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Review

Relationship Between Autism and Cancer

Otizm ve Kanser Arasındaki İlişki

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Abstract

Autism spectrum disorder (ASD) refers to a set of developmental disorders that appear beginning in early infancy. Within the first three years following birth, early warning signs of ASD become apparent. Their difficulties in communicating stem from speech delays as well as difficulties in socializing. Though education and treatment may be somewhat helpful, there are no effective drugs or surgical techniques that can treat it. Researchers have found a relationship between autism and an increased risk of developing neurological, gastrointestinal, and cancer diseases. A comprehensive study of the relationship between autism and cancer has not been clear. Nonetheless, it is important to look into this particular aspect of autism-related cancer risk, paying special attention to the genes and pathways involved. The aim of this article is to provide a holistic perspective by studying the literature of existing evidence on a possible correlation between autism and cancer.

Öz

Otizm spektrum bozukluğu (OSB), erken çocuklukta başlayan bir dizi gelişim bozukluğuna işaret etmektedir. Doğumdan sonraki ilk üç yıl içinde, otizm spektrum bozukluğunun erken uyarı belirtileri görünür hale gelmektedir İletişimdeki zorluklar, konuşma gecikmeleri ve sosyalleşme problemlerinden kaynaklanmaktadır. Eğitim ve tedavi kısmen fayda sağlasa da bu durumu tamamen tedavi edebilecek etkili ilaçlar veya cerrahi teknikler bulunmamaktadır. Araştırmacılar, otizm ile nörolojik, gastrointestinal ve kanser hastalıklarının gelişme riskinin artması arasındaki ilişkiyi incelemiştir. Otizm ve kanser arasındaki ilişki hakkında kapsamlı bir araştırma ise net olarak ortaya konmamıştır. Bununla birlikte, otizmle ilgili kanser riskinin bu özel yönüne bakmak, genlere ve yollara özellikle dikkat etmek önemlidir. Makalenin amacı, otizm ile kanser arasındaki olası bir ilişkiye dair mevcut kanıtları literatürdeki çalışmalar ışığında inceleyerek bütüncül bir bakış açısı sunmaktır.

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INTRODUCTION

In recent years, there has been a notable rise in the prevalence of autism. According to early research, there are 4.5 incidences of autism spectrum disorder (ASD) for every 10.000 live births. According to recent statistics from the US Centers for Disease Control and Prevention (CDC) network, 1 in 54 babies will have ASD in 2020 (1). According to the World Health Organization (WHO), autism is estimated to impact about 1% of the global population. The estimated prevalence ASD in Türkiye is thought to be around 1 in 54 children. However, comprehensive and large-scale epidemiological data is still lacking. While this estimate aligns with global trends, further research is needed in Türkiye to gain a more accurate understanding of autism prevalence (2). A collection of developmental issues known as ASD may surface in the early stages of infancy. People with ASD have a wide range of symptoms and levels of impairment, which is why it is referred to as a "spectrum" disease. The persons in question display repetitive behaviors, have limited areas of interest and may have difficulties with interpersonal contact in Autism spectrum disorders (1). Copy number variations (CNVs), epigenetic changes, and double hit mutations have been found as contributory factors in the development of ASD in affected people. Significant contributions to the issue include variables such as environmental exposures and gender-related risk factors (3). Also, gastrointestinal symptoms have been seen in a majority of individuals diagnosed with autism (4), and many studies have shown the presence of different relationships with a few different diseases in individuals with ASD (5). One of the research areas is the examination of the relationship between autism and cancer development. Cancer, a disease with a long history, has been the subject of treatment efforts dating back to the ancient Egyptian civilization (6). Cancer is a collection of illnesses distinguished by the unregulated proliferation and dissemination of atypical cells (7). Based on a research investigation, it has been shown that females exhibiting signs of ASD tend to possess a higher probability of having a familial background associated with the occurrence of ovarian, uterine, and prostate cancer. Furthermore, studies have shown an increased risk of uterine and breast cancer in mothers of autistic children. Additionally, they are genetically predisposed to uterine and ovarian cancer (8). Many studies have discovered many susceptibility loci connected to potential oncogenes and tumor suppressor genes, which are common genetic variants associated with autism (9). Furthermore, it is well known that copy number changes in autistic people are often connected to genes associated with cancer risk (10). In contrast to the general population, a study examining the potential association between people with autism and their susceptibility to cancer discovered a higher cancer incidence among autistic patients (11). Through the application of molecular genetics and developmental biology, researchers have identified 21 genes in this domain that are most likely to have a significant impact on the onset and manifestation of a number of neuropsychiatric illnesses, including bipolar disorder, schizophrenia, and autism. Furthermore, some types of cancer and neurological conditions, including Parkinson's and Alzheimer's, have also been linked to the development and progression of these genes. A substantial increase in the frequency of oncogenic mutations has been seen in those diagnosed with ASD, also known as autism (9). On the other hand, a small number of studies have shown a significant reduction in the incidence of cancer in people with autism but a significant increase in the rates of gene mutation. The observation that there are shared mutations and signaling pathways across common genes and proteins implies that findings from genetic research in the domain of cancer might potentially have therapeutic implications for autism (11). The objective of this study is to analyze previous research that explores the potential similarities in the mechanisms behind two illnesses and to evaluate the implications of such similarities for the treatment of autism based on existing literature.

EPIDEMIOLOGICAL STUDIES

In epidemiological research examining the etiology of mortality in individuals with autism, findings have indicated that the incidence of cancer-related deaths was 1.9 among participants with mild or no cognitive impairment as a comorbidity, but it was 2.9 among those with moderate, severe, or profound cognitive impairment. Nevertheless, it is worth noting that the study in question primarily focused on groups with an average age of about 15 years. Therefore, researchers have suggested that further research should be conducted with a cohort with a higher average age (12). Further research undertaken throughout the 2000s aimed to examine the epidemiological associations between the occurrence of autism and the risk of cancer in the United States. The study concluded that there exists a strong correlation between the incidence of autism and breast cancer rates (13). In a separate investigation, scholars discovered a correlation between women exhibiting autistic symptoms and a higher prevalence of ovarian, uterine, and prostate cancer within their familial lineage (8).

This finding suggests that variations in people may be influenced by the specific form of cancer. Multiple studies have shown a possible correlation between autistic disorder and an increased susceptibility to cancer, with differences seen among various types of cancer (14, 15). An analysis of data from Taiwan's National Health Insurance and Registry for Catastrophic Illness Patients, encompassing 8438 individuals diagnosed with ASD between 1997 and 2011, identified 20 cases of cancer within this cohort. Elevated cancer rates were observed, particularly in the 15–19 age group, while no significant changes were noted in other age categories. The study found a higher-than-expected incidence of genitourinary cancers, specifically ovarian and testicular cancers, in individuals with autism. Additionally, three individuals were diagnosed with acute myeloid leukemia (AML), two of whom also had either testicular or ovarian cancer. These findings suggest a potential association between autism and an increased risk for certain types of cancer, particularly in the genitourinary system (11).

However, it is important to note that this study was limited to a small sample size, and further research is needed to confirm these observations. Additionally, future studies should also explore the underlying mechanisms that may contribute to this relationship (16). A population-based study in Sweden investigated the potential association between ASD and cancer risk. After analyzing data from more than 2 million people, researchers found that people with ASD have an increased risk of cancer, especially those with narrow autistic disorder or comorbid conditions such as intellectual disability or congenital defects (14).

COMMON RISK GENES AND PATHWAYS IN AUTISM AND CANCER

Several recent studies have presented empirical data indicating the presence of genetically mediated effects that together impact the susceptibility to cancer, autism, and other neurological disorders (17, 18). There may be a link between autism and cancer because of genetic mutations and changes in developmental-metabolic pathways. This could help us understand how these different illnesses are connected. A study compares embryonic Neurodevelopmental Diseases (NDD)-associated mutations to cancer mutations throughout adulthood and examines how these differences affect clinical outcomes. A statistical framework and network analysis were used to find ASD and cancer mutations and disease-specific networks and pathways. Results show signaling strength's therapeutic potential: In cancer, robust signaling promotes cell proliferation, but in ASD, moderate signaling modulates differentiation. Research shows that autism increases the risk of cancer, but NDD reduces the risk of hazardous gene alterations. NDD and cancer share proteins, pathways, and mutations, yet the data show distinctions. Clinical effects also depend on signaling intensity. These findings illuminate the NDD-cancer relationship (19).

A recent study has shown a correlation between oncogene and genetic anomalies that affect the genes responsible for suppressing the PI3K-AKT-mTOR growth signaling pathway (20, 21). The PI3K/AKT/mTOR signaling pathway plays a crucial role in regulating several cellular activities, such as cell growth, proliferation, differentiation, motility, survival, metabolism, and protein synthesis. Components of the PI3K pathway govern synaptic growth and plasticity in the brain. Hence, any disturbance in this system leads to synaptic dysfunction and the emergence of atypical behaviors (22). Furthermore, activation of the PI3K-Akt-mTOR pathway has been firmly associated with the proliferation of several forms of human cancer. A study provides evidence for a causal link between dysregulated eIF4E and the development of ASD, specifically the eIF4E-dependent translational control of neuroligins (NLGNs) and its impact on the excitatory/inhibitory (E/I) balance. The study also suggests that targeting downstream mTOR signaling, specifically eIF4E, 4E-BP2, and NLGNs, may provide a therapeutic benefit for individuals with ASD. The findings suggest that understanding abnormal synaptic protein synthesis and downstream mTOR signaling is crucial in the development of potential treatments for ASD (23).

Fibroblast growth factors (FGFs), known for their pivotal role in cancer, contribute to tumor progression via many mechanisms (24). Research shows that Phosphatase and Tensin Homolog (PTEN) has a higher mtDNA copy number among hamartoma tumor syndrome (PHTS), ASD and cancer. These findings suggest that mtDNA may modify PHTS phenotypes. Future studies need to better understand how mtDNA affects the development of ASD and cancer. These findings are considered an important step toward better predicting the cancer and ASD phenotypes of mtDNA in PHTS individuals (25). A different study analyzed 800 autism genes and 3500 ASD and cancer genes. These genes were analyzed using the VarElect phenotypic software and GeneAnalytics. They found 138 genes associated with ASD and malignancy. GeneAnalytics shows that colorectal, breast, and prostate cancer are most often connected to common genes.

Signal transduction pathways like GPCR and ERK also affect super-pathways linked to common genes. Gene expression regulation mechanisms in gene ontology biological activities were connected to ASD and cancer. The Gene Ontology molecular functions category linked ASD and cancer to protein binding and kinase activity. Both discoveries improve our understanding of the genetic relationship between ASD and cancer, enabling the development of new treatments and approaches. These unexpected similarities between ASD and cancer may lead to future research and treatment advances (26). A study has shown that PTEN-ASD and PTEN-cancer mutations have different effects on the conformational dynamics that arise due to CTT (carboxy-terminal tail) phosphorylation. CTT phosphorylation has different effects on structural flexibility, distant residue contacts, and allosteric communication patterns. In addition, CTT phosphorylation appears to provide a mechanistic basis for allosteric regulation in PTEN-ASD and PTEN-cancer mutations, suggesting a novel approach as a potential therapeutic modality for individuals with various PHTS mutations as allosteric target sites (27). Researchers looked at the molecular and phenotypic traits of germline heterozygous PTEN mutant carriers with ASD. They found that PTEN-ASD patients had cognitive and white matter impairments, and their processing speed and working memory were severely slowed down (28).

Also, mutations in the PTEN gene have been linked to Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Cowden syndrome (CS). These syndromes are associated with ASD and may be associated with cancer risk. Metabolic alterations in the tricarboxylic acid (TCA) cycle have been investigated in individuals associated with PTEN gene mutations. These changes differ between the genotypes and phenotypes of individuals. Specifically, certain metabolites, such as isocitrate, citrate, and lactate, have been associated with clinical features in various ways. Furthermore, it has been emphasized that fumarate levels distinguish individuals with autism from individuals with cancer. These results demonstrate the importance of TCA cycle metabolite alterations in PTEN-related syndromes and autism. These changes could be used as therapeutic interventions or biomarkers (29).

A study has shown that FGF10 and FGF17 have the capability to function as prognostic markers for the survival of individuals diagnosed with AML. Moreover, they might be regarded as potential candidates for therapeutic intervention via the use of small-molecule inhibitors (9).

Scientists have recently achieved the effective generation of a genetically engineered mouse model by specifically deleting the FGF17 gene. FGF17 is a member of FGF gene family and is located in the chromosomal region 8p21.3. The mouse had abnormalities in the development of the frontal cortex and deficiencies in social interaction. Therefore, it is reasonable to think that this specific developmental abnormality might be a substantial contributing factor to certain presentations of autism, schizophrenia, and related disorders. It is noteworthy that the inactivation of the FGF17 gene, which is a therapeutic target in cancer, results in the manifestation of autistic symptoms in mice. This finding contradicts the concept that the FGF17 gene serves as a shared target gene between autism and cancer. Nevertheless, a growing body of data supports the notion that the theory proposing a shared route and gene-specific therapeutic interventions has considerable promise. A different study found that when the PTEN gene was deleted, it caused autism-like symptoms in mice. The PTEN gene stops tumors from growing and is the main inhibitor of PI3K-Akt signaling. These included diminished social interaction, heightened sensitivity to sensory stimuli, enlargement of neurons and the brain, excessive levels of activity, difficulties in cognitive processing, and impaired acquisition of social skills. This study provides evidence linking the aforementioned phenotypes to the presence of autism (30). The presence of germline and somatic PTEN loss-of-function mutations has been linked to the occurrence and progression of early-onset malignancies, such as breast, kidney, prostate, and brain tumors (31). When the PI3K-Akt-mTOR pathway is out of whack, it can have different effects on the body or development, depending on the tissue, stage of development, and type of cell (32). Therefore, in cells during mitosis (as well as in cancer cells), the process of upregulation may result in elevated rates of growth. However, in neurons that have completed mitosis, upregulation can trigger excessive translation, which in turn affects synaptic plasticity and behavior. This excessive translation has been associated with an elevated susceptibility to autism spectrum diseases (9, 33). Given that early detection of ASD has the potential to enhance the effectiveness of interventions, the identification of a dependable biomarker capable of detecting ASD in its early stages might facilitate the implementation of more precise and suitable treatment strategies for affected individuals. The association between Wingless/Integrated Pathway (Wnt) target genes and ASD has been shown (34). By this reasoning, genetic clusters of Wnt pathway genes might show the likelihood of ASD and offer a useful way to sort ASD cases based on how they affect the body and how their genes are expressed.

This would facilitate the early identification of the ASD phenotype. In addition, an examination and assessment may be conducted on some pharmaceutical substances that are recognized for their ability to modulate the Wnt signaling pathway. The objective would be to determine the potential efficacy of these medications in addressing the symptoms of ASD, drawing upon genetic investigations and biomarkers as supporting evidence (34, 35). Recent research has shown a link between the Adenomatous Polyposis Coli (APC) gene and the likelihood of acquiring autism. The APC gene is recognized for its ability to prevent tumor growth (36). Elevated expression of the APC gene has been shown in patients with schizophrenia, indicating a reduced vulnerability to cancer (37). Moreover, this mutation may possibly be associated with a heightened vulnerability to colorectal disease. A previous study has shown that the APC protein plays a vital role in the Wnt-dependent signaling cascade (38). Cancer and schizophrenia have been linked to other constituents of the Wnt pathway (39). Autism and cancer have been genetically linked to many transcription factors, such as ADNP, PAX5, FOXP1, TCF7L2, and TBLXR1 (31). These nuclear factors are located downstream of many important signal transduction pathways that are genetically associated with ASD and cancer, such as PTEN. This is worth mentioning (40). PTEN is a pivotal phosphatase in the AKT signaling pathway. The down-regulation of AKT necessitates engagement in physical activity. Nuclear PTEN also has an impact on the regulation of recombinational DNA repair, a crucial procedure for maintaining the integrity of the genome. The precise relationship between the signaling function of PTEN and its potential outcome as a result of separate PTEN activity remains unclear. However, this dual functionality may provide an explanation for the prominent involvement of PTEN in both cancer and autism.

In addition, neurofibromatosis type 1 (NF1) is an inherited neurocutaneous disorder associated with neurodevelopmental disorders, including ASD. It is the most common inherited tumor predisposition syndrome, affecting approximately 1 in 2500 to 3000 people worldwide. Individuals with NF1 are born with a germline mutation in the NF1 gene, but they can develop neurological problems ranging from inattention and autism to peripheral nerve sheath and brain tumors. A mutation in the NF1 tumor suppressor gene in the germline makes people with neurofibromatosis type 1 more likely to get some cancers and neurological disorders, such as intellectual disabilities and ASD (41-43).

IMMUNE SYSTEM, AUTISM AND CANCER RELATIONSHIP

Numerous studies have provided evidence indicating that there may exist a shared element of immunity in both neurodevelopmental disorders and cancer. During the process of embryonic development, there is a simultaneous development of both the immune and neurological systems (44). Signaling can make changes to the structure of chromatin and the accessibility of genes easier or harder. This can affect the levels of expression of important genes for neurodevelopment.

Dysregulated signaling in cancer may result from random somatic mutations occurring during an individual's lifetime. Neurodevelopmental disorders and cancer have several shared characteristics. Cancer is a pathological state characterized by unregulated cellular proliferation and division. Neurodevelopmental diseases are characterized by the dysregulation of cellular differentiation, leading to changes in cell lineage (45). Neurodevelopmental diseases and cancer have been shown to exhibit dysregulation of small GTPases, such as Toll-Like Receptors (TLRs), IL-1, GIT1, and FGFR signaling pathways (46). In contrast to cancer, neurodevelopmental problems do not often result in fatalities. However, the dysregulation of the mitogen-activated protein kinase (MAPK) pathway, which plays a crucial role in promoting cell proliferation in cancer, is a significant signaling route in both cases (47). The immune system can secrete cytokines, which in turn may stimulate the MAPK signaling pathway in brain cells (48, 49). During embryonic or germline mutations, abnormal signaling can cause changes in chromatin arrangement and gene accessibility within different types of embryonic brain cells. These changes can affect the expression levels of important genes involved in neurodevelopment. Given that cancer primarily arises from sporadic mutations and neurodevelopmental disorders, which are predominantly caused by germline mutations, it is expected that the chromatin organization and accessibility of cancer cells will vary across different cell types and developmental stages of the embryo (50). Hence, despite the similarities in the pathways involved, there is a divergence in the phenotypic results. The primary functions of immunity include the prevention of infections and the facilitation of cell damage repair. Both processes require the release of cytokines. Within the context of cancer, the immune response has the capacity to either induce apoptosis in cancerous cells or facilitate their survival.

Both factors are not relevant in the context of neurodevelopmental disorders. Cytokines have the potential to modulate both the intensity and length of a given signaling pathway in both cancer and neurodevelopmental diseases. Various cell types exhibit distinct sets of accessible genes, resulting in differential protein involvement within certain pathways. Nevertheless, it is worth noting that chromatin accessibility has the potential to explain both phenomena. It is well known that proteins from the innate immune system, such as Toll-like receptors, cytokines, inflammasomes, and phagocytic signals, play a key role in brain development (51). Hence, the impaired functionality of innate immune signaling pathways might potentially be linked to neurodevelopmental diseases, including autism and schizophrenia.

Emerging research underscores a significant relationship between ASD and cancer, revealing shared dysregulation in critical signaling pathways such as MAPK, which plays a pivotal role in both neurodevelopment and oncogenesis (14). Understanding this connection is crucial because it highlights the intricate biological linkages that may underlie both conditions, suggesting that advances in one area of research could inform prevention and treatment strategies in the other. This connection not only deepens our understanding of these complex conditions but also emphasizes the need for comprehensive strategies to reduce the risk of both ASD and cancer, particularly through early intervention.

Early screening for genetic and immune markers is essential because it enables targeted interventions that could modulate immune responses and prevent the onset of these conditions (28). Identifying individuals at risk before symptoms manifest allows for the implementation of personalized preventive strategies, potentially mitigating the progression of both ASD and cancer. Additionally, promoting a healthy environment during pregnancy and early childhood, while minimizing exposure to environmental toxins, is vital in lowering the incidence of ASD and related cancers (8). Environmental factors, including nutrition and exposure to toxins, have been increasingly recognized as significant contributors to the risk of both ASD and cancer, making public health initiatives in this area critically important.

Raising public awareness about the link between ASD and cancer is of paramount importance for several reasons. First, awareness fosters informed decision-making among parents, healthcare providers, and policymakers, which can lead to more effective screening, early diagnosis, and timely intervention strategies. Early intervention is crucial, as it can significantly alter the trajectory of ASD and reduce the long-term burden of the disorder on individuals and their families. Second, increasing awareness can drive research and funding, which are essential for developing better prevention and treatment options. Without adequate public and scientific attention, the opportunities to explore novel therapies that could address both ASD and cancer may be missed.

The need for awareness also stems from the societal and economic impact of these conditions. ASD is a lifelong condition that affects not only the individual but also their family and community, often requiring extensive support and care. When coupled with the increased risk of cancer, the burden becomes even more significant. Therefore, it is imperative to engage in public health campaigns that emphasize the importance of early intervention, healthy lifestyle choices, and the reduction of environmental risks. These campaigns should aim to educate communities about the potential connections between ASD and cancer, dispelling myths and encouraging proactive health behaviors.

To effectively build awareness, multidisciplinary research should be encouraged to explore the connections between ASD and cancer, focusing on the shared biological mechanisms and potential therapeutic targets. Policies should be advocated to support early screening, genetic testing, and environmental protections, as these measures are critical for reducing the incidence of both conditions. Additionally, public health initiatives must prioritize the dissemination of information through awareness campaigns that educate communities about these links. Such initiatives should stress the importance of early intervention, the adoption of healthy lifestyle choices, and the need for ongoing research to improve outcomes for individuals affected by both ASD and cancer. By understanding the relationship between ASD and cancer, and by raising awareness, we can not only improve the quality of life for those affected but also potentially prevent the development of these conditions through early and targeted interventions. The importance of this issue cannot be overstated, as it has the potential to impact public health on a broad scale, reduce healthcare costs, and enhance the well-being of countless individuals and their families.

CONCLUSION AND RECOMMENDATIONS

Genetic characteristics related to autism may increase cancer risk, according to many studies. Thus, conclusions may be drawn, and more research may be suggested to reduce this risk. For instance, several genes, epigenetic factors, and developmental variants linked to autism may also cause cancer. Genomic imprinting or growth pathway control may facilitate these methods. Another option is to reevaluate and investigate several pharmacological approaches that have shown promise in treating autism (52) for cancer therapy, with a focus on targeting common growth signaling pathways. In addition, the idea of using or adapting drugs developed for targeted cancer therapies for neurological disorders such as autism is also very promising. In Türkiye, no large-scale and specific study on this subject has been found in the literature. In conclusion, further epidemiological research is needed to assess autism and family cancer risks

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