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Prostate specific antigen as a biomarker for breast cancer: a meta-analysis study

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Abstract. – OBJECTIVE: To determine whether prostate-specific antigen (PSA) could serve as a biomarker for breast cancer.

MATERIALS AND METHODS: We performed an electronic search on Medline, PubMed, SPRINGER, John Wiley, Science Direct, EBSCO, CNKI and Wanfang Data to identify relevant studies for our meta-analysis. The search terms included ['prostate specific antigen' or 'PSA' (MESH)] and ['breast cancer' or 'breast carcinoma' (MESH)].

RESULTS: A comprehensive meta-analysis of 10 studies comprising of 770 cases and 799 controls were included. Among the studies considered, the sensitivity of the tPSA test for diagnosis was 0.718 (95% CI: 0.630, 0.792), the specificity was 0.528 (95% CI: 0.299, 0.746) and the diagnostic odds ratios (DOR) was 2.852 (95% CI: 1.021, 7.969). The sensitivity of fPSA test for diagnosis was 0.783 (95% CI: 0.541, 0.917), specificity was 0.679 (95% CI: 0.209, 0.944) and diagnostic odds ratio (DOR) was 7.668 (95% CI: 0.331, 177.451).

CONCLUSIONS: Serum PSA could be a useful biomarker for the diagnosis of breast cancer, and a biomarker for the differential diagnosis of breast cancer from benign breast tumors.

Key Words

Prostate-specific antigen, Breast cancer, Meta-analysis.

Introduction

Breast cancer is the most common type of cancer in women worldwide. According to the statistics from the European Society for Medical Oncology, among the 40 countries in Europe, the age-adjusted prevalence of breast cancer reached a prevalence of 94.2/100 000, while the mortality rate reached 23.1/100 000[1]. In Japan, the age-adjusted prevalence of breast cancer was 73.4/100 000 and mortality rate was 20.4/100 000[2]. With economic development, breast cancer has become the main detriment for health and life expectancy in women. The etiology of breast cancer is uncertain, however, several studies have shown that estrogen is associated with the development of breast cancer[3]. Recent studies found that there is a genetic association between breast cancer and prostate cancer[4]. Two large cohort studies found that the genetic link of breast cancer and prostate cancer was BRCA-2[5,6]. Breast cancer and prostate cancer are diseases related to hormones, and there is a significant connection with regards to gene homology. As an important diagnostic indicator for prostate cancer, prostate specific antigen (PSA) has been widely used in the clinic and studies have found that there are low levels of PSA in female serum samples (1000 times less than the normal men)[7]. As early as 1997, Borchert et al[8] investigated the relationship between breast cancer and serum PSA, but strong evidence lacking. This study investigated the levels of PSA on breast cancer patients through META analysis, and provides a scientific basis for its use as a biomarker for clinical application.

Materials and Methods

Publication Search Strategy

Computer-based retrieval of publications using Medline, Pubmed, SPRINGER, John Wiley, Science Direct, EBSCO, CNKI, Wanfang Database, and relevant references was used. Retrieval periods were until August 2017. Retrieval terms included: "prostate-specific antigen", "PSA" as well as "breast cancer", and "breast carcinoma". Retrieval formula used in the search was: ((prostate-specific antigen) OR (PSA)) AND ((breast cancer) OR (breast carcinoma)).

Inclusion and Exclusion Criteria

Research designs for meta-analyses were case-control studies. The included case-control studies had PSA correlation data with breast

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cancer. Studies lacking control group, primary data or incomplete data or article types with case reports, reviews or conference reports, were excluded.

Research Objective

Research and control groups pathologically confirmed breast cancer patients with no limitation on age, pathological types and clinical stages. Control samples in a same study were analyzed with same diagnostic criteria and test methods; research methods were basically identical in the different studies. The research group included patients who were clinically diagnosed with breast benign masses (mainly diagnosed by pathology), while the control group was healthy individuals with no family history of breast cancer.

Research Content

The differences in TPSA and FPSA levels in the serum between the case group and control group retrieved.

Exclusion Criteria

Studies with patients with other tumors were excluded. Articles with undefined pathology diagnosis or studies with STROBE scoring system less than 17.5 were removed.

Evaluation on Methodological Quality

The following data from publications were retrieved by two independent authors: title, the first author, date, research design and basic characteristics of the patients (including age, gender and quantity). The corresponding author for each study was contacted if required to obtain all the relevant information. Article quality assessment was conducted by two researchers; a third researcher performed a review for quality assessment if there was a disagreement between the first two researchers. The quality evaluation was assessed using the STROBE scoring system[9]. STROBE scoring system entails a total of 22 items, with a score of 0, 1 or 2 each (0 points mean that the article doesn't mention the relevant content; 1 point shows that the text refers to the related content with no elaboration; 2 points denote that paper has the relevant content). The STROBE scoring system has a highest attainable mark of 44 points. Low quality publications have scores ranging from 0-17.5, medium quality scores ranging from 17.5-35, and high quality scores ranging from 35-44. The included studies had medium or high quality scores.

Statistical Analysis

Meta-analysis was performed using the stata1.20 software provided by the Cochrane Collaboration (London, UK). This was used to calculate the combined sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic superiority and 95% confidence interval of the included studies. SROC analysis and estimate of the area under curve of SROC were also performed. The above analysis indicators were analyzed using the Cochrane Q heterogeneity and I^2-test prior to comprehensive analysis. If there was heterogeneity ($p<0.05$ or $I^2> 50\%$), then, the aggregate with random effects model was used, otherwise the fixed effect model was used [10].

Results

Literature Retrieval Results

115 articles were retrieved and, after selection using the inclusion and exclusion criteria, a total of 10 articles were selected[11-20] (Figure 1).

Characteristics of the Included Studies

14 articles were published from 2000 to 2016, of which 770 patients were diagnosed with breast cancer and 799 with benign breast mass (Table I).

Total Prostate Specific Serum Antigen

The meta-analysis of serum tPSA diagnosing breast cancer showed that the combined sensitivity of the 7 studies[13-19] was 0.718 (95% CI: 0.630, 0.792), specificity was 0.528 (95% CI: 0.299, 0.746), positive likelihood ratio was 1.522 (95% CI: 0.908, 2.550), negative likelihood ratio was 0.534 (95% CI: 0.315, 0.904), DOR was 2.852 (95% CI: 1.021, 7.969), and the area under curve of SROC was 0.71 (Figures 2, 3 and 4). There was heterogeneity between the studies ($p<0.0001$, $I^2=97.08$); hence, the random effects model were used to analyze the data. There was no significant publication bias ($p> 0.1$, Table II). This indicated that tPSA was moderately effective for the diagnosis of breast cancer.

Free Prostate Specific Serum Antigen

The meta-analysis of serum fPSA diagnosing breast cancer showed that the combined sensitivity of the 7 studies[11,12,14-16,19,20] was 0.783 (95% CI: 0.541,0.917), specificity was 0.679 (95% CI: 0.209, 0.944), positive likelihood ratio was 2.444 (95% CI: 0.474, 12.596), negative likelihood ra-

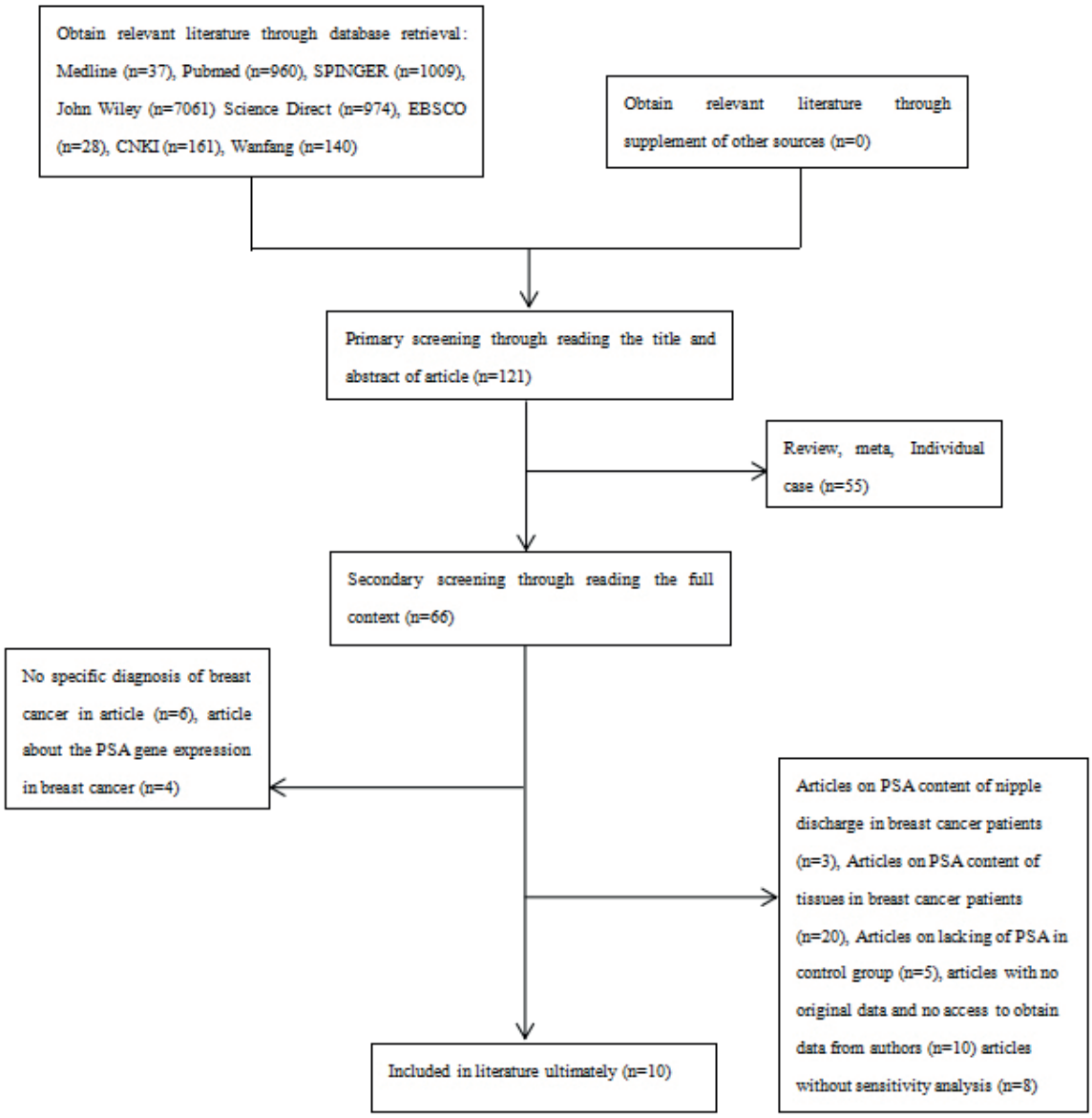

Figure 1. Cytosol. Figure 1. Retrieval flow chart.

Table I. Characteristic of the included Studies.

Author	Year of Publication	Number of Breast Cancer patients	Number of Benign Breast Tumor patients	Measurement Index	Score
Razavi et al[11]	2015	90	90	TPSA, fPSA	27
Luo et al[12]	2010	35	183	fPSA	23
Sun et al[13]	2016	61	108	TPSA	23
Li et al[14]	2012	205	100	TPSA	24
Black et al[15]	2000	118	46	TPSA, fPSA	25
Li et al[16]	2005	38	31	TPSA, fPSA	24
Wang et al[17]	2012	47	34	TPSA, fPSA	22
Zeng et al[18]	2003	26	67	TPSA, fPSA	22
Das et al[19]	2011	107	100	TPSA, fPSA	23
Shiryazdi et al[20]	2015	43	40	TPSA	25

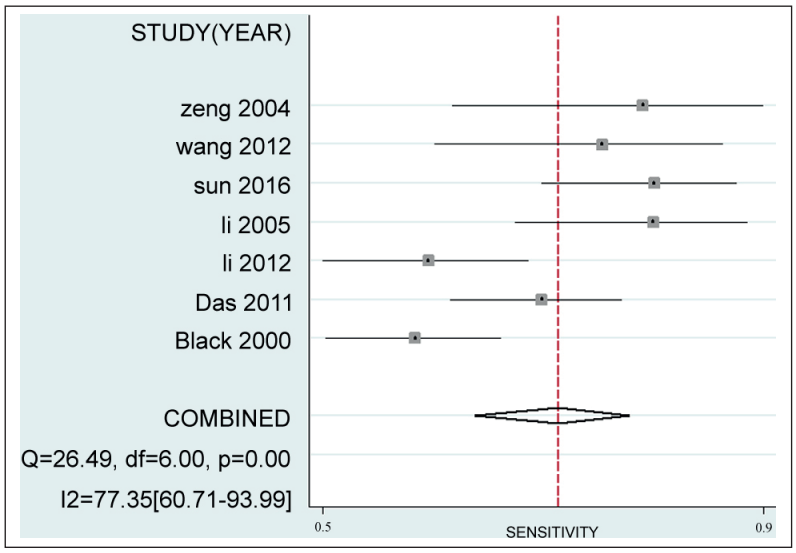

Figure 2. The sensitivity of tPSA in diagnosing breast cancer.

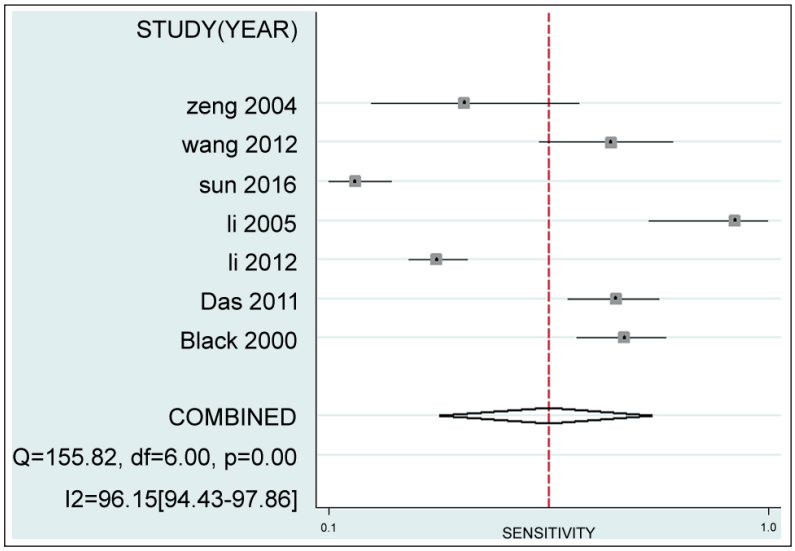

Figure 3. Specificity of tPSA in diagnosing breast cancer.

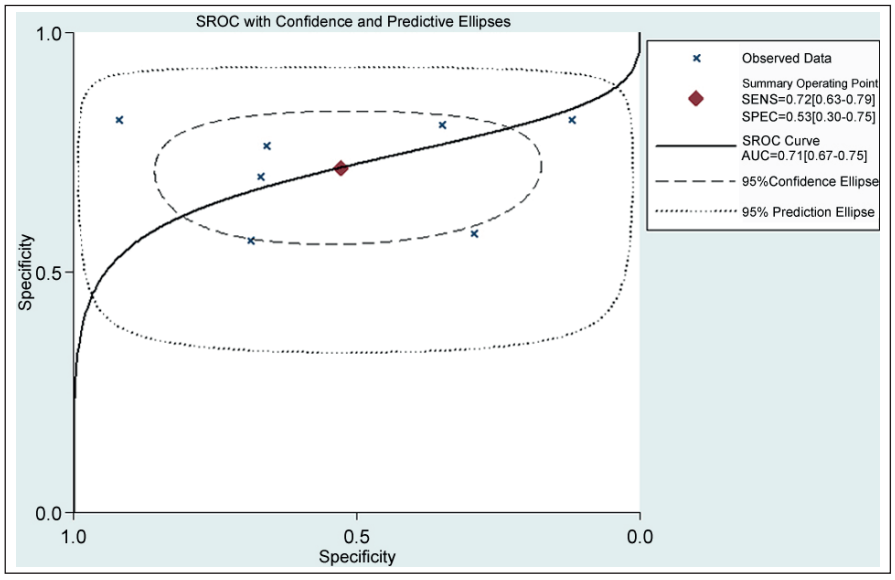

Figure 4. SROC curve of tPSA for diagnosing breast cancer.

Table II. Publication Bias analysis of tPSA in Diagnosing Breast Cancer.

yb	Coef.	Std.Err.	t	P>t	[95% Conf. Interval]	
Bias	27.35745	20.48951	1.34	0.239	-25.31251	80.02741
Intercept	-1.420658	1.703298	-0.83	0.442	-5.799125	2.957809

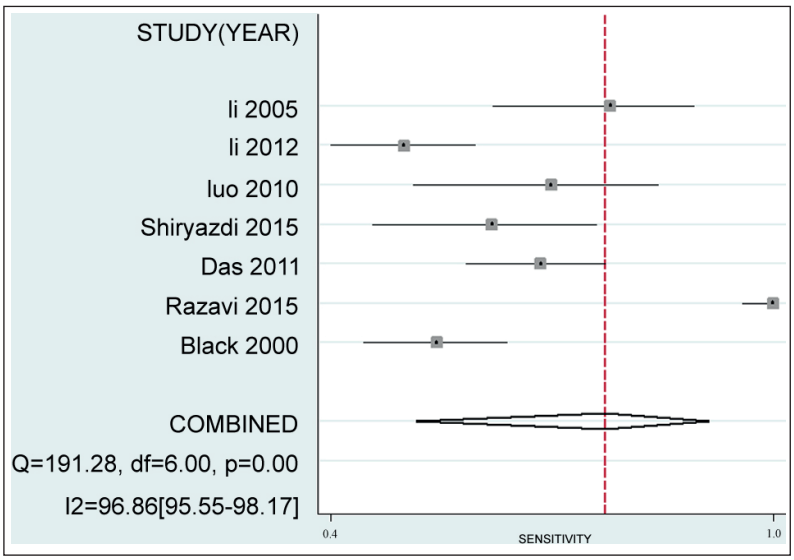

Figure 5. The sensitivity of fPSA for diagnosing breast cancer.

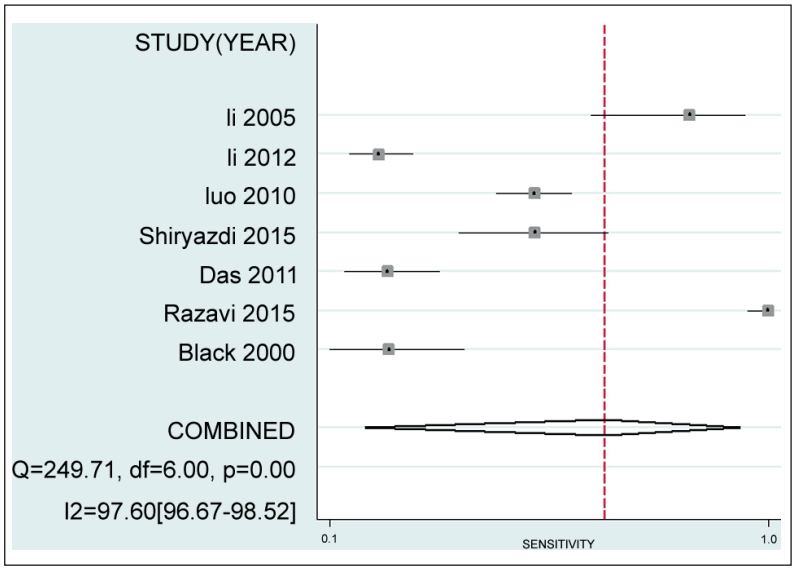

Figure 6. Specificity of fPSA for diagnosing breast cancer.

tio was 0.319 (95% CI: 0.070, 1.449), DOR was 7.668 (95% CI: 0.331, 177.451), and the area under the curve of SROC was 0.81 (Figures 5, 6 and 7). There was heterogeneity between the studies (p=0.009, I^2=75.44); hence, the random effects model was used to analyze the data. There was no significant publication bias (p>0.1, Table III). This indicated that fPSA was moderately effective for the diagnosis of breast cancer.

Discussion

Breast cancer is one of the most common tumors that affect women's health. Its diagnosis mainly relies on clinical screening, pathological biopsy and imaging data. The detection of tumor markers such as CEA, AFP, CA125, CA153 and CA199 is critical for the early diagnosis of breast cancer. However, these markers lack the specifici-

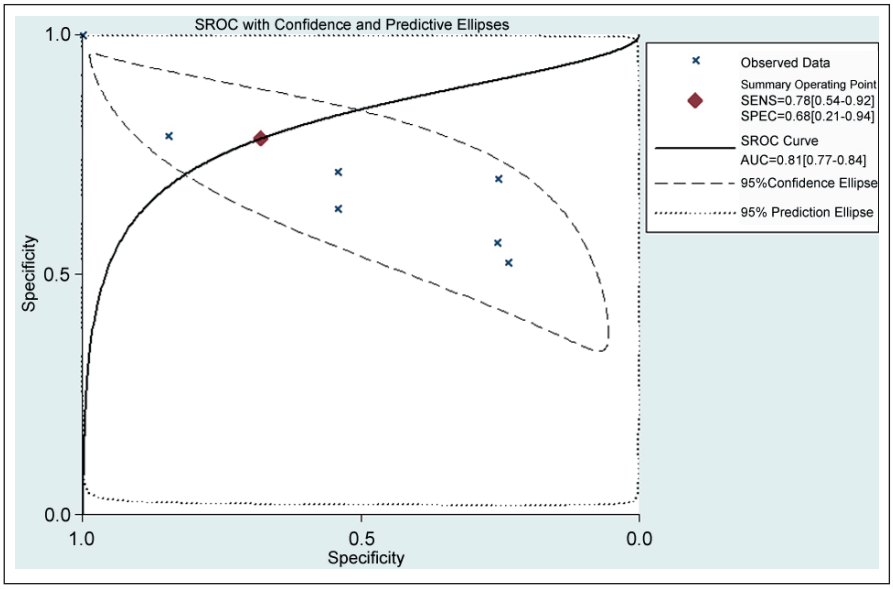

Figure 7. SROC Curve of fPSA for diagnosing breast cancer.

ty for diagnosis. In addition to clinical tests, using tumor markers is expensive[21], and they are unsatisfactory for the early diagnosis of breast cancer. Shiryazdi et al[20] found that PSA has merit for the early diagnosis of breast cancer; however, further verification and the sensitivity of detection techniques still have to be improved. It is necessary to comprehensively explore the value of PSA in the early diagnosis of breast cancer. Meta-analysis comprehensively evaluates and quantitatively analyzes existing studies to determine the value of individual studies. Our meta-analysis re-analyzed and provided a comprehensive assessment of published literature on the value of PSA as a biomarker for breast cancer. The value of PSA for early diagnosis of breast cancer could be invaluable in clinical practice.

PSA is the main component of protein in semen, which is secreted by the epithelial cells of the prostate glands. It has the function of liquefying semen that frees sperm activity[22]. Stamey et al[23] at Stanford University initially identified the important role of PSA for the diagnosis and prognosis of prostate cancer in 1987. However, PSA, which was thought to be only produced in the prostate glands, is being questioned. Researches[24-26] have demonstrated that other than the prostate, PSA also is present in tissues such as breast cyst fluid, amniotic fluid, breast milk, lactation caused by imbalance of pituitary secretion, endometria as well as ascites. The rise of PSA in breast cancer is mainly due to the increase in estrogen and progesterone receptors[27]. The gene of codes for PSA is derived from the gene family of human glandular kallikrein including hKLK1, hKLK2 and hKLK3, respectively encoding three extracellular serine proteases: hK1, hK2 and PSA (hK3)[28,29]. Several researchers have demonstrated that PSA and hK2 are expressed in prostate and other tissues. hK2 is regarded as a potent trypsin like protease, which is capable of hydrolyzing inert PSA precursors and releasing PSA[30,31]. In breast cancer tissues, PSA and hK2 are coordinately expressed[32] by increasing hormone levels. Studies have found that there is a genetic connection between breast cancer and prostate cancer[4]. Two large cohort studies[5,6] discovered that the genetic link between breast cancer and prostate cancer lies in BRCA-2. The increase of PSA in prostate cancer may be due to uncontrollable steroid hormone stimulated by testosterone, which could be an important mechanism for breast can-

Table III. Publication Bias analysis of tPSA in Diagnosing Breast Cancer.

yb	Coef.	Std.Err.	t	P>t	[95% Conf. Interval]	
Bias	28.22959	100.5441	0.28	0.790	-230.2272	286.6863
Intercept	-.5293273	8.095055	-0.07	0.950	-21.33833	20.27967

cer producing PSA[33,34]. Bruner et al[35] showed that prostate cancer has familial inheritance. The incidence of prostate cancer is significantly higher in families with history of female breast cancer[36].

The pathogenesis, diagnosis and treatment of these two cancers are closely related to sex hormones and may be homologous. In this study, we selected 10 high quality studies involving 1569 subjects. The levels of serum tPSA and fPSA in breast cancer patients were significantly higher than those of benign breast mass patients or healthy control groups. Interestingly, PSA levels decreased significantly in patients after surgery, which indicated that tumor cells were producing PSA. These findings suggest the close relationship between prostate cancer and breast cancer. Our findings suggest that PSA, when used as a biomarker, could be invaluable for the early diagnosis of breast cancer. There are advantages for the endocrine treatment of prostate cancer, since hormone therapy of breast cancer has been shown to be invaluable. We aimed to meta-analyze the diagnostic efficacy of changes to TPSA and fPSA levels in serum from breast cancer patients and provide more reliable information derived from multiple reports. However, there are limitations of this meta-analysis: (1) the total cohort sizes were small. This meta-analysis selected both English and Chinese studies by searching relevant database, however it excluded studies published in other languages and sources. This may have resulted in selection and allocation bias. (2) There was publication bias: unpublished literature and undisclosed negative results failed to be included in this study, which influenced the authenticity and objectivity of the meta-analysis. (3) There may have been a high heterogeneity regarding diagnosis and evaluating the various parameters in the different clinics: different research methods and protocols may have affected and thus bias the statistical results.

Conclusions

This meta-analysis included 10 articles that satisfied the selection criteria. The studies included PSA serum levels from breast cancer patients, and determined whether PSA serum levels could be used to diagnose breast cancer. We demonstrated that PSA serum levels were a good indicator for the diagnosis of breast cancer. This meta-analysis needs further validation using a larger cohort from multi-center institutions.

Conflict of Interest:

None.

References

1) Senkus E, Kyriakides S, Penault-Llorca F, Poortmans P, Thompson A, Zackrisson S, Cardoso F, Group EGW. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24 Suppl 6: vi7-23.
2) Horii R, Honma N, Ogiya A, Kozuka Y, Yoshida K, Yoshida M, Horiguchi S, Ito Y, Mukai H. The Japanese breast cancer society clinical practice guidelines for pathological diagnosis of breast cancer, 2015 edition. Breast Cancer 2016; 23: 391-399.
3) Reding KW, Li CI, Weiss NS, Chen C, Carlson CS, Duggan D, Thummel KE, Daling JR, Malone KE. Genetic variation in the progesterone receptor and metabolism pathways and hormone therapy in relation to breast cancer risk. Am J Epidemiol 2009; 170: 1241-1249.
4) Gao X, Zacharek A, Salkowski A, Grignon DJ, Sakr W, Porter AT, Honn KV. Loss of heterozygosity of the BRCA1 and other loci on chromosome 17q in human prostate cancer. Cancer Res 1995; 55: 1002-1005.
5) Sigurdsson S, Thorlacius S, Tomasson J, Tryggvadottir L, Benediktsdottir K, Eyfjord JE, Jonsson E. BRCA2 mutation in Icelandic prostate cancer patients. J Mol Med (Berl) 1997; 75: 758-761.
6) Thorlacius S, Olafsdottir G, Tryggvadottir L, Neuhausen S, Jonasson JG, Tavtigian SV, Tulinius H, Ogmundsdottir HM, Eyfjord JE. A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. Nat Genet 1996; 13: 117-119.
7) Diamandis EP, Yu H. New biological functions of prostate-specific antigen? J Clin Endocrinol Metab 1995; 80: 1515-1517.
8) Borchert GH, Melegos DN, Tomlinson G, Giai M, Roagna R, Ponzone R, Sgro L, Diamandis EP. Molecular forms of prostate-specific antigen in the serum of women with benign and malignant breast diseases. Br J Cancer 1997; 76: 1087-1094.
9) von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007; 335: 806-808.
10) Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.
11) Razavi SH, Ghajarzadeh M, Abdollahi A, Shoar S, Omranipour R. Is serum prostate-specific antigen a diagnostic marker for benign and malignant breast tumors in women? Int J Prev Med 2015; 6: 15.

12) Luo Y, He X, Feng C. Study on early diagnostic value of combined detection of multinomial indexes in breast cancer. Lab Med Clin 2010; 07: 1088-1089.
13) Sun M, Xu Y, Tian J. The optimal cut-off point of PSA in diagnosis female patients with breast cancer by receive operating characteristic curve labeled immunoassays. Clin Med 2016; 23: 1303-1305.
14) Li F. Changes and significance on levels of serum PSA, CYFRA21-1, CA153 and CEA in breast cancer patients. Shandong Medical Journal 2012; 52: 54-56.
15) Black MH, Giai M, Ponzone R, Sismondi P, Yu H, Diamandis EP. Serum total and free prostate-specific antigen for breast cancer diagnosis in women. Clin Cancer Res 2000; 6: 467-473.
16) Li X. Application of serum prostate specific antigen in the diagnosis of breast cancer. Journal of Bengbu Medical College 2005; 30: 546-548.
17) Wang S, Lei M, Feng H. F/T ratio in breast cancer diagnosis and prognosis assessement of application. Medical Research & Education 2012.
18) Zeng X, Zhou H, Yu YK. Clinical value of ratio of f-PSA to t-PSA in the diagnosis of breast cancer. Journal of Regional Anatomy and Operative Surgery 2004.
19) Das S, Paul R, De U, Mukhopadhyay M. The lady with raised prostate specific antigen: do we need to worry? Asian Pac J Cancer Prev 2011; 12: 2051-2053.
20) Shiryazdi SM, Dehestani M, Forat Yazdi M, Soltani Gerdfaramarzi HR, Moghimi M. Can prostate specific antigen be used as new biomarker for early diagnosis of breast cancer? JCHR 2015; 4: 91-98.
21) Ye B, Liu G, Lu J. Low value of application on common serum tumor markers of breast cancer in early diagnosis. China Oncology 2009; 19: 807-808.
22) Lilja H, Oldbring J, Rannevik G, Laurell CB. Seminal vesicle-secreted proteins and their reactions during gelation and liquefaction of human semen. J Clin Invest 1987; 80: 281-285.
23) Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987; 317: 909-916.
24) Mannello F, Miragoli G, Bianchi G, Gazzanelli G. Prostate-specific antigen in ascitic fluid. Clin Chem 1997; 43: 1461-1462.
25) Melegos DN, Yu H, Allen LC, Diamandis EP. Prostate-specific antigen in amniotic fluid of normal and abnormal pregnancies. Clin Biochem 1996; 29: 555-562.
26) Diamandis EP, Yu H. Nonprostatic sources of prostate-specific antigen. Urol Clin North Am 1997; 24: 275-282.
27) Yu H, Diamandis EP, Sutherland DJ. Immunoreactive prostate-specific antigen levels in female and male breast tumors and its association with steroid hormone receptors and patient age. Clin Biochem 1994; 27: 75-79.
28) Riegman PH, Vlietstra RJ, Suurmeijer L, Cleutjens CB, Trapman J. Characterization of the human kallikrein locus. Genomics 1992; 14: 6-11.
29) Clements JA. The human kallikrein gene family: a diversity of expression and function. Mol Cell Endocrinol 1994; 99: C1-6.
30) Kumar A, Mikolajczyk SD, Goel AS, Millar LS, Saedi MS. Expression of pro form of prostate-specific antigen by mammalian cells and its conversion to mature, active form by human kallikrein 2. Cancer Res 1997; 57: 3111-3114.
31) Takayama TK, Fujikawa K, Davie EW. Characterization of the precursor of prostate-specific antigen. Activation by trypsin and by human glandular kallikrein. J Biol Chem 1997; 272: 21582-21588.
32) Diamandis EP. BRCA1 protein products: antibody specificity, functional motifs and secreted tumour suppressors. Nat Genet 1996; 13: 268.
33) Monne M, Croce CM, Yu H, Diamandis EP. Molecular characterization of prostate-specific antigen messenger RNA expressed in breast tumors. Cancer Res 1994; 54: 6344-6347.
34) Diamandis EP, Yu H, Sutherland DJ. Detection of prostate-specific antigen immunoreactivity in breast tumors. Breast Cancer Res Treat 1994; 32: 301-310.
35) Bruner DW, Moore D, Parlanti A, Dorgan J, Engstrom P. Relative risk of prostate cancer for men with affected relatives: systematic review and meta-analysis. Int J Cancer 2003; 107: 797-803.
36) Cerhan JR, Parker AS, Putnam SD, Chiu BC, Lynch CF, Cohen MB, Torner JC, Cantor KP. Family history and prostate cancer risk in a population-based cohort of Iowa men. Cancer Epidemiol Biomarkers Prev 1999; 8: 53-60.