An inconvenient truth: at least three prostate-specific antigen-based screening cycles are needed to reduce subsequent prostate cancer incidence

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The pros and cons of using prostate-specific antigen (PSA) for prostate cancer (PC) screening have been debated in terms of mortality reduction versus overdiagnosis and overtreatment as well as the overall balance of quality-of-life effects and cost-effectiveness. Because PSA is not a PC-specific biomarker, the use of PSA as a biomarker for PC has several limitations. In addition, PSA levels are influenced by several factors, including age, acute prostatitis, ejaculation, catheterization, and certain medications. Furthermore, there is no precise value indicative of a lack of PC risk, and PSA levels cannot distinguish between indolent and aggressive disease, particularly at PSA levels below 20 ng/mL. In addition, approximately 15% men with serum PSA levels below 4 ng/mL are at risk for PC (1).

Several randomized trials evaluating the effect of PSA-based screening on mortality reduction have reported conflicting results. PSA screening for PC showed a significant reduction in the PC mortality rate by 21% in the 13-year follow-up of the European Randomized Study of Screening for Prostate Cancer (ERSPC) (2). However, the Prostate, Lung, Colorectal, and Ovarian trial (PLCO), conducted in the United States, showed no significant decrease in the mortality rate of PC by PSA screening (3). Some reports indicate the incompleteness of PLCO. Pinsky *et al.* surveyed 2,427 participants from the control arm of PLCO and suggested that the high proportion of previous PSA testing (46.6% in the 3 years prior to participation) in this group could be interpreted as "contamination" (4). Together, these findings prompted the United States Preventive Services Task Force to recommend against the use of PSA-based screening in 2012 (5). However, only PLCO showed a negative impact of PSA screening on PC mortality reduction. The randomized control trial in Gothenburg, Sweden, which provided approximately 60% of the ERSPC data, conducted PSA screenings every 2 years, resulting in a high PC mortality reduction of 44% (6). The effect of lowering PC mortality was also proven in a study in Tyrol, Austria, by practical examination of the validity of the screening (7). In that study, the actual mortality rate was decreased by 64% from the predicted mortality rate.

Although several randomized trials have been reported, optimal timing and number of screening rounds required remain unclear. To evaluate how frequently PSA based screening will reduce subsequent PC incidence, Pakarainen *et al.* analyzed the relationships between the number of PSA screenings undergone (number of negative PSA screenings or number of positive PSA screenings with negative prostate biopsy) and the incidence of PC as well as the incidence of high-grade cancer diagnosed after the last screening using data from the Finnish section of the European Organization for Research and Treatment of Cancer (EORTC) study. Of 29,298 men from the screening arm of the Finnish study, the largest domain in the EORTC study, participants were divided into four subgroups based on the number of screenings undergone (0–3 screenings at 4 year intervals, 7,607 of nonparticipants, 4,847 of participated once, 6,958 of twice, 9,886 of three times). To exclude screenings detecting cancer, follow-up for cancer incidence started at 12 months

after the last screening. Age-matched control participants in the Finnish study were selected from the control arm. The results of the study indicated that at least three PSA-based screening cycles are required to reduce subsequent PC incidence. In addition, the incidence of high Gleason grade cancers was not diminished after a single screening round, but was decreased after 2–3 rounds of screening. Pakarainen *et al.* suggested that the incidence was increased following a single screening round because a single screening reveals indolent cases from the prevalence pool, and only repeated screening will detect a substantial proportion of progressive cancers (8). If this is true, the first PSA screening may have increased the probability of overdiagnosis and overtreatment, followed by unnecessary cost and deterioration of QOL; however, compensatory mortality reduction was achieved after three screening rounds. Therefore, the benefit of PSA screening for mortality reduction is still unclear and might be limited using the current methodology in terms of quality-of-life effects and cost-effectiveness. There is an unmet need for a novel biomarker, which can distinguish between indolent and aggressive PC, and can be used in combination with the PSA test (9). Currently, two new tests designed to help determine the need for a prostate biopsy [prostate health index (phi) (10) and PC gene 3 (PCA3) (11)] have recently been approved by the United States Food and Drug Administration. In addition, a new approach to detect aberrant serum PSA glycosylation (S2,3PSA) was reported. The diagnostic accuracy of S2,3PSA was associated with AUC of 0.84, and the sensitivity and specificity of the assay was 95.0% and 72.0%, respectively, which is a significant increase compared with PSA or %fPSA (12). Although the study was small and preliminary, the results suggest that assays measuring cancer-associated glycan alterations in serum S2,3PSA might improve the accuracy of early PC detection and reduce unnecessary prostate biopsies. Although comparative studies evaluating these various biomarker assays are still needed, the use of novel biomarkers that can serve as alternatives to PSA appears to be a promising approach to improve risk assessment strategies and has the potential to improve the outcomes in patients with PC.

In this study, the number of participants who underwent PSA screenings in the control arm is unclear. This contamination may dilute the difference in PC mortality between two arms. Moreover, there are no data on how many participants among the patient undergoing PSA screenings underwent a needle biopsy. In terms of an excessive physical burden, the number of participants with positive PSA screening but negative prostate biopsy should be reported. Furthermore, if there were differences in PC treatment modalities between the two arms, this may cause a bias. Finally, it is important to know the cancer-specific mortality among the four subgroups based on the number of screening undergone. To verify the relationship between the number of screening rounds and PC mortality, further evaluations are necessary.

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Footnote

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