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COMMENTARY

Discoveries and application of prostate-specific antigen, and some proposals to optimize prostate cancer screening

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Abstract: The discoveries and application of prostate-specific antigen (PSA) have been much appreciated because PSA-based screening has saved millions of lives of prostate cancer (PCa) patients. Historically speaking, Flocks et al first identified antigenic properties in prostate tissue in 1960. Then, Barnes et al detected immunologic characteristics in prostatic fluid in 1963. Hara et al characterized γ-semino-protein in semen in 1966, and it has been proven to be identical to PSA. Subsequently, Ablin et al independently reported the presence of precipitation antigens in the prostate in 1970. Wang et al purified the PSA in 1979, and Kuriyama et al first applied an enzyme-linked immunosorbent assay for PSA in 1980. However, the positive predictive value with a cutoff figure of 4.0 ng/mL appeared substantially low (~30%). There are overdiagnoses and overtreatments for latent/low-risk PCa. Controversies exist in the PCa mortality-reducing effects of PSA screening between the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. For optimizing PCa screening, PSA-related items may require the following: 1) adjustment of the cutoff values according to age, as well as setting limits to age and screening intervals; 2) improving test performance using doubling time, density, and ratio of free: total PSA; and 3) fostering active surveillance for low-risk PCa with monitoring by PSA value. Other items needing consideration may include the following: 1) examinations of cell proliferation and cell cycle markers in biopsy specimens; 2) independent quantification of Gleason grading; 3) developing ethnicity-specific staging nomograms based on tumor stage, PSA value, and Gleason score; 4) delineation of the natural history; 5) revisiting the significance of the androgen/testosterone hypothesis; and 6) devoting special attention to individuals with a certain genetic predisposition. Finally, considering the uncertainty that exists in medicine, risk communication on PSA-based screening is indeed due.

Keywords: application, benefits and harm, discovery, optimization, PCa screening, PSA

Commentary

The discoveries and application of prostate-specific antigen (PSA) have been much welcomed because of the hundreds of thousands of prostate cancer (PCa) patients whose lives have been saved by PSA-based screening. However, the early PSA discoveries, in particular, have still not been fully acknowledged.[1] In 1960, Flocks et al[2] first identified antigenic properties in prostate tissue, while the immunologic characteristics in prostatic fluid were detected by Barnes et al[3] in 1963. In 1966, Hara et al[4] isolated and characterized γ-semino-protein in semen for judgment in forensic cases, and it has been proven to be identical to PSA. Subsequently, Ablin et al[5] in 1970 independently reported the presence of precipitation antigens in the prostate. Although these

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discoveries were not specifically related to PCa, the keen observations are valuable. On the basis of these findings and subsequent investigations, Wang et al,[6] from Chu's laboratory, purified the PSA in 1979, and Kuriyama et al[7] in 1980 first developed and applied a sensitive serum immunoassay in PSA testing.

Considering that PSA testing is required as part of a screening battery, PCa is now a disease of priority calling for early detection and treatments. The PSA test is safe and less expensive. However, the test performance of positive predictive value with a cutoff figure of 4.0 ng/mL, in particular, appeared rather low (~30%).[8] There are overdiagnoses (overexaminations and overdetections) and overtreatments for latent/low-risk PCa: that is, the ratio of benefits: harm is not necessarily high. In other words, there are substantial false positives, whereas a high prevalence of PCa is observed in hypogonadal men with PSA level of ≤4.0 ng/mL.[9] Controversies exist in the PCa mortality-reducing effects of PSA screening between the European Randomized Study of Screening for Prostate Cancer (ERSPC)[10] and the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial,[11] and in the interpretations between the Japanese Urological Association[12] and a research group functioning under the auspices of the Ministry of Health, Labour and Welfare (MHLW), Japan.[13] Therefore, PSA testing has not been listed as a population-based screening instrument by the MHLW.[14]

Therapeutic schemes of PCa are literally advancing day by day, while management of PSA-based screening still seems to be developing. Administering PSA testing as the core, collaborative efforts should be used to standardize PCa screening for tailor-made treatments.[15] PSA-related items and auxiliary biomarkers, such as in ongoing trials, may require the following: 1) adjustment of the cutoff values according to age, as well as setting limits to age and screening intervals; 2) improving test performance not only using doubling time (growth speed), density, and ratio of free: total PSA but also adopting validated assays for proenzyme PSA (pro-PSA), together with urinary markers including prostate cancer antigen 3 (PCA3); and 3) fostering active surveillance[16] for low-risk PCa with close monitoring by PSA value because radical therapies, instead of active surveillance, have sometimes been used for such cases. Other items needing consideration may include the following: 1) examinations of cell proliferation and cell cycle markers in biopsy specimens; 2) independent (or automated) quantification of Gleason grading, when distinguishing the score 3+4 from 4+3 for Gleason grade 7, as a typical instance, because the score is directly associated with decision making on treatment modalities; 3) developing ethnicity-specific staging nomograms[17] based on tumor stage, PSA value, and Gleason score; 4) delineation of the natural history of PCa having a wide spectrum of the grade of malignancy; 5) revisiting the significance of the androgen/testosterone hypothesis in the phase of tumor initiation or promotion/progression,[18] including levels of free and conjugated testosterone, as well as the ratio of testosterone/dehydroepiandrosterone (DHEA) or testosterone/estrogen; and 6) paying special attention to individuals with a PCa family history or genetic predisposition, including cancer-causing genes/single-nucleotide polymorphisms, tumor suppressor genes, or genetic polymorphisms associated with metabolisms of steroids and testosterone, alcohol, and vitamin D.

Uncertainty still exists in medicine and there are limits to human knowledge. Informed consent, informed choice, or risk communication (informed decision making) on PSA-based screening are indeed due, as observed in the recommendations recently released by the American Urological Association: "Offer PSA testing for detecting PCa only after engaging in shared decision making."[19] Collaborative attempts should also be made to optimize (ie, maximize pros and minimize cons) PCa screening and to elaborate upon best-available therapies not only for reducing PCa mortality, prolonging patients' healthy life expectancy, and enhancing quality of life but also for downsizing health care expenditures.

Disclosure

The authors report no conflicts of interest in this work.

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