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*Original Article*

# Degree of SUVmax correlates with Ki-67 index in patients with breast cancer: a meta-analysis

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**Abstract:** Positron emission tomography (PET) imaging using the radiotracer $^{18}$F-Fluorodeoxyglucose (FDG) has been proposed as imaging biomarkers of cell proliferation. We aimed to explore the correlation of FDG uptake with the Ki-67 labeling index in patients with breast cancer. Several databases were systematically searched for all relevant literature. The quality of included studies was evaluated according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. The correlation coefficient (rho) and its 95% confidence interval (CI) of individual studies were meta-analyzed using a random-effects model. The sources of heterogeneity were explored by sensitivity and subgroup analysis. The pooled rho value between SUVmax and Ki-67 index was 0.40 (95% CI, 0.35-0.46), which indicated an average correlation, but with a significant heterogeneity ($I^2$=67.4%, P<0.01). Sensitivity analysis revealed that a single study contributed no significant influence to the overall estimate. Study design was a potential source of heterogeneity (rho=0.36 for prospective group vs. rho=0.47 for retrospective group, P<0.05) while other two factors, including scanning modality (PET, PET/CT or both) and sample method (surgery, biopsy or both), were not. In patients with breast cancer, the correlation between $^{18}$F-FDG uptake and tumor cell proliferation is significant but at a low degree.

**Keywords:** Breast cancer, PET/CT, SUVmax, Ki-67, meta-analysis

## Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women, with an estimated 14.1 million new cancer cases and 8.2 million cancer deaths occurring in 2012 worldwide [1]. Its prognostic factors included not only some traditional histologic features such as tumor size, histologic grade, nodal status and vascular invasion, but also some molecular markers involved in breast cancer biology [e.g. Ki-67 proliferation index, epidermal growth factor receptor (EGFR), hormone receptor status, cytokeratin (CK5/6)] [2, 3]. Ki-67, as a nuclear antigen expressed in all active phases of cell cycle (G1, S, and G2) except the G0, is present in all proliferation cells and has been established as a proliferation biomarker in breast cancer [4-6]. Ki-67 positivity confers a higher risk of relapse and a worse survival in patients with breast cancer and is regarded as a prognostic marker in breast cancer [6]. However, the measurement of Ki-67 index involving immunohistochemical staining necessitates an invasive biopsy. If we find a surrogate marker that can be obtained by non-invasive means, it will make response evaluation and prognosis assessment easier for breast cancer patients.

In breast cancer patients, positron emission tomography/computed tomography (PET/CT) with $^{18}$F-fluoro-2-deoxy-2-D-glucose ($^{18}$F-FDG) plays a proven role in the staging, recurrence detection, restaging, and response assessment [7]. Previous studies have focused on its prognostic value for breast cancer, and demonstrated that PET/CT is useful to predict malignancy grades and the prognosis [8-10]. The maximum standardized uptake value (SUVmax) measures glucose metabolism that reflects the growth potential and metabolic activity of malignant tumors, and it is useful for the prediction of malignant behavior and prognosis in breast cancer [11, 12].

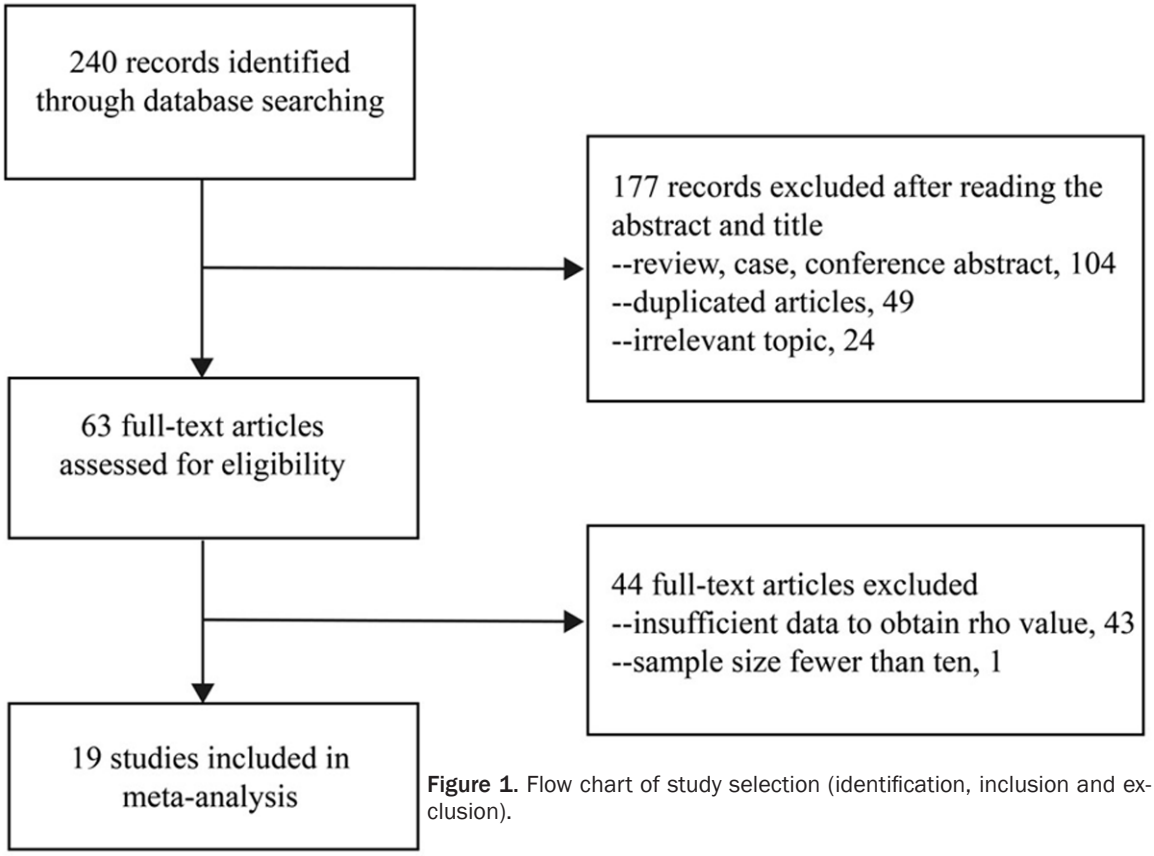


**Figure 1.** Flow chart of study selection (identification, inclusion and exclusion).

Since both Ki-67 proliferation index and FDG uptake (SUVmax) are prognostic markers of breast cancer, it is of value to analysis the association between these two factors, further to evaluate whether calculations of tumor FDG uptake by SUVmax could provide a non-invasive metabolic parameter that is associated with the biological aggressiveness of breast cancer. In this regard, several studies reported a significant correlation between these two factors ranging from 0.4 to 0.73 [13-17] while some studies indicated no significant correlation [3, 18-20]. In consideration of the controversial conclusions on this issue, we performed a meta-analysis to pool the eligible data, and evaluated the correlation of FDG uptake and Ki-67 index, in order to provide an evidence-based conclusion.

## Material and methods

### *Literature search and study selection*

A systematic search of MEDLINE, EMBASE, the Cochrane Library and China National Knowledge Infrastructure (CNKI) (inception to November 2015) was performed for relevant articles about the relationship between $^{18}$F-FDG uptake and Ki-67 expression in breast cancer. All searches were limited to human studies. The search strategy was based on the combination of terms related to PET, FDG, Ki-67 and breast cancer. Inclusion criteria were as follows: (1) studies limited to breast cancer; (2) studies about the relationship between Ki-67 expression and FDG uptake; (3) patients who had undergone PET scans before surgery, chemotherapy or radiotherapy; and (4) tumors confirmed by cytopathology or histopathology. Reviews, case reports, conference abstracts and letters were excluded. Studies with sample size fewer than 10 or studies with insufficient data were also excluded.

### *Data extraction and quality assessment*

Two reviewers independently extracted relevant data from the included studies, and the following information was recorded: first author, publication year, study design, tumor type, number of patients, technical characteristics of PET

**Table 1.** Primary characteristics of $^{18}$F-FDG PET/CT scan

| Author | Year | Study design | Tumor confirmation | Scanner | Dose | Uptake period (min) | Fasted | Scanning time (min) | Uptake index |
|---|---|---|---|---|---|---|---|---|---|
| Cheng | 2013 | P | Pathological evaluation | Biograph 16HR PET/CT (Siemens) | 7.4 MBq/kg | 60 | Y | 2-3 min/table position | SUVmax |
| Cochet | 2012 | P | Pathological evaluation | PET/CT system (Gemini GXL; Philips) | 5 MBq/kg | 90 | Y | 3 min/bed position | SUVmax |
| Ana | 2012 | P | Histopathological analysis | Whole-body PET/CT machine (GE, Discovery DST-E) | 370 MBq | 60 | Y | 3 min/bed position | SUVmax |
| Ana | 2012 | P | The core needle biopsy | Whole-body PET/CT machine (GE, Discovery DST-E) | 370 MBq | 60 | Y | 3 min/bed position | SUVmax |
| Ana | 2013 | P | Histopathological analysis | Whole-body PET/CT (GE) | 370 MBq | 60 | Y | 3 min/bed position | SUVmax |
| Humbert | 2014 | P | Histopathological analysis | CPET Plus scanner and Gemini GXL PET/CT scanner (Philips Medical Systems, Eindhoven, The Netherlands) | 2 MBq/kg for CPET studies and 5 MBq/kg for Gemini studies | 60 | Y | ND | SUVmax |
| Koo | 2015 | R | Surgically diagnosed | PET/CT systems (Biograph, Siemens Medical Solutions, Hoffmann Estates, IL, USA) | 5.2 MBq/kg | 60 | Y | 2 min per bed position for emission scan | SUVmax |
| Koolen | 2012 | P | Core biopsy | PET/CT scanner (Gemini TF, Philips, Cleveland, OH, USA) | 180-240 MBq | 60±10 | Y | 3 min/bed position | SUVmax |
| Kurland | 2012 | P | Biopsy-proven | ADVANCE PET scanner or Discovery STE PET/CT scanner (GE Medical Systems, Waukesha, WI, USA) | 259-370 MBq | 60 | Y | 7-min emission collections per field | SUVmax |
| Tchou | 2010 | R | Histologically proven | Whole-body PET scanner (Allegro; Philips Medical Systems) | ND | 63 | Y | ND | SUVmax |
| Tokes | 2015 | R | Core-biopsy | Whole-body PET/CT scanners (Siemens Biograph™ TruePoint™ HD, Siemens Healthcare; GE Discovery™ ST 8 GE Healthcare) | 185-370 MBq | 60 | Y | ND | SUVmax |
| Garcia | 2014 | P | Pathology diagnosis obtained by core needle biopsy | PET-CT equipment (Biograph; Siemens, Erlangen, Germany) | 5 MBq/kg | 60 | Y | 3 min per table position for emission scan | SUVmax |
| Yang | 2013 | P | Core needle biopsy | Siemens biograph 16HR PET/CT scanner (Knoxville, Tennessee, USA) | 7.4 MBq/kg | 60 | Y | 2-3 min per table position | SUVmax |
| Tokes | 2012 | R | Core biopsy | Siemens Biograph™ TruePoint™ HD PET-CT camera (Siemens Healthcare, Siemens) and GE Discovery™ ST 8 PET-CT (GE Healthcare, GE Medical Systems) | 185-370 MBq | 45-60 | Y | ND | SUVmax |
| Kajáry | 2015 | R | Core needle biopsy | True Point HD PET/CT (Siemens, Knoxville, Tennessee, USA) | 3.7 MBq/kg | 66 | Y | ND | SUVmax |
| Tang | 2013 | R | Biopsy-proven or surgery-proven | GE MINI TFII PET/CT (Philips) | 4.44 MBq/kg | 60 | Y | 1 min per bed position | SUVmax |
| Yang | 2012 | R | Pathologically confirmed | Discovery LS PET/CT (GE, USA) | 3.0-4.5 MBq/kg | 60 | Y | 4 min per bed | SUVmax |
| Yuan | 2013 | R | Pathologically confirmed | GEMINI PET/CT (Philips) | 5.18 MBq/kg | 60 | Y | 3 min per bed | SUVmax |
| Zhu | 2009 | R | Pathologically confirmed | Discovery LS PET/CT (GE, USA) | 5.5 MBq/kg | 45 | Y | 8 min per bed | SUVmax |

ND: not documented; P: prospective; R: retrospective; Y: yes; SUV: standard uptake value.

**Table 2.** The basic characteristics of Ki-67 immunohistochemistry

| Author | Year | Tumor subtype | Stage | No. | Sample methods | Rho (95% CI) |
|---|---|---|---|---|---|---|
| Cheng | 2013 | ER-positive breast cancer | II-IV | 22 | Biopsy + surgical samples | 0.22 (-0.22, 0.59) |
| Cochet | 2012 | Invasive ductal carcinoma for 38; invasive lobular carcinoma for 2 | T2 for 24, T3 for 15, T4a for 1 | 40 | Needle core biopsy | 0.69 (0.48, 0.82) |
| Ana | 2012 | Invasive ductal carcinoma for 55; invasive lobular carcinoma for 6; in situ lobular carcinoma for 1; in situ ductal carcinoma for 1 | IIA for 11, IIB for 21, IIIA for 22, IIIB for 13, IIIC for 1 | 68 | Gross-needle aspiration biopsy and surgical procedures | 0.3 (0.07, 0.5) |
| Ana | 2012 | Invasive ductal carcinoma for 29; invasive lobular carcinoma for 5; in situ lobular carcinoma for 1; in situ ductal carcinoma for 1 | IIB for 4, IIIA for 20, IIIB for 11, IIIC for 1 | 36 | Gross-needle aspiration biopsy and surgical procedures | 0.33 (0, 0.59) |
| Ana | 2013 | Invasive ductal cancer for 61; invasive lobular cancer for 14 | N0 for 17, N1 for 28, N2 for 13, N3 for 17 | 75 | Gross-needle aspiration biopsy | 0.19 (-0.04, 0.40) |
| Humbert | 2014 | Luminal HER2-negative tumors (ductal cancer for 49, lobular cancer for 12) | II or IIIA | 61 | Needle core biopsy | 0.49 (0.27, 0.66) |
| Koo | 2015 | Triple-negative breast cancer (invasive ductal carcinoma for 100, mucinous carcinoma for 1, metaplastic carcinoma for 1, adenoid cystic carcinoma for 1) | IA for 30, IIA for 52, IIB for 15, IIIA for 5 and IIIB for 1 | 103 | Surgical specimens | 0.29 (0.10, 0.46) |
| Koolen | 2012 | Invasive ductal carcinoma for 181, invasive lobular carcinoma for 23, other for 10 | II for 127, III for 60, IV for 27 | 214 | A core biopsy | 0.4 (0.28, 0.51) |
| Kurland | 2012 | Biopsy-proven breast cancer with confirmation of ER or HER2 expression and lesions larger than 3 cm diameter (invasive ductal carcinoma for 23, invasive lobular carcinoma for 10, both for 2, unknown for 5) | ND | 22 | A diagnostic biopsy or remote biopsy | -0.07 (-0.48, 0.36) |
| Tchou | 2010 | Triple negative breast cancer for 21 and non-triple negative for 19 (invasive ductal carcinoma for 21, invasive lobular carcinoma for 19) | ND | 40 | Surgery | 0.485 (0.20, 0.69) |
| Tokes | 2015 | Invasive ductal carcinoma for 39, invasive micropapillary for 2, Invasive medullary for 1 | T1c for 6, T2 for 31, T3 for 3, T4 for 2 | 42 | Core-biopsy specimens | 0.31 (0.007, 0.56) |
| Garcia | 2014 | Ductal carcinoma for 39, lobular carcinoma for 4 | IIA for 13, IIB for 19, IIIA for 7, IIIB for 4 | 43 | Core-biopsy specimens | 0.408 (0.12, 0.63) |
| Yang | 2013 | Invasive ductal breast carcinomas | IIA for 4, IIB for 4, IIIA for 9, IIIB for 1 | 18 | Core-biopsy specimens | 0.28 (-0.21, 0.66) |
| Tokes | 2012 | Invasive ductal carcinoma for 27, micropapillary for 2, invasive medullary for 1 | ND | 30 | Core-biopsy specimens | 0.49 (0.16, 0.72) |
| Kajáry | 2015 | Invasive ductal carcinoma for 75, invasive lobular carcinoma for 4, other for 4 | T1 for 7, T2 for 59, T3 for 5, T4 for 12 | 83 | Core needle biopsy specimens | 0.556 (0.39, 0.69) |
| Tang | 2013 | ND | II for 12, III for 16, IV for 18 | 46 | Surgery and biopsy | 0.73 (0.56, 0.84) |
| Yang | 2012 | Invasive ductal carcinoma | I for 2, II for 12, III for 16, IV for 5 | 35 | Surgery and biopsy | 0.39 (0.07, 0.64) |
| Yuan | 2013 | Invasive ductal carcinoma | II for 16, III for 2 | 18 | Surgery | 0.473 (0.01, 0.77) |
| Zhu | 2009 | invasive ductal carcinoma for 25 cases, invasive lobular carcinoma for 2, ductal carcinoma in situ for 3 | I for 7, II for 14, III for 9 | 30 | Surgery | 0.65 (0.38, 0.82) |

ER: estrogen receptor, HER2: human epidermal growth factor receptor-2; ND: no document, both: both surgery and biopsy.

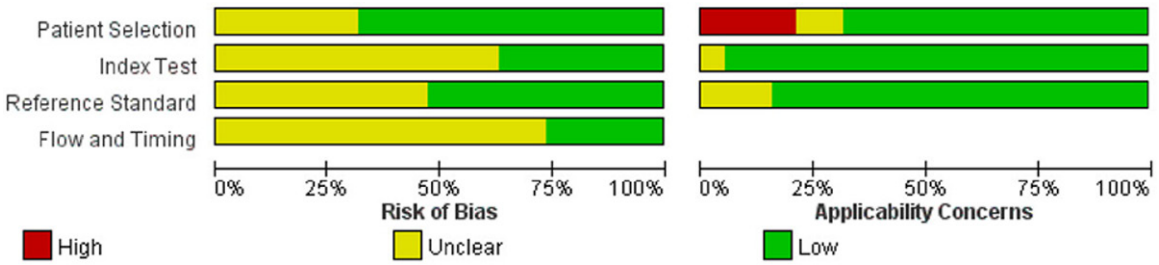


**Figure 2.** Methodological quality of eligible studies with each item presented as percentages across all included studies.

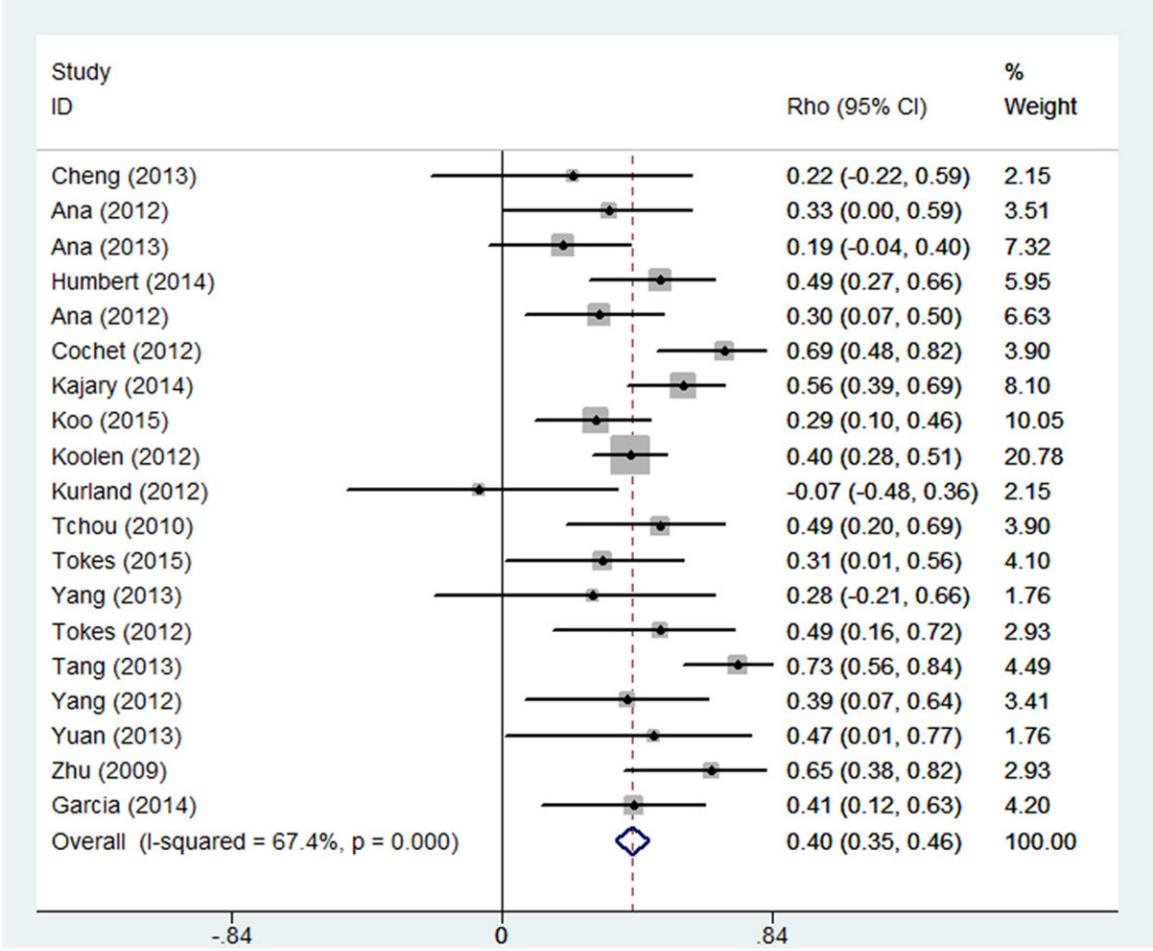


**Figure 3.** The forest plot of the pooled correlation coefficient (rho) with corresponding 95% confidence intervals for the correlation between $^{18}$F-FDG uptake and tumor cell proliferation.

scan and Ki-67 measurement (imaging equipment, agent dose, uptake time, uptake index, and sample method), and correlation coefficient (rho) value.

The methodological quality of included studies was assessed using the Quality Assessment of Diagnostic Studies-2 (QUADAS-2), which consists of four domains (patient selection, reference standard, index test, and low and timing) that each requires a judgment of low, high or unclear for "Risk of bias" [21]. Three of these domains further need to be assessed in terms of concerns regarding applicability with "high", "low" or "unclear" [21]. In our meta-analysis, the PET examination was designated as "index

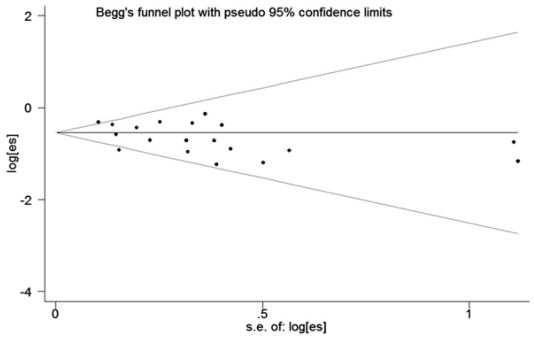


**Figure 4.** The funnel plot of publication bias for SUVmax/Ki-67 correlation. The nonsignificant slope indicates the absence of publication bias (P=0.189).

**Table 3.** Results of subgroup analysis for $^{18}$F-FDG/Ki-67 correlation in breast cancer

| Subgroup | N | Rho value (95% CI) | $I^2$ |
|---|---|---|---|
| Pooled value | 19 | 0.40 (0.35, 0.46) | 67.4% |
| Study design* | | | |
| Prospective | 10 | 0.36 (0.29, 0.43) | 62.6% |
| Retrospective | 9 | 0.47 (0.39, 0.54) | 65.4% |
| Modality | | | |
| PET | 1 | 0.49 (0.20, 0.69) | - |
| PET/CT | 16 | 0.41 (0.35, 0.46) | 69.2% |
| PET+PET/CT | 2 | 0.34 (0.16, 0.52) | 83.1% |
| Sample method | | | |
| Surgery | 4 | 0.41 (0.28, 0.53) | 56.5% |
| Biopsy | 10 | 0.40 (0.34, 0.47) | 64.8% |
| Surgery + Biopsy | 5 | 0.41 (0.29, 0.52) | 82.2% |

**P<0.05.*

test" and the Ki-67 immunohistochemistry as "reference standard".

*Statistical analysis*

The overall correlation coefficient was pooled based on individual Spearman correlation coefficient provided in each article, which was directly extracted from included studies. In cases that the rho value was not reported, it could be calculated based on the raw data using Spearman rank correlation analysis. In addition, the Pearson correlation coefficient was converted to Spearman correlation coefficient based on previously published method [22]. The 95% confidence intervals (CIs) were calculated by Fisher transformation and inverse Fisher transformation [23]. Heterogeneity of included studies was evaluated by $I^2$ index, and it indicated the presence of significant heterogeneity when $I^2$ was more than 50% [24]. In addition, the random-effect model was used to pooled analysis. We performed sensitivity analysis and subgroup analysis to explore the sources of heterogeneity. The publication bias was evaluated by Begg's test.

Statistical analysis was performed using STATA 12 software package (Stata Corporation, College Station, TX, USA). *P*<0.05 was considered significant.

## Results

*Study selection and description*

A total of 240 records were retrieved from the initial search. After reading the titles and abstracts, 177 articles were excluded due to duplication, irrelevant topic or article type. Sixty-three articles underwent full-text screening, and 19 were eventually included for pooled analysis [3, 13-20, 25-34]. The flow chart of study selection was shown in **Figure 1**.

All included studies were published between 2009 and 2015, involving 1026 patients. Of these studies, ten ones [13, 15, 16, 18-20, 26, 27, 30, 32] were prospectively designed while nine [3, 14, 17, 25, 28, 29, 31, 33, 34] were retrospectively designed. The diagnosis of breast cancer was confirmed by core-biopsy or surgery in all of included studies, and the patients were in various stages. With regard to the PET scanning, only one studies [17] used PET scanner while sixteen [3, 14-16, 18, 19, 25-34] used PET/CT scanner, two [13, 20] used both. All of included studies provided SUVmax as the measurement of FDG uptake index. Some variations in acquisition and processing parameters of PET scanning such as PET scanner, dose and scanning time were observed among included studies. For the evaluation of cell proliferation, four studies [3, 17, 25, 31] assessed Ki-67 expression based on surgically-acquired specimens while eight [13, 15, 16, 18, 20, 28, 30, 32, 34] used biopsy-acquired specimens, 5 [14, 19, 26, 27, 29] used both. The basic characteristics of included studies were presented in **Tables 1** and **2**.

*The results of QUADAS-2 for assessing methodological quality*

As presented in **Figure 2**, in six included studies, the patient selection was judged to be at unclear risk of bias because they did not pro-

vide information about patient enrollment that is consecutive or random. Several studies [3, 17, 19, 20] only included breast cancer patients with certain subtypes such as triple-negative or hormonal receptor-positive, which might narrow the range of patient selection, and give rise to high concern about the applicability.

We noted that in many studies, it was not clear if the interpretation of FDG uptake and Ki-67 expression were blind to each other; thus the index test and reference standard were considered to be of unclear risk in these studies. In addition, several studies [17, 18, 32] did not provide enough information about PET scanning or Ki-67 immunohistochemistry, which led to some unclear concerns about the clinical applicability.

With regard to flow and timing, due to lack of an explicit description of the time interval between the PET scanning and immunohistochemistry, fourteen studies were at unclear risk of bias.

*Meta-analysis of FDG/Ki-67 correlation*

The rho values were directly extracted from most of included studies whereas for one study [30], rho was calculated based on the raw data of SUVmax and Ki-67 index. For two studies [14, 29], it was obtained by conversion of Pearson correlation coefficient.

The pooled rho value for all studies was 0.40 (95% CI, 0.35-0.46) with slightly high heterogeneity among studies ($I^2$=67.4%, $P$<0.001) (**Figure 3**). Sensitivity analysis revealed that a single study contributed no significant influence to the overall estimate. In addition, the Begg's test showed that there was no significant publication bias ($P$=0.189) (**Figure 4**).

As shown in **Table 3**, the subgroup analysis for study design revealed that the rho value of retrospective group was significantly higher than that of prospective group (rho=0.36 for prospective group vs. rho=0.47 for retrospective group, $P$<0.05) although there was still significant heterogeneity among these two subgroups ($I^2$=62.6% for prospective group vs. $I^2$=65.4% for retrospective group). The results of subgroup analyses based on scanning modality (PET, PET/CT or both) and sample method (surgery, biopsy or both) did not show any significant difference. With regard to other factors such as tumor type and stage, we cannot perform the relevant subgroup analyses because of insufficient data.

## Discussion

Ki-67 index has been regarded as a biomarker of proliferation activity of malignant cells in various cancers [35], and a higher Ki-67 index is associated with more aggressive biological behavior and worse prognosis in breast cancer [3, 36]. As an invasive method involving biopsy or surgery, it has some drawbacks such as sample error during biopsy and the inability to perform multiple repeat procedures during or after the treatment to monitor the response or predict the prognosis. In the contrary, as a non-invasive method, PET/CT scan can be easily repeated at any point during or after treatment. Although FDG is not tumor-specific and not an indicator directly reflecting the cell proliferation, its uptake is closely associated with cell proliferation for the reason that glycolytic metabolism involves in the proliferation process by providing energy and some molecules [37]. Many studies have focused on evaluating tumor proliferation based on the PET imaging [38-40]. In this study, we investigated whether a correlation existed between tumor $^{18}$F-FDG uptake on PET/CT and cell proliferation activity, expressed as SUVmax and Ki-67 index respectively, for patients with breast cancer. The results showed that for breast cancer, FDG uptake and Ki-67 index displayed an average correlation (rho=0.40), which is a relatively low level [41]. In addition, the heterogeneity among studies was slightly high and its sources needed to be further explored.

The methodological quality of included studies was assessed by QUADAS-2 tool. With regard to the patient selection, we included patients with breast cancer in various tumor subtypes or features, of which the biological behavior and clinical feature were different and this heterogeneity of included patients could have introduced bias. For example, in the studies of Koo HR and Tchou J, they only enrolled women with triple negative breast cancer, which was proved to be more often poorly differentiated and aggressive with higher proliferation index and FDG uptake than ER (estrogen receptor)-positive or HER 2 (human epidermal growth factor receptor 2)-positive breast cancers [42-44], and their results might enhance the correlation relationship in some degree [3, 17]. For the conduct or

interpretation of PET/CT scan and Ki-67 immunohistochemistry, information whether using blind method was not obtained in many articles. This condition might lead to interpreting bias for the reason that knowledge of the previously performed examination may influence the judgment or interpretation of later one. In majority of included studies, the time interval between index test (PET/CT scan) and reference standard (Ki-67 immunohistochemistry) was not clearly stated, which might be a potential source of heterogeneity. If the PET/CT scan was performed after core biopsy, the time interval should be more than 7 days to avoid false positive accumulation of FDG caused by existence of inflammatory cells, as well as less than 1 month to avoid disease progression [15, 16, 38]. If the PET/CT scan was performed before biopsy or surgery, the interval also needed to be controlled.

In addition, subgroup analysis revealed that only study design (retrospective design vs. prospective design) contributed significantly to the overall estimate (rho=0.36 for prospective group vs. rho=0.47 for retrospective group, $P<0.05$) while other two factors, including scanning modality (PET, PET/CT or both) and sample method (surgery, biopsy or both), did not. If a study was retrospective, a potential risk may exist that researchers have known results of PET/CT imaging or Ki-67 index in advance; thus, pooled rho value of retrospective subgroup was significantly higher than that of prospective subgroup. Although further analysis for the factors such as tumor subtypes or stages was not performed, they were still considered to introduce some bias. Finally, based on the result of Begg's test, the publication bias was not significantly observed among included studies.

Although it has been proved to be an effective marker for prognosis in breast cancer [6, 45], Ki-67 has a main disadvantage that is the high degree of interobserver variability in its assessment [46]. The measurement of Ki-67 can vary due to several factors including human error, tumor area selection, specific antibody and analysis method [3, 47]. A recent study showed that for determination of the Ki-67 index, different methods yielded different results with 67% of examined tumor in inconsistent grading [48]. Another study also demonstrated that the Ki-67 labeling index differed according to the measurement methods (hot pot vs. average) and specimen types (core needle biopsy vs. surgery) [47]. In clinical practice, Ki-67 index was assessed only in a few micrometer thick sections that are representative samples not the entire tumor. If the tumor is in high intratumoural heterogeneity, the concordance between selected section and whole tumor is low, and the Ki-67 index of selected sections cannot reveal the true level of proliferation activity of whole tumor [47]. A previous study showed that there were large differences of Ki-67 expression owing to intratumoral heterogeneity, with maximum index ranging from 4.9% to 92.2%, average index ranging from 3.4% to 81.4%, respectively [49]. With regard to the measurement of SUVmax, it is easily calculated with available commercial software. Although it is affected by the voxel size and tumor motion, it is not subject to the interobserver variability because it is not based on the delineation method [50]. For the SUVmax of small lesions, the partial volume effect might be a possible source of measurement error [50].

The present study has some limitations. First, the number of included studies was relatively small, and we cannot perform further analysis for the certain subtype of breast cancer. Further, a wide variation in Ki-67 immunohistochemistry and its measurement method existed among included studies, which was a main source of heterogeneity. Moreover, we only included full-text articles with sufficient data, possibly resulting in a bias; however, Begg's test revealed no significant bias.

In conclusion, in patients with breast cancer, $^{18}$F-FDG uptake showed a positive correlation with tumor cell proliferation; but the degree of correlation is low, which probably limits its application in clinical practice. PET/CT imaging may be a useful non-invasive tool to assess proliferation activity of breast cancer. However, our results need further validation by larger, prospective studies with improved study design, especially for those specific subtypes of breast cancer.

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## Disclosure of conflict of interest

None.

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