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 fPSA 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. In Japan, the age-adjusted prevalence of breast cancer was 73.4/100 000 and mortality rate was 20.4/100 000. 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. Recent studies found that there is a genetic association between breast cancer and prostate cancer. Two large cohort studies found that the genetic link of breast cancer and prostate cancer was BRCA-2. 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). As early as 1997, Borchert et al. 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...
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. 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 I²-test prior to comprehensive analysis. If there was heterogeneity (p<0.05 or I²> 50%), then, the aggregate with random effects model was used, otherwise the fixed effect model was used.

**Results**

**Literature Retrieval Results**

115 articles were retrieved and, after selection using the inclusion and exclusion criteria, a total of 10 articles were selected (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 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, I²=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 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-
Table I. Characteristic of the included Studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of Publication</th>
<th>Number of Breast Cancer patients</th>
<th>Number of Benign Breast Tumor patients</th>
<th>Measurement Index</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Razavi et al11</td>
<td>2015</td>
<td>90</td>
<td>90</td>
<td>TPSA, fPSA</td>
<td>27</td>
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<tr>
<td>Luo et al12</td>
<td>2010</td>
<td>35</td>
<td>183</td>
<td>fPSA</td>
<td>23</td>
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<tr>
<td>Sun et al13</td>
<td>2016</td>
<td>61</td>
<td>108</td>
<td>TPSA</td>
<td>23</td>
</tr>
<tr>
<td>Li et al14</td>
<td>2012</td>
<td>205</td>
<td>100</td>
<td>TPSA</td>
<td>24</td>
</tr>
<tr>
<td>Black et al15</td>
<td>2000</td>
<td>118</td>
<td>46</td>
<td>TPSA, fPSA</td>
<td>25</td>
</tr>
<tr>
<td>Li et al16</td>
<td>2005</td>
<td>38</td>
<td>31</td>
<td>TPSA, fPSA</td>
<td>24</td>
</tr>
<tr>
<td>Wang et al17</td>
<td>2012</td>
<td>47</td>
<td>34</td>
<td>TPSA, fPSA</td>
<td>22</td>
</tr>
<tr>
<td>Zeng et al18</td>
<td>2003</td>
<td>26</td>
<td>67</td>
<td>TPSA, fPSA</td>
<td>22</td>
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<tr>
<td>Das et al19</td>
<td>2011</td>
<td>107</td>
<td>100</td>
<td>TPSA, fPSA</td>
<td>23</td>
</tr>
<tr>
<td>Shiryazdi et al20</td>
<td>2015</td>
<td>43</td>
<td>40</td>
<td>TPSA</td>
<td>25</td>
</tr>
</tbody>
</table>
Prostate specific antigen as a biomarker for breast cancer: a meta-analysis study

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.
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-
ty for diagnosis. In addition to clinical tests, using tumor markers is expensive\(^2\), 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\(^2\). 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 cancer.

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

<table>
<thead>
<tr>
<th></th>
<th>Coef.</th>
<th>Std.Err.</th>
<th>t</th>
<th>P&gt;t</th>
<th>[95% Conf. Interval]</th>
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</thead>
<tbody>
<tr>
<td>Bias</td>
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<td>100.5441</td>
<td>0.28</td>
<td>0.790</td>
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<tr>
<td>Intercept</td>
<td>-.5293273</td>
<td>8.095055</td>
<td>-0.07</td>
<td>0.950</td>
<td>-21.3383 20.27967</td>
</tr>
</tbody>
</table>
cer producing PSA. Bruner et al showed that prostate cancer has familial inheritance. The incidence of prostate cancer is significantly higher in families with history of female breast cancer.

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

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


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.


