisciplinary approach to treating patients with TC, which includes surgery and adjuvant chemotherapy or radiotherapy. As a result, TC is regarded as an example of cancer that can be cured (1).

Despite these undeniable advances, TC still has several challenges that we cannot ignore: Therapeutic Evidence: Despite the efficacy above, self-treatment of TC is often linked to the danger of long-term side effects such as hypogonadism, infertility, metabolic/cardiovascular disease, and osteoporosis, That indicate serious effects of TC treatment (2).

Epidemiological evidence: The occurrence of TC has been duplicated in the last forty years and has increased

over time, particularly in Caucasian men. Information from the continents of Africa and Asia represent less than one per 100,000 men, while the Scandinavian countries show a higher number of new infections globally (from 9.4 to 9.9 per 100,000 men) (3). This racial trend is also approved by information from the US, where TC is very common in whites than in American people (1.2 vs. 6.9 per 100,000 men, respectively) (4).

Clinical evidence

Prior to the background of TC, when treated and closely managed, is a primary element in developing second contralateral carcinoma. Final danger of secondary TC in five years of diagnosis is approximately 5%, and most items occur in two years of initial diagnosis. In this case, the size of the primary testicle and the degree of recurrent testicular invasion are the two main predictors of recurrence (5).

For these purposes, pathogenic mechanisms' identification and risk factors included in testicular carcinogenesis state a clinical challenge. The possibility of expanding TC results from a combination of several factors generally divided into genetic, environmental, and hormonal (6).

Hormones

Testis is a target and a source of hormones similar to other endocrine tissues in the body that are directly involved in a feedback loop regulatory pathway. Specifically, hypothalamic/pituitary/gonadal axis activity is exerted early in embryonic development, regulates testis descent and proper location in the scrotum, and regulates proper spermatogenesis and endocrine function, which have known systemic effects. Slow (7). Primary fluctuation of this hormonal circuit reflects on testicular activity in adulthood and is a serious risk factor for TC (8). RajpertDe Meyts et al., have developed an experimental model for neoplastic transformation of the germ cells. This concept is according to the close relationship of primordial germ cells with gonocytes and cancer tumor cells in situ (CIS), in molecular with genes' co-expression included in pluripotency and proliferation, like NANOG, STELLAR, DPPA-5, GDF3, K-RAS, and CCND2 have been identified. In this context, germ cell latency connected to the embryonic genes' long-term maintenance is crucial for subsequent degeneration into cancer cells (9). Disturbances in hormonal environment of germ cells lead to misleading signals that shift cell phase towards mitosis and meiosis, thereby increasing the danger of neoplastic transformation in adulthood (10). Hormonal risk factors' pattern for TC is asexual growth (DSD) by 46 XY men, often with androgen insensitivity syndrome (AIS), often mild (MAIS), partial (PAIS), complete (CAIS), or as this name suggests, its clinical features vary from the women phenotype of CAIS with an XY karyotype and average androgen production to bitter masculinization in PAIS, like women external genitalia, hypospadias, micropenis (11) or infertility of man and gynecomastia in MAIS. A common characteristic of various structures of AIS is the alteration of androgen receptor function, which leads to be resisted to androgens as active ligands genetic variations of AR gene cause AIS. Specifically, 95% of CAIS connected to inactivating AR mutations. However, AR gene mutations are identified in less than 25% of patients with PAIS. At the same time, an additional causative role is related to protein genetic variants and cofactors associated with the AR signaling pathway, like 17β-hydroxysteroid dehydrogenase deficiency (12). (17β-HSD) is a central enzyme in steroidogenesis. Persistent Müllerian duTC syndrome (PMDS) is a sex-differentiating disorder in 46 XY men caused by an inactivating mutation in the AMH/MIS gene (45% of cases) or its type II receptor (39% of cases) as well (13). Patients with PMDS are genotypically and phenotypically as men with unilateral or bilateral cryptorchidism and childhood inguinal hernia. Overall, DSD and AIS are linked to TC and increase its risk, with an approximate commonness of almost 5.5%, from 0.8% in DSD connected to CAIS and 15% in PAIS to 17% in 17b deficiency. HSD is variable. Even though TC data in PMDS have been described in several cases, there are no studies with large cohorts available (14). In particular, intra-abdominal testicular retention is related to DSD and shows a risk factor for TC, as investigated before. A connection between TC, cryptorchidism, and DSD was reported through AR mutation in PMDS. So, the primary role of pathogenic in DSD related to testicular retention in CT is not excluded. On the other hand, available data on superior hypothalamic/pituitary/gonadal axis abnormalities have shown inconsistent associations with TC. Mainly, mutations in the LR gene function cause DSD types such as puberty and Leydig cell hypoplasia in males (15). Secondary conditions range from usual woman genitalia to hypergonadotropic hypogonadism with microphallus and hypoplastic man external genitalia. Little information exists showing CT alone in patients with homozygous precocious puberty, especially in case of testicular interstitial cell tumors seen in a nine-year-old boy. (without any genetic screening at the analysis time) (16). Moreover, it involves two cases. Of the LHR gene, an activating mutation that causes testicular seminoma in adulthood (17).

Genes

It is widely accepted that the development of TC is based on genetic factors. Although 90% of men with TC have no prior medical history, population studies conducted in the late 1990s and early 2000s found that having a sibling with a background of TC increased the danger of developing the illness by eight in ten, in comparison with the population of men increases (18). Conversely, a father with TC promotes the relative risk for boys by 4-6 times. In 2002, a pioneering population-based registry study

assessing 9.6 million people from the Swedish National Familial Cancer Database made an effort to realize between genetic, purely environmental, and childhood environmental contributions to cancer growth, which is basically according to epidemiological diseases (19). An exciting consideration is that TC is the neoplasms which is related to genetic elements (25%), just after the thyroid gland (53%) and endocrine glands generally (28%).

Furthermore, a new population registry research evaluating monozygous and homozygous individuals showed a known heritable risk of TBI of approximately 40%. However, an important portion was attributable to shared environmental conditions (20). The accessibility of authentic investigations providing quantitative and qualitative information on the genetic basis of family CD development remains a central problem. However, there is evidence to support its genetic origin. Six areas of interest for chromosomes have been found in a linkage study on 237 gene families with one or more incidences of TC during 2006. 2p23, 3p12, 3q26, 12p13-q21, 18q21-q23, and Xq27 (21).

However, further analysis showed that no single region with the most familial clustering was observed in TC, suggesting a central part of multiple susceptibility loci with minor impacts. In this area, great progress has been made through genome-vast association research. (GWAS), Since the mid-2000s, the susceptibility number ofloci with predictive value for the development of TC has gradually increased (22). In a current GWAS and meta-analysis, with more than 5,500 cases and 19,000 controls from Northern Europe, 44 independent TC risk loci (19 recently found and 25 previously stated) were identified and confirmed. Fortunately, chromosomal in situ hybridization analysis in TC cells established a stable pattern of chromatin relationships between susceptible SNPs and target genes and identified 3 potential pathogenic pathways. Specifically, the ten risk regions include genes related to the transcriptional regulation of cell growth, like genes of GATA4 and GATA1 (23). These are transcription elements included in determination and differentiation of postnatal testicular growth; risk allele polymorphisms are connected to progression of tumor. We also found an essential group of PRDM14 and DMRT1 genes included in the definition of stem cells and the SALL4 gene via disruption of binding factor POU5F1, the latter being connected to the pluripotency maintenance of these cells in the embryo (24).

Additionally, 5 TC risk loci were connected to candidate genes in the microtubule assembly and chromosomes, notably the TEX14 gene, the kinetochore microtubule assembly in test germ cells, the WDR73 gene, an essential protein for microtubule organization during interphase, and the assembly-related gene of PMF1 with CENPE and PCNT microtubules In addition, the 3 TC risk loci play an essential role in KIT-MAPK signaling, consistent with current evidence that implicates the KIT gene as a critical somatic driver for development of TC (25). 34% of developing TC is related to a known parent-child relationship, and in the multigenic risk score model, a 1% higher genetic risk corresponds to a 14% lifetime risk for developing TC (26).

From this research, it is evident that TC pathogenesis is based on a vast range of genetic cases. Lately, much attention has been paid to the role of gene copy number variations (CNV) in the growth of cancer, especially in TC. On that point, research team considered inclusion of E2F1 gene CNVs as a TC risk factor (27). E2F1, a member of the E2F protein family, is a transcription factor that manages the transition from G1 to S phase of cell cycle via interaction with the retinoblastoma tumor suppressor protein (RB). Dysregulation of E2F1-pRB binding raises accessibility of the E2F binding site to E2F1 binding target genes, which is thought to increase susceptibility to tumorigenesis (28). Notably, the mTOR signaling pathway is linked to heightened cell proliferation in cancer cell lines upon experimental overexpression of E2F1. It is worth noting that our research team discovered many recurring instances. Specifically, 261 patients were identified with testicular germ cell tumors and 165 controls. The E2F1 gene is found in only 6.5% of TC patients worldwide (29). This was accompanied by increased E2F1 protein expression in tumor tissue samples from patients with only 3 copies of E2F1 while surrounding non-tumor tissues indicated reduced E2F1 protein expression and lower mTOR phosphorylation. Results strongly suggest the inclusion of E2F1 CNVs in TGTC susceptibility via Akt/mTOR signaling pathway. It is noticeable that different clinically relevant risk factors for the development of TC depend mainly on genetic factors. Cryptorchidism, in which the testicle does not descend via the inguinal canal into the scrotum during fetal life, impacts 2 to 9 percent of term boys. Period and is linked to an approximately nine-fold raised risk of TC in comparison to population (30).

The testis migration's embryonic process is partitioned into two successive stages: The transition and inguinoscrotal periods. Information from animal models shows every stage is well-managed by particular elements (31). The migration of the abdominal testis is mainly dependent on insulin-like peptide 3 (INSL3) and its receptor RXFP2, whereas inguinal-breast phase is significantly dependent on androgen signaling. Genetic testing in cryptococcal males has shown that mutations in the INSL3 and RXFP2 genes account for 2% and 4%, respectively, and are predominantly bidirectional. However, there is little agreement on the causative role of polymorphic mutations (32). Interestingly, AR gene mutations are weakly associated with individual cryptorchidism, as the incidence in cryptorchid men is usually less than 2%.

Moreover, expansion sites in the first page of AR gene, recognized as poly-CAG and GGN repeats, known to modulate AR activation activity. However, their downstream regulatory roles in the testis are still debated. Other genetic causes of discrete discharge include mutations in the AMH gene or its receptor in tubular Müller syndrome, described below. Additionally, hypospadias, an abnormality of the urethra during fetal development, is regarded as a risk factor for TC. Specifically, hyperlipidemia is approximately 10% of familial cases, and the approximate heritability of the disease is from 57% to 77% (33).

Environment

Identifying specific environmental factors of TC development presents a challenge of high complexity. Most chemical or physical tumorigenic items indirectly disrupt the hormonal circuits controlling testicular activity or affecting the task of sensitivity genes. By the way, based on the literature, unique environmental risk factors in TC are regularly divided into 4 significant categories: microbiological, physical, mechanical, and chemical (34).

Microbiological

Based on epidemiological information taken in 2002, viral infections are responsible for 12% of cancers in the world, particularly the pathogenic role of infectious agents in testicular tumors in 1980s, according to the epidemiological similarities between Hodgkin's disease and TC (35). The potential role of exposure to Epstein-Barr virus (EBV), such as EBV capsid antigen antibodies, was evaluated in a small group of cases with a background of stage I testicular germ cell tumor undergoing post-orchiectomy care. Interestingly, 80% of the patients indicated higher anti-EBV antibody titers than the control group, indicating a significant connection between cancer and previous exposure to the virus (36). In 1994, they studied EBV DNA detection in testicular samples from patients with testicular germ cell tumors, involving preinvasive CIS. Weak EBV DNA positivity was observed in only 6 of 20 samples. However, the samples displayed no positive staining by anti-EBV immunohistochemical techniques or in situ hybridization, eliminating direct inclusion of EBV and multiple sites for possible causation. Slow down the Stimulatory role of EBV-transformed lymphocytes infiltrating testicular stromal tissue (37). The aim was to measure the potential connection between viral infections and TC using a meta-analysis. Serological markers of exposure to EBV, cytomegalovirus, and parvovirus B19 were connected to TC with odds ratios (OR) of 4.80, 1.885, and 2, respectively (38).

Despite the lack of natural diagnosis and the risk of TC, mechanical and especially traumatic events in testicles are investigated as one of the causes of the disease. The experimental pattern of intratesticular hematoma caused by the injection of autologous blood into the testis of mice linked to important and long-term changes in the shape of the testis, such as a decrease in the size of the testis and its shrinkage (39). In the testicular mass, the size of the spermatogenic epithelium all causes changes in testicular function, like the lack of representation of the population of germ cells in the spermatogenic tubules, changes in sperm parameters and the tendency to decrease testosterone levels (40). According to this substantial change in the functional status of the testes, the reduction of cancer is probably reasonable, especially in the setting of prolonged but subclinical testicular trauma. Despite this simple pattern, the available evidence linking testicular damage to cancer is rare and inconclusive (41).

Another example of long-term microbial damage to the testis is in exercise patients. Of course, testicular contractions and testicular disorders such as urethritis and testicular tumors are common in athletes. Kaldeman et al., stated that cycling, especially in adolescence, was related to an approximately two-fold risk of TC, even after adjusting for confounders such as cryptorchidism or inguinal hernia (42). In addition, horse riding increases the risk of TC by about three times. This remained significantly unchanged after adjustment for confounders, and no significant associations were represented for motorcycling or soccer. But, the following investigations did not find an essential connection between these sports and TBI, suggesting further research (43).

Chemical

Information on chemicals that play a vital role as risk factors for TC is largely taken from occupational research. Special attention is paid to exposure to heavy metals in mining and manufacturing plants (34). Heavy metals are often considered organometallic compounds known to increase in tissues, impair their biological functions, and exhibit long-term deposition, leading to long-term exposure (44). Particularly, transition metals such as cadmium (Cd), mercury, and cobalt have been identified as carcinogenic substances in several experimental papers conducted in animal models and cells. However, the direct relationship between CD and TC exposure is still under investigation (45). In the year of 2011, an investigation into a cancer epidemic in the Kampen area, which straddles the Dutch-Belgian border, revealed that a cadmium and zinc smelter had been in operation for a long time. Environmental exposure to cadmium has been shown to raise the risk of lung cancer in females, bladder cancer in men and women, and prostate cancer in comparison to a control population identified through regional cancer registries. However, the risk Does not increase TC (46). Similarly, another study in the northeastern region of Belgium looked at

cancer incidence over 17 years and found an overall doubling of 24-hour urinary cadmium excretion risk. However, it has no significant connection to TC (47). On the other hand, former investigations of metalworkers in the Hanover region of Germany indicated an almost double risk of TC in comparison to healthy controls. However, no chemical appeared significantly in the association analysis (48). Furthermore, Norwegian metallurgists worked with ferrosilicon and silicon furnaces acknowledged a prevalence of TC that is more than twice the approximate prevalence in the population of Norway based on age and historical period. The other category of environmental chemicals connected to TC is pesticides, as epidemiological investigations indicate a raised occurrence of TC among farmers (49).

Nevertheless, two large meta-analyses conducted in 1992 and 1998 showed no significant risk because of exposure. Pesticides by farmers on this point, appropriate distinctions should be considered. There are significant differences between countries regarding chemicals, formulations, and regulatory principles. Moreover, there are likely large differences in the toxicological effects of different molecular classes in humans. Organochlorine pesticides are endocrine disruptors, while pyrethroids are probably to have an exact impact on cell cycle (50).

Physical

Of the physical risk factors that have been theoretically connected to a raised risk of TC, like exposure to ionizing radiation, UV radiation, and electrical work, exposure to heat stress is the most clinically relevant. As indicated by the external place of the man's genitalia, proper maturation of the germ cells in the spermatogenic tubules is kept at 2-8°C below core body temperature (51). The testis's systematic exposure to physiological hyperthermia is connected to different testicular abnormalities, most of which are reversible, like decreased sperm count, motility, mitochondrial function, and even changes in sperm membrane composition (52). Other environmental cases, potential associations between heat exposure and WA have been considered by occupational research. In 1995, early investigations on TC cases and age-matched healthy subjects showed that exposure to high or severe work temperatures was related to adjusted ORs of 1.2 and 1.7, indicating that ambient temperature is a risk factor (53). An article in 2001 stated that firefighters had an average incidence of TC of 3.0, without increased risk for reasons other than death. However, exposure to milder heat stress, such as showering and bathing, was unrelated to TC risk (54).

Conclusions

TC is a common malignancy in men of reproductive age, with a gradual rise over the last 4 decades. The recent pattern that best describes this process according to clinical and experimental evidence is based on increased exposure to environmental factors, especially chemical pollutants with endocrine-disrupting effects, which are central to hormones that stimulate thyroid growth and function. It changes. Age sensitivity to these changes largely depends on genetic factors, which justifies the high knowledge of TC. A new area of research that links genetic and environmental factors in TC risk is epigenetics, the inheritance of genetic factors is independent on differences in genetic sequence but on gene regulation. Expression through DNA methylation and histone modification: Recent studies have shown that tumor cell DNA exhibits significant hypomethylation in comparison with normal germ cells, possibly because of overexpression of demethylation factors generally suppressed after embryonic development. It is a common belief that the balance between methylating and demethylating factors were managed environmental factors. In the end, it is clear that despite the high sensitivity of TC to chemotherapy, which explains the excellent prognosis of treatment, there are a vast number of patients with drug resistance or resistance to chemotherapy, radiotherapy, or observation. Several critical investigations have clarified genetic markers of positive response or tolerance to therapeutic agents, thereby developing the ultimate effect of treatment. This is to identify a genetic mutation in the SLC16A5 gene strongly associated with cisplatin-induced toxicity. Therefore, the availability of new research strategies to elucidate fundamental dimensions of TC growth, progression, and treatment is critical to improve prevention and treatment of highly treatable diseases with unexplained dissemination.

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Conflict of interest

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Ethical statements

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Data availability

Data will be provided on request.

Abbreviations

AIS	Androgen insensitivity syndrome
CIS	Cells in situ
CNV	Copy number variations

EBV	Epstein-Barr virus
GWAS	Genome-vast association research
INSL3	Insulin-like peptide 3
OR	Odds ratios
PMDS	Persistent Müllerian duTC syndrome
RB	Retinoblastoma
TC	Testicular cancer

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Author (s) biosketches

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