Association between the elevation of tumor-infiltrating lymphocytes in different subtypes of primary breast tumors and prognostic outcomes: A meta-analysis

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Abstract

Purpose To investigate the impact of the elevation of tumor-infiltrating lymphocytes (TILs) in different molecular subtypes of primary breast cancer, i.e. a 10% increment of TILs in tumor and lymphocyte-predominant breast cancer (LPBC), on long-term survival and pathological complete response (pCR) and to compare the presentation of high-level TILs across these molecular subtypes. Methods Citation retrieval was performed in the PubMed, Cochrane Library, Embase and Web of Science databases. All statistical calculations were performed by the software of StataSE version 12.0. Results Twenty-two eligible clinical trials including 15676 unique patients were included for meta-analysis. The 10% increment of TILs in human epidermal growth factor receptor 2 (HER2)-overexpression (pooled Hazard ratio (HR), 0.92; 95% CI, 0.89-0.95) and triple-negative (TN) (pooled HR, 0.90; 95% CI, 0.89-0.92) breast tumors significantly improved overall survival (OS) but in Luminal tumor subtype was inert to improve that (pooled HR, 1.06; 95% CI, 0.99-1.13). It was also associated with an increased pCR rate in breast cancers (pooled Odds ratio (OR), 1.27; 95% CI, 1.19-13.5). LPBC was significantly related with a higher pCR rate (OR, 2.73; 95% CI, 2.40-3.01) than non-LPBC. This significant difference was also shown in different molecular subtypes of LPBC compared with those of non-LPBC. HER2-amplified (OR, 3.14; 95% CI, 1.95-5.06) and TN (OR, 4.09; 95% CI, 2.71-6.19) phenotypes of breast cancers expressed significantly elevated high-level TILs than Luminal tumor subtype, although the presentation of those between the former two subsets was not significantly different (OR, 1.30; 95% CI, 0.83-2.04). Conclusion The elevation of TILs in breast tumors predicts promising prognostic outcomes, particularly in the HER2-overexpression and TN subtypes. These benefits in Luminal tumor subtype need to be warranted.

Introduction
The tumor microenvironment is thought to play an important role in the germination, development, invasion and metastasis of tumors and is composed of immune cells, cytokines, adipocytes, and cancer-related fibroblasts, as well as the extracellular stroma.\textsuperscript{1, 2} The interaction of immune lymphocytes and tumor cells are the most important interactions in these procedures of tumors. In the immune system, lymphocytes can eradicate tumor cells and prevent neoplasm development through immune surveillance;\textsuperscript{3} tumor-infiltrating lymphocytes (TILs) participate in the regulation of the tumor niche and the inhibition of tumor formation and development.\textsuperscript{2}

Lymphocyte-predominant breast cancer (LPBC) favors a good, long-term prognosis and enhanced chemosensitivity in primary aggressive molecular subtypes, including the human epidermal growth factor receptor 2 (HER2)-positive (HER2/neu oncogene overexpressed, hormone-receptor-negative) and triple-negative (TN) subtypes. When TN breast cancer patients undergo chemotherapy, each 10% increment of intratumoral TILs (iTILs) and stromal TILs (sTILs) leads to reductions of the recurrence risk of 17% and 15%, respectively, and to reductions of the death risk of 27% and 17%, respectively.\textsuperscript{4} The presentation of high-level TILs is positively associated with the survival benefits of anthracycline-based chemotherapy and anti-HER2 targeted therapy (trastuzumab) in HER2-positive breast tumors.\textsuperscript{5} Of note, a pooled analysis of 3371 patients who underwent neoadjuvant therapy had a higher concentration of TILs, which led to shorter overall survival (OS) in the Luminal phenotype of breast cancer,\textsuperscript{6} suggesting a different biological feature of immune infiltration in this tumor subtype.

In this context, the purpose of our study is to settle these issues, including how the 10% increment of TILs in different molecular phenotypes of breast cancer and these subtypes of LPBC versus non-LPBC influence the OS and the pathological complete response (pCR).
rate. We also compare the expression of high-level TILs between these phenotypes.

Methods

Search strategy

Electronic retrievals were performed from the PubMed, Web of Science, Cochrane Library and Embase databases accord to the following search strategy: ((primary breast cancer) OR (primary breast tumor) OR (primary breast tumor)) AND ((tumor-infiltrating lymphocytes) OR (immune cells infiltration) OR (immune cells infiltrating) OR (immune cell infiltration) OR (immune cell infiltrating)) NOT (metastasis OR metastatic OR metastasize).

No restrictions were used during the retrieval process. The deadline for retrieval was 25 March 2019.

Inclusion criteria

Clinical trials;
Female patients with primary a breast tumor;
The impact of a 10% increment of TILs in breast cancer or LPBC on the OS or on the pCR rate was reported in publications. Studies that documented at least two molecular tumor subtypes with the expression of high-level TILs were also included. TILs were quantified on hematoxylin and eosin–stained sections and evaluated by the usage of the guideline of the International TILs Working Group. OS referred to the duration from the date of diagnosis to the date of death or lost follow-up. pCR was defined as the pathologically absent residual tumor foci in the breast and local regional lymph nodes. The definition of the LPBC was the TIL’s presentation in breast tumors greater than 50%. The high-level TILs were defined as TILs with a concentration ≥50%.

Exclusion Criteria

Articles not published in English;
Studies referencing forkhead box P3 (FOXP3) + or programmed death 1 (PD-1) + or programmed death ligand-1 (PD-L1) + TILs;
Type of work: reviews, case reports, conference abstracts and conference papers;
Other conditions that did not meet the inclusion criteria.

The retrieved citations were screened by two reviewers (Yaling Wang and Yuhua Song) in terms of duplicated citations, titles, abstract sand full-texts. Only eligible trials that met the inclusion criteria were included. If there were any inconsistencies, they were addressed by a discussion.
Data abstraction

Two co-authors (Yaling Wang and Yuhua Song) independently used Microsoft Excel version 2016 (Microsoft Corporation, Redmond, Washington, USA) to collect the following information from the eligible papers: the first author, publication year, original nation, median follow-up, median age, total number of analyzed patients, the Hazard Ratio (HR) with its 95% confidence interval (CI) indicating the association of the intervention factor and OS, the event number of pCR in different intervention factor or the Odds ratio (OR) with the 95%CI referencing the association between the intervention factor and pCR, as well as the event number of the presentation of high-level TILs in different subtypes. If some divergences existed, they were resolved by the third co-author (Xuezhen Ma).

Statistical analysis

We protocled the 10% increment of TILs in breast tumors and LPBC arms as the study groups and the non–10% increment of TILs in breast tumors and non-LPBC arms as the control groups. If the trials reported the event number of pCRs in the study cohort and the control cohort, respectively, the crude OR with its 95% CI was calculated and pooled with that from the other studies. In the analysis of the impact of the intervention factors on OS, the crude HRs with their 95% CIs from the included studies were directly pooled. The comparison of the expression of high-level TILs across the three subtypes was computed in terms of the event and total numbers. If the publication was lacking the event number, it was obtained according to the incidence rate of the event or other information. The heterogeneity between analyzed trials was assessed by the heterogeneity Chi$^2$ test (significant level of $p<0.1$) with its $I^2$ value. The fixed-effect model was used to pool the data if the heterogeneity test of the meta-analysis was not statistically significant; otherwise, the random-effect model was utilized. The publication bias of these analyses
was evaluated by the Egger’s test (significant level of \( p<0.05 \)). The estrogen receptor (ER) status, primary endpoint, and the chemotherapy strategy and chemotherapy regimen as well as the TILs subset in the eligible studies were also discussed. All the statistical tests were conducted by StataSE software (version 12.0) (StataCorp LP, College Station, TX, USA).

Results

After the systematic retrieval from the abovementioned databases, a total of 914 initial citations were obtained by using the search strategy, and 392 potential citations were left for title and abstract screening following the deletions of duplications (\( n = 285 \)), conference papers (\( n = 219 \)), reviews (\( n = 16 \)) and case reports (\( n = 2 \)). Next, 49 articles remained for full-text assessment due to 343 citations being excluded via title and abstract screening; of these, studies that were reviews (\( n = 2 \)), inconsistent to the criteria of LPBC in our study (\( n = 4 \)), devoid of useful data (\( n = 16 \)) and centered on PD-L1+TILs (\( n = 3 \)) or FOXP3+ TILs (\( n = 2 \)) did not meet the inclusion criteria and hence were excluded. Ultimately, 22 qualified studies were included for meta-analysis.\(^5,\,6,\,8-27\) The procedure of qualified article selection is outlined in Fig. 1.

Of those included studies, the publication year ranged from 2010 to 2019, 14 (63.6%) were retrospective studies with a total of 6958 cases, 10 (45.5%) were originally from Asian countries, 9 (40.9%) documented the breast cancer patients with ER-negative status, and the predominately chemotherapy strategy was in the setting of neoadjuvant therapy. Table 1 also represented the other details involving the median follow-up, the publication year, the median age, the analyzed cases in each analysis, the primary endpoint, and the detailed chemotherapy regimen, as well as the TILs subsets. Four studies recorded the 10% increment of TILs and OS without classification to different
molecular subtypes, and the pooled results showed that the 10% increment of TILs could not significantly improve OS (HR, 0.95; 95% CI, 0.91–1.01). However, there was a significant improvement in OS in terms of the pooled results of multivariate data (HR, 0.92; 95% CI, 0.85–0.98) but not that of univariate data (HR, 1.00; 95% CI, 0.94–1.06) (Fig. 2). In the subgroup analysis of different subtypes, the pooled results showed that, although the 10% increment of TILs in Luminal tumor phenotype did not significantly improve OS (HR, 1.06; 95% CI, 0.99–1.13) (eFig. 1, Supplementary page 1), the improvements in OS were attained by it in HER2-overexpression (HR, 0.92; 95% CI, 0.89–0.95) (eFig. 2, Supplementary page 1) and TN (HR, 0.90; 95% CI, 0.89–0.92) subtypes (eFig. 3, Supplementary page 2). The results were both statistically significant in pooling the univariate data and the multivariate data of the latter two molecular phenotypes (These data were shown in eFig. 2 and eFig. 3, respectively).

Two studies reported the 10% increment of TILs in breast tumors and pCR, and one\(^{25}\) of them divided patients into the training cohort and the validation cohort. Thus, three independently relevant data existed. The pooled results indicated that there was a significantly positive correlation between the 10% increment of TILs in tumor and the increased pCR rate (OR, 1.27; 95% CI, 1.19–1.35). The results of pooling univariate data (OR, 1.33; 95% CI, 1.19–1.47) and multivariate data (OR, 1.21; 95% CI, 1.14–1.28) were still statistically significant (Fig. 3).

Eleven studies provided sufficient data of LPBC and pCR. There was a significant difference in pCR rate between LPBC and non-LPBC (OR, 2.73; 95% CI, 2.40–3.01), and the pooled results of univariate data (OR, 2.84; 95% CI, 2.46–3.21) and multivariate data (OR, 2.35; 95% CI, 1.65–3.05) were also both statistically significant (Fig. 4). In the subgroup analysis, the pooled results all showed a higher pCR rate in Luminal, HER2-overexpression and TN phenotypes of LPBC than those of non-LPBC, respectively (These data were...
Seven studies were collected to perform the comparison of expression of high-level TILs across the different subsets of breast tumors. The pooled data of analysis showed that the presentation of high-level TILs between HER2-overexpression subtype and TN subtype was not significantly different (OR, 1.30; 95% CI, 0.83–2.04), whereas both subtypes experienced significantly elevated expression of high-level TILs as compared to Luminal phenotype (HER2-overexpression vs. Luminal, OR, 3.14; 95% CI, 1.95–5.06; and TN vs. Luminal, OR, 4.09; 95% CI, 2.71–6.19; respectively) (Fig. 5).

Several meta-analyses manifested moderate-to-considerable heterogeneity, and therefore, the random-effect model was employed to pool the data. With the exception of the impact of the 10% increment of TILs in TN tumor subtype on OS ($p = 0.001$) and the impact of LPBC on pCR ($p = 0.007$), there was no likelihood of publication bias in others because the Egg’s tests of them were not statistically significant (eTable 1, Supplementary page 4).

Discussion

Previous meta-analyses have shown that the value of total TILs is that they are associated with an improved outcome in breast cancer following neoadjuvant chemotherapy, but not in hormone receptor-negative subtypes. There is, however, already controversy about whether this benefit is indeed confined to patients with hormone receptor positivity. To investigate this issue, we evaluate all available evidence regarding the Luminal subtype with the hormone receptor-positive and HER2-amplified and TN phenotypes that are both hormone receptor-negative from a pool of clinical studies and demonstrate that a 10% increment of TILs in breast tumors improves OS in HER2-amplified and TN molecular subtypes, but not in the Luminal phenotype. Our results also agree with Denkert’s and West’s trials, which both suggest that a high TILs concentration increases the tumor
response to neoadjuvant chemotherapy and anthracycline-based chemotherapy, and is in association with better long-term survival in the HER2-overexpression and TN breast tumors.

In the study by Denkert et al.,⁶ it is found that the increased TILs may be an adverse factor to OS in breast cancer patients with the Luminal subtype, which differs from our results. This difference may be explained as follows. First, they only evaluated the OS in Luminal-HER2-negative tumors, while our study also includes Luminal-HER-positive of breast cancer patients. Furthermore, they only center on the assessment of the impact of sTILs on OS, but we additionally assess the iTILs. Last, the treatment strategies are not identical, as only neoadjuvant chemotherapy is included in their study but adjuvant chemotherapy is yet included in ours. Collectively, the elevation of the TILs concentration in breast tumors is not advantageous for predicting prolonged OS in patients with the Luminal subtype, largely because of the following reasons: Luminal breast cancer is a predominantly immunologically cold tumor with a low mutation burden of TILs, which can worsen the tumor response to aromatase inhibitor (AIs) treatment;⁶ in addition, the T cell-related mRNA signatures are relevant to a favorable prognosis in breast cancers of the TN or HER2-positive subtypes but not of the Luminal subtype, although B cell-related mRNA signatures indicate good prognosis in Luminal breast cancer;²⁸, ²⁹ third, breast cancer is an immunogenic tumor that can be targeted by immunomodulatory therapy,⁶ but our results show that the expression of high-level TILs in the Luminal subtype is significantly lower than that in the HER2-positive and TN subtypes, making them inefficient in immunomodulatory therapy in Luminal breast tumors.

A large number of clinical trials are enthusiastic about the association between the presence of TILs and the pCR rate after chemotherapy in HR-negative breast cancer. The
2013 San Antonio Breast Cancer Symposium\textsuperscript{5} and 2014 American Society of Clinical Oncology 50th Annual Meeting\textsuperscript{30} reported that the presentation of TILs was associated with a higher pCR rate in breast tumors with the HER2-overexpression and TN phenotypes that underwent neoadjuvant chemotherapy (HER2-overexpression breast cancer routinely received trastuzumab treatment). These results map to our findings that a 10% increment of TILs preages a higher pCR rate in breast carcinoma, but it is imperfect as lack of enough data to perform the subgroup analysis of different disease subtypes. Consequently, the understudied association between the 10% increment of TILs and pCR rate in Luminal breast cancer needs to be warranted. Of note, the association between different molecular subtypes of LPBC and pCR rate is well delineated in our study, i.e. the increased pCR rate favors all subtypes of LPBC when compared to those of non-LPBC. Consistently, West and colleagues reaffirm that HER2-amplified and TN subtypes of LPBC have promising chemosensitivity to anthracycline-based adjuvant or neoadjuvant chemotherapy.\textsuperscript{10}

In our study, breast cancers with the HER2-positive and TN subtypes greatly increase the expression of high-level TILs compared with the Luminal subtype; however, there is no significant difference in expression between the former two tumor subtypes. These disparate results may be attributed to the evaluation of different subtypes of immune cells. A variety of lymphocyte subtypes form TILs, which have different activities, from cytotoxicity to immune escaping effects. In TILs, the infiltration of cytotoxic CD8+ T cells predicts improved responses to anthracycline- and taxane-based regimens in primary breast cancers and significantly prolongs survival of patients. However, the infiltration of FOXP3+ T cells is a predictor of poor prognosis in that these cells mediate tumor immune escape. A meta-analysis of 17 trials demonstrated that FOXP3+ and PD-1+ TILs were
associated with a worse prognosis in breast tumors.\textsuperscript{2} Thus, articles with reference to PD-1+, PD-L1+ and FOXP3+ TILs are included in our study. Our results at a certain extent explain why Luminal breast carcinoma is a predominantly immune cold tumor, the reasons for the good response to anti-HER2 targeted therapy, mediated in part by immune effector mechanisms, of HER2-positive breast cancer and of the strong immunogenic characteristic of breast tumors with the TN subtype.

Admittedly, this meta-analysis has limitations. First, a selection bias might exist because of the inclusion criterion that confined the condition to English publications and the exclusion criteria that omitted the immune cell subsets of PD-1+TILs, PD-L1+TILs and FOXP3+TILs. Second, to obtain more evidence and larger scale of cases, analysis of pCR rate between LPBC and non-LPBC also included trials centering on CD8+LPBC, giving rise to considerable heterogeneity. Finally, there may be clinical heterogeneity among the included studies, such as application of different chemotherapy regimens and treatment strategies, as well as investigation of different TILs subtypes.

Despite these limitations, this was the first meta-analysis that systematically elucidated the influence of a 10% increment of TILs in breast cancer and LPBC on OS and pCR, and compared the presentation of high-level TILs in different molecular subtypes. Moreover, the molecular mechanisms of the antitumor effects of CDK4/6 inhibitors were summarized in the Discussion section. Future studies will need to supplement the underrecognized and understudied landscapes whether a higher pCR rate is related to the 10% increment of TILs in the Luminal subtype of breast cancer and Luminal and HER2-overexpression phenotypes of LPBC is beneficial to improved OS.

Conclusion

The 10% increment of TILs in breast tumors predicts improved OS and pCR rate of
patients, specifically in the HER2-overexpression and TN molecular subtypes. Moreover, all subsets of LPBC benefit greater pCR rate than those of non-LPBC. Although there is no difference between the expression of high-level TILs among HER2-overexpression and TN phenotypes of breast cancer, they both have high expression than that relative to the Luminal tumor subtype.

Declarations

Ethics Statement

*Ethics approval and consent to participate*

This article does not contain any studies with human participants or animals performed by any of the authors.

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Disclosure Statement

*The authors declare that they have no competing interests.*

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**Tables**

| Characteristic                     | Studies, No. (%) (N=22) | Primary Breast Cancer Patients, No. (%) (N=15676) |
|-----------------------------------|-------------------------|-------------------------------------------------|
| Study type                        |                         |                                                 |
| Randomized trial                  | 5 (22.7)                | 3578 (22.8)                                     |
| Retrospective                     | 14 (63.6)               | 6958 (44.4)                                     |
| Pooled                            | 1 (4.5)                 | 3771 (24.1)                                     |
| Prospective-retrospective         | 1 (4.5)                 | 934 (6.0)                                       |
| Prospective                       | 1 (4.5)                 | 435 (2.8)                                       |
| Publication date, median (range), y| 2016 (2010-2019)        |                                                 |
Follow-up, median (range), mo* 90.6 (48.0-190.8)
Median age, median (range), y* 50.0 (46.5-54.0)
10% increment of TILs and OS, total (range), n

| Subtype         | TILs  | OS   |
|-----------------|-------|------|
| All subtypes    | 4460  | (399-2346) |
| Luminal         | 1886  | (463-832)  |
| HER2-enriched   | 1985  | (112-986)  |
| TNBC            | 3847  | (92-897)   |

10% increment of TILs and pCR, total (range), n

| Subtype         | TILs  | pCR  |
|-----------------|-------|------|
| All subtypes    | 1638  | (218-840) |
| Luminal         | 1717  | (91-1366) |
| HER2-enriched   | 1801  | (40-1379) |
| TNBC            | 1425  | (48-906)   |

LPBC and pCR, total (range), n

| Subtype         | LPBC | pCR  |
|-----------------|------|------|
| All subtypes    | 6697 | (40-3771) |
| Luminal         | 1717 | (91-1366) |
| HER2-enriched   | 1801 | (40-1379) |
| TNBC            | 1425 | (48-906)   |

High TILs cross different subtypes, total (range), n

| Subtype         | TILs  |
|-----------------|-------|
| TNBC vs Luminal | 6524  |
| HER2-enriched vs Luminal | 6696  |
| TNBC vs HER2-enriched   | 3722  |

Original area

| Region | Count (Percentage) |
|--------|--------------------|
| Asia   | 10 (45.5)          |
| America| 4 (18.2)           |
| Europe | 8 (36.4)           |

ER status

| ER Status      | Count (Percentage) |
|----------------|--------------------|
| ER-positive    | 0 (0.0)            |
| ER-negative    | 9 (40.9)           |
| ER-combined    | 13 (59.1)          |

Primary endpoint

| Endpoint | Count (Percentage) |
|----------|--------------------|
| pCR      | 10 (45.5)          |
| OS       | 11 (50.0)          |
| Others   | 1 (4.5)            |

Chemotherapy strategy

| Strategy    | Count (Percentage) |
|-------------|--------------------|
| Neoadjuvant | 15 (68.2)          |
| Adjuvant    | 5 (22.7)           |
| Unknown     | 2 (9.1)            |

Chemotherapy regimen
| Treatment Type                        | Count | (%)  | Count | (%)  |
|--------------------------------------|-------|------|-------|------|
| Anthracycline-based                  | 3     | 13.6 | 2113  | 13.5 |
| Taxanes-based                        | 1     | 4.5  | 3771  | 24.1 |
| Anthracycline- and taxanes-based     | 10    | 45.5 | 3822  | 24.4 |
| Methotrexate-based                   | 3     | 13.6 | 1915  | 12.2 |
| Unknown                              | 5     | 22.7 | 4055  | 25.9 |

TILs subsets

| Subset     | Count | (%)  | Count | (%)  |
|------------|-------|------|-------|------|
| TILs       | 11    | 50.0 | 8014  | 51.1 |
| iTILs      | 3     | 13.6 | 4135  | 26.4 |
| sTILs      | 6     | 27.3 | 3199  | 20.4 |
| CD8+TILs   | 1     | 4.5  | 175   | 1.1  |
| CD4+TILs   | 1     | 4.5  | 153   | 1.0  |

**Table 1. Summary of the characteristics of the 21 included Studies.**

Abbreviations: TILs, tumor-infiltrating lymphocytes; OS, overall survival; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; pCR, pathological complete response; LPBC, lymphocyte-predominant breast cancer; ER, estrogen receptor; iTILs, intratumoral tumor-infiltrating lymphocytes; sTILs stromal tumor-infiltrating lymphocytes.

*Median value is calculated in terms of available data.

**Figures**
Figure 1

Flow diagram of eligible article selection.
| Study ID          | HR [95% CI]       | Weight (%) | Hazard ratio |
|-------------------|-------------------|------------|--------------|
| **Univariable analysis** |                   |            |              |
| Denkert (2018)   | 1.01 [0.97-1.05]  | 22.16      |              |
| Loi (2014)       | 1.07 [0.95-1.20]  | 9.57       |              |
| Dieci (2015)     | 0.94 [0.86-1.03]  | 14.50      |              |
| Subtotal (I²=40%; p=0.19) | 1.00 [0.94-1.06] | 46.23      |              |
| **Multivariable analysis** |                   |            |              |
| Sønderstrup (2019) | 0.92 [0.84-1.00]  | 15.28      |              |
| Denkert (2018)   | 0.97 [0.92-1.01]  | 21.31      |              |
| Loi (2014)       | 0.81 [0.61-1.10]  | 3.42       |              |
| Dieci (2015)     | 0.85 [0.77-0.95]  | 13.76      |              |
| Subtotal (I²=56%; p=0.08) | 0.92 [0.85-0.98] | 53.77      |              |
| **Total (I²=64%; p=0.01)** | **0.95 [0.91-1.01]** | **100.00** |              |

**Figure 2**

Impact of a 10% increment of tumor-infiltrating lymphocytes in breast tumor on overall survival.
Figure 3

Impacts of a 10% increment of tumor-infiltrating lymphocytes in breast tumor on the pathological complete response.
| Study ID      | OR [95% CI]       | Weight (%) | Odds ratio |
|--------------|-------------------|------------|------------|
| Denkert (2018) | 2.62 [2.21-3.10]  | 54.51      |            |
| Lee (2013)    | 2.46 [0.93-6.46]  | 1.42       |            |
| Denkert (2010) | 4.12 [2.63-6.47]  | 2.93       |            |
| Denkert (2010) | 6.98 [2.71-17.98] | 0.19       |            |
| Galvez (2018) | 2.60 [1.40-4.84]  | 3.64       |            |
| Watanabe (2018)| 5.73 [2.73-12.03]| 0.50       |            |
| Denkert (2015) | 2.92 [1.98-4.31]  | 7.97       |            |
| West (2011)   | 6.33 [2.49-16.08] | 0.23       |            |
| Seo (2013)    | 7.33 [2.02-26.21] | 0.07       |            |
| Kochi (2018)  | 3.50 [2.43-5.13]  | 5.94       |            |
| Watanabe (2018)| 5.73 [2.73-12.00]| 0.50       |            |
| Subtotal (I²=0%; p=0.50) | 2.84 [2.46-3.21] | 77.90      |            |

**Multivariable analysis**

| Study ID      | OR [95% CI]       | Weight (%) | Odds ratio |
|--------------|-------------------|------------|------------|
| Denkert (2015)| 2.66 [1.76-4.02]  | 8.47       |            |
| West (2011)  | 6.42 [2.08-19.80] | 0.14       |            |
| Seo (2013)   | 2.38 [0.48-11.69] | 0.34       |            |
| Kochi (2018) | 2.02 [1.30-3.14]  | 12.78      |            |
| Watanabe (2018)| 4.97 [1.94-12.80]| 0.37       |            |
| Subtotal (I²=0%; p=0.65) | 2.35 [1.65-3.05] | 22.10      |            |
| **Total (I²=0%; p=0.58)** | **2.73 [2.40-3.01]** | **100.00** |            |

**Figure 4**

Impacts of lymphocyte-predominant breast cancer on the pathological completed response.
### Figure 5

Comparison of the expression of high-level TILs across different subtypes of breast tumors.

| Study ID       | OR [95% CI]        | Weight (%) | Odds ratio                  |
|---------------|--------------------|------------|-----------------------------|
| **TNBC vs Luminal** |
| Denkert (2018) | 2.99 [2.42-3.71]   | 18.10      | **1-V, Random, 95%CI**      |
| Kim (2016)    | 8.68 [4.62-16.30]  | 13.18      |                             |
| Burugu (2017) | 6.87 [5.05-9.34]   | 17.22      |                             |
| Hwang (2018)  | 3.20 [1.61-6.36]   | 12.48      |                             |
| Dieci (2015)  | 3.74 [2.08-6.71]   | 13.77      |                             |
| Watanabe (2017)| 5.39 [2.29-12.67] | 10.47      |                             |
| Galvez (2018) | 1.86 [1.12-3.08]   | 14.79      |                             |
| **Subtotal (I²=82%; p<0.01)** | **4.09 [2.71-6.19]** | **100.00** |                             |

| **HER2+++ vs Luminal** |
| Denkert (2018) | 1.63 [1.32-2.01]   | 18.26      |                             |
| Kim (2016)    | 5.50 [2.48-12.22]  | 12.37      |                             |
| Burugu (2017) | 3.66 [2.49-5.38]   | 16.84      |                             |
| Hwang (2018)  | 3.02 [1.32-6.92]   | 12.05      |                             |
| Dieci (2015)  | 6.69 [3.61-12.38]  | 14.38      |                             |
| Watanabe (2017)| 1.34 [9.52-3.45]  | 10.80      |                             |
| Galvez (2018) | 3.44 [2.02-5.86]   | 15.30      |                             |
| **Subtotal (I²=83%; p<0.01)** | **3.14 [1.95-5.06]** | **100.00** |                             |

| **TNBC vs HER2+++** |
| Denkert (2018) | 1.84 [1.51-2.24]   | 18.81      |                             |
| Kim (2016)    | 1.58 [0.80-3.12]   | 13.42      |                             |
| Burugu (2017) | 1.88 [1.23-2.87]   | 16.58      |                             |
| Hwang (2018)  | 1.06 [0.47-2.39]   | 11.86      |                             |
| Dieci (2015)  | 0.56 [0.31-1.00]   | 14.67      |                             |
| Watanabe (2017)| 4.03 [1.61-10.08] | 10.73      |                             |
| Galvez (2018) | 0.54 [0.28-1.03]   | 13.93      |                             |
| **Subtotal (I²=81%; p<0.01)** | **1.30 [0.83-2.04]** | **100.00** |                             |
Figure 6

Supplementary Files

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