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Association between Autism Spectrum Disorder and Cancer - a Review from the Literature

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Review article

Abstract

Introduction: Autism spectrum disorder (ASD) is neurodevelopmental polygenic disorder with strong genetic component. In the adult period, it is associated with many chronic diseases including diabetes, hypertension, cardiovascular disease, and cancer.

The **aim** of this article is to show possible connection between autism spectrum disorder and some kinds of cancers, and to show the possible pathways for prevention and treatment.

Methodology: The PubMed and Google Scholar databases were searched using the keywords: autism spectrum disorder, genetics, cancer, prevention and treatment.

Results: Autism spectrum disorder is associated with high rates of genomic aberrations, including chromosomal rearrangements and de novo copy-number variations. Autism and cancer share 43 risk genes, suggesting that common mechanisms underlying the functions of some of these genes could conceivably be leveraged to develop therapies not just for cancer but for autism as well. Pleiotropy, whereby gene variants exert effects on multiple phenotypes, has been the source of increasing research attention with ASD and cancer.

Germline loss-of-function PTEN mutations increase the rate of benign and malignant tumours and also manifest as ASD and macrocephaly.

Conclusion: There might be an association between autism and specific forms of cancer, not in the pathophysiologic mechanism, but only in involvement of certain genes in certain forms of cancer. Further epidemiologic research in large populations is needed to elucidate the association between autism and cancer and identify explanatory factors. Approved drugs targeting oncogenic pathways might also have therapeutic value for treating autism spectrum disorder.

Keywords: autism spectrum disorder, cancer, genetics, prevention, treatment

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1. Introduction

Autism Spectrum Disorder (ASD) is a polygenic disorder with predominant genetic ethology that is becoming more common. ASD is characterized by impairment in social interaction and communication, restricted and repetitive behaviours. It affects up to 2% of the world population (Lord et al., 2018). Genetic studies shows high heritability for autism spectrum disorder especially in twin studies, with a range

of 50–90% concordance between monozygotic twins, compared with 0–30% between dizygotic twins and siblings, and a high male: female ratio (Bourgeron, 2015). Pleiotropy, whereby gene variants exert effects on multiple phenotypes, has been the source of increasing research attention with ASD, and other health conditions, such as cancer (Crespi, 2011). Cancer may occur at a variety of different ages and locations in the body. Cancer occurs when cells grow out of control. Treatment usually includes surgery, chemotherapy, and radiation and a variety of side effects may be present because of both cancer and its harsh treatments (American Cancer Society, 2024).

Individuals with ASD may be at higher risk of developing cancer early in life, but this risk seems largely related to the presence of co-occurring birth defects or intellectual disability, according to new findings. While autism spectrum disorder and cancer may appear entirely unrelated, there is actually a significant amount of overlap within the genetic components associated with each condition. Some authors specify that cancer and autism may share some genetic structure. For example, within their research, Gabrielli, Manzardo, and Butler identified approximately 800 genes linked to autism spectrum disorder and approximately 3,500 genes linked to various cancers. In total, 138 of these genes were shared between the two (Gabrielli, Manzardo, and Butler, 2019). Individuals with autism may display increased risk for some types of cancer including brain, kidney, thyroid, and pancreatic cancers. In contrast, individuals with ASD may display protective factors against some types of cancer including lung and prostate cancers (Forés-Martos, et. al, 2019).

Previous studies have reported that children with ASD possess a higher number of genetic aberrations, including higher levels of chromosomal rearrangements (Vorstman et al., 2006) and copy number variations (Szatmari et al., 2007). These studies raise the possibility that there may be correlations to cancer, a disease in which chromosomal aberrations are known to play a role.

ASD is comorbid with several monogenic neurodevelopmental disorders, including Fragile X (*FMR1*), Rett syndrome (*MECP2*), Phelan-McDermid (*SHANK3*), 15q duplication syndrome (*UBE3A*), neurofibromatosis (*NF1*), tuberous sclerosis (*TSC1* and *TSC2*), and Cornelia de Lange syndrome (*NIPBL* and *SMC1A*) (Crawley, Heyer, & LaSalle, 2016).

The **aim** of this article is to show possible connections between autism spectrum disorder and some kinds of cancers, and to show possible pathways for prevention and treatment.

2. Methodology

It is internet-based research. The PubMed and Google Scholar databases were searched using the keywords: autism spectrum disorder, genetics, cancer, prevention and treatment. It was made review and critical analysis of the relevant published literature.

3. Results

Recent studies provide evidence for genetically mediated effects that jointly influence risk of cancer, autism, and other neurodevelopmental disorders. The evidence comes from 4 lines of studies: 1. recent developmental models for the types of genetic, epigenetic, and environmental factors that mediate the ethology of autism, 2. epidemiological studies of cancer risk in relation to autism, 3. genetic-association and molecular genetic studies demonstrating that mutations in tumour suppressor genes, and in other negative regulators of growth-stimulating signal-transduction pathways, are associated with the development of syndromic and idiopathic autism, and 4. altered risk of cancer in other neurological disorders, including schizophrenia, Alzheimer's, and Parkinson's disease (Crespi, 2011).

Some epidemiological studies on large cohorts of patients with neurodevelopmental disorders showed an increased risk for cancer compared to the general population. In one study, a standardized incidence ratio model was applied to a cohort of 8438 patients with autism retrieved from the Taiwan National Health Insurance database during 1997-2011. It implicated an increase in cancers of the genitourinary system and ovary among children and young adults (Chiang et al., 2015). Increased cancer risk was also observed in a population-based study among 2.3 million individuals with ASD from Nordic countries during 1987-2013 with co-occurring birth defects, including intellectual disability (Liu et al., 2022).

Autism spectrum disorder is associated with high rates of genomic aberrations, including chromosomal rearrangements and *de novo* copy-number variations. These observations are reminiscent of cancer, a disease where genomic rearrangements also play a role. It is important to note that individuals with autism can also get cancer. Until we learn more about lessening the severity of autism symptoms that may be caused by a cancer or by cancer treatment, a variety of challenges may be present for an individual with autism presenting to a healthcare facility needing to be treated for cancer. Some difficulties they may encounter may include: trauma, sensory concerns, communication difficulties, behavioural outbursts, repetitive motor movements, and being out of routine (Dell et al., 2008). Autism and cancer share 43 risk genes, suggesting that common mechanisms underlying the functions of some of these genes could conceivably be leveraged to develop therapies not just for cancer but for autism as well. Pleiotropy, whereby gene variants exert effects on multiple phenotypes, has been the source of increasing research attention with ASD and cancer (Kao et al., 2010).

Autism spectrum disorder is comorbid with several monogenic neurodevelopmental disorders, including Fragile X (*FMR1*), Rett syndrome (*MECP2*), Phelan-McDermid (*SHANK3*), 15q duplication syndrome (*UBE3A*), neurofibromatosis (*NF1*), tuberous sclerosis (*TSC1* and *TSC2*), and Cornelia de Lange

syndrome (*NIPBL* and *SMC1A*). (Crawley, Heyer, & LaSalle, 2016).

Cancer is usually a disease of aging, caused by somatic mutations. ASD a developmental disorder, is usually linked to germline malfunctions. It was a surprise when autism studies started picking out genes in pathways typically associated with cancer. In several instances, the crossover emerged in much the same way it did with Cowden syndrome. Neurofibromatosis and tuberous sclerosis are directly associated with tumours, but such tumours are benign and rarely associated, if at all, with malignancies. However, mutations in NF1, TSC1, or TSC2 enhance the risk for developing cancer. NF1, TSC1, and TSC2 function like PTEN in the AKT pathway of mTOR control. Mutations in transcriptional factor genes also mediate downstream signalling pathways that include key proteins implicated in cell proliferation or differentiation pathways implicated in cancer and autism, such as mTOR, RAS GTPases, MAP kinases, AKT, EIF4E, WNT, ERK, PI3K, and CHD8. A risk gene originally identified in individuals with cancer may present as a de novo mutation in a small number of individuals with ASD, or maybe implicated in ASD through analysis of interrelated genes and interacting proteins, such as within a signalling pathway (Martincorena, & Campbell, 2015). Germline loss-of-function PTEN mutations increase the rate of benign and malignant tumours and also manifest as ASD and macrocephaly. Mutations in TSC1 and TSC2 genes cause tuberous sclerosis complex which is characterized by cortical tubers, and neurocognitive phenotypes including epilepsy, ASD, and intellectual disability (ID). (Darbro, et al., 2016). Tuberous sclerosis complex (TSC) is an autosomal dominant disorder resulting from mutations in the *TSC1* or the *TSC2* gene. Neurologic involvement occurs in more than 90% of individuals and comprises several distinct lesions. Seizure disorders are present in 70%–90% of patients and often develop within the first year of life. Developmental and behavioural disorders, including autism spectrum disorders (ASD), are also frequently diagnosed in TSC (Numis et al., 2011). PTEN is a tumour suppressor gene that acts as a key negative regulator of PI3K-AktmTOR signalling (Butler et al., 2005). Deactivation of PTEN in a mouse model resulted in reduced social interaction, increased responsiveness to sensory stimulation, neuronal hypertrophy and macrocephaly, hyperactivity, resistance to handling, and impaired social learning, all phenotypes associated with autism (Kwon et al., 2006). Germline and somatic PTEN loss of function mutations have been associated with the incidence and development of early onset cancers, including cancers of the breast, kidney, prostate, and brain (McBride et al., 2010).

ASD encompasses a broad range of putative causes, symptom presentations, and outcomes, including both macrocephaly and microcephaly, suggesting deficits in the cellular commitment to proliferation versus differentiation, like cancer. This difference may be in the life stage of cellular proliferation. Errors associated with genome maintenance during fatal life may occur at critical time periods for proliferation of neuronal precursors that affect prenatal brain development, resulting in neurodevelopmental disorders, whereas errors more commonly occur during adult life in cell types susceptible to tumours. Biological mechanisms with potential commonalities between genes implicated in both cancers and autism may be revealed from closer investigation of the specific actions of genes and converging pathways identified in both (Pinto, et al., 2014). UBE3A, which is duplicated in approximately 1–2% of ASD, encodes the ubiquitin E3 ligase protein E6-AP, first named as an E6 interacting protein that degrades p53 in human cervical cancer (LaSalle et al., 2015).

ASD has been associated with mutations in the gene eIF4E (eukaryotic translation initiation factor 4E), which codes for a protein that functions in the rate limiting step of eukaryotic translation initiation, downstream of the PI3K-Akt-mTOR pathway (Neves-Pereira et al., 2009). Such mutations involve increased promotor activity, suggesting increased activity of the gene and pathway upregulation. High expression of eIF4E in many cancers has motivated the recent development of chemotherapeutic agents to reduce its activity (Fischer, 2009).

A large cohort of autism and cancer genes affect genome maintenance, including DNA repair factors (*ERCC6* and *SMARCA2*), structural chromosome components, such as cohesions (*NIPBL*, *SMC1A*, and *SMC2*), factors needed for Alternative Lengthening of Telomeres (*ATRX*), and post-translational modifiers (*TRIP12, UBE3A*, and *HERC2*). The functional overlap goes beyond this common gene set, because genomes from individuals with ASD show mutational hotspots and a high incidence of copy number variations. These genetic events signal pathological outcomes of DNA replication stress.

Many neuron-specific genes are rather large, with primary transcripts in the Mbp range. These genes are at particular risk for transcription–DNA replication conflicts that underpin a significant amount of genome instability (Aguilera, & Garcia-Muse, 2013). While such genes are typically transcribed only in terminally differentiated cells, any miscoordination of transcriptional control, DNA replication, differentiation, and cell cycle phasing will greatly increase the risk of mutations targeted to these genes encoding critical brain functions. Transcription coupled repair, the pathway defined by *ERCC6*, is of particular importance for terminally differentiated cells
and long transcription units.

Overall, too little is known about DNA repair in terminally differentiated cells and more studies are needed to evaluate other pathways, such as recombinational DNA repair in differentiated cells and somatic genomic instability in neurons. Thus, like cancer, the inherited risk for autism may be compounded by further somatic mutations associated with

mutations in known risk genes that may be biased for genes with neuronal functions (Crawley, Heyer, & LaSalle, 2016).

4. Discussion

Autism and cancer are two distinct conditions that affect individuals in different ways. While some studies have suggested a link between autism and cancer, the two disorders are not directly comparable in terms of prevalence. Autism spectrum disorder is considered a relatively common condition, with estimates suggesting that 1 in 36 children in the United States has this disorder (CDC, 2023). On the other hand, cancer is less common, with an estimated lifetime risk of developing cancer being around 38% for men and women combined. There are many different types of cancer, each with its own prevalence rates. Some types of cancer, such as breast cancer or prostate cancer, are more common than others. While both autism and cancer can have significant impacts on individuals and their families, it is important to understand the differences between these conditions and to seek appropriate support and treatment for each.

While the studies suggest a link between autism and cancer, correlation does not necessarily equal causation. It is possible that the link between the two conditions is due to other factors such as genetics or environmental factors. Additionally, the studies do not provide a clear understanding of why there may be a link between autism and cancer.

While there is no guaranteed way to prevent either condition, leading a healthy lifestyle can help reduce the risk. Eating a balanced diet, exercising regularly, avoiding smoking and excessive alcohol consumption can all help reduce the risk of developing both cancer and autism.

CNVs identified among children evaluated in an autism diagnostic clinic are clinically significant. The fact that the microdeletions and duplications at the same loci have been found in tissue from malignant neoplasms supports the possibility that gene disruption caused by copy number changes that are associated with autism spectrum disorder and craniofacial dysmorphism can also affect carcinogenesis. Knowing that an individual has an increased susceptibility to cancer is a potential long-term benefit of the utilization of comparative genomic hybridization technology in children with autism and developmental delay (Gannon et al., 2013). Providing care to children, adolescents and adults with cancer requires communicating effectively in an age- and development-specific way. With the increase in the complexity of healthcare systems and sophistication of available cancer therapies, individuals with neurodevelopmental challenges, including autism spectrum disorders (ASD), constitute a particularly vulnerable group for disparities in access and outcomes. Oncology providers need to become progressively more educated to the challenges posed by caring for the ASD population and have the necessary tools to implement effective communication and favourable environments for screening, diagnosis and therapy of cancer in this setting. Giving providers (medical, nursing and affiliated staff) the opportunity of improving their care of individuals with ASD is a global priority. In the absence of higher-grade evidence, they are intended as a call for vigilance of the particularities of these highly vulnerable individuals. (Vuattoux et al., 2021). In one study exploration of the mutations, reconstructed disorder specific networks, pathways, and transcriptome levels and profiles of autism spectrum disorder (ASD) and cancers, point to signalling strength as the key factor: strong signalling promotes cell proliferation in cancer, and weaker (moderate) signalling impacts differentiation in ASD (Yavuz et al., 2023). In this article the role of epigenetics and the post-translation modifications in both disorders is not analysed and that could be a topic for another article.

There are a number of strategies that can be implemented and encouraged by family members, medical staff, occupational therapists, or psychologists. They include following:

- **Coping skills** – deep breathing, progressive muscle relaxation, sensory awareness.
- **Visual schedules and tools** – Provide visuals for things such as schedules, pain rating scales, and labelling needed items.
- **Social stories** – utilized to teach procedures, explain cancer, or prepare for changing events.
- **Positive reinforcement** – provide rewards and praise for good behaviour and treatment compliance.
- **Reduce sensory stimulation** – turning off lights, utilizing a white noise machine, turn off TV, reduce various fabric textures.
- **Staff consistency** – As much as possible, keep staff consistent so that staff can learn unique needs and the patient can become familiar with the staff.
- **Family suppor**t – Allow family in the medical room as much as possible in order to provide support for the patient.

The interconnected relationship between autism and cancer invites further investigation in the pathogenesis of these two disorders, and it warrants a pharmacological basis of treatment. Although invasive drugs and treatments exist for many types of cancer, a drug is yet to be successfully developed to prevent the onset or progression of ASD symptomology.

Neurodevelopment and oncogenesis are multi-step processes, and it is possible that signalling through the same cellular proliferation pathways can have different effects depending on embryological timing, as well as cell type, and mitotic status. Perhaps the most exciting implication here is that interventions are already underway to target cellular pathways shared by many of the mutated genes (Darbro, et al., 2016). One possible medication for PTEN mutation and ASD is Rapamycin, a compound that blocks the mTOR pathway, halts these behavioural problems and seizures.

Rapamycin and related compounds have been shown to prevent the overgrowth of brain cells that leads to macrocephaly and autism-like behaviours in mice lacking PTEN (Boulay, & Lane, 2007). Rapamycin treatment suppressed S6 phosphorylation in valproic acid-exposed mice. Aberrant gene expression was associated with social interaction deficits in valproic acid-exposed mice. Rapamycin may be an effective treatment for non-syndromic ASD in adolescent and adult patients who present impairments in the mTOR signalling pathway (Kotajima-Murakami et al., 2019).

Some authors reported the beneficial effects of enviroximes on autism and attention-deficit hyperactivity disorder (ADHD) symptoms in a group of patients with tuberous sclerosis complex. This drug inhibits mTOR, one of the top 30 super-pathways identified with high scores when comparing shared autism and cancer genes. It is a treatment for TSC in which autism is a finding, along with renal angiomyolipoma's and astrocytoma's. The drug reduced tumour growth, decreased seizures, and improved autistic, ADHD, and depression symptoms. However, there is a paucity of studies on the effects of this drug on neuropsychiatric symptoms, which merit further consideration. Treatment would be a new avenue to pursue and further explore, particularly in those
with ASD, the involvement of shared autism and cancer-related genes (Kilincaslan et al., 2017).

Early detection through regular check-ups and screenings can improve outcomes for both conditions. Understanding any potential links between autism and cancer can help researchers develop new treatments and therapies for both conditions. Regarding cancer prevention there is ongoing COST Action number 21123 entitled "Cancer-Understanding Prevention in Intellectual Disabilities" or shortly CUPID. It is a networking opportunity, which promotes pan European collaboration and indeed, collaboration with stakeholders beyond the European Union. The aim of the COST CUPID Action is to facilitate European stakeholders (researchers, clinicians, advocacy groups, careers and service users) and stakeholders outside of Europe to address an important health and social justice issue – the full recognition and rights of people with intellectual disabilities and autism spectrum disorders as well to access and receive cancer prevention services to equalise their outcomes as part of the general population (Wells, 2023). People with intellectual disabilities and autism spectrum disorder are often underrepresented in cancer prevention and screening policies or have limited access to these services, both of which lead to health disparities and unfavourable health outcomes in this population. Based on the acquired evidence and examples of good practice, CUPID action will provide recommendations for improvement to policy makers across Europe. Participants will benefit from interdisciplinary knowledge exchange and gaining new research skills during the lifetime of the project. By stimulating collaboration between people and organizations and using an interdisciplinary approach, it will build capacity to address the issues of health inequalities for people with intellectual disabilities and autism spectrum disorder. This will increase the network's visibility and have a stronger impact on stakeholders and policy makers, which is particularly important for smaller and EU candidate countries, translating these efforts into a sustainable impact on cancer prevention and equity of access to screening (Vukovic et al., 2023).

5. Conclusions

There is probably an association between autism and specific forms of cancer. Genes encoding nuclear proteins involved in epigenetic functions were frequently shared between cancer and ASD, implicating the importance of aberrant gene regulation in both conditions. The increased cancer risk among individuals with ASD is likely mainly attributable to co-occurring ID and/or birth defects in ASD. Additional research on specific cancer types, perhaps through multinational efforts, should be considered to gain a better understanding of the burden of different cancer types among individuals with ASD and such comorbidities. Further epidemiologic research in large populations is needed to elucidate the association between autism and cancer and identify explanatory factors. Approved drugs targeting oncogenic pathways might also have therapeutic value for treating autism.

The findings raise questions that might have implications for new ways of treating both cancer and ASD. For example, could the genetic variants that seem to provide protection against cancer in people with ASD, be exploited to develop new anticancer treatments? Or could current cancer drugs
that target the genetic pathways found to overlap with ASD also be useful for treating ASD? This last question is already being pursued by other scientists in clinical trials testing the potential benefits of anti-cancer drug for autism patients.

Stratifying individuals with ASD who harbour a risk gene for autism that is also a risk gene for cancer may enable therapeutic development of personalized medicines based on the specific causal mutation. Continued follow-up is required to examine the risk of cancers diagnosed in later life among individuals with ASD, regardless of the presence of comorbidities, as the etiologist of cancers diagnosed in later life likely differ from those diagnosed in early life. Further research is needed to improve our understanding of the impact of cancer – and its therapy (incl. supportive care) on individuals with ASD, which in turn shall help to develop instruments/strategies reliably measuring quality and outcomes in this population during their cancer care trajectory.

Conflict of Interests

The author serves as Editor-in-Chief of the journal but had no role in the editorial handling or peer-review process of this manuscript.

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