**Appendix G -- FDA PRISMA SLR and Meta-Analysis Details**

# Outcomes of Ipsilateral-Breast Tumor Recurrence in Early-Stage, Low-Risk Breast Cancer Patients Following Breast Conserving Treatment: A Systematic Review

## Abbreviations:

T1N0: Tumor stage 1, clinically node-negative cancer

IBTR: In-breast tumor recurrence

ER: Estrogen receptor

PR: Progesterone receptor

HER2: Human Epidermal Growth Factor Receptor-2

BCS/T: Breast-conserving surgery/treatment

RCT: Randomized control trial

WBRT: Whole-breast radiotherapy

PBI: Partial breast irradiation

IORT: Intra-operative radiotherapy


## Abstract:

*Background and Objectives:* Breast cancer is the most common cancer among women in the United States, accounting for about 30% of all new cancers each year in women.[1,2] This systematic review examines the outcomes of in-breast tumor recurrence (IBTR) in early-stage, low-risk breast cancer patients with a focus on elderly women with T1N0 luminal A tumors. The objective of this review is to synthesize existing literature to provide insights into IBTR rates following breast conserving surgery/treatment (BCS/T) with/without radiotherapy.

*Methods:* Data sources included Pubmed/MEDLINE and Embase. Observational studies, randomized control trials (RCTs), and population-based studies were screened. The primary outcome was IBTR at 5-years. Data were extracted and pooled with random effects models.

*Results:* A total of 25 studies were included in the systematic review, with five studies of six cohorts (n=2,062) providing data suitable for pooling in a meta-analysis. Among the studies reporting five-year IBTR rates, the values ranged from 0% to 12% for different treatment arms. The pooled 5-year ipsilateral breast tumor recurrence (IBTR) rate from the five studies included in the meta-estimate was estimated at 0.61% (95% CI; 0.10% to 3.50%), indicating a very low recurrence risk in very low-risk breast cancer patients following breast-conserving surgery. Subgroup analysis meta-estimates showed no statistically significant difference in IBTR rates between patients who received radiotherapy 0.68% (95% CI; 0.15% to 2.94%) across three studies and those who did not 0.47% (95% CI; 0.00% to 35.91%) ($p = 0.6985$) in two studies.

There was insufficient data to complete meta-analysis comparing patients who did and did not receive adjuvant hormone therapy. Heterogeneity across the studies was substantial ($I^2$ = 99.99%, $Tau^2$ = 2.3583), indicating significant variability between studies.

*Discussion:* The meta-analysis confirmed a very low IBTR rate in patients with very low-risk breast cancer, confirming the safety of breast-conserving surgery. While radiotherapy and hormone therapy were associated with slightly lower IBTR rates, their omission in selected patients did not result in significantly higher recurrence rates. The markedly high heterogeneity found highlights the variability in treatment modalities, suggesting that findings be interpreted with these inconsistencies in mind.

## Introduction

Breast cancer is the most common cancer among women in the United States, accounting for about 30% of all new cancers each year in women[1]. In 2024, it is estimated that approximately 310,720 new cases of invasive breast cancer will be diagnosed.[1] With a median age of diagnosis at 62, breast cancer primarily affects middle-aged and older women[1]. The average lifetime risk of developing breast cancer in the U.S. is about 13%, making it a significant public health concern that demands effective screening, treatment, and prevention strategies[1-3].

Among the various breast cancer subtypes, T1N0 tumors are a part of the low-risk category, particularly in elderly women[4]. These tumors are small (≤2 cm) with no lymph node involvement. Many of these low-risk tumors fall under the luminal A molecular subtype, characterized by the presence of estrogen receptor (ER) and/or progesterone receptor (PR), the absence of Human Epidermal Growth Factor Receptor-2 (HER2), and a low expression of the proliferation marker Ki-67. [5,6] Luminal A tumors are typically low-grade, slow-growing, and have the most satisfactory prognosis among breast cancer subtypes.[4,7] Generally, they respond well to hormone therapies, such as tamoxifen or aromatase inhibitors, but derive limited benefit from chemotherapy.[8-10] Despite the favorable outcomes associated with T1N0 luminal A tumors, the risk of in-breast tumor recurrence (IBTR) remains a concern.[11] A recent prospective cohort study of women aged >55 who had undergone BCS for T1N0, grade 1 or 2, luminal A-subtype breast cancer and had received adjuvant hormonal therapy found that recurrence occurred in 2.3% of patients after five years, identifying this specific patient population as very low risk for local recurrence.[12]

This systematic review aims to provide a comprehensive analysis of IBTR outcomes among the aforementioned very low risk population. By synthesizing existing literature, the review will offer clear insights into recurrence rates following breast-conserving surgery/treatment (BCS/T).

## Methods

### *Protocol*

This study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and Cochrane Handbook for Systematic Reviews of Interventions.[13,14]

### *Search Strategy*

The full search strategy is in Supplement 1. We searched Pubmed/MEDLINE and Embase databases on August 6, 2024.

*Inclusion Criteria*

We included observational studies, randomized control trials (RCTs), and population-based studies evaluating the effects of BCS/T (lumpectomy) with/without radiotherapy. Case studies and case series were not eligible for inclusion. The population of interest included female patients ≥50 years at diagnosis of early-stage, low risk breast cancer. This was defined with the following criteria: a) unifocal infiltrating ductal carcinoma b) tumor size ≤2 cm c) Nottingham grade 1-2 d) ER positive e) PR positive f) HER2 negative g) clinically node-negative (N0). The primary outcome of this study was IBTR at 5-years. Studies reporting at least one of the following were considered for inclusion a) cumulative incidence of IBTR at 5-years b) 5-year IBTR free survival rate. Only English language studies published after January 1, 2000, were assessed for eligibility.

*Study Selection and Data Extraction*

Two reviewers divided the total reports to perform title/abstract screening, full text screening and data extraction independently. Conflicts were resolved by a third reviewer. As this was a deviation from standard screening and data abstraction methodology outlined in the Cochrane Handbook for Systematic Reviews of Interventions, necessary due to time constraints, several strategies were implemented to mitigate any potential bias based on only having one reviewer performing screening and data extraction.[14] First, reviewers met to verify inclusion/exclusion criteria and identified eligible seminal papers in alignment with pre-specified inclusion/exclusion criteria to affirm the scope of the review. Prior to data extraction, reviewers piloted the data extraction template and affirmed data extraction strategy by consensus on variable definitions. Reviewers employed the same extraction form to ensure consistency of data abstracted individually. Finally, each reviewer performed checks of data extracted from two papers abstracted by the other to verify consistency in data extraction methodology and content. Data pooled for meta-analysis was independently extracted by two reviewers and verified by a third and fourth reviewer. Both title and abstract screening and full-text screening were managed on EndNote 20 software.[15] Where IBTR was not clearly stated for the population of interest in text, but was available for the population of interest in a figure in the paper, PlotDigitizer was employed to convert IBTR survival curves to numerical data for extraction.[16]

*Risk of Bias*

One reviewer assessed the risk of bias of the individual studies using the Cochrane Risk of Bias 2 (RoB2) tool for RCTs and the Cochrane ROBINS-I tool for observational studies.[14]

*Statistical Analysis*

Data were pooled using random-effects models. All analyses were completed using the *GLIMMIX* procedure in SAS 9.4 software for binary event data (IBTR).[17] The model accounted for between-study variability with inverse-variance weighting based on study precision. Zero-event studies were handled using a continuity correction to prevent bias. The model was structured as follows:

$$logit(p\_ij)=\beta 0+ujlogit(p\_ij)=\beta 0+u\_j$$

In the model, $p\_ij$ represents the IBTR event rate for study $j$, $\beta 0$ is the overall meta-estimate, and $u\_j$ accounts for random effects between studies.

Data not suitable for pooling was summarized via qualitative synthesis. Subgroup analyses were planned to compare IBTR rates between patients receiving radiotherapy and those who did not, and those who received hormone therapy versus those who did not. More detailed methods on meta-analytic methods can be found in Supplement 6, and full SAS Code for these estimates is provided in Supplement 8.

*Heterogeneity and Publication Bias*

Heterogeneity was assessed using the Q statistic, $I^2$ statistic, and $Tau^2$. Additionally, a funnel plot was completed to evaluate publication bias.

## Results

*Included Studies and Characteristics*

A total of 4,391 records were identified through database searches in PubMed/MEDLINE and Embase for screening using EndNote 20 software. After removing 852 duplicates, 3,539 title/abstract records were screened. Of these articles, 2,835 were excluded based on irrelevance to the study inclusion/exclusion criteria. Full texts of 704 articles were assessed for eligibility, resulting in the exclusion of 679 studies for various reasons, including incorrect population (n = 534), incorrect intervention (n = 12), incorrect outcome (n = 41), incorrect study design (n = 17), abstract-only publications (n = 55), non-English articles (n = 19), and retracted studies (n = 1). Subsequently, 25 studies met the inclusion criteria and were found eligible for the systematic review.[4,12,18-40] Please see PRISMA flow chart in Supplement 2. Characteristics of included studies are presented in Supplement 3. The studies were conducted in Canada (n=2), China (n=1), Denmark (n=1), Italy (n=3), Japan (n=1), Spain (n=1), Turkey (n=1), UK (n=4), and USA (n=11). Eligible studies were roughly balanced in terms of study design with 12 experimental trials and 13 observational studies. Of the RCTs four focused on directly comparing IBTR outcomes of arms with and without adjuvant radiotherapy, while three examined the impact of hormone therapy on IBTR.

Amidst the 25 included studies, 23 specified tumors $\leq$2 cm. Furthermore, 21 studies explicitly limited their populations to patients with node-negative disease. With respect to treatment modalities, adjuvant radiotherapy was employed in 21 out of the 25 studies. Hormone therapy was administered in 23 of 25 studies. Both therapies were associated with low recurrence rates in most studies, supporting their use in this very low-risk patient population. Duration of follow up was robust among eligible studies, with 15 studies reporting median follow-up of >5 years and four studies providing $\geq$10-year follow up. Among the studies reporting five-year IBTR rates, the values ranged from 0% to 12% for different treatment arms, and with five studies reporting 0% IBTR in specific cohorts.

*Qualitative Synthesis*

The age of the patients varied slightly, with many studies focusing on older populations (e.g., >70 years in studies like Carleton 2021 and Hughes 2004), while others included a somewhat broader age range (e.g., Blamey 2013 and Arvold 2011).[4,18] For example, the median age among patients followed in Arvold 2011 was 56 (n=905).[18] Blamey 2013 included patients aged 33-69 (mean=57 years).[4] Additionally, 11 studies focused exclusively on patients >60 years old. Among the 25 included studies, there was notable variability in terms of tumor size, histology, and use of adjuvant chemotherapy. While studies mostly focused on patients with small tumors (<2cm), some allowed for slightly larger tumors, such as those up to 3cm in Ohsumi 2022, introducing variability in recurrence risk.[36] Histological subtypes were sometimes inconsistently reported among eligible studies, but where specified invasive ductal carcinoma was the predominant subtype. A few studies allowed for other histological types, such as invasive lobular carcinoma, potentially influencing treatment options and outcomes. Furthermore, administration of adjuvant chemotherapy varied among eligible studies. Many studies omitted chemotherapy for very low-risk patients, those of interest in this review, while others included a small subset of patients who received chemotherapy. Variability in adjuvant chemotherapy adds further complexity to the overall analysis. This heterogeneity in tumor profiles and treatment protocols likely contributed to the substantial between-study differences observed.

All participants were treated with BCS. Radiotherapy was a common component of treatment across nearly all studies (n=21), reflecting its established role in reducing recurrence rates following breast-conserving surgery. Various approaches to radiotherapy were employed. The most frequently reported modality employed either as standard treatment (e.g., Blamey 2013, Coles 2017) or as a comparator in trials assessing the efficacy of omitting radiotherapy (e.g., Hughes 2004).[4,30,34] The outcomes often indicated low recurrence rates with whole-breast radiotherapy (WBRT), underscoring its effectiveness. Some studies explored more localized radiotherapy approaches, such as intra-operative radiotherapy (IORT) (e.g., Abdelsattar 2020), which aims to deliver targeted radiation during surgery.[19] These studies generally reported low recurrence rates, although the shorter follow-up durations in some of these studies warrant cautious interpretation of long-term efficacy. A few studies evaluated the outcomes of omitting radiotherapy in select patient populations. For instance, Hughes 2004 and Kunkler 2015 examined outcomes in older women receiving hormonal therapy alone. These studies found higher recurrence rates in the absence of radiotherapy.[21,34]

Hormonal therapy was widely used across the studies (n=23). In some studies, a high proportion of patients received hormonal therapy, such as in Coles 2017, where 91% of patients were treated.[30] These studies generally reported very low recurrence rates, reinforcing the role of hormonal therapy in reducing IBTR. Other studies showed more varied use, sometimes influenced by patient age, tumor characteristics, or study design. For example, in Demirci 2012, only 46% of patients received hormonal therapy, yet the study still reported high locoregional control rates over a long follow-up period.[24]

Across the studies, the rates of IBTR were generally low, upholding the very low-risk nature of the patient population. Many studies reported IBTR rates close to or below 2% at 5 years, with some reporting 0% recurrence in certain cohorts (e.g., Benitez 2007, Ciervide 2018).[20,27] These findings highlight the effectiveness of BCS/T approaches, even in more conservatively treated populations. The follow-up durations varied, with some studies offering data extending beyond 10 years (e.g., Hughes 2013).[33] Longer follow-up periods provided valuable insights into the robustness of treatment effects, with most studies showing continuing low recurrence rates over time. The variability in recurrence rates was often linked to differences in treatment modalities. For instance, Kunkler 2015 reported higher recurrence rates in patients who underwent lumpectomy alone compared to those who also received WBRT, illustrating the protective effect of radiotherapy.[21] While HER2 status was unknown among the sample leveraged by Kunkler 2015, it was included due to its adherence to the remainder of the inclusion/exclusion criteria, providing valuable insight into recurrence rates between patients who did and did not receive adjuvant WBRT in addition to lumpectomy. Similarly, Hughes 2004 demonstrated that the combination of hormone therapy and radiotherapy significantly reduced IBTR compared to hormone therapy alone.[34]

*Risk of Bias Assessment—RoB2*

Many of the RCTs had moderate risk of bias due to the lack of concealment of allocation until participants were assigned to intervention. Additionally, while blinding was often not possible given the interventions, deviations from the intended interventions were uncommon among included studies. Selection of the reported result is where low risk of bias appeared, as the study staff likely did not choose to report data from multiple eligible measurements. Please see Supplement 4 for full assessment of risk of bias in the individual RCTs.

*Risk of Bias Assessment—ROBINS-I*

Many observational studies were found to have serious risk of bias due to lack of consideration of potential confounders in both the study design and analysis. All observational studies had low risk of bias in classification of the interventions. Several observational studies were found to have either moderate or serious risk of bias due to missing data, as studies did not report on the completeness of data. Please see Supplement 4 for full assessment of risk of bias in the individual observational studies.

*Quantitative Synthesis*

*IBTR - Primary Outcome*

Only five of the 25 eligible studies had data that were suitable for pooling in a meta-analysis, due to slight heterogeneity in study population characteristics such as partial population use of adjuvant chemotherapy or tumor size modestly >2cm. To preserve the validity of meta-estimates, only studies presenting 5-year local IBTR for patients that strictly met the prespecified inclusion/exclusion criteria were pooled for meta-analyses. For a complete breakdown of reasons for inclusion/exclusion into the meta-estimate please see Supplement 5.

Six cohorts in five studies had data suitable for meta-analysis (Table 1). HER2 status was not reported in two studies selected for quantitative analysis.[21,40] One study reported locoregional recurrence via Kaplan-Meier survival estimates—this was included, however, as the IBTR rate would be lower than the locoregional recurrence rate, as IBTR does not include regional recurrences.[37] The pooled meta-analysis of 2,062 total patients yielded an estimated 5-year IBTR rate of 0.61% (95% CI; 0.10% to 3.50%), summarized in Table 2. This reflects a very low rate of recurrence in very low-risk breast cancer patients undergoing breast-conserving surgery. However, heterogeneity was extremely high, with a Q statistic of 62,283.99 ($p < 0.0001$), an $I^2$ of 99.99%, and a $Tau^2$ of 2.3583, indicating substantial between-study [i]variability that could potentially be attributed to zero-events present among the pooled data in additional to differences in treatment protocols.

*Adjuvant Radiotherapy - Subgroup Analysis*

Among studies with data suitable for pooling, only Soyder 2013 and Whelen 2023 did not administer adjuvant radiotherapy. The remaining studies, Ciervide 2018, Kunkler 2015, and Offersen 2022 provided adjuvant radiotherapy to their eligible cohorts. The subgroup analysis found that patients who did not receive radiotherapy (n=516) had a 5-year IBTR rate of 0.47% (95% CI; 0.00% to 35.91%). Patients who received radiotherapy (n=1546) had a 5-year IBTR rate of 0.68% (95% CI; 0.15% to 2.94%). While this study was not designed to detect differences in IBTR between patients treated with concomitant radiotherapy or without concomitant radiotherapy, on post hoc analysis the difference in IBTR between the radiation and no radiation groups was not statistically significant ($p = 0.6985$). Additionally, the wide confidence interval for the no radiation group indicates considerable uncertainty in this estimate, which is unsurprising as it was based on only two studies with very disparate sample size and different effect estimates.

*Adjuvant Hormone Therapy - Subgroup Analysis*

There was not sufficient data to perform subgroup meta-analysis comparing participants who did and did not receive adjuvant hormonal therapy.

*Publication Bias*

The funnel plot for assessment of publication bias for the studies included in the meta-analysis may be found in Supplement 7. The plot appears asymmetrical around the overall effect size (indicated by the red dashed line). This asymmetry suggests the presence of publication bias.

**Table 1.** Summary of characteristics among studies included for meta-analysis.

| Study ID | Year | Country | Study Design | Sample Size^ (n=) | Age | Tumor Size | Histology | Radio-therapy | Hormonal Therapy | In-breast tumor recurrence (IBTR) at 5-years | Follow-up Duration |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ciervide 2018 | 2021 | Spain | Prospective cohort | 23 | Median = 74, (Range 63-90) | <2.2cm | T1N0 | Yes | No | 0% | Median = 4 years |
| Kunkler 2015 | 2015 | UK | Randomized control trial | 1326 | ≥65 | 0-1.0cm 39.5%; 1.1-2.0cm 49.5%; 2.0-3.0cm 12% | T1N0M0 | Yes, for treatment group only | Yes | 1.3% for WBRT** + lumpectomy patients; 4.1% for lumpectomy only patients | Median = 5 (Range 3.84-6.05 years) |
| Offersen 2022 | 2022 | Denmark | Randomized control trial | 865 | Median = 66 (Range: 60-86) | *Not specified* | T1N0M0 | Yes | Yes, for treatment group only | 18 locoregional recurrences in total (6 in WBRT** and 10 PBI†) | Median = 7.6 years (IQR, 6.1-9.2) |
| Soyder 2013 | 2013 | Turkey | Retrospective cohort | 16 | Mean = 74.5 | <2cm | T1N0 | No | Yes | 0% | Mean = 32.2 months |
| Whelen 2023 | 2023 | Canada | Prospective cohort | 500 | Median = 67.1 (IQR = 62.9–71.6) | <2cm | pN0 | No | Yes | 2.3% (95% CI, 1.2 to 4.1) | Median = 5 years |

**WBRT: Whole-breast radiotherapy

† PBI: Partial breast irradiation

^Sample size is provided for relevant population within the study

**Table 2.** Meta-Analysis of 5-Year IBTR Rates from Selected Studies

| Study ID | 5-year IBTR Rate (%) (Lower 95% CI - Upper 95% CI) | Initial Sample Size | Number at Risk at 5-year | Number of Events at 5-year | Radiation Group |
|---|---|---|---|---|---|
| Ciervide 2018 | 0.0% (0.0% - 0.0%) * | 23 | 16* | 0* | Yes |
| Soyder 2013 | 0.0% (0.0% - 0.0%) * | 16 | 11* | 0* | No |
| Kunkler 2015_2 (RT Arm) | 0.5% (0.0% - 1.0%) | 658 | 324 | 5 | Yes |
| Offersen 2022_1 (WBI Arm) | 0.7% (0.2% - 1.9%) | 434 | 396 | 3 | Yes |
| Offersen 2022_2 (PBI Arm) | 1.2% (0.40% - 2.6%) | 431 | 379 | 5 | Yes |
| Whelen 2023 | 2.3% (1.3% - 3.8%) | 500 | 246 | 10 | No |
| **IBTR Random Effect Weighted Meta-Estimate** | **0.61% (0.10% - 3.50%)** | 2062 | 1372* | 23* | |
| **With Radiation IBTR Random Effect Weighted Meta-Estimate** | **0.68% (0.15% 2.94%)** | 1546 | 1115 | 11 | |
| **Without Radiation IBTR Random Effect Weighted Meta-Estimate** | **0.47% (0.00% 35.91%)** | 516 | 257* | 10* | |

* Indicates corrected values where imputation and zero correction were applied for missing or zero event rates. Corrected values are based on SAS output where missing data for number at risk or events were imputed or corrected as described in methods.

## Discussion

The findings from this meta-analysis confirm that very low-risk breast cancer patients have an extremely low risk of IBTR following BCS/T, with an estimated overall recurrence 5-year IBTR of 0.61%. This supports the current practice of using breast-conserving surgery for such patients, alongside adjuvant therapies where appropriate. Despite the low pooled IBTR rate, the high degree of heterogeneity observed ($I^2 = 99.99\%$) suggests that individual patient factors and treatment protocols significantly influence outcomes. This variability is also likely partially attributable to the multiple studies with zero-events and treatment modalities across the studies. As such, the pooled estimate should be interpreted with caution, as it may not fully reflect the variability in individual patient outcomes.[41,42]

The subgroup analysis of radiotherapy showed no statistically significant difference in IBTR rates between patients receiving and not receiving radiotherapy. However, the wide confidence interval in the no-radiotherapy group suggests uncertainty and highlights the need for more targeted research to determine whether omission of radiotherapy is safe without compromising local control of cancer recurrence.

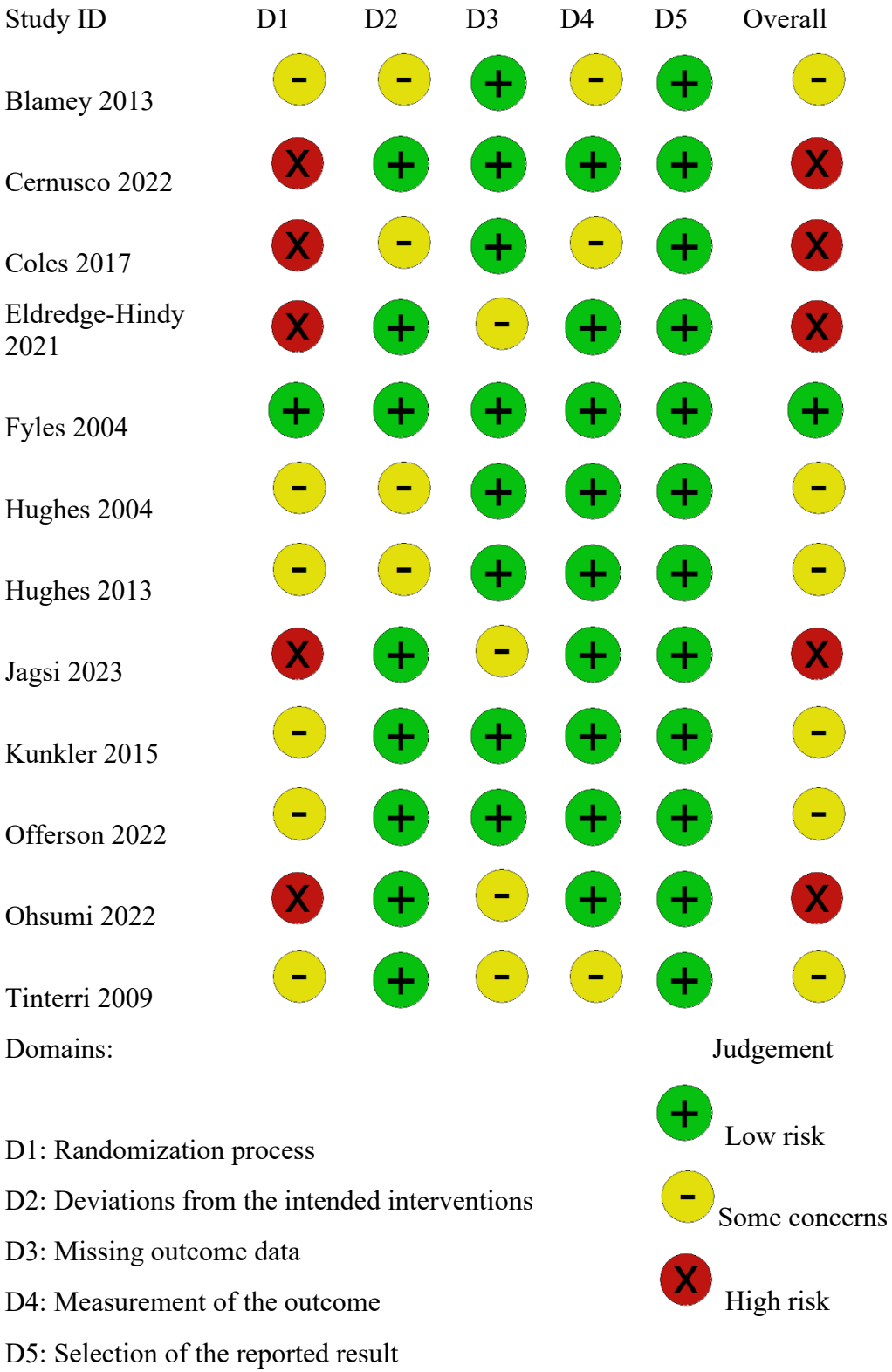
## Conclusion

From the qualitative assessment of these 25 studies, there was consistency in results across study designs, across geographic locations, in patients receiving different adjunctive therapies, and these were maintained over longer follow-up when reported. In the meta-analysis of the five studies meeting the most stringent inclusion/exclusion criteria to the ICE3 population point estimates for IBTR recurrence were also low. The consistency in low recurrence rates suggests that BCS/T, with or without adjuvant therapies, is a safe and effective treatment option for this population.

**Supplement 1.** Search Strategy

| Database | Search Terms |
|---|---|
| Pubmed/MEDLINE | (breast neoplasms OR breast tumor OR breast cancer OR breast carcinoma) AND ("Mastectomy, Segmental"[MeSH Terms] OR breast-conserving surgery OR breast conserving surgery OR breast conservation surgery OR breast-conservation surgery OR breast conserving therapy OR breast-conserving therapy OR breast conservation therapy OR breast-conservation therapy OR breast sparing surgery OR breast-sparing surgery OR breast sparing therapy OR breast-sparing therapy OR partial mastectomy OR lumpectomy OR quadrantectomy OR segmental mastectomy OR limited resection OR tylectomy OR wide local excision OR BCS) AND (neoplasm recurrence, local OR recurrence OR ipsilateral breast tumor OR IBTR OR relapse OR ipsilateral OR in-breast recurrence OR IBR) AND ("Early Stage" OR "Stage I" OR "Early Detection of Cancer" OR "Low Risk" OR "Low-Risk" OR "Nottingham Grade" OR "Grade 1" OR "Grade 2" OR "Tumor Size" OR "≤1.5cm" OR "1.5 centimeters" OR "Luminal A" OR "Ki67" |
| Embase | ('breast neoplasms'/exp OR 'breast neoplasms' OR 'breast tumor'/exp OR 'breast tumor' OR 'breast cancer'/exp OR 'breast cancer' OR 'breast carcinoma'/exp OR 'breast carcinoma') AND ('mastectomy, segmental'/exp OR 'mastectomy, segmental' OR 'breast-conserving surgery'/exp OR 'breast-conserving surgery' OR 'breast conserving surgery'/exp OR 'breast conserving surgery' OR 'breast conservation surgery'/exp OR 'breast conservation surgery' OR 'breast-conservation surgery'/exp OR 'breast-conservation surgery' OR 'breast conserving therapy'/exp OR 'breast conserving therapy' OR 'breast-conserving therapy' OR 'breast conservation therapy'/exp OR 'breast conservation therapy' OR 'breast-conservation therapy' OR 'breast sparing surgery'/exp OR 'breast sparing surgery' OR 'breast-sparing surgery'/exp OR 'breast-sparing surgery' OR 'breast sparing therapy' OR 'breast-sparing therapy' OR 'partial mastectomy'/exp OR 'partial mastectomy' OR 'lumpectomy'/exp OR 'lumpectomy' OR 'quadrantectomy'/exp OR 'quadrantectomy' OR 'segmental mastectomy'/exp OR 'segmental mastectomy' OR 'limited resection'/exp OR 'limited resection' OR 'tylectomy'/exp OR 'tylectomy' OR 'wide local excision'/exp OR 'wide local excision' OR 'bcs') AND ('neoplasm recurrence, local'/exp OR 'neoplasm recurrence, local' OR 'recurrence'/exp OR 'recurrence' OR 'ipsilateral breast tumor' OR 'ibtr' OR 'relapse'/exp OR 'relapse' OR 'ipsilateral' OR 'in-breast recurrence' OR 'ibr') AND ('early stage'/exp OR 'early stage' OR 'stage i' OR 'early detection of cancer'/exp OR 'early detection of cancer' OR 'low risk' OR 'low-risk' OR 'nottingham grade' OR 'grade |

**RoB2 for Randomized Control Trials**



## Supplement 5. Screening for Inclusion into Meta-Estimate

We have attempted to closely follow the Inclusion Criteria when screening full text studies, the targeted group of interest included female patients ≥50 years at diagnosis of early-stage, low risk breast cancer.

This was defined with the following criteria:

a) unifocal infiltrating ductal carcinoma
b) tumor size ≤2 cm
c) Nottingham grade 1-2
d) ER positive
e) PR positive
f) HER2 negativeP
g) clinically node-negative (N0). The primary outcome of this study was IBTR at 5-years.

Studies reporting at least one of the following were considered for inclusion a) cumulative incidence of IBTR at 5-years b) 5-year IBTR free survival rate. Only English language studies published after January 1, 2000, were assessed for eligibility.

Since recurrence rate in the targeted group "low risk, early-stage breast cancer" expected to be small, any deviation from the factors identified in the inclusion criteria might influence the meta estimate rate found. Therefore, this meta-analysis exclusively incorporated studies that demonstrated close alignment with these specified factors (meta-analysis studies highlighted in blue in the table below). We provided caveats and explanation when we deviated from the criteria.

| NO. | Included in the Meta Analysis | Study Name/Year | Total Sample Size | Meta Studies Sample size | Applicable Rate at 5 Year | Meta Analysis Exclusion/Inclusion Reason |
|---|---|---|---|---|---|---|
| **1** | No | Arvold 2011 | 905 | NA | 0.8% (95% CI, 0.4-1.8) | Not able to extract an appropriate age group without chemotherapy, please refer to "Table 3. Patient Baseline Characteristics Stratified by Subtype" |
| **2** | No | Blamey 2013 | NA | NA | NA | Not able to extract the targeted group, age (range 33–69 years), PR positive, and HER2 negative breast cancers status are unknown. |
| **3** | Yes | Ciervide 2018 | 23 | 23 | 0 | 99% alignment with the SLR criteria, 100% of patients with T size (.5-2.2 cm), Grade 1–2, Ki-67 < 25%, Positive Hormonal Receptors |
| **4** | No | De Paula 2016 | 65 | NA | 0 | Not able to extract a group that is free from the following: Lobular, G3, T II, Chemo, Luminal B, N2 |
| **5** | No | Demirci 2012 | 295 | NA | NA | Not able to extract the targeted age group. Age range (18-89) also other excluded factors LVI, N1, T2, Lobular |
| **6** | No | Fyles 2004 | 611 | NA | Tamoxifen arm = 5.9% | Not able to extract the targeted group there are patients with T size 2 to 5, Hormone Receptors negative, grade 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | Tamoxifen and radiation arm = 1 | |
| **7** | No | Khan 2013 | 224 | NA | NA | Not able to extract targeted group, 15 patients received Chemotherapy between the two arms of the study, Hormone receptors status is unknown |
| **8** | No | Kirbky-Bott 2005 | 121 | NA | NA | Not able to extract the targeted age group. Age range 43–84 years |
| **9** | No | Liao 2011 | 12 | NA | 0 | Not able to extract targeted group: Age range 40-71, Chemotherapy, PR and Er negative, HER positive |
| **10** | Yes | Soyder 2013 | 522 | 16 | 0 | Targeted group is BCS+HT T1N0M0 98% alignment with the SLR criteria, all other groups excluded because of stage II, there are 4 patients with Grade 4 in the total cohort that are unknown if they are included in this subgroup, HER2 status unknown |
| **11** | No | Eldredge-Hindy 2021 | 158 | NA | 2.17% (95% CI 0.58–5.78) | Not able to extract the targeted group there are patients with DCIS, Lobular, T 2 and T3, N1, Hormone receptors negative, Chemotherapy |
| **12** | No | Cernusco 2022 | 295 | NA | 2% | Chemotherapy was administered to patients |
| **13** | No | Dahn 2020 | 460 | NA | Radiation alone = 1.5%<br><br>Hormone therapy alone = 4.2%<br><br>No adjuvant therapy = 12% | Targeted group was not extractable: LVI, HER 2 positive, G3 |
| **14** | No | Coles 2017 | 2018 | NA | 0.89% | Targeted group was not extractable there are patients with T3, Node positive, Lymph vascular invasion, Hormone poor, HER2 status positive, chemotherapy in all groups in the study |
| **15** | No | Benitez 2007 | 36 | NA | 0 | Targeted group couldn't be extracted: 5 patients had chemotherapy, age >=45 |
| **16** | No | Hughes 2004 | 636 | NA | Tamoxifen only arm = 4% | Targeted group couldn't be extracted: there are with Hormone negative and T size >2 cm patients in the two arms of the study. |

| | | | | | | |
|---|---|---|---|---|---|---|
| **17** | No | Jagsi 2023 | 186 | NA | 50-59 age group = 3.3%<br><br>60-69 age group = 3.6% | Targeted group couldn't be extracted there are 24 patients with Lobular, 3 patients with Mucinous, 4 patients with Tubular, 6 patients with G3, 16 patients with LVI |
| **18** | No | Kunkler 2015_1* | 1326 | NA | 4.1% (95% CI, 2.4 to 5.7) | Targeted group couldn't be extracted, in the "No radiotherapy group" 6 patients T > 2 cm, 3 patients G3, 2 patients LVI, Estrogen poor 6 patients had recurrences (Table 2) |
| **18** | Yes | Kunkler 2015_2* | 1326 | 658 | 1.3% (95% CI, 0.2 to 2.3) | Targeted group is the RT Arm, 98% alignment with the SLR criteria, in the "radiotherapy group" only 1 patient T > 2 cm had recurrence (Table 2), HER2 status unknown |
| **19** | Yes | Offersen*** 2022_1 | 865 | 434 | 0.7% (95% CI, 0.2 to 1.9) | Targeted group is the WBI group, 99% alignment with the SLR criteria since there is 3 lobular (1%), 12% Other Invasive Cancer, PR status is unknown |
| **19** | Yes | Offersen*** 2022_2 | 865 | 431 | 1.2% (95% CI, 0.4 to 2.6) | Targeted group is the PBI group, 99.9% alignment with the SLR criteria since there is 1 lobular (0%), 12% Other Invasive Cancer, PR status is unknown |
| **20** | No | Ohsumi 2022 | 321 | NA | 3% | Targeted group couldn't be extracted there are patients with hormone negative, T size >2 cm, DCIS, Chemotherapy, Her2 positive in the two arms of the study, also total age range was 50-83 |
| **21** | No | Tinterri 2009 | 649 | NA | Lumpectomy and radiation arm = 0.7% | Targeted group couldn't be extracted, there are patients with T size >2 cm, Lobular, Ostergren and Progesterone negative, Her2 status unknown |
| **22** | Yes | Whelen 2023** | 500 | 500 | 2.3% (95% CI, 1.2-4.1) | 100% alignment with the SLR criteria. |
| **23** | No | Carleton 2021 | 2109 | NA | 1.2% | Targeted group couldn't be extracted, there are patients with T size > 2, Grade III, DCIS, and Mastectomy in all arms in the study.<br>Full information about patients' characteristics is in the supplement not the paper "eTable 3. Baseline Characteristics of Patients " |
| **24** | No | Abdelsattar 2020 | 117 | NA | 1.9% of IORT patients | Targeted group couldn't be extracted, IORT group: 1 patient T2, 3 patients with chemo, 2 patients with N1, Ki 67 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 0% of WBRT patients | max is 19.2<br>WBRT group: 6 patients with T2, 8 patients with chemo, 2 patients with N1, K67 max is 23.3 |
| **25** | No | Hughes 2013 | 636 | NA | NA | Targeted group couldn't be extracted,<br>TamRT group: 4 patients with ER negative, 7 patients<br>with T size > 2, HERs2 Unknown<br>Tam group: 6 patients with ER negative, 6 patients with T size > 2, HERs2 Unknown |

***In Kunkler (2016) Table 2**, recurrence rates were broken down by factors (tumor size, margin, grade, age, lymphovascular invasion, and estrogen status).
For the **no radiotherapy group**, most high-risk factors, like the 20 to 30 mm tumor size group, showed recurrence rate more than 1% (Tumor size (mm) 20·1–30 6/84 (7%)). However, it was difficult to determine if this rate was due to tumor size alone or a combination of another factor. The uncertainty made it challenging to focus on the indicated SLR population, leading us to exclude the no radiotherapy group. On the other hand, **the radiotherapy group** had 0% recurrence rates for most high-risk factors, with only a 1% recurrence in the 20 to 30 mm tumor size group. This suggests that the recurrence rates in the radiotherapy group were more representative of the indicated SLR population, making it more suitable for assessing outcomes. So, we only included the radiotherapy group in the meta-analysis.
****Notes:** 4 patients received radiotherapy, 8 patients didn't receive endocrine therapy
*****Offersen reported only locoregional recurrence, they didn't report local recurrence, the IBTR rate would be lower than the locoregional recurrence rate because IBTR (Local recurrence) does not include regional recurrences.

**Supplement 6. Meta-analysis Model Description**

**Methods for Model**

1. **Meta Estimate Model Description: GLIMMIX Procedure**

The meta-analysis used the GLIMMIX procedure in SAS to fit a weighted random-effects model for binary event data (IBTR rates). This model is suited for meta-analyses where studies report event rates and allows for the incorporation of both fixed and random effects.

- Model Structure:

$\text{logit}(p_{ij}) = \beta_0 + u_j$

  - Where:
    - $p_{ij}$ is the estimated event rate for study j,
    - $\beta_0$ is the overall meta-estimate (fixed effect),
    - $u_j$ is the random effect for study j, which accounts for between-study variability.

**2. Weighting in Meta-Analysis**

The meta-analysis assigns weights to studies based on their precision. Inverse-variance weighting was used in this analysis to give more weight to studies with smaller standard errors.

- Standard Weighting:

$\text{weight} = 1 / (SE_{logit}^2)$

  - Where $SE_{logit}$ is the standard error of the logit-transformed event proportion.

Higgins, Julian P. T et al. *Cochrane Handbook for Systematic Reviews of Interventions*. Second edition. Newark: John Wiley & Sons, Incorporated, 2019. Web.

**3. Weighting for Zero-Event Studies**

For studies with zero events, the standard inverse-variance weight is undefined due to the zero-event rate. A modified weighting method was applied:

- Modified Weight for Zero-Event Studies:

$\text{weight} = \mathbf{1} / (\mathbf{0.5} / (\text{Number at Risk} + \mathbf{0.5}))$

This adjustment to account for the influence of zero-event studies while still including them in the analysis. These studies are important because they contribute information about the absence of events, especially in rare-event meta-analyses.

Friedrich JO, Adhikari NK, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. BMC Med Res Methodol. 2007;7:5. Published 2007 Jan 23. doi:10.1186/1471-2288-7-5

**4. Continuity Correction for Zero Events**

To handle studies reporting zero events, a continuity correction was applied to allow for logit transformation and inclusion in the model. This adjustment is made as follows:

- Continuity Correction:

Events Corrected = Events + 0.5

At Risk Corrected = Number at Risk + 0.5

5. Why Include Zero-Event Studies?

Excluding studies with zero events could introduce bias and overestimate event rates. Including these studies with appropriate corrections allows for a more accurate and generalizable estimate of the event rate.

Reference for handling Zero Event Studies: aJ. Sweeting, M., J. Sutton, A. and C. Lambert, P. (2004), What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Statist. Med., 23: 1351-1375. https://doi.org/10.1002/sim.1761

## Results

**Fit Statistics for Meta-Estimate of 5-yr IBTR included in SLR and Executive Summary:**

**Overall 5-yr IBTR Meta-Estimate Weighted Random Effect Model:**

The overall 5-year ipsilateral breast tumor recurrence (IBTR) rate across all studies included in the quantitative analysis, adjusting for between-study variability and study precision, is estimated at 0.61% (95% CI: 0.10% to 3.50%).

**Final Meta-Estimate of Overall IBTR Rate**

| Overall IBTR Rate | Lower 95% CI | Upper 95% CI |
|---|---|---|
| 0.60684% | 0.10256% | 3.50349% |

**Final Meta-Estimate of Overall IBTR Rate**

```
Interpretation of Results:
1. The overall IBTR rate across all studies, adjusting for between-study variability and study preci
sion, is estimated at the value shown above.
2. Interpretation of the Effect: The intercept on the logit scale can be transformed to a probabilit
y using the formula: exp(intercept) / (1 + exp(intercept)).
3. This rate represents the expected 5-year IBTR rate for a typical study in this population, weight
ed by study precision.
4. The 95% confidence interval provides a range of plausible values for the true overall IBTR rate.
5. This analysis accounts for heterogeneity between studies using a weighted random-effects model.
6. Studies with more precise estimates (usually larger studies) contribute more to the overall estim
ate.
7. The magnitude of the IBTR rate suggests the effectiveness of the treatments studied in preventing
 ipsilateral breast tumor recurrence.
8. Note: The rates are presented with four decimal places due to their small magnitude. This level o
f precision is necessary for accurate interpretation of these low event rates.
```

**Heterogeneity:**

**Heterogeneity Analysis Results**

| Q | DF | I_squared | Tau_squared |
|---|---|---|---|
| 63316.1996 | 6 | 99.9921 | 2.6000 |

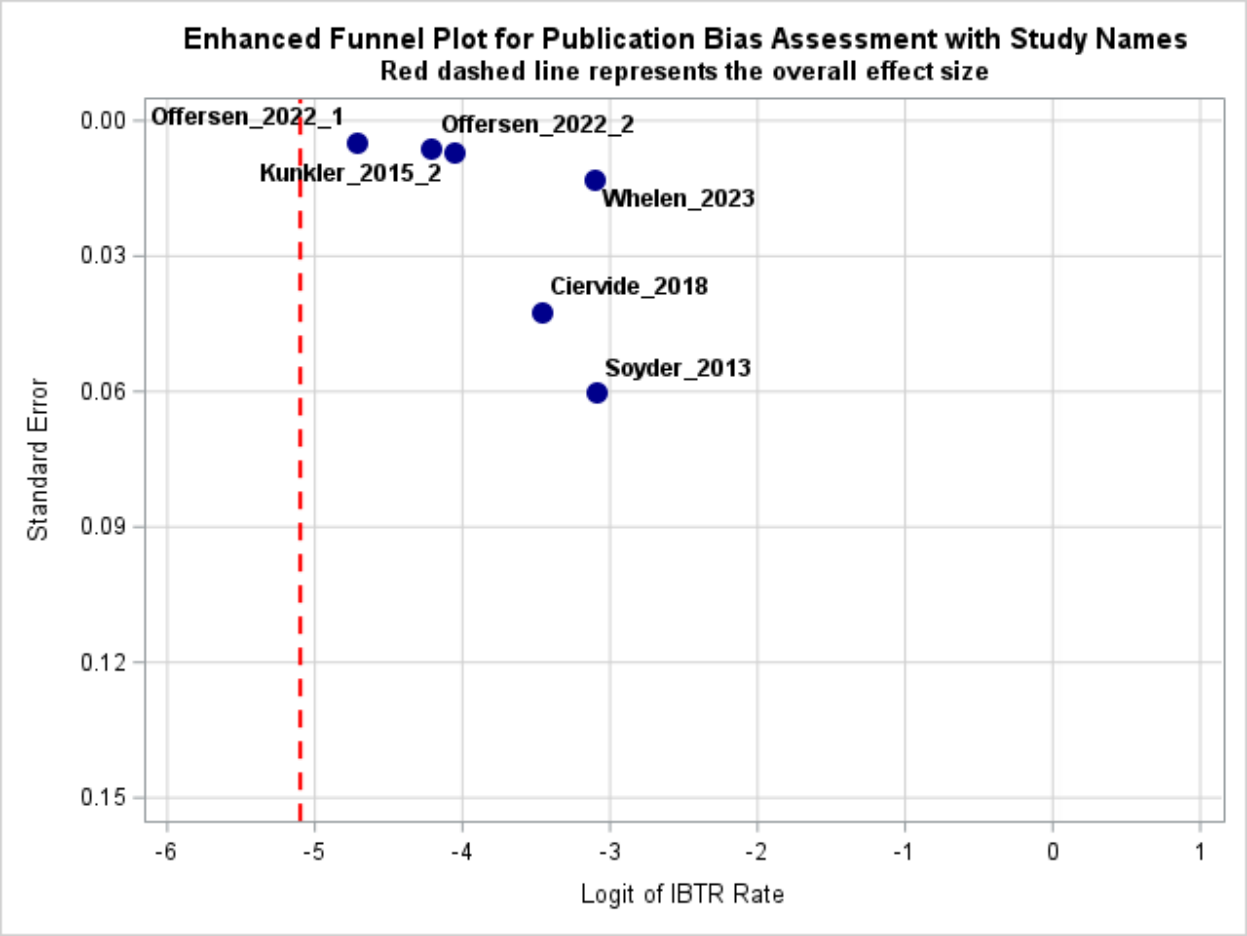
**Heterogeneity Analysis Results**

```
Heterogeneity Analysis Interpretation:
1. Q statistic:   63316.1996 (df = 6 )
   - p-value:       0.0000
   - A significant p-value (< 0.05) suggests the presence of heterogeneity.
2. I² index:      99.9921%
   - This represents the percentage of variability in effect estimates that is due to heterogeneity
rather than sampling error.
   - I² values of 25%, 50%, and 75% might be considered as low, moderate, and high heterogeneity, re
spectively.
3. Tau² (between-study variance):       2.6000
   - This quantifies the total amount of heterogeneity in the true effects across studies.
   - Larger values indicate greater heterogeneity.
```

Q statistic: 63316.1996 (df = 6, $p < 0.0001$)
$I^2$ index: 99.99%
$Tau^2$ (between-study variance): 2.6000

The heterogeneity remains very high, indicating substantial variability between studies that is not due to chance. This suggests that differences in study populations, designs, or other factors significantly influence the IBTR rates.

**Publication Bias Assessment for Overall Meta-Estimate of IBTR:**




1. **Symmetry**: The plot appears asymmetrical around the overall effect size (indicated by the red dashed line). This asymmetry suggests the presence of publication bias.
2. **Study Distribution**: More precise studies, particularly Offersen_2022_1, Offersen_2022_2, and Kunkler_2015_2, are located towards the top of the plot, showing smaller standard errors. Their positioning closer to the dashed line suggests their results are closely aligned with the meta-analytic average.
3. **Potential Outliers**: The study Whelen_2023 deviates slightly from the central cluster. This might indicate unique characteristics or effects within this study, warranting further examination to understand its impact on the meta-analysis.

Reference for Publication Bias Assessment: Higgins, Julian P. T et al. *Cochrane Handbook for Systematic Reviews of Interventions*. Second edition. Newark: John Wiley & Sons, Incorporated, 2019. Web.

**Subgroup Meta-analysis by Radiation Treatment for Meta-Estimate of 5-year IBTR:**

**Subgroup Analysis Results by Radiation Treatment**

| Obs | Radiation | IBTR_Rate | Lower_CI | Upper_CI |
|---|---|---|---|---|
| 1 | 0 | 0.47% | 0.00% | 35.91% |
| 2 | 1 | 0.68% | 0.15% | 2.94% |

No radiation group (Radiation 0): IBTR rate = 0.47% (95% CI: 0.00% to 35.91%)
Radiation group (Radiation 1): IBTR rate = 0.68% (95% CI: 0.15% to 2.94%)

This study was not designed to detect differences in IBTR between patients treated with concomitant radiotherapy or without concomitant radiotherapy. However, on post hoc analysis the difference between the radiation and no radiation groups is not statistically significant (p = 0.6985). Additionally, the wide confidence interval for the no radiation group indicates considerable uncertainty in this estimate, which is unsurprising as it was based on only two studies with very disparate sample size and different effect estimates.

**Sensitivity Analysis:**
The leave-one-out analysis shows that removing any single study does not substantially change the overall heterogeneity, which remains very high ($I^2 > 99\%$ in all cases). This suggests that the high heterogeneity is a fundamental characteristic of this set of studies rather than being driven by any single outlier.

**Table: Leave-one-out analysis on the probability scale**

| Removed_Study | Rate_Estimate | Rate_SE | zval | pval | Rate_CI_lb | Rate_CI_ub | Q | df | Tau_squared | I_squared | H2 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Offersen_2022_1 | 0.627946 | 1.838969 | -1.71839 | 0.085726 | 0.001959 | 67.08544 | 56953.58 | 5 | 2.66 | 99.99 | 14238.39 |
| Offersen_2022_2 | 0.547144 | 1.533692 | -1.84592 | 0.064904 | 0.002194 | 57.97010 | 55508.92 | 5 | 2.63 | 99.99 | 13877.23 |
| Kunkler_2015_2 | 0.315902 | 1.899183 | -.954128 | 0.340019 | 0.000002 | 99.76858 | 143775.6 | 5 | 4.87 | 100.00 | 35943.90 |
| Whelen_2023 | 0.334159 | 1.203651 | -1.57659 | 0.114890 | 0.000281 | 79.99028 | 142378.0 | 5 | 2.37 | 100.00 | 35594.49 |
| Ciervide_2018 | 1.346124 | 1.015619 | -5.61526 | 0.000000 | 0.303853 | 5.757125 | 26320.47 | 5 | 0.69 | 99.98 | 6580.12 |
| Soyder_2013 | 1.044189 | 1.685206 | -2.79071 | 0.005259 | 0.043140 | 20.50821 | 22717.36 | 5 | 1.46 | 99.98 | 5679.34 |

**Table: Leave-one-out analysis on the probability scale**

```
Sensitivity Analysis Interpretation:
1. This analysis shows how the heterogeneity measures (Q, I², and Tau²) change when each study is re
moved from the meta-analysis.
2. Large changes in these measures when a particular study is removed suggest that this study has a
substantial impact on the overall heterogeneity.
3. Studies whose removal leads to a notable decrease in I² or Tau² may be considered as potential so
urces of heterogeneity.
4. However, high heterogeneity remaining after removal of any single study suggests that the heterog
eneity is not driven by a single outlier study.
5. Consider the clinical and methodological characteristics of studies that have a large impact on h
eterogeneity when removed.
6. If heterogeneity remains high in all scenarios, it suggests that the variation between studies is
 a fundamental characteristic of this set of studies, rather than being driven by one or two outlier
s.
```

**Conclusions:**

The overall IBTR estimate remains very low at 0.61%, suggesting generally effective treatments for preventing ipsilateral breast tumor recurrence.
The extremely high heterogeneity ($I^2 = 99.99\%$) indicates that the true IBTR rates likely vary substantially between different study populations or treatment protocols.
The subgroup analysis does not show a statistically significant difference in IBTR rates between radiation and no radiation groups, but the wide confidence interval for the no radiation group limits the reliability of this comparison.

The persistent high heterogeneity in the sensitivity analysis suggests that the variation between studies is a fundamental characteristic of this set of studies, rather than being driven by one or two outliers.

The high heterogeneity suggests that patient-specific factors and treatment protocols may significantly influence IBTR rates, and individualized risk assessment may be necessary.

**Additional Analyses:**

We conducted additional analyses to enhance transparency and understanding. Comparing fixed and random effect models provides insight into how heterogeneity among studies impacts the overall estimate. Also, showing the effect of adjusting weights for the zero-event studies emphasize the importance of accounting for zero-event studies in order to obtain more reliable estimate.

1. **Fixed Effect Model:**

**Final Meta-Estimate of Overall IBTR Rate**

| Overall IBTR Rate | Lower 95% CI | Upper 95% CI |
|---|---|---|
| 1.95724% | 1.68247% | 2.27584% |

While we selected to utilize random effects models for meta-estimates, we are also providing the meta-estimate calculated using a fixed effect model (shown above). We do not believe a fixed effect is appropriate as this model assumes homogeneity among studies. Homogeneity across the studies selected for this meta-analysis is unlikely given differences in study design, population, and effect (including the zero event studies) estimates.

2. **Random Effect Model without Adjusting Weights for the Zero events Studies:**

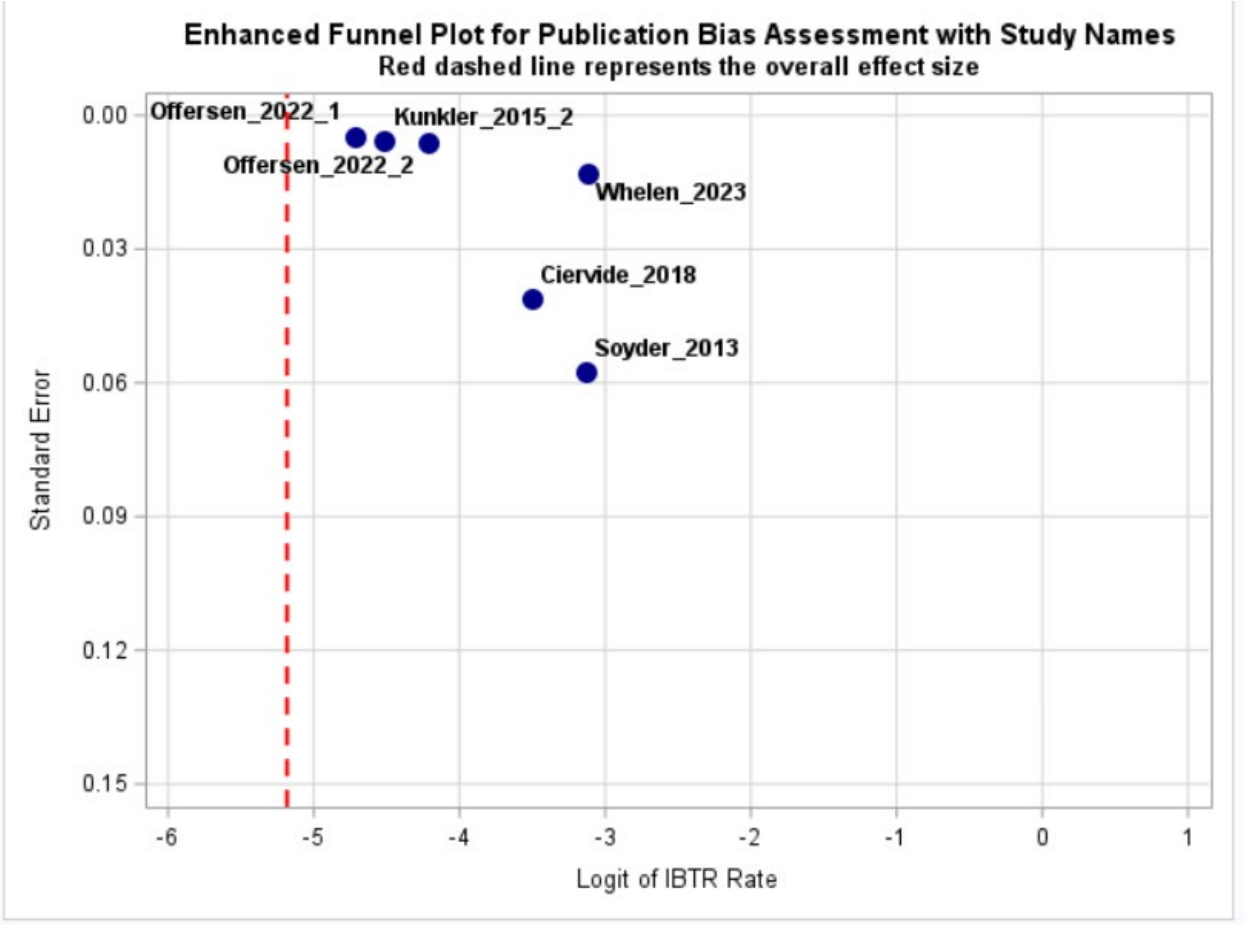
**Final Meta-Estimate of Overall IBTR Rate**

| Overall IBTR Rate | Lower 95% CI | Upper 95% CI |
|---|---|---|
| 1.85971% | 0.97733% | 3.51048% |

In this meta-estimate (1.86), we employed inverse variance weighting only without adjusted weighting for zero rates studies (please see section 3. Weighting for Zero-Event Studies). Employing inverse weighting without adjusting the weights for the zero events studies can misrepresent their impact, equivalent to excluding these studies completely from the analysis.

The estimated rate here without weight adjustments is 1.86, however, when weights are adjusted for zero events, this rate adjusts to 0.6 (Overall IBTR Rate for the Random Effect Model).

**Supplement 7.** Publication Bias Assessment



## Supplement 8. SAS code

```
/* Overall estimate: Run weighted GLIMMIX */
proc glimmix data=meta_prop method=quad;
    class Study_ID;
    model Events / Number_at_Risk = / dist=binomial link=logit solution;
    random intercept / subject=Study_ID type=vc;
    weight weight;  /* Apply the calculated weights */
    ods output ParameterEstimates=PE_glmm CovParms=CP_glmm;
    /* Note: This analysis uses a weighted random-effects model to account
for between-study variability
       and different precisions of study estimates */
run;


/* Step 2: Subgroup Analysis by Radiation */
%macro subgroup_analysis(radiation_group);
    proc glimmix data=meta_prop(where=(Radiation=&radiation_group))
method=quad;
        class Study_ID;
        model Events / Number_at_Risk = / dist=binomial link=logit solution;
        random intercept / subject=Study_ID type=vc;
        weight weight;
        ods output ParameterEstimates=PE_glmm_&radiation_group
CovParms=CP_glmm_&radiation_group;
    run;

    data Results_&radiation_group;
        set PE_glmm_&radiation_group;
        where Effect = "Intercept";
        IBTR_Rate = exp(Estimate) / (1 + exp(Estimate));
        Lower_CI = exp(Estimate - 1.96*StdErr) / (1 + exp(Estimate -
1.96*StdErr));
        Upper_CI = exp(Estimate + 1.96*StdErr) / (1 + exp(Estimate +
1.96*StdErr));
        Radiation = &radiation_group;
    run;
%mend;

%subgroup_analysis(0);
%subgroup_analysis(1);
```

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