Vulnerability and Protection: Integrative Literature Review on the Contrasting Risk of Leukemias and Solid Tumors in Down Syndrome

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Vulnerabilidade e Proteção: Revisão Integrativa da Literatura sobre o Risco Contrastante de Leucemias e Tumores Sólidos na Síndrome de Down

Vulnerabilidad y Protección: Revisión Integradora de la Literatura sobre el Riesgo Contrastante de Leucemias y Tumores Sólidos en el Síndrome de Down

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ABSTRACT

Introduction: Down syndrome (DS), characterized by trisomy of chromosome 21, is associated with an increased risk of leukemia and a reduced incidence of solid tumors. **Objective:** To analyze the epidemiological patterns and molecular mechanisms that explain the increased susceptibility to leukemias and protection against solid neoplasms in individuals with DS. **Method:** Seventeen studies with different designs were selected, totaling 62,121 individuals. **Result:** The overall prevalence of cancer was 2.02%, with 1.18% of leukemias (predominantly AML and ALL) and 0.22% of solid tumors (testicular cancer being the most common). The standardized incidence ratio (SIR) was low for solid tumors (0.69), with especially low values for lung (0.10), skin (0.24), and breast (0.35). In contrast, there was an increased risk of testicular (SIR: 4.28) and liver (SIR: 3.72) cancer. From a molecular point of view, the GATA1 mutation was found in virtually all cases of AML in DS, while increased expression of tumor suppressor genes, such as RCAN1 and DYRK1A, may explain the lower incidence of solid tumors in this population. **Conclusion:** It is concluded that DS presents a unique oncological profile, with a specific predisposition to leukemias in childhood and protection against solid neoplasms, especially in adulthood.

Key words: Down syndrome/complications; Leukemia/epidemiology; Neoplasms/genetics; Genetic Predisposition to Disease.

RESUMO

Introdução: A síndrome de Down (SD), caracterizada pela trissomia do cromossomo 21, está associada a risco aumentado de leucemias e redução da incidência de tumores sólidos. **Objetivo:** Analisar os padrões epidemiológicos e os mecanismos moleculares que explicam a susceptibilidade aumentada a leucemias e a proteção contra neoplasias sólidas em indivíduos com SD. **Método:** Foram selecionados 17 estudos de diferentes delineamentos, totalizando 62.121 indivíduos. **Resultado:** A prevalência global de câncer foi de 2,02%, sendo 1,18% de leucemias (predomínio de LLA e LMA) e 0,22% de tumores sólidos (câncer testicular como o mais comum). A razão de incidência padronizada (SIR) foi reduzida para tumores sólidos (0,69), com valores especialmente baixos para pulmão (0,10), pele (0,24) e mama (0,35). Em contrapartida, houve aumento de risco para câncer testicular (SIR: 4,28) e hepático (SIR: 3,72). Do ponto de vista molecular, a mutação GATA1 foi encontrada em praticamente todos os casos de LMA em SD, enquanto a expressão aumentada de genes supressores de tumor, como RCAN1 e DYRK1A, pode explicar a menor incidência de tumores sólidos. **Conclusão:** Conclui-se que a SD apresenta um perfil oncológico singular, com predisposição específica a leucemias na infância e proteção contra neoplasias sólidas, especialmente na vida adulta.

Palavras-chave: Síndrome de Down/complicações; Leucemia/epidemiologia; Neoplasias/genética; Predisposição Genética para Doença.

RESUMEN

Introducción: El síndrome de Down (SD), caracterizado por la trisomía del cromosoma 21, se asocia con un mayor riesgo de leucemia y una menor incidencia de tumores sólidos. **Objetivo:** Analizar los patrones epidemiológicos y los mecanismos moleculares que explican la mayor susceptibilidad a las leucemias y la protección contra neoplasias sólidas en individuos con SD. **Método:** Se seleccionaron diecisiete estudios con diferentes diseños, con un total de 62 121 individuos. **Resultado:** La prevalencia general de cáncer fue del 2,02%, con un 1,18% de leucemias (predominantemente LMA y LLA) y un 0,22% de tumores sólidos (siendo el cáncer testicular el más común). La razón de incidencia estandarizada (SIR) fue baja para los tumores sólidos (0,69), con valores especialmente bajos para pulmón (0,10), piel (0,24) y mama (0,35). En contraste, se observó un mayor riesgo de cáncer testicular (SIR: 4,28) y hepático (SIR: 3,72). Desde un punto de vista molecular, la mutación GATA1 se encontró en prácticamente todos los casos de LMA en el síndrome de Down, mientras que el aumento de la expresión de genes supresores de tumores, como RCAN1 y DYRK1A, podría explicar la menor incidencia de tumores sólidos. **Conclusión:** Se concluye que el síndrome de Down presenta un perfil oncológico único, con una predisposición específica a las leucemias en la infancia y protección contra las neoplasias sólidas, especialmente en la edad adulta.

Palabras clave: Síndrome de Down/complicaciones; Leucemia/epidemiología; Neoplasias/genética; Predisposición Genética a la Enfermedad.

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INTRODUCTION

Down syndrome (DS) arises from trisomy of chromosome 21 (T21), it is the most prevalent aneuploidy in human beings at an incidence rate of one in each 600 – 1,000 global births and is associated with various clinical comorbidities as hematological disorders and specific oncologic predisposition[2]. Individuals with DS are at a significant high risk of acute leukemias, including megakaryoblastic leukemia (MKL) which encompasses transient forms (TL) or pre-leukemias and acute megakaryoblastic leukemia (AMKL) corresponding to acute clinical manifestation, being observed a 10-20-fold growth or more compared to children without DS[3].

Curiously, from the epidemiological perspective, the incidence of solid tumors in individuals with DS is remarkably small than the overall population with biological motives suggesting an intrinsic protection connected to the increased gene expression of chromosome 21[4,5]. Robust epidemiologic studies reveal a global prevalence of cancer in DS around 2% with leukemias accounting for approximately 1.18% and solid tumors of only 0.22%, being testicular cancer the most frequent solid type for this population[1,4].

A comprehensive analysis involving more than 34 thousand individuals with DS observed that the incidence of solid tumors in this population is around 95 cases per 100 thousand individuals/year, a frequency considerably low when compared to the overall population. The standardized incidence ratio (SIR) for all solid tumors was 0.69 with confidence interval between 0.51 and 0.94, indicating a substantially reduced risk. Among the specific types of cancer with low occurrence are breast (SIR: 0.35), skin (SIR: 0.24), lung (SIR: 0.10) and female genital tract (SIR: 0.44). On the other hand, there are important exceptions: tumors on the testicles and liver have high incidence rates with SIR of 4.28 and 3.72, respectively. These results reinforce that, although there is a protective pattern against solid neoplasms, certain organs remain vulnerable in individuals with T21[6].

From the molecular perspective, the predisposition to leukemias in DS is related to somatic mutation of GATA1 present in almost all the cases of MKL together with additional mutations in genes JAK2 and CRLF2 in ALL[5,6]. The pathogenesis of DS associated leukemias involves a multi-phase models that starts with an overlap of genes of chromosome 21 followed by primary mutations (e.g., GATA1), rearrangements in CRLF2 and mutations in JAK2. The evolution of these neoplasms follows the multi-hit evolution somatic model where T21 creates a permissive genetic environment, promoting transcriptional deregulation, genes overexpression and hematopoietic instability. In addition to this initial context, primary mutational events (mutation GATA1) and, later, secondary genetic alterations that contribute to the clonal expansion and progression to frank leukemia. This model implies in a gradual and cumulative evolution trajectory of genetic events, characteristic of DS associated pediatric leukemias[7-10].

On the other hand, the protective profile against solid tumors has been associated with the triplication of tumor suppressor genes as Ets2 and RCAN1, that inhibit tumoral angiogenesis, promoting regulation of apoptosis and stromal microenvironment[4,11]. Evidences indicate yet the influence of microRNAs located on the critical region of T21 as well as alterations in the immune and metabolic system, reducing the vulnerability to the tumoral development in many organs[4].

The thorough understanding of the epidemiologic differences and molecules involved is essential to guide customized tracking strategies and improve therapeutic protocols since children with DS present differential toxicity to chemotherapy as well as specific prognostic profiles, especially MKL with 5-year survival above 90% and less favorable outcomes[10] in ALL.

In face of this context, the goal of this study is to gather, summarize and critically analyze the scientific knowledge available so far in individuals with DS, integrating studies with different methodological designs, attempting to respond to the following research question: "which genetic, molecular and epidemiological factors contribute to increase the predisposition to leukemias and to the apparent protection against solid tumors of individuals with DS?"

METHOD

Integrative literature review to allow the inclusion of quantitative epidemiologic studies and qualitative theoretical and molecular analyzes that elucidate the oncologic particularities of individuals with DS.

The review followed the six stages proposed by Whittemore and Knafl[12]: problem identification, search criteria, categorization of the studies selected, critical evaluation of the studies included, interpretation and synthesis of the data and presentation of the results.

The literature search was performed on the electronic databases: PubMed/MEDLINE, Scopus, Web of Science, Embase and SciELO utilizing the following descriptors in English and Portuguese: "Down Syndrome", "Leukemia", "Solid Tumors", "Cancer", "Neoplasms", "Epidemiology", "Risk", "Genetics", "MicroRNAs", "Angiogenesis", "Gene Dosage". Specific terms "MicroRNAs" and "Angiogenesis" were included because it was necessary to identify studies

investigating specific molecular mechanisms subjacent to the predisposition to leukemias and protection against solid tumors in individuals with DS. These terms allowed to capture evidences related to genetic regulation, signaling pathways and cellular factors involved in the differential oncogenesis of this population.

The search strategy combined terms utilizing operators AND and OR according to PICO adapted to the integrative review: Population (P): individuals with DS; Intervention/Exposure (I): presence of genetic, molecular, immune or epidemiologic factors associated with neoplasms; Comparator (C): population without DS and Outcomes (O): incidence, prevalence or risk of leukemias and solid tumors and their molecular and clinical characteristics.

Original studies, systematic reviews and meta-analyzes published between 2000 and 2025 addressing incidence, prevalence or relative risk of leukemias and solid tumors in individuals with DS have been included, in addition to genetic, molecular or immune bases related to these oncologic patterns, studies with human samples, publications in English, Portuguese or Spanish, peer-reviewed studies published in journals.

Duplicate studies, abstracts, letters to the editor, opinion without scientific evidences, studies with animals specimen only or *in vitro* cellular models were excluded.

Two independent investigators selected the studies reading the titles, abstracts and later the full texts and discrepancies were settled by consensus. The data extracted included types of neoplasm (leukemia/solid tumor), type of study, target-population, country, main findings, genetic or molecular factors quoted and epidemiological estimates as SIR or prevalence.

The data were organized in summary charts and analyzed quantitatively allowing the comparison among studies and identification of patterns, gaps and recurring hypotheses in the literature. Statistics, whether present, were described as referenced by the authors, respecting the formulas and original indicators (CI 95%, *p*, OR, SIR). No additional statistical analysis was conducted in the study.

Because only secondary and deidentified data were utilized, the review and approval by the Ethics Committee was waived in compliance with Directive 510/2016 of the National Health Council[13]. However, all the sources utilized were found in peer-reviewed scientific journals and in compliance with ethical international research principles.

RESULTS

The review included 17 studies with quantitative and qualitative design, totaling a combined sample of 62,121 individuals with DS. The global prevalence of cancer in this population was estimated in 2.02% (CI 95%: 1.63–2.50). The prevalence of leukemia was 1.18% (CI 95%: 0.86–1.62) as primary outcomes with predominance of ALL, accounting for 0.86% followed by AMKL with 0.51%. Solid tumors were considered as secondary outcomes with prevalence of 0.22% (CI 95%: 0.12–0.43), being testicular cancer, the most common type identified in this group[14]. The studies selection process followed the criteria of literature integrative review, beginning with the identification of 1,310 articles in five databases: PubMed/MEDLINE (n = 410), Scopus (n = 372), Web of Science (n = 295), Embase (n = 198) and SciELO (n = 35). After duplicates removal, 972 articles were screened by title and abstract, 812 of which that did not meet the criteria were excluded. Next, 160 articles were fully read of which 143 were excluded due to the utilization of animal models or *in vitro* (n = 47), lack of relevant data on DS and cancer (n = 56), design out of the scope (letters, editorials) (n = 25) and redundant data (n = 15). Eventually, the final sample consisted in 17 studies included in the qualitative analysis (Figure 1)[15].

SIR estimates for solid tumors was 0.69 (CI 95% 0.51–0.94), indicating low frequency than the overall population. SIR for breast cancer was 0.35, 0.24 for skin and 0.10 for lungs. However, increased risk was observed for testicular tumors (SIR: 4.28; CI 95% 2.61–7.03) and liver (SIR: 3.72; CI 95% 1.09–12.75)[16].

A robust cohort study conducted with 3,530 individuals with DS and a reference cohort with 89,570 individuals-year, revealed different oncologic patterns associated with karyotype and age range. Most of the participants presented classic T21 (92.7%) followed by Robertsonian translocations (4.1%) and mosaicism (3.2%). The global risk of cancer in DS was not significantly different than the overall population (SIR: 0.84; CI 95%: 0.70–1.02), although an accentuated elevation in cases of leukemia and lymphomas have been observed (SIR: 5.5; CI 95%: 4.17–7.11) and a substantial reduction of solid tumors (SIR: 0.45; CI 95%: 0.34–0.59). This tendency was found in practically all the groups of solid tumors, standing out lung cancer (SIR: 0.10), skin (0.24), breast (0.16) and cervix (0.0). In counterpart, testicular cancer was the most prevalent than anticipated (SIR: 2.87), being diagnosed in 14 men with predominance of seminomas between 33 and 41 years of age. The risk of leukemia was extremely high in younger than 5-year children with SIR of 27 for ALL and 114 for AMKL. Although the incidence of solid tumors tends to approach the expected between 15 and 30 years of age, it drops drastically after 40 years old, reaching a SIR of 0.27 after 50 years old. Cumulative rates of lifelong cancer reinforce this pattern, with incidence of

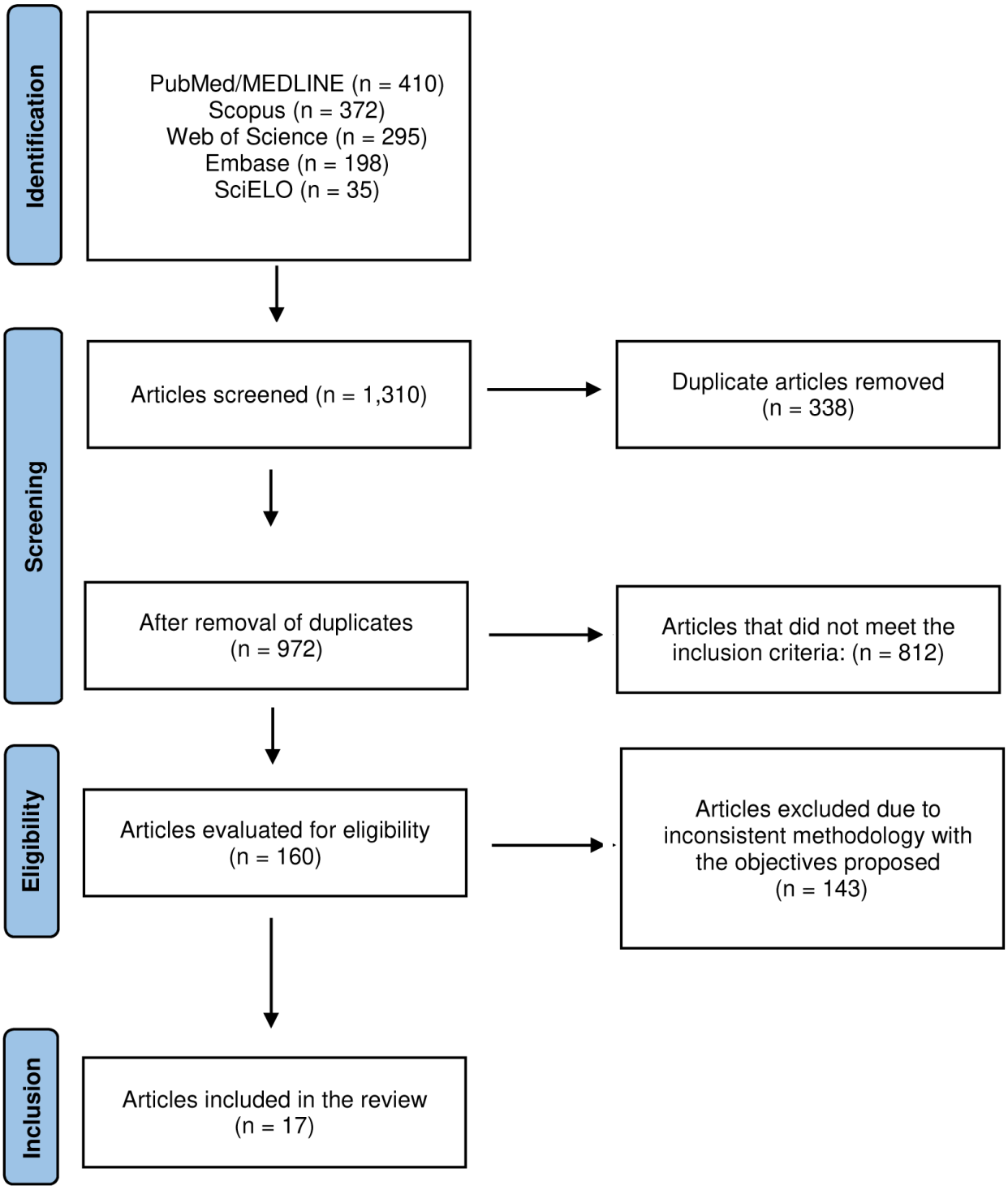

Figure 1. PRISMA flowchart of studies selection
Source: Adapted from PRISMA[15].

leukemias reaching 2.9% at 60 years old in individuals with DS *versus* 0.32% in the overall population and 5.0% of solid tumors *versus* 11.3%, respectively[17].

Hitzler et al.[18] investigated mutations of the gene GATA1, specifically in exon 2, in peripheral blood samples and bone marrow of patients with DS diagnosed with TL and MKL. Mutations in nine of 12 patients with TL and in all three patients with AMKL have been identified, consisting mainly of insertions and deletions that induce premature stop codons, resulting in truncated proteins of approximately 330 amino-acids. These mutated proteins lose the N-terminal transcriptional activation domain, essential for the normal function of GATA1 during erythroid and megakaryocytic differentiation.

The presence of the same mutations in samples obtained during TL and after progression to AMKL but absent after remission, suggests that AMKL appears from the clonal expansion of persistent TL. The findings support the multi-hit evolution model of leukemogenesis in DS where T21 provides a permissive genetic context while the mutation GATA1 acts as starting event and later accompanied by additional cytogenetic anomalies in the progression to frank malignancy. These mutations were not found in individuals with DS reinforcing their specific role in leukemogenesis associated with T21.

In contrast with the high incidence of childhood leukemia, studies show that the rate of occurrence of the neoplasm in adults with DS is considerably small, especially in common epithelial tumors at advanced ages as colon, prostate and breast. A study involving older than 50 years women with T21 showed that no breast or colorectal cancers have been identified, reinforcing the hypothesis of protection against epithelial carcinogenesis. Genomic data obtained by studies with biopsies and molecular analyzes showed the increased expression of tumor suppressor genes located in chromosome 21 as RCAN1 and DYRK1A, involved in the inhibition of the signaling pathway of VEGF (angiogenesis), in addition to the modulation of the apoptosis via NFAT (NFATC1–C4) and calcineurin. This increased gene expression is correlated with resistance to formation of favorable tumor microenvironment in solid tissues[18].

The results show that the global prevalence of cancer in individuals with DS was 2.02 %, standing out leukemias (1.18 %) with low incidence of solid tumors (0.22 %)[14,16]. These data corroborate the literature indicating elevated risk for leukemias – between 10 and 20-fold higher for ALL and until 150-fold higher for AMKL than children without DS – while confirming the rarity of epithelial tumors typical of adult age. The predominance of leukemia in the population analyzed with ALL of 0.86% and AMKL of 0.51% is consistent with studies describing a cumulative risk of nearly 2.0% until five years of age and 2.5 % until 30 years old, reinforcing the clinical impact of this neoplasm in *infantile* DS[19].

The low incidence of solid tumors in individuals with DS shown by a global SIR of 0.69 has been consistently demonstrated in multigenerational cohort studies. These studies reveal still lower SIR for specific types of cancer as breast, skin and lung whose incidence are 0.35, 0.24 and 0.10, respectively. In some cases, certain types of cancer weren't even detected in these populations, suggesting a complete absence of occurrence. These data reinforce robustly the hypothesis that there is a specific genetic protection mechanism associated with DS that confers resistance to the development of solid tumors. This protection can be related to T21 own genetic properties as the overexpression of tumor suppressor genes, in addition to changes of the cellular microenvironment, regulation of the cellular cycle and pathway of apoptosis. These factors appear to contribute synergically to a remarkable reduction of the risk of solid neoplasm in this population, in contrast with higher susceptibility to certain types of leukemia, which highlights the complexity of the interaction between genetics and oncogenesis in DS[20].

Increased risk of testicular (SIR: 4.28) and liver (SIR: 3.72) tumors observed in the present study are consistent with former reports describing enhanced sensitiveness of germinative and liver cells in DS, suggesting selective susceptibility in these tissues[14,16,17]. In addition, lower risk of solid tumors in older than 50 years adults with reduced SIR of 0.27 without cases of breast or colorectal cancers was observed, revealing a potential prolonged protection until later stages of life[16,19].

The ubiquity of mutation GATA1 in cases of AMKL associated with DS (ML), present in more than 90% of the cases, confirms the characteristic molecular pattern, marked by progression of TL to ML in the majority of the cases until five years of age[18]. The molecular analysis reinforces the model of multiple mutations where the combination between GATA1 and the gene triplication by DS is essential for the leukemic transformation, corroborated by studies that also identify additional targets as JAK2 and CRLF2 in ALL[19]. The enhanced expression of tumor suppressor genes as RCAN1 and DYRK1A, able to inhibit VEGF–calcineurin–NFAT signaling allows a plausible mechanism for observed protection against solid tumors according to experiment in murine models and human induced pluripotent stem cells (iPSC)[20].

The functional duality of DYRK1A – pro-leukemic in childhood and antitumor in adulthood – highlights the pleiotropic character of these genes as observed by Malinge et al. in murine models[21] and confirmed in broader studies about immune and inflammatory functions connected to cancer[19].

The limitations of the integrative review are the combination of heterogeneous methodology of the original studies, lack of comparable longitudinal data and not running its own statistical analyzes. However, the strengthening of molecular and epidemiologic evidence was highlighted, suggesting future studies targeted to specific genes interactions in DS, longitudinal adults cohorts, clinical tests to prevent MKL and specific screening strategies for testicular and liver cancers.

CONCLUSION

The findings of this integrative review confirm that DS is associated with a unique neoplastic profile where it is observed an expressive predisposition to the

development of acute leukemia, mainly in childhood and a substantial reduction in the incidence of solid tumors. This affirmation reinforces the importance of considering DS not only as a genetic condition, but also as a model of study to understand oncogenesis and tumor resistance mechanisms.

According to the objectives proposed, it was possible to identify and quantify the relative risks for different types of cancer in individuals with DS. Leukemia, especially ALL and ML was the most prevalent, while solid tumors as breast, lung, skin and colon presented rates significantly lower than those observed in the overall population. Testicular and liver tumors, though solid, contrast with this tendency and presented increased risk, indicating selectiveness of the susceptibility pattern.

In addition to describing the epidemiologic distribution, this study allowed to explore the main molecular genetic mechanisms implied in this differentiated oncologic behavior. The mutation GATA1, virtually present in all cases of ML was highlighted as a determinant factor for the progression of leukemia in DS. Similarly, the genes overexpression located in chromosome 21 as RCAN1 and DYRK1A, was pivotal to protect against the formation of solid tumors by inhibiting associated pathways with angiogenesis and cellular proliferation.

The presence of these specific molecular characteristics contributes to the understanding of the processes that favor or inhibit the development of several types of cancer with significant implications for translational medicine. For instance, understand how T21 acts as tumor suppressor mechanism can inspire new therapeutic strategies for other populations, especially in diseases related to angiogenesis and unregulated growth.

The data have also demonstrated that age range exerts relevant influence over the neoplastic patterns. Children with DS present extremely elevated risk of leukemia while adults, especially those older than 50 years rarely develop common epithelial neoplasms as breast, prostate and colorectal. This implies in the necessity of lifetime different clinical and screening approaches targeted as a priority to hematologic neoplasms in childhood and special attention to testicular and liver tumors in all ages.

This study does not only responds to the initially designed objectives but also emphasizes the necessity of incorporating genetic knowledge in clinical/epidemiological management of patients with DS. Risk stratification based on molecular profiles can benefit both early diagnosis and customization of therapeutic protocols, particularly considering the increased sensitiveness of patients with DS to certain chemotherapeutic agents.

Notwithstanding its contributions, this review has limitations as heterogeneous methodological design of the studies included and absence of quantitative meta-analyzes. However, its integrative character favored a broad analysis of the available evidences and a holistic and updated perspective on the theme.

DS is a natural model of modulation of oncologic risk with important implications for the understanding of the biology of cancer. The knowledge consolidated herein indicates the urgency of future studies focused to the individual genetic characterization, development of target therapies and refinement of the clinical guidelines of oncologic care of individuals with DS. At the same time, these findings can lead to advances applicable to the overall population, especially in prevention and control of solid tumors.

CONTRIBUTIONS

Igor Gabriel Araújo Medeiros contributed substantially to the conception and design of the study, acquisition and interpretation of the data, writing and critical review. Francylene Malheiros Macedo da Cunha Rego contributed to the critical review. Both authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

DATA AVAILABILITY STATEMENT

All content underlying the text is contained in the manuscript.

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REFERENCES

1. Rabin KR, Whitlock JA. Malignancy in children with trisomy 21. Oncologist. 2009;14(2):164-73. doi: https://doi.org/10.1634/theoncologist.2008-0217

2. Hasaart KAL, Bertrums EJM, Manders F, et al. Increased risk of leukaemia in children with down syndrome: a somatic evolutionary view. 2021;23:e5. doi: https://doi.org/10.1017/erm.2021.6

3. Baruchel A, Bourquin JP, Crispino J, et al. Down syndrome and leukemia: from basic mechanisms to clinical advances. Haematologica. 2023;108(10). doi: https://doi.org/10.3324/haematol.2023.283225

4. Fosu K, Quarshie JT, Sarpong KAN, et al. Inverse Comorbidity between down syndrome and solid tumors:

insights from in silico analyses of down syndrome critical region genes. Genes (Basel). 2023;14(4):800. doi: https://doi.org/10.3390/genes14040800

5. Mason NR, Cahill H, Diamond Y, et al. Down syndrome-associated leukaemias: current evidence and challenges. Ther Adv Hematol. 2024;15:20406207241257901 doi: https://doi.org/10.1177/20406207241257901

6. Taherifard E, Taherifard E, Bouffet E, et al. Solid tumor incidence and patterns in individuals with down syndrome: a systematic review and meta-analysis. Pediatr Blood Cancer. 2025;72(8):e31775. doi: https://doi.org/10.1002/pbc.31775

7. Clemente AB, Ferreira BA, Carneiro LMF, et al. Risco aumentado de leucemia em crianças com síndrome de Down: mini revisão integrativa. RESU. 2024;12(supl2):179-84.

8. Gu Z, Izraeli S. All about down syndrome all. Blood. 2023;142(2):126-8. doi: https://doi.org/10.1182/blood.2023020508

9. Barwe SP, Kolb EA, Gopalakrishnapillai A. Down syndrome and leukemia: an insight into the disease biology and current treatment options. Blood Rev. 2024;64:101154. doi: https://doi.org/10.1016/j.blre.2023.101154

10. Lupo PJ, Schraw JM, Desrosiers TA, et al. Association between birth defects and cancer risk among children and adolescents in a population-based assessment of 10 million live births. JAMA Oncology. 2019;5(8):1150-8. doi: https://doi.org/10.1001/jamaoncol.2019.1215

11. Sussan TE, Yang A, Li F, et al. Trisomy represses ApcMin-mediated tumours in mouse models of down's syndrome. Nature. 2008;451:73-5. doi: https://doi.org/10.1038/nature06446

12. Whittemore R, Knafl K. The integrative review: update methodology. J Adv Nurs. 2005;52(5):546-53. doi: https://doi.org/10.1111/j.1365-2648.2005.03621.x

13. Conselho Nacional de Saúde (BR). Resolução nº 510, de 7 de abril de 2016. Dispõe sobre as normas aplicáveis a pesquisas em Ciências Humanas e Sociais cujos procedimentos metodológicos envolvam a utilização de dados diretamente obtidos com os participantes ou de informações identificáveis ou que possam acarretar riscos maiores do que os existentes na vida cotidiana, na forma definida nesta Resolução [Internet]. Diário Oficial da União, Brasília, DF. 2016 maio 24 [acesso 2025 abr 7]; Seção 1:44. Disponível em: http://bvsms.saude.gov.br/bvs/saudelegis/cns/2016/res0510_07_04_2016.html

14. Satgé D, Seidel MG. The pattern of malignancies in down syndrome and its potential context with the immune system. Front. Immunol. 2018;9(3058):1-6. doi: https://doi.org/10.3389/fimmu.2018.03058

15. Page MJ, Moher D, Bossuyt PM, et al. Prisma 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160. doi: https://doi.org/10.1136/bmj.n160

16. Moretti NR, Silva ABN, Guimarães LV, et al. The prevalence of solid tumors and hematologic malignancies among patients with down syndrome: a systematic review and meta-analysis. Crit Rev Oncol Hematol. 2025;205:104558. doi: https://doi.org/10.1016/j.critrevonc.2024.104558

17. Hasle H, Friedman JM, Olsen JH, et al. Low risk of solid tumors in persons with Down syndrome. Genet Med. 2016;18(11):1151-7. doi: https://doi.org/10.1038/gim.2016.23

18. Hitzler JK, Cheung J, Li Y, et al. GATA1 mutations in transient leukemia and acute megakaryoblastic leukemia of down syndrome. Br J Haematol. 2003;101(11):4301-4. doi: https://doi.org/10.1182/blood-2003-01-0013

19. Baek KH, Zaslavsky A, Lynch RC, et al. Down's syndrome suppression of tumour growth and the role of the calcineurin inhibitor RCAN1. Nature. 2009;459(7250):1126-30. doi: https://doi.org/10.1038/nature08062

20. Krieg S, Krieg A, Loosen SH, et al. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Cancers. 2024;16(6):1103. doi: https://doi.org/10.3390/cancers16061103

21. Malinge S, Bliss-Moreau M, Kirsammer G, et al. Increased dosage of the chromosome 21 ortholog dyrk1a promotes megakaryoblastic leukemia in a murine model of down syndrome. J Clin Invest. 2012;122(3):948-62. doi: https://doi.org/10.1172/jci60455

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