In the 1990s, several studies were published showing that serum prostate specific antigen (PSA) aided in the diagnosis of localized prostate cancer (1,2). Widespread screening was adopted quickly in the United States, where it is dogma that early detection and aggressive treatment saves lives.

This bias toward screening would delay and hinder study to determine whether screening truly saves lives. It would be more than 20 years before the results of well-designed prospective randomized studies would be published assessing the effectiveness of PSA screening—notably, the Prostate, Lung, Colon and Ovarian Cancer Screening Trial (PLCO)(3,4), which suggested that screening does not reduce mortality at 13 years median follow-up, and the European Randomized Study of Prostate Cancer (ERSPC)(5,6) study and Goteborg (7) trial, which suggested that
screening does save lives after 11 and 14 years median follow-up, respectively.

In this issue of the Journal, Haines and Gabor Miklos (8) provide some much-needed critical examination of these trials. Biases are preventing us from determining which finding is correct. No clinical study is perfect. The scientific process is at its best when there is publication of studies and thorough discussion in the literature. When proper analysis of a study defines its limitations, it actually increases the value of the study. Careful examination of a study and its results leads to a better understanding of the truth and, often, defines additional important questions.

Many show bias in their interpretation of these trials. Those who had faith in the value of screening were quick to point out the weaknesses of the PLCO and claim that the ERSPC and Goteborg trial justified screening. Also, the ERSPC is commonly referred to as a trial that showed that screening saves lives. In truth, it is a pooled analysis of seven clinical trials from seven countries. Each trial has different inclusion criteria, different screening schedules, and different PSA cutoffs; some have different randomization schema. When presented in meta-analysis format, five of the seven clinical trials do not show a statistically significant benefit to screening at the time of analysis. The ERSPC finding of a 20% decrease in relative risk is driven by substantial benefits found in the Dutch and Swedish trials (9). Also, 60% of men in the Goteborg trial were included in the Swedish component of ERSPC (7). Goteborg might be considered a prolonged follow-up of a subset of ERSPC.

The randomization methods of some of the European trials may be biased in favor of a finding that screening is beneficial. This phenomenon was first described in analysis of some colorectal screening trials. Studies in which the control group did not know they were in a trial tend to demonstrate a greater benefit to the intervention compared with trials in which patients were enrolled and randomized to a screening or control arm (10).

The ideal prospective screening trial is a study of screening and effective treatment vs no screening and effective treatment if diagnosed. Some of the European trials may be studies of screening and one type of prostate cancer treatment vs no screening and a different type of treatment if cancer is diagnosed. Men in the European intervention groups are perhaps more likely treated by expert physicians running the trial, and those diagnosed in the control group are perhaps more likely to receive care common to the community. Evidence of this is the imbalance in type of treatment received, as discussed by Haines and Gabor (8).

Is it possible that screening and treatment did not lower risk of death in the intervention arms of the European trials but treatment in the control arms increased risk of death attributed to prostate cancer? The realization that men in the control groups with high-risk localized disease were twice as likely to receive hormonal therapy compared with men in the control groups is concerning (29.5% vs 14.7%) (11).

Could the excess use in hormonal therapy in the control group have contributed to a number of deaths attributed to prostate cancer? For now it can only be presented as a hypothesis that merits further consideration. A small negative effect of androgen deprivation therapy (ADT) could be powerful. ERSPC was a study of 182,160 men. Haines and Gabor (8) point out ERSPC had a difference of 158 men in the high-risk groups and only 11 deaths attributed to prostate cancer in the control group would have negated the apparent improvement in prostate cancer mortality.

Like PSA screening, ADT with gonadotrophin-releasing hormone analogs and oral antiandrogens was a promising medical intervention developed in the 1980s. Because of a bias toward newer therapies, there was early widespread uptake in Europe and the United States without full assessment of its benefits and risks. By 1999, more than half of all American patients with prostate cancer were being treated with ADT within 1 year of diagnosis. One pattern-of-care study suggested that nearly half of all American men treated with gonadotrophin-releasing hormone agonists were receiving them for inappropriate reasons (12).

If ADT does increase risk of cardiovascular and thrombotic events, it is an amazing treatment bias in these screening studies. It is also ironic that overuse of ADT in the United States and Europe may account for some of the decline in prostate cancer death rates over the past 20 years in a very unfortunate way (13). Early deaths due to ADT-induced cardiovascular and thrombotic disease would prevent later deaths actually caused by prostate cancer.

In truth, the evidence of harm from hormonal therapies is mixed. A number of retrospective studies have demonstrated that hormonal therapy for prostate cancer increases surrogate markers for cardiovascular disease and diabetes (14). Several retrospective studies suggest increased risk of death from cardiovascular disease (15–20). Some studies show increased risk of thromboembolic events (21, 22), as does one prospective cohort study (23). Increased risk of death from cardiovascular disease is not seen in major prospective randomized trials using short-term hormonal therapy or hormonal therapy with radiation. Indeed, a meta-analysis that incorporated data from eight prospective randomized trials showed that the incidence of cardiovascular death was not substantially different in those treated with ADT compared with placebo (24).

A handicap in analyses of screening as well as ADT studies is the fact that cause-of-death analyses are imprecise and vary by country and even within country over time. Indeed, it has been suggested that changes in the interpretation of the cause of death on death certificates may have caused some of the decline in mortality attributed to prostate cancer seen over the past two decades in the United States and Europe (13,25).

The controversies in prostate cancer screening and treatment will only be further settled if these large trials are rigorously analyzed by an objective panel of experts with access to all the data. This may be the most appropriate way to deal with bias.

Until then, a few things are true. The harms of screening, such as overdiagnosis and the risk of overtreatment, have been consistently demonstrated in all screening trials to date. Benefits of screening have only been seen in the studies done in Sweden and the Netherlands. Most respected professional organizations have appropriately warned against mass screening and incorporated recommendations for informed decision-making regarding the risks and benefits of screening within the physician–patient relationship. There are clear benefits to ADT when used appropriately, even though the risks are incompletely understood. Therefore, the potential for harm from ADT should be balanced against the potential benefits (26).
References


Note
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From Papanicolaou to Papillomaviruses: Evolving Challenges in Cervical Cancer Screening in the Era of Human Papillomavirus Vaccination

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February 2012 marked the 50th anniversary of the death of George Papanicolaou, the inventor of the Pap test for cervical cancer screening. Pap test screening has contributed to sharp reductions in cervical cancer incidence and mortality throughout the developed world (1-5). Despite the success of the Pap test, recognition that it suffers from inadequate single-test sensitivity and frequent