Also, quality control measures were in place for the cytology and histopathological analysis to ensure optimum results. Care was taken before designing the study to calculate the sample size to give a power of 80% to detect a 50% decline in cumulative death rates due to cervical cancer. Also, allowance was made for loss to follow up.

This study has major implications for countries such as India where resources are scarce and there is a major difficulty in ensuring repeated screening at regular intervals, so it is important to chalk out alternative low-cost and effective strategies. VIA performed by health workers is the least expensive of all screening options. This study did not find a reduction in the rate of cervical cancer with VIA, although a previous randomized trial from southern India had found a 25% reduction in the incidence of cervical cancer and a 35% reduction in mortality.[7] VIA is an operator-dependent method with high inter-observer variation, which requires proper quality control and training-assessment protocols. HPV testing has emerged as a superior test with greater sensitivity, accuracy and objectivity. Presently, the drawback is that the hc2 method is very expensive. However, a rapid affordable test is expected to be available by 2011.[8,9] Thus, implementation of a nationwide programme of once-in-a-lifetime HPV testing at 40 years of age holds promise for reducing the burden of cervical cancer. An appropriate protocol for management of HPV-positive women must be developed. In areas with very high prevalence, colposcopy of all patients may not be cost-effective or feasible. VIA may be used to triage patients. In some regions, screen-and-treat protocols using cryotherapy for HPV-positive women (>30 years of age) without clinical evidence of invasive cancer may minimize cost and loss to follow up, especially if there are no facilities for colposcopy and histopathological analysis.[10] Proper implementation of this strategy in developing countries could save the lives of countless women in the years to come.

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Screening for cancer of the prostate: Do we have an answer?

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Center, New York; Oncology Center Antwerp, Antwerp, Belgium; Finnish Cancer Registry, Helsinki; Department of Urology, Centre Hospitalier Regional Universitaire, Lille, France; Department of Urology, Clinique de Beau Soleil, Montpellier, France; and the Cancer Screening Evaluation Unit, Surrey, United Kingdom.) Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;**360:**1320–8.

SUMMARY

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer screening trial is a randomized controlled trial (RCT) that has been ongoing at 10 study centres in the USA since 1993. In this study, 76 693 participants (between 55 and 74 years of age) received either annual screening (38 343 subjects) or usual care as the control group (38 350 subjects). Individual randomization was performed within blocks stratified according to the centre and age. Prostate-cancer specific mortality was the primary end-point. In addition, cancer incidence, staging and survival were monitored as secondary end-points.

Screening group: Subjects in this group were offered annual prostate-specific antigen (PSA) testing for 6 years and annual digital rectal examination (DRE) for 4 years. A serum PSA level of >4 ng/ml was considered abnormal. Men with positive results of screening tests (i.e. PSA and/or DRE) were advised to seek further evaluation. The rate of compliance with screening (calculated as the number of subjects who were screened divided by the number of those who were expected to be screened) was 85% for PSA and 86% for DRE.

Control group: The 'usual care' received by the control group also included screening, thereby resulting in the observation of PSA testing in the control group. The rate of PSA testing observed in the control group was 40% in the first year and it increased to 52% in the sixth year. The rate of screening by DRE in this group ranged from 41% to 46%.

Results: At 7 years, screening was associated with a relative increase of 22% in the rate of diagnosis of prostate cancer as compared with the control group even though there was more-than-expected screening in the control group. The same trend continued at 10 years of follow up. The large majority of prostate cancers were stage II at diagnosis (95.5% in the screening and 93.8% in the control group) and approximately 60% had a Gleason score of ≤6. Overall, the number of subjects with advanced (stages III or IV) tumours was similar in the two groups (122 in the screening *v.* 135 in the control group), though the number of subjects with a Gleason score of 8–10 was higher in the control group (341 subjects in the control *v.* 289 in the screening group). The treatment distribution was similar in the two groups within each tumour stage. There was no reduction in prostate-cancer mortality during the first 7 years of the trial (rate ratio: 1.13), with similar results through 10 years. There was a little difference between the two groups in terms of the proportion of deaths according to tumour stage.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) was started in the early 1990s in 7 European countries. A total of 182 160 men (between 50 and 74 years of age) were randomized to either the screening (offered PSA at an average of once every 4 years) or the control groups (no PSA). The predefined core age group for this study included 162 243 men between 55 and 69 years of age. Of these, 72 952 were assigned to the screening group and 89 435 to the control group. Prostate-cancer specific mortality was the primary end-point.

Screening group: The PSA screening interval at 6 of the 7 centres (87% of subjects) was 4 years. Most centres used a PSA cut-off value of 3 ng/ml as an indication for a biopsy. In total, 82.2% of the men in this group were screened at least once. An average of 2.1 PSA-based tests per subject was performed; 16.2% (range 11.1%–22.3%) of all tests were positive, 85.8% of the subjects complied with the biopsy recommendation.

Result: After a median follow up of 9 years, the cumulative incidence of prostate cancer was 8.2% in the screening group and 4.8% in the control group. The additional prostate cancer diagnosed by screening resulted in an increase in cumulative incidence of 34 per 1000 men as compared with the control group. In those who developed cancer, a greater proportion of men had a Gleason score of ≥7 in the control group (45.2%) compared with the screening group (27.8%). A significant absolute reduction of 0.71 prostate cancer deaths per 1000 men was noted with intention-to-screen analysis of the data. This corresponded to a relative reduction of 20% in the rate of death from prostate cancer in the core age group (i.e. 55–69 years).

COMMENT

Two major studies from Europe and the USA have flared the controversy regarding benefit and cost-effectiveness of widespread screening for prostate cancer. Even 2 decades after its introduction, PSA screening for prostate cancer remains controversial as its role continues to evolve. Most of the recommendations for PSA screening are based on population-based observational studies, which have reported conflicting findings.[1] The above two RCTs (i.e. PLCO and ERSPC trials) were conducted to clarify the impact of population-based screening on prostate cancer mortality and assist in making decisions about the benefits and limitations of PSA screening.

In the USA, the PLCO trial found no mortality benefit for PSA screening after 7–10 years, whereas in Europe, the ERSPC trial reported a 20% mortality benefit after 10 years. There is a concern that the mortality results from these two studies are being interpreted prematurely. Considering the slow growth of prostate cancer, the follow up of 7–10 years is too short to know exactly what effect screening may ultimately have. In the ERSPC trial, the mortality curve did not begin to diverge until 7–8 years. Thus, results from a further follow up extending up to 13–15 years should provide more information.

One of the factors that may have affected the difference in the incidence of prostate cancer diagnosed in the two trials and the mortality benefit of screening is the high cross-contamination in the control cohort in PLCO trial (up to 50% men in the control arm received PSA testing). Not only the subjects in the control arm were allowed to have one screening within 3 years before enrolment, but also, many of these men might have received PSA screening without their knowledge during routine physical examination.[2] By contrast, in the European trial, fewer men in the control arm seem to have received PSA testing.

In addition, the European trial used a lower cut-off for a positive PSA test (i.e. 3 ng/ml) compared with the PLCO trial (4 ng/ml), resulting in increased sensitivity but reduced specificity. This difference also helps account for the discrepancy between the two trials. However, lower cut-off values also probably lead to over-detection, over-treatment and impact quality-of-life issues.

These studies have vindicated at least one of the practice of 'Not screening men with a short life expectancy of <10 years'. The PLCO trial shows no mortality benefits at 7–10 years while in the ERSPC trial, the mortality curve did not begin to diverge until 7–8 years.

Regarding the utility of screening in a younger population, the ERSPC trial has (with a lower contamination of control cohort) shown a relative reduction of 20% in death from prostate cancer in men 55–69 years of age at entry into the study. Adjusting for non-compliance, a decrease of 27% in the rate of death from cancer was expected in the ERSPC trial. The difference observed

in mortality benefit of PSA screening in the two trials were probably the result of difference in the baseline exposure rate of PSA screening in the two populations in which the trials were conducted. Owing to the high ongoing level of PSA screening in the USA[3] (PLCO trial) and the resulting cross-over contamination of the control cohort, the PLCO trial may have lost its original power to detect the benefit of annual screening versus no screening. In view of its shorter follow up and above methodological issues, the investigators of the US study decided to continue the trial till everyone is followed for a minimum of 13 years.[4]

Although both the above studies could not conclusively establish the benefit of PSA screening on the prostate cancer-specific mortality, it is important to note that the most recent reliable research on screening for prostate cancer, excluding RCTs, also revealed a possible reduction in mortality.[5,6] Furthermore, a recent RCT demonstrated that the incidence of advanced prostate cancer decreased about 50% in the screening arm compared with the control arm over 10 years.[7] Thus, the system of PSA screening should not be an 'all or none phenomenon' but the aim should be to establish an optimal screening system (utilizing PSA and other biomarkers), which minimizes over-detection and over-treatment of indolent cancers and maximizes the decrease in mortality rate and development of metastatic prostate cancer. More insight into the role of PSA is expected from 13–15-year follow up in both PLCO and ERSPC trials.

Therefore, it is important to look at this debate from a scientific perspective and identify future directions of research. The current challenges are as follows:

Current inability to differentiate between indolent versus aggressive cancer

The key issue that prevents planning of optimal treatment is related to our own inability to differentiate toothless tigers (indolent cancer) from potential killers (aggressive cancers). In 2009, we often see patients who were considered to have indolent prostate cancers but when operated have significant and sometimes incurable cancers. About 25%–40% of men with presumed low-risk prostate cancer at needle biopsy, as defined by Gleason score of $\leq$6, turn out to have more aggressive features at final pathology when the prostate is removed and comprehensively evaluated.[8–11] This phenomenon, referred to as Gleason sum upgrading and pathological upstaging, arises because of several limitations associated with current needle biopsy protocols such as insufficient tissue for accurate pathological assessment of cancer aggressiveness; inter-observer variability between pathologists; and microscopic extension of cancer outside the prostate not detected on needle biopsy. Having adverse features on the final pathology report is associated with a higher risk of cancer recurrence and progression.[8,12]

As such, a considerable number of men are being advised to consider watchful waiting when they actually harbor more aggressive cancer *in situ* based on inadequate appreciation of the true cancer biology. While we continue our debate on planning better treatment options, we must focus on tools for more accurate imaging and staging for precise identification of prostate cancers. Better imaging, real-time tissue characterization and molecular markers of aggression will help us in differentiating aggressive from indolent cancers. Several research projects are currently under way.

Does aggressive treatment prolong life?

While both radiation and surgery have side-effects, in appropriate cases they save life. There is good evidence that aggressive treatment gives superior long-term survival than watchful waiting for patients with early prostate cancer. The large Scandinavian randomized study by Bill-Axelson *et al.*, published in the *New England Journal of Medicine* in 2005, and more recently updated in the *Journal of National Cancer Institute* in 2008, showed that radical prostatectomy significantly reduced death from prostate cancer (10% *v.* 15%, p=0.01) and the risk of distant metastases (15.2% *v.* 25.4%) at 10 years of follow up compared with watchful waiting.[13,14] Similar findings have been published using large retrospective cohorts based on propensity modelling.[15,16]

Several large retrospective studies[15,17,18] have also reported that definitive treatment with either radical prostatectomy, external beam radiation or interstitial radiation therapy significantly reduce the risk of PSA progression in patients with intermediate- to high-risk prostate cancer, the latter being a harbinger of eventual clinical disease progression and metastatic disease.

What happens if we deny or delay the aggressive treatment in non-indolent cancers?

Delaying surgery for aggressive prostate cancer potentially results in worse functional outcomes and complications. Recent single- and multi-institutional studies have reported good results with active surveillance as a safe treatment strategy for men with presumed low risk prostate cancer, and associated with low risk of systemic progression.[19,20] However, surgeons when faced with operating on patients with more aggressive cancers, will invariably adopt a more cautious approach to nerve-sparing during radical prostatectomy, excising more of the tissue around the gland to minimize the chance of leaving viable cancer behind. In our personal observations, patients who undergo multiple biopsies have significant changes in peri-prostatic tissues including nerves and veins. The surgical planes are more adherent and nerve preservation becomes more difficult. As a result, more of the nerves responsible for erection and urinary control will invariably be sacrificed, resulting in poorer continence and sexual function outcomes after surgery. These complications, and the secondary therapies required to redress them, place an onerous financial burden on the national healthcare system and considerable psychological distress to individual patients and their partners.[21,22]

Given the ubiquity of this disease spectre, we desperately need better staging, imaging and biomarkers and well-designed randomized trials comparing various treatments for early prostate cancer to shed much-needed light on this current 'black box'. Meanwhile, we as physicians need to involve patients in shared decision-making and highlight current limitations of staging and provide them with decision tools and encourage them to participate in clinical trials to further elucidate the risk and benefits of various approaches.

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