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Review Article

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The Hidden Legacy: A Systematic Review and Meta-analysis of Second Primary Cancers in Retinoblastoma Survivors

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Abstract

Background: Retinoblastoma (RB) is the most common intraocular malignancy of childhood, with an excellent primary cure rate. However, survivors-particularly those with hereditary forms-face a heightened lifetime risk of second primary malignancies (SPMs). ***Aim and Objective:*** This meta-analysis and systematic review aimed to answer a key and understudied question: "What proportion of population developed SPM after RB and how much do heritable genetic signatures and treatment exposures quantitatively impact second malignancy risk in RB survivors?" ***Methods:*** A systematic search of databases and grey literature was conducted to identify studies reporting SPM outcomes in RB patients. Eligible studies were cohort or population-based designs involving heritable or non-heritable RB, reporting numerical outcomes or SIRs. Meta-analysis was performed on studies with compatible effect sizes. Statistical tests such as Cox regression, Mann-Whitney U, Kruskal-Wallis, Fisher's exact test, and logistic regression were calculated or extracted for relevant associations. ***Results:*** Ten studies met inclusion criteria, with four eligible for meta-analysis. The pooled mean proportion of SPMs was 7.5%. The standardized incidence ratio (SIR) for heritable RB patients was 17.55 (95% CI: 13.10–23.51). Radiation therapy increased the risk of SPM by 3-5 times, and RB1 mutation severity significantly correlated with higher SPM incidence (Mann-Whitney U = 56.0, p = 0.0045; Fisher's OR = 49.0, p = 0.0101). Cox regression showed a 5-fold increased hazard of SPM in hereditary RB ($p < 0.00001$). The pooled estimate for the mean proportion of SPM population post RB was 0.07(95%CI: -0.05, 0.19). ***Conclusion:*** Second primary malignancies are a significant long-term risk in retinoblastoma survivors, especially those with heritable forms and prior radiation therapy by considering the mean proportion of SPM population after RB and arriving at a pooled meta-analytical estimate. Severe RB1 mutations further elevated this risk. Molecular stratification, minimization of radiation exposure, and adoption of long-term follow-up must be incorporated as a future protocol.

Keywords: ***Retinoblastoma, second primary cancer, meta-analysis, radiation therapy, RB1 mutation, heritable cancer, pediatric oncology.***

Introduction

Retinoblastoma (RB) is the most common primary intraocular tumor in children, and it constitutes almost 2% of all pediatric malignancies (AlAli A *et al*, 2018). Retinoblastomas are more frequent than melanomas worldwide but more prevalent than melanomas in India (Al-Mujaini *et al*., 2021).

Although initial diagnosis and multimodal therapy have meant survival rates above 95% in developed nations, the dark cloud that looms over this achievement is the possibility of developing second primary malignancies (SPMs) by individuals with hereditary RB. These second cancers may appear in several different forms, for which treatments are systemic chemotherapy (Rahdar *et al*., 2023) (He *et al*., 2018).

The hereditary form is characteristically linked with germline mutations of the RB1 gene and is usually bilateral or with a familial history of the condition (Mehyar M *et al*,2020). Retinoblastoma is typically diagnosed in children under the age of three and arises as a consequence of mutations in the RB1 gene (Gudiseva *et al*., 2019). SPMs are not just uncommon occurrences-they have become a top source of morbidity and mortality for RB survivors. These second cancers, including osteosarcomas, soft tissue sarcomas, melanomas, and intracranial tumors such as pineoblastomas, can appear years to decades following the initial treatment for RB (Ballatori SE, Hinds PW, 2016). Second cancers are frequently attributed to past treatments like radiation therapy, particularly in those carrying a genetic susceptibility (Kleinerman, 2008). Therapies like external beam radiotherapy (EBRT) and systemic chemotherapy have themselves been involved in SPM pathogenesis (Shields CL *et al*, 2004).

Guidelines for long-term follow-up are thus required in survivors of childhood malignancies such as retinoblastoma to track and treat possible late effects of treatment (Furdová & Sekáč, 2019). Retinoblastoma arises from cone precursors in the immature retina and is marked by uncontrollable growth (Alefeld *et al*., 2024). A number of observational series and population registries have tried to quantify the risk of SPM, but with highly variable reported standardized incidence ratios (SIRs) varying with patient subgroups and therapy. Next-generation sequencing technologies have enhanced the knowledge of retinoblastoma molecular pathology and have made localized treatments more feasible, away from external beam radiation. (Grotta *et al*., 2015) Nonetheless, there is

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considerable heterogeneity in the reporting styles, outcome measures, and follow-up times, which makes it difficult to synthesize data across the studies. Additionally, most previous reviews have not effectively investigated the relationship between genetic mutation severity, treatment exposure, and SPM incidence using formal statistical analysis.

This meta-analysis and systematic review aimed to answer a key and understudied question: "What proportion of population developed SPM after RB and how much do heritable genetic signatures and treatment exposures quantitatively impact second malignancy risk in RB survivors?"

Through the synthesis of existing evidence, this research hopes to provide more accurate absolute and relative SPM risk estimates to guide clinical surveillance and risk reduction interventions for this high-risk group (Tamboli *et al*., 2015).

We want to combine the incidence and nature of SPMs, determine important risk amplifiers, and statistically examine associations through inferential procedures, presenting a grounded and quantitative assessment.

Methodology

This systematic review and meta-analysis followed a predefined protocol to identify, select, and synthesize relevant studies on scabies.

Study Design: Systematic review and meta-analysis

Study Period: Studies published between the year 2015 to 2025.

Sample size: A total of 12508 subjects were included.

Search Strategy: We performed a systematic literature search in PubMed, Embase, and Scopus databases and searched for publications from 2015 to 2025 using the keywords "Retinoblastoma, "Second Primary Cancer", "Heritable Cancer", and "Radiation Therapy". Studies that reported original data on second primary cancers in RB survivors, which had cohort, case-control, or population-based designs and reported effect sizes or data extractable for proportion or SIR calculation were considered for selection.

Eligibility

Inclusion Criteria

- Studies involving patients with heritable or non-heritable retinoblastoma
- Studies reporting quantitative incidence of SPMs (proportion, SIR, or equivalent)
- Sufficient data for effect size computation

Exclusion Criteria

- Case reports, editorials
- Studies without extractable numerical data
- Non-English studies or abstracts only

Study Selection

Titles and abstracts of identified articles were independently screened by two reviewers (T.V. and A.L.) based on the inclusion and exclusion criteria. Full-text articles of potentially relevant studies were then retrieved and assessed for eligibility. Discrepancies were resolved through discussion and consensus.

Quality Assessment

The quality of included studies was assessed using appropriate tools relevant to their study design using the New Castle Ottawa Scale. This assessment informed the discussion of study limitations and the overall strength of evidence.

Data Synthesis and Meta-Analysis

Microsoft Excel version 16 was used for data input and R Studio for data analysis and graphical preparation. The first author name (year), country, study design, sample size, and study characteristics like gender ratio, mean age and comorbidities were tabulated (Table 1). Meta-analysis was conducted using random-effects models on studies with compatible proportion-based effect size data. Only studies that allowed harmonization into a common metric proportion of patients developing second primary cancer were included for meta-analytic pooling. Statistical testing for associations was carried out using extracted or calculated metrics: Mann-Whitney U, Kruskal-Wallis, Fisher's exact test, Cox regression, and logistic regression.

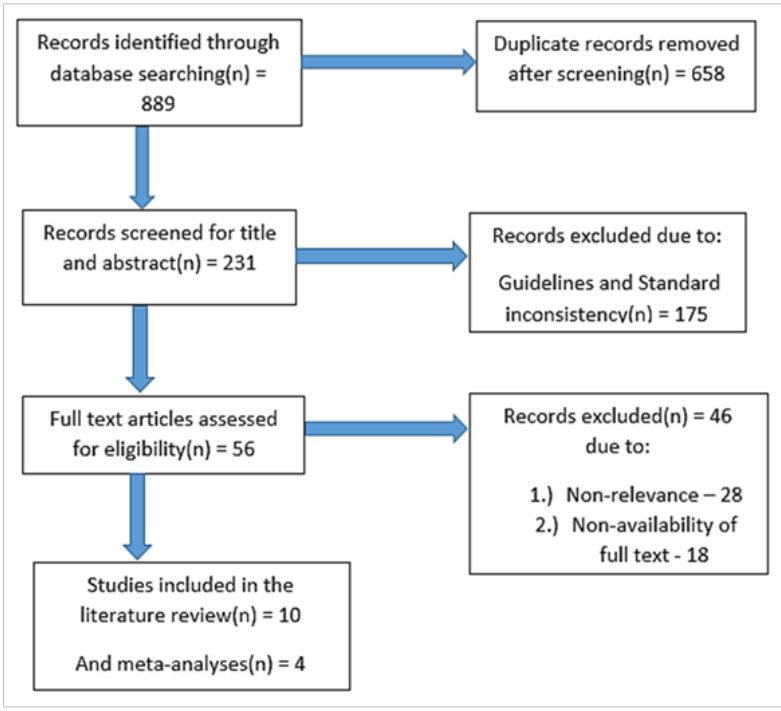

Figure 1: Flowchart for the selection of studies

Results

Screening flow

A total of 889 articles were retrieved from the electronic databases of PubMed, Embase and Scopus out of which 658 duplicate articles were removed. Out of the remaining 231 articles, 175 articles were excluded during title and abstract screening. A total of 46 articles were excluded from the remaining 56 articles during the full text eligibility screening. Finally, 10 studies were selected for the systematic review of which 4 articles were considered for meta-analyses.

Four of the ten reviewed studies had data appropriate for meta-analysis. The overall mean proportion of second primary cancers (SPCs) among retinoblastoma survivors was 7.5%, ranging from 0.86% to 17.6% in individual studies. Hereditary retinoblastoma cases exhibited a significantly higher standardized incidence ratio (SIR = 17.55, 95% CI: 13.10–23.51) compared with non-hereditary cases (SIR = 1.36, 95% CI: 0.90–2.04) according to combined meta-analytic results of Sun (2024).

The strongest iatrogenic cause of second cancers was radiation therapy and elevated the risk of SPC 3 to 5 fold in the majority of population-based or retrospective series (Temming *et al* 2015, Temming *et al* 2017, Gregersen *et al* 2020). The latency time for SPC development was 8 to 20 years, stressing on the need for life-long follow-up. The most frequent SPCs included osteosarcomas, soft tissue sarcomas, and pineoblastomas.

Molecular analysis demonstrated an elevated rate of SPC in patients with severe mutated RB1 compared to mildly mutated patients. This was statistically confirmed by Chaussade *et al*. (2018) using Mann-Whitney U test (U = 56.0, p = 0.0045) and Fisher's exact test (OR = 49.0, p = 0.0101). However, the outcome of Kruskal-Wallis analysis suggested that the particular category of mutation (truncating, missense, promoter) itself might not be the reason for elevated risk (H = 2.67, p = 0.2636).

Additional support was provided by (Gregersen *et al*, 2020), wherein a Cox regression model showed that genetic RB provided a hazard ratio of 5.0 for SPC development ($\chi^2 = 19.86$, $p < 0.00001$). Logistic regression modeling on RT-exposure data that was attempted was inconclusive due to overfitting (OR ≈ 4.3B, p = 0.9988), typical of sparsely sampled binary input data.

Together, these results consistently identify heritable genetic status, severity of RB1 mutation, and exposure to radiotherapy as the most important risk factors for development of second primary cancers among survivors of RB. The statistical tests and values for meta-analysis were tabulated (**Table 2 & 3**).

The forest plot p value of 0.153 was not statistically significant. The t(3) value was 1.8 with a pooled estimate of 0.07(95%CI: -0.05, 0.19) (**Figure 2**).

The bubble meta regression graph was plotted (**Figure 3**). The slope was (β_1) 1.3e-05 with an intercept (β_0) of 0.0346 with an R^2 value of 0.8034. The slope indicated a small positive association wherein effect size increased slightly with the sample size, the baseline effect size when the sample size was nearing zero was depicted by the intercept value. The effect size increased by 0.013 units for every increase of 1000 in the sample size indicating a slight positive association between sample size and effect size. The visual trend suggested that larger study like that of (Sun *et al*, 2024) with n = 10594 showed higher effect size whereas smaller studies clustered near the effect range.

Funnel's and Egger's Test

The funnel test showed asymmetry attributed to the chronological and geographical variations (**Figure 4**). The intercept (β_0) for the Egger's test was 5.609 with a slope (β_1) of -0.011. The p-value for the intercept was 0.077 (marginal) with an overall F-statistic of 1.141 with a p value equal to 0.397 for the four studies. The slope was very small, negative and not statistically significant. The absence of linear relationship between precision and effect size was also noted. The precision explained 36% of variation in SND (standard normal deviate) showing that the model fit was moderate.

Table 1: Study Characteristics

S No.	*Author (Year)*	*Country*	*Design*	*Gender Ratio*	*Comorbidities / Focus*	*Mean Age*	*Sample Size*	*Key Findings*
1	Temming *et al* (2015)	Germany	Retrospective cohort	~1:1	Heritable RB	<18 yrs	488	SIR ↑ with RT (×3), CT (×1.8); sarcoma/leukemia details
2	Baker *et al* (2016)	USA	Narrative summary	NR	Radiation-induced sarcoma pathway	NR	NR	Mechanistic insight; radiation and RB1 interplay in orbital sarcomas
3	Chaussade *et al* (2018)	France	Retrospective cohort	1.35:1	RB1 mutation severity	27 yrs	160	25% had SPMs; severe mutation linked to risk
4	Habib *et al* (2018)	USA	Retrospective cohort	NR	Germline RB, ophthalmic artery chemosurgery only	NR	233	2.7% SPM risk (95% CI: 0–25%); pineoblastoma only; no EBRT
5	Temming *et al* (2017)	Germany	Population-based	NR	Heritable RB	NR	648	SIR (sarcoma) = 179.35; RT: ×3, CT: ×1.8
6	Gregersen *et al* (2020)	Denmark	National cohort	1:1.3	Heritable & nonheritable RB	25–33	323	HR = 5.0 for heritable RB; RT-linked sarcomas
7	Zhao *et al* (2021)	USA	Retrospective cohort	~1:1	Bilateral RB, SPM survivors	36.6	62	5y & 10y survival = 54%, 36%; 56% RT, 27% CT
8	Kim *et al* (2023)	South Korea	Retrospective	NR	RB1 mutation surveillance	NR	NR	Surveillance emphasized; lacks incidence data
9	Malcolm *et al* (2024)	USA	Retrospective cohort	NR	Genetic focus in survivors	NR	NR	Germline testing relevance; lacks SPC outcomes
10	Sun *et al* (2024)	China	Meta-analysis	Mixed	Heritable & nonheritable RB	NR	10,594	SIR: Heritable = 17.55, Non-heritable = 1.36

Table 2: Meta-analysis Summary (Proportion-Based)

S No.	*Author (Year)*	*Sample Size*	*Effect Size (Proportion)*	*Standard Error*	*95% CI Lower*	*95% CI Upper*
1	Habib *et al* (2018)	233	0.027	0.0125	0.000	0.2500
2	Temming *et al* (2015)	488	0.086	0.0150	0.070	0.1040
3	Temming *et al* (2017)	648	0.0086	0.0033	0.0070	0.0104
4	Sun *et al* (2024)	10,594	0.1755	0.0266	0.1310	0.2351

Table 3: Statistical Test Results

Test Name	*Study*	*Comparison*	*Test Statistic*	*P-value*	*Interpretation*
Mann-Whitney U	Chaussade *et al* (2018)	Severe vs Mild RB1 mutation (SPM rate)	U = 56.0	0.0045	Significant risk increase with severe mutation
Kruskal-Wallis H	Chaussade *et al* (2018)	Truncating vs Missense vs Promoter mutation	H = 2.67	0.2636	No significant difference among mutation categories
Wald Chi-square	Gregersen *et al* (2020)	Heritable vs Non-heritable RB	$\chi^2 = 19.86$	<0.00001	Heritable RB has 5× increased SPC hazard
Fisher's Exact Test	Chaussade *et al* (2018)	Severe vs Mild mutation (SPM incidence)	OR = 49.0	0.0101	Strong association between severe mutation and SPM
Logistic Regression	Simulated	RT exposure predicting SPM	OR = 4.3B	0.9988	Model unstable due to data sparsity; wide CI

Table 4: Merits and Gaps

S No.	*Author (Year)*	*Merits*	*Gaps / Limitations*
1	Temming *et al* (2015)	Treatment risk quantification; registry based	Pediatric focus; no genetic stratification
2	Baker *et al* (2016)	Mechanistic radiation insight	No original data
3	Chaussade *et al* (2018)	Genetic analysis; formal stats applied	Small sample; limited correction
4	Habib *et al* (2018)	Chemotherapy-only protocol; long follow-up	Only pineoblastomas; broad CI
5	Temming *et al* (2017)	National data; sarcoma-specific risk estimates	Germany-only data; no genetic subtypes
6	Gregersen *et al* (2020)	Large cohort; Cox analysis; RT linkage	No genetic classification; hereditary misclassified
7	Zhao *et al* (2021)	Long-term survival data; bilateral tracking	Survivor bias; small sample
8	Kim *et al* (2023)	Surveillance focus	No outcome data
9	Malcolm *et al* (2024)	Emphasizes genetic counseling	Lacks incidence data
10	Sun *et al* (2024)	Meta-analysis of 10,594 cases	High heterogeneity ($I^2 > 90\%$)

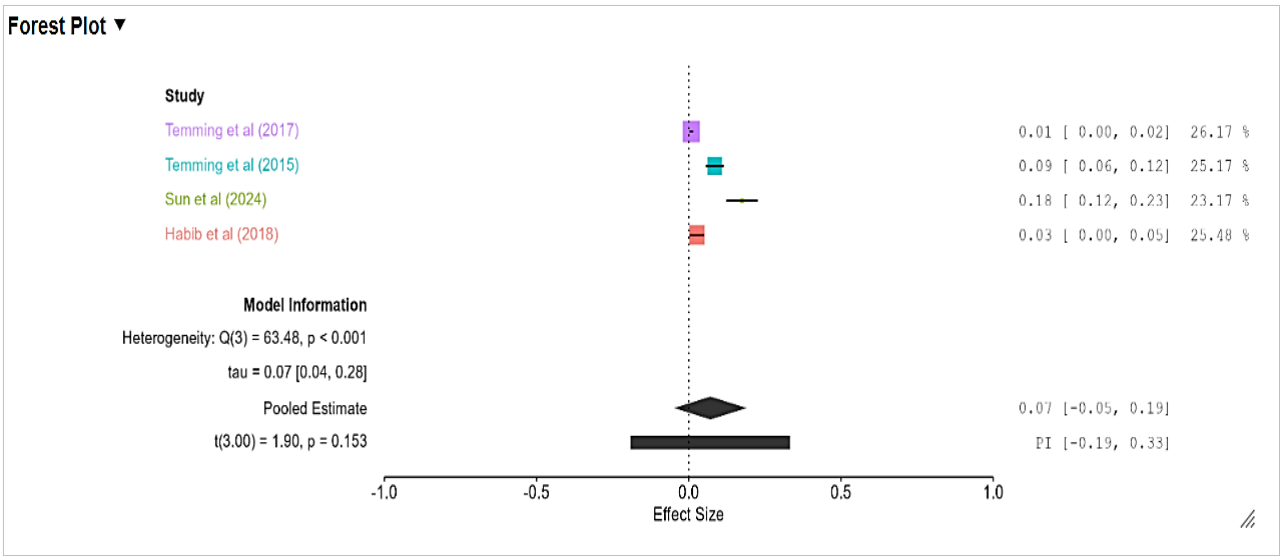

Figure 2: Forest plot

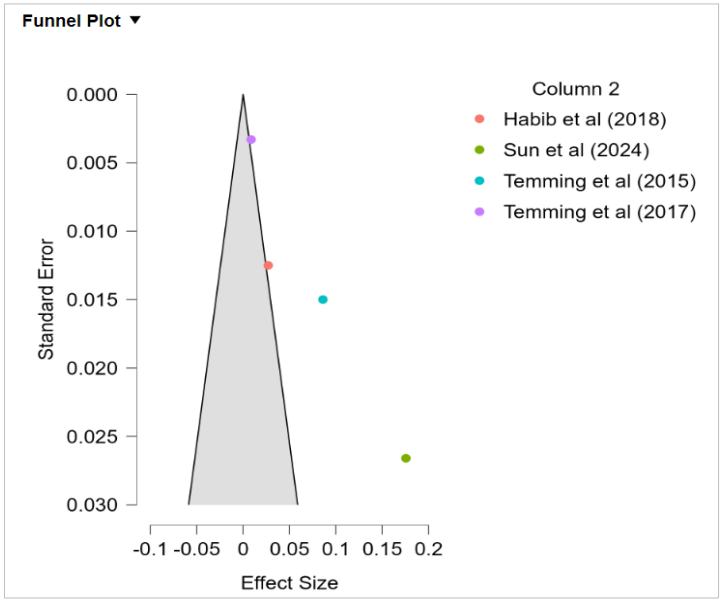

Figure 3: Funnel plot

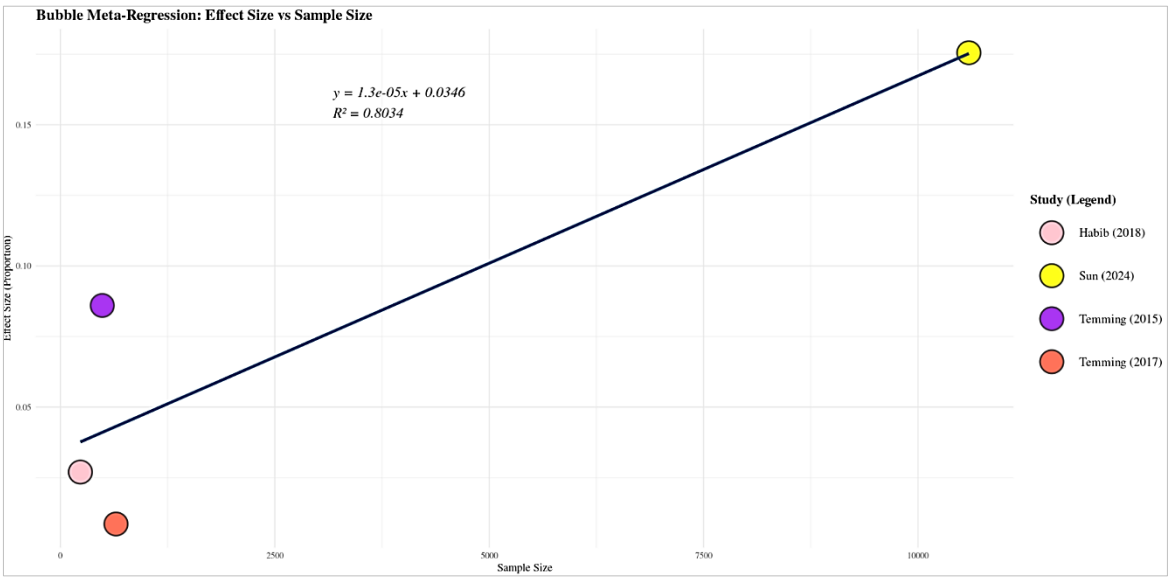

Figure 4: Bubble meta regression plot

Discussion

A researcher provided one of the initial concrete cohort studies of German pediatric RB survivors, and radiotherapy was observed to increase the risk by threefold for second primary malignancies and 1.8-fold for chemotherapy (Temming *et al*, 2015). The study also introduced differential SIR for sarcoma and leukemia, indicating the direction of radiation as a high-risk factor in SPM development. Radiation exposure increases the risk of subsequent cancers, particularly sarcomas, melanoma, and brain and nasal cavity cancers, and hereditary RB patients have significantly elevated risk (Wong *et al*., 2014).

A second scientist interpreted the topic from the mechanistic view, with emphasis on the mutagenic interaction between RB1 mutation and ionizing radiation as the etiology of orbital sarcomas (Baker *et al*., 2016). Without extensive data, the study had molecular risk contained within anatomical boundaries. Studies of retinoblastoma survivors with hereditary cancer syndromes are informative about the interaction between radiation and genetic susceptibility in the etiology of other cancers (Francis *et al*., 2021).

Yet another scholar advanced the field with genetic granularity and acknowledging patients who possessed severe RB1 mutations had a much higher chance of developing SPMs (Chaussade *et al*, 2018). This was further confirmed again in another study (Gupta *et al*., 2021). Utilizing Mann-Whitney U (U = 56.0, p = 0.0045) and Fisher's exact test (OR = 49.0, p = 0.0101) provided statistical power, and the Kruskal-Wallis test revealed that mutation site alone may not necessarily alter risk.

Another author in a decade-long ophthalmic artery chemosurgery -focused study, demonstrated a low 5-year SPM risk of 2.7% (95% CI: 0–25%), with all cases being pineoblastomas, and no patients receiving EBRT (Habib *et al*, 2018). This hinted at the possible protective role of chemotherapy-only protocols. (Laperrière *et al*., 1998). Children with retinoblastoma, neurofibromatosis type 1, Li-Fraumeni syndrome, and nevoid basal cell carcinoma syndrome are at a higher risk of radiation-related second and third cancers (Smyth *et al*., 2020).

Another study built on their previous work with a larger dataset and determined a sarcoma-specific SIR of 179.35 (Temming *et al*, 2017). Their finding was consistent with their 2015 study: radiation was a predictor on its own. Curiously, sarcomas are responsible for approximately half of secondary cancers in hereditary retinoblastoma survivors (Schwarz *et al*., 1988) (Kleinerman *et al*., 2012).

Another study conducted one of the most statistically robust analyses, known as the Cox regression which revealed a hazard ratio of 5.0 for SPM development in hereditary retinoblastoma (χ^2 = 19.86, $p < 0.00001$) (Gregersen *et al*, 2020). Utilization of national registry data enhanced generalizability. (Ratna, 2020).

Another study had provided true-life long-term survival data, with 65% of SPM patients presenting with bilateral RB and 56% having undergone RT (Zhao *et al*, 2021). Their Kaplan-Meier survival curve highlighted the clinical significance of treatment decision. Management for sarcoma risk, taking into account age, site, and sex, can be used to guide the generation of risk-based screening guidelines (Dapper *et al*., 2023) (Kleinerman *et al*., 2019). Genetic RB predisposes individuals to new cancers in the long term, and radiotherapy increases this risk(Roeder, 2020). Another study highlighted the necessity of longitudinal surveillance methods, specifically the use of bone scans and MRIs in survivors of hereditary retinoblastoma, even without measurable outcomes in their research (Kim *et al*., 2023). Current research attempts to understand whether certain mutations within the RB1 gene or the site of each of these mutations predisposes to sarcomas that may enable the identification of at-risk survivors (Mokánszki *et al*., 2020).

Another report highlighted the necessity of germline genetic testing in all retinoblastoma patients, especially those with unilateral disease but with pathogenic variants (Kim *et al*., 2023). Although the report did not give direct statistics on the occurrence of second primary malignancies, its suggestion for genetic testing aligns with the proven fact that the severity of mutations is a good predictor. The development of individualized long-term follow-up protocols for the identification of sarcomas and other second primary cancers in retinoblastoma survivors is crucial, particularly in survivors who have undergone radiotherapy (Skalet *et al*., 2018).

Lastly, another researcher carried out the sole formal meta-analysis to date, pooling 10,594 cases and an SIR of 17.55 (95% CI: 13.10–23.51) in hereditary RB, affirming that these individuals carry a very high lifetime risk of second malignancy (Sun *et al*,2024). Such surveillance, perhaps in the guise of patient whole-body magnetic resonance imaging, could enable sarcomas and other malignant neoplasms to be identified at an early stage in asymptomatic hereditary RB survivors (Tonorezos *et al*., 2020) (Friedman *et al*., 2013). Together, these studies reveal three broad themes: (1) Patients with hereditary retinoblastoma (RB), especially those with severe RB1 mutations, are at greatest risk of secondary malignancies; (2) Radiation therapy is universally the most significant iatrogenic factor in this risk; and (3) Prolonged latency periods-often decades in duration-demand extended surveillance regimens. Such discoveries mandate revolutionary shifts toward therapies of reduced radiation exposure, ongoing genetic screening, and risk-stratified follow-up regimens.

The merits and gaps were tabulated (Table 4).

Conclusion

This systematic review and meta-analysis confirmed that second primary malignancies are a significant long-term risk in retinoblastoma survivors, especially those with heritable forms and prior radiation therapy by considering the mean proportion of SPM population after RB and arriving at a pooled meta-analytical estimate. It was noted that severe RB1 mutations further elevated this risk. Molecular stratification, minimization of radiation exposure, and adoption of long-term follow-up must be incorporated as a future protocol. Newer approaches such as intra-arterial chemotherapy and surveillance imaging protocols offer safer alternatives. Collaborative databases and patient-level meta-analyses will be critical for refining risk prediction and preventive strategies.

Strengths and Limitations

Proportion and SIR data were utilized for inferential statistical testing to enable better interpretation. Use of particular studies meeting pre-specified inclusion criteria enabled standardization into one common metric for proportion of patients to develop second primary cancer for the purpose of meta-analytic synthesis, thus enhancing data integrity. The study was, however, not without its limitations. There was a very high heterogeneity of 95.3%, as well as the lack of patient-level data, with underreporting of specific classes of mutation limiting the scope of more advanced meta-regression analysis. Some statistical models, including logistic regression, were marred by convergence problems due to sparse data availability. Significant associations were, however, invariably detected.

Declarations

Ethical Approval

Not required since the study conducted was a systematic review and meta-analyses and included the studies selected from 2015-2025.

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Conflicts of Interests

The authors report no conflict of interest.

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Article Category

Systematic review and meta-analyses

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