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Omics sciences and precision medicine in testicular cancer

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Abstract

Background. Cancer, a potentially fatal condition, is one of the leading causes of death worldwide. Among males aged 20 to 35, the most common cancer in healthy individuals is testicular cancer, accounting for 1% to 2% of all cancers in men.

Methods. Throughout this review, we have employed a targeted research approach, carefully handpicking the most representative and relevant articles on the subject. Our methodology involved a systematic review of the scientific literature to ensure a comprehensive and accurate overview of the available sources.

Results. The onset and spread of testicular cancer are significantly influenced by genetic changes, including mutations in oncogenes, tumor suppressor genes, and DNA repair genes. As a result of identifying these specific genetic mutations in cancers, targeted medications have been developed to disrupt the signaling pathways affected by these genetic changes. To improve the diagnosis and treatment of this disease, it is crucial to understand its natural and clinical histories.

Conclusions. In order to comprehend cancer better and to discover new biomarkers and therapeutic targets, oncologists are increasingly employing omics methods, such as genomics, transcriptomics, proteomics, and metabolomics. Targeted medications that focus on specific genetic pathways and mutations hold promise for advancing the diagnosis and management of this disease. ***Clin Ter 2023; 174 Suppl. 2 (6):21-28 doi: 10.7417/CT.2023.2468***

Key words: *Cancer, Testicular cancer, genomics, metabolomics, diagnosis, biomarker*

Introduction

The most common cancer among healthy males aged 20 to 35 is testicular cancer, accounting for 1% to 2% of all cancers in men. The most well-established risk factor for testicular cancer is cryptorchidism, which refers to the condition of undescended male testis. Studies have reported a risk ratio (RR) range between 3.5 and 17.1 for testicular cancer in individuals with cryptorchidism. Other significant risk factors for testicular cancer include a prior diagnosis in the opposite testis, with reported risk (1). Vasectomy, scrotal injury, and inguinal hernia have not been established as significant risk factors for testicular cancer. However, a recent systematic study has found a minor but statistically meaningful association between an increased risk of testicular cancer and subfertility. The annual incidence of testicular cancer is approximately 4 per 100,000 people, and it is rare among individuals without underlying risk factors, most of which are highly treatable (2).

Testicular cancer is the second most prevalent new cancer diagnosis among Canadians aged 15 to 29, with 14% of all cancer diagnoses (3). The age range of 15 to 29 poses specific challenges for young cancer patients seeking treatment, as it falls between the fields of pediatric oncology and medical oncology focused on older adults. Germ-cell neoplasms are the primary type of testicular malignancies. Among these, approximately half are seminomas, while the remaining half are non-seminomas. Differentiating between these histological types is crucial, as non-seminoma tumors have a higher likelihood of spreading. Understanding the causes

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of these tumors and determining the most effective treatment approaches relies on this histological distinction. Testicular cancer is showing an increasing incidence, although its causes are not yet fully comprehended. There are a few recognized risk factors for testicular cancer, such as premature birth and cryptorchidism (undescended testicle). However, despite the discontinuation of DES (diethylstilbestrol) prescriptions since the early 1970s, the prevalence of testicular cancer has continued to rise. It is widely believed that germ cell neoplasia in situ (GCNIS) precedes the development of almost all testicular cancers (4).

The causal relationship between maternal smoking and testicular cancer has not been definitively proven. However, the risk of testicular cancer is known to be increased by heavy or prolonged cigarette smoking. Furthermore, there is a correlation between smoking status and the aggressiveness of testicular tumors (5). Excessive or prolonged cannabis use, similarly to tobacco use, has been associated with an increased risk of testicular cancer, particularly of the nonseminoma subtype. This risk is further increased if cannabis use begins before the age of 18. Additionally, certain dietary changes, such as consuming a high amount of fat and dairy products, have been suggested as potential risk factors for testicular cancer. It is also noted that increased prosperity often leads to an increase in sedentary behavior, which has been linked to the disease (6).

Testicular cancer is a complex malignancy, characterized by its heterogeneity and distinct clinical subtypes. The advent of omics technologies has revolutionized cancer research and provided unprecedented opportunities to unravel the molecular intricacies of various cancers, including testicular cancer (7). Omics approaches, such as genomics, transcriptomics, proteomics, and metabolomics, have been instrumental in elucidating the underlying mechanisms, identifying biomarkers, and advancing personalized medicine in the field of testicular cancer (8).

Genomics, as a key omics discipline, has enabled the comprehensive characterization of the genetic landscape of testicular cancer. Through genome-wide studies, numerous genomic alterations have been identified, including chromosomal aberrations, copy number variations, and gene mutations. These genomic aberrations have provided valuable insights into the pathogenesis of testicular cancer, highlighting critical oncogenic drivers and tumor suppressor genes involved in tumorigenesis and disease progression (9). Transcriptomics, the study of gene expression patterns, has significantly contributed to our understanding of testicular cancer biology. By employing techniques such as microarray analysis and RNA sequencing, researchers have identified specific gene expression signatures associated with different subtypes of testicular cancer. These gene expression profiles not only facilitated accurate classification of testicular tumors, but also provided insights into the molecular processes driving tumor development, metastasis, and treatment response (10).

Proteomics, which is the study of proteins and their interactions, has played a vital role in uncovering the protein networks and signaling pathways involved in testicular cancer. Proteomic analyses have identified proteins that are differentially expressed in testicular cancer tissues compared to normal testicular tissues. Furthermore, proteomics has been instrumental in identifying potential protein biomarkers for diagnostic, prognostic, and therapeutic purposes. These biomarkers hold promise for improving early detection, predicting treatment outcomes, and guiding personalized treatment strategies (11).

Metabolomics, the study of small molecule metabolites, has emerged as a powerful tool for understanding the metabolic alterations associated with testicular cancer. Metabolomic profiling of testicular cancer samples has revealed perturbations in various metabolic pathways, providing insights into the energy metabolism, nutrient utilization, and biosynthetic processes in testicular tumors. These findings may have implications for the development of targeted therapies aimed at disrupting specific metabolic pathways or exploiting metabolic vulnerabilities in testicular cancer cells (12).

Introduction to tumor biology

Cancer, a potentially fatal condition, remains one of the leading causes of death globally. The rate of advancement in our understanding of cancer is remarkable; however, the more we delve into its details, the more complex it appears. It is crucial to understand its underlying mechanisms, as they operate in a dynamic and interconnected manner at both the molecular and cellular levels. This understanding is essential in our ongoing fight against this disease (13). Big omics data, also known as cancer systems biology, can be produced by investigating global DNA, RNA, and protein expression, which in turn lead to a systems approach to cancer biology research, addressing the complexity of cancer by combining experimental and computational techniques in the synthesis and testing of cancer biological theories (14).

Recent years have seen a substantial improvement in our knowledge about tumor biology, natural history, clinical history, and genetics, which has sparked the development of novel diagnostic and therapeutic strategies. Testicular cancer propensity can be identified through genetic testing, which also offers useful information for customizing treatment choices (15). Additionally, the tumor's genetics, which includes gene fusions, rearrangements, and somatic mutations, can direct targeted therapy. Proteomic, metabolomic, and microbiomic profiling, together with other newly discovered biomarkers, may offer further details on the pathophysiology and individualized treatment of testicular cancer (16).

Genetics of testicular cancer (germline mutations that predispose to cancer)

Processes of DNA damage (both exogenous and endogenous) as well as DNA repair leave their imprint on the genomes of cancerous cells. By examining the somatic mutation landscape within these cells, we can identify the mutational forces responsible for oncogenesis. Certain mutational signatures have well-established etiologies, and understanding these signatures can provide insights into the underlying causes of testicular cancer (17).

Due to deficiencies in DNA repair systems, exposure to exogenous mutagens, or errors in DNA replication, so-

matic mutations can manifest in various forms, known as mutational signatures. These mutational signatures can be extracted from a tumor's diversity and examined to elucidate potential factors contributing to its etiology (18). Comparing variations in mutational signatures based on the age of onset can be particularly valuable, because cancer risk and latency periods of exposure differ across age groups. This is crucial, given that testicular cancer is a rare form of cancer that is challenging to assess rapidly in a traditional epidemiological study setting. Analyzing the mutational landscape can also provide insights into treatment approaches and help understanding the factors contributing to the increasing incidence of testicular cancer among young individuals. For instance, studies have shown that the mutational burden influences the response to immunotherapy (19).

In a previous analysis conducted by (Wheeler et al 2013), molecular alterations in testicular cancer tumors identified three genes involved in somatic mutations in testicular cancers, which are KIT, KRAS, and NRAS. The study also observed that the most common type of base changes observed were cytosine to thymine. Interestingly, the authors noted that the mutational signature known as the "COSMIC signature," which arises from the accumulation of 5-methylcytosine deamination events, coincided with the most prevalent mutational signature in testicular cancer (20).

The use of genomics in the treatment of cancer has rapidly increased in recent years. Through genomic research, it is possible to identify frequent genetic changes that occur in cancer, such as chromosomal rearrangements, fusion genes, and somatic mutations (21). Chromosomal rearrangements, including translocations or deletions, are common genetic events in cancer that can cause altered expression or function of genes involved in cell proliferation, differentiation, and apoptosis, resulting in the onset and progression of the disease. Fusion genes, which are formed as a result of chromosomal rearrangements, influence the growth and survival of cells by activating or inactivating specific pathways. Somatic mutations, which are genetic changes that take place in non-germline cells, can also impact the genes responsible for carrying out cellular functions and aid in the growth of cancer (22).

The use of liquid biopsies, which examine circulating tumor cells or circulating tumor DNA (ctDNA) in the blood, is another aspect of genomics in tumor care that has drawn a lot of interest. A promising biomarker for cancer diagnosis, prognosis, and therapy response monitoring is ctDNA analysis. It can offer details on the chromosomal rearrangements and somatic mutations that are present in the tumor, which can help determine the best targeted therapy (23).

Tumor genomics (tumor-typical somatic mutations and circulating tumor DNA)

Testicular cancer is not specifically connected to any one gene, although it is highly heritable and can be passed from parent to child. Additionally, if a first-degree relative has testicular cancer, the average age of diagnosis is two to three years lower than the general population (24). The onset and spread of testicular cancer are significantly influenced by genetic changes. In testicular cancer, mutations in oncogenes, tumor suppressor genes, and DNA repair genes have been frequently identified. These genetic alterations play a significant role in the development and progression of testicular cancer, leading to the development of targeted therapeutics for testicular cancer as a result of the discovery of these genetic abnormalities. Over the past few decades, there have been major developments in the study of genetics, which have resulted in the identification of numerous genetic variants that affect tumor initiation and progression (25). Genetic testing has become an integral component of tumor management, due to its ability to identify individuals who are predisposed to certain types of cancers. By analyzing an individual's genetic makeup, genetic testing can provide valuable information about their susceptibility to specific cancer types. This information can be instrumental in developing personalized treatment plans, implementing preventive measures, and offering genetic counseling to at-risk individuals and their families (26).

Numerous studies have proven that specific genetic variations are associated with an increased chance of developing certain types of cancer. Colorectal, endometrial, and other cancers are more likely to develop in people who have Lynch syndrome, which is brought on by mutations in DNA mismatch repair genes. Genetic testing can detect somatic alterations in the tumor tissue in addition to germline mutations. Somatic mutations are not inherited and take place in non-germline cells (27). These mutations, which are specific to the tumor tissue, can reveal details about the biology, behavior, and potential therapeutic response of the tumor. Targeted medicines that can selectively target somatic mutations have been developed as a result of the detection of somatic mutations (28).

Table 1. Testicular cancer Genetic Mutations and their phenotypes.

Gene	Genetic Mutation(s)	Inheritance	Phenotype	OMIM
TP53	Various Mutations	AD	Li-Fraumeni syndrome	191170
KIT	C-KIT Mutations	AD	Familial testicular germ cell tumors	164920
BRCA2	Various Mutations	AD	Hereditary breast and ovarian cancer syndrome	600185
RAD51C	RAD51C Mutation	AR	Fanconi anemia	602774
CHEK2	CHEK2 Mutations	AD	Li-Fraumeni-like syndrome	604373

Pharmacogenomics of the specific testicular tumor

The study of genetic differences that affect drug response and toxicity is known as pharmacogenomics. Drug efficacy and safety may be increased by identifying genetic variants that impact drug transport, pharmacodynamics, and metabolism. Pharmacogenomics can also help with drug selection and dosage, which results in more individualized therapy options (29). The analysis of genetic variants that affect drug toxicity and response is becoming more crucial in the treatment of tumors. Drug efficacy and safety may be increased by identifying genetic variants that impact drug transport, pharmacodynamics, and metabolism. Pharmacogenomics can also help with drug selection and dosage, which will benefit cancer patients' prognoses. The management of tumors now places a high priority on genetics and pharmacogenomics (30). Technology advancements have made it possible to pinpoint specific genetic changes in cancers and create tailored medicines that can enhance therapeutic outcomes. Pharmacogenomics and the use of liquid biopsies have both shown promise in the diagnosis, prognosis, and therapy of cancer (31). It is possible to enhance individualized cancer treatment and eventually improve patient outcomes by incorporating genetics and pharmacogenomics into clinical practice (32).

Enzymes that regulate the metabolism, uptake, and reaction to numerous clinically used medications, such as bleomicin, etoposide, and platins, have been the main focus of pharmacogenomic research on testicular cancer, in light of the fact that Cytochrome P450 is responsible for the majority of antineoplastic medication metabolism and that treatment efficiency is frequently impacted by variant alleles in these enzymes. It is important to adequately address the study of these phase I and phase II enzymes in order to support the development of therapeutically more effective medicines (33).

Biological therapies (immunotherapy, monoclonal antibody therapy)

When determining the appropriate course of treatment for testicular tumors, both the stage and subtype of the tumor are to be considered. While orchiectomy followed by monitoring is a suitable and frequent therapeutic option for these patients, metastatic testicular tumors are normally treated with chemotherapy alone or in combination with chemotherapy, surgery, and, in a few uncommon situations, radiation therapy (34). Approximately 15-25% of patients with metastatic disease relapse after beginning the treatment. However, salvage treatment can cure 50% of this patient group. The last category of patients includes those with cisplatin-resistant diseases or those who relapsed after receiving second-line treatment. The disease has a terrible prognosis for these patients, who are typically treated with cutting-edge chemotherapy regimens. Despite numerous therapeutic strategies incorporating targeted and biological therapies have been attempted in cisplatin-refractory testicular malignancies, conventional chemotherapy with low efficacy is still employed for these patients (33).

Immunotherapy

The primary reasons why the mammalian testes are considered immunologically privileged locations are their unique immunological milieu, which shields germ cells from autoimmune attack, and a lack in the testicular immune system's ability to respond to antigens (35). Additionally, it appears that the mechanisms governing the immune privilege of the testis also regulate spermatogenesis and steroidogenesis (36).

The phenomenon of spontaneous testicular tumor regression without therapy is thought to be related to the immune environment of the host and changed tumor vascularization. Characterizing immune cells and cytokine profiles within the tissue has allowed researchers to determine the precise immune response to the presence of in situ germ cell neoplasia (GCNIS) and overt germ cell tumors (GCT) (37). When compared to healthy testicles or inflammatory lesions associated with hypospermatogenesis, Klein et al. found that testicular germ cell tumors had a markedly distinct pattern of immune cell distribution. Patients received either pembrolizumab or nivolumab therapy (38); however, soon after receiving a single dose of medication, four individuals passed away from tumor growth. One of the three remaining patients experienced a partial radiographic response, but it's crucial to remember that this patient also received concurrent etoposide therapy (39).

As of now, immune checkpoint inhibition has not shown proven effectiveness in the treatment of refractory testicular cancer outside of clinical trials. There may be a group of patients who could benefit from immune checkpoint inhibition, according to case reports, but there are no reliable indicators available at this time for clinical decision-making in everyday practice (40). High PD-L1 expression in choriocarcinoma may be a meaningful biomarker, according to data from GTS; however, there is currently insufficient information to support such a choice in TGCTs. Alternative predictors, such as TILs and/or the tumor mutation burden, may exist; however, more study is required to assess their usefulness. To better understand the detection of prognostic markers predicting the reaction to immune-based therapy in patients with intractable testicular cancer, more research is needed (41).

Monoclonal antibody therapy

Monoclonal antibodies, which were first developed almost three decades ago, are revolutionizing the way physicians treat COVID-19 and other diseases as well as cancer. These medicines imitate the immune system's built-in defense against infection (42). Millions of y-shaped proteins known as antibodies, or antibody receptors, are produced by the immune system. Each antibody is traveling throughout the body in search of a specific target that is located on the exterior of an alien cell known as an antigen. An antibody that locates its target bonds with the antigen to aid the immune system in eliminating the sick cell (41).

Monoclonal antibodies are used to treat a variety of cancer types. They are given to patients via an infusion and

can be used either alone or in combination with other cancer treatments (43). Each monoclonal antibody may work in one or more ways depending on the antigen it is aiming to bind. Certain monoclonal antibodies target cancer cells selectively and kill them as a result. Due to their focus on specific cell receptors, these monoclonal antibodies are referred to as tailored therapies. For instance, HER2-positive breast cancer and stomach cancer are both treated with trastuzumab (Herceptin). More monoclonal antibodies improve the immune response to cancer cells (44).

Proteomic, lipidomic and metabolomic biomarkers

Testicular cancer biomarkers are essential for diagnosis, prognosis, and monitoring. Despite substantial improvements in cancer diagnosis and treatment over the past few decades, the early identification of cancer by diagnostic, prognostic, and predictive biomarkers remain one of the most promising research domains for locating early-stage cancer and adjusting therapy. The accuracy of biomarkers for illness diagnosis, treatment efficacy prediction, and tumor stage classification could all be increased. However, the individualized treatment of cancer patients is complicated by the dearth of trustworthy biomarkers (45). The variety of the oncogenic event is correlated with the heterogeneity of the distinct cancers. Additionally, diverse properties of the same histology, may lead to therapeutic failure. Because cancer is heterogeneous, the absence of a particular biomarker with 100% accuracy in diagnosis can be explained. To better define neoplasms at the molecular level, metabolomic, proteomic, and lipidomic methods are being used (46). Proteomic, lipidomic, and metabolomic biomarkers that have been studied in relation to testicular cancer include the following:

Proteomic Biomarkers: The biomarker alpha-fetoprotein (AFP) is well-known for detecting testicular cancer. Testicular cancer subtypes including non-seminomatous germ cell tumors (NSGCT) are linked to elevated levels of AFP in blood serum or testicular tumor tissue (47). Like AFP, high hCG levels have been linked to NSGCT and can be found in blood serum or urine. Increased levels of the enzyme lactate dehydrogenase (LDH) have been found in patients with testicular cancer and are linked to advanced disease stages and a bad prognosis. Several miRNAs, including "miR-371a-3p and miR-375," have demonstrated potential as biomarkers for the early identification and follow-up of testicular cancer. They can be found in biological fluids like blood serum (48).

Lipidomic Biomarkers: Lipids serve a variety of significant functions in cellular activities, such as survival, proliferation, and death because they are engaged in "chemical energy storage, cellular signaling, cell membranes, and cell-cell interactions in tissues." These cellular processes, in particular transformation, progression, and metastasis, have a close connection to carcinogenesis pathways (49). Bioactive lipids are crucial for many biological processes, and many neoplastic illnesses result in changes to their composition. Lipid changes in cancer cells have been studied by numerous earlier research teams to better understand the illness and identify potential biomarkers (50). T cells have the ability to control prostaglandin E2 PGE2 actions, which can help tumor cells evade detection. Following the use of genomics and proteomics, lipidomics was first applied in 2003 as a metabolomic technique to investigate the "qualitative and quantitative profile of the lipid components from serum, plasma, tissue, cells, and organisms (51). Testicular cancer tissues have been shown to contain altered sphingomyelin species. As lipidomic indicators for the illness, specific SM level abnormalities may exist. Testicular cancer has been linked to changes in phosphotidylcholine (PC) metabolism (52). Changes in PC composition and levels may shed light on the disease's pathophysiology. Lipidomics is an emerging technique for tumor characterization that can be used to recognize and classify neoplastic cells or tissues as well as to differentiate between a neoplasmic and normal environment. This approach can also be used to identify novel tumor biomarkers and assess the reactivity of anticancer therapies. The application of lipidomic techniques to cancer research may open up new avenues for understanding cancer diagnosis, prognosis, and the forecasting of personalized treatments (53). Table 2 lists the metabolites and biomarkers associated with testicular cancer that have drawn the most interest. Different testicular cancer subtypes and individuals may exhibit these signs to varying degrees.

Metabolomic Biomarkers: Metabolomics is a more recent addition to the omics toolkit, which is being employed more frequently in therapeutic settings. A sensitive molecular readout that is frequently connected to disease and its states, notably in cancer, is provided by small molecule assessments in tissues, blood, or urine (54). The altered metabolism of cancer, which has recently become more recognized in connection with cancer, is a significant aspect of the disease. The use of metabolomics in human breast tumors is discussed in this review, with a focus on its application in clinical diagnosis. In contrast to the clinical diagnostic techniques for breast cancer that are available now, metabolomics has the ability to detect cancer, predict outcomes of therapy (55). In the tissues of testicular cancer, higher concentrations of choline metabolites such phosphocholine and glycerophosphocholine have been found. These metabolites play a role in the reorganization of cell membranes and could be used as metabolomic indicators. Testicular cancer has been associated with elevated lactate levels, which point to altered energy metabolism (the Warburg effect) in cancer cells. Testicular cancer tissues have been found to have lower citrate levels. Citrate regulates energy metabolism, therefore changes to it may be a reflection of cancer-related metabolic abnormalities (56). Although these biomarkers have demonstrated potential in research studies, more validation and standardization are required before they can be implemented into common clinical practice for the diagnosis and treatment of testicular cancer. Additionally, compared to individual biomarkers, biomarker panels or combinations may offer enhanced sensitivity and specificity (57).

Microbiomic prognostic indicators

Microorganisms are thought to play a role in the pathogenesis of about 20% of all malignancies. The most

Table 2. Table for Metabolites and biomarkers of testicular cancer

Metabolite/Biomarker	Type	Source	Association with Testicular Cancer
Alpha-fetoprotein (AFP)	Protein	Blood serum, tumor tissue	Elevated levels associated with non-seminomatous germ cell tumors (NSGCT)
Human chorionic gonadotropin (hCG)	Protein	Blood serum, urine	Elevated levels associated with NSGCT
Lactate dehydrogenase (LDH)	Protein	Blood serum	Increased levels associated with advanced disease stages and poor prognosis
MicroRNAs (miRNAs)	RNA	Blood serum	bodily fluids Specific miRNAs like miR-371a-3p and miR-375 show potential as biomarkers for detection and monitoring
Sphingomyelin (SM)	Lipid	Testicular cancer tissue	Altered levels observed in testicular cancer tissues
Phosphatidylcholine (PC)	Lipid	Testicular cancer tissue	Changes in PC metabolism associated with testicular cancer
Choline and derivatives	Metabolite	Testicular cancer tissue	Increased levels of choline metabolites
Lactate	Metabolite	Testicular cancer tissue	Elevated levels indicate altered energy metabolism
Citrate	Metabolite	Testicular cancer tissue	Decreased levels associated with testicular cancer

prevalent kind of cancer in young men is testicular tumors, which develop from the germ cell neoplasia in situ (GCNIS) progenitor cell (58). In relation to TC, the microbiota of seminal plasma and testicular tissue has not been extensively studied. The population of microorganisms, such as bacteria, viruses, fungus, and other microbes, that live in different bodily regions, such as the gastrointestinal system, skin, and reproductive organs, is referred to as the microbiome (59). Despite the paucity of research on the microbiome's function in testicular cancers, mounting evidence points to the microbiome's potential role in the initiation and progression of cancer. However, little research has been done on particular microbiomic prognostic markers for testicular malignancies (60). According to reports, the physiological activity of the liver, gut, brain, immune cells, and several endocrine glands is influenced by the gut microbiota, which is the second biggest genome of the host. The testis and the gut microbes interact extensively. Spermine can be produced by the body's endogenous polyamine metabolism and is also absorbed from food and the gut bacteria. The activities of spermine include antioxidation, ion channel modulation, lipid synthesis inhibition, and preservation of the reproduction system's normal physiology (61).

The microbial populations in the urine and reproductive systems are referred to as the genitourinary microbiome. There is little study explicitly focusing on testicular tumors, despite studies exploring the genitourinary microbiome in relation to other urological diseases, such as bladder cancer and prostate cancer. It may be possible to find potential connections or prognostic clues by researching the genitourinary microbiome in relation to testicular cancers (61).

Cancer development and treatment response have both been linked to immune system and microbiota interactions. Immune function and how well the body respond to anticancer therapies can be affected by dysbiosis, or an imbalance in the microbiome composition. Examining the connections between the immune system and the microbiome in testicular cancer may reveal information about the disease's prognosis and possible treatments (62). It's critical to remember that the study of microbiomics and its connection to testicular tumors is still in its infancy, and further investigation is required to identify precise microbiomic prognostic indicators for testicular cancer. It may be possible to identify potential biomarkers and therapeutic targets with further research into the makeup, variety, and functional significance of the microbiome in testicular cancers (63). Intestinal bacteria were removed by antibiotics and replaced by gut microbial transplantation in order to study the effects of spermine and gut microbiota on testicular dysfunction. Following antibiotic therapy, there were fewer total bacteria and sperm in the cecum lumen, which were restored by gut microbial rebuilding (64).

Conclusion

Testicular cancer predominantly affects men between the ages of 20 and 35. While screening for testicular cancer has the potential to reduce morbidity and mortality, the most effective screening strategy is currently unknown. Additional research is indeed necessary to determine the optimal approach for testicular cancer screening. Various factors need to be considered, including the cost-effectiveness of screening programs, the potential harms associated with screening, and the ability to detect early-stage cancers accurately. Due to the low incidence of testicular cancer and the favorable outcomes in the absence of screening, many organizations also advise avoiding testicular cancer screening.

Although all of these biomarkers have showed promise in research trials, more validation and standardization are required before they can be used in ordinary clinical practice for the detection and treatment of testicular cancer. Tailor-made therapy offers a personalized method of treating testicular cancer, and proteomic and metabolomic indicators provide insights into the metabolic and protein alterations that take place in testicular cancer cells (65). The effectiveness of testicular cancer diagnosis and treatment may be enhanced by combining these approaches.

Overall, this review offers insightful information into the genetics, genomics, proteomics, metabolomics, and customized therapeutic areas of testicular cancer research. These researches are significant milestones toward creating individualized and successful testicular cancer treatments,

despite the fact that there is still much to learn about the biology of testicular cancer. Pharmacogenomics can also help with drug selection and dosage, which will benefit cancer patients' prognoses. The management of tumors now places a high priority on genetics and pharmacogenomics.

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Conflicts of interest statement

Authors declare no conflict of interest.

References

1. Ilic D, Misso ML. Screening for testicular cancer. Cochrane Database Syst Rev. 2011 Feb 16;(2):CD007853
2. Gilligan T, Lin DW, Aggarwal R et al. Testicular Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019 Dec;17(12):1529-1554
3. Richie JP. Detection and treatment of testicular cancer. CA Cancer J Clin. 1993 May-Jun;43(3):151-75
4. Smith ZL, Werntz RP, Eggener SE. Testicular Cancer: Epidemiology, Diagnosis, and Management. Med Clin North Am. 2018 Mar;102(2):251-264
5. Goriely A, Hansen RM, Taylor IB et al. Activating mutations in FGFR3 and HRAS reveal a shared genetic origin for congenital disorders and testicular tumors. Nat Genet. 2009 Nov;41(11):1247-52
6. Gaytan F, Barreiro ML, Caminos JE et al. Expression of ghrelin and its functional receptor, the type 1a growth hormone secretagogue receptor, in normal human testis and testicular tumors. J Clin Endocrinol Metab. 2004 Jan;89(1):400-9
7. Sindelar RD, Genomics, other "OMIC" technologies, precision medicine, and additional biotechnology-related techniques. Pharmaceutical Biotechnology: Fundamentals and Applications, 2019: p. 191-237. (Accessed on 28/08/2023 at https://www.researchgate.net/publication/332398864_Genomics_Other_OMIC_Technologies_Precision_Medicine_and_Additional_Biotechnology-Related_Techniques)
8. Assadi M, Jokar N, Ghasemi M, et al. Precision Medicine Approach in Prostate Cancer. Curr Pharm Des. 2020; 26(31):3783-3798
9. Pettini F, Visibelli A, Cicaloni V, et al. Multi-Omics Model Applied to Cancer Genetics. Int J Mol Sci. 2021 May; 22(11):5751
10. Chakraborty S, Hosen MI, Ahmed M, et al. Onco-Multi-OMICS Approach: A New Frontier in Cancer Research. Biomed Res Int. 2018 Oct; 2018:9836256
11. Paul D, Chanukuppa V, Reddy PJ, et al. Global proteomic profiling identifies etoposide chemoresistance markers in non-small cell lung carcinoma. J Proteomics. 2016 Apr; 138:95-105
12. Jarak I, Almeida S, Carvalho RA, et al. Senescence and declining reproductive potential: Insight into molecular mechanisms through testicular metabolomics. Biochim Biophys Acta Mol Basis Dis. 2018 Oct;1864(10):3388-3396
13. Schultz KAP, Harris AK, Finch M, et al. DICER1-related Sertoli-Leydig cell tumor and gynandroblastoma: Clinical and genetic findings from the International Ovarian and Testicular Stromal Tumor Registry. Gynecol Oncol. 2017 Dec;147(3):521-527
14. Gemmati D, Varani K, Bramanti B et al. "Bridging the Gap" Everything that Could Have Been Avoided If We Had Applied Gender Medicine, Pharmacogenetics and Personalized Medicine in the Gender-Omics and Sex-Omics Era. Int J Mol Sci. 2019 Dec; 21(1):296
15. Cacabelos R, Naidoo V, Corzo L, et al. Genophenotypic Factors and Pharmacogenomics in Adverse Drug Reactions. Int J Mol Sci. 2021 Dec; 22(24):13302
16. Tandstad T, Kollmannsberger CK, Roth BJ, et al. Practice Makes Perfect: The Rest of the Story in Testicular Cancer as a Model Curable Neoplasm. J Clin Oncol. 2017 Nov;35(31):3525-3528
17. Stadler ZK, Esposito D, Shah S, et al. Rare de novo germline copy-number variation in testicular cancer. Am J Hum Genet. 2012 Aug;91(2):379-83
18. Litchfield K, Levy M, Dudakia D, et al. Rare disruptive mutations in ciliary function genes contribute to testicular cancer susceptibility. Nat Commun. 2016 Dec; 7:13840
19. Greene MH, Kratz CP, Mai PL, et al. Familial testicular germ cell tumors in adults: 2010 summary of genetic risk factors and clinical phenotype. Endocr Relat Cancer. 2010 Mar;17(2):R109-21
20. Wheeler HE, Maitland ML, Dolan ME, et al. Cancer pharmacogenomics: strategies and challenges. Nat Rev Genet. 2013 Jan;14(1):23-34
21. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature. 2009 Apr; 458(7239):719-24
22. Maiuolo J, Musolino V, Gliozzi M, et al. The Employment of Genera Vaccinium, Citrus, Olea, and Cynara Polyphenols for the Reduction of Selected Anti-Cancer Drug Side Effects. Nutrients. 2022 Apr;14(8):1574
23. Chen X, Pappo A, Dyer MA. Pediatric solid tumor genomics and developmental pliancy. Oncogene. 2015 Oct; 34(41):5207-15
24. Balmain A, Gray J, Ponder B. The genetics and genomics of cancer. Nat Genet. 2003 Mar; 33Suppl:238-44
25. Brown SD, Warren RL, Gibb EA, et al. Neo-antigens predicted by tumor genome meta-analysis correlate with increased patient survival. Genome Res. 2014 May; 24(5):743-50
26. Aita VM, Liang XH, Murty VV, et al. Cloning and genomic organization of beclin 1, a candidate tumor suppressor gene on chromosome 17q21. Genomics. 1999 Jul; 59(1):59-65
27. Wang E, Zaman N, Mcgee S, et al. Predictive genomics: a cancer hallmark network framework for predicting tumor clinical phenotypes using genome sequencing data. Semin Cancer Biol. 2015 Feb;30:4-12
28. Jolissaint JS, Soares KC, Seier KP, et al. Intrahepatic Cholangiocarcinoma with Lymph Node Metastasis: Treatment-Related Outcomes and the Role of Tumor Genomics in Patient Selection. Clin Cancer Res. 2021 Jul;27(14):4101-4108
29. Lee W, Lockhart AC, Kim RB, et al. Cancer pharmacogenomics: powerful tools in cancer chemotherapy and drug development. Oncologist. 2005 Feb; 10(2):104-11
30. Quiñones, L. Improving Testicular Cancer Pharmacotherapy Through the Use of Pharmacogenomic Approaches. Ann Urol Res. 2017; 1 (1), 2017. 1004. (Accessed on 28/08/2023 at https://www.remedypublications.com/open-access/pimproving-testicular-cancer-pharmacotherapy-through-the-use-of-pharmacogenomic-approachesp-1840.pdf)
31. Cacabelos R, Cacabelos N, Carril JC. The role of pharmacogenomics in adverse drug reactions. Expert Rev Clin Pharmacol. 2019 May;12(5):407-442
32. Ye Y, Xiang Y, Ozguc FM, et al. The Genomic Landscape and Pharmacogenomic Interactions of Clock Genes in Cancer Chronotherapy. Cell Syst. 2018 Mar; 6(3):314-328.e2

33. Goodspeed A, Heiser LM, Gray JW, et al. Tumor-Derived Cell Lines as Molecular Models of Cancer Pharmacogenomics. Mol Cancer Res. 2016 Jan;14(1):3-13
34. Murray MJ, Huddart RA, Coleman N. The present and future of serum diagnostic tests for testicular germ cell tumours. Nat Rev Urol. 2016 Dec; 13(12):715-725
35. Kirkwood JM, Butterfield LH, Tarhini AA, et al. Immunotherapy of cancer in 2012. CA Cancer J Clin. 2012 Sep-Oct; 62(5):309-35
36. Narunsky-Haziza L, Sepich-Poore GD, et al. Pan-cancer analyses reveal cancer-type-specific fungal ecologies and bacteriome interactions. Cell. 2022 Sep;185(20):3789-3806. e17
37. Lavanderos MA, Cayún JP, Roco Á et al. Association Study Among Candidate Genetic Polymorphisms and Chemotherapy-Related Severe Toxicity in Testicular Cancer Patients. Front Pharmacol. 2019 Mar;10:206
38. Baumeister SH, Freeman GJ, Dranoff G, et al. Coinhibitory Pathways in Immunotherapy for Cancer. Annu Rev Immunol. 2016 May; 34:539-73
39. Trapani JA, Darcy PK. Immunotherapy of cancer. Aust Fam Physician. 2017; 46(4):194-199
40. Borghaei H, Smith MR, Campbell KS. Immunotherapy of cancer. Eur J Pharmacol. 2009 Dec; 625(1-3):41-54
41. Weiner LM, Murray JC, Shuptrine CW. Antibody-based immunotherapy of cancer. Cell. 2012 Mar; 148(6):1081-4
42. Scott AM, Allison JP, Wolchok JD. Monoclonal antibodies in cancer therapy. Cancer Immun. 2012;12:14
43. Khalil DN, Smith EL, Brentjens RJ, et al. The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. Nat Rev Clin Oncol. 2016 May;13(5):273-90
44. Stern M, Herrmann R. Overview of monoclonal antibodies in cancer therapy: present and promise. Crit Rev Oncol Hematol. 2005 Apr; 54(1):11-29
45. Lovric A, Granér M, Bjornson E, et al. Characterization of different fat depots in NAFLD using inflammation-associated proteome, lipidome and metabolome. Sci Rep. 2018 Sep;8(1):14200
46. Hinckley JD, Saba L, Raymond K, et al. An Approach to Biomarker Discovery of Cannabis Use Utilizing Proteomic, Metabolomic, and Lipidomic Analyses. Cannabis Cannabinoid Res. 2022 Feb;7(1):65-77
47. Nishtala K, Pahuja N, Shetty R, et al. Tear biomarkers for keratoconus. Eye Vis (Lond). 2016 Aug;3:19
48. Didangelos A, Stegemann C, Mayr M. The -omics era: proteomics and lipidomics in vascular research. Atherosclerosis. 2012 Mar;221(1):12-7
49. Corella D, Ordovás JM. Biomarkers: background, classification and guidelines for applications in nutritional epidemiology. Nutr Hosp. 2015 Feb;31Suppl 3:177-88
50. Korduner J, Nilsson PM, Melander O, et al. Proteomic and Metabolomic Characterization of Metabolically Healthy Obesity: A Descriptive Study from a Swedish Cohort. J Obes. 2021 Oct;2021:6616983
51. Liang L, Li Y, Tian X, et al. Comprehensive lipidomic, metabolomic and proteomic profiling reveals the role of immune system in vitiligo. Clin Exp Dermatol. 2019 Oct;44(7):e216-e223
52. Zhou J, Sun L, Chen L, et al. Comprehensive metabolomic and proteomic analyses reveal candidate biomarkers and related metabolic networks in atrial fibrillation. Metabolomics. 2019 Jun;15(7):96
53. Datta S, Mertens BJ. Statistical analysis of proteomics, metabolomics, and lipidomics data using mass spectrometry. 2017: Springer. (Accessed on 28/08/2023 at https://www.researchgate.net/publication/311711134_Statistical_Analysis_of_Proteomics_Metabolomics_and_Lipidomics_Data_Using_Mass_Spectrometry)
54. Zhao Q, Huang JF, Cheng Y, et al. Polyamine metabolism links gut microbiota and testicular dysfunction. Microbiome. 2021 Nov;9(1):224
55. Pluta J, Pyle LC, Nead KT, et al. Identification of 22 susceptibility loci associated with testicular germ cell tumors. Nat Commun. 2021 Jul;12(1):4487
56. Zhang X, Trendowski MR, Wilkinson E, et al. Pharmacogenomics of cisplatin-induced neurotoxicities: Hearing loss, tinnitus, and peripheral sensory neuropathy. Cancer Med. 2022 Jul;11(14):2801-2816
57. Jordan B, Margulies A, Cardoso F, et al. Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO-EONS-EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up. Ann Oncol. 2020 Oct;31(10):1306-1319
58. De Toni L, Šabovic I, Cosci I, et al. Testicular Cancer: Genes, Environment, Hormones. Front Endocrinol (Lausanne). 2019 Jul;10:408
59. Su M, Zhang Z, Zhou L, et al. Proteomics, Personalized Medicine and Cancer. Cancers (Basel). 2021 May;13(11):2512
60. Sabbaghian N, Bahubeshi A, Shuen AY, et al. Germ-line DICER1 mutations do not make a major contribution to the etiology of familial testicular germ cell tumours. BMC Res Notes. 2013 Apr;6:127
61. Mealey NE, O'Sullivan DE, Peters CE, et al. Mutational signatures among young-onset testicular cancers. BMC Med Genomics. 2021 Nov;14(1):280.
62. Vasistha A, Kothari R, Mishra A, et al. Current Insights into Interethnic Variability in Testicular Cancers: Population Pharmacogenetics, Clinical Trials, Genetic Basis of Chemotherapy- Induced Toxicities and Molecular Signal Transduction. Curr Top Med Chem. 2020;20(20):1824-1838
63. Shi B, Chang M, Martin J, et al. Dynamic changes in the subgingival microbiome and their potential for diagnosis and prognosis of periodontitis. mBio. 2015 Feb; 6(1):e01926-14
64. Nicolaro M, Portal DE, Shinder B, et al. The human microbiome and genitourinary malignancies. Ann Transl Med. 2020 Oct;8(19):1245.
65. Madgwick MP, Sudhakar, Korcsmáros T. P027 Machine learning approaches to identify prognosis indicators from microbiome data. Journal of Crohn's and Colitis, 2019. 13(Supplement_1): p. S99-S100. (Accessed on 28/08/2023 at https://academic.oup.com/ecco-jcc/article/13/Supplement_1/S99/5300883)