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Prognostic and clinical significance of focal adhesion kinase expression in breast cancer: A systematic review and meta-analysis

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ABSTRACT

Background: The prognostic significance of focal adhesion kinase (FAK) in breast cancer remains controversial. Here, we conducted a meta-analysis to explore the prognostic value of FAK expression in breast cancer.
Materials and methods: Possible prognostic significance of protein or mRNA expression of FAK in breast cancer was investigated with searches of electronic databases for relevant publications. Pooled hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) were extracted from eligible studies.
Results: A total of eight eligible studies which included 2604 participants were analyzed in this meta-analysis. Increased expression of FAK protein was found to significantly correlate with shorter overall survival (OS) (HR = 1.43, 95% CI: 1.12–1.83; $P = 0.004$), and not with disease-free survival (HR = 1.31, 95% CI: 0.92–1.85; $P = 0.14$). Elevated FAK protein expression was also associated with negative estrogen receptor (ER) expression (OR, 1.34; 95% CI, 1.06–1.68; $P = 0.01$), negative progesterone receptor (PR) expression (OR, 1.54; 95% CI, 1.22–1.93; $P < 0.001$), positive human epidermal growth factor receptor 2 (HER2) expression (OR, 1.64; 95% CI, 1.28–2.09; $P < 0.001$), triple-negative breast cancer (TNBC) (OR, 1.57; 95% CI, 1.14–2.17; $P = 0.006$), high nuclear grade (OR, 1.70; 95% CI, 1.05–2.78; $P = 0.03$), high Ki-67 expression level (OR, 2.87; 95% CI, 1.94–4.24; $P < 0.001$), and positive p53 status (OR, 2.28; 95% CI, 1.58–3.29; $P < 0.001$).
Conclusion: Our meta-analysis identifies an association between increased FAK protein expression and worse OS among breast cancer patients. Moreover, enhanced FAK expression is associated with negative ER expression, negative PR expression, positive HER2 expression, TNBC, high nuclear grade, high Ki-67 expression level, and positive p53 status in breast carcinoma.

Contents

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Introduction

Breast cancer is becoming an increasingly serious public health concern. Worldwide, it is predicted that approximately 2.1 million cases of breast cancer among females will have been diagnosed in 2018 [1]. Furthermore, despite the reduced mortality of breast cancer due to individualized treatment encompassing early diagnosis, surgery, chemotherapy, radiotherapy, endocrine, and targeted therapy [2], distant metastasis remains one of the major challenges in the treatment of breast cancer cases. It is recognized that the mechanism(s) mediating metastasis are complex. Thus, it has been proposed that novel prognostic markers are needed to provide insight into these molecular mechanisms and improve treatment management of breast cancer cases.

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase which contributes to cellular physiological processes through the activation of integrins and focal adhesions of cell receptors [3,4]. Previous studies have demonstrated that FAK promotes malignancy by regulating numerous cellular processes, including adhesion, motility, proliferation, migration, invasion, and angiogenesis. Both highly coordinated signaling networks and activated cancer stem cells mediate the roles of FAK [5,6]. For example, Rigiracciolo et al. [7] have demonstrated that FAK promotes the migration of triple-negative breast cancer (TNBC) cells by activating signaling via the estrogenic G-protein coupled estrogen receptor pathway. Bianchi-Smiraglia and coworkers [8] have also reported that integrin β5 promotes breast cancer cell migration via the Src-FAK and MEK-ERK signaling pathways. Correspondingly, FAK expression has been detected in various cancers, including breast cancer [9], pancreatic cancer [10], head and neck squamous cell carcinoma [11], rectal cancer [12], hepatocellular carcinoma [13], and lung cancer [14].

Previous studies have revealed that up-regulation of FAK expression is associated with poor survival outcome in breast carcinoma [15,16], while other studies have reported no significance [17,18]. Therefore, we performed a pooled meta-analysis in order to investigate a possible correlation between FAK expression and its prognostic value in breast cancer.

Materials and methods

Search strategy

Searches were conducted of the PubMed, Embase, Cochrane Library, and Web of Science databases through August 12, 2019 with the following keywords: “breast neoplasms”/“breast cancer” and “focal adhesion kinase”/“FAK” and “prognosis”/“survival”.

Study inclusion/exclusion criteria

Inclusion criteria were: (1) research focused on breast cancer patients, (2) investigations of associations between FAK protein or gene expression and clinical parameters and prognosis, and (3) articles with sufficient information for extraction of hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (CI) data. Exclusion criteria were: non-human studies, studies of cell lines or animals, conference reports, letters, reviews, and studies lacking sufficient information to estimate associations.

Data extraction

Two authors independently extracted baseline characteristics from the studies selected. Author surname, year of publication, country where study conducted, number of patients, outcomes, detection method, staining location, cut-off score, and proportion of up-regulated FAK expression were recorded for each study. From eligible studies, information focused on prognosis and clinicopathologic features were also extracted. The Newcastle Ottawa Scale (NOS) was applied to assess quality of the included studies [19]. Studies with a NOS score ≥ 7 were considered to be of high quality.

Statistical analysis

This meta-analysis was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [20]. All analyses were performed with Review Manager version 5.3 (Cochrane Collaboration, Copenhagen, Denmark) and STATA version 12.0 (Stata Corporation, TX, USA) software programs. Heterogeneity was evaluated by using the Chi-squared test and I^2 statistics [21]. I^2 values >50% and *P*-values <0.05 indicated significant heterogeneity. A fixed effects model or random effects model was applied according to heterogeneity [22]. Sensitivity analysis was used to estimate stability of the pooled results. Publication bias was assessed with Begg's and Egger's tests [23,24]. Triple sequential analysis (TSA) was performed to estimate required sample information [25]. False-positive report probability (FPRP) analysis was performed to verify true correlations [26]. *P*-values less than 0.05 were considered statistically significant.

Results

Search results

As shown in Fig. 1, a total of 1178 articles were identified from our search strategy (S1 Table). After removing duplicates ($n = 298$), titles and abstracts were screened. A total of 854 studies were excluded because they either involved cell culture or animal model studies, or were reviews, case reports, or meeting abstracts. Overall text of the remaining 26 studies were then reviewed. Four reviews, eleven no endpoint studies, and three studies lacking relevant data were excluded. Finally, a total of 8 eligible studies involving 2604 participants were selected for a meta-analysis [15–18,27–30].

Search characteristics

Baseline characteristics of the qualifying studies are summarized in Tables 1 and 2. The included studies were retrospective or observational in a nature, and were of high quality according to NOS criteria (score ≥ 7) (S2 Table). For the integrity of the publication data, we considered relapse-free survival (RFS) equivalent to disease-free survival (DFS) [18], and cancer-specific survival (CSS) equivalent to overall survival (OS) [15] in the eligible studies. In addition, *FAK* mRNA expression studies were excluded due to insufficient data. Therefore, our eligible studies included detection of FAK expression by immunohistochemistry. However, the antibodies used, the staining locations, and the cut-off values used for FAK expression varied in the eligible studies. Correspondingly, the reported proportion of increased FAK expression ranged from 18.5% to 88%.

Association of FAK protein expression and DFS and OS

Two studies assessed the relationship between FAK protein expression and DFS in breast cancer, and no significant correlation was observed (HR = 1.31, 95% CI: 0.92–1.85; $P = 0.14$) (Fig. 2A). Therefore, a fixed effects model was applied according to an absence of heterogeneity ($P = 0.85$, $I^2 = 0\%$). Importantly, increased FAK protein expression was found to significantly correlate with worse OS ($n = 4$; HR = 1.43, 95% CI: 1.12–1.83; $P = 0.004$) in the populations of breast cancer patients analyzed

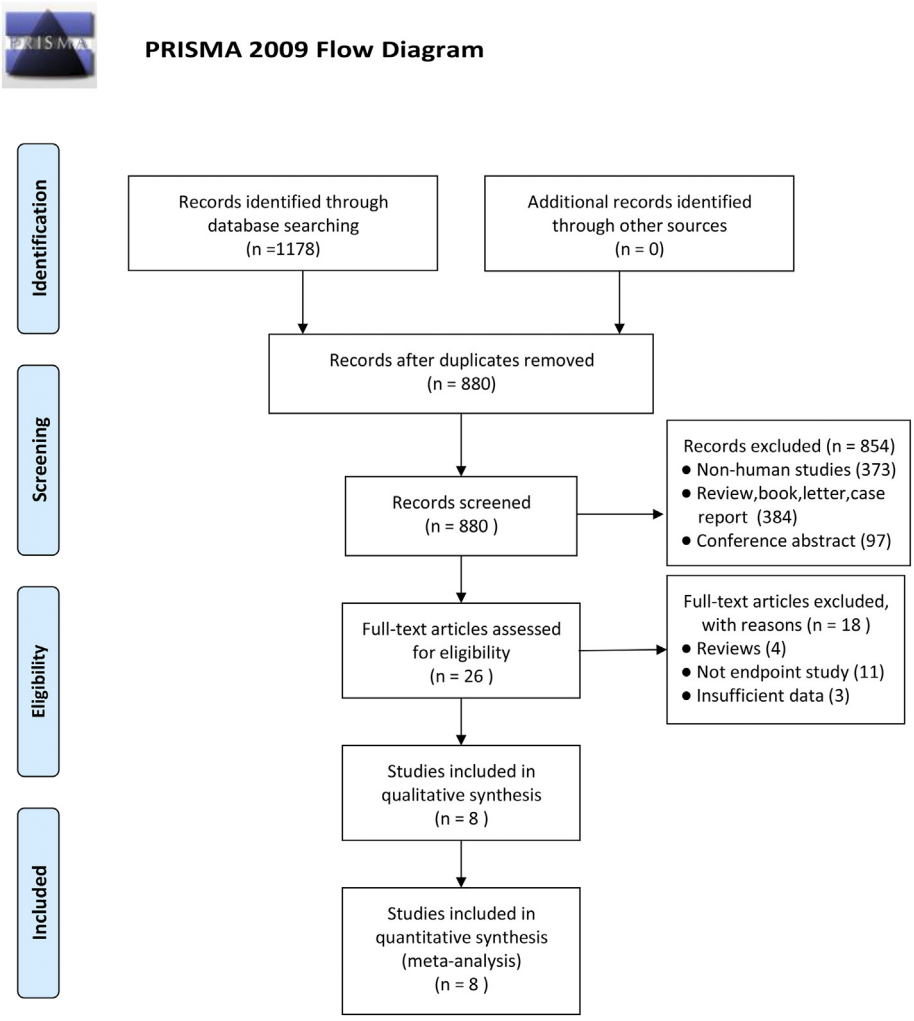

Fig. 1. Flow chart of the process used to select eligible studies.

(Fig. 2B). Therefore, a fixed effects model was applied based on insignificant heterogeneity ($P = 0.24$, $I^2 = 29\%$).

Association between FAK protein expression and clinicopathologic characteristics

Correlations between increased FAK protein expression and clinicopathologic factors are summarized in Table 3. Overexpression of FAK protein was found to be related to negative estrogen receptor (ER) expression ($n = 6$; OR, 1.34; 95% CI, 1.06–1.68; $P = 0.01$) (S1 Fig. A), negative progesterone receptor (PR) expression ($n = 4$; OR, 1.54; 95% CI, 1.22–1.93; $P < 0.001$) (S1 Fig. B), positive human epidermal growth factor receptor 2 (HER2) expression (n = 6; OR, 1.64; 95% CI, 1.28–2.09; $P < 0.001$) (S1 Fig. C), TNBC ($n = 3$; OR, 1.57; 95% CI, 1.14–2.17; $P = 0.006$) (S1 Fig. D), high nuclear grade ($n = 5$; OR, 1.70; 95% CI, 1.05–2.78; $P = 0.03$) (S2 Fig. A), high Ki-67 expression level ($n = 2$; OR, 2.87; 95% CI, 1.94–4.24; P < 0.001) (S2 Fig. B), and positive p53 status (n = 2; OR, 2.28; 95% CI, 1.58–3.29; P < 0.001) (S2 Fig. C). However, no significant associations between FAK protein expression and other features, including age (n = 3; OR, 0.82; 95% CI, 0.63–1.08; $P = 0.15$) (S3 Fig. A), lymph node involvement (n = 5; OR, 1.18; 95% CI, 0.96–1.46; $P = 0.12$) (S3 Fig. B), and tumor size ($n = 4$; OR, 0.45; 95% CI, 0.14–1.43; $P = 0.17$) (S3 Fig. C), were identified.

Table 1
Characteristics of the eligible studies examined.

Publication	Year	Country	Cancer subtype	No. of patients	Age, years (median, range)	Follow-up time, months (median, range)	Outcome	Survival analysis	NOS (score)
Almstedt	2017	Germany	Node-negative BC	335	58 (range, 32–90)	183 (range, 0–348)	DFS,OS	Multivariate	8
Andisha	2019	UK	Primary BC	474	50	150	OS	Multivariate	8
Golubovskaya	2014	USA	Stage II-IV BC	196	56 (range, 27–91)	NR	NR	NR	7
Guo	2017	China	BC	300	56.9 (range, 29–88)	NR	OS	Multivariate	7
Lark	2005	USA	Invasive BC	629	48 (range, 23–74)	NR	NR	NR	7
Schmitz	2005	Germany	BC	162	59	89.8	NR	NR	7
Theocharis	2009	France	BC	73	59 (range, 31–85)	NR	NR	NR	7
Yom	2011	Korea	Invasive BC	435	46 (range, 25–79)	53 (range, 7–85)	DFS, 0S	Multivariate	8

BC, breast cancer; NR, not reported; DFS, disease-free survival; OS, overall survival; NOS, Newcastle Ottawa Scale.

Table 2
Methods of quantitative FAK measurement of eligible studies.

Publication	Year	FAK phenotype	Detection method	FAK expression	Staining location	Antibody	Cut-off value (low/high level)	High FAK expression
Almstedt	2017	FAK	IHC	protein	cytoplasmic and membranous	anti-FAK (1:100,Dako,Germany)	high (IHC score ≥ 6)	45.1% (151/335)
Andisha	2019	nuclear ph-FAK Y^{397}	IHC	protein	nuclear Ph-FAK Y^{397}	anti-FAK (1:200,ab39967,Abcam)	high (stained ≥ + 2x%)	50.8% (213/419)
Golubovskaya	2014	FAK	IHC	protein	NR	anti-FAK (Millipore #05–537)	high (stained score > 4)	27%(53/196)
Guo	2017	FAK	IHC	protein	membranous	anti-FAK (1:50,#3285,USA)	high (grade 4–7)	74.7% (215/288)
Lark	2005	FAK	IHC	protein	cytoplasmic	anti-FAK (1:250,4.47,USA)	high (stained ≥3+)	25%(154/629)
Schmitz	2005	FAK	IHC	protein	cytoplasmic and membranous	anti-FAK (1:100,Polyclonal)	high (stained ≥3+)	18.5%(30/162)
Theocharis	2009	FAK	IHC	protein	cytoplasmic and membranous	anti-FAK (sc-1688,USA)	high (stained ≥5%)	88%(64/73)
Yom	2011	FAK	IHC	protein	cytoplasmic	anti-FAK (monoclonal,4.47)	high (stained score > 3)	27.5% (108/393)

IHC, immunohistochemistry; NR, not reported.

Sensitivity analysis and publication bias

Sensitivity analysis was conducted for DFS (Fig. 3A) and OS (Fig. 3B) data, and pooled HRs were stable. Application of Begg's test ($P = 0.734$) and Egger's test ($P = 0.836$) to the OS data further revealed no evidence for publication bias.

Trial sequential and FPRP analyses

Trial sequential analysis was conducted to evaluate the required sample information of the selected studies. The cumulative *Z*-curve (blue line) does not cross either the traditional boundary line or the trial sequential monitoring boundary (red line) for DFS (Fig. 4A). However, the cumulative Z-curve (blue line) crosses both the traditional boundary line and the trial sequential monitoring boundary (red line) for OS (Fig. 4B). In addition, the cumulative information reaches the required information size for OS. Therefore, the involved sample size is sufficient for OS, yet insufficient for DFS, in the meta-analysis.

Prognosis information was also subjected to FPRP analysis. With a prior probability of 0.01, the FPRP values for DFS and OS were both >0.2, indicating that the pooled HRs were not truly significant (Table 4).

Discussion

We performed a meta-analysis to clarify a potential association between FAK expression and prognosis of breast cancer. In a previous meta-analysis, a correlation between FAK expression and OS in various types of cancer was investigated. No significant correlation was observed, although this meta-analysis only included two studies which focused on breast cancer cases [31]. In contrast, the present meta-analysis included a total of eight breast cancer articles to investigate an association between FAK protein expression and clinicopathologic factors of breast cancer. In the latter, higher FAK protein expression was found to be related to worse OS (HR, 1.43; 95% CI, 1.12–1.83; $P = 0.004$). However, the high probability of false-positive reports in the FPRP analysis performed indicates that additional research is needed to confirm this relationship. Meanwhile, no significant correlation was observed between DFS and FAK protein expression (HR, 1.31; 95% CI, 0.92–1.85; $P = 0.14$). It is possible that this insignificant correlation to DFS may be due to an insufficient sample size was verified with the TSA analysis.

As indicated above, enhanced FAK expression was linked to shorter OS, yet not to DFS, in the breast cancer cases examined. Aglan et al. [32] previously demonstrated that increased total FAK (tFAK) expression correlates with poor DFS in breast cancer. Similarly, Charpin et al. [33] reported that high FAK expression is related to worse DFS in breast cancer. These results, in combination with those of the present study, prove that FAK may represent a valuable prognostic marker of shorter DFS and OS in patients with breast cancer. Indeed, previous studies have reported a relationship between FAK expression and survival outcome for various types of tumors. For example, Thanapprapasr et al. [34] observed that elevated pFAKY397 expression is associated with poor OS in metastatic osteosarcoma. Similarly, de Vicente et al. [35] observed that enhanced expression of FAK correlates with adverse disease-specific survival (DSS) in oral squamous cell carcinoma (OSCC). Min et al. [36] also demonstrated that FAK regulates

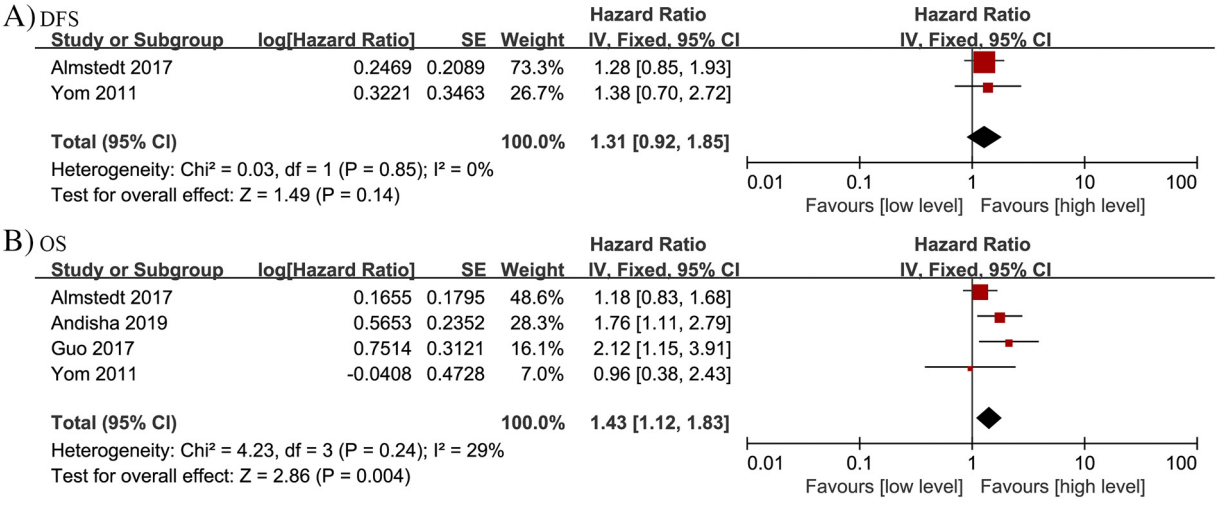

Fig. 2. Forest plots depicting correlations between FAK protein expression and (A) DFS, and (B) OS among the breast cancer patients examined.

Table 3
Meta-analysis of the correlation between FAK expression and clinicopathological factors of breast cancer.

Clinicopathological parameter	No. of studies	No. of patients	OR (95% CI)	*P*-value	Heterogeneity	
					I^2 (%)	*P*-value
ER (− vs. +)	6	1680	1.34 (1.06–1.68)	0.01	22	0.27
PR (− vs. +)	4	1546	1.54 (1.22–1.93)	< 0.001	1	0.39
HER2 (+ vs. −)	6	2057	1.64 (1.28–2.09)	< 0.001	48	0.08
TNBC (TNBC vs. non-TNBC)	3	1068	1.57 (1.14–2.17)	0.006	0	0.73
Nuclear grade (3 vs. 1 and 2)	5	1897	1.70 (1.05–2.78)	0.03	76	0.002
Ki-67 (high vs. low)	2	650	2.87 (1.94–4.24)	< 0.001	0	0.57
p53 (+ vs. −)	2	671	2.28 (1.58–3.29)	< 0.001	0	0.92
Age (≥50 vs. < 50)	3	1099	0.82 (0.63–1.08)	0.15	7	0.34
Lymph node (+ vs. −)	5	1766	1.18 (0.96–1.46)	0.12	0	0.78
Tumor size (large vs. small)	4	1155	0.45 (0.14–1.43)	0.17	91	< 0.001

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; OR, odds ratio.

increased migration and invasion by carcinoma-associated fibroblasts (CAFs) in OSCC via an increase in MCP-1/CCL2 expression. In hepatocellular carcinoma, Ko et al. [37] revealed that elevated expression of FAK is associated with reduced OS. Ko et al. [37] further indicated that FAK may collaborate or crosstalk with 14–3-3ε to promote hepatocellular cancer progression by activating the NFκB signaling pathway. Albasri et al. [38] found that positive nuclear P-FAK expression correlates with poor DSS in colorectal cancer. Meanwhile, Bian et al. [39] further demonstrated that ACP5 promotes colorectal cancer cell proliferation via the FAK/PI3K/AKT signaling pathway. However, Giaginis et al. [40] reported that enhanced FAK expression correlates with favorable OS in patients with diffuse-type gastric cancer. In non-small cell lung cancer, Dy et al. [14] did not find a significant association between FAK expression and OS. Thus, in various tumor types, FAK expression has been associated with variable prognosis. This variability potentially contributes to the value of FAK expression for clinical pathological and cellular characteristics in different carcinomas. Thus, FAK represents a novel and pivotal indicator for evaluating the biological behavior and prognosis of carcinomas. Moreover, FAK represents an effective therapeutic target for regulating the expression and activity of FAK, and for controlling and treating cancer by promoting apoptosis and inhibiting the proliferation of tumor cells.

Numerous studies have demonstrated that certain molecular markers, including negative ER expression, negative PR expression, positive HER2 expression, TNBC, and a high Ki-67 expression level, indicate poor prognosis in breast cancer [41,42]. In the present study, all of these factors were associated with increased FAK expression, and those results support our finding that increased FAK expression was correlated with worse OS in breast cancer. Moreover, Abubakar et al. [43] revealed that up-regulation of the proliferating cell nuclear antigen, Ki-67, is associated with an adverse prognosis in breast cancer. The present results also demonstrate that increased FAK protein expression correlates with a high Ki-67 expression level, thereby suggesting that elevated FAK expression promotes the proliferation of breast cancer cells. Kaur et al. [44] have revealed that *p53* also contributes to the pathogenesis of breast cancer via its roles in various cellular processes, including DNA damage repair, cell cycle arrest, and apoptosis. The present results demonstrate that enhanced FAK expression correlates with positive p53 status. Therefore, these results support the hypothesis that FAK plays a role in regulating p53 to affect tumor growth and proliferation.

There were limitations associated with the present meta-analysis. First, the numbers of included studies and patients were relatively small. Thus, further studies involving more samples are needed to confirm our results. Second, the antibodies used, staining locations, and cut-off values for FAK expression varied among the eligible studies. Therefore, it is possible that these factors contributed to the heterogeneity observed among the eligible studies examined.

In conclusion, the present meta-analysis demonstrates that increased FAK protein expression is associated with worse OS in breast cancer. Moreover, elevated FAK protein expression correlates with negative ER expression, negative PR expression, positive HER2 expression, TNBC, high nuclear grade, high Ki-67 expression level, and positive p53 status in breast cancer. Thus, support is provided for FAK to serve as an indicator of the biological behavior and prognosis of carcinomas, while also serving as an effective therapeutic target.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tranon.2020.100835.

Author contributions

Miao Deng: Conceptualization, Methodology, Software. **Weiqiang Qiao**: Data curation, Writing - Original draft preparation. **Wenhui Wang**: Visualization, Investigation. **Heyang Liu**: Supervision. **Wanying Guo**: Software, Validation. **Peng Li**: Writing - Reviewing and Editing.

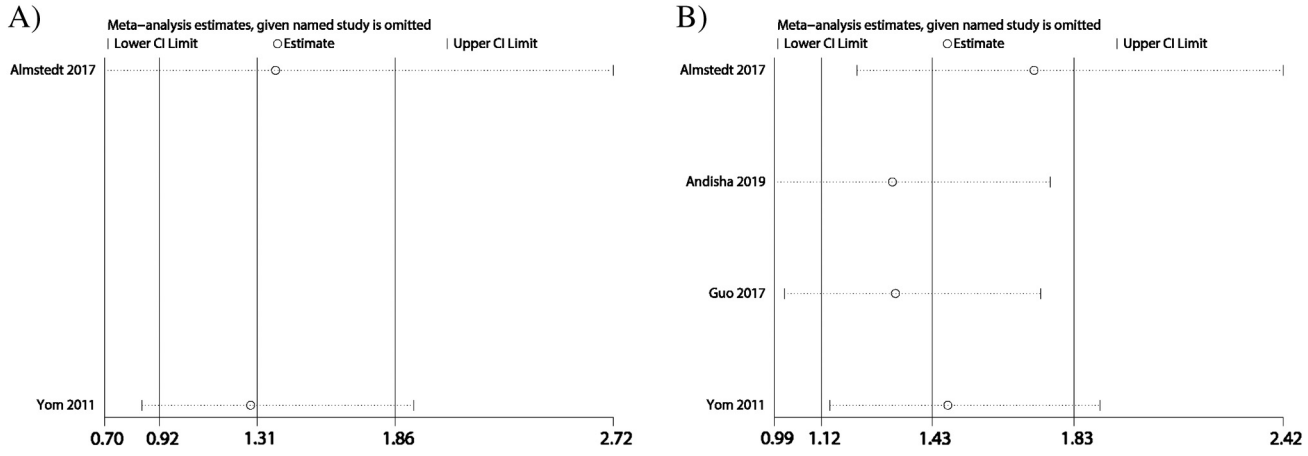

Fig. 3. Sensitivity analysis of FAK protein expression in relation to (A) DFS and (B) OS.

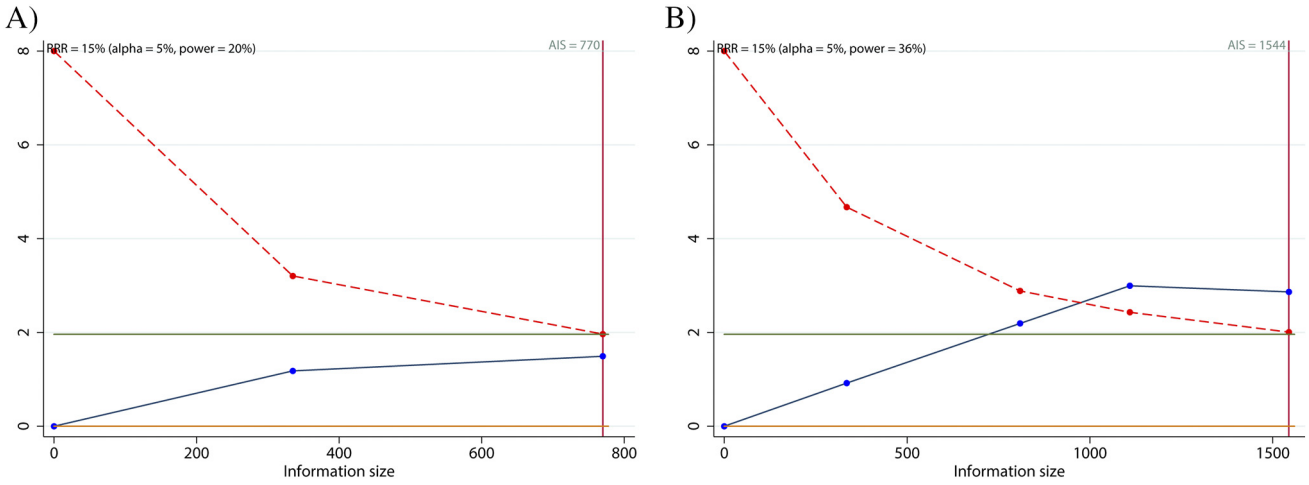

Fig. 4. Trial sequential analysis (TSA) assessing the required sample information in (A) DFS and (B) OS.

Table 4
False-positive report probability analysis values for DFS and OS.

Survival outcome	Crude HR (95% CI)	*P*-value	Statistical power	Prior probability				
				0.25	0.1	0.01	0.001	0.0001
DFS	1.31 (0.92–1.85)	0.125	0.779	0.325	0.591	0.941	0.994	0.999
OS	1.43 (1.12–1.83)	0.004	0.648	0.020	0.059	0.406	0.873	0.986

DFS, disease-free survival; OS, overall survival.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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