EDITORIALS

Early Detection of Prostate Cancer — Time to Fish or Cut Bait

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Approaches to early detection of cancer often seem contentious, but the big-picture view is actually one of remarkable consensus. All major guideline groups recommend the Papanicolaou smear, mammography, colonoscopy, and — in older adults with a substantial history of smoking — lung imaging; none recommend CA-125 for early detection of ovarian cancer or ultrasonography of the neck for thyroid cancer screening. These recommendations are largely mirrored in the services provided by national cancer screening programs, such as that of the U.K. National Health Service.

Prostate-specific antigen (PSA) screening for prostate cancer remains the great exception. Since first becoming available nearly four decades ago, PSA testing has been mired in controversy. With minor exceptions, there are no national PSA screening programs, yet PSA testing has been widely implemented in clinical practice. Most older men in high-income countries have had a PSA test, and in some countries, the number of PSA tests ordered each year far outweighs the number that would be given as a result of population-based screening.[1]

For many years, the controversy about PSA screening was whether it had any benefits at all. The hypothesis was reasonable: PSA levels might only indicate the sort of prostate cancers that grew so slowly that they would never threaten a patient's health but would miss the more rapidly developing tumors that would lead to cancer death.

The European Randomized Trial of Screening for Prostate Cancer (ERSPC) is one of the largest and most mature studies to evaluate the question of whether PSA screening results in lower mortality. In this issue of the *Journal*, Roobol et al.[2] report the results of long-term follow-up of the ERSPC — at a median follow-up of 23 years, PSA screening had led to a 13% relative reduction in the risk of death from prostate cancer. Such an effect size is broadly in line with those for breast cancer screening (relative risk reduction of 15 to 20%) and colon cancer screening (relative risk reduction of 10 to 25%, depending on screening method). The only serious threat to the validity of the ERSPC findings that has been raised in the literature is that treatment differed between the screening and control groups. This difference has been shown to be a result of stage shift and could not explain the observed between-group differences in mortality.[3] Taking into consideration the results of the other two major randomized trials of PSA screening (the Cluster Randomized Trial of PSA Testing for Prostate Cancer[4] in the United Kingdom and the Prostate, Lung, Colorectal and Ovarian[5] trial in the United States) as well as population trends (prostate cancer mortality in the United States has fallen by approximately one half since the introduction of PSA screening), there can be little doubt that PSA screening reduces prostate cancer mortality.

However, the critical question remains whether the benefit of a reduced mortality outweighs the harms of PSA screening, namely, overdiagnoses of prostate cancers that never would have caused symptoms and consequent overtreatment with the attendant risk of long-term urinary, sexual, and bowel dysfunction. The problem with using the ERSPC to address the question of net benefit is one that is inevitable to the study of early detection in cancer: by the time long-term results are available, diagnostic and treatment methods have evolved, leaving us with an effect estimate for an outdated approach.

The benefits of PSA screening are probably underestimated in the ERSPC because the testing regimen that was evaluated included starting PSA screening at a random point between 55 and 69 years of age and stopping at age 70. In contrast, international guidelines call for screening to start at 50 years of age or earlier, with the stopping point determined by the patient's health and PSA level.[6] The age at the first PSA screening has a particularly strong influence on the effectiveness of screening; initiation of testing at 50 years of age has resulted in risk reductions that are more than double those among men who start testing at age 60, which is the median age of the first PSA screening test in the ERSPC.[7] The ERSPC results also underestimate screening benefits because the treatments given to participants were far from being the current state of art, with radiotherapy doses much lower and surgery performed by low-volume surgeons.

Moreover, the harms of PSA screening are probably overestimated in the ERSPC findings, because nearly all men with elevated PSA underwent biopsy and nearly all men who subsequently received a diagnosis received curative treatment. To reduce the risk of overdiagnosis, current guidelines recommend biopsy only in men with a positive result on a secondary test, whether magnetic resonance imaging or any one of an array of molecular markers,[8] an approach that has been shown to be of value in randomized trials.[9] To reduce overtreatment, current guidelines recommend conservative management for patients with low-risk disease.[6,8]

Whether PSA screening does more good than harm depends on how it is performed. Of concern, current PSA screening policies that encourage men to make their own decisions about PSA testing exacerbate harms and reduce benefits. Rates of PSA testing are low among young men in their 50s and high among men over 70 years of age, the group most likely to be overdiagnosed and least likely to benefit from screening.[1]

The ERSPC was a monumental effort, a 30-year trial that involved hundreds of researchers and more than 150,000 patients. To best use the results of that research to improve the lives of our patients, we have to do better than abdicate the responsibility for PSA decision making to individual patients and instead formulate policies on PSA screening that maximize benefits and minimize harms.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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EGFR-Mutated Lung Cancer — Letting the Butterfly Out of the Cocoon

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Somatic mutations in *EGFR* (epidermal growth factor receptor) account for approximately one third of lung cancer cases worldwide.[1] A point mutation in exon 21 (L858R) or a short deletion in exon 19 are the most common *EGFR* variants. Tyrosine kinase inhibitors (TKIs) are the cornerstone of