Assessing Clinical Significance of Serum CA15-3 and Carcinoembryonic Antigen (CEA) Levels in Breast Cancer Patients: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Breast cancer is the most common malignant cancer in women worldwide. The tumor markers Cancer Antigen 15-3 (CA15-3) and Carcinoembryonic Antigen (CEA) are frequently used for screening and monitoring breast cancer.

Material/Methods: We conducted a meta-analysis of 13 published case-control studies to assess the associations between serum levels of CA15-3 and CEA with breast cancer susceptibility, including 1179 cases and 493 controls. The analyses were performed on malignant tumor and benign tumor, as well as in different subgroups with respect to the patient ethnicities and clinical tumor stages.

Results: This systematic review and meta-analysis of association studies shows that serum levels of CA15-3 and CEA are potential biomarkers for breast cancer monitoring. When stratified by clinical stage, we noticed that although malignant tumors in all stages show elevated levels of CA15-3, it is greatly associated with the tumor stage, as it increases as breast tumor stage worsens.

Conclusions: This study clarifies the inconsistent conclusions from multiple studies, and provides a precise estimation for clinical utility of 2 important biomarkers, CA15-3 and CEA, in breast cancer monitoring. Thus, our study will shed lights on the prognosis of breast cancer patients.

MeSH Keywords: Breast Neoplasms, Male • Cetacea • Meta-Analysis as Topic • Nuclear Receptor Coactivator 3

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Background

Breast cancer is reported as the most common malignant cancer, which accounts for 25% of all cancer cases in women worldwide [1,2]. It resulted over half a million deaths in 2012 [2]. Traditional diagnostic tools, including two-dimensional and three-dimensional mammography, use radiological scanning technique for tumor detection, but these methods are usually not recommended for young women (≤40 years old) due to the false-positive rate and over-diagnosis [3,4]. More practical methods are still needed to provide a fast and non-invasive quantitative estimate of tumor growth. Tumor markers are frequently used for screening and monitoring cancers. Cancer Antigen 15-3 (CA15-3) and Carcinoembryonic Antigen (CEA) are 2 Food and Drug Administration (FDA)-approved tumor markers for monitoring breast cancer [5,6]. CA15-3 is a mucinous glycoprotein, which is one of products of Mucin1 (MUC-1) gene [7]. MUC-1 is found in nearly all epithelial cells, and its overexpression is often associated with colon, breast, ovarian, lung, and pancreatic cancers [8,9]. CEA is a member of the immunoglobulin superfamily. A total of 29 genes have been found in the human CEA gene family, including 11 pregnancy-specific glycoprotein subgroup genes [7]. Previous studies show that elevated levels of serum or salivary CA15-3 and CEA are usually detected in patients with breast malignancies. Many studies have been conducted to quantitatively evaluate the serum level of these 2 tumor markers in breast cancer patients [10–24]. For example, Moazzezy et al. reported that CA15-3 and CEA serum levels were independent of the breast cancer staging [25]. Uehara et al. [6] and Atoum et al. [11] found significant differences in CA15-3 expression levels in different stages of breast cancer. In addition, Thriveni et al. found that serum CEA levels did not have any significant correlation in breast cancer patients prior to treatment [17]. Samy et al. showed that preoperative serum levels of CEA of breast cancer patients were significantly higher compared with the levels of the control group [15]. Nevertheless, the results of many studies are inconsistent, even conflicting with each other. Therefore, to clarify the change of serum levels of CA15-3 and CEA in breast cancer, we performed a meta-analysis on 13 eligible case-control studies [10–12,14–23] that have been published to date, including 1179 cases and 493 controls, as well as subgroup analysis in terms of ethnicity distribution and breast cancer clinical stages. We used the Mantel-Haenszel (M-H) fixed-effects model set to analyze datasets at low statistical inconsistency, and used the DerSimonian and Laird (D-L) random-effects model for those showing obvious heterogeneity, to calculate the standardized mean difference (SMD) and 95% confidence interval (CI) for the strength of the associations between serum levels and breast cancer risk. We believe our study can deliver a more precise estimation of association of CA15-3 and CEA with breast cancer susceptibility.

Material and Methods

Search strategy

All studies reporting associations between the serum levels of CA15-3 and CEA with breast cancer published from 2000 to 2014 were collected by comprehensive internet-based searches of PubMed, Google Scholar, and CNKI databases. The relevant key words, including "CA15-3", "CEA", and "breast cancer" were used for searching.

Data collection

A total of 385 results (220 from PubMed, 135 from Google Scholar, and 30 from CNKI) were found in the first-round screening. To narrow the selection, the criteria for studies to be considered for this meta-analysis were as follows: (i) relative articles, non-duplicated articles; (ii) case–control studies published in peer-reviewed journals with full text available; (ii) studies focus on the relationship between serum levels of CA15-3 and CEA with breast cancer; and (iv) statistic information of mean, standard deviation, and number of cases/controls being available. With the restrictions mentioned above, a total of 13 articles are eventually selected for our meta-analysis. For each article, the following data were collected: the first author's last name, year of publication, country of origin, patient ethnicity, mean/standard deviation, and number of cases or controls, as well as the clinical information. The procedure of article collection is shown in Figure 1.

Statistical methods

In this study, statistics software STATA (release 12.0, College Station, TX) was used to conduct all the meta-analyses. The strength of the associations between serum levels and breast cancer susceptibility were assessed using all databases, and the average differences of each included trial were expressed as the standardized mean difference (SMD) and 95% confidence interval. Analyses of CA15-3 and CEA were performed separately. We also performed subgroup analyses according to patient ethnicities (Caucasian or Asian) and tumor stages (stage I, II, and III). I^2 index was calculated to estimate the heterogeneity among trials, as the higher the I^2, the more significant the heterogeneity. Values of $I^2=50\%$ represent a dividing point between low and high heterogeneity. When $I^2 \leq 50\%$, we assumed that there was no significant heterogeneity between pooled data. Correspondingly, $I^2 >50$ was treated as significant heterogeneity. Moreover, based on the I^2 index, we choose a different model in analysis: the Mantel-Haenszel (M-H) fixed-effects model set should be used to analysis datasets at low statistical inconsistency and the DerSimonian and Laird (D-L) random-effects model should be used for datasets showing obvious heterogeneity. In our meta-analysis,
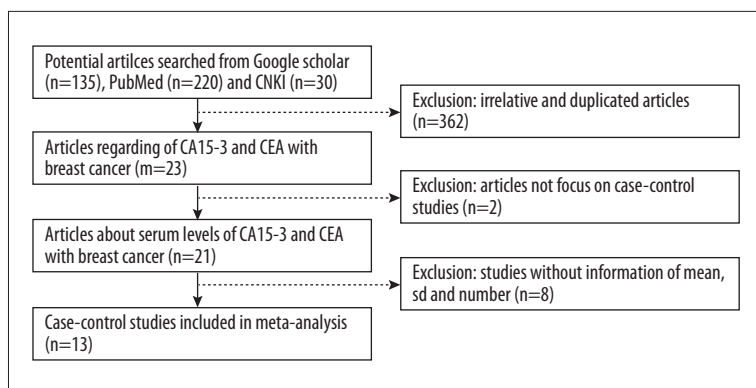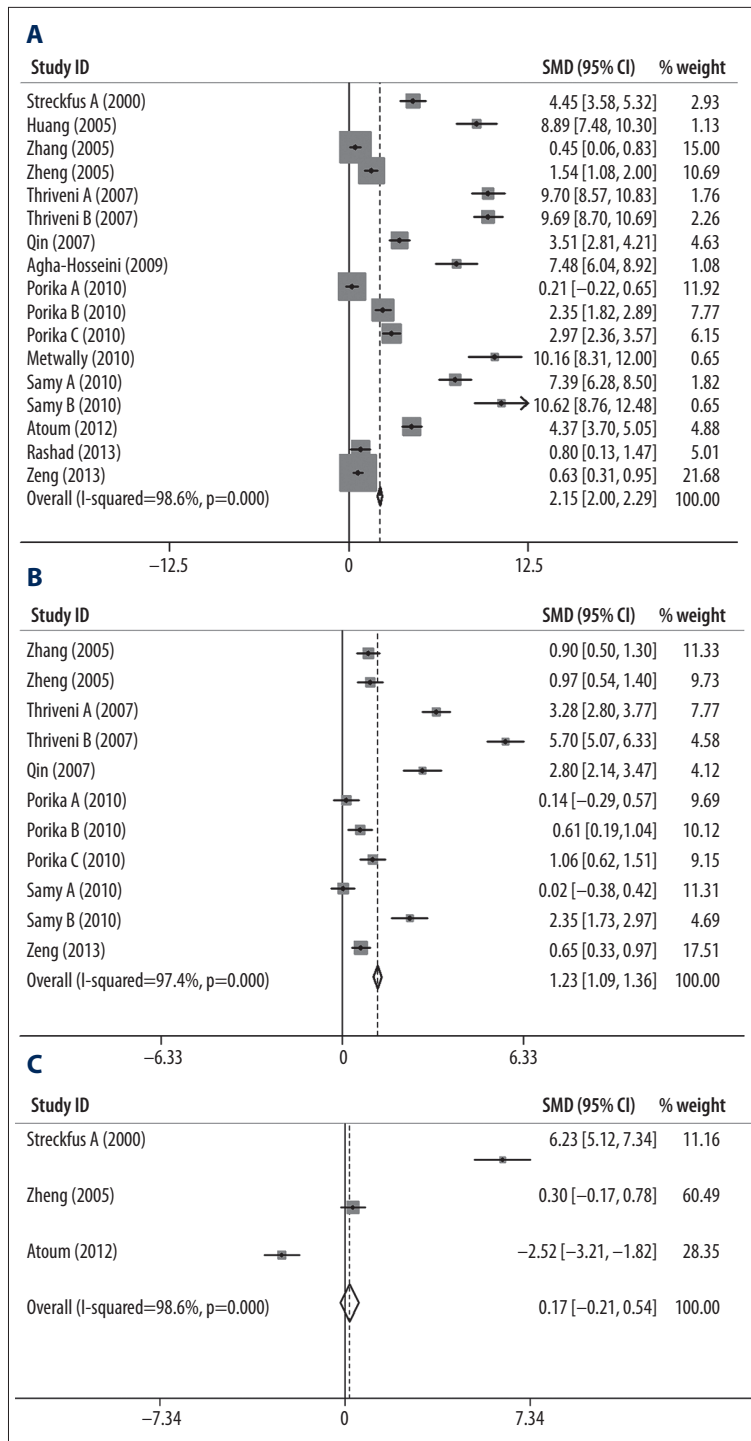
Figure 1. Flow diagram of article collection.

Table 1. Characteristics of studies included in the meta-analysis.

Author	Year	Country	Ethnicity	Description	No. of patients (case/control)	Age (average)	CA15-3-method	CEA-method
Zeng	2013	China	Asian	Malignant	100/64	51.4	MEIA, Abbott AxSYM	MEIA, Abbott AxSYM
Rashad	2013	Egypt	Caucasian	Malignant	80/10	49.6	ELISA, MyBioSource	
Atoum	2012	Jordan	Caucasian	Benign & malignant	91/45		MEIA, Abbott AxSYM	
Porika	2010	India	Caucasian	Stage I,II & III	153/38	44.9	ELISA, Antuos	ELISA, Antuos
Metwally	2010	Egypt	Caucasian	Malignant	44/21	36	MEIA, Abbott AxSYM	
Samy	2010	Egypt	Caucasian	Stage I & II	89/40		ELISA, CIS Bio International	ELISA, Quorum
Agha-Hosseini	2009	Iran	Caucasian	Malignant	26/35	42.6	ELISA, CanAg	
Thriveni	2007	India	Caucasian	Stage I & II, III & IV	207/75		ELISA, Calbiotech	ELISA
Qin	2007	China	Asian	Malignant	67/24		ELISA	ELISA
Huang	2005	China	Asian	Malignant	63/25	53.4	IRMA	
Zhang	2005	China	Asian	Malignant	66/44	47	CLIA, Bayer	CLIA, Bayer
Zheng	2005	China	Asian	Benign & malignant	130/30	45	ELISA, CanAg	ELISA, CanAg
Streckfus	2000	USA	Caucasian	Benign & malignant	63/42	50.8	ELISA,CIS Bio International	

Table 2. Results of meta-analysis for CA15-3 and CEA using malignant and benign tumor database.

Biomarker	Analysis method	Heterogeneity		Odd ratio (OR)				Publication bias	
		I² (%)	p-value	Overall	Lower	Upper	p-value	Begg	Egger
Malignant									
CA15-3	Random	98.6	3.7×10^{-30}	2.15	2.00	2.30	1.8×10^{-10}	0.149	1.0×10^{-5}
CEA	Random	97.4	3.1×10^{-25}	1.23	1.09	1.36	1.8×10^{-21}	0.020	0.149
Benign**									
CA15-3	Random	98.8	2.2×10^{-18}	0.17	−0.21	0.54	0.382	−*	−*

* Results are not available because there were too few studies; ** Analysis on CEA was not performed due to the lack of studies.

A

Study ID	SMD (95% CI)	% weight
Streckfus A (2000)	4.45 [3.58, 5.32]	2.93
Huang (2005)	8.89 [7.48, 10.30]	1.13
Zhang (2005)	0.45 [0.06, 0.83]	15.00
Zheng (2005)	1.54 [1.08, 2.00]	10.69
Thriveni A (2007)	9.70 [8.57, 10.83]	1.76
Thriveni B (2007)	9.69 [8.70, 10.69]	2.26
Qin (2007)	3.51 [2.81, 4.21]	4.63
Agha-Hosseini (2009)	7.48 [6.04, 8.92]	1.08
Porika A (2010)	0.21 [−0.22, 0.65]	11.92
Porika B (2010)	2.35 [1.82, 2.89]	7.77
Porika C (2010)	2.97 [2.36, 3.57]	6.15
Metwally (2010)	10.16 [8.31, 12.00]	0.65
Samy A (2010)	7.39 [6.28, 8.50]	1.82
Samy B (2010)	10.62 [8.76, 12.48]	0.65
Atoum (2012)	4.37 [3.70, 5.05]	4.88
Rashad (2013)	0.80 [0.13, 1.47]	5.01
Zeng (2013)	0.63 [0.31, 0.95]	21.68
Overall (I-squared=98.6%, p=0.000)	2.15 [2.00, 2.29]	100.00

−12.5   0   12.5

B

Study ID	SMD (95% CI)	% weight
Zhang (2005)	0.90 [0.50, 1.30]	11.33
Zheng (2005)	0.97 [0.54, 1.40]	9.73
Thriveni A (2007)	3.28 [2.80, 3.77]	7.77
Thriveni B (2007)	5.70 [5.07, 6.33]	4.58
Qin (2007)	2.80 [2.14, 3.47]	4.12
Porika A (2010)	0.14 [−0.29, 0.57]	9.69
Porika B (2010)	0.61 [0.19, 1.04]	10.12
Porika C (2010)	1.06 [0.62, 1.51]	9.15
Samy A (2010)	0.02 [−0.38, 0.42]	11.31
Samy B (2010)	2.35 [1.73, 2.97]	4.69
Zeng (2013)	0.65 [0.33, 0.97]	17.51
Overall (I-squared=97.4%, p=0.000)	1.23 [1.09, 1.36]	100.00

−6.33   0   6.33

C

Study ID	SMD (95% CI)	% weight
Streckfus A (2000)	6.23 [5.12, 7.34]	11.16
Zheng (2005)	0.30 [−0.17, 0.78]	60.49
Atoum (2012)	−2.52 [−3.21, −1.82]	28.35
Overall (I-squared=98.6%, p=0.000)	0.17 [−0.21, 0.54]	100.00

−7.34   0   7.34

Figure 2. Forest plots of (**A**) CA15-3 for malignant tumor, (**B**) CEA for malignant tumor, and (**C**) CA15-3 for benign tumor.

we used the M-H fixed-effect model to test the heterogeneity first, and then choose different models based on the testing results. SMDs were calculated with each model within 95% confidence intervals. Forest plots were generated to summarize the results. Potential publication bias was assessed by Begg's funnel plots and Egger's test. All reported p-values were from two-sided tests.

Results

To systematically study the association between the levels of CA15-3 and CEA in the serum with the risk of breast cancer, we performed a meta-analysis of a total of 13 eligible case-control studies, the main characteristics of which are shown in Table 1. These studies involved a total of 1179 cases and 493
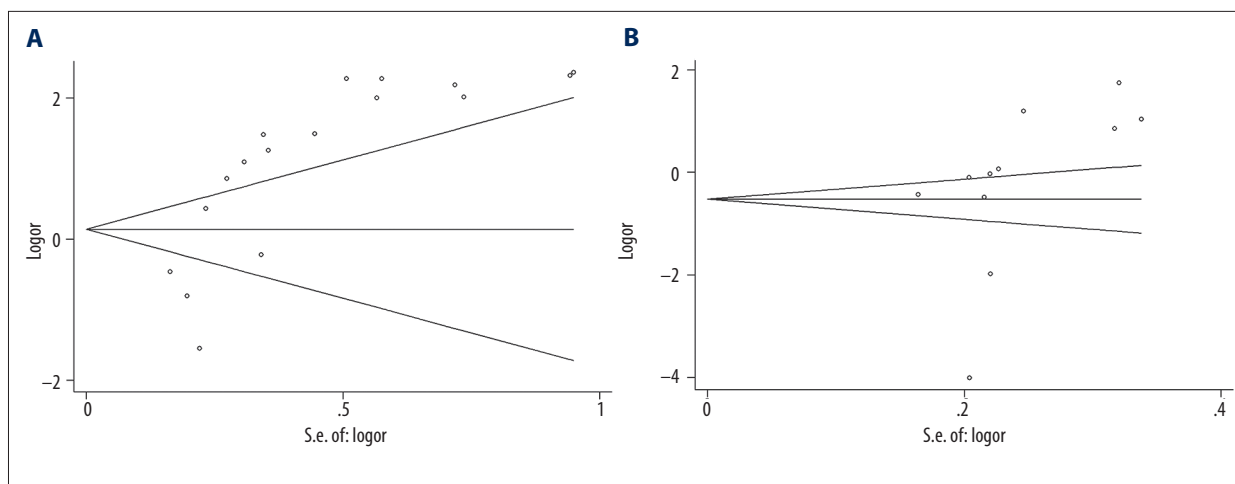
Figure 3. Funnel plots of (**A**) CA15-3 for malignant tumor and (**B**) CEA for malignant tumor.

Table 3. Results of subgroup meta-analysis for CA15-3 and CEA using Caucasian and Asian database.

Biomarker	Caucasian				Asian			
	I^2 (%)	ph*	OR (95%CI)	pOR**	I^2 (%)	ph*	OR (95%CI)	pOR**
CA15-3	98.5	1.6×10^{-32}	3.23 (3.01–3.45)	9.6×10^{-27}	97.8	3.1×10^{-19}	1.19 (0.98–1.39)	2.1×10^{-25}
CEA	98.2	6.5×10^{-30}	1.40 (1.22–1.58)	1.3×10^{-18}	91.0	1.6×10^{-7}	1.00 (0.79–1.20)	1.2×10^{-20}

* P-value from heterogeneity test; ** P-value from OR test.

controls. Among them, there are 13 studies of CA15-3 and 7 studies of CEA. For ethnicity distribution, there were 5 studies in Asians and 8 studies in Caucasians.

The results of the meta-analysis are shown in Table 2. We found that the I^2 was larger than 90% in all 3 groups (malignant tumor with CA15-3 marker, malignant tumor with CEA marker, and benign tumor with CA15-3 marker), suggesting statistically significant heterogeneity in all cases. Given the large I^2 indexes, the random-effects model was used for further calculating standardized mean difference (SMD) and 95% confidence interval (CI) calculation. Forest plots for each group are shown in Figure 2. From the analysis, we found significant associations between the levels of CA15-3 and CEA with breast cancer susceptibility for malignant tumors (CA15-3: SMD=2.15, 95% CI (2.00–2.30), p-value=1.8×10^{-8}, Figure 2A; CEA: SMD=1.23, 95% CI (1.09–1.36), p-value=1.8×10^{-21}, Figure 2B). These results indicate that the levels of CA15-3 and CEA in the serum were significantly associated with the risk of developing malignant breast cancer. However, further analysis revealed that there was no significant association between the level of CA15-3 with breast cancer susceptibility for benign tumors (CA15-3: SMD=0.17, 95% CI (–0.21–0.38), p-value=0.382, Figure 2C). For publication bias, we noticed that Egger's test of the CA15-3 level in malignant tumors and Begg's test of the CEA level

in benign tumors demonstrated slightly significant bias. The funnel plots of each group are shown in Figure 3.

We performed subgroup meta-analyses for CA15-3 and CEA with respect to Caucasian and Asian populations, and the results are shown in Table 3. Based on the information from the above analyses, only the malignant tumors database was used in this section. Generally, the I^2 indexes were still very large (>90% in all cases) for all analyses, indicating a significant heterogeneity in these comparison models (p-values <0.05). Due to these results, a random-effects model was used for assessing the association in the analysis. The forest plots of CA15-3/CEA for Caucasian and Asian populations are shown in Figures 4 and 5, respectively. From these results, we found that both CA15-3 and CEA were significantly associated with breast cancer, regardless of ethnicity (CA15-3 (Caucasian): SMD=3.23, 95% CI (3.01–3.45), p-value=9.6×10^{-27}, Figure 4A; CA15-3 (Asian): SMD=1.19, 95% CI (0.98–1.39), p-value=2.1×10^{-25}, Figure 4B; CEA (Caucasian): SMD=1.40, 95% CI (1.22–1.58), p-value=1.3×10^{-18}, Figure 5A; CEA (Asian): SMD=1.00, 95% CI (0.79–1.20), p-value=1.2×10^{-20}, Figure 5B). These results indicate that the levels of CA15-3 and CEA in serum can be used to effectively predict breast cancer susceptibility and provide a useful prognosis for breast cancer detection.
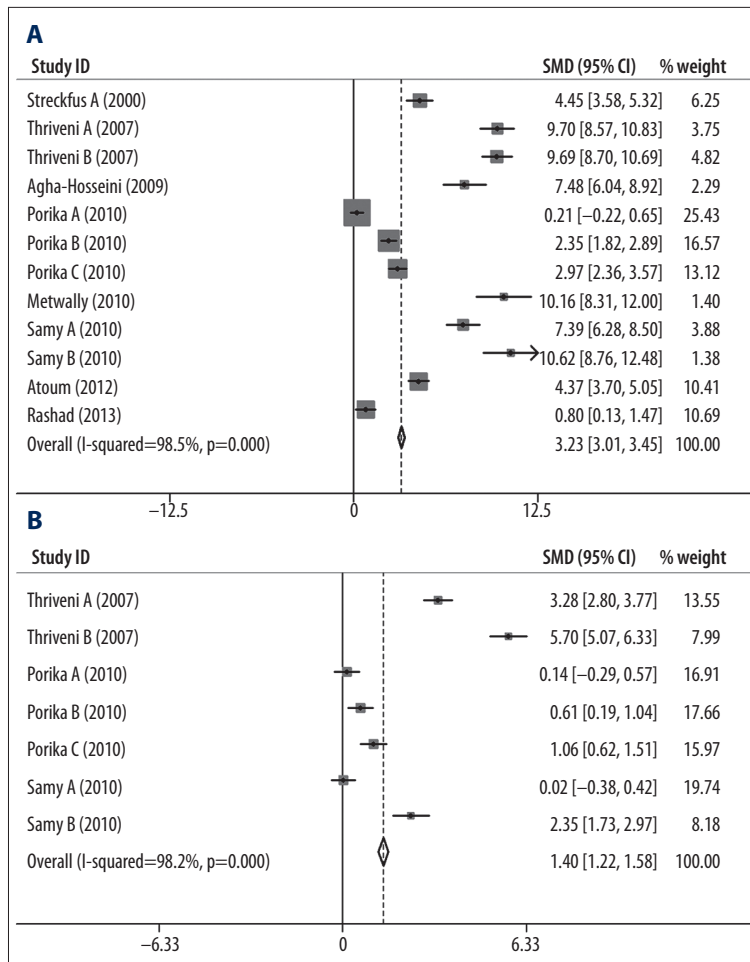
Figure 4. Forest plots of CA15-3 for (**A**) Caucasian population and (**B**) Asian population.

Discussion

Similar to the strategy detailed above, we performed subgroup meta-analyses for CA15-3 in terms of different tumor clinical stages (stage I, II, and III), and the results are shown in Table 4. Again, we found significant heterogeneity in these subgroup analyses (P-values <0.05). The forest plots of all 3 stages are shown in Figure 6. Based on the meta-analysis, CA15-3 is significantly associated with breast cancer in all stratified stages (Stage I: SMD=2.03, 95% CI (1.66–2.40), p-value=9.8×10^{-27}, Figure 6A; Stage II: SMD=3.88, 95% CI (3.40–4.35), p-value=5.1×10^{-41}, Figure 6B; Stage III: SMD=5.12, 95% CI (4.63–5.61), p-value=6.7×10^{-48}, Figure 6C). Although all malignant tumors show elevated levels of CA15-3, we noticed that the level of CA15-3 keeps increasing as the breast tumor progresses. These results suggest that the level of CA15-3 might be more efficient for monitoring advanced tumors than early diagnosis. On the other hand, for publication bias, only statistically significant biases were observed for stage I and II in Egger's test with explicit database stratification. The funnel plots are shown in Figure 7.

Several different tumor-specific antigens are usually generated by tumor cells or by host cells in response to tumorigenesis. These unique antigens are termed tumor markers and can be used in cancer screening and monitoring. The sensitivity and specificity of an individual tumor marker may be low, but the combination of multiple tumor markers can be very helpful as a clinical tool in oncology. CA15-3 and CEA are frequently used in clinical treatment of breast cancer [10–23]. In this study, we investigated the associations between serum levels of CA15-3 and CEA with breast cancer susceptibility by a systematic meta-analysis. We found significantly elevated serum levels of CA15-3 and CEA in patients with malignant breast cancer, but not in those with benign tumors. Further subgroup analyses involving patients with malignant tumors showed that both Caucasian and Asian populations had a similar significant association. In addition, we found that the level of CA15-3 is greatly associated with tumor stages. However, Gion et al. reported that there was no difference in CA15-3 expression between benign tumors and stage I and II [24]. Moazzezy et al. also reported that CA15-3 and CEA serum levels were independent of the breast
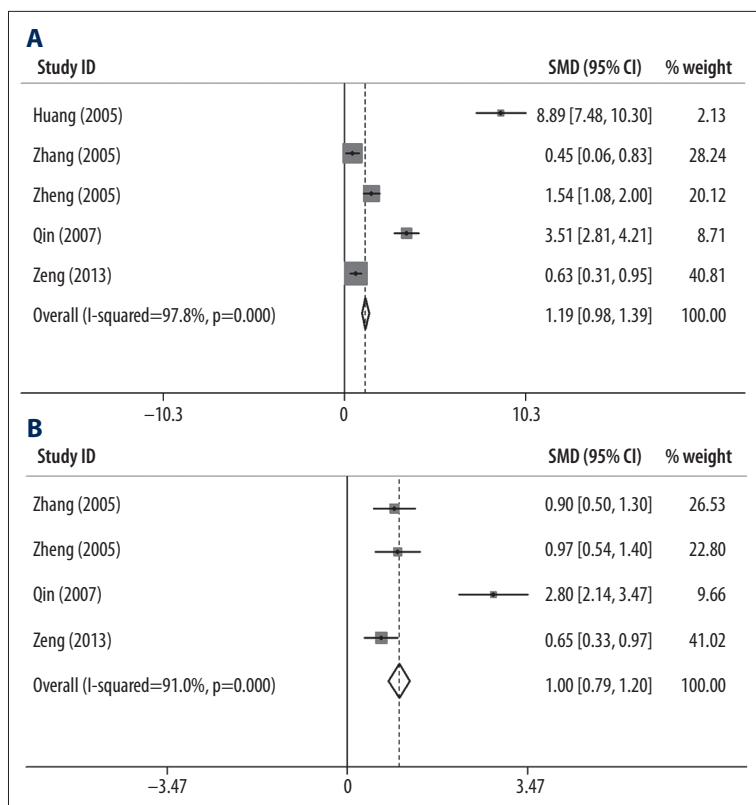
Figure 5. Forest plots of CEA for (**A**) Caucasian population and (**B**) Asian population.

**Table 4.** Results of subgroup meta-analysis for CA15-3 using stage I, II, and III database.

Tumor stage	Analysis method	Heterogeneity		OR				Publication bias	
		I² (%)	p-value	Overall	Lower	Upper	p-value	Begg	Egger
Stage I	Random	98.4	2.7×10⁻²³	2.03	1.66	2.40	9.8×10⁻²⁷	0.806	0.029
Stage II	Random	97.7	2.7×10⁻¹⁹	3.88	3.40	4.35	5.1×10⁻⁴¹	1.000	0.010
Stage III	Random	98.2	1.0×10⁻²⁶	5.12	4.63	5.61	6.7×10⁻⁴⁸	0.734	0.308

cancer staging [25]. However, the sample size in this study was small: only 30 patients and 30 controls, which may not be able to represent the population accurately. In contrast to these and consistent with our results, Uehara et al. found that breast cancer stage II patients with normal CA15-3 levels had a better prognosis than those with elevated CA15-3 levels [6]. Sutterlin et al. also reported significant differences in CA15-3 expression levels between those in benign tumors and those in stage III and IV [26]. The inconsistency could come from different sensitivities of detecting CA15-3 levels in different studies. It is also possible that differences in the age, BMI, tumor size, menopause status, lifestyle, environment, and other variables between different patients may affect the tumor marker levels. Hence, elevated CA15-3 levels may be one factor that predicts a poor prognosis. In addition, a heterogeneous disease such as breast cancer may require combining multiple biomarkers to allow the detection of different subtypes.

Despite our consistent results, there are some limitations in this study. First, the patients included in this study had an average age between 36 and 53.4 years old, with most between 40 and 50 years old. As use of traditional tools such as mammography increase more dramatically for the older people, and the probability of over-diagnosis also usually increases with age, the biomarker screening for breast cancer would really benefit women over 55 years old. Therefore, in the context of an aging society, more research is needed to fully understand the natural history of breast cancer and to improve its screening and treatment in older age groups. Secondly, the 13 studies in our analysis used different methods/assays to test CA15-3 and CEA levels, including 11 for CA15-3: MEIA, Abbott AxSYM, ELISA, MyBioSource, Antuos, CIS Bio International, CanAg, Calbiotech, IRMA, CLIA and Bayer, and 8 for CEA: MEIA, Abbott AxSYM, ELISA, Antuos, Quorum, CLIA, Bayer and CanAg. Previous research compared 3 different
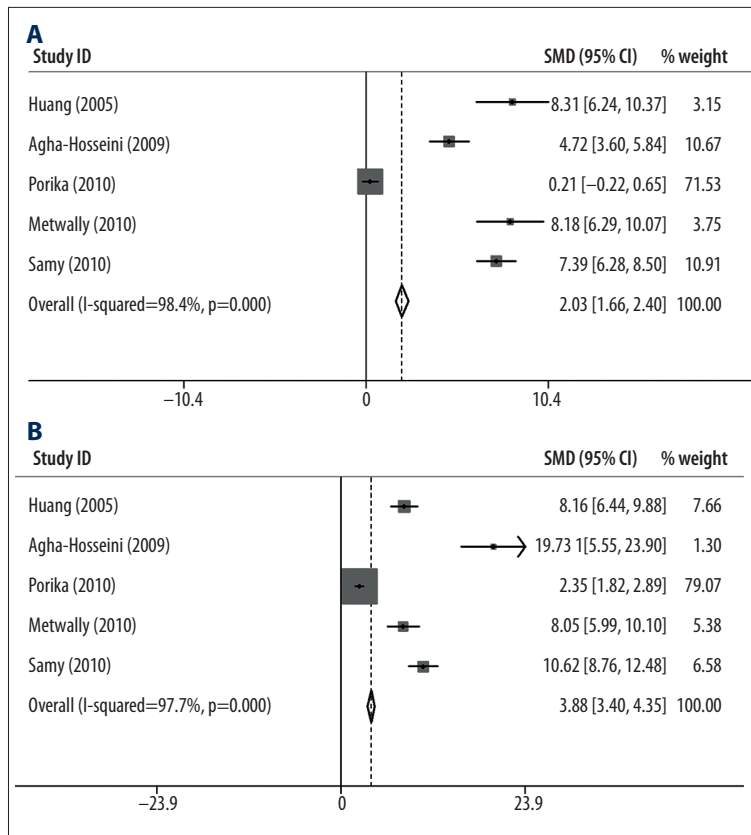
Figure 6. Forest plots of CA15-3 for (**A**) stage I, (**B**) stage II and (**C**) stage III tumor.
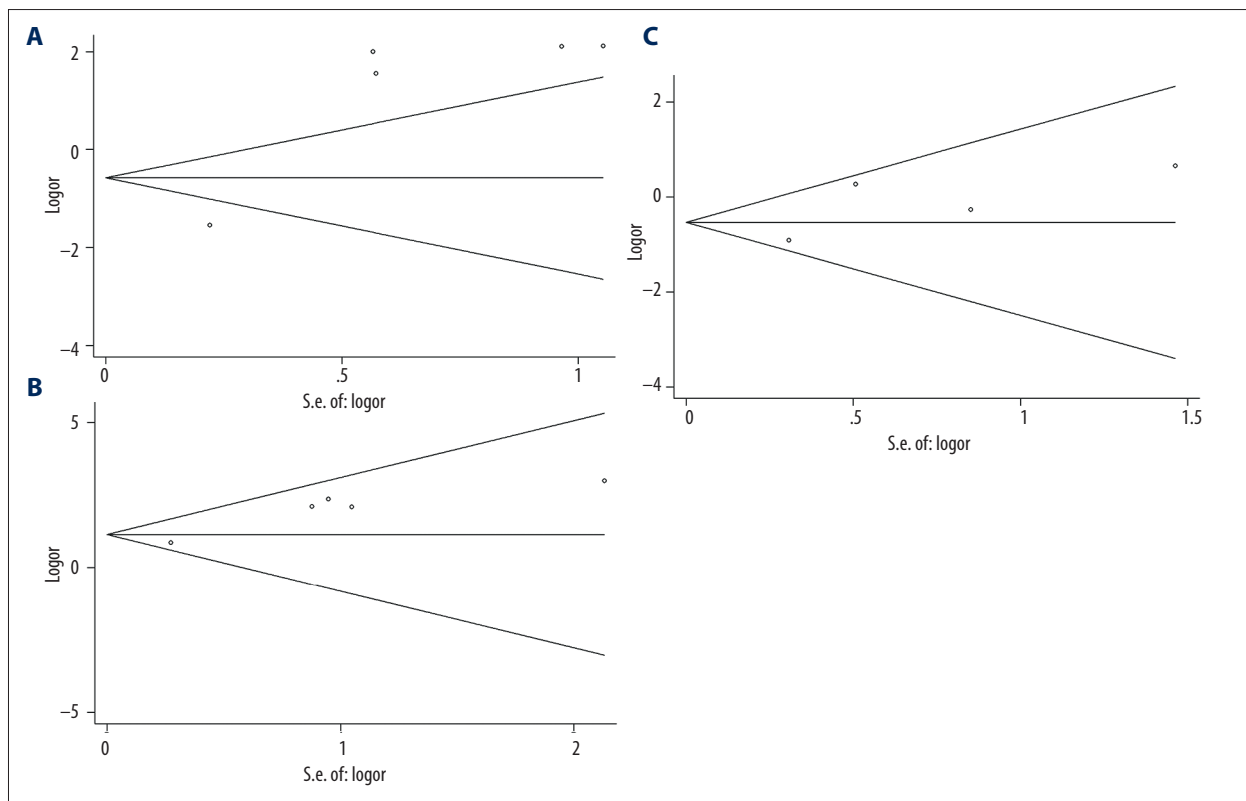
Figure 7. Funnel plots of CA15-3 for (**A**) stage I, (**B**) stage II and (**C**) stage III tumor.

CA15-3 assay kits (the manual IRMA Centocor and 2 fully automated methods, the ELISA-Boehringer Mannheim-ES300 and the Abbott IMx) and showed that they have different sensitivity and could yield inconsistent results [27,28]. Positive rates of the IRMA CA15-3 did not show any significant variations related to stage, while CA15-3 levels obtained by both ELISA and Abbott assays showed higher values in stage I than in stage II patients [27,28]. Therefore, it may be necessary to find a uniform method to screen for CA15-3 and CEA levels. As diagnostic and clinical techniques improve, tumor markers will likely become more important in cancer screening and treatment.

Conclusions

In this study, we presented a meta-analysis investigating the associations between serum levels of CA15-3 and CEA with breast cancer susceptibility. A total of 13 studies, including 1179 cases and 493 controls, were involved in our analysis, which shows that serum levels of CA15-3 and CEA are potential biomarkers for breast cancer monitoring. Specifically, we found statistically significant elevated levels of serum CA15-3 and CEA in the patients with malignant breast tumors, but not in the patients with benign tumors. Further subgroup analyses focusing on patients with malignant tumors showed that both Caucasian and Asian populations demonstrated a similar significant association. When stratified by the clinical stage, we noticed that although malignant tumors in all stages show elevated levels of CA15-3, the level of CA15-3 is greatly associated with the tumor stage, meaning that the level of CA15-3 becomes higher as the breast tumor stage progresses. This study clarifies the inconsistent conclusions from multiple studies, and provides a precise estimation for clinical values of 2 important biomarkers in breast cancer monitoring. We believe our study will shed light on future breast cancer research.

Conflict of interest

The author(s) declare that they have no competing interests.

References:

1. Greenlee RT, Murray T, Bolden S, Wingo PA: Cancer statistics, 2000. Cancer J Clin, 2000; 50(1): 7–33

2. Stewart BW, Wild C, International Agency for Research on Cancer, World Health Organization. World cancer report, 2014

3. Taplin S, Abraham L, Barlow WE et al: Mammography facility characteristics associated with interpretive accuracy of screening mammography. J Natl Cancer Inst, 2008; 100(12): 876–87

4. Mandelblatt JS, Cronin KA, Bailey S et al: Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. Ann Intern Med, 2009; 151(10): 738–47

5. O'Hanlon DM, Kerin MJ, Kent P et al: An evaluation of preoperative CA 15-3 measurement in primary breast carcinoma. Br J Cancer, 1995; 71(6): 1288–91

6. Uehara M, Kinoshita T, Hojo T et al: Long-term prognostic study of carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3) in breast cancer. Int J Clin Oncol, 2008; 13(5): 447–51

7. Thompson JA, Grunert F, Zimmermann W: Carcinoembryonic antigen gene family: molecular biology and clinical perspectives. J Clin Lab Anal, 1991; 5(5): 344–66

8. Gendler SJ: MUC1, the renaissance molecule. J Mammary Gland Biol Neoplasia, 2001; 6(3): 339–53

9. Roy LD, Sahraei M, Subramani DB et al: MUC1 enhances invasiveness of pancreatic cancer cells by inducing epithelial to mesenchymal transition. Oncogene, 2011; 30(12): 1449–59

10. Agha-Hosseini F, Mirzaii-Dizgah I, Rahimi A: Correlation of serum and salivary CA15-3 levels in patients with breast cancer. Med Oral Patol Oral Cir Buca, 2009; 14(10): e521–24

11. Atoum M, Nimer N, Abdeldayem S, Nasr H: Relationships among Serum CA15-3 tumor marker, TNM staging, and estrogen and progesterone receptor expression in benign and malignant breast lesions. Asian Pac J Cancer Prev, 2012; 13(3): 857–60

12. Metwally FM, El-mezayen HA, Ahmed HH: Significance of vascular endothelial growth factor, interleukin-18 and nitric oxide in patients with breast cancer: Correlation with carbohydrate antigen 15.3. Med Oncol, 2011; 28(Suppl.1): S15–21

13. Park BW, Oh JW, Kim JH et al: Preoperative CA 15-3 and CEA serum levels as predictor for breast cancer outcomes. Ann Oncol, 2008; 19(4): 675–81

14. Rashad YA, Elkhodary TR, El-Gayar AM, Eissa LA: Evaluation of serum levels of HER2, MMP-9, nitric oxide, and total antioxidant capacity in Egyptian breast cancer patients: Correlation with clinico-pathological parameters. Sci Pharm, 2014; 82(1): 129–45

15. Samy N, Ragab HM, El Maksoud NA, Shaalan M: Prognostic significance of serum Her2/neu, BCL2, CA15-3 and CEA in breast cancer patients: A short follow-up. Cancer Biomark, 2010; 6(2): 63–72

16. Zeng RC, Zhang W, Yan XQ et al: Down-regulation of miRNA-30a in human plasma is a novel marker for breast cancer. Med Oncol, 2013; 30(1): 477

17. Thriveni K, Krishnamoorthy L, Ramaswamy G: Correlation study of Carcino Embryonic Antigen & Cancer Antigen 15.3 in pretreated female breast cancer patients. Indian journal of clinical biochemistry: IJCB, 2007; 22(1): 57–60

18. Porika M, Malotu N, Veldandi UK et al: Evaluation of tumor markers in southern Indian breast cancer patients. Asian Pac J Cancer Prev, 2010; 11(1): 157–59

19. Zheng H, Luo RC: [Diagnostic value of combined detection of TPS, CA153 and CEA in breast cancer]. Di Yi Jun Yi Da Xue Xue Bao, 2005; 25(10): 1293–94, 1298

20. Streckfus C, Bigler L, Dellinger T et al: The presence of soluble c-erbB-2 in saliva and serum among women with breast carcinoma: A preliminary study. Clin Cancer Res, 2000; 6(6): 2363–70

21. Huang Y, Zheng X, Huang S et al: Expression and significance of P53 and CA153 in patients with breast carcinoma. Chin J Lab Diagn, 2005; 2005-2

22. Jiyong Qin, Kangming Li, Juyun He, Li Y: Clinical value of tumor marker CA15-3 in diagnosis and treatment of breast carcinoma. Xiandai Zhongliu Yixue, 2007; 15(4)

23. Zhang J, Chen L, Yao Y, Chen Z: Diagnostic value of combined detection of serum CA15-3, CEA, SF contents in patients with breast cancer. J Radioimmunology, 2005; 2005-1

24. Gion M, Mione R, Leon AE et al: CA27.29: A valuable marker for breast cancer management. A confirmatory multicentric study on 603 cases. Eur J Cancer, 2001; 37(3): 355–63

25. Moazzezy N, Farahany TZ, Oloomi M, Bouzari S: Relationship between preoperative serum CA 15-3 and CEA levels and clinicopathological parameters in breast cancer. Asian Pac J Cancer Prev, 2014; 15(4): 1685–88

26. Sutterlin M, Bussen S, Trott S, Caffier H: Predictive value of CEA and CA 15-3 in the follow up of invasive breast cancer. Anticancer Res, 1999; 19(4A): 2567–70

27. Bon GG, von Mensdorff-Pouilly S, Kenemans P et al: Clinical and technical evaluation of ACS BR serum assay of MUC1 gene-derived glycoprotein in breast cancer, and comparison with CA 15-3 assays. Clin Chem, 1997; 43(4): 585–93

28. Lynch DM, Rogers PE, Love JC et al: Clinical evaluation comparing AxSYM CA 15-3, IMx CA 15-3 and Truquant BRTM RIA. Tumour Biol, 1998; 19(6): 421–38