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Temporal Trends and Sociodemographic Determinants of Multiple Primary Cancers in Individuals Aged 0 to 24 Years: Analysis of the SEER Program (1975-2022)

Tendências Temporais e Determinantes Sociodemográficos de Cânceres Primários Múltiplos em Indivíduos de 0 a 24 Anos: Análise do Programa SEER (1975-2022)

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ABSTRACT

Background: Multiple primary cancers (MPCs) represent an emerging challenge in pediatric and young adult oncology, influenced by genetic, environmental, and iatrogenic factors. Understanding temporal trends and associated determinants is essential for cancer surveillance strategies and integrated care planning. **Objective:** To analyze the epidemiological profile and factors associated with multiple primary cancer diagnoses in individuals aged 0-24 years registered in the SEER database (1975-2022). **Methods:** Retrospective, population-based observational study following STROBE guidelines. Data from 65,535 individuals diagnosed with primary malignant tumors between 1975 and 2022 were analyzed. The outcome was defined as presence of multiple primary diagnoses of malignant cancer. Binary logistic regression and Poisson regression with robust variance were employed to identify associated factors, estimating odds ratios (OR) and β coefficients with 95% confidence intervals. **Results:** The prevalence of MPCs was 7.1% (n=4,635). Significant differences were identified for sex, race/ethnicity, age group, and year of diagnosis (p<0.001). Female sex (OR=1.33), older age (OR=3.11 for 20-24 years vs. 0 years), and earlier diagnosis years showed positive association with MPCs. A marked temporal decline was observed, from approximately 15% (1975-1985) to 2% (2015-2022). **Conclusion:** Female sex and advanced age are independent predictors of MPCs. The progressive temporal reduction reflects improvements in diagnostic accuracy, standardization of coding criteria, and therapeutic advances with reduced iatrogenic toxicity. These findings support differentiated surveillance strategies and continued investment in less toxic therapies for long-term cancer survivors.

Keywords: Multiple primary neoplasms; Childhood cancer; Adolescent and young adult oncology; Cancer epidemiology; SEER Program.

Resumo

Introdução: Os cânceres primários múltiplos (CPMs) representam um desafio emergente na oncologia pediátrica e de adultos jovens, influenciados por fatores genéticos, ambientais e iatrogênicos. Compreender as tendências temporais e os determinantes associados é essencial para as estratégias de vigilância oncológica e o planejamento de cuidados integrados. **Objetivo:** Analisar o perfil epidemiológico e os fatores associados ao diagnóstico de cânceres primários múltiplos em indivíduos de 0 a 24 anos registrados no banco de dados SEER (1975-2022). **Métodos:** Estudo observacional, retrospectivo, de base populacional, seguindo as diretrizes STROBE. Foram analisados dados de 65.535 indivíduos diagnosticados com tumores malignos primários entre 1975 e 2022. O desfecho foi definido como a presença de múltiplos diagnósticos primários de câncer maligno. Regressão logística binária e regressão de Poisson com variância robusta foram empregadas para identificar os fatores associados, estimando razões de chances (RC) e coeficientes β com intervalos de confiança de 95%. **Resultados:** A prevalência de CPMs foi de 7,1% (n=4.635). Diferenças significativas foram identificadas para sexo, raça/etnia, faixa etária e ano de diagnóstico (p<0,001). O sexo feminino (RC=1,33), a maior faixa etária (RC=3,11 para 20-24 anos vs. 0 anos) e os anos de diagnóstico mais antigos apresentaram associação positiva com os CPMs. Observou-se um marcado declínio temporal, de aproximadamente 15% (1975-1985) para 2% (2015-2022). **Conclusão:** O sexo feminino e a idade avançada são preditores independentes de CPMs. A redução temporal progressiva reflete melhorias na precisão diagnóstica, na padronização dos critérios de codificação e nos avanços terapêuticos com redução da toxicidade iatrogênica. Esses achados apoiam estratégias de vigilância diferenciadas e o investimento contínuo em terapias menos tóxicas para sobreviventes de câncer a longo prazo.

Palavras-chave: Neoplasias primárias múltiplas; Câncer infantil; Oncologia do adolescente e adulto jovem; Epidemiologia do câncer; Programa SEER.

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INTRODUCTION

Cancer remains one of the leading causes of global morbidity and mortality, with increasing impact on health systems and the quality of life of affected individuals. It is estimated that in the United States, approximately 50% of men and 33% of women will be diagnosed with some type of neoplasm during their lifetime.[1,2] The age range from zero to 24 years encompasses childhood (0 to 10 years), adolescence (10-19 years, according to the World Health Organization - WHO), and young adulthood (15-24 years, according to the United Nations - UN). In this population, cancer continues to present significant clinical and socioeconomic impact, being the leading cause of death by disease, particularly in economically disadvantaged regions. Therapeutic and diagnostic advances in recent decades have substantially increased survival rates but have also contributed to the increased occurrence of multiple primary cancers (MPCs), that is, the manifestation of two or more independent primary tumors in the same individual.[1,3] Among hematological malignancies, leukemia stands out as the most prevalent neoplasm in the pediatric age group, accounting for approximately 30% of childhood cancers and representing an important epidemiological marker of the cancer burden in this population, with documented incidence patterns across different Brazilian regions.[4]

The occurrence of MPCs represents a complex phenomenon influenced by genetic, environmental, and iatrogenic factors, including germline mutations, carcinogenic exposures, and late effects of chemotherapy or radiotherapy.[3,5] These cases are clinically and epidemiologically important as they are associated with greater morbidity burden, need for prolonged surveillance, and impacts on screening policies and cancer survivor follow-up.[5]

The Surveillance, Epidemiology, and End Results (SEER) Program, maintained by the National Cancer Institute (NCI), constitutes the primary source of population-based cancer data in the United States, with coverage initiated in 1973 and standardized criteria for collection, coding, and validation.[6] Beyond its use in multiple primary cancer research, SEER data have also been applied in comparative epidemiological analyses of cancer mortality across different countries and racial/ethnic groups, enabling temporal trend studies and cross-national comparisons of cancer outcomes.[7] The SEER multiple primary coding rules, more comprehensive than those of the International Agency for Research on Cancer (IARC), allow identification of MPC incidence patterns and risk factors across different age groups, sexes, and ethnicities.[8]

Despite this, there are important methodological gaps in the literature regarding temporal trends and sociodemographic determinants of multiple primary diagnoses, especially in younger age groups and in long historical series. Thus, understanding the evolution of frequency and factors associated with multiple diagnoses in SEER is essential to support cancer surveillance strategies, secondary prevention, and integrated care planning for cancer survivors. Therefore, the present study aimed to analyze the epidemiological profile and factors associated with the occurrence of multiple primary cancer diagnoses in the SEER database (1975-2022).

METHODS

This is an observational, retrospective, population-based study conducted according to STROBE Statement recommendations. The objective was to estimate the frequency and factors associated with the occurrence of multiple primary diagnoses in patients registered in the Surveillance, Epidemiology, and End Results (SEER) program, covering the period from 1975 to 2022.

Data were obtained from SEER Research Data, a program maintained by the National Cancer Institute (USA), which aggregates cancer registry records from multiple regions of the United States. SEER uses standardized methodologies for collection, coding, and consistency verification, ensuring high completeness and temporal comparability.

The target population comprised all incident cases of primary malignant tumors registered between 1975 and 2022. Individuals aged 0 to 24 years at the time of initial diagnosis were included, aiming to capture the pediatric and young adult spectrum. As this is a population-based study, the sample size corresponded to the census of available records. Therefore, no prior sample calculation was applied.

INCLUSION AND EXCLUSION CRITERIA

Records with valid information on the following were included:

i. Year of diagnosis (year_dx);
ii. Biological sex (sex);
iii. Race/ethnicity (race_recode);
iv. Age group at diagnosis (agegrp);
v. Number of malignant tumors (n_tumors_malig).

Observations with the following were excluded:

i. Missing year of diagnosis or outside the 1975-2022 interval;
ii. Missing essential information for outcome calculation;
iii. Duplicate, inconsistent, or incompletely coded records.

Initially, all incident malignant tumor records from 1975 to 2022 were identified in SEER Research Data. Subsequently, individuals aged 0 to 24 years at the time of initial diagnosis were selected. After this stage, the study eligibility criteria were applied, excluding: (i) records with missing year of diagnosis or outside the 1975-2022 interval; (ii) observations with missing essential information for outcome and/or covariate definition (sex, race/ethnicity, age group, and/or number of malignant tumors); and (iii) duplicate, inconsistent, or incompletely coded records. After the curation process and application of exclusion criteria, the analytical sample consisted of 65,535 eligible individuals.

VARIABLE DEFINITION

Primary outcome: Presence of multiple primary diagnoses in the same individual, defined hierarchically:

i. Native SEER variable (multi_primary = 1), when available; Secondary operational proxy based on number of malignant tumors ≥2 (n_tumors_malig ≥ 2).
ii. The outcome was coded as binary: one diagnosis (0) and more than one diagnosis (1).

INDEPENDENT VARIABLES:

i. Sex (male/female);
ii. Race/ethnicity (white, black, other origins, unknown);
iii. Age group (ordered categories: 0, 1-4, 5-9, 10-14, 15-19, and 20-24 years);
iv. Year of diagnosis (continuous).

DATA COLLECTION AND PROCESSING

Data were obtained from the SEER Research Data, 8 Registries, Nov 2024 Sub (1975–2022) [Ref. 38], a program maintained by the National Cancer Institute (USA). Data were extracted using SEER*Stat software (version 9.0.42) [Ref. 37] and organized in Stata 18.0 environment (StataCorp, College Station, TX, USA).

Curation stages:

1. Cleaning and typing: conversion of string variables to numeric format and label standardization;
2. Category recoding: normalization of categorical variables and creation of factor variables;
3. Outcome validation: cross-checking between multi_primary, seq_central, and n_tumors_malig;
4. Time series construction: annual aggregation of proportions of patients with multiple diagnoses, including filling of years without observations.

BIAS CONTROL

Strategies were adopted to mitigate biases related to:

i. Historical changes in SEER geographic coverage;
ii. Differences in diagnostic and coding criteria over decades;
iii. Reduced follow-up time in recent cohorts (underestimation of multiple tumors).

These limitations were mitigated through:

i. Use of hierarchical redundant outcome definition (native variable + proxy);
ii. Multivariate modeling adjusted for demographic and temporal covariates;
iii. Sensitivity analysis via Poisson model with robust variance.

STATISTICAL METHOD

Initially, descriptive characterization of the sample was performed, with presentation of categorical variables in absolute and relative frequencies, and continuous variables in mean and standard deviation. Participants were stratified into two groups: "one diagnosis" and "more than one diagnosis," according to the total number of registered primary tumors.

Comparisons between groups were conducted using Pearson's chi-square test for categorical variables and Student's t-test for continuous variables with normal distribution, complemented by the Mann-Whitney test in cases of asymmetry. Variables with statistical significance in bivariate analysis ($p < 0.05$) were included in multivariate models. To identify factors associated with the presence of multiple diagnoses, binary logistic regression was applied and, as a robustness measure, Poisson regression with robust variance, both estimating odds ratios (OR) and β coefficients with respective 95% confidence intervals (95% CI). The significance level adopted was 5% ($\alpha = 0.05$). Data were analyzed using Stata® software, version 18.0 (StataCorp, College Station, TX, USA).

MISSING DATA MANAGEMENT

Observations with missing essential data (year of diagnosis or outcome variable) were excluded. The race/ethnicity variable was maintained with an "Unknown" category to avoid loss of analytical power.

Multiple imputation method was not applied, since the percentage of missing data was less than 5% and its distribution did not show differential patterns between groups.

ETHICAL CONSIDERATIONS

Data used in this study were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program, maintained by the National Cancer Institute (NCI, USA). SEER provides public, secondary, and fully de-identified data, in compliance with current privacy regulations in the United States and the ethical principles of the Declaration of Helsinki.

As this involves an anonymous and public domain database, this study was considered exempt from review by a Research Ethics Committee/Institutional Review Board (IRB exemption), according to U.S. federal regulation 45 CFR 46.101(b)(4).

RESULTS

A total of 65,535 individuals were analyzed, of whom 7.1% (n = 4,635) presented more than one primary diagnosis, while 92.9% (n = 60,900) presented only one diagnosis. Male predominance was observed (52.8%) as well as white race (83.5%), with age distribution predominantly concentrated between 15 and 24 years.

In the comparison between groups, significant differences were identified for sex, race/ethnicity, age group, and year of diagnosis ($p < 0.001$ in all cases) (Table 1).

Female individuals presented a higher proportion of multiple diagnoses (8.1%) compared to males (6.1%). Among racial categories, the highest percentages of multiple diagnoses occurred among white individuals (7.4%) and those of other origins (6.1%), whereas cases classified as "unknown race" exhibited markedly lower prevalence (1.5%).

Age distribution demonstrated an ascending trend in the proportion of multiple diagnoses with advancing age: from 3.4% in 0-year-old children to 11.5% in individuals aged 20 to 24 years. Furthermore, a relevant temporal difference was observed: patients with multiple diagnoses presented a lower mean year of diagnosis (1993.6 ± 12.8) compared to single cases (1999.2 ± 13.4; $p < 0.001$), suggesting greater occurrence of multiple tumors in diagnoses made in previous decades.

Values expressed as absolute (n) and relative (%) frequencies. Differences between groups evaluated by Pearson's chi-square test for categorical variables and Student's t-test (or Mann–Whitney test, according to distribution) for continuous variables. SD: standard deviation; p: statistical significance level.

In multivariate analysis, it was observed that male sex presented lower odds of multiple diagnoses (OR = 0.75; 95% CI: 0.70–0.80; $p < 0.001$). Regarding race/ethnicity, individuals classified as "unknown" showed lower probability of being diagnosed with multiple tumors (OR = 0.31; 95% CI: 0.17–0.56; $p < 0.001$), while the "other" category showed a trend toward positive association (OR = 1.17; $p = 0.070$).

Age group exhibited a gradually increasing effect: compared to the reference group (0 years), the odds of multiple diagnoses were 1.50 times higher among 5–9 years, 2.16 times among 10–14 years, 2.47 times among 15–19 years, and 3.11 times among 20–24 years (all $p < 0.001$).

Table 1. Demographic and clinical characteristics of patients according to number of primary diagnoses, SEER 1975–2022.

Variable	One diagnosis	More than one diagnosis	p-value
Sex (%)			
Female	91.9	8.1	<0.001
Male	93.9	6.1	
Race/Ethnicity (%)			
Black	94.5	5.5	<0.001
Other (Ind./Asian/Pacific)	93.9	6.1	
White	92.6	7.4	
Unknown	98.5	1.5	
Age group (years) (%)			
0	96.6	3.4	<0.001
1–4	96.8	3.2	
5–9	95.1	4.9	
10–14	93.2	6.8	
15–19	92.2	7.8	
20–24	88.5	11.5	
Year of diagnosis (mean ± SD)	1999.25 ± 13.37	1993.57 ± 12.84	<0.001

Year of diagnosis presented an inverse association (OR = 0.97; p < 0.001), indicating a reduction in the probability of multiple diagnoses in more recent periods (Table 2).

Table 2. Factors associated with the presence of multiple primary diagnoses, adjusted binary logistic regression model.

Variable	OR (95% CI)	p-value
Sex (ref: Female)		
Male	0.75 (0.70–0.80)	<0.001
Race/Ethnicity (ref: Black)		
Other (Ind./Asian/Pacific)	1.17 (0.99–1.39)	0.700
Unknown	0.31 (0.17–0.56)	<0.001
White	0.95 (0.83–1.09)	0.505
Age group (ref: 0 years)		
1–4 years	0.97 (0.79–1.19)	0.759
5–9 years	1.50 (1.22–1.84)	<0.001
10–14 years	2.16 (1.77–2.62)	<0.001
15–19 years	2.47 (2.05–2.99)	<0.001
20–24 years	3.11 (2.58–3.76)	<0.001
Year of diagnosis	0.97 (0.97–0.97)	<0.001

Model adjusted for sex, race/ethnicity, age group, and year of diagnosis. Odds ratios (OR) with respective 95% confidence intervals (95% CI). The significance level adopted was p < 0.05. OR: odds ratio; 95% CI: 95% confidence interval; ref: reference category.

The negative coefficient for male sex (β = -0.26; p < 0.001) reinforces the lower relative risk (~23% lower) of multiple diagnoses compared to females. Age group remained the main independent predictor, with progressive elevation of risk, ranging from 47% (β = 0.39) in 5–9 years to 187% (β = 1.05) in 20–24 years.

Year of diagnosis maintained an inverse correlation (β = -0.026; p < 0.001), suggesting that the risk of multiple diagnoses decreases with each more recent year of notification.

These results indicate that sex, age, and year of diagnosis are independent determinants for the development of multiple primary tumors, while the race/ethnicity variable exerted marginal influence, without robust statistical significance (Table 3).

Table 3. Poisson regression with robust variance for factors associated with the presence of multiple primary diagnoses.

Variable	Coefficient (β)	p-value	Interpretation
Male	-0.26	<0.001	Lower risk (~77%)
Race "Other"	0.15	71	Trend toward higher risk
Race "Unknown"	-1.14	<0.001	Lower risk
Age group 5–9 years	0.39	<0.001	Risk increase (~47%)
Age group 10–14 years	0.72	<0.001	Risk increase (~106%)
Age group 15–19 years	0.85	<0.001	Risk increase (~134%)
Age group 20–24 years	01.05	<0.001	Risk increase (~187%)
Year of diagnosis	-26	<0.001	Risk reduction in more recent diagnoses

Poisson regression model with robust variance estimates. β coefficients, p-values, and interpretation of approximate relative risk. β: regression coefficient; p: statistical significance; 95% CI: 95% confidence interval.

Figure 1 demonstrates the declining temporal trend in the proportion of patients with multiple primary diagnoses registered in the SEER (Surveillance, Epidemiology, and End Results Program) database between 1975 and 2022. It is observed that in the initial decades of the historical series, especially between 1975 and 1985, approximately 10% to 15% of patients presented more than one diagnosis. From the mid-1990s onwards, this proportion began to decline consistently, reaching values below 5% after the year 2000, and stabilizing around 2% in the most recent periods (2015–2022).

This progressive reduction suggests improvement in registry accuracy and standardization of multiple primary tumor coding criteria over time. It is also plausible that clinical and methodological factors contribute to the phenomenon, including diagnostic and therapeutic advances, greater effectiveness in controlling initial tumors, and reduced follow-up time for patients diagnosed in more recent cohorts.

Overall, the graph demonstrates a structural change in the pattern of multiple diagnoses over five decades, reflecting both developments in epidemiological surveillance and progress in oncological clinical management.

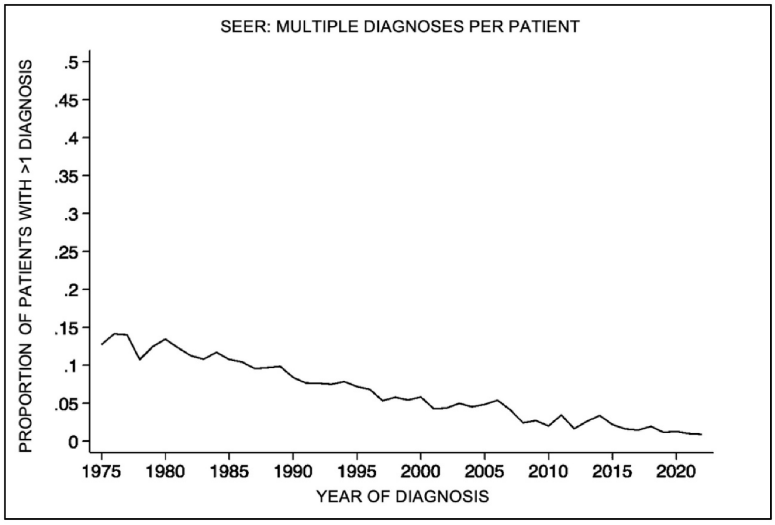

Figure 1. Temporal trend of the proportion of patients with multiple primary diagnoses in the SEER database, 1975–2022.

Annual proportion of patients with more than one primary diagnosis (proxy for multiple tumors). Values smoothed by simple annual average. SEER: Surveillance, Epidemiology, and End Results Program; prop.: proportion; p: statistical significance level.

DISCUSSION

The present study analyzed a cohort of 65,535 individuals diagnosed with cancer between 0 and 24 years of age in the SEER database (1975-2022), identifying a prevalence of 7.1% of multiple primary diagnoses (MPDs) of malignant cancers. This rate aligns with the spectrum reported in the literature, although direct comparison is challenging due to crucial methodological variations. For example, studies in Korea and the Netherlands reported slightly lower incidences (2.3% and 3.7%-4.8%, respectively).[9,10] This discrepancy is largely attributable to the multiple primary coding rules employed. Factors related to different population genetic backgrounds may also have contributed to the observed prevalence differences. Additionally, SEER uses more comprehensive criteria than those of the International Agency for Research on Cancer (IARC), which results in greater case detection and, consequently, higher prevalence estimates.[8,11] This methodological difference underscores the need for international standardization to allow reliable comparisons between population registries.

The results of multivariate analysis demonstrated that female sex and older age at diagnosis are independent predictors of MPDs. The higher prevalence in women (8.1% versus 6.1% in men) represents a notable finding, as it contrasts with the overall cancer incidence, which is consistently higher in men for most shared anatomical sites.[12,13] This contrasts with findings observed in other cancer types; for example, in lung cancer epidemiology, male sex has been identified as an independent predictor of mortality risk (OR=2.07; 95%CI: 1.16–3.69), reinforcing the notion that the influence of sex on cancer outcomes is tumour-type and age-group specific.[14]

The higher proportion of multiple primary diagnoses observed in females cannot be attributed to differences in self-care or health service-seeking behavior, since in the pediatric and young adult population, diagnosis and follow-up are conducted predominantly by family members and caregivers. Thus, it is more likely that this finding is related to biological and clinical factors. From puberty onwards, hormonal influences may modulate carcinogenic processes, while sex differences in DNA repair mechanisms, gene expression, and response to cancer treatments may impact the risk of subsequent tumors. Furthermore, in this age group, genetic cancer predisposition syndromes and late effects of antineoplastic therapies play a central role in the occurrence of multiple primary tumors.[15,16] Particularly for post-pubertal girls, hormonal factors play a complex role in carcinogenesis, with effects that may modulate the risk of second tumors.[17] Additionally, differences in cellular receptor expression and DNA repair mechanisms between sexes may influence both initial cancer susceptibility and the risk of developing subsequent tumors.[18,19] In the studied population (0-24 years), the uniqueness of the age range implies that genetic syndromes and iatrogenic effects of cancer treatments assume relatively greater importance than in adults, potentially differentially modulating MPD patterns between sexes.

The positive and gradual association between age and MPDs (from 3.4% at 0 years to 11.5% at 20-24 years) reflects the convergence of biological and epidemiological factors. The age gradient is explained, in part, by longer follow-up time, which allows detection of metachronous tumors.[20,21] However, in the pediatric population, intrinsic factors such as genetic predisposition and congenital anomalies are the main etiological determinants, given that cumulative environmental exposures are limited in children.[20,22] It is estimated that for every 10 pediatric and young adult cancer diagnoses, 1 to 2 occur in the context of germline mutations associated with cancer predisposition syndromes. With advancing knowledge in the field and greater access to genetic testing, identification of these cases has become more frequent, allowing better clinical follow-up and targeted surveillance.[23]

A finding of great epidemiological relevance is the inverse and progressive association between year of diagnosis and occurrence of MPDs. The proportion of MPDs declined from approximately 15% in the initial years (1975-1985) to about 2% in the most recent period (2015-2022). This declining trend is multifactorial, reflecting the confluence of methodological, technological, and clinical advances. Furthermore, therapeutic adaptation to reduce the risk of second neoplasms, such as avoiding radiotherapy and unnecessary ionizing radiation exposures in syndromes like Li-Fraumeni, could also, at least partially, contribute to decreasing the occurrence of MPDs in this scenario. Additionally,[24] improvement in diagnostic accuracy and standardization of multiple primary tumor coding criteria in SEER contributed to the reduction of registry artifacts and more precise case classification over time.[25-27]

Moreover, and importantly, therapeutic advances have fundamentally modified the risk profile of second cancers. Childhood cancer survivors present a 14% higher risk of developing new primary tumors compared to the general population.[26] Radiotherapy and chemotherapeutic agents (particularly alkylating agents and topoisomerase II inhibitors) are well-established iatrogenic risk factors, associated with the development of solid tumors (related to irradiation) and secondary leukemias, respectively.[23,28] However, the reduction of chemotherapy and radiotherapy doses, replacement of more genotoxic agents, and implementation of high-precision radiotherapeutic techniques (such as conformal and proton radiotherapy) in recent decades have contributed to the reduction of iatrogenic risk.[29-31] These therapeutic advances largely explain the observed declining temporal trend.

Finally, the observed progress in temporal reduction of multiple primary cancers, reflecting advances in less genotoxic treatments and more precise radiotherapeutic techniques, should stimulate continuous investment in translational research and development of innovative therapies. The pursuit of equally effective but less toxic cancer treatments, including immunotherapies, molecular targeted therapies, and precision medicine approaches, represents a priority for additional reduction of the burden of second primary cancers in long-term survivors.[32-36]

LIMITATIONS AND CLINICAL IMPLICATIONS

This study is subject to limitations inherent to a retrospective design with population registry data. The unavailability of detailed information on individual risk factors, such as family history, genetic syndromes, and detailed information on cancer treatments, precludes a more in-depth etiological analysis.

Nevertheless, the findings have direct implications for clinical practice and public health policies. The identification of higher-risk groups, particularly female patients, adolescents, and young adults, should inform differentiated surveillance strategies. Long-term follow-up protocols for childhood cancer survivors should incorporate individualized risk assessment based on age at treatment, therapeutic modalities employed, and genetic predispositions. The progress observed in the temporal reduction of MPDs should stimulate continued investment in translational research and development of less toxic therapies, such as immunotherapies and molecular targeted therapies, as a priority for reducing the burden of second primary cancers.

REFERENCES

1. Okeke O, Onoh R, Mbah C, et al. Multiple primary malignancies: Patterns, risk factors, and outcomes. Cureus. 2023;15(5):e44993. PMid:37829945.

2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660. PMid:33538338.

3. Eberl MM, Dreyer MS, Pratte KA, et al. Cancer survivorship and risk of subsequent primary malignancies: a population-based study. BMC Med. 2024;22(1):3398. PMid:38702684.

4. Almeida SVS, Cruz AJF, Oliveira CVB, Silva MEP, Junior IFS, Castro JWG. Perfil epidemiológico dos casos de leucemia na Região do Cariri do Estado do Ceará, no período de 2011 a 2021. Rev Epidemiol Saúde Pública. 2023;1(3). https://doi.org/10.59788/resp.v1i3.31.

5. He Y, Tang W. Epidemiological trends and survival outcomes of multiple primary cancers: A population-based analysis. Arch Public Health. 2024;82(1):1463.

6. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER). Oncologist. 2007;12(1):20-37. https://doi.org/10.1634/theoncologist.12-1-20. PMid:17227898.

7. Borba LR, Fonseca JM, Pinho AGSF, et al. Análise comparativa da mortalidade por melanoma no Brasil vs. Estados Unidos de 2010 a 2020. Rev Epidemiol Saúde Pública. 2024;2(2). https://doi.org/10.59788/resp.v2i2.65.

8. Weir HK, Johnson CJ, Ward KC, et al. The effect of multiple primary rules on cancer incidence rates and trends. Cancer Causes Control. 2016;27(3):377-90. https://doi.org/10.1007/s10552-016-0714-9. PMid:26809509.

9. Kwon JH, Kim H, Lee JK, Hong YJ, Kang HJ, Jang YJ. Incidence and characteristics of multiple primary cancers: a 20-year retrospective study of a single cancer center in Korea. Cancers (Basel). 2024;16(13):2346. https://doi.org/10.3390/cancers16132346. PMid:39001408.

10. van der Meer DJ, Husson O, Schaapveld M, et al. Long-term second primary cancer risk in adolescent and young adult (15-39 years) cancer survivors: a population-based study in the Netherlands between 1989 and 2018. Ann Oncol. 2024;35(1):98-106. PMid:37871701.

11. Weir HK, Johnson CJ, Thompson TD. The effect of multiple primary rules on population-based cancer survival. Cancer Causes Control. 2013;24(6):1231-42. https://doi.org/10.1007/s10552-013-0203-3. PMid:23558444.

12. Jackson SS, Marks MA, Katki HA, et al. Sex disparities in the incidence of 21 cancer types: quantification of the contribution of risk factors. Cancer. 2022;128(19):3531-40. https://doi.org/10.1002/cncr.34390. PMid:35934938.

13. Rubin JB, Lagas JS, Broestl L, et al. Sex differences and cancer: the roles of sex chromosomes, gonadal steroids and microenvironmental factors. Trends Cancer. 2020;6(10):906-18.

14. Diniz CMM, Santos FG, Silva JRS, et al. Câncer de pulmão e riscos ocupacionais em municípios do Estado de Pernambuco: uma análise epidemiológica. Rev Epidemiol Saúde Pública. 2025;3(1):230-44. http://doi.org/10.59788/resp.v3i1.191.

15. Kim HI, Lim H, Moon A. Sex differences in cancer: Epidemiology, genetics and therapy. Biomol Ther. 2018;26(4):335-42. https://doi.org/10.4062/biomolther.2018.103. PMid:29949843.

16. Li H, Jiang W, Liu S, et al. Connecting the mechanisms of tumor sex differences with cancer therapy. Mol Cell Biochem. 2024;479(2):213-31. https://doi.org/10.1007/s11010-023-04723-1. PMid:37027097.

17. Lee ML, Chen GG, Vlantis AC, Tse GM, Leung BC, van Hasselt CA. Induction of thyroid papillary carcinoma cell proliferation by estrogen is associated with an altered expression of Bcl-xL. Cancer J. 2005;11(2):113-21. https://doi.org/10.1097/00130404-200503000-00006. PMid:15969986.

18. Yang X, Schadt EE, Wang S, et al. Tissue-specific expression and regulation of sexually dimorphic genes in mice. Genome Res. 2006;16(8):995-1004. https://doi.org/10.1101/gr.5217506. PMid:16825664.

19. Rubin JB, Lagas JS, Broestl L, et al. The spectrum of sex differences in cancer. Trends Cancer. 2020;6(4):303-15. https://doi.org/10.1016/j.trecan.2022.01.013. PMid:35190302.

20. Spector LG, Pankratz N, Marcotte EL. Genetic and nongenetic risk factors for childhood cancer. Pediatr Clin North Am. 2015;62(1):11-25. https://doi.org/10.1016/j.pcl.2014.09.013. PMid:25435109.

21. Williams LA, Ulrich CM, Larson T, et al. Causes of childhood cancer: a review of the recent literature: part I - childhood factors. Pediatr Blood Cancer. 2024;71(6):e30930.

22. Johnson KJ, Carozza SE, Chow EJ, et al. Parental age and risk of childhood cancer: a pooled analysis. Epidemiology. 2009;20(4):475-83. https://doi.org/10.1097/EDE.0b013e3181a5a332. PMid:19373093.

23. Brodeur GM, Diller LR, Nichols KE, Plon SE, Porter CC, Malkin D. Pediatric cancer predisposition and surveillance update: Summary perspective and future directions. Clin Cancer Res. 2025;31(13):2581-8. https://doi.org/10.1158/1078-0432.CCR-25-0423. PMid:40327330.

24. Thariat J, Chevalier F, Orbach D, et al. Avoidance or adaptation of radiotherapy in patients with cancer with Li-Fraumeni and heritable TP53-related cancer syndromes. Lancet Oncol. 2021;22(12):e562-74. https://doi.org/10.1016/S1470-2045(21)00425-3. PMid:34856153.

25. Morton LM, Onel K, Curtis RE, Hungate EA, Armstrong GT. The rising incidence of second cancers: patterns of occurrence and identification of risk factors for children and adults. ASCO Educ Book. 2014;34:e57-67. PMid:24857148.

26. Zahnreich S, Schmidberger H. Childhood cancer: occurrence, treatment and risk of second primary malignancies. Cancers. 2021;13(11):2607. https://doi.org/10.3390/cancers13112607. PMid:34073340.

27. Curtis RE, Freedman DM, Ron E, et al. New malignancies among cancer survivors: SEER cancer registries, 1973-2000. Bethesda (MD): National Cancer Institute; 2006. (NIH Publ; no. 05-5302).

28. Berrington de Gonzalez A, Curtis RE, Kry SF, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol. 2011;12(4):353-60. https://doi.org/10.1016/S1470-2045(11)70061-4. PMid:21454129.

29. Allodji RS, Tucker MA, Hawkins MM, et al. Role of radiotherapy and chemotherapy in the risk of leukemia after childhood cancer: an international pooled analysis. Int J Cancer. 2021;148(9):2079-89. https://doi.org/10.1002/ijc.33361. PMid:33105035.

30. Travis LB, Ng AK, Allan JM, et al. Second malignant neoplasms and cardiovascular disease following radiotherapy. J Natl Cancer Inst. 2012;104(5):357-70. https://doi.org/10.1093/jnci/djr533. PMid:22312134.

31. Crocetti E, Buiatti E, Falini P. Multiple primary cancer incidence in Italy. Eur J Cancer. 2001;37(18):2449-56. https://doi.org/10.1016/S0959-8049(01)00314-8. PMid:11720842.

32. Surveillance E, Results E. Multiple primary and histology coding rules [Internet]. Bethesda (MD): National Cancer Institute; 2024 [cited 2024]. Available from: https://seer.cancer.gov/tools/mphrules/

33. Liu L, de Vries E, Louwman M, et al. Prevalence of multiple malignancies in the Netherlands in 2007. Int J Cancer. 2011;128(7):1659-67. https://doi.org/10.1002/ijc.25480. PMid:20503267.

34. McGuire V, Lichtensztajn DY, Tao L, et al. Variation in patterns of second primary malignancies across U.S. race and ethnicity groups: a Surveillance, Epidemiology, and End Results (SEER) analysis. Cancer Causes Control. 2024;35(5): 799-815. https://doi.org/10.1007/s10552-023-01836-2. PMid:38206498.

35. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12-49. https://doi.org/10.3322/caac.21820. PMid:38230766.

36. Yang J, Luo G, Xiang Q, Li S, Feng Y. Global burden of cancer in adolescents and young adults aged 10-24 years: a trend analysis. Front Oncol. 2025;15:1663523. https://doi.org/10.3389/fonc.2025.1663523. PMid:41256315.

37. Surveillance Research Program, National Cancer Institute. SEER*Stat software (seer.cancer.gov/seerstat) version 9.0.42.

38. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER Research Data, 8 Registries, Nov 2024 Sub (1975–2022), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2025, based on the November 2024 submission.

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