

Grand Rounds

Current Controversies in Screening: Cholesterol, Breast Cancer, and Prostate Cancer

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Abstract

Physicians must make decisions in day-to-day practice even when the balance of benefit and harm is not yet known. Adopting a clinical policy about screening is a case in point. Three controversies in screening healthy adults illustrate different aspects of resolving a dispute when the evidence is incomplete.

The major controversy in cholesterol screening is whether to screen young adults. There has never been a randomized trial of treatment, let alone a trial of screening, in young adults. However, a patchwork of evidence strongly suggests that, because the baseline risk of coronary heart disease (CHD) is very small in young adults, the absolute reduction in risk from treatment would be very small.

In breast cancer screening, randomized trials do not show conclusively that periodic mammography for women aged 40–49 years reduces breast cancer mortality. A 7–10 year delay between the first mammogram and a reduction in deaths from breast cancer suggests the hypothesis that the only benefit of screening women aged 40–49 years occurs from mammograms performed after age 50.

There is no high quality evidence that early detection and treatment reduce the death rate from prostate cancer. In lieu of randomized trial data, we must depend on a decision analysis that shows that screening middle-aged men is cost-effective relative to other preventive services. However, this result depends on using optimistic survival data in the decision model, and most organizations do not recommend routine screening. The best strategy is to discuss the harms and benefits, and let the patient decide.

Key Words: Screening, breast cancer, prostate cancer, coronary heart disease.

Several contemporary controversies about routine screening illustrate the challenges in developing recommendations for clinical practice when the evidence is of poor quality, incomplete, or conflicting. Controversy develops under these circumstances because physicians differ in how they respond to the need to take a stand in the care of individual patients. Some physicians believe that the best way to serve the patient is to provide a service until it has been discredited, while others believe that the patient is best served by withholding a service until it has been proven effective.

This article updates a 1995 review of preventive services (1). I write as the chair of the second U.S. Preventive Services Task Force, which made its report in December 1995 (2). The Task Force began by selecting target conditions on the basis of their prevalence, severity, and susceptibility to successful treatment. A systematic search of the literature and assessment of study methods identified high-quality studies. The Task Force was at pains to link its recommendations to the evidence in these studies. The final step was extensive external review, in which experts had a chance to persuade the Task Force to adopt their perspective on specific preventive methods. The Task Force graded the strength of its recommendations. Some recommendations had a strong base of evidence for (A or B recommendations) or against (D and E recommendations), but many recommendations received a C rating, which meant that it was not possible to make a firm recommendation, either because the studies were of poor quality or because they were of good quality, but with conflicting findings. The rating scale serves partly to spotlight opportunities for research, but mostly to help physicians set priorities for using a limited time in the office. Physicians should spend time on A- and B-rated services and not find themselves doing C-rated items, let alone D- and E-rated services, at the expense of the A- or B-rated services.

Screening is a low-yield activity on a year-to-year basis, yet it will repay persistent effort, since the lifetime incidence of many diseases is quite high (**Table 1**). The annual incidence of invasive cervical cancer is only 20 women per 100,000, aged 40 years. Yet, in a lifetime, 0.7% of all women will develop cervical cancer. So, physicians should not get discouraged with screening because they can't remember the last time they made a diagnosis of cancer with a screening test.

TABLE 1
Annual and Lifetime Incidence of Some Common Cancers

	Annual incidence at age 35–39 years per 100,000 persons	Annual incidence at age 75–79 years per 100,000 persons	Lifetime incidence
Breast cancer	63	327	9.3%
Colon cancer (men)	5.9	411	6.0%

Source: Reference 3. Reprinted with permission of the Annals of Internal Medicine.

When to Start Screening for High Serum Cholesterol?

The first topic is when to start screening for high serum cholesterol levels. The resolution of this issue is methodologically challenging. It pits two points of view against one another.

The National Cholesterol Education Project recommends that the screening of men and women begin at age 20 and continue every 5 years thereafter (4). The authors do not explain the logic of screening every 5 years regardless of whether the patient's cholesterol is very close to a treatment threshold, or is 150 mg/dL and would never reach a treatment threshold. The rationale for the recommendation to start at age 20 is that arteriosclerosis is a progressive disease that begins early in life and is linked to an elevated serum cholesterol; so the earlier one begins to reduce any contributing factor, the better. This position is based on physiologic reasoning, not experimental evidence. Lowering serum cholesterol does lower the risk of heart disease in individuals in their 40s, 50s and 60s. Because there have been no studies of the effect of lowering cholesterol in individuals who are in their 20s and 30s, there is no direct evidence that treating young people reduces the incidence of coronary heart disease.

The U.S. Preventive Services Task Force (2) and the American College of Physicians-American Society of Internal Medicine (ACP-ASIM) (5) both recommend that screening begin when the risk of coronary heart disease becomes appreciable. Their logic is the following: Screen only at an age when you are willing to treat. (Some would take issue with this premise, believing that people are more likely to reduce their dietary intake of cholesterol and saturated fat if they know that their serum cholesterol is high. This belief is unsubstantiated by any evidence that knowing one's cholesterol alters behavior). Moreover, treatment of high cholesterol may not be entirely safe. Some treatments for high cholesterol have increased the risk of all-cause mortality in populations at low risk for coronary heart disease. Therefore, in the lifetime of a person with high serum cholesterol, there may be periods in which the risk of coronary disease, and therefore the probability of benefit from treatment, is very low, yet the person may suffer side effects or long-term harms, to which everyone is susceptible. Why treat during a time of life in which harms exceed benefit, as long as there is no penalty for delaying treatment until an age in which benefit exceeds harms? In fact, with treatment, a person's risk of coronary disease falls remarkably quickly to the same level as the risk of someone who had spent a lifetime at the post-treatment cholesterol level. This crucial piece of evidence suggests that it is not necessary to begin treatment very early in life in order to reduce the risk of coronary disease. Therefore, treat when the immediate risk of coronary disease starts to rise and avoid treating at an age when the harm may exceed the benefit. The evidence supporting this line of argument is strong.

As the risk of a disease increases, the benefits of treatment increase relative to the harms. The best way to understand this principle is to consider a hypothetical circumstance: a fatal disease that, because it cannot be diagnosed in an early, treatable stage, requires prophylactic treatment for everyone (**Table 2**). The treatment reduces the risk of death by 50% in those who have the disease and increases the risk of death by a tenth of a percent in those who don't have the disease. Treating a population in which there are 20 people per 100,000 with the disease reduces the number of deaths with the disease from 20 to 10 per 100,000. However, this treatment will cause 100 deaths per 100,000 (one death per 1,000) in those who don't have the disease. The number of deaths in those fated to die decreases, but the overall number of deaths increases (**Table 2**). If the risk of death from the disease is much higher (1%), the balance of harms and benefits changes dramatically. Treatment

saves 500 of the 1,000 people who had the disease. Although treating those who don't have the disease causes 100 deaths, the overall number of deaths decreases by 400. Clearly, the balance between harm and benefit depends on the baseline risk of the condition to be treated.

TABLE 2
Effect of a Prophylactic Treatment for a Hypothetical Fatal Disease

	Number who have disease		Number who don't have disease		
	die	live	die	live	net deaths
Low-risk population					
Status quo	20	0	0	99,980	
Treat	10	10	100	99,880	+90
High-risk population					
Status quo	1,000	0	0	99,000	
Treat	500	500	100	98,900	-400

Assumptions:

Disease fatal unless treated

Treatment reduces the risk of death by 50% in those with disease

Treatment increases the risk of death by 0.1% in those who don't have disease

The treatment of high cholesterol is an excellent example of the changing balance of benefits and harms, as disease risk increases. In a meta-analysis of a very large number of studies of different drug treatments for high cholesterol, the authors grouped the studies according to the coronary heart disease (CHD) mortality rate in the study population, as indicated by the death rate in the untreated group (6). The high risk population clearly benefited from treatment, with an odds ratio (O.R.) of 0.75 for total mortality. However, in the group with the lowest CHD mortality rate, treatment was associated with an increased total mortality rate (O.R.=1.3). Clearly, the balance of harms and benefits shifted from net benefit to net harm with a falling risk of CHD in the population, a relationship that supports the view that cholesterol-lowering drugs might cause harm in low-risk populations, such as young adults.

However, this meta-analysis included studies of treatments that are no longer used, in part because of adverse effects. Perhaps, modern cholesterol-lowering drugs are so safe that they would not cause net harm in low-risk adults. Clinical trials of several statins have shown a reduction in risk of future CHD events in hypercholesterolemic patients with angina pectoris or myocardial infarction (7), asymptomatic hypercholesterolemic high-risk middle-aged men (8), men and women with a normal cholesterol level who have survived a myocardial infarction (9), and men and women with average cholesterol levels but below-average HDL levels (10). A meta-analysis of 16 clinical trials of statin drugs showed a 22% reduction in total cholesterol, 29% reduction in risk of stroke, 22% reduction in total mortality, and 28% reduction in cardiovascular disease mortality (11). This

structured review did not detect an increase in non-cardiovascular disease mortality, including cancer. However, as the authors pointed out, the confidence intervals on the estimated risk were wide, and the average period of follow-up was only 3.3 years. In one study (9), breast cancer occurred in 12 patients in the group taking pravastatin and one patient in the placebo group ($p=0.002$). These results underscore the need for caution in prescribing statins to patients who are at low risk of heart disease. None of these clinical trials enrolled healthy young men and women, the population in question when considering the age to start screening healthy individuals.

The rationale for screening at an early age hinges on the early onset of atherosclerosis and the purported advantage of intervention at an early stage in the development of atherosclerotic plaque. Without studying the effect of cholesterol lowering in young people, it is very difficult to test this rationale. One approach, however, is to examine the rate at which the incidence of CHD falls after starting cholesterol-lowering drugs and the extent to which it approaches the incidence of CHD in cohort studies of people who had spent their lifetime with a serum cholesterol equal to the post-treatment cholesterol level. Delaying screening and treatment until an age when the CHD incidence started to rise would be safe if the annual incidence of CHD rapidly fell to the lowest level that one could expect, that of individuals who had always been at the post-treatment cholesterol level.

Law and colleagues (12) compared the incidence of CHD before and after treatment achieved a 10% reduction in serum cholesterol with the CHD incidence in cohorts whose lifetime cholesterol levels differed by 10%. The left-hand bar in **Fig. 1** represents a 27% difference in CHD incidence

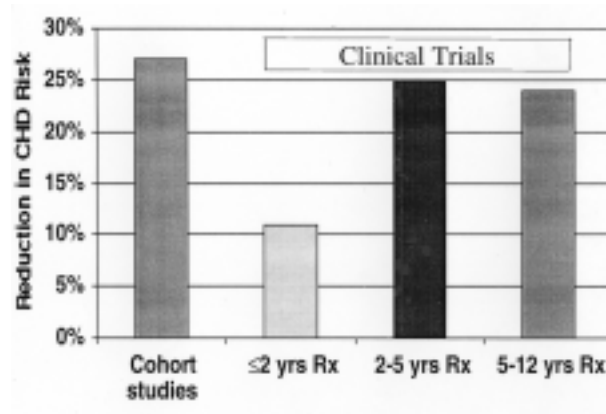


Fig. 1. Effect of a 10% reduction in serum cholesterol on risk of coronary heart disease. The left-hand bar represents the difference in risk for two cohorts of middle-aged men whose cholesterol levels are 10% apart and whose age at death was 55–64 years. The other bars represent the change in coronary heart disease risk seen in randomized trials of cholesterol lowering in the first two years of treatment, between the second and fifth years of treatment, and between the fifth and twelfth years of treatment. Adapted from tables that appeared in Reference 12 and used with permission of the British Medical Journal.

between two cohorts of men aged 55–64 who differ by 10% in their serum cholesterol concentration. The 27% difference in CHD incidence is the maximum effect that one could expect from reducing the serum cholesterol concentration by 10%. The middle bar represents the fall in CHD incidence in the first two years (a 7% drop) after achieving a 10% reduction in serum cholesterol concentration. At five years, the fall in CHD incidence is 25% (95% confidence interval, 15–35%), which is not substantially different from the 27% theoretical maximum fall in CHD incidence. So, cholesterol treatment does not require fifteen years to achieve a desirable risk reduction. Five years is enough. Put another way, people don't have to pay a penalty for waiting to lower cholesterol until an age when the incidence rises to the point where the benefits of lowering cholesterol exceed the potential harms.

The reduction in the probability of developing CHD (often called absolute risk reduction or attributable risk) is the most useful measure of the effect of lowering cholesterol. The inverse of the reduction in the probability of developing CHD is the number of people who must undergo treatment for one person to avoid developing CHD, which is a crude measure of cost-effectiveness. The reduction in the probability of developing CHD is the reduction in relative risk (e.g., 25% reduction in CHD incidence) multiplied by the pre-treatment incidence of CHD. The relative-risk reduction decreases with age, from 54% at ages 35–44 to 19% at ages 75–84 (12), but the incidence of CHD increases at a much faster rate with advancing age, as shown for men and for women in **Fig. 2**, so that the absolute risk reduction should increase with age.

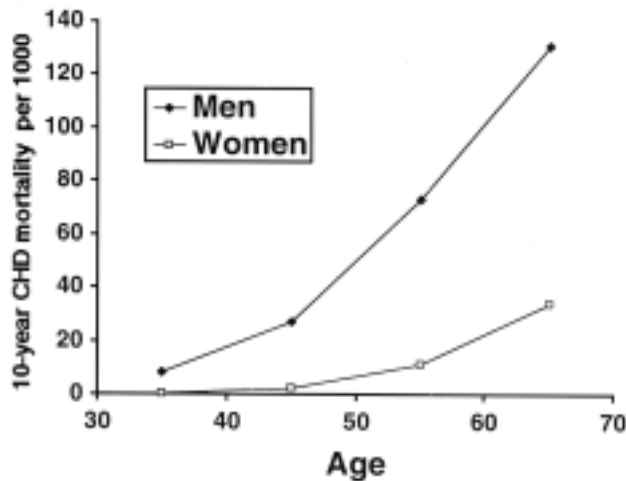


Fig. 2. Age and risk of CHD: the findings represent average risk individuals with serum cholesterol equal to 280 mg/dL. Adapted from a table in Reference 5 with permission of the Annals of Internal Medicine.

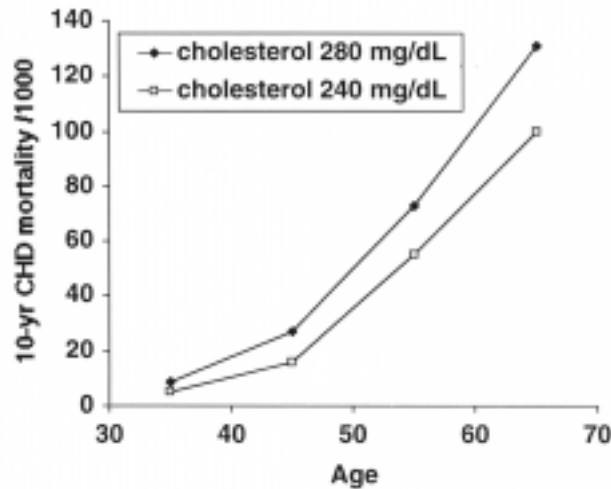


Fig. 3. Effect of lowering cholesterol on risk of coronary heart disease. The data represent the effect of lowering serum cholesterol from 280 mg/dL to 240 mg/dL in men. Adapted from a table in Reference 5 with permission of the Annals of Internal Medicine.

In fact, the absolute reduction in risk of CHD does increase dramatically with advancing age (5). **Fig. 3** shows the effect of lowering cholesterol from 280–240 mg/dL as a function of age (5). Because the pre-treatment risk of CHD is so low in men and women in their 30s (and would be even lower in the 20s), the absolute risk reduction is very small. On the other hand, the absolute reduction in the risk of CHD becomes larger as the pre-treatment risk increases with advancing age.

To summarize, physicians should delay cholesterol screening in healthy people until an age when it is reasonable to prescribe cholesterol-lowering medication. Because there is reason to be concerned about possible ill effects of long-term treatment to reduce serum cholesterol, physicians should be sensitive to the balance of harms and benefits, which shift toward benefits as the baseline risk of CHD increases. The expected benefit of cholesterol reduction, an absolute reduction in the incidence of CHD, is very small until age 35 in low-risk men, and age 45 in women. Since treatment achieves the maximum achievable reduction within five years of starting treatment, there is no penalty for delaying treatment until the age at which the benefit begins to increase. Both the U.S. Preventive Services Task Force and the American College of Physicians — American Society of Internal Medicine (ACP-ASIM) recommend starting to perform screening at age 35 in healthy men and age 45 in women.

These recommendations contrast sharply with those for people with risk factors for CHD, or people with established CHD. These individuals have a much higher incidence of subsequent CHD events than do healthy people. The same logic that applies to healthy people (screen when the incidence of CHD is appreciable) applies to people at high risk of CHD, whom physicians should screen for hypercholesterolemia irrespective of the patient's age.

When to Start Screening for Breast Cancer?

Breast cancer is the second leading cause of cancer death in women. The incidence increases with advancing age, but it is appreciable before age 50 (Fig. 4). The age at which to start screening is a matter of great controversy. Fortunately, there have been many large-scale randomized

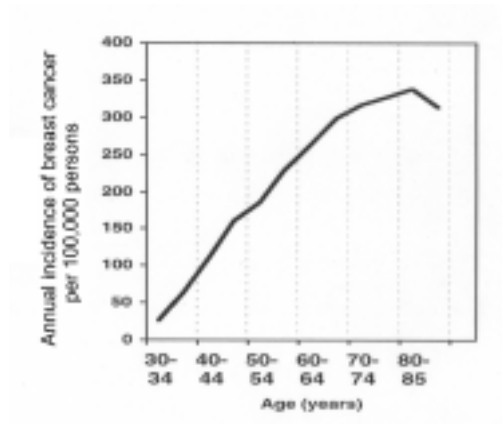


Fig. 4. Incidence of breast cancer according to age. Data obtained from a table in *Common Screening Tests* (Reference 3) and used with permission of the American College of Physicians.

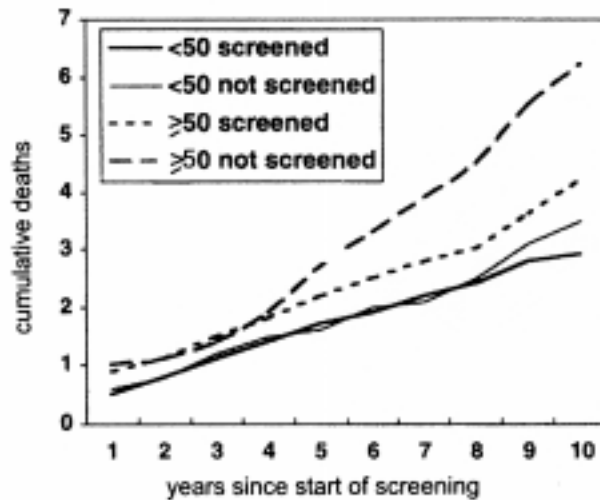


Fig. 5. Cumulative deaths after starting screening in two cohorts. The graphical representation is not based on actual data obtained from Reference 14, but illustrates the differences in the various cohorts which have been studied.

trials which randomly allocated women to regular mammography or to usual care. The endpoint in these studies was death from breast cancer. A meta-analysis of eight randomized trials (and two case-control studies) shows that performing mammography every 1–2 years on women aged 50 and older reduces by 26% the risk of dying of breast cancer (95% confidence interval, 17%–34%) (13). The same meta-analysis (applied to eight randomized trials and one case-control study) showed different results in women aged 40–49 years. Only five of the nine studies reported a relative risk of dying of breast cancer less than 1.0, although the relative risk was not statistically significantly different from 1.0 in any study. The combined relative risk was 0.93 (95% confidence interval, 0.75–1.13). The apparent difference in breast cancer screening effectiveness in younger women has caused a great deal of discussion about whether the difference is real and, if so, about the reasons for the difference.

An apparent delay in benefit from screening is the most remarkable aspect of screening women who are aged 40–49 at the time of the first mammogram. In women aged 50–69, the relative risk is 0.73 for those who have been followed for 7–9 years, and 0.76 for those who have been followed for 10–12 years (13). In women aged 40–49, the relative risk is 1.02 (95% confidence interval, 0.82–1.27) for those who have been followed for 7–9 years and 0.83 (95% confidence interval, 0.65–1.06) for those who have been followed for 10–12 years (13). The difference between younger and older women is even clearer in the curves describing breast cancer deaths in the first 12 years after screening, in a meta-analysis of five Swedish randomized trials (14). In women aged 50–69, the curves describing mortality in the screened group and the control group separate at about 4 years and diverge progressively with each year of follow-up. In women aged 40–49, the curves are essentially superimposable for the first 11 years, diverging thereafter. **Fig. 5** illustrates this effect.

Why does it take at least several years for the survival curve for screened women to diverge from the curve for unscreened women? Regardless of the age of the patient, the survival curve for screened women should be very close to the curve for unscreened women for the first few years after the first mammogram. Immediately prior to the first mammogram, a cohort of screened women should have the same proportion of metastatic cancers as a cohort of unscreened women. Consequently, screened and unscreened women should have the same death rate for the first few years, as deaths from these metastatic cancers occur. However, the first mammogram detected cancers that were successfully treated in screened women but would go on to metastasize in unscreened women. If the second mammogram is close enough to the first mammogram, fewer of the cancers it detects will have metastasized, relative to the cancers in the cohort of unscreened women. Therefore, the survival curves should begin to diverge.

Given this rationale, why does it take so much longer for the survival curves to diverge in women aged 40–49 years (15)? One hypothesis is that breast cancer metastasizes earlier in younger women, so that the interval between mammograms is too long to detect many cancers before they metastasize. Breast cancer does grow more rapidly in younger women (16). In addition, breast cancer is more likely to have metastasized in younger women: at diagnosis, 44% of women under

age 50 years have metastases, as compared with 36% of women aged 50 years and older (17).

Is the benefit of screening women in their 40s due entirely to improved survival from breast cancer detected in their 50s? This hypothesis receives some support from the HIP study (18). The authors divided women who were 45–49 years old at their first screen into two groups. One group had a diagnosis of breast cancer at age 45–49; the other had breast cancer diagnosed at age 50–54 years. Only the group whose diagnosis of breast cancer occurred at ages 50–54 had better survival than unscreened women. The HIP study findings suggest that the effectiveness of screening in women who are over age 50 may explain effectiveness in women who are age 40–49 at the time they began screening. The number of patients in the HIP study was too small to draw a strong conclusion, but the authors are the only ones to analyze their findings according to the age at diagnosis. Age may simply be an imprecise marker for menopausal status, which is physiologically important in tumor growth. Many women who began these studies before their menopause were probably menopausal at the time of detection of cancer. In some randomized trials, screening did not begin until age 45.

Reasons for the effectiveness of mammography in women over age 50 years include better accuracy and the slower growth rate of cancer in post-menopausal women. The breasts of post-menopausal women have a higher fat content relative to the breasts of pre-menopausal women. The contrast between a breast mass, which has the radiodensity of water, and the surrounding tissue is better if the surrounding tissue is fat, which has a lower radiodensity than water. In fact, the frequency of a positive mammogram in women with breast cancer is 0.87 in women aged 40–49 and 0.94 in women aged 50–59 (19).

The magnitude of harm in mammography is relatively small, but women aged 40–49 need to know about these harms before agreeing to screening, especially since the evidence of benefit is weak in this age group. Compared with women over age 50, women younger than age 50 require approximately 2.5 times as many biopsies and 3 times as many tests to diagnose one cancer (20). False-positive mammograms are very common; in one study, 56% of women aged 40–49 experienced at least one false-positive mammogram, as compared with 47% of women aged 50–74 (21). Anxiety after screening is one reason for concern about a false-positive result. In one study 26% of women who had a false-positive mammogram remained worried, as compared with 9% of women with a normal mammogram (22).

The U.S. Preventive Services Task Force gave an "A" recommendation for breast cancer screening between ages 50–69. The recommendation for women aged 40–49 was a "C" (no compelling evidence for or against screening) (2). In 1997, the National Institutes of Health Consensus Development Conference (23) concluded that "the data currently available do not warrant a universal recommendation for mammography for all women in the forties." Further, they recommended, "Each woman should decide for herself whether to undergo mammography." This advice reflects the panel's feeling that the decision in 40–49-year-old women is a toss-up, a decision between actions that, repeated over many patients, have essentially the same outcome.

Screening for Prostate Cancer

Unlike the situation with breast cancer, there are no randomized trials for prostate cancer screening, nor any useful trials of treatment of early-stage prostate cancer. To evaluate prostate cancer screening, we will use a heuristic called the "chain of evidence." The first link in the chain of evidence is a reasonably priced, safe test that can detect prostate cancer before symptoms occur. The second link is evidence that the prognosis is better in screen-detected cancer. The third link is evidence that screening leads to better outcomes in clinical practice. A strong recommendation for prostate cancer screening would require that each of these links be intact. The next three sections examine the evidence for each of these three links in the chain of evidence.

Prevalence and Detection of Prostate Cancer

Prostate cancer is a common disease, which makes it a potentially attractive target for screening. Autopsies on men who did not have clinical evidence of prostate cancer provide the best information on the prevalence of prostate cancer in candidates for screening. The prevalence of intracapsular prostate cancer that is large enough to cause significant future problems (a tumor volume of 0.5 mL or greater) is 3.5% in men aged 40–49 and increases with age (**Table 3**) (24). The

TABLE 3

Prevalence of Prostate Cancer in Autopsies of Men Dying Without Known Prostate Cancer

Age (years)	Prevalence of prostate cancer	
	tumor size (Vol. <0.5 mL)	tumor size (Vol. >0.5 mL)
40–49	0.072	0.035
50–59	0.090	0.044
60–69	0.132	0.064
70–79	0.234	0.114
>80	0.258	0.126

Source: Reference 24. Reprinted with permission of the Annals of Internal Medicine.

prevalences in **Table 3** are the best approximations of the pretest probability of prostate cancer at the time of screening. How much does the probability change after a rectal examination or a serum prostate-specific antigen (PSA)? **Table 4** shows the likelihood ratios for the rectal examination and the serum PSA (24). A suspicious rectal examination increases the odds of intracapsular prostate cancer by a factor of 1.5–2.0, according to the odds ratio form of Bayes' theorem, which states that the post-test odds equal the pre-test odds times the likelihood ratio. A non-suspicious rectal examination decreases the odds of cancer to 0.9 of the starting odds; effectively, a non-suspicious examination has no effect on the probability of cancer. A single measurement of the serum PSA is

TABLE 4
Performance of Screening Tests for Prostate Cancer

	Likelihood ratio	
	intracapsular tumor (>0.5 mL)	extracapsular tumor (>0.5 mL)
Serum PSA		
<4.0 ng/mL	0.8	0.5
4.0–10.0 ng/mL	2.8	3.2
>10.0 ng/mL	3.0	23.7
Rectal Examination		
Suspicious (Study A)	1.5	8.6
Suspicious (Study B)	2.0	2.7
Non-suspicious (Study A)	0.96	0.53
Non-suspicious (Study B)	0.83	0.73

Source: Reference 24. Reprinted with permission of the Annals of Internal Medicine.

only slightly better than the rectal examination in predicting localized prostate cancer (**Table 4**). Still, because the prevalence of prostate cancer is relatively high (pre-test odds of 6:100 in men aged 60–69), the post-test odds are 18:100, corresponding to a probability of 15%. If everyone who had a serum PSA in the range of 4–10 ng/mL had a prostate biopsy, it would require between 6 and 7 prostate biopsies to detect one clinically significant, localized cancer. This price might be reasonable if people with localized cancer could be sure that treatment had a high probability of prolonging their period of healthy life. In fact, there is considerable doubt about the effect of early detection on prognosis in prostate cancer, mainly because the prognosis is good, at least relative to other cancers, in most men with prostate cancer.

The Natural History of Localized Prostate Cancer

“Does treatment in the early stage of disease improve the prognosis of prostate cancer?” That question, surprisingly, does not have an answer. An expert panel of the American Urological Association analyzed the literature on the outcomes of radical prostatectomy and radiation therapy. The panel (25) stated its main conclusion as follows: “The panel found the outcomes data inadequate for valid comparison of treatments.” In other words, deficiencies in the design of published studies made it impossible to decide if treatment prolongs life. Given this shortcoming, another approach to analyzing the effectiveness of treatment is to ask how good treatment would have to be to improve on the natural history of early stage prostate cancer.

The best study of the natural history of early stage prostate cancer is a 15-year study of a prospectively collected cohort of Swedish men with clinically localized prostate cancer (26). None of the men in the final cohort received curative treatment for prostate cancer. The original cohort comprised 642 men with consecutively diagnosed prostate cancer of any stage. The median age of the cohort was 72 years. Three hundred men had localized disease, and 223 elected no curative treatment. Survival was the same in the men who elected no treatment and those who did undergo treatment with curative intent. Among all untreated men with clinically localized cancer, the 15-year survival was 81% (95% confidence interval, 72%–89%). The authors pointed out that this excellent survival left little room for improvement by radical treatment.

There are several important caveats in interpreting this careful study. First, the men were relatively old. Older men are more likely to die of other diseases, and the findings of this study may therefore underestimate the effect of prostate cancer on the death rate. Second, the clinical examination, rather than serum PSA, was the basis for diagnosis. In the Swedish cohort, nearly 50% of those with localized disease had highly differentiated tumors, and only 4.0% had highly undifferentiated tumors. In a population of patients who underwent prostate biopsy after having a serum PSA of 2.4–4.0 ng/mL, 80% had tumors that were intermediate in histological differentiation (27). Apparently, a population discovered by PSA testing has less well-differentiated cancers than men discovered by clinical examination. The mean age of the patients detected by PSA screening was 65 years, somewhat lower than the Swedish cohort.

The histologic grade of the tumor has an important effect on mortality. In the Swedish cohort, the 15-year rate of death caused by prostate cancer was 6% for highly differentiated tumors, 17% for moderately differentiated tumors, and 56% for poorly differentiated tumors (26). In a group of patients who met criteria for radical prostatectomy (age < 70 years at diagnosis, clinically localized to the prostate, and highly or moderately differentiated tumors), 15% died of prostate cancer.

To summarize, the natural history of clinically localized prostate cancer is unusually favorable as compared with many other common cancers. In addition to low mortality, disease progression was the exception: only 33% of the Swedish cohort had local progression and 13% had distant metastases after 15 years. This favorable natural history leaves little room for improvement by radical treatment strategies.

Effect of Treatment

There has been only one randomized clinical trial that compared treatment with no treatment (28). This study enrolled 111 men with localized cancer and randomly assigned them to radical surgery or watchful waiting. At 15 years, 21% of the controls and 26% of the radical surgery patients were still alive, and the two survival curves were identical. There was, therefore, no hint of a treatment effect. Because of the small number of patients, there was a large chance of missing a clinically important difference in survival rates. As discussed earlier, the American Urological Association expert panel reported that it was not possible to conclude that radical treatment reduced

the prostate cancer death rate (25). Fortunately, several clinical trials are randomly assigning patients with localized prostate cancer to radical treatment or watchful waiting. However, these studies will require at least 10 years to accumulate enough study endpoints to form any conclusions.

What should one do while waiting for the results of randomized trials? Decision analysis offers a method for predicting the results of a randomized trial, based on guesses about the effectiveness of treatment and what is known about the natural history of prostate cancer. There have been several decision analyses of prostate cancer and treatment. The analysis that forms the basis of the practice guidelines of the ACP-ASIM is illustrative of the approach and results (29). These authors performed a cost-effectiveness analysis, which is a method for estimating the costs of screening (as compared with no screening) per added year of healthy life gained by screening. The authors of the decision model used existing knowledge of the prevalence of prostate cancer and the accuracy of tests (**Tables 3 and 4**), the death rate from surgery, long-term survival with no treatment, the side effects of treatment, and the costs of diagnosis, treatment, and management of metastatic prostate cancer. The data that they used included the following: 56% and 33% of men with localized disease had well-differentiated and moderately differentiated tumors, respectively; 0.5% surgical mortality rate; long-term incontinence, 23%; long-term erectile dysfunction, 61%. They tested several assumptions about the cure rate from radical prostatectomy, 50%, 75% and 100%. They also assigned values between zero and 1.0 to a year of life with incontinence and with erectile dysfunction (quality-adjustment). The main results from this study appear in **Table 5**.

TABLE 5
Marginal Cost-Effectiveness Analysis of Prostate Cancer Screening

Outcome measure	Age 50–59	Age 60–69	Age 70–79
Days gained per person screened (discounted)	11	7	3
Years gained per person treated for prostate cancer	3.2	1.6	0.49
Dollars per quality-adjusted life-year gained (assumes 100% cure rate)	\$16,029	\$27,507	\$162,095
Dollars per quality-adjusted life-year gained (assumes 75% cure rate)	\$24,868	\$46,976	\$612,095

Source: Reference 29. Reprinted with permission of the Annals of Internal Medicine.

Overall, the authors found that screening offered potential benefit to men aged 50–69. The cost-effectiveness of screening in this age range was comparable to many other commonly employed

screening and treatment practices, even when they made the realistic assumption that the cure rate is only 75%. For men over age 70, the gain from screening was much smaller, and the cost-effectiveness of screening was well outside the range of other widely used medical interventions. The authors generally made assumptions that were favorable to screening. When they substituted cancer-specific mortality rates from studies other than the one they used, the cost per extra year of life increased by a factor of three to four.

The cost-effectiveness analysis provides a best estimate of benefit from prostate cancer screening. These benefits are speculative, albeit well grounded, until ongoing clinical trials report their results. In contrast, the harms of prostate cancer screening are not speculative. Radical prostatectomy is a well-established procedure. A telephone survey of Medicare patients who underwent radical prostatectomy (1988–1990) provides the best estimate of the harms of radical prostatectomy as performed in community practice (30). Forty-seven percent (47%) of the men had some incontinence every day; 23% lost more than a few drops of urine, 32% used pads or a penile clamp, and 2% needed an indwelling catheter. Before surgery, 91% of the men had erections sufficient for intercourse. After surgery, 61% had never had an erection; in the month before the interview, only 11% had erections that were firm enough for sexual intercourse. The authors also asked about follow-up treatments for prostate cancer. Thirteen percent had radiation therapy at least one year after surgery. (The presumed purpose of radiation therapy so long after surgery would be to control metastatic disease.) By that time, 10% had anti-androgen therapy, 15% had orchiectomy, and 28% had at least one of the three treatments. Thus, in the community setting, the cure rate of radical prostatectomy is no better than 72%.

The U.S. Preventive Services Task Force gave prostate cancer screening a “D” recommendation, which means “fair evidence against” routine screening (2). The recommendation of the ACP-ASIM (31) reflected the cost-effectiveness analysis shown in **Table 5**, which suggested that screening could be useful and cost-effective in men aged 50–69 years. The ACP-ASIM recommended against routine screening, proposing that physicians should describe the potential benefits and known harms of screening, diagnosis and treatment, listen to the patient's concerns, and then individualize the decision to screen. In other words, the ACP-ASIM recommended informed consent before screening.

Will educating patients about the harms and potential benefits of prostate cancer screening have any effect? A randomized trial of patient education addressed this question (32). The study subjects were patients attending a scheduled general internal medicine clinic appointment. Based on random assignment, they saw either a videotape about prostate cancer screening or no video. Among the study endpoints was the answer to the following question: “What treatment would you prefer if you had prostate cancer?” Patients who didn't see the video were about evenly split between watchful waiting (39.5%) and radical prostatectomy (41%). Most patients (86%) who saw the video preferred watchful waiting ($p < 0.0001$). In follow-up studies, 12% of the video group had a PSA done at the next opportunity, as compared with 23% of the control group ($p = 0.041$). The results were similar but the differences were smaller in a study of men attending a free prostate cancer

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screening clinic.

Questions and Answers

Audience: Will knowing the cholesterol increase the likelihood that the patient will comply with sensible recommendations about diet?

Dr. Sox: We don't know. There has been one study, and I believe that it did not show any effect of knowing one's cholesterol on compliance with diet, or the degree of which the cholesterol was lowered. So, we don't have the evidence right now to argue that you ought to know your cholesterol as a motivator to follow the sensible diet that most physicians recommend to all of their patients. Diet is of limited efficacy. A Step 1 diet only reduces the cholesterol by about 2% in free living subjects. Even a Step 2 diet only reduced cholesterol by about 6% in a study where the authors made extensive efforts to assure compliance.

Audience: Should we be recommending radiation therapy rather than surgery for cancer of the prostate?

Dr. Sox: We don't know whether radiation therapy is as effective as radical prostatectomy for the same reasons that the American Urological Association said that extant clinical trials of radical prostatectomy had too many design flaws to allow any interpretation of the results.

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