Prostate Cancer — Uncertainty and a Way Forward
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Three important studies published in the *Journal* during the past 3 years have addressed key issues related to prostate cancer. Two articles described large trials of prostate-specific antigen (PSA) screening and reached opposite conclusions regarding the impact of screening on the risk of death from prostate cancer.¹² In this issue of the *Journal*, Wilt and colleagues³ report the results of a study that asked whether radical prostatectomy, as compared with observation, improved survival among men with prostate cancer. Collectively, these three studies suggest that a national focus on PSA screening and treatment for prostate cancer may have a marginal benefit on the lifespan of men but at a considerable cost. Nonetheless, there was a 44% reduction in prostate-cancer mortality between 1993 and 2009.⁴ How can this be, if screening and treatment do not reduce deaths from prostate cancer? One explanation could be the flaws of the studies themselves. In the U.S. screening trial,¹ more than 50% of the men in the control group underwent PSA testing, which blunted the effect of screening. The use of a PSA cutoff value of 4.0 ng per milliliter in the two large screening studies probably reduced the chance that some cancers could have been cured.¹²,⁵

The original design of the study by Wilt and colleagues included a challenging randomization of 2000 patients to surgery or observation; the authors should be congratulated for their foresight with regard to a question that remains important today. Unfortunately, this goal could not be achieved, and the design was modified to justify a randomization goal of 740 patients. Median survival was assumed to be 15 years in the original study design and 10 years in the updated design. If we take the median survival of 12 years in the study's observation group and assume 7 years for enrollment and 8 years of follow-up, as specified in the study report, the sample should be 1200 patients in order to detect a 25% relative reduction in mortality with 90% power and a two-sided alpha level of 0.05. With an actual enrollment of 731 patients, the study was thus underpowered to detect this relatively large clinical effect. The wide 95% confidence interval around the hazard ratio for death in the treatment group illustrates this point. A relative increase of 8% to a relative reduction of 29% in the risk of death in the prostatectomy group, as compared with the observation group, cannot be excluded with 95% confidence. Also, only 15% of the deaths were attributed to prostate cancer or its treatment. Although overall mortality is an appealing end point, in this context, the majority of end points would be noninformative for the comparison of interest. The expectation of a 25% relative reduction in mortality when 85% of the events are noninformative implies an enormous treatment effect with respect to the informative end points. In addition, the finding that one fifth of patients did not adhere to the assigned treatment further reduces the ability to discern a treatment effect. Despite these limitations, a trend toward a reduction in mortality was seen among men with high-risk cancers who were undergoing radical prostatectomy.

The U.S. demographic characteristics are sobering: an aging population will be at increasing risk for death from prostate cancer. What is a rational approach to control this disease? The most efficient solution will probably include biopsy only for men with lethal cancer, treatment focused on this type of cancer, and individualized treatment approaches.

The Early Detection Research Network of the
National Cancer Institute and other groups are conducting studies designed to preferentially detect high-grade (often lethal) cancer, using either biomarker combinations or novel biomarkers such as PCA3 (prostate cancer gene 3).\(^6,7\) These are the first steps toward the goal of performing biopsy only in men with lethal cancer.

Subset analyses in the study reported by Wilt and colleagues showed no benefit of radical prostatectomy for men with lower-risk disease. This finding is consistent with the results of a study of active surveillance in men with localized prostate cancer, in which low-risk tumors were monitored and treatment was given only if a high-risk tumor developed.\(^8\) The 99.7% and 97.2% cancer-specific survival rates for those men at 5 and 10 years, respectively, strongly support this approach, which should be offered to men with low-risk cancer. On the other hand, high-grade, aggressive prostate cancers usually have a lethal course if left untreated. Those of us who treat this disease are heartened to see men we treated years or decades ago for aggressive, high-grade cancer who remain cancer-free today. It is these men who are at greatest risk for death from cancer and who are most likely to benefit from therapy but whom we must treat effectively. Effective treatments often require multiple therapeutic approaches; for example, mortality is reduced among men with high-risk tumors in whom radiation therapy and surgery are augmented by androgen deprivation.\(^9,10\)

Prostate cancer is not a monolithic cancer but a spectrum of disease. The screening, detection, and treatment we provide must focus on cancers that matter, and future clinical trials must do so as well.

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

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**The Search for Genetic Links in ANCA-Associated Vasculitis and Its Variants**

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Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis encompasses three distinct yet overlapping syndromes: granulomatosis with polyangiitis (formerly Wegener’s granulomatosis), microscopic polyangiitis, and the Churg–Strauss syndrome. These vasculitides are lumped together, not only because of their clinical and histopathologic similarities but also because of their common serologic marker, ANCA, which may contribute importantly to the pathogenesis of vascular inflammation. ANCA encompasses two major specificities: proteinase 3, more commonly encountered in the context of granulomatosis with polyangiitis, and myeloperoxidase, more frequently occurring in association with microscopic polyangiitis and the Churg–Strauss syndrome.

The pathogenesis of ANCA-associated vasculitis remains incompletely understood. Environmental, autoimmune, and genetic factors are probably relevant. Autoimmunity is supported...