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Associations Between PET Parameters and Expression of Ki-67 in Breast Cancer[1,2,3]

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Abstract

OBJECTIVES: Numerous studies investigated relationships between positron emission tomography and proliferation index Ki-67 in breast cancer (BC) with inconsistent results. The aim of the present analysis was to provide evident data about associations between standardized uptake value (SUV) and expression of Ki-67 in BC. *METHODS:* MEDLINE library, SCOPUS and EMBASE data bases were screened for relationships between SUV and Ki-67 in BC up to April 2018. Overall, 32 studies with 1802 patients were identified. The following data were extracted from the literature: authors, year of publication, number of patients, and correlation coefficients. Associations between SUV and Ki-67 were analyzed by Spearman's correlation coefficient. *RESULTS:* Associations between SUV_{max} derived from ^{18}F-FDG PET and Ki-67 were reported in 25 studies (1624 patients). The pooled correlation coefficient was 0.40, (95% CI = [0.34; 0.46]). Furthermore, 7 studies analyzed associations between SUV_{max} derived from ^{18}F-fluorthymidin (FLT) PET and Ki-67 (178 patients). The pooled correlation coefficient was 0.54, (95% CI = [0.37; 0.70]). *CONCLUSION:* SUV_{max} correlated moderately with expression of Ki-67 and, therefore, cannot be used as a surrogate marker for tumor proliferation. Further studies are needed to evaluate associations between PET parameters and histopathological findings like hormone receptor status in breast cancer.

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Introduction

Breast cancer (BC) is one of the most frequent malignancies in humans [1]. Imaging methods, especially mammography, ultrasound and magnetic resonance imaging, play a fundamental role in the diagnosis of BC [2]. Nowadays, also positron emission tomography (PET) is increasingly used in BC [3–7]. It has been shown that PET besides detection of distant metastases can also provide additional information about tumor histopathology [5–8]. For example, numerous reports suggested that PET parameters, such as the maximal standardized uptake value (SUV_{max}), depended on the histologic and biologic characteristics of the breast tumor [5,6]. Invasive tumors classified exhibit higher uptake than lower-grade tumors [5–7]. Furthermore, PET parameters can also predict behavior of BC [8–12]. For instance, Higuchi et al. showed that the prognosis of patients with high SUV_{max} of primary tumors at baseline is significantly worse than that of patients with low SUV_{max} in operated BC [9]. In addition, PET can predict patient's response to chemotherapy in BC [10]. According to Ohara et al., the 3-year disease-free survival rates were 90.9 % for patients with a tumor of SUVmax <8.6 and only 42.9 % for patients with a tumor of SUV_{max} >8.6 ($P < .002$) [11].

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Presumably, metabolic activity showing by PET may be associated with biological patterns of BC. In fact, some studies also indicated that PET parameters can also provide information about tumor microstructure in BC [4,5,7]. For example, Heudel et al. observed significant correlations between SUV and histological grade ($P < 0.0001$), histological type ($P = 0.001$), tumor size ($P < 0.0435$), estrogen receptor status ($P < 0.0005$), and progesterone receptor status ($P = 0.002$) [13].

In clinical practice, associations between PET parameters like SUV_{max} and expression of proliferation marker Ki-67 are of great importance. Ki-67 is a non-histone, nuclear protein synthesized throughout the whole cell cycle except the G0 phase [14]. According to the literature, BC with high expression of Ki-67 (<25%) are associated with a greater risk of death compared with lower expression rates [14]. Moreover, a higher Ki-67 labeling index is associated with a greater risk of recurrence (64 % increased risk) [14].

However, the reported data about relationships between PET and Ki-67 are controversial. While some authors identified significant correlations between the parameters, others did not. Therefore, it is unclear, if SUV_{max} can be used as imaging biomarker reflecting proliferation activity in BC or not.

The purpose of this meta-analysis was to provide evident data about associations between SUV_{max} and expression of Ki-67 breast cancer.

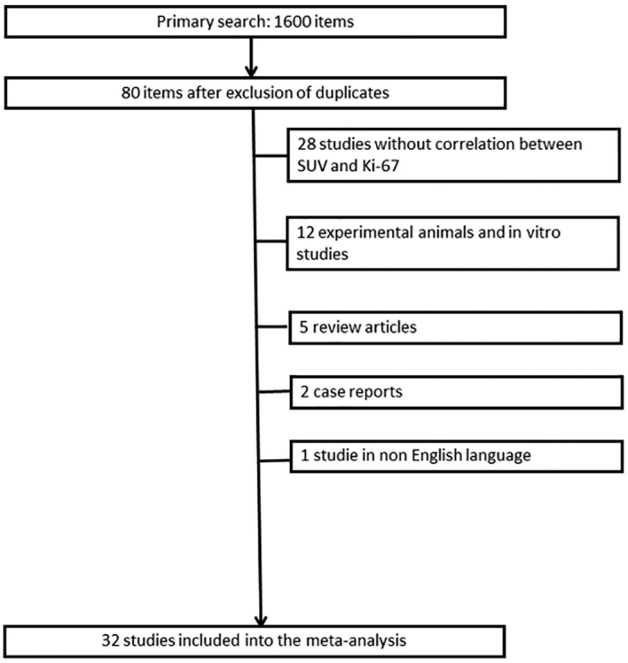

Figure 1. Flowchart of the data acquisition.

Materials and Methods

Data Acquisition

MEDLINE library, EMBASE data base and SCOPUS data base were screened for associations between PET parameters and proliferation marker Ki-67 in breast cancer up to April 2018. The strategy of data acquisition is shown in Figure 1.

The following search words were used: "breast cancer OR breast carcinoma AND PET OR positron emission tomography OR SUV OR standardized uptake value AND Ki-67 OR KI 67 OR Ki 67 OR KI67 OR ki67 OR ki-67 OR mitotic index OR proliferation index OR MIB 1 OR MIB-1 OR mitosis index". Secondary references were also recruited. Overall, 1600 records were identified. Duplicate articles, review articles, case reports, non-English publications, and articles, which not contain correlation coefficients between PET and Ki-67 were excluded (n= 1568). Therefore, the present analysis comprises 32 studies with 1801 patients (Table 1) [15–46]. The following data were extracted from the literature: authors, year of publication, number of patients, histopathological parameters, and correlation coefficients.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) was used for the research [47].

Meta-Analysis

On the first step, the methodological quality of the acquired 32 studies was independently checked by two observers (A.S. and H.J. M.) using the Quality Assessment of Diagnostic Studies (QUADAS) instrument [48]. The results of QUADAS proving are shown in Table 2. The involved studies originated from several work groups world-wide and included different breast carcinomas. Study design was reported for all researches and it was prospective in 50% and retrospective in other 50%.

Secondly, the acquired correlations between SUV_{max} and Ki-67 were re-analyzed by Spearman's correlation coefficient. Therefore, the reported Pearson`s correlation coefficients in some studies were converted into Spearman`s correlation coefficients according to the previous description [49].

Furthermore, the meta-analysis was undertaken by using RevMan 5.3 (Computer program, version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity was calculated by means of the inconsistency index I^2 [50,51]. Finally, DerSimonian and Laird random-effects models with inverse-variance weights were performed without any further correction [52].

Results

Associations between SUV_{max} derived from ^{18}F-FDG (fluoro-D-glucose) PET and Ki-67 were reported in 25 studies (Figure 2). Overall, these studies included 1620 patients. The correlation coefficients between SUV_{max} and Ki-67 ranged from -0.07 to 0.69 (Figure 2). The pooled correlation coefficient was 0.40, (95% CI = [0.34; 0.46]).

Furthermore, 7 studies analyzed associations between SUV_{max} derived from ^{18}F-fluorthymidin (FLT) PET and Ki-67 (181 patients) [21,22,32,35,37,40,45]. The reported correlation coefficients between the parameters ranged from 0.02 to 0.73 (Figure 3). The pooled correlation coefficient was 0.54, (95% CI = [0.37; 0.70]).

Discussion

The possibility to predict biological features and, therefore, tumor behavior based on imaging, in particular on PET findings, is very important. In fact, if PET parameters, for instance, SUV_{max}, can reflect proliferation activity of lesions, so PET can be used as surrogate biomarker. Theoretically, metabolic activity measuring by PET may predict tumor cellularity and proliferation in malignancies. Therefore, PET parameters like SUV_{max} may well correlate with expression of Ki-67. However, some reports suggested that this does not apply for all tumors. In fact, it has been shown that different tumor types exhibited varied

Table 1. Data About the Involved Studies

Autors	Year	Country	Design	Histo-pathology	Patients	Receptor status	Tracer
Avril et al. [15]	2001	Germany	retrospective	different	46	different	^{18}F-FDG
Bitencourt et al. [16]	2014	Brazil	prospective	different	50	different	^{18}F-FDG
Buck et al. [17]	2002	Germany	retrospective	different	75	different	^{18}F-FDG
Cheng et al. [18]	2013	China	retrospective	n.r.	20	ER positive	^{18}F-FDG
Choi et al. [19]	2018	South Korea	retrospective	different	117	Triple negative	^{18}F-FDG
Cochet et al. [20]	2012	France	prospective	n.r.	40	different	^{18}F-FDG
Contractor et al. [21]	2011	United Kingdom	prospective	n.r.	18	different	^{18}F-FLT
Crippa et al. [22]	2015	Italy	prospective	different	15	different, none triple negative	^{18}F-FLT
De Cremoux et al. [23]	2018	France	retrospective	different	75	Luminal types	^{18}F-FDG
Ege Aktas et al. [24]	2017	Turkey	retrospective	IDC	65	different	^{18}F-FDG
Garcia Vicente et al. [26]	2012	Spain	prospective	different	68	different	^{18}F-FDG
García-Esquinas et al. [25]	2014	Spain	prospective	n.r.	43	different	^{18}F-FDG
Groheux et al. [27]	2018	France	prospective	different	55	Triple negative	^{18}F-FDG
Humbert et al. [28]	2014	France	prospective	different	61	Luminal types	^{18}F-FDG
Ikenaga et al. [29]	2007	Japan	retrospective	different	45	different	^{18}F-FDG
Jacobs et al. [30]	2011	USA	prospective	different	6	different	^{18}F-FDG
Jena et al. [31]	2017	India	retrospective	IDC	69	different	^{18}F-FDG
Kenny et al. [32]	2005	United Kingdom	prospective	different	15	n.r.	^{18}F-FLT
Koo et al. [33]	2015	South Korea	retrospective	different	103	Triple negative	^{18}F-FDG
Koolen et al. [34]	2012	The Netherlands	prospective	different	214	different	^{18}F-FDG
Kostakoglu et al. [35]	2015	USA	prospective	different	72	different	^{18}F-FLT
Kurland et al. [36]	2012	USA	prospective	different	40	different	^{18}F-FDG
Marti-Climent et al. [37]	2014	Spain	prospective	different	30	different	^{18}F-FLT
Nishimukai et al. [38]	2017	Japan	retrospective	n.r.	163	different, none triple negative	^{18}F-FDG
Shimoda et al. [39]	2007	Japan	retrospective	different	37	different, none triple negative	^{18}F-FDG
Smyczek-Gargya et al. [40]	2004	Germany	prospective	n.r.	12	different	^{18}F-FLT, ^{18}F-FDG
Soussan et al. [41]	2014	France	retrospective	different	54	different	^{18}F-FDG
Tchou et al. [42]	2010	USA	retrospective	different	41	different	^{18}F-FDG
Tokes et al. [43]	2015	Hungary	retrospective	different	42	different	^{18}F-FDG
Tural et al. [44]	2015	Turkey	retrospective	different	73	different	^{18}F-FDG
Woolf et al. [45]	2014	United Kingdom	prospective	IDC and ILC	19	different	^{18}F-FLT
Yang et al. [46]	2013	China	retrospective	n.r.	18	different	^{18}F-FDG

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; HER 2, human epidermal growth factor receptor 2; ^{18}F-FLT, ^{18}F-fluorthymidin; ^{18}F-FDG (fluoro-D-glucose)

degree of correlation between SUV_{max} and Ki-67 [53]. So, correlation coefficients ranged from 0.81 in thymic carcinoma to -0.22 in malignant melanoma [53]. In most malignancies, only moderate correlations between the analyzed parameters were identified [53].

Previously, numerous reports analyzed relationships between PET parameters and expression of Ki-67 in BC with very inconsistent results. So, a very wide spectrum of correlation coefficients between SUV_{max} and Ki-67 was reported. Furthermore, most studies investigated small samples ranging from 6 to 75 patients/tumors and only four studies investigated samples over 100 patients [20,33,34,38]. Therefore, the reported data cannot be considered as evident. These facts question the possibility to use PET parameters as surrogate biomarkers for proliferation activity in BC.

The present analysis identified moderate correlations between SUV_{max} derived from FDG PET and expression of Ki-67 in BC (0.40). In most acquired studies, slightly-to-moderate correlations were observed. Only in the study of Kurland et al., the reported correlation coefficient was -0.07 [36] and must be seen as an outlier [36]. In this study, the decline of FDG-PET uptake and Ki-67 after aromatase inhibitors and trastuzumab therapy was investigated [36]. The negative correlation at baseline might be caused by a heterogenous patient sample comprising metastasized and not metastasized patients. However, in the aromatase group a strong correlation regarding therapeutic induced decline of Ki-67 and FDG-PET was identified (r=0.77), indicating that in specific subgroups the associations between imaging and histopathology substantial can differ.

Table 2. Methodological Quality of the Involved 32 Studies According to the QUADAS Criteria

Quadas criteria	No bias (%)	Bias (%)	Unclear (%)
Was the spectrum of patients representative of the patients who will receive the test in practice?	32 (100)		
Were selection criteria clearly described?	19 (59.38)	4 (12.5)	9 (28.12)
Is the reference standard likely to correctly classify the target condition?	32 (100)		
Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	32 (100)		
Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	32 (100)		
Did patients receive the same reference standard regardless of the index test result?	32 (100)		
Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	32 (100)		
Was the execution of the index test described in sufficient detail to permit replication of the test?	32 (100)		
Was the execution of the reference standard described in sufficient detail to permit its replication?	32 (100)		
Were the index test results interpreted without knowledge of the results of the reference standard?	16 (50.0)		16 (50.0)
Were the reference standard results interpreted without knowledge of the results of the index test?	12 (46.15)		20 (30.77)
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	32 (100)		
Were uninterpretable/intermediate test results reported?	30 (93.76)	1 (3.12)	1 (3.12)
Were withdrawals from the study explained?	27 (84.38)	3 (9.37)	2 (6.25)

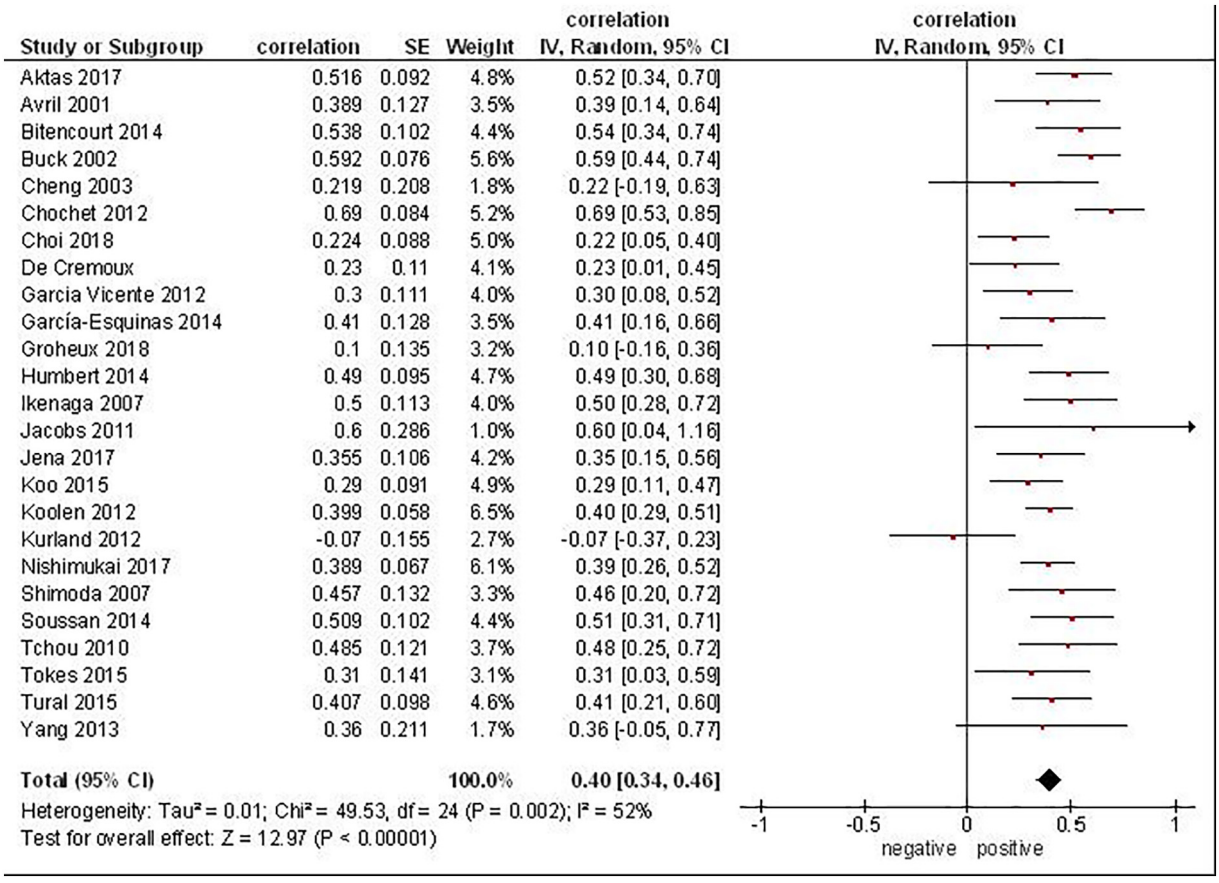

Figure 2. Forest plots of correlation coefficients between SUV_{max} derived from ^{18}F-FDG PET and Ki-67 in patients with breast cancer.

Furthermore, we found that SUV_{max} derived from FLT PET had stronger associations with Ki-67 in BC (0.54). This finding is not unusual. Similar results were reported also for other malignancies. For example, in a meta-analysis investigated relationships between SUV_{max} and Ki-67 in lung cancer, FLT-PET showed a higher correlation coefficient (r = 0.65) than FDG-PET (r=0.45) [54]. FLT is phosphorylated by thymidine kinase-1 and is a marker of cells in the S-phase of the cell cycle [55,56]. Therefore, the uptake of FLT is linked to cell proliferation rate. Thus, FLT PET is more sensitive than FDG PET to predict proliferation potential.

However, overall, our findings suggest that it is problematically to use SUV_{max} as predictor of proliferation activity in BC. This finding is difficult to explain. Presumably, glucose metabolism and cell proliferation are not associated directly. Furthermore, Ki-67 is one of numerous proliferation markers. Possibly, glucose metabolism might be stronger associated with other proliferation factors than with Ki-67. In fact, Nishimukai et al. showed that SUV_{max} correlated stronger with proliferation marker geminin than with Ki-67 [38]. The authors also suggested that geminin is preferable to Ki-67 evaluating the proliferative activity of breast cancer cells [38].

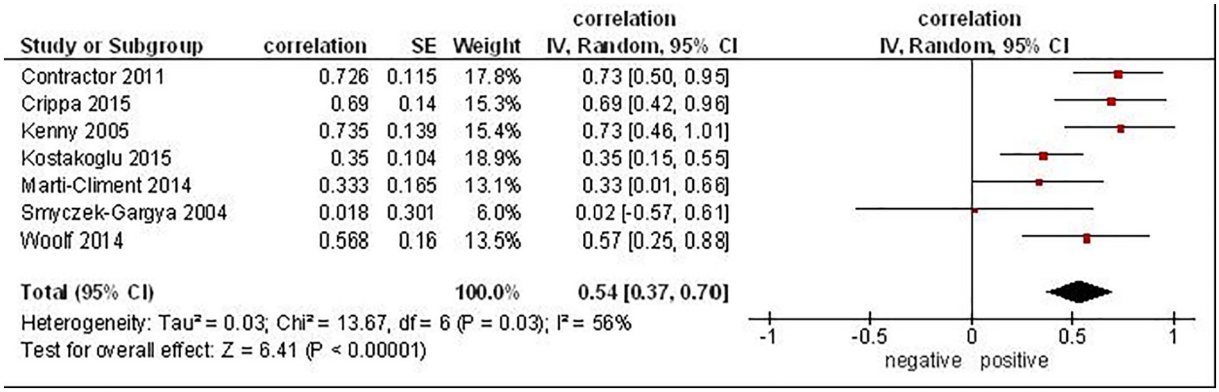

Figure 3. Forest plots of correlation coefficients between SUV_{max} derived from ^{18}F-fluorthymidin PET and Ki-67 in patients with breast cancer.

The present analysis identified another interesting aspect. BC represents a heterogenous group of carcinomas with different histopathological features and behavior. Presumably, different subtypes of BC may have also different associations between PET and Ki-67. Further prospective studies are needed to confirm this hypothesis.

Our analysis identified also methodological problems of the previous reports. Half of the acquired studies were of retrospective design. Furthermore, according the QUADAS criteria, 28.12% of the acquired studies had unclear selection criteria. Additionally, 30.77% of the studies may have diagnostic review bias. Clearly, studies with well-defined inclusion and exclusion criteria are needed to investigate associations between PET and Ki-67 in BC.

In conclusion, the present meta-analysis showed that SUV_{max} correlated moderately with expression of Ki-67 and, therefore, cannot be used as a surrogate marker for tumor proliferation. Further studies are needed to evaluate associations between PET parameters and histopathological findings like hormone receptor status in breast cancer.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

The data that support the findings of this study are available from professor Surov but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of professor Surov.

Authors' Contributions

- **AS, HJM, AW** made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data;
- **HJM, AW** been involved in drafting the manuscript or revising it critically for important intellectual content;
- **HJM, AW** given final approval of the version to be published. Each author have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and
- **AS, HJM,** agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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