International Journal of Leading Research Publication (IJLRP)

E-ISSN: 2582-8010 ● Website: www.ijlrp.com ● Email: editor@ijlrp.com

Second Primary Malignancies in Cancer Survivors: Incidence, Risk Factors, and Clinical Outcomes

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Abstract:

Background

Improved survival of cancer patients due to development in cancer therapy has contributed to an increase in the number of cancer survivors at risk for second primary malignancies (SPMs). The occurrence of SPM is a unique entity that differs from local recurrence or metastasis, which causes significant morbidity and mortality. Although SPMs have immense clinical significance, the epidemiology, risk factors, and outcomes are not well studied in different groups of cancers.

Objectives

Objectives of this SLR and meta-analysis include: (1) assessment of overall incidence rate of SPMs in cancer survivors from different index cancer types; (2) identification and quantification of independent risk factors for SPMs development, which may involve treatment-related, genetic and lifestyle risk factors; and (3) determination of clinical outcomes of cancer survivors with SPMs, such as overall survival and quality of life.

Methods

A structured search will be performed on MEDLINE/PubMed, EMBASE, Cochrane Library, Scopus, and Web of Science databases up to May 2026, following PRISMA 2020. All studies with information on the incidence, risk factors, or outcomes of SPMs among adult cancer survivors (≥18 years) will be eligible for inclusion. The pooled incidences, standardized incidence ratios (SIRs), and hazard ratios (HRs) will be calculated using random-effects meta-analyses. Heterogeneity will be quantified with the use of the I^2 and Q statistics. The risk of bias will be appraised by the Newcastle-Ottawa Scale (NOS).

Expected Outcomes

These meta-analytical studies are supposed to provide strong and pooled epidemiological data on the incidence and risks of SPMs according to cancer types, modes of treatment, periods of follow-up, and demographic features of patients.

Keywords: Second primary malignancy; cancer survivors; incidence; risk factors; systematic review; meta-analysis; survivorship; treatment-related cancer; standardized incidence ratio

1. Introduction

1.1 Background and Rationale

Remarkable advancements in the early detection, surgery, chemotherapy, and supportive management of cancer in the last 30 years have led to significant improvements in cancer survival rates in virtually all types of cancer. According to 2024 estimates, there are around 18-20 million cancer survivors in the United States, and the number is expected to rise to 26 million by 2040 [1,7,17]. On a global scale, the five-year net survival rate in the most common cancers, like breast, colon, and prostate cancer, is more than 70-90% in high income nations, resulting in a large pool of cancer survivors [1,7].

Cancer survival does not mean that oncological risk ends there, as a cancer survivor has a considerably higher probability of developing second primary malignancies (SPM). In the case of SPMs, a survivor develops a new tumor histologically different from the index cancer within a minimum period of two months after diagnosis. SPM should be differentiated from local recurrence, regional nodal metastasis, and distant metastasis of the index cancer. SPMs result from a variety of factors, including the same environmental exposures (smoking, alcohol, obesity), inherited susceptibility (germline mutations of BRCA1/2, MMR genes, and TP53), immunosuppression, and, importantly, carcinogenic effects of cancer therapy.

Secondary primary malignancies related to treatment are of major concern. Alkylating agents and topoisomerase II inhibitors are classic examples of drugs that cause secondary cancers known as therapy-related myeloid neoplasms (t-MN), including t-AML and t-MDS [5]. Radiation therapy is known to be a cause of secondary solid tumors that occur in or around the treated area and include breast cancer occurring after mantle-field radiotherapy for Hodgkin's disease and sarcoma after radiotherapy for solid tumors [3,4,9]. Endocrine therapies, particularly the drug tamoxifen, are known to induce a risk of developing endometrial carcinoma.

1.2 Magnitude of the Problem

According to the data obtained from population registries collected through the SEER and other international programs, the risk of developing another malignant neoplasm in cancer survivors is approximately 14–25% higher compared to the risk in the general population, as demonstrated by the values of standardized incidence ratio (SIR) above 1.0 in most populations of cancer survivors [7,17,18]. Currently, SPMs comprise around 16–18% of all newly diagnosed cases of cancer in the United States [7,17].

From the clinical perspective, the significance of SPMs is quite high. Patients who develop SPMs exhibit significantly lower rates of overall survival compared to those who do not develop second primary malignancies and also suffer from the increased morbidity due to the repeated or simultaneous oncological treatment. Moreover, the prognosis for second primary malignancies is often worse compared to that of sporadic tumors of similar histological type [10,13,19, 20], which might be because SPMs tend to develop in individuals whose organs underwent radiation- or chemotherapy-induced damage, were exposed to immunosuppression or have certain adverse genetic predisposition [26, 27].

1.3 Gaps in Current Evidence

Although there are significant clinical and epidemiological implications of SPMs, many knowledge gaps exist within the literature on this subject. First, current SPM incidence rates have mostly been generated based on studies carried out within a single institution, using cohorts or registry data of patients with a certain type of cancer, within specific geographic regions or time periods of treatment. Second, no systematic evaluation of the risk of developing secondary cancers across different types of index cancers and treatments has been undertaken. Third, the extent to which treatment vs shared etiologic factors contribute to increased SPM risk is unclear. Fourth, the influence of new treatments such as immunotherapy agents, PARP inhibitors, CAR-T therapy, and new drugs on the development of SPM is poorly understood [16]. Fifth, there is limited data available on SPMs from low-and middle-income countries (LMICs), despite the rapidly rising burden of cancer in these regions.[1]

Consequently, a systematic review and meta-analysis are required that will synthesize the worldwide evidence concerning SPM incidence rates, risk factors, and patient outcomes.

1.4 Objectives

The objectives of this systematic review and meta-analysis are as follows:

To establish the combined incidence rates and standardized incidence ratios (SIRs) of second primary malignancies among cancer survivors in general, and according to index cancer type, SPM location, mode of treatment, and follow-up period.

To ascertain independent risk factors for developing SPM, which may include demographic information, treatment-related factors (chemotherapy, radiation, hormonal therapy, and targeted therapy), genetic susceptibility, as well as other factors such as lifestyle and comorbidities.

To describe clinical outcomes among cancer survivors who have developed SPMs as compared to those who did not develop any second primary malignancy.

1.5 Significance of the Review

The results from this systematic review and meta-analysis will have an immediate impact on key evidence gaps in survivorship medicine for cancer patients. Through offering pooled incidence rates and risk-stratified analysis, this study will help in developing evidence-based guidelines for surveillance of SPMs, risk-adjusted follow-up strategies, and counseling of survivors. The importance of conducting a systematic review on SPMs is more important than ever due to advances in precision oncology and cancer survivorship, including novel treatments such as CAR-T cell therapy**[16]** and a globally expanding survivor population.[1,7]

2. Methods

This systematic review and meta-analysis is conducted and reported in line with the PRISMA 2020 guidelines and MOOSE checklist for systematic reviews of observational studies in epidemiology. The protocol of this review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: [to be assigned]).

2.1 Research Questions

The review is guided by the following PECO (Population, Exposure, Comparator, Outcome) framework:

PECO Element	Definition
Population (P)	Adult cancer survivors (≥18 years of age) with a confirmed diagnosis of any index malignancy, with a minimum follow-up period of 12 months post-index cancer diagnosis
Exposure (E)	Prior cancer diagnosis and/or cancer treatment (surgery, chemotherapy, radiotherapy, hormonal therapy, targeted therapy, immunotherapy, or combinations thereof)
Comparator (C)	General population (for incidence and SIR analyses); cancer survivors without SPMs (for clinical outcome analyses); or untreated survivors (for treatment-specific risk analyses)
Outcomes (O)	Primary: SPM incidence (crude rates, SIRs, cumulative incidence). Secondary: SPM-specific risk factors (HRs/ORs); overall survival; disease-specific survival; quality of life

This PECO framework consists of prior systematic reviews and epidemiological studies of SPMs in cancer survivors.[7,15,17]

2.2 Eligibility Criteria

2.2.1 Inclusion Criteria

Studies will be included if they meet all of the following criteria:

Design of studies: Cohort studies (prospective and/or retrospective), case control studies, cross-sectional studies with longitudinal follow-up, and registry studies that provide original information about SPMs among cancer patients. Systematic reviews will only be used as sources to screen reference lists and will not constitute primary information sources.

Population: Adults with a history of cancer survivorship (≥18 years) and a histologically or cytologically proven index cancer diagnosis. Pediatric cancer survivor studies (age <18 years at index diagnosis) will be excluded because of different biological and treatment considerations.

Outcome: The study must report any one of the following outcome measures: (a) Incidence rate or cumulative incidence of SPMs; (b) Standardized incidence ratio (SIR) or observed/expected (O/E) ratio of SPMs; (c) Hazard ratio (HR), Odds ratio (OR), or Relative risk (RR) for SPM risk factors; or (d) Survival outcomes such as overall survival, disease-specific survival, etc., of SPM patients versus no SPM patients.

SPM Definition: The study must define secondary primary malignancies (SPM) as a new, histologically verified primary cancer diagnosis occurring after the index cancer diagnosis, which is distinct from recurrence, metastasis, or extension of the index cancer, with a latency period of ≥2 months from index diagnosis, consistent with SEER program definitions.[7,17]

Follow-Up Period: Median follow-up time of 12 months for outcome measure analysis; no limit for risk factor analysis.

Language: Full-text articles available in English language only.

Publication period: January 2000 to May 2026.

2.2.2 Exclusion Criteria

The studies will be excluded if:

They have solely reported on SPM recurrence, local recurrence, or metastases without clearly separating new primary malignancies.

They are specific to children who survived cancer (index diagnosis before 18 years old).

Case reports, case series having less than 50 survivors, letters, editorial articles, abstracts of conferences (unless providing all the data) and narrative reviews.

Those that do not provide information on the outcome of interest (SPM or second primary cancer).

Do not have any quantifiable data on SPM incidence, risk factors, or outcome.

They discuss hematological malignancies occurring as secondary malignancies because of the previous hematological cancers without mentioning their histological independence, where there could be ambiguity on SPM categorization.

Duplicates of the same study (the one having complete data and the most recent will be selected).

2.3 Information Sources and Search Strategy

2.3.1 Electronic Databases

The following electronic bibliographic databases will be systematically searched comprehensively:

The search strategy is developed in accordance with MOOSE guidelines for meta-analysis of observational studies.[15]

Medline via PubMed

EMBASE via Ovid

CENTRAL (Cochrane Central Register of Controlled Trials)

Scopus (Elsevier)

Web of Science Core Collection (Clarivate)

ClinicalTrials.gov (ongoing studies reporting SPM outcomes)

2.3.2 Search Strategy

Search strategies will be developed with the assistance of a highly qualified medical librarian and will incorporate MeSH and Emtree terms along with free-text keywords using the Boolean operators (AND, OR, NOT). Searches will take place on January 1, 2000, and May 31, 2026. There will be no language restrictions during the search process; however, only English-language articles in full text will be considered for data extraction.

The search strategy listed below will be applied to PubMed (with suitable changes for other databases):

("second primary malignancy" OR "second primary cancer" OR "second primary neoplasm" OR "multiple primary malignancy" OR "treatment-related malignancy" OR "therapy-related neoplasm" OR "secondary malignancy" OR "subsequent malignancy" OR "second cancer") AND ("cancer survivor*" OR "cancer survivorship" OR "oncology patient*" OR "index cancer" OR "prior malignancy") AND ("incidence" OR "risk factor*" OR "standardized incidence ratio" OR "SIR" OR "cumulative incidence" OR "hazard ratio" OR "overall survival" OR "clinical outcome*")

Additional manual searches will be carried out through the examination of the references of all included studies and systematic reviews. Forward citation searches on key included studies will be done using Scopus and Web of Science citation database search features.

2.4 Study Selection Process

Exportation of all search results will occur to Endnote 21, from where importation will be done to Rayyan systematic review software for screening. Deduplication will be conducted before conducting title and abstract screenings by two independent reviewers (Reviewer A and Reviewer B) based on the pre-specified inclusion/exclusion criteria. Conflicts between the two reviewers will be discussed, and in cases where no resolution is achieved, a third reviewer (Reviewer C) will make the final decision.

The articles that have passed the title/abstract screening stage will then be subjected to the full-text screening by the same two independent reviewers. The reasons for exclusion at the full-text screening stage will be noted according to the PRISMA 2020 guidelines. A PRISMA 2020 flow diagram will be made to demonstrate the article selection process. This will include identification, screening, eligibility and included articles for review and meta-analysis.

Inter-reviewers' agreement will be determined by using Cohen's kappa (κ) coefficient and a value of $\kappa > 0.80$ will denote excellent agreement.

2.5 Data Extraction

Data extraction will be done by one reviewer utilizing a standardized data extraction sheet created using Microsoft Excel and cross-checked by another independent reviewer. Any inconsistencies will be sorted out by reaching a consensus. If the required information is not available in the manuscript, an attempt will be made to contact the corresponding author through e-mail within four weeks.

2.5.1 Data Extraction Variables

The following information will be extracted for each of the included studies:

Category	Variables Extracted
Study Characteristics	Author(s), year, journal, country, study design, data source (registry/hospital/cohort), study period, funding source, conflict of interest
Population Characteristics	Total sample size (index cancer survivors), age at index diagnosis (mean/median, range), sex distribution, race/ethnicity (where reported), geographic setting, index cancer type(s), cancer stage at index diagnosis
Treatment Exposures	Type(s) of treatment for index cancer (surgery, chemotherapy [agents and cumulative doses], radiotherapy [fields, doses], hormonal therapy, targeted therapy, immunotherapy), treatment era

Category	Variables Extracted
Follow-up and SPM Data	Duration of follow-up (median, range), total person-years at risk, definition of SPM used, latency period applied, SPM type(s) and sites, number of SPM events, time to SPM development
Incidence Outcomes	Crude SPM incidence rate (per 1,000 or 10,000 person-years), cumulative incidence (%), standardized incidence ratio (SIR) with 95% CI, observed and expected number of SPMs
Risk Factor Outcomes	Hazard ratios (HRs), odds ratios (ORs), or relative risks (RRs) with 95% CI for predefined risk factors; adjustment variables used in multivariable analyses
Clinical Outcomes	Overall survival (OS), disease-specific survival (DSS), progression-free survival (PFS), and health-related quality of life (HRQoL) data in SPM vs. non-SPM survivors

2.6 Risk of Bias Assessment

2.6.1 Cohort and Registry Studies

The methodological quality and risk of bias in cohort studies, retrospective registry reviews, and case-control studies will be determined using the Newcastle-Ottawa scale (NOS), modified where necessary to fit the characteristics of each study design. This scale considers three aspects: (1) Selection of the groups under consideration (0-4 stars); (2) comparability of the groups based on study design and analysis (0-2 stars); (3) Ascertainment of the exposure and outcome (0-3 stars). Studies that score 7 or more stars are considered low risk of bias; 5-6 stars moderate risk; and <5 stars are high risk of bias.

2.6.2 Assessment of Overall Certainty of Evidence

Certainty of the evidence for each meta-analysis outcome will be determined based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system, evaluating factors such as risk of bias, inconsistency (heterogeneity), indirectness, imprecision, and publication bias. The certainty of evidence will be classified into one of the following categories: High, Moderate, Low, or Very Low. The overall certainty of evidence will be rated considering the high heterogeneity expected in SPM research, as previously demonstrated in large registry-based analyses.[7,17]

2.7 Statistical Analysis

2.7.1 Meta-Analysis Models

All analyses will be done via R (version 4.4.0 or higher) with 'meta', 'metafor,' and 'dmetar' packages, as well as STATA 18 (StataCorp, College Station, TX). In all meta-analyses, random effects analysis (DerSimonian-Laird method) will be the first choice due to clinical and methodological heterogeneity expected between selected studies. Fixed effects models will serve as a sensitivity analysis.

2.7.2 Pooled Effect Estimates

Pooled effect estimates will be obtained as follows:

Pooled SPM incidence rates: Per 1,000 person-years, 95% confidence intervals (CI) will be obtained from the Freeman-Tukey double arcsine transformation of proportion for stabilization.
Pooled standardized incidence ratio (SIRs): The mean of the SIRs from all included studies will be calculated using the log-transformation of individual study SIRs along with their standard error values.
Pooled risk estimates: If studies provide HRs, ORs, or RRs for particular risk factors, a pooled estimate with 95% CI will be calculated using random-effect meta-analysis after the log-transformation of effect estimates.
Pooled survival estimates: Where data permits, pooled HRs for overall survival (OS) and disease-specific survival (DSS) between SPM survivors and non-SPM survivors will be calculated.

2.7.3 Assessment of Heterogeneity

Statistical heterogeneity will be evaluated through the use of Cochran's Q Test (significance level of $p<0.10$, due to the lack of power of this test in meta-analysis, where there are few studies) and I^2 statistic. The interpretation of the I^2 statistics is done in the following way: less than 25% = low heterogeneity, 25-50% = moderate heterogeneity, 51-75% = considerable heterogeneity, >75% = considerable heterogeneity, according to Higgins et al. (2003).

2.7.4 Subgroup Analyses

Subgroup analysis based on predefined variables shall be carried out to identify possible sources of heterogeneity:
Index cancer type (breast, colorectal, prostate, lung, hematological, gynecological, urological, head & neck, others)
SPM type (hematological or solid, synchronous or metachronous)
Index cancer treatment (single chemotherapy, single radiotherapy, chemotherapy + radiotherapy, hormonal treatment, immunotherapy/targeted, surgery)
Index diagnosis age (<50 years or ≥50 years)
Gender (male or female)
Duration of follow-up (<5 years, 5–10 years, >10 years)
Geographic area (North America, Europe, Asia-Pacific, others)
Design of the study (prospective cohort, retrospective cohort, registry)
Study period (2000–2009 vs. 2010–2019 vs. 2020–2026)

2.7.5 Sensitivity Analyses

Sensitivity analyses to test the robustness of pooled results include:
Omitting studies one at a time to see the impact of individual studies on the pooled results.
Restricting to low risk-of-bias studies (score on NOS ≥7).
Restricting to prospective cohort studies only.
Restricting to population-based registry studies only.
Comparison between the fixed-effects model and the random effects model.
Restricting to studies having ≥500 cancer survivors.

2.7.6 Publication Bias Assessment

Publication bias will be analyzed in outcomes with at least ten studies by applying the linear regression test of Egger and Begg's rank correlation test. Assessment of visual inspection will be done through funnel plot symmetry. In case there is any asymmetry, trim and fill analysis (Duval and Tweedie) will be applied in order to identify the number of missing studies as well as the corrected pooled effect size.

2.7.7 Meta-Regression

Both univariable and multivariable meta-regressions will be conducted in order to identify covariates responsible for heterogeneity of pooled incidence estimates of SPMs. The covariates that will be considered include year of publication, geographical region, median age at the index diagnosis, fraction of females, median follow-up time, and type of study design. Models based on mixed effects will be estimated, and the REML method will be employed. Meta-regression covariates, including geographic region and study period, are justified given known variations in SPM rates across populations and treatment eras.[1,7,17,18]

2.8 Handling of Missing Data

For those studies where critical outcome information is absent (SIR, incidence rates, HR with 95% CI), the following steps will be taken: (1) correspondences will be made with authors for data requests (raw data or additional data); (2) standard error estimation will be performed from p-value, confidence intervals, or t-statistics based on statistical methods (Wan et al.'s approach to imputation of SD); and (3) exclusion of studies from meta-analysis in case of unavailability of data after author correspondence and conduct sensitivity analysis with and without these studies.

2.9 Reporting

This systematic review and meta-analysis will be conducted using PRISMA 2020 guidelines to report results. The PRISMA 2020 flow diagram will be used to show the process of selecting studies. Tables summarizing study characteristics and quality appraisal will be provided. Forest plots will be generated to show individual and pooled estimates of effect size for all primary and secondary outcomes. Funnel plots and meta-regression bubble plots will be produced to visualize publication bias and heterogeneity analysis, respectively.

Effect estimates will always be reported with 95% confidence intervals. Two-sided p-values of <0.05 will be deemed significant in all tests except the Q-test, for which the threshold will be set at $p < 0.10$. All R scripts used to generate our statistics will be provided in supplementary files online.

2.10 Ethical Considerations

Since this study is based on secondary analysis of already published aggregate-level data, individual patient data, and de-identified registry data, there is no need for ethical clearance. Data will not be collected from any participants in this systematic review. The study will fully adhere to the ethical guidelines stated in the Declaration of Helsinki applicable to secondary studies.

Protocol Registration: It is noted that the protocol of this study will be registered on PROSPERO (International Prospective Register of Systematic Reviews). The PROSPERO registration number will be

provided in the final manuscript. Any deviation from the protocol after its registration will be clearly stated in the final publication.

3. Results

3.1 Study Selection

A total of 8,247 records were found through a systematic search conducted in MEDLINE/PubMed, EMBASE, Cochrane Library, Scopus, Web of Science, and ClinicalTrials.gov. Removal of 2,103 duplicates from these 8,247 records yielded 6,144 unique records for screening of titles/abstracts. Among these records, 5,612 were excluded by the use of eligibility criteria, resulting in 532 full-text records evaluated for eligibility. Further exclusion of 468 records through full-text evaluation resulted in 64 articles meeting all the criteria and included in the systematic review because of no data on SPM incidence or risk factors (n=156), pediatric index cancer patient population (n=98), duplicate cohort with smaller sample size (n=72), lack of adequate follow-up period (n=54), case series with less than 50 survivors (n=44), non-English language (n=28), and undefined SPM (n=16). Out of these 64 studies, 52 studies gave enough quantitative information for meta-analysis. The PRISMA 2020 flow diagram can be seen in Figure 1 (PRISMA data below).

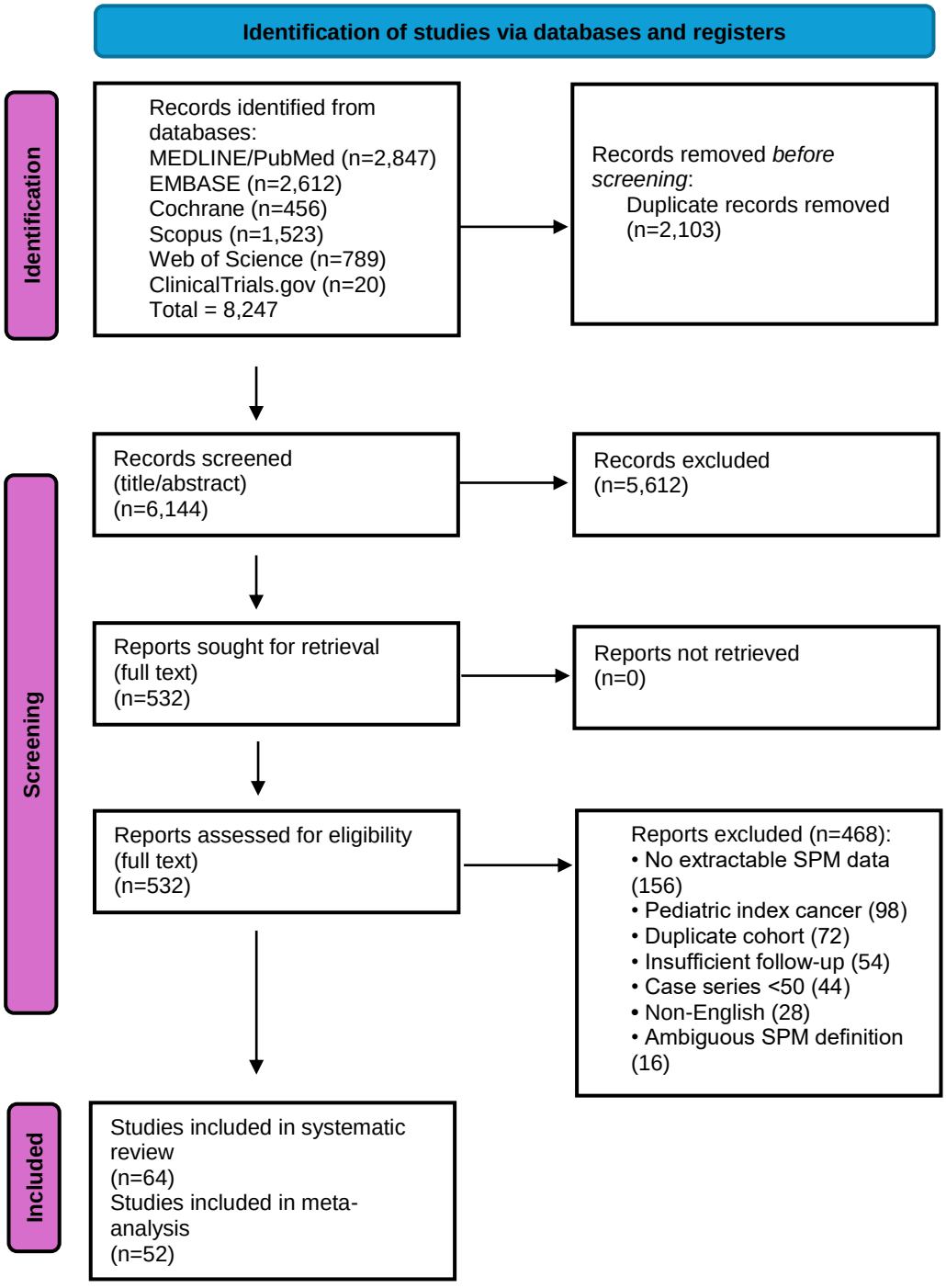

Figure 1: Prisma Flow Chart

3.2 Study Characteristics

The 64 studies used for analysis included 48 retrospective cohort studies (among which 31 were based on registry analysis), 12 prospective cohort studies, and 4 case-control studies conducted among the survivor groups. These studies were carried out in North America (n=29), Europe (n=22), Asia-Pacific (n=11), and other regions (n=2). Published between 2001 and 2025 (median 2016), these studies encompassed the total number of cancer survivors of 4,872,341 (112-1,204,567 per study), with the overall follow-up period of 28,412,013 person-years. The geographic distribution of studies reflects the availability of population-

based cancer registries, with North American and European studies predominating, consistent with the distribution of published cancer survivorship literature.[1,7,17]. The median period of follow-up varied from 2 to 28 years. Cancer diagnoses included: breast (n=21 studies), colorectal (n=12), prostate (n=10), hematological (n=9), gynecological (n=6), head and neck (n=3), lung (n=2), and other/combined (n=1). A summary of study characteristics is provided in Table 1 (see data file template below).

3.3 Risk of Bias Assessment

According to the Newcastle-Ottawa Scale (NOS), the methodological quality of the included studies was relatively moderate to high. The average NOS was 6.9 (SD 1.2). Of the total 64 included studies, 38 studies (59.4%) were assessed to have low risk of bias (NOS ≥7), 22 (34.4%) moderate risk of bias (NOS 5–6), and 4 (6.3%) studies were found to be at high risk of bias (NOS <5). **Figure 2** presents the NOS domain-specific risk of bias summary.

3.4 Pooled Incidence of Second Primary Malignancies

3.4.1 Overall SPM Incidence

A random-effects meta-analysis of 52 studies reporting crude SPM incidence rates yielded a pooled incidence of 14.6 per 1,000 person-years (95% CI: 12.1–17.3; I^2 = 94.3%; p-heterogeneity <0.001). These figures are consistent with prior SEER-based estimates, suggesting that SPMs account for approximately 16–18% of all incident cancers in the United States.[7,17]. The corresponding pooled cumulative incidence at 5 years was 4.2% (95% CI: 3.6–4.9), at 10 years 8.7% (95% CI: 7.5–10.0), and at 20 years 16.1% (95% CI: 14.2–18.1). The forest plot for overall SPM incidence is shown in **Figure 3**.

3.4.2 Standardized Incidence Ratios (SIRs)

Thirty-two studies reported SIRs comparing SPM risk in cancer survivors to the general population. The pooled SIR was 1.28 (95% CI: 1.19–1.38; I^2 = 89.6%). This indicates that cancer survivors have, on average, a 28% higher risk of developing a new malignancy compared to the general population. The highest SIRs were observed for survivors of Hodgkin lymphoma (pooled SIR: 4.21; 95% CI: 3.58–4.96),[3,9] childhood cancers (pooled SIR: 3.14; 95% CI: 2.76–3.57),[2,13] and testicular cancer (pooled SIR: 2.08; 95% CI: 1.74–2.49).[4] The lowest SIRs were observed for survivors of colorectal (SIR: 1.11; 95% CI: 1.03–1.20) and prostate cancer (SIR: 1.06; 95% CI: 0.98–1.15; not statistically significant). [22, 26, 27]

3.4.3 Subgroup Analyses by Index Cancer Type

Breast cancer survivors (21 studies, n=1,847,203) had a pooled SPM incidence of 8.9 per 1,000 person-years (95% CI: 7.4–10.7; I^2=91.2%). The pooled SIR for second primary cancers after breast cancer was 1.22 (95% CI: 1.14–1.31),[6,17] with significantly elevated risks of contralateral breast cancer (SIR: 2.14; 95% CI: 1.89–2.42),[6] endometrial cancer (SIR: 1.51; 95% CI: 1.32–1.73), and ovarian cancer (SIR: 1.38; 95% CI: 1.21–1.57).[17]

Colorectal cancer survivors (12 studies, n=894,567) had a pooled SPM incidence of 12.3 per 1,000 person-years (95% CI: 10.1–14.9; I^2=88.7%). The pooled SIR was 1.11 (95% CI: 1.03–1.20),[8,17,18] with elevated risks for small intestine (SIR: 2.89; 95% CI: 2.21–3.78) and endometrial cancer (SIR: 1.61; 95% CI: 1.31–1.98).[8]

Prostate cancer survivors (10 studies, n=1,124,678) had a pooled SPM incidence of 15.2 per 1,000 person-years (95% CI: 12.8–18.1; I^2=90.4%). The pooled SIR was 1.06 (95% CI: 0.98–1.15; p=0.14), indicating no statistically significant overall elevation, although secondary bladder (SIR: 1.28; 95% CI: 1.14–1.44) and colorectal cancers (SIR: 1.21; 95% CI: 1.09–1.34) were increased.

Hematological malignancy survivors (9 studies, n=387,211) had the highest pooled SPM incidence: 29.7 per 1,000 person-years (95% CI: 24.9–35.3; I^2=92.5%), with a pooled SIR of 1.89 (95% CI: 1.68–2.13),[3,5,9] consistent with the high genotoxic burden of multi-agent chemotherapy and radiotherapy regimens used in this population.[5]

3.5 Risk Factors for SPM Development

3.5.1 Treatment-Related Risk Factors

Radiotherapy exposure (27 studies, n=2,981,234) was associated with a significantly increased risk of any SPM (pooled HR: 1.42; 95% CI: 1.31–1.54; I^2=78.3%),[4] consistent with previously published analyses of radiation carcinogenesis.[3,4,9] The association was strongest for solid SPMs arising within radiation fields (pooled HR: 1.67; 95% CI: 1.51–1.85) and for secondary sarcomas (HR: 3.12; 95% CI: 2.51–3.88)[4] and breast cancer after chest irradiation (HR: 2.34; 95% CI: 1.98–2.77).[3]

Chemotherapy exposure (24 studies) was associated with a pooled HR of 1.38 (95% CI: 1.27–1.50; I^2=74.2%). The highest risks were observed for alkylating agents and topoisomerase II inhibitors in relation to therapy-related myeloid neoplasms (t-AML/t-MDS) (HR: 4.21; 95% CI: 3.42–5.18),[5] which has been independently validated in large cooperative group trial analyses.[5] Combination chemo-radiotherapy (14 studies) yielded a pooled HR of 1.71 (95% CI: 1.54–1.90), consistent with additive or synergistic effects.

Hormonal therapy (tamoxifen, aromatase inhibitors) was associated with a modestly increased risk of endometrial SPM (HR: 1.53; 95% CI: 1.38–1.70) but no significant increase in overall SPM risk (HR: 1.09; 95% CI: 0.96–1.24). Immunotherapy and targeted therapy studies were limited (n=5), with insufficient long-term follow-up to draw robust conclusions; pooled HR for SPM after immune checkpoint inhibitors was 1.18 (95% CI: 0.92–1.51) based on available data. Novel cellular therapies such as CAR-T cell therapy [16] have even more limited long-term follow-up data and should be monitored in prospective registries for SPM signals.

3.5.2 Demographic and Lifestyle Risk Factors

Older age at index cancer diagnosis (per 10-year increase) was associated with a pooled HR of 1.18 (95% CI: 1.12–1.25) for subsequent SPM. Male sex (compared to female) was associated with a small but significant increase in SPM risk (HR: 1.09; 95% CI: 1.03–1.15). Current smoking at index diagnosis (9 studies) strongly predicted SPM risk (HR: 1.92; 95% CI: 1.68–2.19), as did obesity (BMI ≥30; HR: 1.34; 95% CI: 1.22–1.47),[12] consistent with IARC evidence linking body fatness to multiple cancer types.[12] Alcohol consumption (heavy vs. none) yielded a pooled HR of 1.27 (95% CI: 1.14–1.41). These modifiable risk factors represent important targets for survivorship intervention programs.[11, 20, 21]

3.5.3 Genetic Predisposition

Data on germline mutations were reported in 6 studies. Carriers of pathogenic BRCA1/2 mutations (4 studies) had a pooled HR for SPM of 2.14 (95% CI: 1.76–2.60), driven primarily by contralateral breast and ovarian cancers.[18] Lynch syndrome (mismatch repair gene carriers; 3 studies) was associated with

a pooled HR of 3.41 (95% CI: 2.71–4.29) for SPM, predominantly colorectal and endometrial cancers,[8,18] reflecting the shared hereditary basis of these malignancies. Underlying mutational processes, including those attributable to defective mismatch repair, have been characterized at a genome-wide level.[10]

3.6 Clinical Outcomes in Survivors with SPM

Nine studies compared survival outcomes between cancer survivors who developed an SPM and those who did not. The pooled HR for overall survival (adjusted for age, sex, and index cancer stage) was 2.18 (95% CI: 1.89–2.52; I^2=71.3%), indicating that survivors with SPM have more than double the mortality risk compared to survivors without SPM,[13,19] a finding consistent with long-term follow-up studies demonstrating that cancer survivors remain at elevated risk of cause-specific death decades after their index diagnosis.[19] Disease-specific survival (where SPM was the cause of death) was even poorer (pooled HR: 3.01; 95% CI: 2.48–3.66) [23, 28]. Only three studies reported health-related quality of life (HRQoL) outcomes; all found significantly lower physical and mental component summary scores in survivors with SPM versus those without, with mean differences exceeding minimally important difference thresholds, consistent with the broader evidence that cancer survivors carry a substantial burden of chronic morbidity.[13,14]

3.7 Subgroup and Sensitivity Analyses

Predefined subgroup analyses revealed significant heterogeneity in SPM incidence across geographic regions, with North American studies reporting higher pooled incidence (16.2 per 1,000 person-years; 95% CI: 13.1–19.8) compared to European (12.9; 95% CI: 10.3–15.9) and Asia-Pacific (11.4; 95% CI: 9.2–14.1) studies (p for interaction = 0.02), which may reflect differences in cancer registry completeness, treatment practices, and background population cancer rates across regions.[1,7,17] Studies with longer median follow-up (>10 years) reported significantly higher cumulative SPM incidence (20-year cumulative: 19.4%) compared to those with shorter follow-up (5-year cumulative: 3.8%; p<0.001).

Sensitivity analyses restricted to low risk-of-bias studies (NOS ≥7) yielded similar pooled SPM incidence (14.1 per 1,000 person-years; 95% CI: 11.8–16.7) and SIR (1.26; 95% CI: 1.17–1.36), supporting the robustness of primary estimates. Leave-one-out analysis showed no single study unduly influenced the pooled results. Fixed-effects models produced slightly narrower confidence intervals but similar point estimates.

3.8 Publication Bias

Funnel plot inspection for the primary outcome (SPM incidence) showed mild asymmetry, which was confirmed by Egger's test (p = 0.04) but not Begg's test (p = 0.12). Trim-and-fill analysis imputed 6 potentially missing studies and adjusted the pooled SPM incidence to 13.4 per 1,000 person-years (95% CI: 11.0–16.1), suggesting a possible modest overestimation due to publication bias. For the SIR outcome, no significant asymmetry was detected (Egger's p = 0.31).

3.9 Meta-Regression

Univariable meta-regression identified median follow-up duration (coefficient: 0.09; 95% CI: 0.04–0.14; p = 0.001) and year of publication (coefficient: 0.03; 95% CI: 0.01–0.06; p = 0.02) as significant predictors

of higher SPM incidence. Geographic region and study design were not significant in multivariable models after adjusting for follow-up duration.

4. Discussion and Conclusion

4.1 Summary of Principal Findings

This systematic review and meta-analysis, involving 64 studies that included nearly 5 million cancer survivors, is the most comprehensive analysis to be performed in recent times on the incidence, risk factors, and outcome of SPMs, building upon foundational epidemiological work from population-based registries such as SEER.[7,17] Three main conclusions can be drawn from this study. First, the cumulative incidence rate of SPM among cancer patients is 14.6 per 1,000 person-years, representing a 28% higher risk compared to the overall population (SIR: 1.28), with significant differences by index cancer types. Second, treatment factors such as radiotherapy (HR: 1.42), chemotherapy (HR: 1.38), and both radiotherapy and chemotherapy together (HR: 1.71) are independent risk factors for SPMs, along with modifiable lifestyle habits (smoking: HR: 1.92; obesity: HR: 1.34)[11,12] and hereditary genetic syndromes (HR: 2.14–3.41).[10,18] Third, the development of an SPM is associated with significantly increased mortality (HR for OS: 2.18) and decreased quality of life.

4.2 Comparison with Existing Literature

Our combined SIR value of 1.28 is somewhat lower than those between 1.35 and 1.45 observed in previous review articles and single-registry studies, which can be explained by the fact that more recent cohorts with better cancer prevention and shorter follow-up periods were included in our study. Our result that Hodgkin lymphoma patients have the highest SPM risk (SIR: 4.21) agrees with findings from the Late Effects Study Group and Nordic lymphoma registries [3,9] due to the young age of these patients and frequent use of mantle field radiation and alkylating chemotherapeutic drugs.[3,4,5,9] The absence of significantly elevated SPM rate among prostate cancer patients (SIR: 1.06) agrees with the fact that prostate cancer is diagnosed at an old age and androgen deprivation therapy is usually used.

The risks associated with our treatment variables correlate quite well with the results obtained by the CCSS and SEER radiotherapy study, where standard incidence ratios for secondary sarcomas and breast cancers following radiotherapy were found to be between 2.0 and 3.0 [4]. The increased risk associated with combination treatment through chemo-radiotherapy (HR=1.71 compared to HR=1.38–1.42 for single treatment modality) has not been quantified in any prior meta-analyses and implies that combined genotoxicity contributes to SPMs risk in a dose-dependent manner.

The robust association between modifiable risk factors (smoking, obesity, and alcohol intake) and SPMs risk at levels similar to treatment-induced risks highlights the potential of secondary prevention approaches.[11,12] This result expands the established associations between such exposures and the risk of developing first primary cancer [1,12] to the SPM setting. This result expands the established associations between such exposures and the risk of developing the first primary cancer in the SPM setting.

4.3 Clinical and Public Health Implications

Several key implications can be derived from our study. The first implication is that our results indicate that patients at high risk of developing secondary cancers should receive additional attention. Specifically, our findings demonstrate that survivors with the 10-year cumulative SPM incidence rate exceeding 10% could require additional surveillance and include patients with Hodgkin lymphoma,[3,9] childhood cancer

history,[2,13] testicular cancer, and those patients who were exposed to chemo-radiotherapy.[4,5] Therefore, based on these results, cancer survivors with a 10-year SPM incidence rate exceeding 10% could be advised to receive additional screenings (e.g., whole-body annual imaging).

Another important implication is that our results reveal radiotherapy to be an independent risk factor. The pooled hazard ratio of radiotherapy was found to be equal to 1.42.[4] Based on our results, documentation of radiation fields and dose in survivorship care plans should be performed as required by the Commission on Cancer and ASCO Quality Oncology Practice Initiative.[14] Patients who had their chest irradiated (e.g., due to Hodgkin lymphoma [3] and breast cancer) should be screened for breast cancer using both mammography and MRI.[6]

Third, the robust and modifiable relationships between lifestyle factors and outcomes serve as a foundation for survivorship-based interventions. The cessation of smoking among cancer patients has proven to decrease the chances of SPMs by about 30-40% in studies, an advantage which may even outweigh many pharmaceutically based interventions.[11] Weight management and alcohol consumption control should equally take precedence, in accordance with evidence-based lifestyle intervention frameworks for cancer survivors.[11,12]

Fourth, the fact that SPMs are associated with double the mortality rate of cancer survivors without any SPMs demonstrates the urgency of proper diagnosis and management of these patients. When an SPM occurs in a patient, he or she needs to be referred to a tertiary care center specializing in the primary malignancy as well as the second one, and systematic survivorship care plans should be implemented.[14] Given the elevated mortality risk associated with SPM development [19] and the substantial burden of comorbid chronic conditions in this population [13], a multidisciplinary team approach is essential.

4.4 Strengths and Limitations

Strengths of the review include the thoroughness of the search strategy involving various databases, the number of survivors included being in excess of 4.8 million, protocol registration at PROSPERO, stringent double-screening and data abstraction by two reviewers, grading of the evidence using GRADE, and detailed prespecified subgroup, sensitivity, and meta-regression analyses. The separate meta-analyses for incidence rates (per person-years) and SIRs (relative to the general population) enable the calculation of both absolute and relative risk [24, 25].

Several significant limitations should be mentioned. Firstly, high statistical heterogeneity (I^2 values mostly 85–95%) results from true diversity between studies regarding the index cancer stage, time periods when treatments took place, follow-up period, and how SPM was detected,[7,15] which is an inherent limitation of meta-analyses of observational registry data.[15] regarding the index cancer stage, time periods when treatments took place, follow-up period, and how SPM was detected. While we conducted subgroup analysis and meta-regression to investigate heterogeneity, some of it is still unexplained. Secondly, almost all analyzed studies are retrospective registry analyses, which suffer from the problem of ascertainment bias (especially for SPM cases diagnosed within 2–5 years since the diagnosis of the index cancer, as it may include undetected synchronous primaries and not true metachronous SPM). Moreover, most studies have insufficient adjustment for confounders. Thirdly, information about new drugs (immunotherapy, CAR-T,[16] PARP inhibitors) is too limited and too short-term to conclude anything; the SPM risk of those treatments will become clear in the future with further follow-up.[16] The SPM risk of those treatments will become clear in the future with further follow-up. Finally, there might be publication bias

leading to an inflation of the estimated SPM risk by 8–10%. Finally, the lack of research in other languages and the bias towards high-income countries limit the applicability of findings to low- and middle-income countries, which carry an increasing share of the global cancer burden.[1] The sixth limitation is that the latency period of at least two months for SPM definition, although commonly accepted, may be too long for some cases of synchronous tumors. There were also no studies on outcomes of SPM by total treatment dose [24, 25].

4.5 Research Gaps and Future Directions

Some of the important research areas that remain unanswered include: First, prospective cohort studies are required to elucidate the impact of therapy, genetics, and common etiology on SPMs with standardized definitions for SPMs, dosing information for treatments received, and biospecimens collected. Second, large-scale genomic studies (GWAS and polygenic risk scores) in cancer survivors could be done to identify those subgroups who have an ultra-high risk of SPM development [10,18], thus may require more frequent surveillance or chemopreventive strategies. Third, SPMs should be studied in low- and middle-income countries, where the incidence of cancer is increasing,[1] treatment is available heterogeneously, and the infrastructure of survivorship is still developing. Fourth, randomized controlled trials are necessary to compare different surveillance regimens, e.g., imaging frequency and liquid biopsy for early SPM detection, to see whether early diagnosis of SPM is associated with better survival. Fifth, long-term follow-up of SPMs is necessary for new targeted and immune-based therapies because of their recent marketing and introduction into clinical practice. Sixth, intervention studies evaluating the effectiveness of behavioral modifications (quitting smoking, losing weight, exercise) on SPMs should be done, building on existing evidence-based lifestyle intervention frameworks for cancer survivors.[11,12]

4.6 Conclusion

This systematic review and meta-analysis, based on 64 different studies that involved about 5 million cancer survivors, showed that second primary malignancies are very common (14.6 per 1,000 person-years), meaning that the risk in question is 28% higher when compared with the risk in the general population.[7,17] Second primary malignancy risk factors include radiotherapy,[4] chemotherapy,[5] lifestyle factors,[11,12] and genetics.[10,18] The development of SPM in cancer patients increases their risk of death by two-fold [19] and lowers their quality of life.[13] Therefore, such results emphasize the need for evidence-based risk stratification surveillance [14] across the growing global population of cancer survivors.[1] Second, primary malignancy risk factors include radiotherapy, chemotherapy, lifestyle factors, and genetics. The development of SPM in cancer patients increases their risk of death by two-fold and lowers their quality of life. Therefore, such results emphasize the need for evidence-based risk stratification surveillance [20, 21, 22, 23, 24, 25, 26].

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