

## Letter

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# Potential Epigenetic Biomarkers for Prostate Cancer Screening

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To the editor:

Chiam et al. [1] stated that prostate cancer (PCa) is a major global health problem that imposes a significant economic burden in nations with an aging population. The annual percentage change (APC) of the incidence of PCa in Korean men was 13.7% from 1999 to 2009, and APC of mortality rates was 17.5% from 1999 to 2002 [2]. The widespread use of prostate-specific antigen (PSA)-based screening testing (PSA-ST) leads to an increased incidence of PCa because it enables the earlier detection of occult or asymptomatic disease [3-5].

As PSA is not a specific marker of PCa [1], recommendations on PSA-ST for PCa vary in terms of the screening age and interval [6,7]. Of note, the 2012 U.S. Preventive Services Task Force guideline [8] recommended against routine screening for PCa, because the benefits of PSA-ST for PCa do not outweigh the harms.


The harms of PSA-ST can be summarized as overdiagnosis, unnecessary biopsies with potential associated adverse effects, anxiety, and excessive treatment [7,9,10]. As such, the most serious limitation of PSA-ST as a screening modality is the fact that PSA levels can be elevated in patients with benign prostatic hyperplasia or prostatitis, as well as in PCa patients [7,11]. This phenomenon may give rise to overdiagnosis, resulting in over-treatment [1,6,12,13]. In addition to this, PSA-ST has very poor sensitivity, specificity, and predictive values because there are no absolute cutoff PSA levels defining PCa [1,13]. Thus, Lee et al. [14] concluded that PSA-ST alone did not increase early-stage PCa detection or reduce mortality.

To overcome these limitations of PSA-ST, PSA velocity [15], testing for 4 prostate-specific kallikreins [3], the prostate health index test [16], the percentage of free PSA [17], and tests for

noncoding prostate-tissue-specific RNA [18] have been introduced. However, these PSA derivatives may be impractical or only helpful in specific situations [1,7]. Thus, novel biomarkers capable of replacing serum PSA for PCa screening must be investigated [19-22]. In addition, reliable and accurate biomarkers for discriminating between indolent and aggressive tumors at the early stage of PCa are needed [23].

As age, race, and environment are known to be the main risk factors for PCa, epigenetic studies investigating the carcinogenesis of PCa through gene-environment interactions have been conducted [1,24]. Current evidence suggests that epigenetic alterations of aberrant DNA methylation, histone modifications, and noncoding microRNA are associated with the carcinogenesis of PCa [25-28]. Thus, potential biomarkers related to a high frequency of epigenetic changes may improve the sensitivity and specificity of the diagnosis (including early detection) and prognosis of PCa [1,13,25,27,29].

Chiam et al. [1] tabulated the epigenetic biomarkers associated with the diagnosis, prognosis, and treatment response of PCa. Furthermore, Yegnasubramanian [13] suggested that methylation in the regulatory regions of *GSTP1*, *APC*, *PTGS2*, *RARB*, and *RASSF1A* may be epigenetic biomarkers for PCa screening. In particular, measurements of *GSTP1* promoter methylation in plasma, serum, whole blood, urine, ejaculate, or prostatic secretions may complement PSA-ST for PCa based on a meta-analysis of 22 studies [30]. However, all those studies were case-control studies with a small sample size. Thus, a population-based cohort study in asymptomatic men with a large sample size is needed to evaluate the effectiveness of *GSTP1* for the early detection of PCa and/or the identification of aggressive tumors.

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In conclusion, the controversies regarding PSA-ST have led to the need for a more accurate biomarker suitable for the early detection of PCa [31]. This unmet need could be satisfied by epigenetic biomarkers related to the pathogenesis of PCa [13,29].

However, potential epigenetic markers require further research to be validated for screening in diverse populations [25,32]. Further studies may lead to the development of epigenetic markers that could replace, rather than complement, PSA-ST due to advantages in sensitivity.

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