Challenging the Conventional Wisdom on Colorectal and Prostate Cancer Screening

Kenneth W. Lin, MD
Assistant Professor of Clinical Family Medicine
Georgetown University School of Medicine

ABSTRACT

In the U.S., men over 50 years of age are often encouraged to obtain screening tests for colorectal and prostate cancer in order to improve future health outcomes. The evidence supporting the effectiveness of screening tests for each of these cancers differs, however, as does the magnitude of potential harm from each test. This article reviews the implications for clinical practice of both the U.S. Preventive Services Task Force recommendations, as well as recent studies of the effectiveness of colorectal and prostate cancer screening. It highlights specific situations in which "conventional wisdom" about screening tests has been based on a misunderstanding of the scientific evidence.

INTRODUCTION

The recent emphasis of state and national health reform initiatives for disease prevention has cast a spotlight on screening tests for cancer. Colorectal and prostate cancers lead to more than 80,000 premature deaths each year, and screening tests for these cancers have the potential to prevent considerable morbidity and mortality. Unfortunately, there remains a great deal of misunderstanding among physicians and patients about which screening tests have proven to be effective in clinical studies, and how current tests compare in effectiveness and potential for harm. The most authoritative evidence-based recommendations about cancer screening are made by the U.S. Preventive Services Task Force (USPSTF), an independent panel of experts in primary care and preventive medicine. The USPSTF last updated its recommendations on screening for colorectal and prostate cancer in 2008, and new evidence has become available since then.

THE BURDEN OF COLORECTAL CANCER

In 2005, more than 145,000 new cases of colorectal cancer were diagnosed in the U.S., and 62% had already spread beyond the colon. Each year 57,000 adults in the U.S. die of colorectal cancer. African American adults have disproportionately high occurrence and mortality rates from colorectal cancer, though it is not clear how much of this racial disparity is due to biology versus disparities in health care access and utilization.[1] Since only 1 in 5 persons who will develop colorectal cancer can be identified through family history, it is an optimal disease for routine screening in primary care populations. In 2008, the USPSTF recommended that average-risk adults aged 50 to 75 years undergo routine screening with fecal occult blood testing (FOBT), flexible sigmoidoscopy, or colonoscopy.[2] (They acknowledge that the risks and benefits of these methods vary.) The USPSTF found insufficient evidence to assess the balance of benefits and harms of newer screening technologies such as CT colonography or fecal DNA testing.

THE CONVENTIONAL WISDOM: COLLECTING A FECAL OCCULT BLOOD SAMPLE FOR SCREENING DURING THE DIGITAL RECTAL EXAMINATION IS "BETTER THAN NOTHING AT ALL;" SCIENTIFIC EVIDENCE SHOWS: IT'S NOT

The recommended protocol for fecal occult blood testing is collection by the patient of a total of 6 stool samples obtained at home on 3 different occasions. The USPSTF does not endorse screening a single fecal sample obtained in the office during a digital rectal examination. Primary care physicians often perform this test as part of a comprehensive physical examination because they believe that doing so is "better than nothing at all."

A national survey conducted from 2006–7 found that 53% of primary care physicians perform in-office tests in addition to recommending home testing, while another 25% perform *only* in-office tests for colorectal cancer screening.[3] However, a 2005 study in the Annals of Internal Medicine found that testing a single fecal sample obtained in the office missed more than 95% of colorectal cancers diagnosed with a subsequent colonoscopy, producing a negative predictive value for the in-office test that was almost identical to not having performed the test.[4] In other words, this test was not better than nothing at all,

since many patients with a "negative" test feel falsely reassured and do not think it necessary to undergo effective screening tests.

THE CONVENTIONAL WISDOM: COLONOSCOPY IS THE GOLD STANDARD FOR COLORECTAL CANCER SCREENING; SCIENTIFIC EVIDENCE SHOWS: FECAL OCCULT BLOOD TESTING AND FLEXIBLE SIGMOIDOSCOPY HAVE COMPARABLE BENEFITS AND FEWER RISKS

Over the past decade, there has been a remarkable shift in the nature of recommended colorectal cancer screening tests by primary care physicians. In a recent survey, 95% of physicians reported recommending colonoscopy, 80% recommended FOBT, and only 26% recommended flexible sigmoidoscopy.[5] Many primary care physicians feel that colonoscopy is the screening "gold standard," since it is the only recommended test that visually examines the entire colon, and other tests are inferior because they do not do so. Not surprisingly, an expert consensus guideline from the American College of Gastroenterology supports this position. However, only FOBT and flexible sigmoidoscopy have been shown to reduce colorectal cancer mortality in randomized controlled trials, and colonoscopy, despite its potential for higher detection rates, is associated with increased risk from anesthesia and colon perforation.[6]

Recent studies have also cast some doubt on the widely held premise that colonoscopy is superior to flexible sigmoidoscopy because the former is able to reduce mortality from cancers in the ascending colon (right-sided cancers). A population-based case-control study in Ontario, Canada found that colonoscopy was associated with a 67% reduction in deaths from left-sided cancers (i.e., those within the reach of a flexible sigmoidoscope) but no difference in deaths from right-sided cancers.[7] A subsequent cross-sectional study from Germany found that adults who had undergone colonoscopy within the last 10 years had a lower prevalence of left-sided, but not right-sided cancers. An accompanying editorial noted that the study raised important questions about the comparative effectiveness of colonoscopy and older screening tests:

Is there an incremental benefit of colonoscopy over flexible sigmoidoscopy for colorectal cancer screening? If so, is the incremental benefit of sufficient magnitude to justify the additional risks and costs of colonoscopy for screening in the population? Simply put, is the effectiveness of colonoscopy "good enough" for population-based screening?[8]

The bottom line is that as long as the above questions remain unanswered by a randomized controlled trial, FOBT and flexible sigmoidoscopy should not be considered or portrayed as "inferior" to colonoscopy in shared decision-making discussions with patients about screening test preferences. Even when colonoscopy is available and affordable, some patients still prefer FOBT, demonstrating the importance of providing multiple screening options.[9]

THE BURDEN OF PROSTATE CANCER

The American Cancer Society estimates that 27,360 men died of prostate cancer in 2009. Although medications for primary prevention have reduced the incidence of prostate cancer in randomized trials, the secondary prevention strategy of screening based on prostate-specific antigen (PSA) is far more common in the United States. Data from nationally representative surveys and community primary care practices consistently show that a majority of American men age 50 and older receive regular PSA tests.

THE CONVENTIONAL WISDOM: SCREENING FOR PROSTATE CANCER LEADS TO DRAMATIC HEALTH BENEFITS; SCIENTIFIC EVIDENCE SHOWS: BENEFITS OF PSA SCREENING ON MORTALITY ARE LIKELY SMALL TO NONE

It is estimated that since PSA screening began in the early 1990s, one million additional U.S. men have been diagnosed and treated for prostate cancer. Nonetheless, there is considerable debate about how much of the decreased mortality rate observed since then is attributable to screening. In 2008, the USPSTF recommended against screening for prostate cancer in men age 75 years and older due to the high likelihood that most of these men would die from other causes before receiving any benefit from treatment of asymptomatic prostate cancer. In men younger than age 75 years, the USPSTF concluded that evidence was insufficient to assess the balance of benefit and harm from screening for prostate cancer due to a lack of direct evidence from randomized trials that mortality was reduced by screening.[10]

Two major randomized controlled trials of PSA-based screening for prostate cancer published their initial mortality results in the spring of 2009. The prostate cancer component of the U.S. Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening trial[11] randomized 76,693 men between the ages of 55 and 74 years to usual care vs. annual screening with PSA for 6 years and digital rectal examination for 4

years. Abnormal results, defined as a PSA level greater than or equal to 4.0 ng/ml or suspicious examination findings, were provided to the patient's primary care clinician of record, and further testing and treatment were based on patient and physician preferences. Overall, 89% of men in the screening group and 90% of men in the control group who received a prostate cancer diagnosis chose active treatment (surgery, radiation, and/or hormonal therapy). Treatment choices stratified by prostate cancer stage were similar between the screening and control groups.

The overall prostate cancer mortality rate was surprisingly low; the 94 deaths from prostate cancer at 7 years represented only 1.5% of the 6137 deaths from all causes other than PLCO study cancers. But the more significant finding was that despite having 22% more prostate cancers detected, the screening group had a statistically non-significant 13% *higher* prostate cancer mortality rate than the control group—which is exactly the opposite of what we would expect if screening was effective in detecting cancers at earlier, more curable stages.

In contrast, the European Randomized Study of Screening for Prostate Cancer (ERSPC)[12] randomized 182,000 men from 7 European countries aged 50 to 74 years to PSA testing every 2 to 7 years versus usual care. PSA cutpoints for additional diagnostic testing and/or biopsy ranged from 2.5 ng/ml to 4.0 ng/ml. After a median follow-up of 9 years, the ERSPC found a 15% reduction in prostate cancer mortality in the screened group. In a pre-specified subgroup analysis of 162,243 men aged 55 to 69 years, the relative mortality risk reduction was 20%. Based on an absolute risk difference of 7.1 deaths per 10,000 men between the screening and control groups, the authors calculated that 1410 men would need to be subjected to screening and 49 additional men would need to be treated to prevent a single prostate cancer death.

Both of these trials have been criticized for flaws in their methods, and it remains controversial which trial's results more accurately represent the effect of instituting routine PSA screening in the U.S. Until recently, there was little information about the natural history of localized prostate cancers detected through PSA testing, since most men with a prostate cancer diagnosis immediately undergo curative treatment.

In 2009, Lu-Yao and colleagues published the results of a cohort study of 90,000 men aged 65 years and older who chose conservative management for PSA-detected prostate cancers from 1992 and 2002. Of men with well-differentiated or moderately differentiated (Gleason score less than or equal to 7) tumors, between 8 and 9 percent of men had died of prostate cancer 10 years later, between 57 and 60 percent of the group *had died of some other cause* (most often heart disease). In other words, this analysis indicates that an older man diagnosed with PSA-detected prostate cancer who declined active therapy was 5 times as likely to still be alive, and 7 times as likely to have died of some other cause, than to have died of prostate cancer 10 years later. Consequently, the population-level benefits of screening and treatment of PSA-detected cancers are likely to be small indeed.

THE CONVENTIONAL WISDOM: HARMS FROM PROSTATE CANCER SCREENING ARE "MINIMAL" SCIENTIFIC EVIDENCE SHOWS: OVERDIAGNOSIS AND OVERTREATMENT CAUSE SUBSTANTIAL HARMS

Many physicians routinely order PSA tests on men over age 50 years with minimal to no informed discussion, in the mistaken belief that "it's only a blood test." While there are few harms associated with the simple act of drawing a blood sample, PSA testing has the potential to subject a large number of men with elevated levels to a "diagnostic cascade" of multiple biopsies, repeated PSA tests, and unnecessary treatment for cancers that would not have been detected in their lifetimes (a phenomenon known as "overdiagnosis"). Less than half of U.S. men with "lower risk" (defined as well-differentiated tumors in all age groups or moderately-differentiated tumors in men aged 70 years and older) prostate cancers chose conservative management between 2000 and 2002.[14]

Current prostate cancer treatments cause time-limited or permanent erectile dysfunction, urinary leakage, and bowel urgency in up to a third of patients, depending on the intervention.[15] If we use the ERSPC trial as a benchmark for the number of men needing to be treated, approximately 15-20 men will experience persistent adverse health effects from curative therapies for every one man who does not die from prostate cancer. Whether this price is worth paying on a societal level can be debated, but there is little doubt that screening for prostate cancer leads to substantial harm from overdiagnosis and overtreatment for many more men than it helps.

CONCLUSIONS

The decision to perform screening for colorectal or prostate cancer can be complex, and should take in

account evidence-based recommendations, the implications of recent studies, and patient preferences. In order to give patients accurate information on the benefits and limitations of cancer screening tests, physicians should discard "conventional wisdom" that has not been supported by scientific evidence. To briefly review:

1) Collecting a fecal occult blood sample for screening during the digital rectal examination is not "better than nothing at all."

2) FOBT and flexible sigmoidoscopy have comparable benefits and fewer harms than screening colonoscopy.

3) Benefits of PSA screening on mortality are likely small to none.

4) Overdiagnosis and overtreatment of PSA-detected prostate cancers cause substantial harms.

REFERENCES

1. Laiyemo AO, Doubeni C, Pinsky P, et al. Race and colorectal cancer disparities: health-care utilization vs different cancer susceptibilities. J Natl Cancer Inst 2010;102:538-546.
2. U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008;149:627-37.
3. Nadel MR, Berkowitz Z, Klabunde CN. Fecal occult blood testing beliefs and practices of U.S. primary care physicians: serious deviations from evidence-based recommendations. J Gen Intern Med early online pub DOI: 10.1007/s11606-010-1328-7.
4. Collins JF, Lieberman DA, Durbin TE, Weiss DG, Veterans Affairs Cooperative Study #380 Group. Accuracy of screening for fecal occult blood on a single stool sample obtained by digital rectal examination: a comparison with recommended sampling practice. Ann Intern Med 2005;142:81–5.
5. Klabunde CN, Lanier D, Nadel MR, et al. Colorectal cancer screening by primary care physicians: recommendations and practices, 2006-2007. Am J Prev Med 2009;37:8-16.
6. Whitlock EP, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review. Ann Intern Med 2008;149:638-58.
7. Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. Ann Intern Med 2009;150:1-8.
8. Baxter NN, Rabeneck L. Is the effectiveness of colonoscopy "good enough" for population-based screening? J Natl Cancer Inst 2010;102:70-71.
9. Sarfaty M, Feng S. Choice of screening modality in a colorectal cancer education and screening program for the uninsured. J Cancer Educ 2006;21:43-49.
10. U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008;149:185-91.
11. Andriole GL, Grubb RL, Buys SS, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360:1310-19.
12. Schroder FH, Hugosson J, Roobol M, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320-8.
13. Lu-Yao GL, Albertsen PC, Moore DF, et al. Outcomes of localized prostate cancer following conservative management. JAMA 2009;302:1202-9.
14. Miller DC, Gruber SB, Hollenbeck BK, et al. Incidence of initial local therapy among men with lower-risk prostate cancer in the United States. J Natl Cancer Inst 2006;98:1134-41.
15. Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. Ann Intern Med 2008;148:435-48.

Kenneth W. Lin, MD
Assistant Professor of Clinical Family Medicine
Georgetown University School of Medicine
KWL4@georgetown.edu

see Editorial Comments on p. 78-79

Editorial Comment by Bruce H. Pokorney, M.D.

on Challenging the Conventional Wisdom on Colorectal and Prostate Cancer Screening

The article by Dr. Kenneth Lin in this quarter's *Journal* regarding colorectal cancer screening is very well constructed, scientifically valid, important to read, and bold in its willingness to challenge conventional wisdom based upon evidence. Nonetheless, as accurate as the comment might be, it presents only part of the overall story. As is often the case, the absence of adequate double blind controlled studies to provide evidence for a position is not the same as confirmation of that position as invalid. In the case of colorectal cancer screening, as well as many other issues in medicine, there are different guidelines created by well-intentioned professionals looking at the same available evidence. In the case of colorectal cancer screening there are at least three different published guidelines for screening. In each case there are differences in the final recommendations which at first seem coincidentally contradictory at best or based upon a biased literature review for self-serving reasons at worst. A deeper look reveals that neither is the case.

The joint guidelines from the American Cancer Society, the United States Multi-Society Task Force on Colorectal Cancer (ACS-MSTF), and the American College of Radiology were published in 2008. While the USPSTF Guidelines discussed in detail in Dr. Lin's article did not consider the value of identifying and removing premalignant lesions to prevent colon cancer, the joint guidelines differentiate recommendations that only screen for existing colon cancer as a means for early detection from those that serve as tools for both detection of cancer as well as preventing cancer by detecting and removing pre-malignant polyps. Likewise, the American College of Gastroenterology (ACG) in their published 2008 guidelines recommend colonoscopy as a "preferred" strategy for both screening and prevention. The ACG believes there is evidence that presenting a "preferred" strategy to patients not only shortens and clarifies the discussions with the patient but also makes it more likely for the patient to proceed with screening than in cases where a "menu of options" are presented.[1]

In addition, I believe that one can say that the USPSTF requires a higher level of evidence to promote a definitive recommendation than the ACS-MSTF and the ACG. Indeed, the evidence that colonoscopy reduces the mortality from colorectal cancer is indirect as there have been no double blind, controlled studies comparing colonoscopy screening and no screening. Nonetheless, the indirect evidence is overwhelming and a discussion of all of this evidence is beyond the scope of a brief editorial comment. Suffice it to say that there are cohort studies showing that the clearance of colorectal neoplasia (polyps) in patients undergoing colonoscopy has decreased the incidence of colorectal cancer compared to a reference population by 76-90%.[2,3] Even with some recent studies suggesting that right-sided colon cancers are often missed or at least not prevented by colonoscopy screening, the polyp-to-cancer theory has not been refuted or rejected and the body of evidence still speaks to the benefit of removing premalignant polyps from anywhere they may be found in the colon. There has been much criticism of the Canadian study referenced by Dr. Lin based upon the study design and the fact that only a small minority of the colonoscopy exams were done by trained gastroenterologists.

To end on a note of universal agreement, I think we can all concur from current evidence that, as Dr, Lin concludes, collecting a fecal occult blood sample during a digital rectal exam, in spite of what we may have been taught in medical school, is NOT "Better than Nothing at All".

REFERENCES

1. Inadomi J , Kuhn L , Vijan S et al. Adherence to competing colorectal cancer screening strategies . Am J Gastroenterol 2005 ; 100 : S387 – 8 .
2. Winawer SJ , Zauber AG , Ho MN et al. Prevention of colorectal cancer by colonoscopic polypectomy. _ e National Polyp Study Workgroup . N Engl J Med 1993 ; 329 : 1977 – 81 .
3. tCairda F , oTmaselli G , aCpocaccia R e t al. _ e Italian Multicentre Study Group. EO cacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence . Gut 2001 ; 48 : 812 – 5 .

Editorial Comment by Paul R. Sieber, M.D.

Dr Lin's article lays out the current dilemma in prostate cancer screening. He is correct and valid in his references, but his conclusions are clearly in agreement with expert panels that contain no urologists. The frequently quoted USPSTF contains neither a urologist nor an oncologist. Earlier this decade the USPSTF was uncertain that we should even treat prostate cancer since we had no data that intervention was better than no treatment!

The first Level 1 evidence of survival advantages for treatment of advanced prostate cancer came from a comparison of combined neoadjuvant androgen deprivation therapy with radiation therapy versus radiation therapy alone.[1] Subsequently, the study by Bill-Axelson and coworkers of radical prostatectomy provided Level 1 evidence that treatment is clearly superior to observation in men with prostate cancer.[2] According to statistics from the American Cancer Society, the death rates for prostate cancer have fallen since the advent of PSA screening in 1991 from nearly 40,000 deaths per year to 28,000 deaths in 2009. Urologists now face a very different clinical landscape, since there has been a vast stage migration due to identification of early stage cancer by PSA screening. Though simultaneity does not prove causality, the fall in cancer deaths coincident with the advent of PSA screening for prostate cancer is highly suggestive.

The PLCO and ESPRC share a similar shortcoming when reviewed by urologists. Surprisingly, the non-urologist study comes in on the non-screening side of the argument and the urologist driven study comes to a different conclusion. The main concern I have between the two studies involves trial design. The PLCO was largely completed by non-urologists and biopsies were at the patients' and doctors' discretion, while the ESPRC mandated biopsies for all abnormal exams and PSA's. Greater than 50% of the control arm in PLCO had PSA screening as well. The ESPRC had a more rigorous biopsy scheme which changed over time to include data from the Prostate Cancer Prevention Trial(PCPT). The PCPT found that a PSA cutoff of 4 missed a number of cancers,[3] so the cutoff for biopsy was made even more aggressive. The two studies are thus not really comparable.

The second question Dr Lin raises is whether screening does harm by leading to treatments which cause loss of sexual function, and bladder and bowel dysfunction. With the average age of diagnosis for prostate cancer in excess of 65 years I would reference the Massachusetts Male Aging study.[4] The majority of men already have ED at the time of diagnosis and I believe there is undue weight given to this harm. However, I agree overtreatment in men at low risk certainly puts them at risk for unnecessary side effects.

I have 3 conclusions that differ from those of Dr Lin:

1. Screening seems to be moving from both extremes of the argument toward a policy of screening only men with a 10+ year life expectancy. The cost/benefit ratio will rapidly become more complex. A myriad of new treatments for advanced prostate cancer are already here or coming soon; all with very expensive price tags (Dendreon's Provenge costs $93,000/patient)
2. The vast stage migration of prostate cancer in this country toward detection of early stages, which is a downside to aggressive screening, is leading to overtreatment of low risk prostate cancer. Better prognostic/predictive criteria are badly needed.
3. I believe we need to better identify men who should have aggressive screening, and I believe recording of a baseline PSA at a younger age may be one simple yet economical way to identify high risk patients.[5]

REFERENCES

1. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Bolla M, Collette L, Blank L, et al. Lancet. 2002 Jul 13;360(9327):103-6.
2. Radical prostatectomy versus watchful waiting in early prostate cancer.Bill-Axelson A, Holmberg L, Ruutu M, et al. N Engl J Med. 2005 May 12;352(19):1977-84
3. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. Thompson IM, Pauler DK, Goodman PJ, et al. N Engl J Med. 2004 May 27;350(22):2239-46. Erratum in: N Engl J Med. 2004 Sep 30;351(14):1470.
4. The health of normally aging men: The Massachusetts Male Aging Study (1987-2004).O'Donnell AB, Araujo AB, McKinlay JB. Exp Gerontol. (Review) 2004 Jul;39(7):975-84.
5. Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50 years. Lilja H, Ulmert D, Björk T, et al. J Clin Oncol. 2007 Feb 1;25(4):431-6.