Low Dose Radiation and Cancer: Systematic Review with ☸SAIMSARA.

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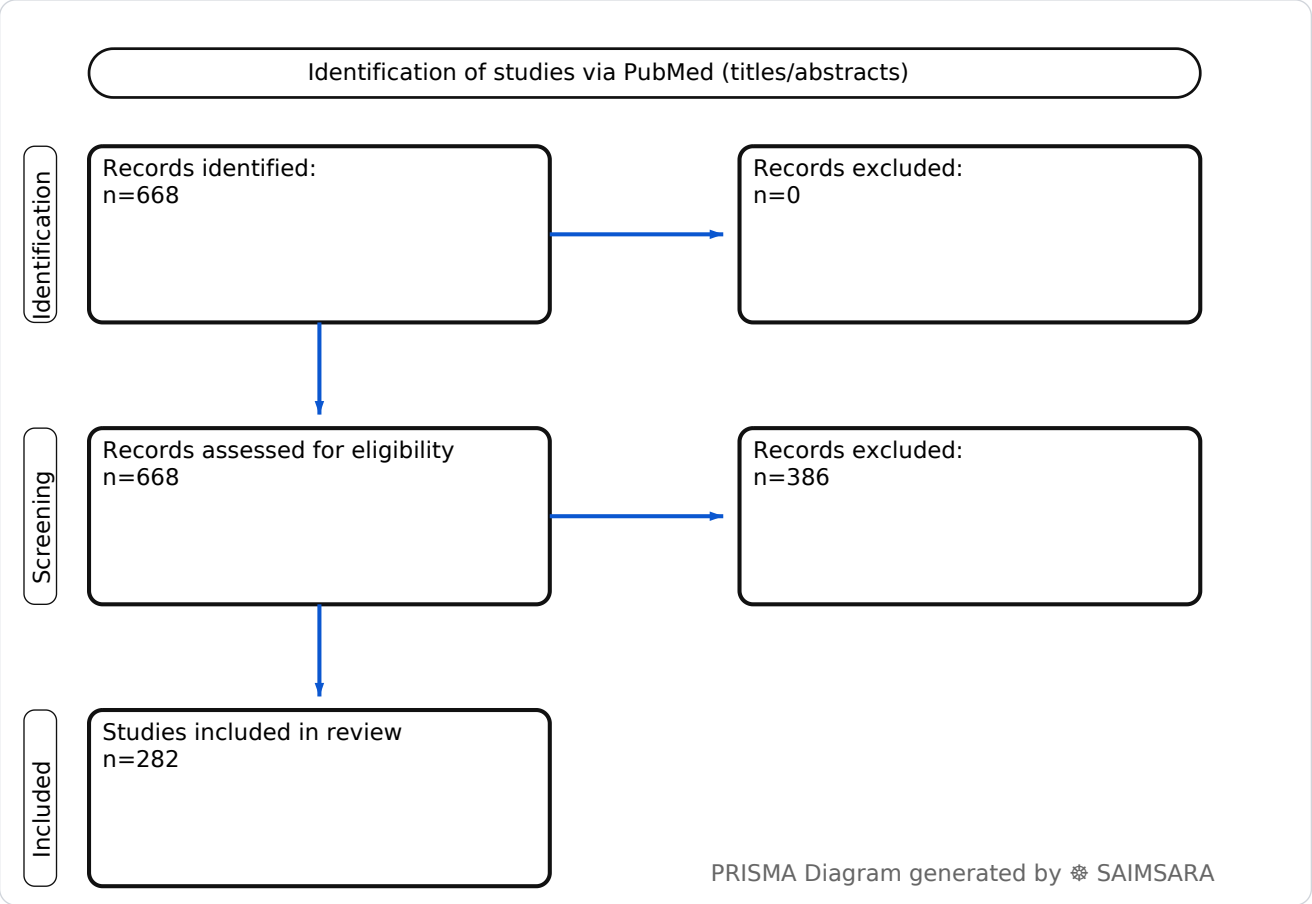
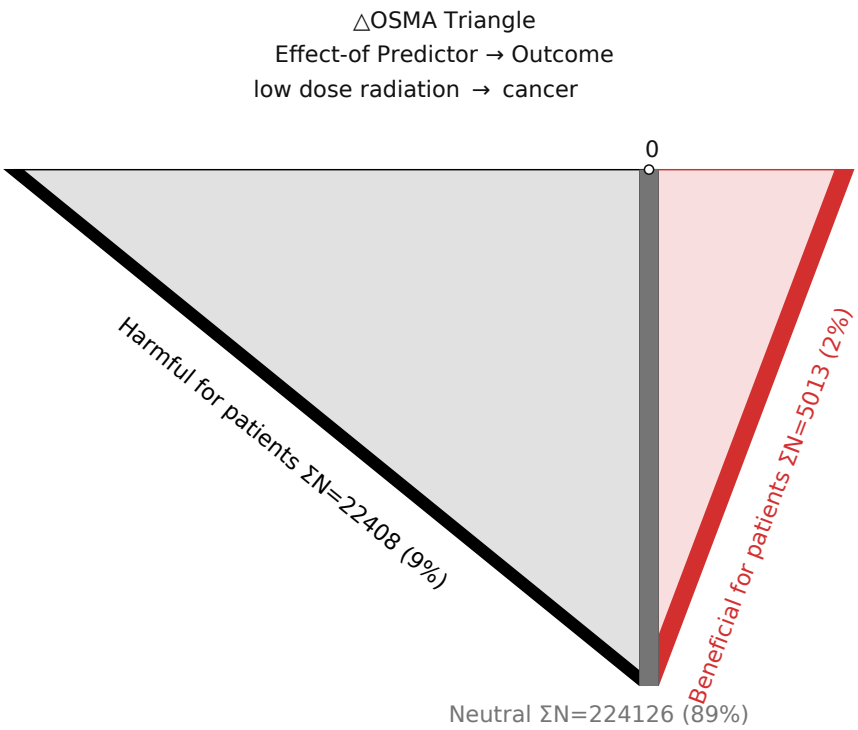
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
- Total Abstracts/Papers: 668
- Downloaded Abstracts/Papers: 668
- Included original Abstracts/Papers: 282
- Total study participants (naïve ΣN): 251547





△OSMA Triangle generated by ☸SAIMSARA

Outcome-Sentiment Meta-Analysis (OSMA): *(LLM-only)*

Frame: Effect-of Predictor → Outcome • *Source*: PubMed

Outcome: cancer Typical timepoints: 3-mo, 3-day. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: mortality, survival, recurrence.

Predictor: low dose radiation — exposure/predictor. Routes seen: subcutaneous. Typical comparator: the general population, observation, pca alone for acetabular, control….

- **1) Beneficial for patients** — cancer with low dose radiation — [5], [6], [7], [8], [9], [11], [14], [21], [26], [31], [32], [36], [37], [45], [48], [51], [52], [61], [67], [76], [80], [82], [84], [87], [90], [91], [92], [94], [96], [101], [106], [108], [111], [112], [114], [119], [120], [122], [125], [126], [127], [132], [133], [134], [135], [137], [141], [142], [143], [145], [146], [151], [156], [161], [165], [169], [175], [176], [181], [182], [184], [190], [196], [199], [205], [213], [218], [219], [222], [245], [246], [247], [252], [260], [274], [275], [280] — ΣN=5013
- **2) Harmful for patients** — cancer with low dose radiation — [13], [41], [43], [55], [63], [68], [73], [74], [78], [81], [85], [89], [93], [98], [100], [102], [103], [107], [110], [113], [118], [121], [129], [131], [138], [139], [147], [148], [152], [160], [164], [166], [171], [172], [188], [189], [192], [194], [195], [198], [204], [206], [212], [214], [221],

[227], [228], [230], [231], [232], [233], [234], [237], [241], [244], [248], [251], [256], [258], [261], [263], [267], [271], [277], [282] — ΣN=22408

- **3) No clear effect** — cancer with low dose radiation — [1], [2], [3], [4], [10], [12], [15], [16], [17], [18], [19], [20], [22], [23], [24], [25], [27], [28], [29], [30], [33], [34], [35], [38], [39], [40], [42], [44], [46], [47], [49], [50], [53], [54], [56], [57], [58], [59], [60], [62], [64], [65], [66], [69], [70], [71], [72], [75], [77], [79], [83], [86], [88], [95], [97], [99], [104], [105], [109], [115], [116], [117], [123], [124], [128], [130], [136], [140], [144], [149], [150], [153], [154], [155], [157], [158], [159], [162], [163], [167], [168], [170], [173], [174], [177], [178], [179], [180], [183], [185], [186], [187], [191], [193], [197], [200], [201], [202], [203], [207], [208], [209], [210], [211], [215], [216], [217], [220], [223], [224], [225], [226], [229], [235], [236], [238], [239], [240], [242], [243], [249], [250], [253], [254], [255], [257], [259], [262], [264], [265], [266], [268], [269], [270], [272], [273], [276], [278], [279], [281] — ΣN=224126

1) Introduction

The relationship between low-dose radiation (LDR) exposure and cancer risk remains a complex and highly debated topic in radiobiology and public health. Historically, the linear no-threshold (LNT) model has guided radiation protection policies, positing that any radiation dose, however small, carries a proportional risk of cancer. However, recent research, particularly on LDR, has challenged this paradigm, with studies suggesting both potential beneficial (hormetic) effects, adaptive responses, and enhanced therapeutic applications, alongside continued concerns about carcinogenesis from diagnostic and occupational exposures. This paper synthesizes current findings to provide a comprehensive overview of LDR's multifaceted role in cancer, encompassing epidemiological observations, mechanistic insights, and emerging therapeutic strategies.

2) Aim

To systematically review the current scientific literature on low-dose radiation and its association with cancer risk and therapeutic outcomes.

3) Methods

Systematic review with multilayer AI research agent: keyword normalization, retrieval & structuring, and paper synthesis (see SAIMSARA About section for details).

- **Bias:** Qualitatively inferred from study design fields. The included studies exhibit a range of designs, from large cohort studies and randomized controlled trials (RCTs) offering higher

evidence levels, to retrospective analyses, mixed studies (combining *in vitro*, *in vivo*, and clinical data), and reviews. The heterogeneity in study designs, populations, and endpoints introduces potential for selection bias, reporting bias, and confounding, particularly in observational studies assessing cancer risk from environmental or occupational exposures. Experimental and preclinical studies, while providing mechanistic insights, may have limited generalizability to human clinical outcomes.

4) Results

4.1 Study characteristics

The structured extraction summary includes 282 studies, predominantly mixed designs (combining experimental, preclinical, and/or clinical components), alongside numerous cohort studies and randomized controlled trials (RCTs). Populations range widely, from human cancer patients (e.g., recurrent high-grade gliomas, metastatic cancer, breast cancer, prostate cancer, esophageal cancer) to radiation workers, general populations exposed environmentally or diagnostically, and various animal and cell models (e.g., triple-negative breast cancer mouse models, human white blood cells, lung cancer cells). Follow-up periods, when specified, varied from short-term (e.g., 24 hours) to long-term (e.g., 108 months, decades, or lifetime).

4.2 Main numerical result aligned to the query

The evidence regarding low-dose radiation (LDR) and cancer risk is highly heterogeneous and often contradictory across studies, precluding a single comparable numeric outcome for risk assessment. While some large cohort studies, such as the Korean Radiation Workers Study (KRWS) and analyses of Life Span Study data, reported a decrease or no apparent increase in overall cancer incidence or mortality among exposed populations compared to general populations or non-exposed groups [1, 11, 79, 101, 250, 262], other epidemiological studies found increased risks for specific cancers, particularly in children exposed to diagnostic LDR [121, 138, 139]. For instance, a meta-analysis reported an excess relative risk (ERR) at 100 mGy of 0.029 (95% CI = 0.011 to 0.047) for solid cancers and 0.16 (95% CI = 0.07 to 0.25) for leukemia, with a higher ERR for childhood leukemia [110]. Similarly, a cohort of South Korean youths exposed to diagnostic LDR showed an increased incidence rate ratio (IRR) of 1.64 (95% CI, 1.56-1.73) for all cancers [121]. In contrast, therapeutic applications of LDR for various cancers often demonstrate promising efficacy, such as improved tumor response or survival, often in combination with other treatments [e.g., 2, 5, 6, 14, 16, 36, 67, 96, 114, 176].

4.3 Topic synthesis

- **Epidemiological Risk Assessment & Models:** Conflicting evidence on LDR cancer risk, with some studies showing decreased overall cancer incidence (e.g., Korean Radiation Workers Study [1], Life Span Study [11]) and others indicating increased risks (e.g., meta-ERR at 100 mGy of 0.029 for solid cancers, 0.16 for leukemia [110]). The debate between the linear no-threshold (LNT) model and threshold/random threshold models for individualized susceptibility persists [15, 18, 22, 54, 56, 60, 74, 79, 101, 110, 237, 248].
- **Diagnostic Radiation & Cancer Risk:** Increased incidence of various cancers (e.g., myeloid leukemias, myelodysplasia, breast, thyroid) in children and youths exposed to low-dose diagnostic imaging (CT scans) [121, 138, 139, 206, 214, 228, 230, 234]. Occupational exposure in medical X-ray workers also showed positive relationships with liver, esophagus, thyroid, and non-melanoma skin cancers [63, 172, 229, 256, 258].
- **Therapeutic Efficacy in Cancer Treatment:** LDRT (low-dose radiation therapy) is explored as monotherapy or in combination with chemotherapy, immunotherapy, or nanoparticles for various cancers, including triple-negative breast cancer (6 Gy X-ray with nanosensitizer [2]), recurrent high-grade gliomas (0.5 Gy LDRFT [5]), metastatic colorectal cancer (LDRT plus FOLFIRI-bevacizumab achieving 10/10 clinical PR/CR [176, 199]), and locally advanced gastric/gastroesophageal junction adenocarcinoma (LDRT with chemotherapy and tislelizumab [16]).
- **Immunomodulation by Low-Dose Radiation:** LDR enhances antitumor immunity by transiently increasing NK cell frequency and IFN-γ production [4], boosting vaccine-induced antitumor CD8 T cell responses [9], promoting M1 macrophage polarization [106], and upregulating immune checkpoint molecules like CD47 and PD-L1 in lung cancer cells [82, 19]. LDR also improves the immune microenvironment and sensitizes tumors to immune checkpoint inhibitors [48, 51, 80, 87, 96, 114, 120, 125, 137, 146, 179].
- **Mechanisms of LDR Effects:** LDR influences DNA damage and repair pathways (e.g., DNA-PKcs [127], γ-H2AX foci [64, 187, 217]), modulates oxidative stress (e.g., ROS generation [37, 100, 188], NADPH oxidase upregulation [43, 55]), and alters gene expression (e.g., p21 [239], c-Myc [93], miR-30a/b [132], NF-κB [113, 204, 225]). These effects contribute to tumor microenvironment remodeling, cellular proliferation, apoptosis, senescence, ferroptosis, cuproptosis, and hypoxia reversal [2, 6, 10, 23, 31, 33, 34, 39, 47, 59, 61, 66, 69, 70, 75, 83, 91, 92, 99, 103, 115, 126, 141, 142, 144, 149, 161, 162, 167, 168, 173, 174, 178, 181, 183, 185, 189, 190, 192, 198, 208, 215, 223, 224, 243, 264, 265].
- **Radiation Adaptive Response & Hormesis:** LDR can induce an adaptive response (AR), enhancing an organism's ability to withstand subsequent higher doses [27, 75, 141, 158, 167, 225]. Some studies suggest LDR is associated with positive health effects, including reduced cancer risk and increased life expectancy, challenging the LNT model and supporting radiation hormesis [11, 21, 32, 79, 101, 140, 169, 181, 188, 205, 213, 246, 266].

- **Toxicity and Safety Considerations:** While LDRT is generally well-tolerated [7], concerns exist regarding acute hematologic toxicity (HT) associated with large volumes of bone marrow (BM) receiving low-dose radiation (e.g., V20 LSBM > 64% for endometrial cancer [13], V5Gy ≥98% for cervical cancer [73], BM-V10 >=90% for anal cancer [232, 241]). Other toxicities include pseudoprogression [5], minor hematologic changes [40], and potential lifetime risks of lung cancer and heart disease from pulmonary LDRT [42, 86, 98, 107, 207].

5) Discussion

5.1 Principal finding

The evidence regarding low-dose radiation (LDR) and cancer risk is highly heterogeneous and often contradictory across studies, precluding a single comparable numeric outcome for risk assessment, with some studies showing decreased overall cancer incidence [1, 11] while others report increased risks, particularly from diagnostic exposures [110, 121].

5.2 Clinical implications

- **Therapeutic Potential:** LDRT, particularly when combined with novel agents (e.g., nanosensitizers, PARP inhibitors, immune checkpoint inhibitors), offers a promising strategy for various cancers, including triple-negative breast cancer [2], recurrent high-grade gliomas [5], and metastatic disease [96, 114, 176].
- **Immunotherapy Enhancement:** LDR's ability to remodel the tumor microenvironment and enhance anti-tumor immune responses suggests its increasing role as an immunomodulator, potentially improving the efficacy of existing immunotherapies [9, 14, 36, 48, 51, 82, 106, 111, 120].
- **Diagnostic Risk Management:** Given the observed increased cancer risks in children from diagnostic low-dose ionizing radiation (e.g., CT scans) [121, 138, 139], careful consideration of necessity and dose reduction strategies (e.g., EOS scans [45], prospectively ECG-gated CTA [227]) is crucial, especially for radiosensitive subgroups [18].
- **Toxicity Monitoring:** When employing LDRT, clinicians should be mindful of potential toxicities, such as acute hematologic toxicity associated with bone marrow exposure [13, 73, 232, 241], and monitor for pseudoprogression, which may correlate with improved outcomes [5].
- **Individualized Risk Assessment:** The concept of individual susceptibility to radiation-induced cancer, potentially influenced by genetic factors and adaptive responses [15, 18, 136, 244], highlights the need for personalized risk assessment rather than a universal linear no-threshold (LNT) approach [22, 46, 54, 56, 60, 62].

5.3 Research implications / key gaps

- **Dose-Response Curve Elucidation:** Further research is needed to precisely define the dose-response relationship for LDR in various human populations, especially at very low doses, to clarify if a threshold or hormetic effect exists for cancer risk [11, 21, 27, 74, 101, 237].
- **Biomarker Identification:** Developing robust and sensitive biomarkers (e.g., PAX5-related CpG sites [64], miR-622 [189], plasma proteins [97]) for LDR exposure and individual radiosensitivity would enable more accurate risk stratification and personalized treatment strategies [30, 62, 186].
- **Long-Term Epidemiological Studies:** Continued long-term cohort studies with detailed individual dose data and comprehensive health outcomes are essential to resolve the conflicting epidemiological findings on LDR cancer risks, especially in occupational settings and populations exposed to environmental radiation [1, 72, 78, 81, 85, 89, 116, 117, 148, 152, 154, 155, 166, 171, 172, 194, 212, 231, 233, 240, 250, 258].
- **Mechanistic Pathways in Adaptive Response:** Deeper investigation into the molecular and cellular mechanisms underlying radiation adaptive response (AR) and hormesis, particularly the interplay between DNA repair, immune modulation, and oxidative stress, could unlock novel therapeutic targets [27, 33, 75, 140, 141, 158, 167, 213, 225].
- **Optimized Combination Therapies:** Prospective randomized controlled trials are needed to optimize LDRT dosing, fractionation, and sequencing in combination with emerging immunotherapies, targeted agents, and nanotechnologies to maximize anti-tumor efficacy while minimizing toxicity [2, 5, 6, 14, 16, 36, 61, 87, 96, 114, 176, 179].

5.4 Limitations

- **Heterogeneous Study Designs** — The diverse range of study designs (cohort, RCT, mixed, *in vitro*, *in vivo*) limits direct comparability and meta-analysis of outcomes.
- **Inconsistent Dose Definitions** — "Low dose" is not uniformly defined, making it challenging to synthesize findings across studies with varying radiation levels and dose rates.
- **Lack of Unified Endpoints** — Studies report a wide array of endpoints, from cancer incidence and mortality to tumor response rates, immune cell changes, and molecular alterations, hindering a singular conclusion on LDR and cancer.
- **Confounding Factors** — Epidemiological studies are often susceptible to confounding by lifestyle factors (e.g., smoking [85, 89]), genetic predispositions, and other environmental exposures, which can bias radiation risk estimates.

- **Limited Long-Term Follow-up** — While some studies offer long follow-up, many preclinical and early clinical trials lack the extensive follow-up needed to fully assess long-term cancer risks or late effects of LDR.

5.5 Future directions

- **Standardized Dose Reporting** — Implement consistent reporting of LDR doses, dose rates, and fractionation schemes to improve comparability.
- **Biomarker Validation Studies** — Conduct large-scale studies to validate LDR-specific biomarkers for risk assessment and treatment response.
- **Personalized Risk Models** — Develop and test models that integrate individual genetic susceptibility and lifestyle factors into LDR cancer risk predictions.
- **Adaptive Response Mechanism Trials** — Design clinical trials that leverage LDR-induced adaptive responses to enhance radioprotection or therapeutic efficacy.
- **Immunomodulatory LDRT Trials** — Further investigate LDRT in combination with novel immunotherapies through robust randomized controlled trials.

6) Conclusion

The evidence regarding low-dose radiation (LDR) and cancer risk is highly heterogeneous and often contradictory across studies, precluding a single comparable numeric outcome for risk assessment, with some studies showing decreased overall cancer incidence [1, 11] while others report increased risks, particularly from diagnostic exposures [110, 121]. This complexity underscores the dual nature of LDR, which can be both a potential carcinogen, especially in vulnerable populations, and a promising therapeutic tool for various cancers. The lack of unified endpoints and consistent dose definitions across studies remains the most significant limitation affecting certainty. A crucial next step is to conduct large-scale, long-term epidemiological studies with standardized dose reporting and comprehensive health outcomes to resolve the conflicting findings on LDR cancer risks.

References

SAIMSARA Session Index — session.json

Figure 1. Publication-year distribution of included originals

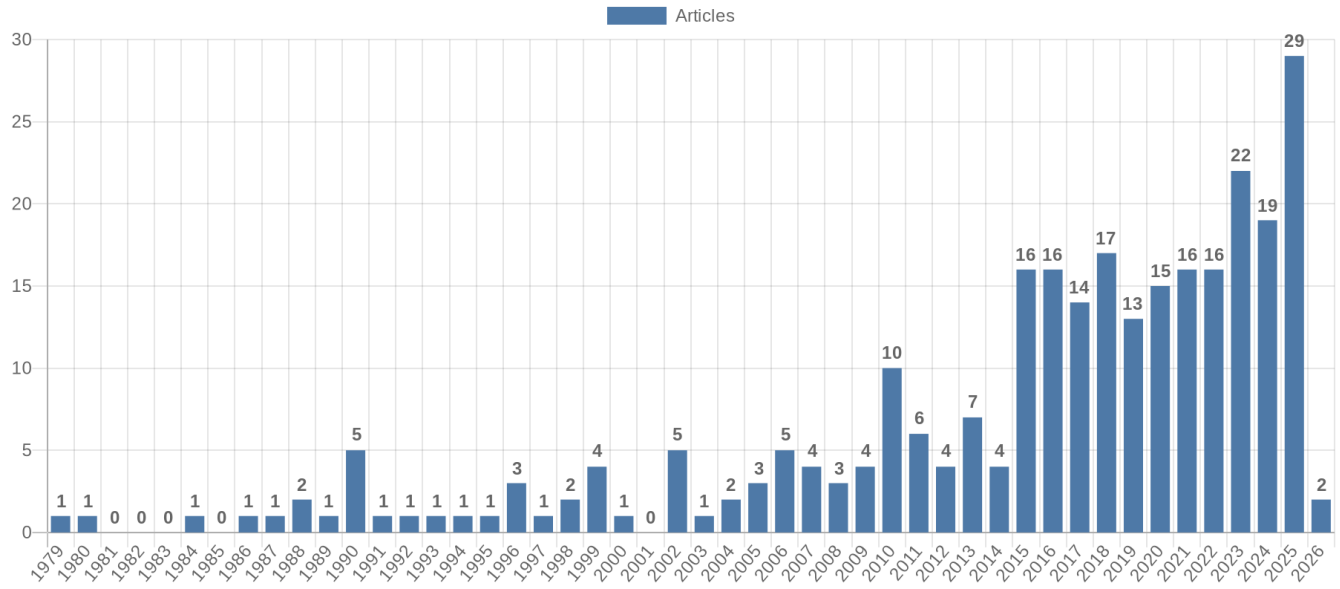


Figure 2. Study-design distribution of included originals

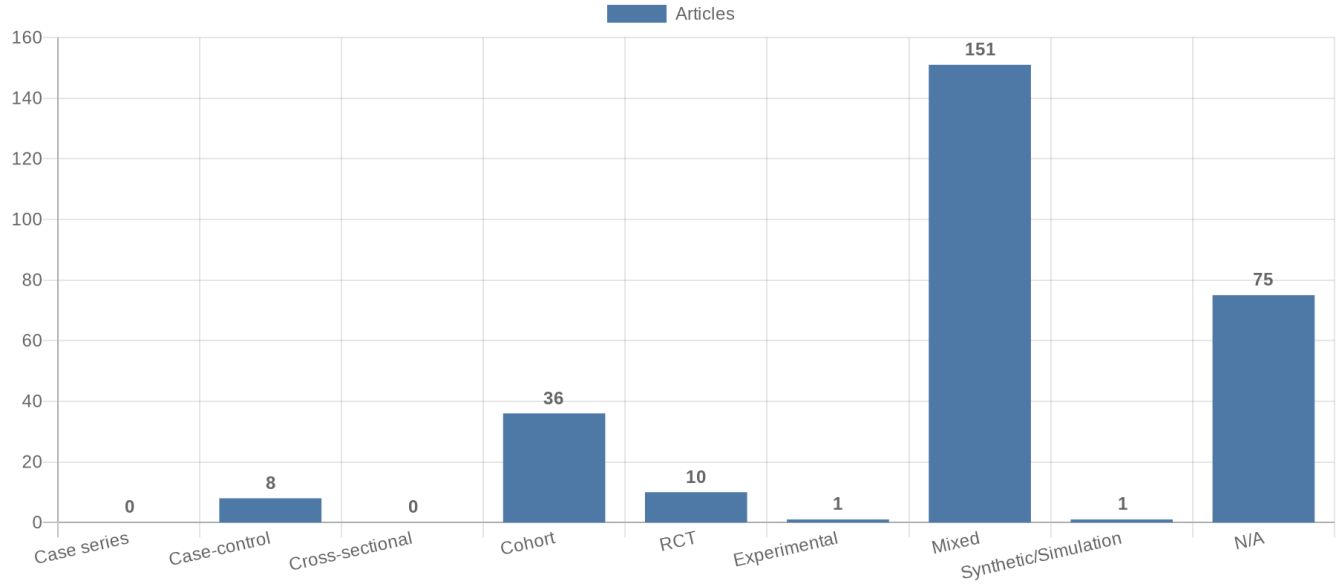


Figure 3. Study-type (directionality) distribution of included originals

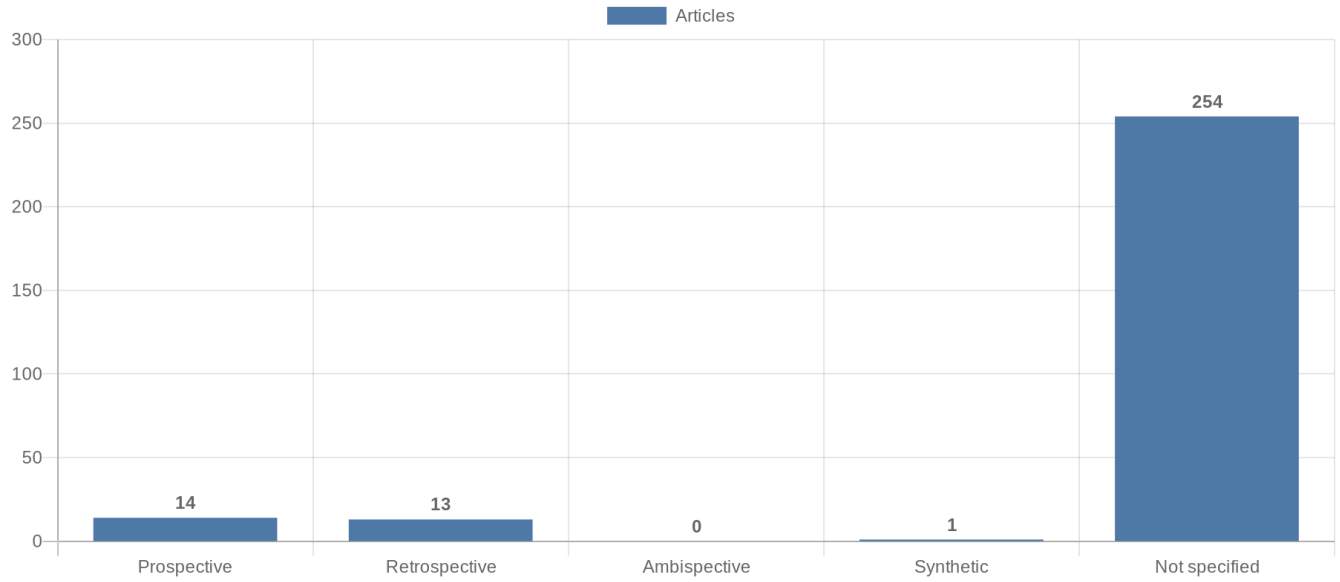


Figure 4. Main extracted research topics

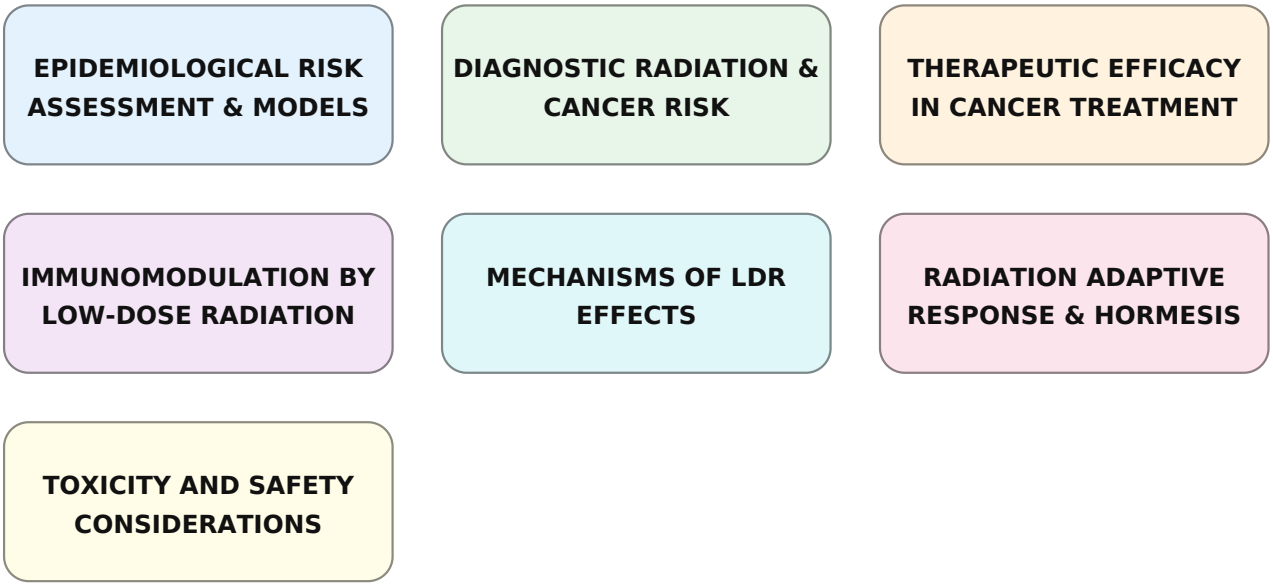


Figure 5. Limitations of current studies (topics)

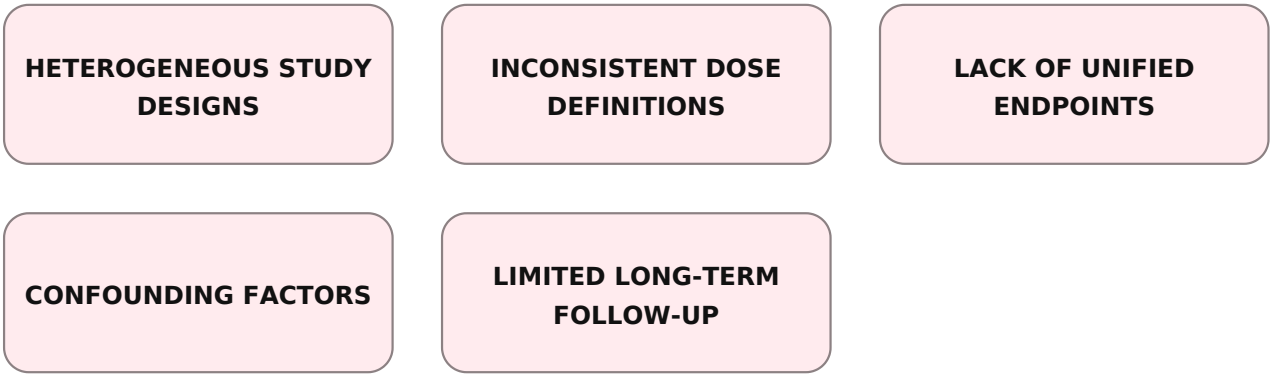


Figure 6. Future research directions (topics)