I'm Dr. Therese Bevers, Medical Director of the Cancer Prevention Center and Professor of Clinical Cancer Prevention at The University of Texas MD Anderson Cancer Center. Today’s lecture is on screening for cancer.

The objectives of this program are to identify characteristics of screening tests; describe populations for whom cancer screening is appropriate; and identify reliable sources of cancer screening recommendations and guidelines.

Since 1991, mortality from cancer has been decreasing. This has been attributable not only to improved treatment, but also to cancer prevention activities. This encompasses both cancer risk reduction, such as healthy lifestyle changes like tobacco cessation, but also cancer screening or early detection. It has been suggested that up to 35% of deaths may be preventable by early detection.

I want to start out by describing the difference between a screening and a diagnostic test. Screening tests are tests that are performed on asymptomatic individuals to detect cancer at an early stage before the development of symptoms. Screening tests do not diagnose cancer. In fact, if the screening test is abnormal, more testing, diagnostic testing, will need to be done to determine if it is cancer. Diagnostic tests, as just alluded to, are tests done to evaluate a problem, either a symptom or an abnormal screening test.

Why would we screen for cancer? Well, the intent is to find cancer at an earlier stage when it is more treatable and outcomes are better. Screening not only decreases the chance of dying or mortality from cancer, but also reduces morbidity or associated illnesses related to the cancer and the treatment itself. It’s been estimated that over 50% of new cancers occur at sites where screening has the potential to reduce mortality.

There are, however, reasons not to screen. If the cancers are very rare affecting a very tiny proportion of the population, if the cancer itself does not cause significant morbidity or mortality, or if early diagnosis doesn’t lead to better outcomes. Additionally, if there is not effective treatments, then there is no reason to try to find cancers earlier when you don’t have something to offer the patient.

Who should we screen? The individual should have at least a ten-year life expectancy. It is estimated that it takes approximately five to seven years for most cancer screening tests to have an impact on a population. So if an individual has a very short life expectancy due to other diseases, say end stage liver disease, heart disease, kidney disease, they are probably not good candidates to screen. And again they should be asymptomatic.

Who should we not screen? Again, individuals with clinical findings are not candidates for screening. They are candidates for diagnostic evaluation. Patients who have significant comorbidities that would limit the treatment of abnormal findings...
are not good screening candidates. And individuals who don’t want to undergo diagnostic evaluation or treatment of the abnormal findings shouldn’t undergo screening in the first place.

There are at least two requirements that must be met for a cancer screening test to be considered efficacious. It must be a test that is available to detect cancers at an earlier stage than if the cancer were detected as a result of the development of symptoms. There must also be evidence that treatment initiated earlier as a consequence of the screening results in an improved outcome, in other words, fewer individuals dying of the disease.

Let’s look a minute at the evidence supporting current cancer screening recommendations.

A randomized controlled trial with a mortality reduction as the endpoint is considered the gold standard for determining the usefulness of a screening test.

Fortunately, we are getting more and more cancer screening tests with randomized controlled trials with cancer mortality reduction as the end point. There are a number that have shown a beneficial outcome from mammography, fecal occult blood test, spiral CT of the lung, and sigmoidoscopy. There are also some randomized controlled trials that have shown a negative outcome, such as for breast self-exam, chest x-rays for lung cancer detection and CA-125 for ovarian cancer detection. There are also some that have had a controversial outcome, such as prostate cancer screening using the prostate specific antigen with or without a digital rectal exam.

However, it may surprise you to know that not all cancer screening tests that are commonly utilized have randomized controlled trials with mortality reduction as an end point. In fact, one of the best known cancer screening tests and probably the greatest success of modern medicine is the Pap smear and there is no randomized controlled trial studying its effectiveness. It’s --- All the data that we have is indirect or observational. However, there is a wealth of that that has demonstrated a reduction in cervical cancer mortality. Additionally, colonoscopy does not have randomized controlled trials showing its benefits. However, it is used as a test to evaluate a positive fecal occult blood test and that provides the indirect evidence of its benefit.

There are also a number of tests that are utilized in spite of a lack of high level data regarding cancer mortality reduction. For example, breast MRI is utilized in women at increased risk of the disease. We have identified that breast MRI can detect breast cancers that may not be found on exam or mammogram, but we have not yet demonstrated that fewer women will die of breast cancer by getting a breast MRI.

So to evaluate a screening test, there are a number of efficacy measures.

To briefly review, if the test is positive and the patient actually has cancer that is considered a true positive of the test. If the test is negative and the patient does not
have cancer that is considered a true negative. However, if the test is positive, but the patient does not have cancer, that is considered a false positive. And conversely if the test is negative, but the patient actually does have cancer, that is a false negative. The goal is to optimize true positives and true negatives while minimizing the harms of false positives and false negatives.

Sensitivity is the proportion of persons with a condition who correctly test positive when screened. Here is the formula for calculating the sensitivity. Our goal is to have a high sensitivity, which means we will have low false negatives and less missed disease.

Specificity is the proportion of persons without the condition who correctly test negative when screened. And the goal is to have low false positives so that we can avoid unnecessary diagnostic testing.

A positive predictive value is the proportion of persons with a positive test who actually have the condition. And here is the formula for a positive predictive value.

A negative predictive value is the proportion of persons with a negative test who are truly disease free.

There can be a number of biases that can be inherent in evaluating cancer screening tests. This is a list of some.

The selection in healthy volunteer bias occurs in that the population that is screened may tend to be a healthier or more health conscious population than is the general population. Especially, those who volunteer to participate in cancer screening tests. This may make it appear that the test has greater value when, in fact, it may be due to other variables, such as their healthier lifestyle.

Lead time bias is when the screening test advances the diagnosis by a period of time before symptoms develop but death results at the same point in time as if it had been detected by the symptom diagnosis itself. In this case, the patient is actually harmed by being diagnosed earlier, because they are aware of it for a longer period of time with all the associated anxiety. However, it doesn’t change the outcome. They still die from the disease.

Length bias is when we see that slower growing cancers are more likely to be picked up by a screening test and as a result would be picked up at an earlier stage. That means that they’re slower growing. They also tend to be better outcomes overall as opposed to a cancer that is so rapidly growing that it starts after a screening test was done and becomes clinically apparent before the next screening test is due. These cancers because they are more aggressive tend to have poorer outcomes.

Now overdiagnosis bias is actually a length bias extreme. This is where we are diagnosing cancers that are so indolent or so slowly progressing that they never would become clinically relevant in that person’s lifetime. In other words, if we hadn’t
screened for them, we would never have found this cancer. And the person would never have been diagnosed and never had known that they had cancer in their lifetime nor would they have undergone the treatment for such. Clearly a situation we want to avoid.

However, I would propose to you that overdiagnosis not the real problem of screening. --- It's actually the problem is the inability to distinguish which cancers are life-threatening and require treatment from those that are not. This results in over treatment and all the harms that are associated with over treatment. A common example is prostate cancers that are over diagnosed. Men undergo treatment that can cause incon --- incontinence or impotence. It can also cause significant psychological distress. Patients assume that cancer left untreated will kill them. And they very much want to be treated because of this concern. However, we do know that for certain cancers, such as prostate cancers, many will not progress, at least in that individual's lifetime to become a clinical problem.

We need to better understand which cancers will progress and need treatment versus those that do not progress and don’t need treatment. If we could identify that, we would then want to establish a new nomenclature, so that we’re not calling these diseases cancer where patients become concerned that we’re not treating the cancer.

Review a bit about the harms of screening. This has increasingly come to the fore in the press lately that not only are there benefits to cancer screening, but there are associated harms.

We’ve talked about them briefly. False positives, when the screening tests appear to be abnormal, even though there is no cancer. This not only can cause anxiety but often will result in additional testing and maybe even biopsies. Even worse, however, is false negatives, when the screening test appears to be normal even though there is cancer. This may result in delay in seeking medical care even if the individual ends up developing symptoms feeling that they are reassured by having a negative screening test.

Some possible harms from the screening test itself could be due to, for example, a perforated colon at a colonoscopy. An example of a significant false positive would be an individual who went --- underwent a screening lung CT scan that was read as positive. And they ended up needing a biopsy of the lung, which is a significant biopsy, ending up proving that it was benign. And then we’ve already talked about overdiagnosis that would result in treatment that may be the patient never would have needed to undergo and which can carry significant harms.

So whenever we look at a cancer screening test, we want to weigh the benefits and the harms. If the benefits outweigh the harms, it is considered to have a net benefit and screening should be considered.
If, however, the harms are greater than the benefits, then it’s a net harm and screening likely is not appropriate.

Always ask, “Are screen-detected outcomes better than outcomes from disease that is clinically detected?” In other words, waiting until clinical symptoms present.

Remember, it’s hard to improve on asymptomatic. And that’s the population that we are screening. If we are going to medically intervene on people with no symptoms, we should do so based only on strong evidence of good benefits.

As a physician I took an oath, “First, do no harm.” In reality, we try to do more good than harm. We recognize that all intervention have harms in additions to benefits including screening tests. It’s the balance in trying to find those which have greater benefits than harms.

A number of organizations have developed cancer screening guidelines. MD Anderson has a number of cancer screening guidelines and they are available on our website. Other organizations have also produced cancer screening guidelines, such as the American Cancer Society, the National Comprehensive Cancer Network, and the U. S. Preventive Services Task Force.

Also, available at the NCI website is a review of evidence for cancer screening tests.

In summary, screening should make sense. We should screen the appropriate populations and screen only when it will change the outcome. Specifically, fewer people dying from the disease. It’s important to understand and review with the patient the risk or cost associated with the test versus the benefits and make sure that the benefits outweigh the harms. Remember, first do no harm. That concludes this lecture. We welcome your comments. Thank you.