Clinicopathological significance of forkhead box protein A1 in breast cancer: A meta-analysis

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Abstract. The aim of the present study was to investigate the associations between the expression of forkhead box protein A1 (FOXA1) and differential clinicopathological characteristics in breast cancer using a meta-analysis method. Eligible studies that investigated the correlation between FOXA1 expression and the clinical characteristics of breast cancer were collected through searching numerous databases, including PubMed, EMBASE, the Chinese National Knowledge Infrastructure and the VIP database. In total, eight studies were included in the meta-analysis. Following a systematic analysis, the expression of FOXA1 was found to be significantly associated with the estrogen receptor α status, the progesterone receptor status, lymph node metastasis and the histological grade in breast cancer. However, no statistically significant association was observed between FOXA1 expression and the human epidermal growth factor receptor-2 status in breast cancer patients.

Introduction

Breast cancer is one of the most common cancer types in females. The incidence of breast cancer has increased in previous years, with the annual rate of increase reaching 3.1% (1). Therefore, an in-depth understanding of the molecular mechanisms underlying breast cancer, and the identification of novel anticancer drug targets are of great significance.

At present, several clinical features, including the estrogen receptor α (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor-2 (HER-2) status, lymph node metastases and histological grade, have major prognostic value in breast cancer (2). These parameters reflect the biological features of the tumor; however, they are not useful as outcome predictors for the individual patient. Thus, the identification of novel prognostic markers, which are associated with the clinical features, is required to provide a more accurate prediction of clinical outcome, in addition to the identification of new therapeutic targets.

Forkhead box protein A1 (FOXA1) plays an important role in the occurrence and development of various human tumors, and FOXA1 expression has been shown to be closely associated with breast cancer (3,4). Therefore, FOXA1 may be a new target for breast cancer prevention and control. Increasingly, studies have investigated the associations between FOXA1 expression and the clinical pathological features of breast cancer; however, the conclusion of each study has not always been consistent (5-12). Therefore, a comprehensive analysis was required to clarify the inconsistencies. In the present study, a meta-analysis was performed based on the collected literature, and the association between FOXA1 expression and the clinical pathological features of breast cancer was investigated comprehensively. Subsequently, the use of FOXA1 as a biomarker for the diagnosis, treatment and prognosis of breast cancer was assessed.

Materials and methods

Search strategy. A systematic search for eligible studies that reported on the expression of FOXA1 and the associations in patients with breast cancer was conducted in PubMed, EMBASE, the Chinese National Knowledge Infrastructure and the VIP databases. Publications were first identified by using combinations of the following words: FOXA1 and breast cancer. Subsequently, the references in the identified publications were screened and examined for any other potentially relevant studies. Retrieval time range from the time when the databases were established to May 2014. If certain studies lacked information, the authors were contacted to obtain as much available information as possible.

Inclusion and exclusion criteria. Inclusion criteria were as follows: i) Texts were published and available on line; ii) studies investigated the association between FOXA1 and clinical features of breast cancer; iii) sufficient information was provided to estimate the odds ratio (OR) and 95% confidence interval (CI); iv) measurement methods

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Table I. Main characteristics of the studies included in the meta-analysis.

Authors, year	Country	Cases (n)	Method	Cut-off	(Ref)
Hisamatsu *et al*, 2011	Japan	239	IHC	Median	(5)
Wolf *et al*, 2007	USA	100	IHC	Not mentioned	(6)
Habashy *et al*, 2008	UK	880	IHC	Median	(7)
Thorat *et al*, 2008	UK	245	IHC	3	(8)
Albergaria *et al*, 2009	UK	249	IHC	3	(9)
Liu *et al*, 2010	China	213	IHC	3	(10)
Ijichi *et al*, 2012	Japan	113	IHC	2	(11)
Jiang *et al*, 2012	China	113	IHC	3	(12)

IHC, immunohistochemistry.

and experimental groups were similar among the studies. Exclusion criteria were as follows: i) Review articles or letters; ii) included investigation of non-human samples; iii) articles with duplicated data.

Data extraction. Eligible articles were reviewed independently by two investigators and disagreements were resolved by consensus. The following data were retrieved from the studies: Name of the first author, year of publication, country of origin, methods of testing and definition of positivity (cut-off value).

Statistical analysis. The strength of an association was expressed as pooled OR values along with the corresponding 95% CI. Heterogeneity between studies was assessed by χ^2-based Q-tests and I^2 tests, where $I^2 > 50\%$ or $P < 0.10$ was considered to indicate significant heterogeneity (13). A random-effects model (DerSimonian-Laird) was used to assess the pooled ORs when significant heterogeneity was observed (14). In cases without significant heterogeneity, a fixed-effects model (Mantel-Haenszel) was used. Rev-Man 4.2 software (The Cochrane Collaboration, Oxford, UK) was used to conduct the meta-analysis.

Results

Study selection. A selection flow chart is shown in Fig. 1. In total, 15 articles were eligible for detailed reading. The studies by Ademuyiwa *et al* (15), Kawase *et al* (16), Imamura *et al* (17) and Badve *et al* (18) were excluded due to insufficient data. In addition, the studies by McCune *et al* (19) and Bernardo *et al* (20) were excluded due to the inclusion of non-human-sample-based trials. There were two studies (5,21) that used the same samples; thus, the study with the smaller sample size was excluded. Finally, there were eight studies included in the meta-analysis (5-12).

Study characteristics. Major characteristics of the eight eligible publications are reported in Table I. The studies were conducted in four countries (USA, UK, China and Japan). Six studies were published in English, and the remaining two were published in Chinese. The eight articles used an immunohistochemistry method to determine the FOXA1 status.
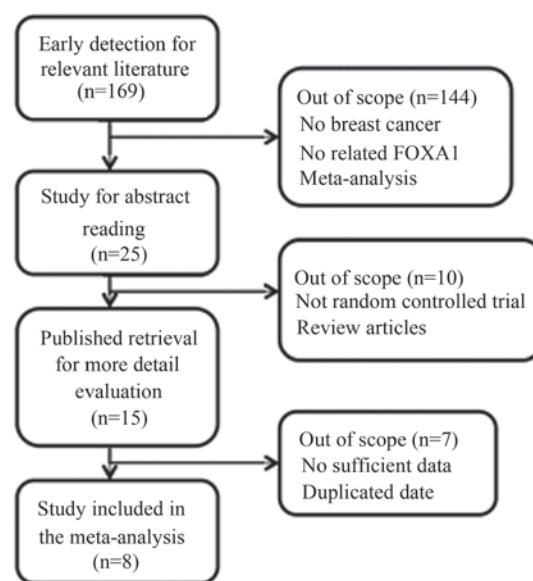

Figure 1. Literature screening and result. FOXA1, forkhead box protein A1.

Meta-analysis results. No significant heterogeneity was encountered across the studies with regard to the association between FOXA1 and any of the prognostic factors, with the exception of the ER status and HER-2 status. Thus, the random-effects model was selected for the ER status and HER-2 status, while the fixed-effects model was selected for each of the remaining three clinical features.

A total of seven studies were selected (5-11) to analyze the association between FOXA1 expression and the ER status in breast cancer. In total, 1,127 patients were included in the ER positive group, while 576 patients comprised the ER negative group. The FOXA1 expression level was shown to be higher in the ER positive breast cancer group when compared with the ER negative breast cancer group, and the difference was statistically significant (OR, 4.15; 95% CI, 2.89-5.95; P<0.0001), as shown in Fig. 2.

The same seven studies were included to assess the association between FOXA1 expression and the PR status in breast cancer (5-11). In total, 876 patients were included in the PR positive group and 830 patients were included in the PR negative group. The FOXA1 expression level was

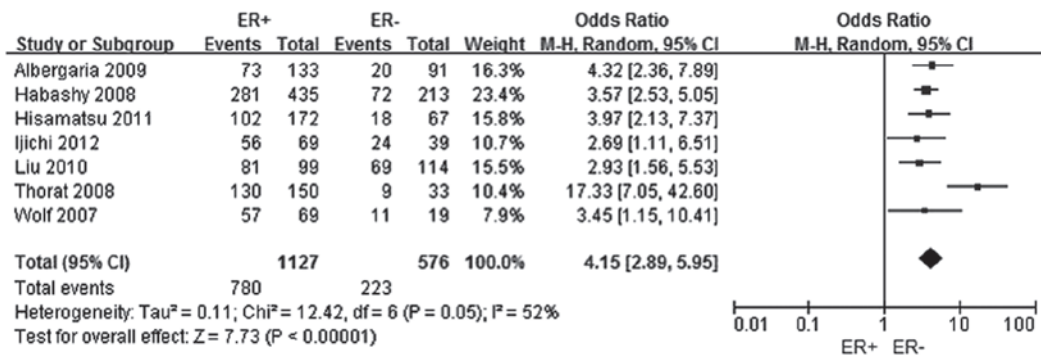| Study or Subgroup	ER+ Events	Total	ER- Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Albergaria 2009	73	133	20	91	16.3%	4.32 [2.36, 7.89]
Habashy 2008	281	435	72	213	23.4%	3.57 [2.53, 5.05]
Hisamatsu 2011	102	172	18	67	15.8%	3.97 [2.13, 7.37]
Ijichi 2012	56	69	24	39	10.7%	2.69 [1.11, 6.51]
Liu 2010	81	99	69	114	15.5%	2.93 [1.56, 5.53]
Thorat 2008	130	150	9	33	10.4%	17.33 [7.05, 42.60]
Wolf 2007	57	69	11	19	7.9%	3.45 [1.15, 10.41]
Total (95% CI)		1127		576	100.0%	4.15 [2.89, 5.95]
Total events	780		223			
Heterogeneity: Tau² = 0.11; Chi² = 12.42, df = 6 (P = 0.05); I² = 52%						
Test for overall effect: Z = 7.73 (P < 0.00001)						

Figure 2. Forest plot assessing the association between forkhead box protein A1 expression and the ER status in breast cancer. The center of the square indicates the study-specific OR and the horizontal lines correspond to the study-specific 95% CI. The area of the square reflects the study-specific variance. The diamond represents the pooled OR and 95% CI. ER, estrogen-receptor α; OR, odds ratio; CI, confidence interval.

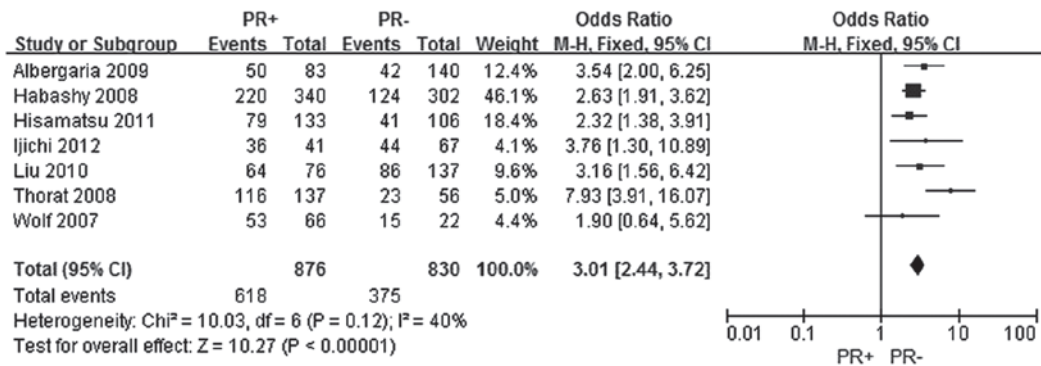| Study or Subgroup	PR+ Events	Total	PR- Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Albergaria 2009	50	83	42	140	12.4%	3.54 [2.00, 6.25]
Habashy 2008	220	340	124	302	46.1%	2.63 [1.91, 3.62]
Hisamatsu 2011	79	133	41	106	18.4%	2.32 [1.38, 3.91]
Ijichi 2012	36	41	44	67	4.1%	3.76 [1.30, 10.89]
Liu 2010	64	76	86	137	9.6%	3.16 [1.56, 6.42]
Thorat 2008	116	137	23	56	5.0%	7.93 [3.91, 16.07]
Wolf 2007	53	66	15	22	4.4%	1.90 [0.64, 5.62]
Total (95% CI)		876		830	100.0%	3.01 [2.44, 3.72]
Total events	618		375			
Heterogeneity: Chi² = 10.03, df = 6 (P = 0.12); I² = 40%						
Test for overall effect: Z = 10.27 (P < 0.00001)						

Figure 3. Forest plot assessing the association between forkhead box protein A1 expression and the PR status in breast cancer. The center of the square indicates the study-specific OR and the horizontal lines correspond to the study-specific 95% CI. The area of the square reflects the study-specific variance. The diamond represents the pooled OR and 95% CI. PR, progesterone receptor; OR, odds ratio; CI, confidence interval.
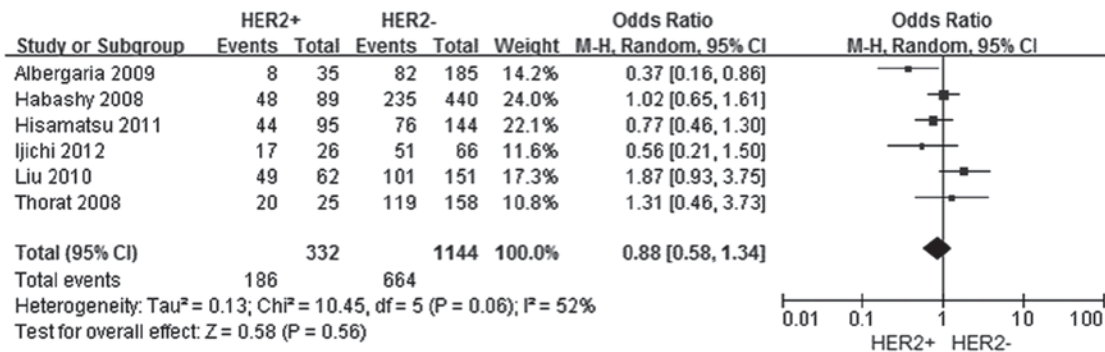
Study or Subgroup	HER2+ Events	Total	HER2- Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Albergaria 2009	8	35	82	185	14.2%	0.37 [0.16, 0.86]
Habashy 2008	48	89	235	440	24.0%	1.02 [0.65, 1.61]
Hisamatsu 2011	44	95	76	144	22.1%	0.77 [0.46, 1.30]
Ijichi 2012	17	26	51	66	11.6%	0.56 [0.21, 1.50]
Liu 2010	49	62	101	151	17.3%	1.87 [0.93, 3.75]
Thorat 2008	20	25	119	158	10.8%	1.31 [0.46, 3.73]
Total (95% CI)		332		1144	100.0%	0.88 [0.58, 1.34]
Total events	186		664			
Heterogeneity: Tau² = 0.13; Chi² = 10.45, df = 5 (P = 0.06); I² = 52%						
Test for overall effect: Z = 0.58 (P = 0.56)						

Figure 4. Forest plot assessing the association between forkhead box protein A1 expression and the HER-2 status in breast cancer. The center of the square indicates the study-specific OR and the horizontal lines correspond to the study-specific 95% CI. The area of the square reflects the study specific variance. The diamond represents the pooled OR and 95% CI. HER-2, human epidermal growth factor receptor-2; OR, odds ratio; CI, confidence interval.

demonstrated to be increased in the PR positive breast cancer group when compared with the PR negative breast cancer group, and the difference was statistically significant (OR, 3.01; 95% CI, 2.44-3.72; P<0.0001), as shown in Fig. 3.

In total, six studies were selected (5-11) to investigate the association between FOXA1 expression and the HER-2 status, among which 332 patients comprised the HER-2 positive group and 1,144 patients were included in the HER-2 negative group. However, no significant association was identified between FOXA1 expression and the HER-2 status in breast cancer patients (OR, 0.88; 95% CI, 0.58-1.3; P=0.56), as shown in Fig. 4.

With regard to the analysis of the association between lymph node metastasis and FOXA1 expression in breast cancer, seven studies were selected (5-11). In total, 664 patients were included in the lymph node metastasis positive group and 1,034 patients were included in the lymph node metastasis negative group. FOXA1 expression levels were shown to be higher in the lymph node metastasis negative breast cancer group when compared with the lymph node metastasis positive
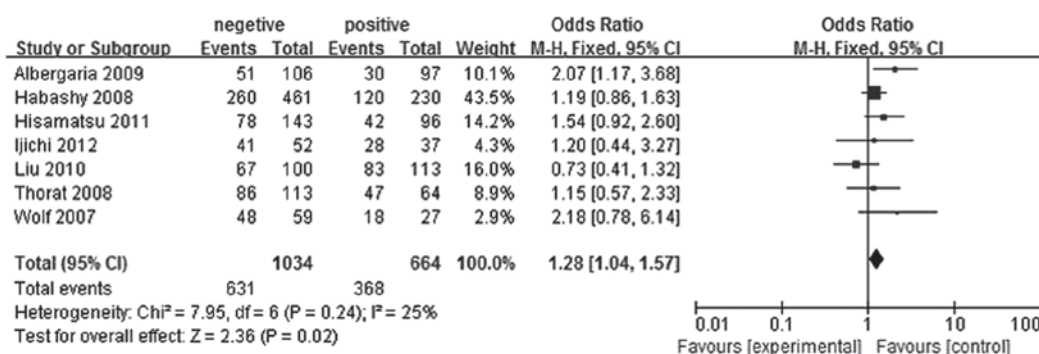
Study or Subgroup	negetive Events	Total	positive Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Albergaria 2009	51	106	30	97	10.1%	2.07 [1.17, 3.68]
Habashy 2008	260	461	120	230	43.5%	1.19 [0.86, 1.63]
Hisamatsu 2011	78	143	42	96	14.2%	1.54 [0.92, 2.60]
Ijichi 2012	41	52	28	37	4.3%	1.20 [0.44, 3.27]
Liu 2010	67	100	83	113	16.0%	0.73 [0.41, 1.32]
Thorat 2008	86	113	47	64	8.9%	1.15 [0.57, 2.33]
Wolf 2007	48	59	18	27	2.9%	2.18 [0.78, 6.14]
Total (95% CI)		1034		664	100.0%	1.28 [1.04, 1.57]
Total events	631		368			

Heterogeneity: Chi² = 7.95, df = 6 (P = 0.24); I² = 25%
Test for overall effect: Z = 2.36 (P = 0.02)

Figure 5. Forest plot assessing the association between forkhead box protein A1 expression and lymph node metastasis in breast cancer. The center of the square indicates the study-specific OR and the horizontal lines correspond to the study-specific 95% CI. The area of the square reflects the study-specific variance. The diamond represents the pooled OR and 95% CI. OR, odds ratio; CI, confidence interval.

Study or Subgroup	Grade 1-2 Events	Total	Grade 3 Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Albergaria 2009	74	149	19	75	11.4%	2.91 [1.58, 5.36]
Habashy 2008	240	364	138	325	44.6%	2.62 [1.93, 3.57]
Hisamatsu 2011	94	164	26	75	13.7%	2.53 [1.44, 4.46]
Ijichi 2012	58	74	3	8	1.1%	6.04 [1.30, 28.03]
Jiang 2012	46	67	26	46	8.7%	1.68 [0.77, 3.67]
Liu 2010	122	160	28	53	9.0%	2.87 [1.50, 5.49]
Thorat 2008	61	71	75	109	7.5%	2.77 [1.27, 6.04]
Wolf 2007	50	59	25	38	4.2%	2.89 [1.09, 7.67]
Total (95% CI)		1108		729	100.0%	2.64 [2.15, 3.25]
Total events	745		340			

Heterogeneity: Chi² = 2.62, df = 7 (P = 0.92); I² = 0%
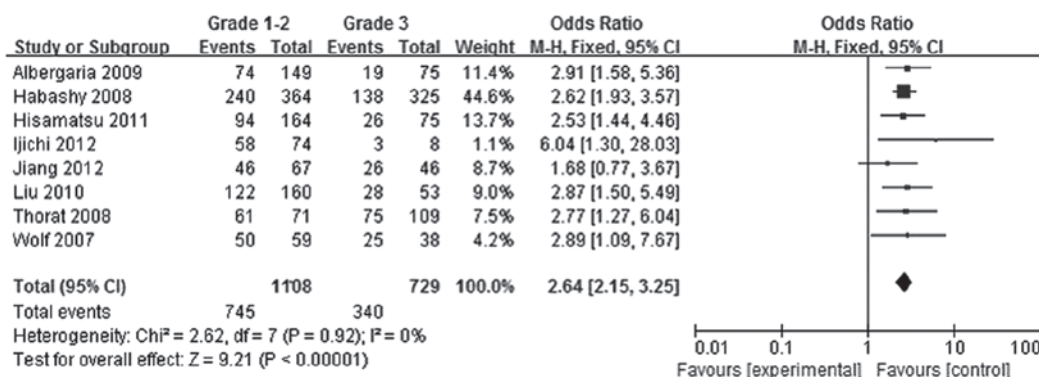Test for overall effect: Z = 9.21 (P < 0.00001)

Figure 6. Forest plot assessing the association between forkhead box protein A1 expression and histological grade in breast cancer. The center of the square indicates the study-specific OR and the horizontal lines correspond to the study-specific 95% CI. The area of the square reflects the study-specific variance. The diamond represents the pooled OR and 95% CI. OR, odds ratio; CI, confidence interval.

breast cancer group (OR, 1.28; 95% CI, 1.04-1.57; P=0.02), as shown in Fig. 5.

Tumors were divided according to histological grade into a grade 1-2 group and grade 3 group. Using eight studies (5-12), 1,108 patients were included in the grade 1-2 group, while 729 patients were included in the grade 3 group. FOXA1 expression levels in the grade 1-2 breast cancer group were found to be greater compared with those in the grade 3 breast cancer group (OR, 2.64; 95% CI, 2.15-3.25; P<0.00001), as shown in Fig. 6.

Discussion

As a member of the FOX family of transcription factors, FOXA1 expression has been observed not only in breast cancer, but also in colon, lung, thyroid, esophageal, prostate and endometrial cancers (22-26). FOXA1 can bind to the promoters of numerous genes associated with regulation of cell signaling and the cell cycle (27). In addition, FOXA1 was identified to not only stimulate growth, but also function as a growth inhibitor (28). When functioning as a trigger, FOXA1 is a 'pioneer factor' that binds to chromatinized DNA, and opens the chromatin to enhance the combination of ER and target genes (29). While functioning as an inhibitor, FOXA1 expression has been shown to block metastatic progression by influencing the expression of the breast cancer susceptibility

gene (BRCA1)-associated cell cycle inhibitor, p27, and promoting E-cadherin expression (30,31). These observations indicate that FOXA1 plays an important role in regulating the growth and activity of cancer cells. In previous years, a number of studies have demonstrated differential expression of FOXA1 in breast cancer, and that FOXA1 plays an important role in the occurrence, development and prognostics of breast cancer, which has attracted further studies (7,32,33). Certain studies have suggested that there is an association between FOXA1 expression and prognostic factors of breast cancer, such as ER, PR, HER-2, lymph node metastasis and histological grade (5-9), which has subsequently lead to the investigation of whether FOXA1 may be a significant prognostic factor. The expression of certain receptors in breast cancer is associated with a variety of factors, of which FOXA1 expression may be one (5-12). The results, however, remain controversial. The majority of studies indicate that the ER and PR status are significantly associated with FOXA1 expression in breast cancer; however, there is no association with the HER-2 status (5,7,8,10-12). By contrast, Wolf *et al* (6) found that there was no association between FOXA1 expression and PR status in breast cancer, while Albergaria *et al* (9) reported that FOXA1 expression was associated with the HER-2 status. In the present meta-analysis, the results were consistent with the majority of studies in that the expression of FOXA1 in the ER positive or PR positive groups was significantly higher

compared with that in the ER negative or PR negative groups. However, no statistically significant difference was observed between the HER-2 positive and HER-2 negative groups. With regard to the breast cancer process (lymph node metastasis and histological grade), the result for FOXA1 expression at different stages was also divided. Albergaria *et al* (9) found that FOXA1 expression was associated with lymph node metastasis; however, this was inconsistent with the results observed by Ijichi *et al* (11) and Thorat *et al* (8). Albergaria *et al* (9) and Habashy *et al* (7) hypothesized that FOXA1 expression was associated with histological grade, while Jiang *et al* (12) demonstrated no correlation between FOXA1 expression and histological grade. In the current meta-analysis, the combined results indicated that FOXA1 expression was associated with lymph node metastasis and histological grade. The expression levels of FOXA1 in the lymph node negative or low histological grade groups were significantly higher compared with that in the lymph node positive or high histological grade groups, which demonstrated that FOXA1 expression was associated with the development, cell differentiation and prognosis of breast cancer.

Limitations of the present analysis should be acknowledged. Firstly, the cut-off values in the present study were not consistent. Four studies defined a score of 0-3 as FOXA1 expression negative, one study defined a score of 0-2 as FOXA1 expression negative, whereas different thresholds (median) were used in the two additional studies. The remaining study did not discuss cut-off values. Secondly, heterogeneity is a potential problem that may have affected the interpretation of the results of the meta-analysis. When investigating the correlation between FOXA1 expression and the ER status or HER-2 status, high heterogeneity was observed in selected articles. The sources of heterogeneity may be attributed to differences in the ethnicity and histological type. Thirdly, the study was restricted to papers published in English and Chinese, which is likely to have introduced bias. Despite a number of limitations in the present study, to the best of our knowledge, this is the first meta-analysis focusing on the association between FOXA1 expression and the clinical characteristics of breast cancer.

In conclusion, the results of the meta-analysis demonstrated a significant association between FOXA1 expression and the clinical characteristics of breast cancer, which may be valuable to the diagnosis, treatment and prognosis of breast cancer. However, due to the aforementioned limitations, future studies evaluating the significance of FOXA1 expression on the clinical characteristics of breast cancer are strongly recommended.

Acknowledgements

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