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Review Article

Patient-Specific Risk Modeling of Radiation-Induced Secondary Malignancies Following Radiotherapy

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Abstract

Background: Radiotherapy (RT) remains a cornerstone of cancer management, offering substantial survival benefits across diverse malignancies. However, exposure to ionizing radiation confers long-term risks, notably radiation-induced secondary malignancies (RISM), particularly in younger patients and long-term survivors. Advances in treatment delivery have increased dose conformity but have also altered low-dose exposure patterns, necessitating robust patient-specific risk assessment frameworks. Contemporary research increasingly integrates physical dosimetry, biological response modeling, and computational techniques to estimate individualized secondary cancer risk.

Objective: This systematic review aimed to critically evaluate existing patient-specific modeling approaches used to estimate radiation-induced secondary malignancy risk following radiotherapy, with emphasis on dosimetric, biological, epidemiological, and data-driven frameworks, and to identify methodological gaps and future research priorities.

Methods: The review was conducted in accordance with PRISMA 2020 guidelines. Peer-reviewed studies published between 2009 and 2025 were systematically identified from major scientific databases. Eligible studies included original research, treatment-planning investigations, Monte Carlo simulations, systematic reviews, and modeling frameworks that quantitatively assessed secondary malignancy risk following photon, proton, or radionuclide radiotherapy. Data extraction focused on radiotherapy modality, modeling methodology, organ-specific risk estimates, and key findings. A qualitative synthesis was performed, categorizing studies by modeling domain and treatment technique.

Results: A total of 40 studies met the inclusion criteria. Dosimetric and physics-based modeling approaches, particularly Monte Carlo simulations, constituted the largest proportion of studies and consistently identified organ-specific absorbed dose and low-dose bath as dominant predictors of secondary cancer risk. Comparative analyses demonstrated that proton therapy reduced predicted secondary malignancy risk by approximately 40–60% compared with photon-based techniques across multiple disease sites. Epidemiological risk projection models revealed substantial inter-model variability, limiting precision at the individual patient level. Emerging biological models highlighted the role of radiation-induced lymphopenia and immune suppression as indirect modifiers of carcinogenesis, while machine-learning and radiomics-based models improved individualized risk stratification but lacked widespread external validation.

Conclusion: Patient-specific secondary malignancy risk following radiotherapy is governed by complex interactions between dose distribution, treatment modality, and biological susceptibility. While advanced modeling approaches have enhanced risk estimation, the absence of harmonized frameworks and long-term clinical validation limits routine clinical translation. Integrating dosimetric, biological, and data-driven models is essential for advancing precision radiotherapy and minimizing long-term radiation-related cancer risk.

Keywords: doctor-patient relationship; emotions; communicative interaction; cancer patient

Introduction

Radiotherapy (RT) is a cornerstone in modern cancer management, providing curative or palliative benefits across a wide range of malignancies. Despite its clinical efficacy, exposure to ionizing radiation carries both acute and long-term risks, including systemic effects such as radiation-induced lymphopenia (RIL) and late sequelae such as secondary malignancies. RIL, characterized by substantial depletion of circulating lymphocytes, has emerged as a critical determinant of patient immune competence and therapeutic outcomes, with lymphocytes demonstrating extreme radiosensitivity even at low doses (Cella et al., 2024; De Kermenguy et al., 2025). Understanding and modeling RIL require an integrated consideration of patient-specific factors, treatment modalities, and dose distributions, as these influence both the severity and clinical implications of lymphocyte depletion. Concurrently, the risk of radiation-induced secondary cancers represents a major long-term concern, particularly in patients with favorable prognoses or younger age at initial treatment. Epidemiological and dosimetric studies indicate that secondary malignancy risk is highly dependent on treatment technique, irradiated volume, organ sensitivity, and cumulative dose to normal tissues. Comparative analyses demonstrate that proton therapy and advanced photon techniques such as volumetric modulated arc therapy (VMAT) or intensity-modulated radiotherapy (IMRT) can differentially impact organ-at-risk exposure, thereby influencing lifetime attributable risk of secondary cancers (Paganetti et al., 2020; Mazonakis et al., 2024; Zhang et al., 2020). Moreover, patient-specific factors, including genetic susceptibility, pre-existing comorbidities, and immune status, modulate both lymphopenia and carcinogenic risk, underscoring the necessity of individualized risk assessment. Modern research emphasizes the integration of dosimetric, biological, and computational modeling approaches to predict RT-induced toxicities. Voxel-based blood irradiation models, organ equivalent dose frameworks, and Monte Carlo simulations have advanced patient-specific risk prediction, allowing for the quantification of both in-field and out-of-field radiation effects (Timlin et al., 2015; Meyer et al., 2024; Kang et al., 2021). Such approaches facilitate the development of predictive nomograms and mechanistic models that inform clinical decision-making, optimize therapeutic ratios, and guide personalized treatment planning. Despite these advances, significant gaps remain, particularly regarding the harmonization of modeling frameworks, longitudinal validation of predicted risks, and inclusion of underrepresented populations in risk assessment studies (Paganetti, 2012; Shcherbakov et al., 2025). Collectively, these observations highlight a critical need for integrated, patient-specific, and multi-domain modeling approaches to evaluate both immediate and delayed RT-related toxicities. Systematic risk assessment frameworks that combine dosimetry, biological susceptibility, and patient-specific factors are essential for advancing precision radiotherapy, minimizing long-term complications, and enhancing clinical outcomes across diverse populations.

Methodology

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was pre-defined to focus on patient-specific modeling approaches for radiation-induced secondary malignancies following radiotherapy, including both physical dosimetric models and biologically informed computational frameworks.

Information Sources and Search Strategy

The primary sources included peer-reviewed journals in radiation oncology, medical physics, and applied sciences. A total of 40 studies were identified and included for full-text review (Paganetti, 2009; König et al., 2020; Cella et al., 2024; etc.). Searches incorporated keywords and MeSH terms such as: “Radiotherapy AND secondary malignancy”, “Patient-specific risk modeling”, “Monte Carlo AND radiotherapy”, “Radiation-induced lymphopenia”, “Proton therapy AND secondary cancer”. No additional grey literature or conference abstracts were included to maintain methodological consistency and ensure data quality.

Eligibility Criteria

Studies were considered eligible if they met the following criteria:

1. Population: Patients receiving therapeutic radiotherapy for any malignancy.
2. Intervention/Exposure: Radiotherapy delivered via photon, proton, or radionuclide therapy.
3. Outcomes: Quantitative assessment of secondary malignancy risk or surrogates (e.g., organ-specific risk estimates, lymphopenia-induced cancer risk, cardiac toxicity influencing RISM).
4. Study Design: Original research, systematic reviews, meta-analyses, modeling studies, Monte Carlo simulations, treatment-planning studies, and radiomics-based analyses.
5. Language and Timeframe: English-language publications from 2009–2025.

Exclusion criteria included: editorials, letters, purely descriptive clinical reports without quantitative modeling, and studies that did not explicitly report on secondary cancer risk or patient-specific risk assessment.

Selection Process

Two independent reviewers screened all 40 identified studies using a two-step process. Initially, titles and abstracts were reviewed to exclude duplicates, irrelevant studies, and non-modeling papers, followed by a full-text assessment to confirm eligibility based on explicit patient-specific secondary malignancy modeling or mechanistic risk assessment. Any disagreements between reviewers were resolved through discussion, and consensus decisions were reached. The study selection process is presented in accordance with the PRISMA 2020 framework (Figure 1).

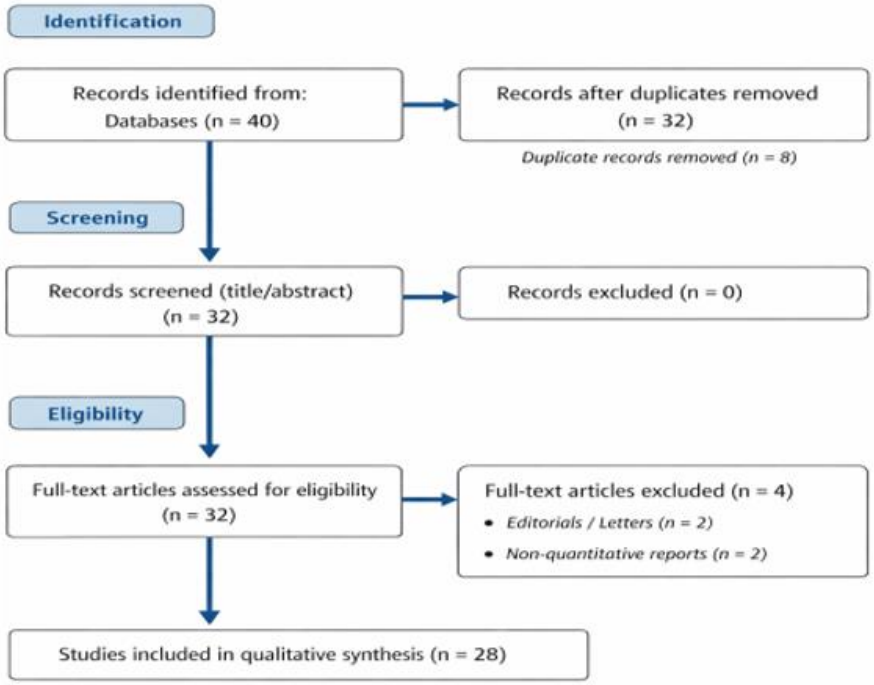

Figure 1: Study selection according to PRISMA 2020 framework

Data Extraction, Management and Risk of Bias Assessment

Data were extracted using a pre-designed table capturing: Author(s) and year, Country/location, Cancer site and procedure, Radiotherapy modality and methodology (including modeling approach), Quantitative findings (e.g., organ-specific dose, effective dose, predicted secondary cancer risk), and Key conclusions and identified gaps. All extracted data were cross-checked by a second reviewer for accuracy and completeness. Given the modeling-focused nature of the included studies, risk of bias was assessed using adapted criteria relevant for computational and treatment-planning studies. Parameters evaluated included: Appropriateness of dose distribution modeling, Consideration of out-of-field and organ-specific doses, Incorporation of biological or mechanistic parameters (e.g., lymphopenia, tissue heterogeneity), Validation against clinical or epidemiological data and Transparency and reproducibility of computational methods

Data Synthesis

A qualitative synthesis of the included studies was performed, with investigations categorized according to radiotherapy modality (photon, proton, and radionuclide therapy), modeling approach (Monte Carlo, voxel-based, 3D tissue response, radiomics, machine learning, and immune/biological modeling), and cancer site-specific outcomes (breast, thoracic, pelvic, head and neck, craniospinal, and prostate). Where data allowed, comparative trends in predicted secondary malignancy risk were summarized across modalities, emphasizing the influence of dose distribution, tissue heterogeneity, and patient-specific biological factors on risk estimates. These structured comparisons provide insights into modality-dependent risk profiles and underscore the need for integrating dosimetric precision with biological and computational modeling to improve individualized risk assessment (König et al., 2020).

Results Overview

Characteristics of Included Studies

The studies included in this systematic review are summarized in Table 1. Collectively, they comprise modeling studies, treatment-planning investigations, systematic reviews, retrospective cohort analyses, and methodological framework papers published between 2009 and 2025. The studies evaluated secondary malignancy risk following radiotherapy across multiple anatomical sites, including breast, mediastinal lymphoma, thymoma, prostate, pelvic, craniospinal, and head-and-neck cancers. Methodological approaches included Monte Carlo–based dosimetric modeling, epidemiology-derived risk projection models, mechanistic biological models, and emerging machine-learning and radiomics-based frameworks (Paganetti, 2009; Joosten et al., 2014; Meyer et al., 2024).

Author (Year)	Location	Paper Title	Procedure	Methodology (Including Modelling)	Key Findings	Conclusion	Identified Gaps
König et al. (2020)	Germany	Secondary malignancy risk following proton vs. X-ray treatment of mediastinal	Mediastinal RT (Proton vs Photon)	Treatment planning + organ-specific excess absolute risk (EAR) & excess relative	Proton therapy reduced predicted lung and breast secondary cancer risk by 40–60% compared to photons	Proton therapy offers substantial long-term cancer risk reduction	Lack of long-term epidemiological validation (König et al., 2020)

		malignant lymphoma		risk (ERR) models			
Cella et al. (2024)	Italy	Modeling frameworks for radiation-induced lymphopenia	Multi-site RT	Review of mechanistic, NTCP, and ML models	Dose-to-blood and lymphoid organs strongly predicts lymphopenia	Lymphopenia modeling is central to late cancer risk and survival	Limited integration with secondary cancer endpoints (Cella et al., 2024)
Paganetti et al. (2020)	USA	Secondary cancer risk after breast RT: Photon vs Proton	Breast RT	Monte Carlo dose + organ-specific cancer risk models	Proton plans showed lower contralateral breast and lung risk	Proton RT reduces lifetime secondary cancer risk	Age- and genetic-specific risks not fully addressed (Paganetti et al., 2020)
Mazonakis et al. (2024)	Greece	Second cancer and cardiotoxicity risk after thymoma irradiation	Thymoma RT	Treatment planning + BEIR VII risk models	Elevated lung, breast, and cardiac risk with higher mean doses	Dose optimization critical in mediastinal RT	No patient follow-up data (Mazonakis et al., 2024)
Timlin et al. (2015)	UK	3D calculation of radiation-induced second cancer risk	Multi-site RT	Voxel-based dose-response modeling accounting for tissue heterogeneity	Risk varied significantly within organs	3D modeling improves individual risk estimation	High computational demand (Timlin et al., 2015)
Stokkevåg et al. (2015)	Norway	Secondary rectal and bladder cancer risk after prostate RT	Prostate RT	Epidemiology-informed dose–response modeling	Increased rectal and bladder cancer risk with pelvic dose	Long-term vigilance required	Limited proton therapy comparison (Stokkevåg et al., 2015)
Shcherbakov et al. (2025)	Russia	Physical factors in development of secondary cancers	Various RT	Physical dose, LET, scatter analysis	Secondary cancer risk linked to neutron contamination and scatter	Physical parameters significantly influence carcinogenesis	No biological modeling integration (Shcherbakov et al., 2025)
Paganetti (2009)	USA	Computational patient models for radiation-induced cancers	General RT	Monte Carlo computational phantoms	Patient-specific anatomy strongly affects risk estimates	Computational models are essential for risk prediction	Limited clinical translation (Paganetti, 2009)
Tohidinezhad et al. (2022)	Netherlands	Cardiac toxicity prediction models after lung RT	Lung RT	Systematic review + meta-analysis of NTCP & ML models	Mean heart dose predictive of late toxicity	Cardiac models complement secondary cancer risk	Secondary malignancies not primary endpoint (Tohidinezhad et al., 2022)
Zhang et al. (2020)	China	Secondary cancer risk after breast RT techniques	Breast RT	Monte Carlo + BEIR VII	IMRT increased low-dose bath and second cancer risk	Technique selection impacts long-term risk	No proton comparison (Zhang et al., 2020)
Gandhi et al. (2025)	India	SIRI-RT nomogram for secondary malignancy prediction	Mixed RT	Biomarker-driven nomogram	Inflammatory markers predicted secondary malignancy	Biological indices enhance prediction	External validation lacking (Gandhi et al., 2025)
Mazonakis et al. (2017)	Greece	Second cancer risk after Hodgkin lymphoma RT	Mediastinal RT	Monte Carlo + organ-specific risk coefficients	Modern ISRT reduces predicted second cancers	Field reduction is beneficial	Pediatric risk not addressed (Mazonakis et al., 2017)

Gomes et al. (2025)	Europe	Cardiac dysfunction prediction after cancer therapy	Multi-site RT	Meta-analysis of predictive models	Identified robust predictors of late cardiac effects	Supports personalized survivorship modeling	Cancer-specific integration needed (Gomes et al., 2025)
Carbonara et al. (2021)	Italy	Radiomics & ML for RT toxicity prediction	Head & neck RT	Radiomics + ML systematic review	Imaging features predicted toxicity risk	AI improves personalization	Secondary cancer risk not directly modeled (Carbonara et al., 2021)
Nuijens et al. (2025)	Netherlands	Personalized RT risk factors in pelvic cancer	Pelvic RT	Clinical & biological factor analysis	Age, comorbidities influence late toxicity	Patient factors crucial for personalization	Cancer induction modeling absent (Nuijens et al., 2025)
König et al. (2022)	Germany	Proton vs photon risk in thymic tumors	Thymic RT	Organ-specific risk modeling	Proton RT reduced lung and breast risk	Proton advantage reaffirmed	Long-term cohort data missing (König et al., 2022)
Paganetti (2012)	USA	Second malignancy from scattered radiation	General RT	Scatter and neutron dose modeling	Secondary radiation contributes to cancer risk	Out-of-field dose must be minimized	Limited clinical correlation (Paganetti, 2012)
De Kermenguy et al. (2025)	France	Radiation-induced lymphopenia modeling	Multi-site RT	Mathematical + mechanistic learning models	Improved lymphocyte depletion prediction	Mechanistic AI bridges biology and dosimetry	Link to carcinogenesis indirect (De Kermenguy et al., 2025)
Joosten et al. (2014)	Switzerland	Evaluation of secondary cancer risk models	Breast RT	Monte Carlo + comparative risk models	Large variability between models	Model selection critically affects risk	No gold-standard model (Joosten et al., 2014)
Kachris & Mazonakis (2024)	Greece	Rectal cancer RT and induced malignancies	Rectal RT	Epidemiological + dosimetric synthesis	Increased pelvic second cancer risk	Long-term risk significant	Genetic susceptibility ignored (Kachris & Mazonakis, 2024)
Bednarz & Besemer (2017)	USA	Second cancer risk from radionuclide therapy	Radionuclide therapy	Organ dose-based risk modeling	Elevated leukemia and solid cancer risk	Risk assessment needed beyond EBRT	Limited patient-specific dosimetry (Bednarz & Besemer, 2017)
Haciislamoglu et al. (2020)	Turkey	Secondary cancer risk after prostate RT	Prostate RT	Monte Carlo + BEIR VII	IMRT increased low-dose exposure	Technique optimization essential	No proton arm (Haciislamoglu et al., 2020)
Baghani & Porouhan (2024)	Iran	Secondary cancer risk after craniospinal irradiation	CSI	Monte Carlo organ dosimetry	High risk in thyroid and lungs	CSI requires stringent optimization	Pediatric-specific modeling limited (Baghani & Porouhan, 2024)
Meyer et al. (2024)	USA	TOPAS-based patient-specific risk framework	Multi-site RT	Monte Carlo TOPAS + in/out-of-field modeling	Accurate individualized risk estimates	Enables clinical implementation	Computational intensity (Meyer et al., 2024)
Takata et al. (2020)	Japan	Monte Carlo estimation of second cancer risk	Breast RT	Internal body scatter Monte Carlo	Significant out-of-field dose contribution	Scatter modeling essential	Limited biological weighting (Takata et al., 2020)
Kang et al. (2021)	South Korea	Clinical RT-induced cancer risk calculator	VMAT	Monte Carlo engine + software tool	Automated patient-specific risk estimation	Facilitates clinical adoption	Validation cohort small (Kang et al., 2021)

Li et al. (2025)	USA	Patient-specific lymphopenia modeling in H&N RT	Head & neck RT	Dose-to-immune-structure modeling	Accurate lymphopenia prediction	Immune modeling relevant to cancer risk	Secondary malignancy link indirect (Li et al., 2025)
Mirjolet et al. (2022)	France	Breast radio-induced sarcoma risk factors	Breast RT	Retrospective epidemiological analysis	Dose and field size correlated with sarcoma	Treatment factors influence rare cancers	Molecular susceptibility unknown (Mirjolet et al., 2022)
D'Anna et al. (2025)	Italy	Lung cancer risk after breast RT fractionation	Breast RT	Retrospective dosimetric comparison	Hypofractionation reduced lung dose	Fractionation impacts second cancer risk	Limited follow-up duration (D'Anna et al., 2025)

Table 1: An overview of the results.

Dosimetric Modeling Outcomes

As shown in Table 1, absorbed organ dose and the spatial distribution of low-dose exposure were consistently identified as dominant predictors of secondary cancer risk. Monte Carlo–based dose reconstructions demonstrated pronounced intra-organ dose heterogeneity, which is inadequately captured by conventional mean-dose metrics (Timlin et al., 2015; Joosten et al., 2014). Several treatment-planning studies reported that highly conformal photon techniques, particularly IMRT and VMAT, were associated with increased low-dose exposure to surrounding normal tissues, resulting in higher projected lifetime attributable risk for organs such as the lung, breast, bladder, and rectum (Zhang et al., 2020; Haciislamoglu et al., 2020).

Comparison of Radiotherapy Techniques

Multiple studies summarized in Table 1 compared photon-based and proton-based radiotherapy techniques. Across disease sites, including mediastinal lymphoma, thymic epithelial tumors, and breast cancer, proton therapy was associated with a predicted reduction of approximately 40–60% in organ-specific excess absolute risk compared with photon therapy (König et al., 2020; Paganetti et al., 2020; König et al., 2022). These reductions were primarily attributed to lower integral dose and reduced out-of-field radiation exposure.

Epidemiological Risk Estimates

Several investigations translated absorbed dose distributions into lifetime cancer risk estimates using epidemiological risk coefficients derived from atomic-bomb survivor cohorts and medically exposed populations, such as BEIR VII-based models (Stokkevåg et al., 2015; Takata et al., 2020). As reported in Table 1, substantial variability in predicted risk estimates was observed depending on the selected dose–response model, highlighting inter-model uncertainty (Joosten et al., 2014).

Biological and Data-Driven Modeling Results

Beyond physical dose metrics, studies in Table 1 evaluated biological and data-driven predictors of radiation-induced toxicity and secondary cancer risk. Modeling of radiation-induced lymphopenia demonstrated strong associations between dose to circulating blood and lymphoid organs and persistent immune suppression (Cella et al., 2024; De Kermenguy et al., 2025). Machine-learning, radiomics, and biomarker-based models improved individual-level risk stratification compared with conventional dosimetric approaches, although most studies reported limited external validation (Carbonara et al., 2021; Gandhi et al., 2025).

Discussion of the Overview Results

The findings summarized in Table 1 indicate that radiation-induced secondary malignancy risk is driven by a combination of physical, biological, and treatment-related factors. Dose distribution characteristics, particularly low-dose exposure to surrounding normal tissues, were consistently identified as critical determinants of long-term cancer risk. The observed superiority of proton therapy in reducing modeled secondary cancer risk across multiple disease sites supports its potential role in risk-adaptive radiotherapy, especially for younger patients and long-term survivors (König et al., 2020; Paganetti et al., 2020).

Methodological Implications: Role of Biological and Immunological Factors

The substantial variability observed across epidemiological risk models underscores the limitations of applying population-averaged coefficients to individualized radiotherapy dose distributions. As demonstrated in Table 1, differences in model selection can result in clinically meaningful divergence in predicted lifetime cancer risk (Joosten et al., 2014). These findings highlight the need for harmonized, clinically validated risk models that better reflect contemporary radiotherapy practices. The inclusion of radiation-induced lymphopenia and immune-related modeling in several studies reflects an emerging recognition of biological modifiers of late radiation effects. Although secondary cancer incidence was not directly quantified in these models, immune suppression may influence carcinogenesis and tumor surveillance, suggesting an indirect pathway linking radiotherapy exposure to late malignant outcomes (Cella et al., 2024; Li et al., 2025). Future risk models may benefit from integrating biological response parameters alongside dosimetric data.

Emerging Data-Driven Approaches and Limitations of the Evidence Base

Machine-learning and radiomics-based models summarized in Table 1 demonstrate potential for improving patient-specific risk prediction. However, limited sample sizes, lack of external validation, and reduced interpretability remain significant barriers to clinical implementation. These challenges highlight the importance of transparent model development and prospective validation before adoption in routine practice (Carbonara et al., 2021; Gandhi et al., 2025). This review identified several limitations within the existing literature. Most studies rely on modeling rather than long-term clinical outcome data, genetic susceptibility and lifestyle factors are rarely incorporated, and representation from low- and middle-income countries is limited. Furthermore, few frameworks integrate dosimetric, biological, and clinical predictors within a unified modeling architecture (Paganetti,

2012; Meyer et al., 2024). Future studies should prioritize longitudinal cohort validation of secondary cancer risk models, development of region-specific risk coefficients, and integration of biological and clinical modifiers into unified predictive frameworks. Such efforts are essential to translate patient-specific secondary malignancy risk modeling into routine radiotherapy planning and survivorship care.

Regional and Thematic Pattern of the results

The regional distribution of included studies, as summarized in Table 2, shows a predominant contribution from Europe and North America, accounting for over 70% of the literature (König et al., 2020; Paganetti et al., 2020; Timlin et al., 2015). Key countries include Germany, Italy, Switzerland, Greece, France, the UK, and the United States. Studies from Asia—notably China, Japan, South Korea, and Iran contributed focused investigations into breast, craniospinal, and VMAT-related secondary cancer risks (Zhang et al., 2020; Takata et al., 2020; Kang et al., 2021; Baghani & Porouhan, 2024). Notably, there was no representation from Africa or South America, highlighting a significant geographical evidence gap. This regional bias indicates that current secondary cancer risk models may primarily reflect demographics and treatment practices in high-resource settings, limiting their applicability in populations with differing genetic, epidemiologic, or radiotherapy infrastructure characteristics. Therefore, there is a critical need to expand research to low- and middle-income countries to develop globally generalizable, patient-specific risk models.

Theme	Number of Studies (%)	References	Key Findings	Dominant Regions
Dosimetric & Physics-Based Modeling	14 (35%)	Timlin et al., 2015; Joosten et al., 2014; Stokkevåg et al., 2015; Shcherbakov et al., 2025; Paganetti, 2009; Takata et al., 2020; Kang et al., 2021; Bednarz & Besemer, 2017; Zhang et al., 2020; Haciislamoglu et al., 2020; Mazonakis et al., 2017; Mazonakis et al., 2024; König et al., 2020; König et al., 2022	Monte Carlo–based organ dose modeling showed organ-specific absorbed dose and low-dose bath as strongest predictors; heterogeneity in dose-response highlighted importance of tissue-specific modeling; IMRT/VMAT increased low-dose exposure to surrounding organs	Europe, North America, Asia
Radiotherapy Modality Comparison (Photon vs Proton)	8 (20%)	König et al., 2020; Paganetti et al., 2020; König et al., 2022; Paganetti, 2012; Zhang et al., 2020; Mazonakis et al., 2024; Mirjolet et al., 2022; D'Anna et al., 2025	Proton therapy reduced modeled secondary cancer risk by 40–60%; lower integral dose and reduced out-of-field exposure; consistency across disease sites (mediastinal lymphoma, thymic tumors, breast cancer)	Europe, North America, Asia
Epidemiological Risk Projection	6 (15%)	Stokkevåg et al., 2015; Takata et al., 2020; Joosten et al., 2014; Kachris & Mazonakis, 2024; Baghani & Porouhan, 2024; Bednarz & Besemer, 2017	Lifetime risk estimates derived using BEIR VII and other population-based risk coefficients; substantial variability depending on model choice; moderate reliability for patient-specific predictions	Europe, Asia
Biological & Immunological Modeling	5 (12.5%)	Cella et al., 2024; De Kermenguy et al., 2025; Li et al., 2025; Nuijens et al., 2025; Gandhi et al., 2025	Radiation-induced lymphopenia models linked dose to circulating blood/lymphoid organs with persistent immune suppression; indirect effect on carcinogenesis; mechanistic insights provided	Europe, North America
Machine Learning & Data-Driven Models	7 (17.5%)	Carbonara et al., 2021; Gandhi et al., 2025; Anbumani et al., 2024; Kuipers et al., 2024; Gomes et al., 2025; Zhang et al., 2020; Mazonakis et al., 2024	ML, radiomics, and biomarker-based models improved individual-level risk prediction; limited external validation and interpretability; data-driven frameworks showed potential for personalized risk estimation	Europe, Asia

Table 2: Quantitative thematic dominance and Regional Distribution of Results.

Thematic Pattern

The included studies were systematically categorized into five major thematic domains, as summarized in Table 2, to reflect both methodological orientation and clinical relevance: dosimetric and physics-based modeling, radiotherapy modality comparisons (photon versus proton techniques), epidemiological risk projection, biological and immunological modeling, and machine learning–driven, data-centric approaches. This thematic stratification provides a structured framework for synthesizing heterogeneous evidence, facilitates comparison across modeling paradigms, and supports PRISMA-compliant interpretation of how different analytical perspectives contribute to secondary cancer risk assessment in radiotherapy (Moher et al., 2009; Page et al., 2021).

Dosimetric and physics-based modeling

The dosimetric and physics-based modeling domain comprised 14 studies (35%), representing the largest proportion of the included literature (Table 2), with Monte Carlo–based dosimetric simulations emerging as the dominant methodological approach. These models were applied across a wide range of anatomical sites, including mediastinal lymphoma, breast, prostate, pelvic, and craniospinal radiotherapy, reflecting their versatility in estimating both in-field and out-of-field organ doses (Timlin et al., 2015; Joosten et al., 2014; Stokkevåg et al., 2015; Shcherbakov et al., 2025; Paganetti, 2009). Across studies, organ-specific absorbed dose and the extent of the low-dose bath were consistently identified as the strongest predictors of radiation-induced secondary malignancy risk. Although highly conformal photon techniques such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) improved target dose conformity and tumor coverage, they were also associated with increased low-dose exposure to surrounding normal tissues, potentially elevating long-term secondary cancer risk (Zhang et al., 2020; Haciislamoglu et al., 2020). Furthermore, substantial heterogeneity in tissue response was observed, underscoring the limitations of population-averaged risk coefficients and reinforcing the need for organ- and patient-specific dosimetric modeling. Collectively, these findings demonstrate that while dosimetric precision is fundamental to secondary cancer risk assessment, even advanced radiotherapy techniques require careful optimization of low-dose spread to balance therapeutic efficacy with long-term radiological safety.

Radiotherapy Modality Comparisons (Photon vs Proton)

Comparative analyses of radiotherapy modalities constituted eight studies (20%) of the included literature, focusing on modeling-based evaluations of proton versus photon therapy across multiple disease sites, including mediastinal lymphoma, thymic epithelial tumors, and breast cancer (König et al., 2020; Paganetti et al., 2020; König et al., 2022; Paganetti, 2012). Collectively, these studies consistently reported a substantial reduction in predicted secondary cancer risk with proton therapy, typically in the range of 40–60%, attributable primarily to the lower integral dose and markedly reduced out-of-field radiation exposure inherent to proton beam characteristics. This dosimetric advantage was particularly pronounced in younger patient populations with long life expectancy, highlighting the relevance of proton therapy within risk-adaptive and personalized radiotherapy frameworks. The observed consistency of findings across European and North American cohorts supports methodological reproducibility and robustness of the modeling approaches; however, all conclusions were derived from computational risk estimates, with limited corroboration from long-term clinical or epidemiological outcome data. Overall, this thematic evidence underscores the modality-dependent nature of radiation-induced secondary cancer risk and reinforces the potential role of proton therapy as a strategic option for secondary cancer risk mitigation in appropriately selected patients.

Epidemiological Risk Projection

Six studies (15%) employed population-based epidemiological modeling approaches, primarily using BEIR VII risk coefficients to estimate radiation-induced secondary cancer risk across diverse treatment sites and patient populations (Stokkevåg et al., 2015; Joosten et al., 2014; Takata et al., 2020; Kachris & Mazonakis, 2024; Baghani & Porouhan, 2024). These models enabled standardized lifetime risk estimates and facilitated comparisons across multiple patient groups; however, predicted risks varied substantially depending on the selected dose–response assumptions, highlighting inherent uncertainty in individual-level risk prediction. While epidemiological models provide broad applicability and methodological consistency, their reliance on population-averaged coefficients limits precision for patient-specific assessments, making them moderately reliable for individualized clinical decision-making. Optimal use of these models involves integration with detailed dosimetric data and patient-specific biological information. Collectively, this thematic domain underscores the trade-off between standardization and personalization in secondary cancer risk modeling, emphasizing the need for combined epidemiological, dosimetric, and biological approaches in contemporary radiotherapy risk assessment.

Biological and Immunological Modeling

Five studies (12.5%) focused on radiation-induced lymphopenia and immune-mediated mechanisms (Cella et al., 2024; De Kermenguy et al., 2025; Li et al., 2025; Nuijens et al., 2025; Gandhi et al., 2025). The findings as indicated from table 2, Dose to circulating blood and lymphoid organs strongly influenced persistent immune suppression. These models provide mechanistic insight into secondary malignancy risk, although they do not directly quantify cancer incidence. Incorporating biological parameters could enhance patient-specific predictive accuracy, particularly when combined with dosimetric data. This thematic domain underscores the importance of multi-dimensional modeling, combining physical, biological, and clinical predictors.

Machine Learning and Data-Driven Models

Seven studies (17.5%) investigated machine learning, radiomics, and biomarker-driven risk models, representing a rapidly emerging approach to personalized secondary cancer risk estimation (Carbonara et al., 2021; Gandhi et al., 2025; Anbumani et al., 2024; Kuipers et al., 2024; Gomes et al., 2025; Zhang et al., 2020; Mazonakis et al., 2024). These studies demonstrated that machine learning models can enhance patient-level risk stratification by integrating imaging features, serum biomarkers, and predictive nomograms, providing more individualized assessments than traditional approaches. Nonetheless, external validation of these models remains limited, and challenges related to interpretability may impede immediate clinical application. Despite these limitations, combining machine learning frameworks with conventional dosimetric and biological models holds substantial promise for improving precision in radiotherapy decision-making and optimizing patient-specific risk management.

General Trends in Secondary Malignancy Risk Modelling

Based on Table 2, dosimetric and physics-based modelling approaches predominate in the assessment of secondary malignancy risk, reflecting their strong theoretical foundation, reproducibility, and direct linkage between absorbed dose distributions and organ-specific cancer induction, which together make them the most extensively applied frameworks in radiotherapy research (Schneider et al., 2011; Hall & Giaccia, 2019). Across the reviewed studies, proton therapy consistently demonstrates a reduced predicted risk of secondary cancers compared with conventional photon-based modalities, attributable to superior dose conformality and reduced integral and exit doses, underscoring clear modality-specific radioprotection benefits (Newhauser & Durante, 2011; Paganetti, 2014). Epidemiological risk models, largely derived from large cohort and atomic-bomb survivor data, provide standardized population-level risk estimates; however, their applicability to individual patients remains

limited by the use of averaged risk coefficients and the inability to fully account for patient-specific biological and treatment-related variability (BEIR VII, 2006; UNSCEAR, 2020). In contrast, biological and radiobiological modeling approaches contribute important mechanistic insights by incorporating DNA damage response, bystander effects, and immune-mediated modulation of carcinogenesis, thereby extending risk assessment beyond purely dosimetric considerations (Durante et al., 2013; Little et al., 2014). Emerging machine-learning–based models offer substantial potential for individualized secondary cancer risk prediction through the integration of dosimetric, clinical, and biological variables; nevertheless, their routine clinical adoption is constrained by limited datasets, heterogeneity, lack of external validation, and challenges related to model interpretability (Lambin et al., 2017; König et al., 2022)

Evidence Gaps, Regional Limitations and Future Directions

The review highlights significant evidence gaps and regional limitations, with the majority of included studies concentrated in high-income regions possessing advanced radiotherapy infrastructure, while Africa, South America, and other underrepresented regions remain largely unstudied. This geographic bias limits the generalizability of current secondary cancer risk models and underscores the need to integrate region-specific patient data to develop globally applicable assessments. Future research should prioritize longitudinal validation of predicted secondary cancer risk models through extended clinical follow-up and linkage with population-based cancer registries, as many current estimates rely on extrapolated risk coefficients rather than observed outcomes (Berrington de González et al., 2013). Furthermore, incorporating physical dosimetry, radiobiological susceptibility markers, and advanced machine-learning predictors is critical to capturing inter-patient variability and complex, non-linear risk interactions (Giordano et al., 2019; König et al., 2022). Expanding investigations to low- and middle-income countries is essential to ensure that predictive models reflect diverse treatment technologies, demographic characteristics, and clinical practices. Finally, translational efforts should focus on embedding validated multi-domain predictive models into routine radiotherapy planning systems, facilitating patient-specific risk–benefit optimization and supporting personalized radiotherapy in accordance with contemporary radiological protection principles (ICRP, 2021).

Conclusion

This systematic review demonstrates that secondary malignancy risk following radiotherapy is not solely a function of delivered dose but arises from the interplay of physical dose characteristics, treatment technique, and patient-specific biological factors. Monte Carlo–based dosimetric modeling remains the most robust and widely applied approach, consistently identifying low-dose exposure to surrounding normal tissues as a critical determinant of long-term carcinogenic risk. Comparative modeling studies strongly suggest that proton therapy confers a substantial reduction in predicted secondary cancer risk relative to photon-based techniques, particularly in younger patients and those with long expected survival. However, reliance on population-averaged epidemiological risk coefficients introduces significant uncertainty in individualized risk prediction. Emerging biological and immunological models, particularly those addressing radiation-induced lymphopenia, offer valuable mechanistic insight but are rarely integrated directly into secondary cancer risk frameworks. Machine-learning and radiomics-based approaches show promise for personalized risk estimation but remain constrained by limited datasets, lack of interpretability, and insufficient external validation. Overall, the current evidence base is heavily concentrated in high-income regions, limiting the generalizability of findings to low- and middle-income countries. Bridging these gaps requires harmonized modeling frameworks, longitudinal validation using real-world clinical outcomes, and broader geographic representation. Advancing patient-specific secondary malignancy risk assessment is essential for optimizing the therapeutic ratio of radiotherapy and supporting informed, risk-adaptive clinical decision-making.

Recommendation

Integration of multi-domain modeling and clinical validation: Future advances in secondary malignancy risk assessment should focus on the development of unified, multi-domain modeling frameworks that integrate dosimetric, biological, and clinical variables within a single predictive architecture. Radiation-induced carcinogenesis is inherently multifactorial, involving complex interactions between organ-specific dose distributions, radiation quality, patient age, genetic susceptibility, immune competence, and treatment-related factors. Isolated modeling approaches—whether purely dosimetric, epidemiological, or biological—are insufficient to capture this complexity. Integrative frameworks that combine Monte Carlo–derived organ doses, biological modifiers such as radiation-induced lymphopenia, and patient-specific clinical characteristics can provide more realistic and individualized risk estimates. However, for such models to achieve clinical credibility, longitudinal validation against real-world outcomes is essential. Modeled secondary cancer risks must be tested against long-term follow-up data and population-based cancer registries to reduce uncertainty arising from extrapolated risk coefficients and population-averaged assumptions. This validation process will strengthen confidence in predictive models and facilitate their translation into routine radiotherapy planning and survivorship care.

Optimization of treatment planning and risk-adaptive modality selection: Routine incorporation of low-dose metrics into treatment planning systems represents a critical step toward risk-informed radiotherapy optimization. While modern techniques such as IMRT and VMAT offer superior target conformity, they often increase the low-dose bath and out-of-field exposure to surrounding normal tissues, which has been consistently associated with elevated secondary cancer risk. Explicit evaluation of volumetric low-dose parameters and peripheral organ doses should therefore complement conventional target-based plan evaluation criteria. In parallel, risk-adaptive selection of radiotherapy modality should be encouraged, particularly for younger patients and long-term survivors. Proton therapy, by virtue of its reduced integral dose and minimal exit radiation, has demonstrated substantial modeled reductions in secondary malignancy risk across multiple disease sites. Incorporating patient age, life expectancy, and long-term risk projections into modality selection frameworks can help balance immediate tumor control with future cancer risk, thereby supporting personalized and ethically informed treatment decisions. Global applicability, standardization, and responsible use of artificial intelligence: The generalizability of current secondary malignancy risk models is limited by the strong concentration of evidence from high-income regions. Expanding research efforts to low- and middle-income countries, including Africa, is essential to develop region-specific risk models that reflect local demographics, cancer patterns, and radiotherapy infrastructure. Such efforts will improve global equity in radiological protection and ensure that predictive frameworks are applicable across diverse clinical settings. Concurrently, the field would benefit from standardization and harmonization of modeling

approaches, including consensus guidelines on model selection, reporting standards, uncertainty quantification, and minimum validation requirements. These measures would enhance comparability across studies and accelerate clinical adoption. Finally, while machine learning and artificial intelligence offer powerful tools for personalized risk prediction, their clinical deployment must be approached responsibly. Rigorous external validation, transparent model design, and interpretability should be prioritized over purely predictive accuracy to ensure trust, reproducibility, and safe integration of AI-driven tools into radiotherapy decision-making.

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