

# The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis

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## Abstract

**Background.** Patients with metastatic breast cancer (MBC) are living longer, but the development of brain metastases often limits their survival. We conducted a systematic review and meta-analysis to determine the incidence of brain metastases in this patient population.

**Methods.** Articles published from January 2000 to January 2020 were compiled from four databases using search terms related to breast cancer, brain metastasis, and incidence. The overall and per patient-year incidence of brain metastases were extracted from studies including patients with human epidermal growth factor receptor-2 positive (HER2+), triple negative, and hormone receptor (HR)+/hormone receptor negative (HER2–) MBC; pooled overall estimates for incidence were calculated using random effects models.

**Results.** 937 articles were compiled, and 25 were included in the meta-analysis. Incidence of brain metastases in patients with HER2+ MBC, triple negative MBC, and HR+/HER2– MBC was reported in 17, 6, and 4 studies, respectively. The pooled cumulative incidence of brain metastases was 31% for the HER2+ subgroup (median follow-up: 30.7 months, IQR: 24.0–34.0), 32% for the triple negative subgroup (median follow-up: 32.8 months, IQR: 18.5–40.6), and 15% among patients with HR+/HER2– MBC (median follow-up: 33.0 months, IQR: 31.9–36.2). The corresponding incidences per patient-year were 0.13 (95% CI: 0.10–0.16) for the HER2+ subgroup, 0.13 (95%CI: 0.09–0.20) for the triple negative subgroup, and only 0.05 (95%CI: 0.03–0.08) for patients with HR+/HER2– MBC.

**Conclusion.** There is a high incidence of brain metastases among patients with HER2+ and triple negative MBC. The utility of a brain metastases screening program warrants investigation in these populations.

## Key Points

1. Brain metastases occur in almost 1 in 3 patients with human epidermal growth factor receptor-2 positive (HER2+) or triple negative metastatic breast cancer (MBC).
2. Incidence per patient-year is 13% for both HER2+ and triple negative MBC.
3. Screening for brain metastases in high-risk MBC populations warrants investigation.

## Importance of the Study

Patients with human epidermal growth factor receptor-2 positive (HER2+) or triple negative metastatic breast cancer (MBC) are living longer, but their survival is often limited by the development of brain metastases. To evaluate the possible benefit of a brain metastases screening program, we conducted a systematic review and meta-analysis to determine the incidence of brain metastases in this patient population. To account for variable follow-up durations across included studies, the incidence of brain metastases per patient-year was

also calculated. We found that almost one-third of patients with HER2+ or triple negative MBC will develop brain metastases during their lifetime, with a 13% incidence per patient-year among those with HER2+ MBC and a 13% incidence per patient-year among those with triple negative MBC. To our knowledge, this is the first meta-analysis to investigate the incidence of breast cancer brain metastases among patients with MBC. Our findings support further investigation of an MRI-based screening program in high-risk MBC populations.

The incidence of brain metastases has steadily increased over time as women with metastatic breast cancer (MBC) survive longer to be at risk for developing metastasis to the central nervous system (CNS).<sup>1-10</sup> Women with human epidermal growth factor receptor-2 positive (HER2+) or triple negative (hormone receptor negative [HER2-]) MBC, which represent approximately 30–40% of the MBC population, are at particularly high risk of brain metastases.<sup>11-18</sup> In fact, retrospective data reveal that 30–50% of women with these high-risk breast cancer subtypes ultimately develop and succumb to CNS disease.<sup>1-5,8-10</sup>

Many studies confirm that brain metastases afford women with MBC a very poor prognosis.<sup>1,19</sup> In a large retrospective study of 557 patients with MBC, for example, the presence of symptomatic brain metastases was independently prognostic for a shorter overall survival with a hazard ratio of 1.58 (95%CI: 1.04–2.41,  $P = 0.033$ ).<sup>19</sup> In the prospective “registHER” study, women with HER2+ MBC who developed CNS metastases also had adverse outcomes; the median survival was 26.3 months among women with brain metastases as compared to 44.6 months among those women who did not develop brain metastases.<sup>3</sup> Although the cause of death was not reported in this specific study, approximately 50% of patients with HER2+ brain metastases are thought to die from the neurologic progression of their disease.<sup>10</sup>

Given that the overall incidence of brain metastases is fairly low in the general breast cancer population, screening procedures are not recommended in the National Comprehensive Cancer Network (NCCN) consensus or American Society of Clinical Oncology (ASCO) guidelines. Rather, patients with breast cancer undergo imaging of the brain only after symptoms suggestive of CNS involvement develop. Unfortunately, by the time that patients experience potentially debilitating symptoms of brain metastases, they often have a significant burden of disease with limited treatment options.<sup>20,21</sup>

Whether early detection of brain metastases via a magnetic resonance imaging (MRI)-based screening program may allow for early intervention and, ultimately, improved outcomes for patients with certain “high risk” populations of MBC is unknown. A very high incidence of brain metastases in certain breast cancer populations may prompt the revisiting of guidelines regarding screening practices. Hence, we conducted a systematic review and

meta-analysis to determine the incidence of brain metastases among patients with a new diagnosis of MBC subtypes, which are known to portend a high risk of brain metastases.<sup>22</sup>

## Methods

This systematic review was conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>23</sup> (see [Supplementary Figure 1](#)).

### Study Selection

A literature search was conducted in the MedLine, EMBASE, CENTRAL, and CDSR databases using Medical Subject Headings (MeSH) indexing terms and keywords related to breast neoplasm, breast cancer, incidence, and brain metastasis (see [Supplementary Figure 2](#) for the full search strategy). Databases were chosen per recommendations from the Cochrane Handbook for Systematic Reviews.<sup>24</sup> The search was conducted by a library information specialist; the search was conducted in the English language without any further publication restrictions. Experimental or observational studies that reported the first incidence of brain metastases among patients with MBC and were published between January 2000 and January 2020 were included in this systematic review. This time period was selected to capture more modern studies, which reflect the use of trastuzumab-based chemotherapy regimens that are currently administered to patients with MBC. Studies were excluded if they did not report a median follow-up of their study cohort, if they were reviews, editorials, or conference abstracts, if they investigated very specific breast cancer populations that were not representative of the MBC population in general (e.g., inflammatory breast cancer), or if they only reported on patients with symptomatic brain metastases at baseline. Furthermore, two studies that excluded patients with asymptomatic brain metastases at study entry were ineligible. References of included publications were scanned as part of the review process; however, a search of the grey literature was not conducted. In cases where studies queried the same

patient database (i.e., Surveillance, Epidemiology, and End Results [SEER]) during the same time period, only the study with the largest number of patients was included, while the rest were excluded.

Two reviewers (YG and AJD) independently reviewed the abstracts of all papers and selected papers for inclusion. Any discrepancies or conflicts were adjudicated by a third reviewer (MK).

### Data Extraction

Two authors reviewed the papers and extracted the data (MK, KJJ). The reported incidence of brain metastases and follow-up duration were extracted from studies. Some studies presented two arms of data (i.e., control and treatment): where possible, we calculated median follow-up times to obtain a value for the entire cohort. Notably, the treatment arm of one randomized control trial<sup>20</sup> that studied the efficacy of prophylactic cranial irradiation was omitted from our analysis because this practice is not standard-of-care. In cases where our patient population of interest was a subgroup of the originally reported publication, or if certain patients in the study group did not fit our inclusion criteria (i.e., patients with brain metastases at baseline), we removed those patients from the values reported in the studies. If there was no reliable way to adjust the incidence values, the studies were excluded. This was unfortunately the case with two large randomized phase III trials. While the EMILIA<sup>25</sup> and CLEOPATRA<sup>26</sup> trials are both important trials in the field, both studies screened for asymptomatic brain metastases prior to study entry and excluded patients with CNS involvement of their disease. Given a systematic reduction in the incidence of brain metastases, both studies were excluded from our analysis.

During the data extraction process, a level of evidence was assigned to each paper based on the hierarchy for “Prognosis” in the Australian National Health and Medical Research Council (NHMRC) guidelines.<sup>27</sup>

### Statistical Analysis

The primary outcome of interest was the incidence rate of brain metastases per patient-year among patients with MBC. The secondary endpoint was the cumulative incidence of brain metastases. The incidence rate per patient-year was calculated to adjust for variable follow-up durations, with 2-sided 95% confidence intervals (95% CI) based on the measured variances. Subgroup analyses were performed for HER2+ and triple negative breast cancer subtypes; the incidence of brain metastases among studies that did not specify breast cancer subtypes were also pooled. Finally, raw data regarding the overall incidence of brain metastases for each breast cancer subtype (as opposed to incidence per unit time) were reported with median follow-up durations.

In order to compute the pooled estimate for incidence of brain metastases, a random effects model (RE Model) was carried out for the overall cohort as well as each of the three subgroups. A forest plot was generated, based on

the random intercept Poisson regression model with the computed 95% CI. For each RE model, a test of heterogeneity (Q-statistic) was calculated using a restricted maximum likelihood estimator. The total heterogeneity ( $\tau^2$ ) and the total heterogeneity relative to the variance ( $I^2$ ) was also calculated.

Publication bias was evaluated and presented as funnel plots, which illustrate the incidence of brain metastases against standard error with 2-sided 95% confidence intervals. To test for publication bias, a regression analysis was performed using Egger’s test to assess the symmetry of the funnel plot ( $\alpha = 0.05$ ). An Egger’s test was appropriate as there were fewer than 25 studies for each subgroup.<sup>28</sup>

A within-study assessment of bias was performed for all studies included in the analysis. The Newcastle Ottawa Scale was used to assess bias in case-control and cohort studies while the Cochrane Risk of Bias 2.0 tool was used for randomized controlled trials (RCTs).

### Data Analysis

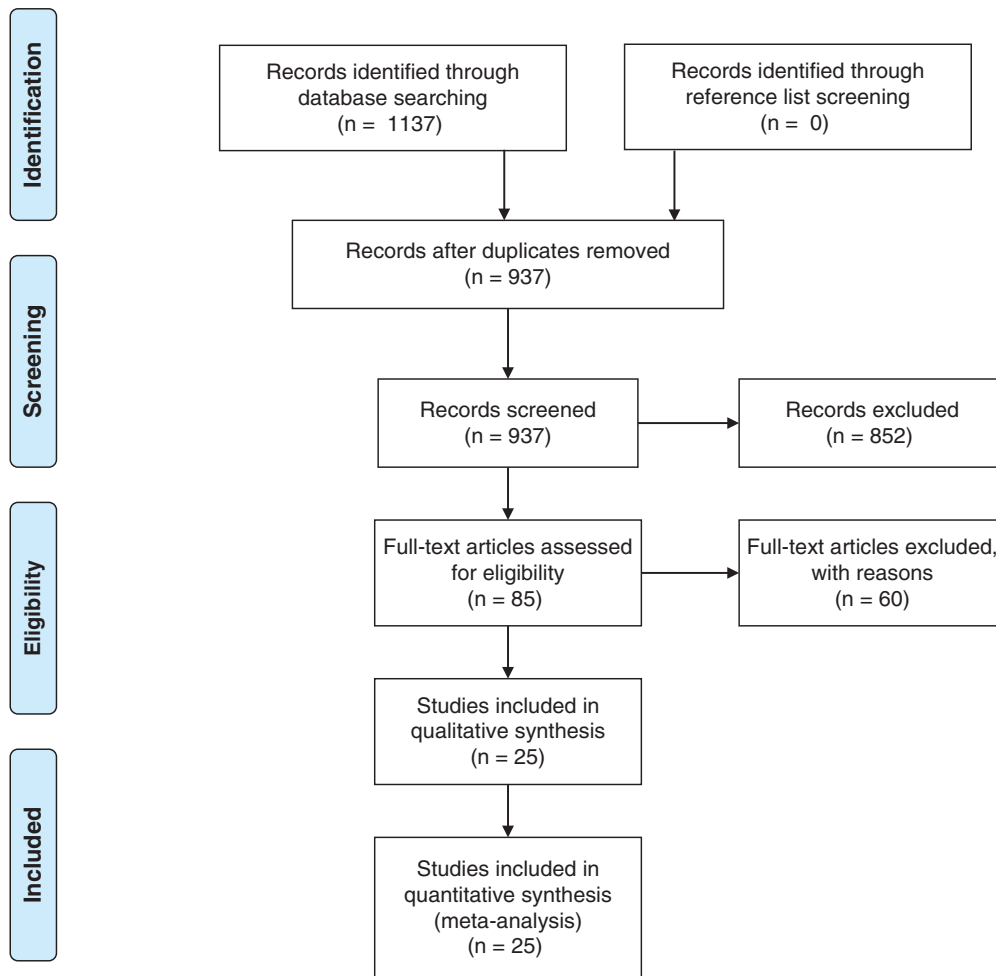
Data analysis was carried out using the methods previously described.<sup>29</sup> All data analysis was performed using SAS (Version 9.4; SAS Institute, Cary, NC, USA) and R Statistics (Version 3.6.1; R Core Team, 2019). R Statistics Version 3.6.1 and GraphPad Prism 8.4.3 (GraphPad Software Inc, CA, USA) were used to create the figures. Subgroup analyses were carried out for HER2+, triple negative, and HR+/HER2– metastatic breast cancer subtypes.

## Results

After the removal of duplicates, 937 studies were identified in our literature review. After assessment by reviewers, 85 papers were assessed for inclusion. During the full-text screen, an additional 60 papers were excluded based on specific exclusion criteria, including if they did not report a median follow-up of their study cohort. This is detailed in [Supplementary Figure 3](#). 25 trials were included in the final analysis ([Figure 1](#)—Adapted from PRISMA 2009 Flowchart).<sup>1–4,14,15,20,30–47</sup> Data extracted from the selected studies is summarized in [Table 1](#) and the full data is included in [Supplementary Figure 4](#). In total, 3 studies were randomized controlled trials, 1 study was a non-randomized controlled trial, and 21 studies were observational studies.

### Pooled Incidence of Brain Metastases Among Patients with HER2+ MBC

Seventeen studies including 5971 patients reported brain metastasis incidence among patients with HER2+ MBC. The pooled cumulative incidence of brain metastases was 0.31 (95% CI: 0.22–0.38) with a median follow-up of 30.7 months (IQR: 24.0–34.0). Using a random effects model, the pooled incidence of brain metastases per patient-year was 0.13 (95% CI: 0.10–0.16). Corresponding forest and funnel plots are presented in [Figure 2A](#) and [B](#), respectively. An Egger’s test did not find asymmetry in the funnel plot and,



**Fig. 1** Schematic illustrating study selection process. Adapted from PRISMA flow diagram 2009. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

therefore, publication bias in this subset of data was unlikely ( $P = 0.30$ ).

Six studies reported brain metastasis incidence among patients with HER2+ MBC and also provided hormone receptor (HR) status. The pooled incidence value of brain metastases per patient-year was calculated for each subgroup using a random effects model; the HR-/HER2+ group (comprising of 2092 patients) had a higher pooled incidence of 0.13 (95% CI: 0.08–0.20) than the HR+/HER2+ group (0.08 [95% CI: 0.05–0.13]), which comprised of 3480 patients. Forest and funnel plots for the HR-/HER2+ and HR+/HER2+ groups are presented in [Supplementary Figures S5](#) and [S6](#), respectively. Compared to patients with HR-/HER2+ MBC, those with HR+/HER2+ disease were less likely to develop brain metastases with an incidence rate ratio of 0.71 (95% CI: 0.64–0.78).

#### Pooled Incidence of Brain Metastases Among Patients with HR+/HER2– MBC

Four studies including 14656 patients reported the incidence of brain metastases specifically in patients with

HR+/HER2– MBC. Pooled cumulative incidence of brain metastases among this subgroup was 0.15 (95% CI: 0.078–0.27), with a median follow-up of 33.0 months (IQR: 31.9–36.2). Using a random effects model, the pooled incidence per patient-year was found to be 0.05 (95% CI: 0.03–0.08); corresponding forest and funnel plots are displayed in [Figure 3](#). Because only four studies were included in this subgroup, an Egger's test was not performed.

#### Pooled Incidence of Brain Metastases Among Patients with Triple Negative MBC

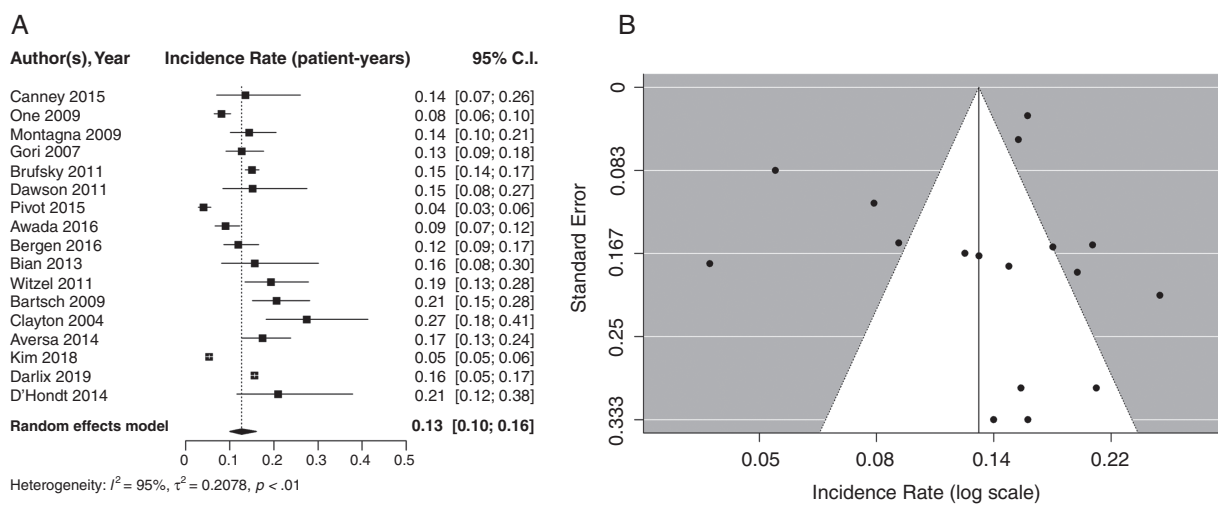
Six studies including 4102 patients reported the incidence of brain metastases among patients with triple negative MBC. The pooled cumulative incidence of brain metastases was 0.32 (95% CI: 0.19–0.49) with a median follow-up of 32.8 months (IQR: 18.5–40.6). Using a random effects model, the pooled incidence of brain metastases per patient-year was 0.13 (95% CI: 0.09–0.20). A forest plot of these data is presented in [Figure 4A](#). The incidence of

**Table 1** Characteristics and Incidence of Brain Metastases in the Included Studies

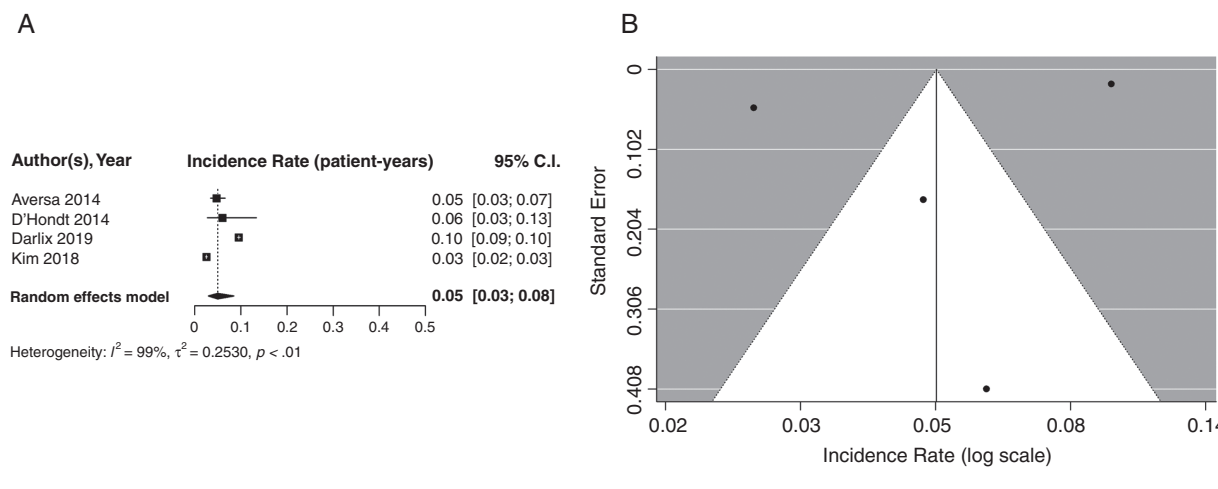
	Type of study	Sample size	Cumulative incidence	Median follow-up (months)	Time to brain metastasis (months)	Level of evidence <sup>a</sup>
<b>HER2+</b>						
Canney et al. 2015	RCT	26	0.346	30.7	NR	III-2
Ono et al. 2009	Case control	204	0.363	53.6	13.6	III-3
Montagna et al. 2009	Case control	73	0.425	35.3	35.8	III-3
Gori et al. 2007	Retrospective cohort	118	0.297	28.0	12.0	III-3
Brufsky et al. 2011	Prospective cohort	997	0.363	29.0	13.3	II
Dawson et al. 2006	Retrospective cohort	28	0.393	31.0	11.2	III-3
Pivot et al. 2015	RCT	501	0.064	19.0	5.0	II
Awada et al. 2016	RCT	237	0.173	23.0	NR	III-2
Bergen et al. 2014	Retrospective cohort	76	0.474	47.5	NR	III-3
Bian et al. 2013	Nonrandomized controlled clinical trial	120	0.075	5.8	NR	II
Witzel et al. 2011	Retrospective cohort	75	0.387	24.0	NR	III-3
Bartsch et al. 2009	Retrospective cohort	97	0.412	24.0	NR	III-3
Clayton et al. 2004	Retrospective cohort	93	0.247	10.8	10.0	III-3
Aversa et al. 2013	Retrospective cohort	79	0.494	34.0	NR	III-3
Kim et al. 2018	Retrospective cohort	1045	0.138	31.0	NR	III-3
D'Hondt et al. 2014	Retrospective cohort	20	0.550	31.5	NR	III-3
Darlux et al. 2019	Retrospective cohort	2182	0.558	42.8	NR	III-3
<b>Triple negative</b>						
Jin et al. 2018	Retrospective cohort	415	0.263	48.1	10	III-3
Lin et al. 2008	Retrospective cohort	100	0.370	14.2	NR	III-3
Aversa et al. 2014	Retrospective cohort	64	0.219	34	NR	III-3
Kim et al. 2018	Retrospective cohort	1441	0.124	12	NR	III-3
D'Hondt et al. 2014	Retrospective cohort	36	0.417	31.5	NR	III-3
Darlux et al. 2019	Retrospective cohort	2046	0.670	42.8	NR	III-3
<b>MBC (irrespective of subtype)</b>						
Ren et al. 2019	Case control	13066	0.0718	19	NR	III-3
Ryberg et al. 2005	Case control	579	0.2142	137	NR	III-3
Azim et al. 2018	Case control	246	0.0935	43.2	NR	III-3
Danese et al. 2012	Retrospective cohort	562	0.2224	13.7096	NR	III-3
Yan et al. 2013	Retrospective cohort	291	0.1718	12	8.0	III-3
Aversa et al. 2014	Retrospective cohort	488	0.2357	34	NR	III-3
Kim et al. 2018	Retrospective cohort	10432	0.0851	29	NR	III-3
Heitz et al. 2011	Prospective cohort	626	0.1054	48	NR	II
D'Hondt et al. 2014	Retrospective cohort	169	0.2840	31.5	NR	III-3
Darlux et al. 2019	Retrospective cohort	15499	0.188	42.8	NR	III-3

NR, not reported; RCT, randomized controlled trial.

<sup>a</sup>Based on the hierarchy for "Prognosis" in the Australian National Health and Medical Research Council (NHMRC) guidelines.<sup>25</sup>



**Fig. 2** A) Forest plot of pooled incidence rate (patient-years) for HER2+ MBC. Random effects model presented. Incidence per year of follow-up ranged from 0.04 to 0.27. Median follow-up times ranged from 5.8 to 53.6 months. B) Funnel Plot for publication bias according to studies reporting brain metastasis in HER2+ MBC. Egger's test;  $P = 0.30$ . HER2+, human epidermal growth factor receptor-2 positive; MBC, metastatic breast cancer.



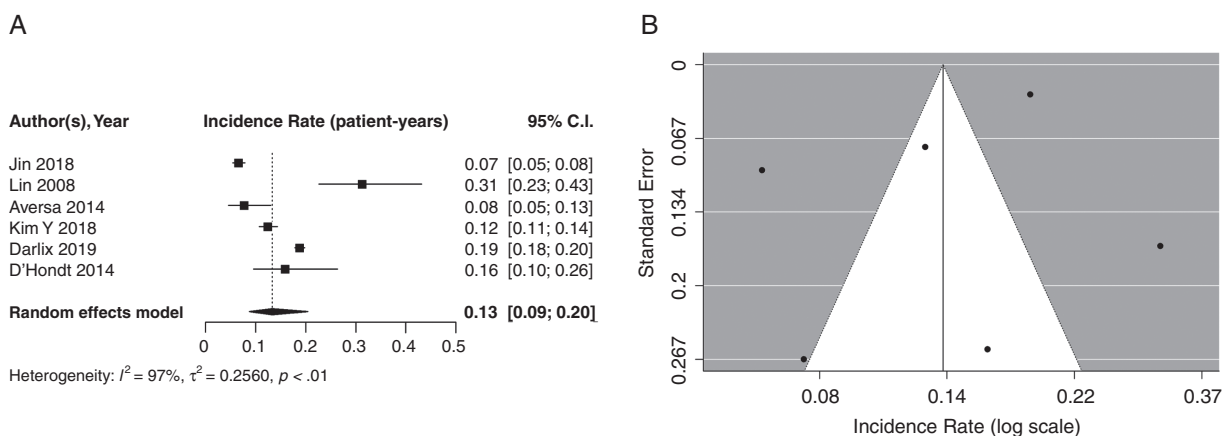
**Fig. 3** A) Forest plot of pooled incidence rate (patient-years) for HR+/HER2- MBC. Random effects model presented. Incidence per year of follow-up ranged from 0.03–0.10. Median follow-up times ranged from 32.0–42.8 months. B) Funnel plot for publication bias according to studies reporting brain metastasis in HR+/HER2- MBC. HER2-, hormone receptor negative; HR+, hormone receptor; MBC, metastatic breast cancer.

brain metastases plotted against the standard error and presented with 95% CIs is illustrated in Figure 4B. Because only 6 studies were included in this subset, an Egger's test was not performed.

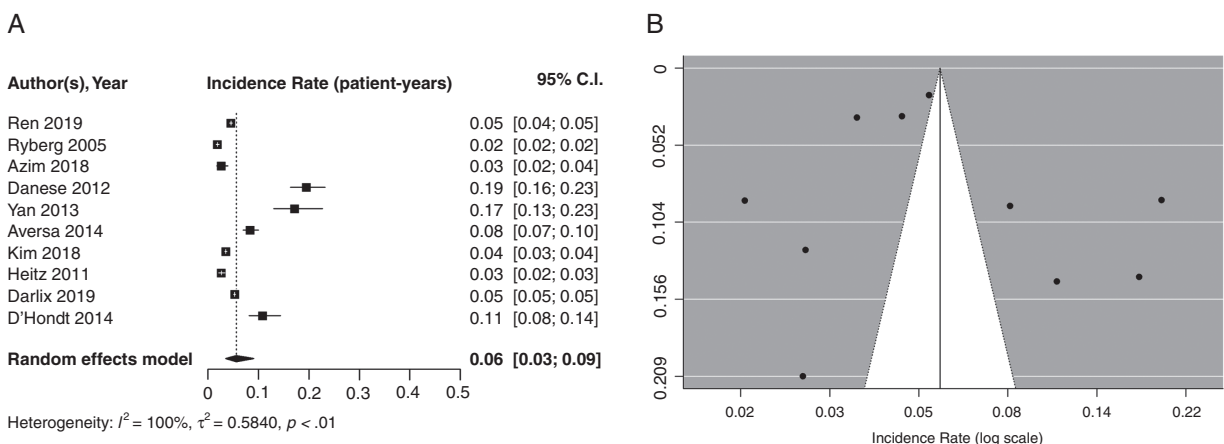
### Pooled Incidence of Brain Metastases Among Patients, Irrespective of Breast Cancer Subtype

In total, 10 studies including 41,958 patients reported the incidence of brain metastases irrespective of breast cancer

subtype. The pooled cumulative incidence of brain metastases in all patients with MBC was 0.15 (95% CI: 0.11–0.20) with a median follow-up of 32.7 months (IQR: 21.5–43.1). Using a random effects model, the pooled incidence of brain metastases per patient-year was 0.06 (95% CI: 0.03–0.09) (Figure 5A). In the assessment of publication bias, we plotted the incidence of brain metastases against the standard error and presented it with 95% CI in a funnel plot (Figure 5B). An Egger's test did not find asymmetry in the funnel plot, which suggests publication bias in this subset of data is unlikely ( $P = 0.88$ ).



**Fig. 4** A) Forest plot of pooled incidence rate (patient-years) for triple negative MBC. Random effects model presented. Incidence per year of follow-up ranged from 0.07 to 0.31. Median follow-up times ranged from 12.0 to 48.1 months. B) Funnel plot illustrating studies reporting brain metastasis in triple negative MBC. MBC, metastatic breast cancer.



**Fig. 5** A) Forest plot of pooled incidence rate (patient-years) for MBC, irrespective of subtype. Random effects model presented. Incidence per year of follow-up ranged from 0.02 to 0.19. Median follow-up times ranged from 12.0 to 137.0 months. B) Funnel Plot for publication bias according to studies reporting brain metastasis in MBC, irrespective of subtype. Egger's test,  $P = 0.88$ . MBC, metastatic breast cancer.

### Pooled Incidence of Brain Metastases Among All Patients from 2000 to 2010 Compared to 2011 to 2020

When comparing the incidence rates of brain metastases in studies published in 2000–2010 and 2011–2020, the brain metastasis incidence did not differ between the 2 groups ( $P = 0.23$ ). It is worth noting that all 3 studies with the largest patient populations were published after 2010.

### Assessment of Bias

The Newcastle Ottawa Scale for estimating the risk of bias in the cohort and case-control studies is illustrated in [Supplementary Figure 7](#). The average score (out of 9) for

all studies included was 7.38, and only 3 studies ranked “Poor” in their assessment of bias. Results of The Cochrane Risk of Bias 2.0 assessment of included RCTs are presented in [Supplementary Figure 8A](#) and [B](#), respectively.

## Discussion

Our study is the first meta-analysis to investigate the incidence of brain metastases among patients with MBC. Given that patients with HER2+ or triple negative MBC are known to have the highest risk of brain metastases, our analyses focused on these subgroups. Further, to account for wide variations in median follow-up times in the

literature, we report the incidence of brain metastases per patient-year, in addition to pooled cumulative incidence. For patients with HER2+ MBC, the pooled cumulative incidence of brain metastases was 31% with a median follow-up of 30.7 months (IQR: 24.0–34.0). The incidence of brain metastases per patient-year was 13%. For patients with triple negative MBC, the pooled cumulative incidence of brain metastases was 32% with a median follow-up of 32.8 months (IQR: 18.5–40.6); when accounting for follow-up duration, the incidence of brain metastases per patient-year was 13%.

This study builds upon a narrative review of the literature, which was previously published by our group.<sup>22</sup> The present study included a systematic literature search utilizing a larger number of databases and search terms, as well as a formal meta-analysis to pool incidence rates of brain metastases. Our results indicate a high incidence of brain metastases among patients with HER2+ or triple negative MBC (13% per patient-year). The largest and highest quality study (based on our level of evidence assessment) included in our analysis was the prospective “registHER” observational study.<sup>3</sup> RegistHER reported an incidence of brain metastases in patients with HER2+ MBC of 37%,<sup>3</sup> with a median follow-up of 29.0 months, which is consistent with our results.

Unfortunately, only six studies reported the incidence of brain metastases in triple negative MBC, with a large range in reported cumulative incidences of 12.4%–41.7% (pooled estimate of 13% per patient-year). The largest, highest quality paper that assessed the incidence of brain metastases among patients with triple negative MBC was published by investigators at the Fudan University Shanghai Cancer Center; with a median follow-up of 48.1 months, the incidence of brain metastases was 26.3%.<sup>40</sup> Unfortunately, clinical trials for patients with metastatic triple negative breast cancer do not typically capture brain metastases as “events,” limiting our understanding of the incidence and CNS-specific efficacy of systemic therapies in this high-risk patient population.

Importantly, most of the studies in our pooled analysis did not screen patients for asymptomatic brain metastases. Brain metastases were typically detected after the onset of neurological symptoms, which necessitated a CT scan or MRI of the brain. This suggests that while the pooled incidence estimates for brain metastases are high, they may be under-estimated. Furthermore, while not all studies specified the type of imaging that was used to detect brain metastases; at least three studies indicated that a CT scan was performed while 11 studies indicated that either a CT scan or MRI scan were used to detect brain metastases. Given that MRI is the recommended method for the detection of brain metastases,<sup>48</sup> studies that did not use MRI to detect brain metastases have likely underestimated the incidence of brain metastases in their patient populations. Given that almost one-third of patients with triple negative or HER2+ metastatic breast cancer will experience brain metastases in their lifetime, there may be a role for an MRI-based brain metastases screening program in this patient population. It is possible that the early detection of brain metastases and early intervention may improve patient outcomes, but properly conducted randomized controlled

trials that incorporate quality-of-life endpoints, as well as CNS-specific progression and ideally overall survival, are required before screening for brain metastases can be recommended in practice guidelines.

Historically, the brain was considered to be a sanctuary site for breast cancer progression given that systemic therapies were felt to have poor penetration through the blood-brain barrier.<sup>49</sup> However, even large antibodies such as trastuzumab have been shown to penetrate the CNS in radiolabelled positron emission tomography (PET) studies.<sup>50</sup> The clinical activity of anti-HER2 antibodies in the CNS has since been demonstrated in the CLEOPATRA study, which suggests that the addition of pertuzumab to trastuzumab plus docetaxel delays the onset of CNS metastases.<sup>26</sup> Trastuzumab emtansine (T-DM1) has also demonstrated CNS-specific benefit in patients with HER2+ MBC and brain metastases in the KAMILLA study.<sup>51</sup> Given the approval of these CNS-penetrating therapies over the previous decade, we compared the incidence of brain metastases in studies published in 2000–2010 to studies published in 2011–2020 and found no statistical difference. This may be due to delayed uptake and funding of pertuzumab and T-DM1 in certain jurisdictions, reducing their impact on the incidence of brain metastases in studies that were published between 2011 and 2020. It is also possible that two competing effects on brain metastases incidence may be at play. While CNS penetrating drugs may delay or foreseeably even prevent brain metastases (although data for the latter is currently lacking), improved control of extra-cranial disease and longer survival times may conversely increase the incidence of brain metastases.

With an evolving landscape of CNS-penetrating systemic therapies for patients with MBC, particularly those with HER2+ disease, the outcomes of patients with breast cancer brain metastases are likely to improve over time. In fact, the addition of tucatinib (small molecule tyrosine kinase inhibitor of HER2) to trastuzumab plus capecitabine has recently demonstrated significant intracranial response, reduced risk of intracranial progression or death, and even improved survival in a randomized controlled trial.<sup>52</sup> In addition, the poly(adenosine diphosphate-ribose) inhibitor talazoparib has shown efficacy among patients with HER2 negative MBC and a germline BRCA mutation, irrespective of the presence of CNS metastases.<sup>53</sup> Unfortunately, despite rationale for intracranial efficacy of immunotherapy,<sup>54</sup> particularly among patients with triple negative, programmed death-ligand 1 (PD-L1) positive metastatic breast cancer, patients with brain metastases were not well represented in relevant phase III randomized controlled trials.<sup>55–57</sup> Evidence for CNS-specific activity of CDK4/6 inhibitors<sup>58,59</sup> and PI3K inhibitors<sup>60,61</sup> in combination with endocrine therapy among patients with HR+/HER2– MBC is emerging but still limited.

### Study Limitations

Overall, we included 25 studies in our analysis. This number represents only a portion of all the studies that assessed the incidence of brain metastases in patients



with MBC. This is largely due to inconsistencies in the way that data were reported across studies, limiting our ability to pool results. Many studies made no mention of median follow-up time, and others varied in how follow-up times were measured (e.g., from initial diagnosis of early breast cancer, from diagnosis of MBC, from initiation of treatment).

It is noted that few studies reported data for HER2+ and triple negative MBC subgroups, and brain metastasis incidence was rarely broken down by hormone receptor status. Even fewer studies differentiated between parenchymal brain metastases and leptomeningeal disease. Future studies should acknowledge these types of CNS involvement, as their prognoses and treatment options vary significantly. Quality-of-life data among patients with brain metastases were also lacking. Importantly, one limitation of the incidence rate ratio analysis to compare HR-/HER2+ and HR+/HER2+ subgroups is that the same median follow-up time between the two groups had to be assumed, as separate follow-up times were not reported. Finally, it is noted that small sample sizes lead to wide confidence intervals and reduced precision around estimates in some cases. As the calculation of true confidence intervals require at least 12 samples within a group,<sup>62</sup> assessment of publication bias was omitted for the triple negative and HR+/HER2- subgroups.

## Conclusion

Patients and clinicians should be aware of the high risk of brain metastases among patients with HER2+ and triple negative MBC. Vigilant monitoring for neurologic symptoms may help to identify CNS spread of disease early and enable appropriate and timely treatment. Although clinical practice guidelines do not currently recommend screening for brain metastases, this is largely due to a lack of available data to demonstrate the merits of an MRI-based screening program for early detection. Clinical trials, such as the "MRI Screening Versus SYMptom-directed Surveillance for Brain Metastases Among Patients With Triple Negative or HER2+ MBC" (SYMPToM trial; NCT03881605), are ongoing to investigate the potential risks and benefits of early detection of brain metastases and subsequent early intervention.

## Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

## Keywords

brain metastases | human epidermal growth factor receptor-2 positive (HER2+) | incidence | metastatic breast cancer | triple negative

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