The PSA Debate

A Point Counterpoint Discussion

The Prostate Net

The Prostate Net

Prostate Cancer & the PSA Debate

By John Andrews

Prostate cancer is the most common cancer and the second leading cause of cancer-related deaths in American men. Although the use of the prostate-specific antigen (PSA) test for prostate cancer screening since the 1990s has led to increased early diagnoses, the most recent studies are in conflict about the risks and benefits of routine prostate cancer screening.

On September 11, 2010, The Prostate Net and The Robert H. Lurie Cancer Center in conjunction with the Prostate SPORE, a consortium of Northwestern University, University of Chicago and North Shore University Health System presented their Inaugural Prostate Cancer Forum. This dual track educational initiative for patients/spouses, Advocates and Healthcare professionals convened a world-class faculty of medical professionals to present and discuss the most contemporary treatment options and issues surrounding prostate cancer, including PSA screening.

The initial symposium topic; PSA Testing: Is There An Answer? was introduced by Virgil Simons, Founder and President of The Prostate Net and continued with presentations by two well-known, leading prostate cancer experts, William Catalona, MD, Professor, Northwestern University, Feinberg School of Medicine, Department of Urology and Otis Brawley, MD, Chief Medical and Scientific Officer Executive Vice President American Cancer Society, and Professor of Hematology, Medical Oncology, Medicine and Epidemiology Emory University.

A point-counter-point discussion by Dr. Catalona and Dr. Brawley followed and has been captured for review on The Prostate Net's Symposium Portal: http://prostatenet.com/page/

You are encouraged to read the articles here, visit the site and investigate and decide for yourself the value of routine PSA screening.

Prostate Cancer Screening

Brian Stone, MD

Brian Stone, MD

This is a year of controversy in health care. The economic crisis and the aggressive move towards healthcare reform have further stimulated cost cutting measures by Medicare and private insurance carriers. Reimbursements for cancer early detection are being heavily scrutinized.

The AUA believes that the wide spread use of PSA screening has led to the earlier diagnosis of prostate cancer and improved short term outcomes after diagnosis. However, this belief has not been supported by randomized trials. The current position by many opponents of screening, that prostate cancer early detection is not warranted is fueled by those lobbying for "healthcare cost containment" and not necessarily for the preservation of male lives. This is especially true in high risk populations such as men of African descent and those with a strong family history of prostate cancer.

By the end of our discussion I am certain that you will be convinced that early detection is warranted in high risk populations, especially African American men when offered in an informed manner.

Facts:

Prostate cancer remains the most frequently diagnosed cancer in men. An estimated 192,280 new cases are expected to be diagnosed in 2009 along with 27,360 deaths from this disease. There is a significant disparity is the incidence and mortality of prostate cancer between men of African descent and the rest of the American population (specifically African American and Jamaican men).

Several screening trials are currently underway attempting to provide the much needed data but they have severe under representation of high risk populations making their conclusions useless for men of color. There was never comparable scrutiny for mammography and breast cancer early detection, why????

Quebec Trial (Labrie et al)

This trial enrolled 46,486 men aged 45 -80 years which were randomly assigned to screening and no screening in 1988. The 11 year follow up showed a 62% reduction in prostate-specific mortality among the screened men (P = .005).

Study Drawback: There are concerns over the design of this trial leaving this the least robust data set addressing PSA screening. No data on men of African descent.

The Tyrol Study

This study involved [12] different projects. The PSA screening study enrolled 21,079 men in Tyrol, Austria in 1993 and study published in 1999. These data suggest that PSA-based screening with low PSA cut-off values increase the detection rate of clinically significant, organ confined and potentially curable prostate cancer.

Study Drawback: Follow up period not long enough and there were no men of African descent in the study.

European Randomized Study of Screening for Prostate Cancer (ERSPC)

This study evaluated the effects of screening on advancing the time of diagnosis (i.e., lead time) and detecting cancers that would not have been diagnosed in the absence of screening (i.e., over detection). Investigators identified 182,000 men 50 to 74 years of age from seven European countries in the early 1990's (enrollment dates in each country varied). These men were randomized in to screening vs. control group. The screening group received a PSA test every 4 years and the men in the control group "supposedly" did not receive a PSA test at all. The 162,243 men included in this analysis were 55 to 69 years of age. This study concluded that while prostate cancer deaths were reduced by 20%, over detection of incidental prostate cancers is a consequence of screening.

Study Drawback: Follow-up period not long enough to assess true mortality impact and no data of men of African descent.

PLCO Cancer Screening Trial

The prostate, lung, colorectal and ovarian cancer study is a large-scale clinical trial to determine whether certain screening tests reduce the mortality from these cancers. This study enrolled 154,942 men and women between the ages of 55 and 74. Men entering the prostate cancer component of the study were randomized into either the cancer screening arm or to continue their normal health care routine. Men in the screening arm received PSA blood testing and a DRE upon entry.

The PLCO data six rounds of annual screening led to the diagnosis of 22% more prostate cancers by 7 years after the start of screening and 17% more prostate cancers by 10 years from the start of screening. The difference in the number of prostate cancer deaths between the two study groups was not statistically different.

Study Drawback: Follow-up period not long enough and no analysis of data in AA men available.

Screening Guidelines:

US Preventative Services Task Force

In 2008, the USPSTF concluded that there was insufficient data to support / recommend PSA screening in men 75 years of age or older.

American College of Preventive Medicine

They concluded in February 2008 that there is not enough evidence to recommend routine population screening for prostate cancer using DRE and PSA testing.

The National Comprehensive Cancer Network Guidelines

They recommend baseline risk assessment with DRE and PSA at age 40. Men with a baseline PSA of <0.6 ng/ml can wait until

age 45 for additional prostate cancer screening, but men with a PSA >0.6 ng/ml should proceed with follow-up screening.

American Urological Association Guidelines

The AUA recommends that the PSA blood test be offered to well informed men aged 40 years or older who have a life expectancy of at least 10 years. The AUA recognizes that the use of PSA in the detection of prostate cancer is very controversial; however, they believe that when the test is offered and interpreted appropriately, the PSA blood test may provide essential information for the diagnosis, pre-treatment staging or risk assessment and post-treatment monitoring of prostate cancer.

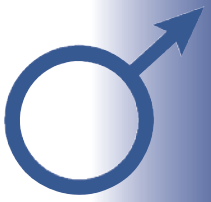
R. Frank Jones Urological Society Guidelines

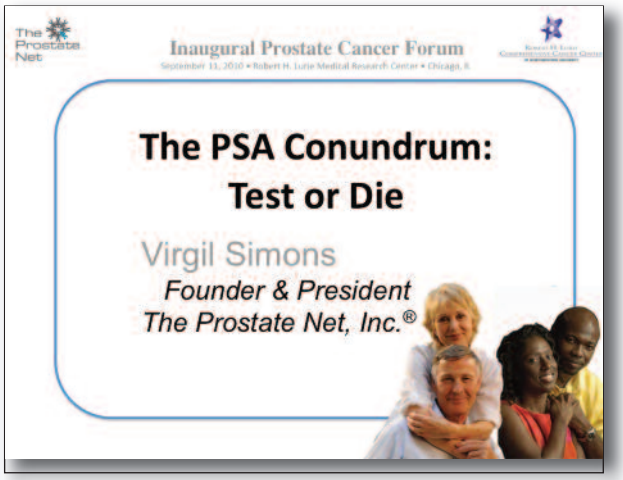
The RFJUS represents the interests of the nations African American urologists (and patients) and established guidelines that were published in 1998 that recommended that all high risk males began annual PSA testing and DRE at the age of 40. We are currently a recognized society within the AUA and have embraced its current guidelines.

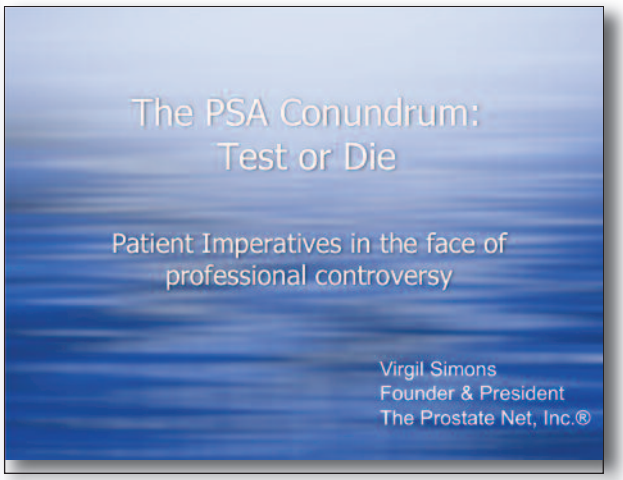
American Cancer Society Guidelines

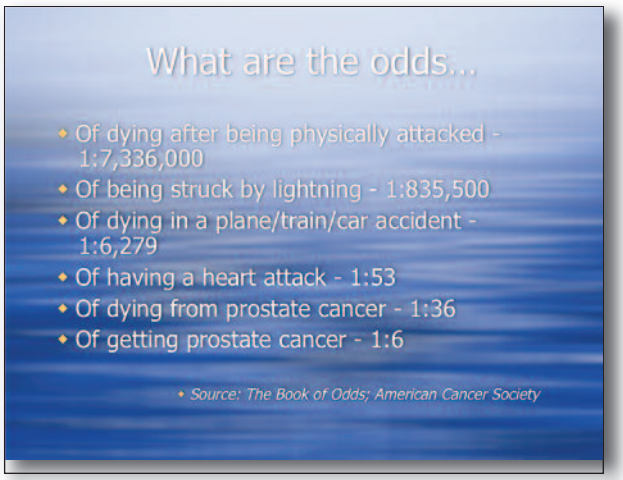
The ACS does not support routine testing for prostate cancer at this time. However, they do believe that health professionals should "discuss" the potential risks and benefits of prostate cancer early detection testing with men before any testing is initiated. This discussion should include an "offer" of testing with PSA blood testing and the DRE annually starting at the age of 50 in men with an "average" risk of prostate cancer and a life expectancy of 10-years. This discussion should take place at the age of 45 in high risk populations.

Editor's Note: The Prostate Net® supports the importance of PSA testing for all men in order to, at minimum, establish a baseline level of prostate health, from which informed decision making can be made.









PSA Testing: Is There an Answer?

Virgil Simons: The Patient's Perspective

I. The PSA Conundrum: Test or Die

We're going to talk about what the PSA test means in today's world and in the future. The controversy around the PSA test has been building, and ultimately men are saying should I test or should I just die? They don't have any ideas in terms of how to best handle the controversy.

Virgil Simons

II. What are the odds. . .

The odds of dying from prostate cancer are 1:36, and the odds of getting prostate cancer are 1:6. If you look at the African American community and the Latino community to a lesser degree, the numbers are even higher. From an odds standpoint, the experience that we all could potentially have with prostate cancer is very high compared to a lot of other risks.

III. Early Disease Detection Barriers

Most of you have read about the controversy between the U.S. and European tests in terms of what screening means. We have seen a whole host of recommendations from a variety of agencies in the U.S., and there has also been the question of how we really determine risk. Ultimately, what we want to know is whether we have a disease that is potentially going to kill us or if it is a disease that we can live with.

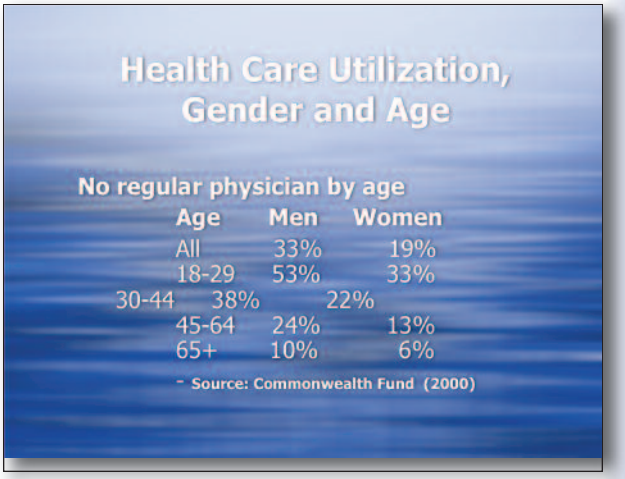
In terms of looking at risk, men sometimes exacerbate the risk in the following ways: Compared to women, men are less likely to use the health care system. They are less likely to have health insurance, and they are more likely to delay seeking care.

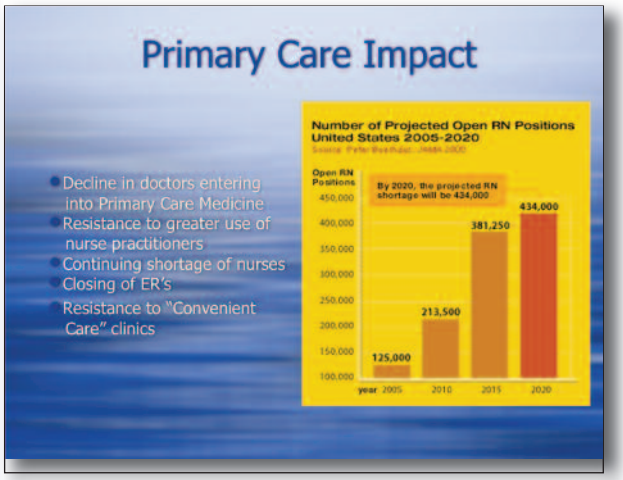
IV. Defining Barriers to Men's Participation in Health Care

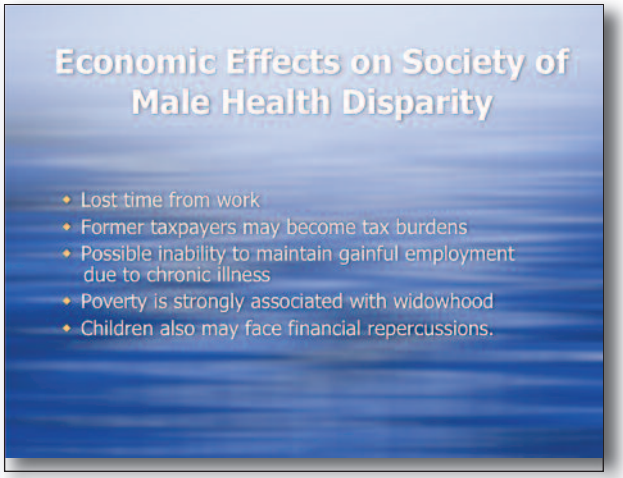
In terms of attitudinal barriers, there tends to be a lot of gender role stoicism. There is also work role stoicism—can't take off from work because I'm sick. There is in many cases a lack of trust in the health care system, and another issue is that there is a lot of fatalism that exists—you have to die from something. We have to look at our own risk in terms of changing this paradigm.

V. Health Care Utilization, Gender and Age

Women utilize healthcare 100% more than men, which may explain why women outlive men on average.





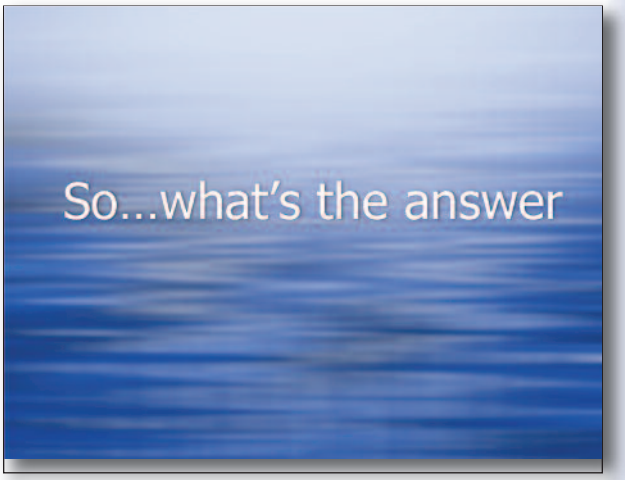


VI. Primary Care Impact

In terms of systemic issues, there is a situation now where there are fewer doctors that are going into primary care medicine. There is a resistance on the part of many people in the establishment to nurse practitioners taking up that role, and by 2014 there is going to be a shortage of over 400,000 nurses in America. Emergency rooms are closing for financial reasons, and there is a resistance to "convenient care clinics." The primary care system of early detection is going away, which will result in more and more advanced stage cases at first diagnosis. Despite the PSA test and the ability to find the disease earlier, if there is not a system in place to administer the test and monitor health, we will in effect go back to the old days when men go to the doctor with bleeding and pain and find out that they have advanced stage disease.

VII. Economic Effects on Society of Male Health Disparity

We should also look at the economic effects of male health disparity on society. The lost time from work means lost revenues. People who have been taxpayers all of the sudden become tax burdens. They have to go on welfare or other kind of social help. If a debilitating bout of prostate cancer progresses, continuity of work becomes an issue as well. When men die from prostate cancer and even other diseases, the people they leave behind carry another greater burden. Women have difficulty at a more mature age finding a partner, which puts them at reduced financial circumstances. The children of the families, again, are going to be in reduced financial straits. It becomes less likely that they will have the ability to go to college and have the future that you planned for them.


So…what's the answer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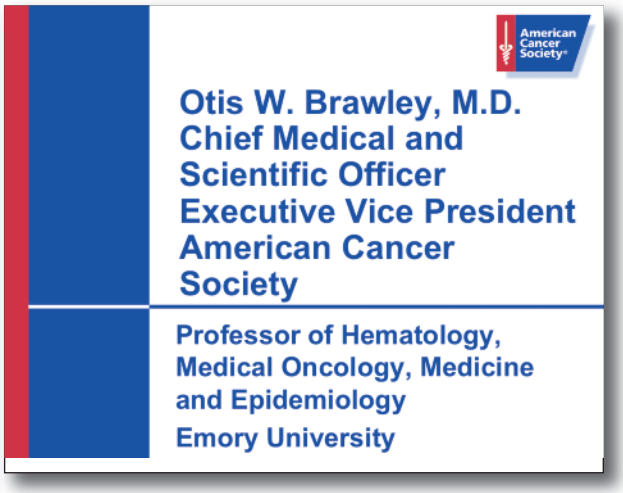
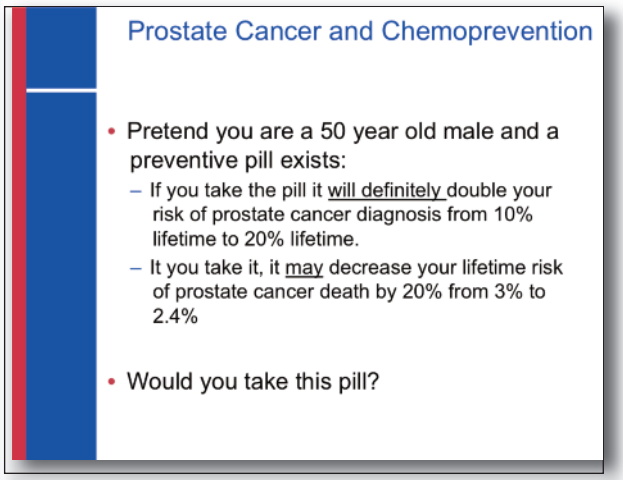


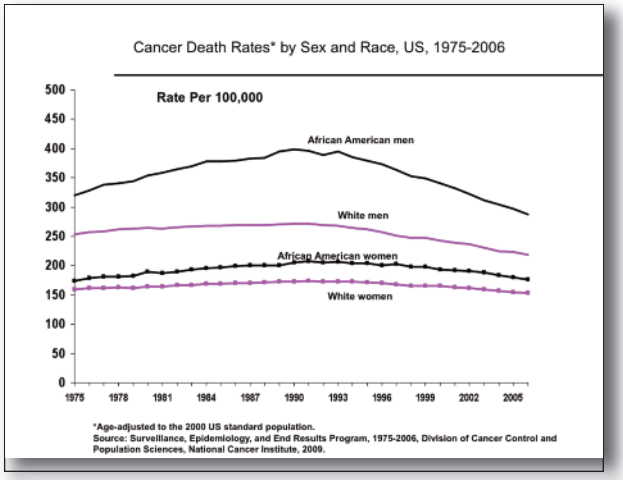
Otis Brawley, MD

I. Introduction

Otis Brawley, MD

I'm a medical oncologist; I treat prostate cancer patients. I'm also an epidemiologist. I'm a scientist who studies what happens in the population—outcomes. The reason why epidemiologists are important is because we need to keep an open mind. When individuals in medicine keep a closed mind, they get into a lot of trouble and actually start hurting people. We can define the scientific questions that need to be addressed, the treatments that are successful, and the treatments that are not successful. If we can convince people and doctors of the important scientific questions, we can then do the studies that help us figure out if something works or find out if something works better than something else. Those who are in medicine have a long history of adopting things before they are actually adequately assessed.



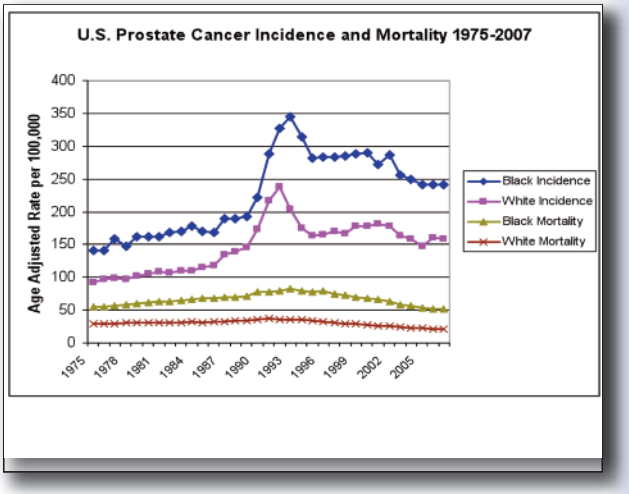


II. Cancer Death Rates

In 1975, for every 100,000 Black men alive in the United States, 325 died of cancer. Over time, that number increased. In 1992 and 1993 it peaked, and since then it has gone down. The disparity between Black and White men is decreasing as the mortality rate for Black men in the United States is going down faster than any other group. The death rate decline in Black men is overwhelmingly driven by declines in lung cancer deaths because Black men either stopped or didn't start

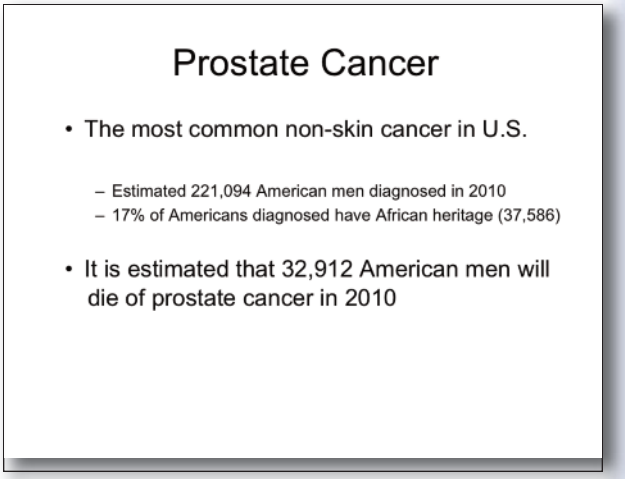
smoking in the 1960s and 1970s, and colorectal cancer screening was utilized. There is no debate that colorectal cancer screening saves lives. It clearly decreases the risk of death by 35%.

In terms of the U.S. prostate cancer incidence in mortality from 1975-2007, there was a dramatic rise in the incidence in the 1990s, which was due for the most part to prostate specific antigen screening.



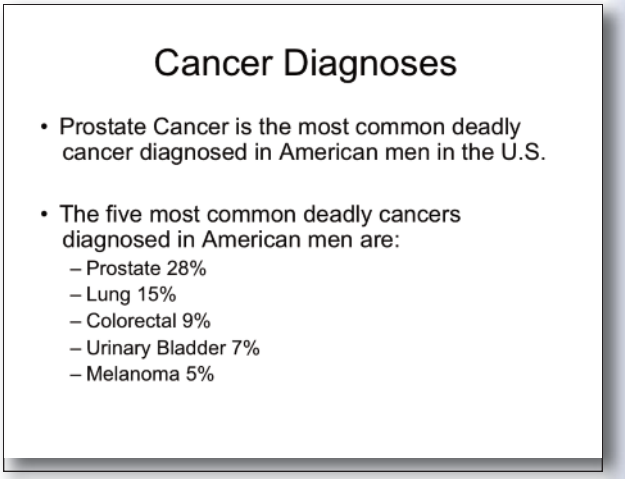
III. Prostate Cancer

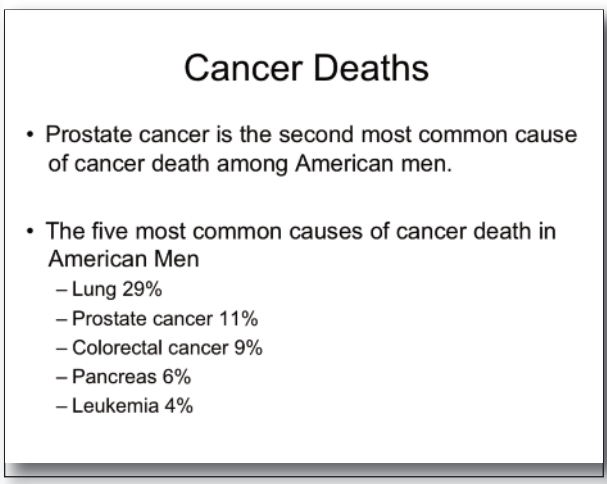
Prostate cancer is the most common non-skin cancer in the United States. It is estimated that 221,094 American men will be diagnosed with prostate cancer in 2010. About 32,912, American men will die from prostate cancer in 2010, and we know that in screening populations today between 20 and 25% of screen-detected men with apparently localized disease at diagnosis, about one in five to one in ten, ultimately die from the disease. We need a better screening test than PSA. It is an advancement over what we had before, but we still need a better test.



IV. Cancer Diagnoses

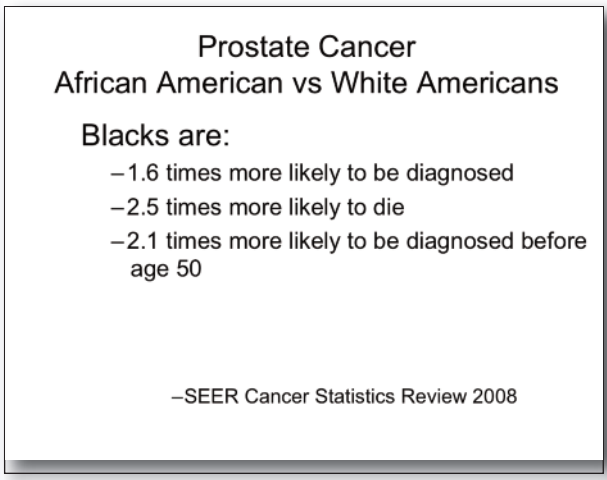
Prostate cancer is the most common deadly cancer diagnosed in American men in the U.S., and it is approximately 28% of all cancers diagnosed.





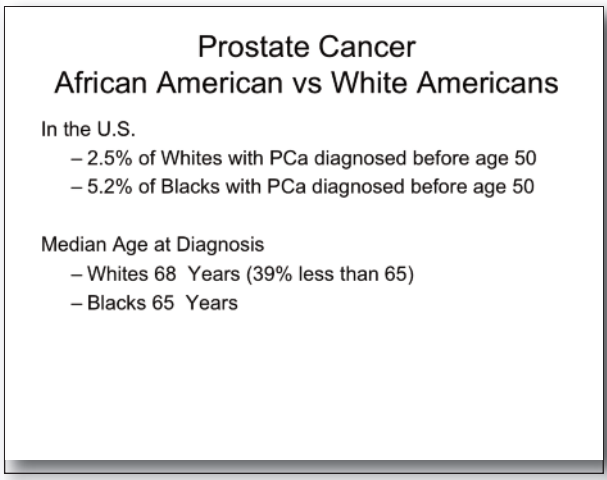
V. Cancer Deaths

Prostate cancer is the second most common cause of cancer death among American men.



VI. African Americans vs. White Americans

We have gone to Africa and found that there are huge disparities in prostate cancer death rates in various parts of Africa among Africans. In the United States and in the Caribbean, Blacks are 1.6 times more likely to be diagnosed with prostate cancer than Whites and 2.5 times more like to die. They are 2.1 times more likely to be diagnosed before the age of 50.



In the U.S., 2.5% of Whites with prostate cancer are diagnosed before the age of 50, and 5.2% of Blacks are diagnosed before the age of 50. That is about one out of twenty Black men with prostate cancer who are diagnosed before the age of 50. The median age at diagnosis of prostate cancer for Whites is 68, and the median age for Black men is 65.

VII. Aggressiveness/Grade of Disease at Diagnosis

I often hear that prostate cancer is more aggressive in Black men than White men, but nobody ever shows the data. In terms of Gleason scores, however, in the United States the proportion of men diagnosed with Gleason 3+4, Blacks and Whites, are essentially the same.

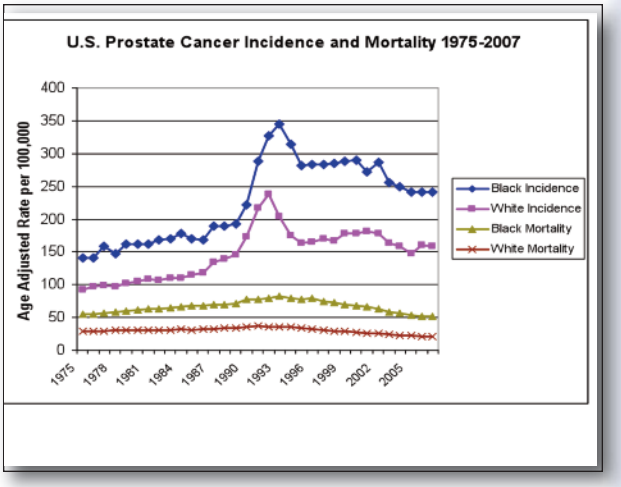
Prostate Cancer
Aggressiveness/Grade of Disease at Diagnosis

Gleason Score	All	Whites	Blacks
2-6	46.3%	46.8%	42.8%
3+4	23.7%	23.5%	25.1%
4+3	9.3%	9.2%	9.8%
8-10	14.2%	14.1 %	14.9%
Unknown	6.5%	6.4 %	7.4%

NCI SEER Program 2009

VIII. Prostate Cancer Screening

The thing about PSA screening, which is widely done, is it clearly leads to increased numbers of men who are diagnosed. It clearly misses as much cancer as it finds; however, and we need a better test.



IX. Cancer Screening

People make money in the business of cancer screening, and we have a moral obligation to tell people what we scientifically know, what we don't know and what we believe. We must label these things accordingly. The quandary in prostate cancer is that there clearly are cancers that do not need to be cured but can be cured. There are also cancers that need to be cured but cannot be cured, but we do not know if we cure any disease that needs to be cured. We must approach the issue ethically, logically and rationally.

Prostate Cancer Screening

- Prostate Specific Antigen testing is widely done in U.S. despite questions regarding its efficacy.
  - It clearly leads to increased numbers of diagnoses
  - It clearly misses as much cancer as it finds
  - It is unclear that it finds disease that is life threatening but treatable

Prostate Cancer Screening

- The quandary of prostate cancer screening
  - There are cancers that do not need to be cured but can be cured.
  - There are cancers that need to be cured but cannot be cured. (The patient dies).
  - We do not know if we cure any disease that needs to be cured. ("Do we save lives?" is an open question).

Several studies have shown that PSA screening finds a lot of cancer, but these studies have failed to show that the screening saves lives. In an interim analysis, a French study showed a 20% decline in relative risk of prostate cancer death with a P value that was statistically significant. It was, however, an interim analysis, and the P value was very close to not being statistically significant. The European study showed you had to treat 48 men in order to save one life.

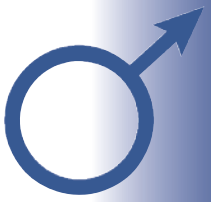
Cancer Screening

- An issue that must be approached ethically, logically and rationally
- We must realize:
  - What we know.
  - What we do not know.
  - What we believe.

Biomarkers for Early Detection

The Biotech Revolution

- Methods for detecting colon polyps
- Methods to detect cervical dysplasia
- PSA – Prostate Cancer
- CA 125 – Ovarian Cancer
- Numerous Others



Cancer Screening

- Well designed clinical studies have demonstrated the mortality reduction through:
  - –Mammography and CBE for Breast Cancer
  - –Stool Blood Testing, Sigmoidoscopy and Colonoscopy for Colorectal Cancer

Prostate Cancer Screening

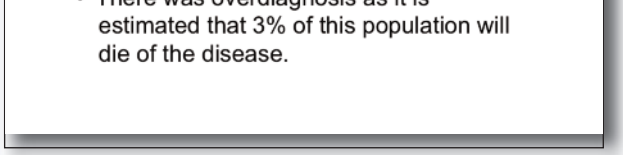
- Several studies have shown PSA screening finds a lot of cancer, but have failed to show that prostate cancer screening saves lives.
- The large study suggesting that screening may save lives had a tenuous p value and showed that 48 men needed to be treated to save one life at ten years of follow-up.

X. Prostate Cancer Prevention Trial

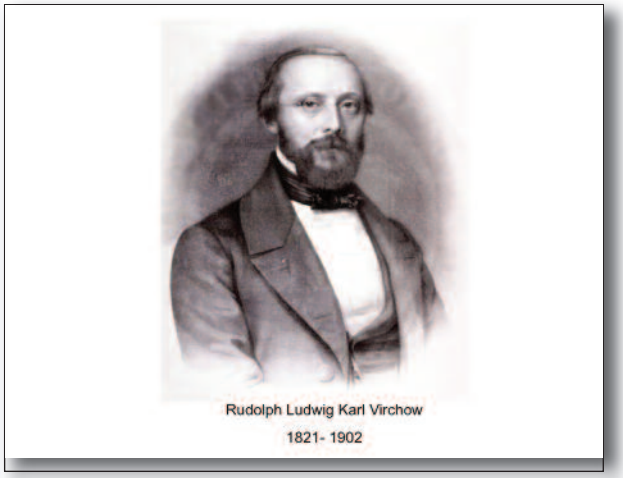
More than 18,000 men were randomized to finasteride or placebo for the Prostate Cancer Prevention Trial. The median age was 62, and they were followed over a period of time. The placebo control group is the best screened cohort of men in the history of prostate cancer screening with eight screens over seven years in men at the median age of 62 with a PSA of less than 3 to get on to the trial. Ultimately, once the trial was completed 14% of the men were diagnosed with prostate cancer due to those eight PSA screens over seven years. Per

The Prostate Cancer Prevention Trail (the placebo arm)

- Median age 62 with PSA less than 3.0 and screened annually for seven years.
- 14% diagnosed with cancer due to screening during the seven years.
- 14% diagnosed with cancer on terminal biopsy done per protocol among those with a “normal screen” for seven years.

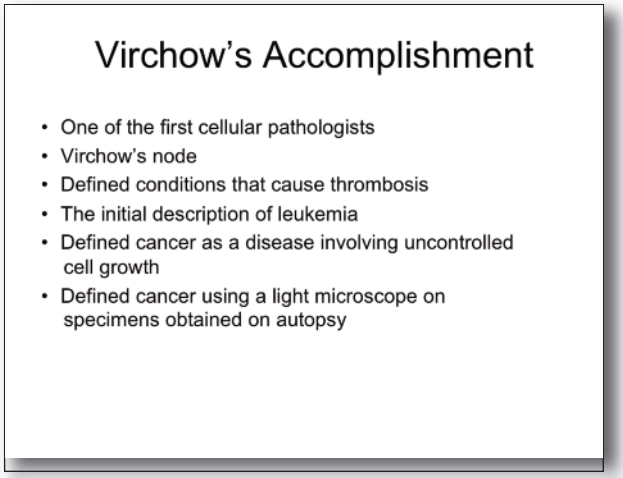


protocol, anyone who had a normal screen for at least seven years got a biopsy of their prostate anyway, and 14% of those guys were diagnosed with prostate cancer. We were able to diagnose 28% of men in their late sixties with prostate cancer, but the epidemiologists tell us that only 3% of men who are age 60 are ever destined to die from the disease.



XI. Rudolph Ludwig Karl Virchow

Virchow was one of the first cellular pathologists. He was the person who initially described leukemia as a disease, and he defined cancer as uncontrolled cellular growth. Cancer had been around for thousands of years, but nobody realized that it was uncontrolled cell growth until Virchow. He did this with a light microscope, and he went on to make drawings of normal cells versus abnormal cells defining the rules under which we define cancer. We need, however, a 2010 definition of cancer.



XII. Greatest Need in Prostate Cancer Screening and Diagnosis

We need a better test than PSA to find cancer, and we also need a test to determine when a patient has cancer that is a threat to their life versus cancer that is not a threat. The ultimate test is likely to involve genomics, the study of the presence of genes and their expression.

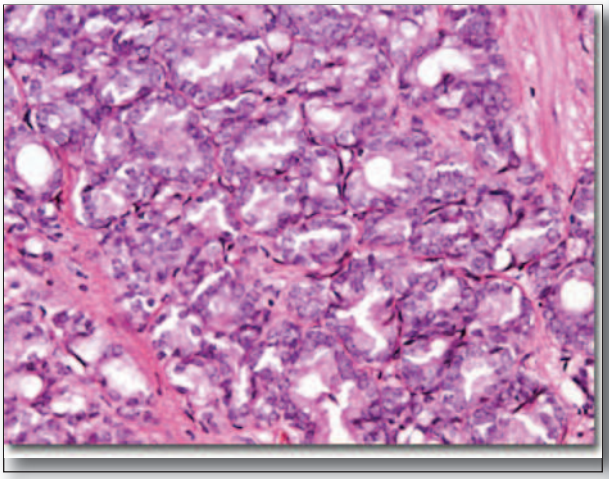
XIII. Consensus

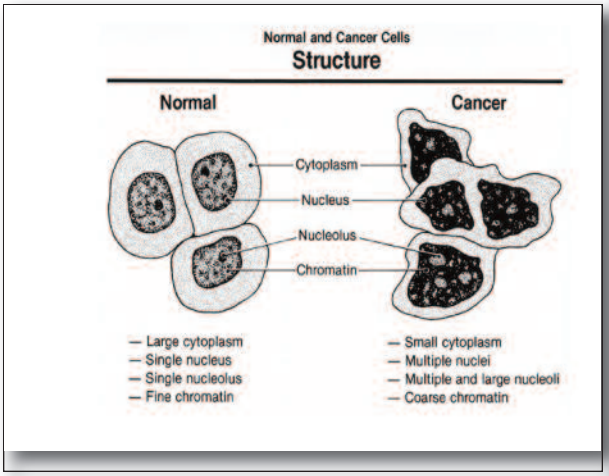
There is consensus. After the trials that were published last year, the American Urological Association did say that because we have one study that suggests that screening may save lives, they were in favor of screening, which was reasonable. They also said that given the uncertainty that PSA testing results in more benefit than harm, a thoughtful and broad approach to PSA is critical. They said patients need to be informed of the risks and benefits of testing before it is undertaken, and the risks of over detection and over treatment should be included in that discussion.

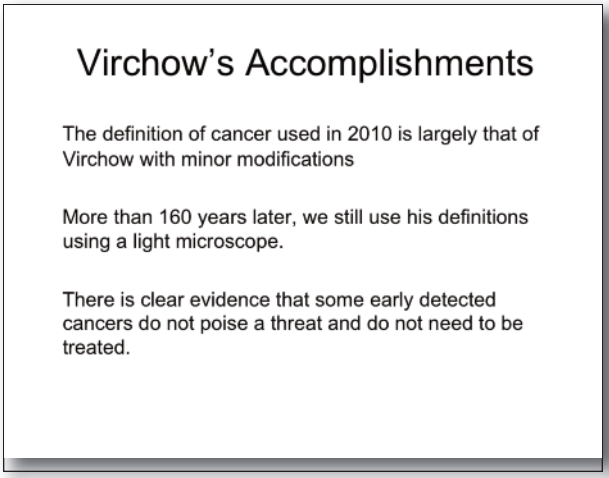
The European Association of Urology recommends first against mass screening because they are for informed decision making within the physician-patient relationship. Their concern is that appropriate discussions can't happen during mass screenings.

According to the American Cancer Society 2010 Prostate Cancer Screening Guideline, "Men should have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer, after receiving information about the uncertainties, risks, and potential benefits associated with prostate cancer screening."

Every man that wants to be screened should be supported, and every man that doesn't want to be screened should not be criticized. I am not against prostate cancer screening, but I am against over stating its possible benefits while recognizing the fact that there are possible benefits.







The Greatest Need In Prostate Cancer Screening and Diagnosis

- A test to determine who has cancer that is a threat to one's life vs cancer that is no threat to one's health.
- It is reasonable to ask why did it take two decades for American Medicine to realize this.
- This test is likely to involve genomics, the study of the presence of genes and their expression

Cancer Screening

- An issue that must be approached ethically, logically and rationally
- We must realize:
  - What we know.
  - What we do not know.
  - What we believe.

American Urological Association

Given the uncertainty that PSA testing results in more benefit than harm, a thoughtful and broad approach to PSA is critical.

Patients need to be informed of the risks and benefits of testing before it is undertaken. The risks of overdetection and overtreatment should be included in this discussion.

PSA Best Practice Statement 2009

I am not optimistic that the question, "does PSA screening save lives?" can be answered. To do so would require a concerted, expensive effort lasting for fifteen or more years. It is unfortunate that prostate cancer screening was implemented before it was adequately assessed to determine if it saved lives. I believe the question will never be answered because too many people believe rather naively that "early detection always saves lives." Because of this belief in screening, some of the screening studies that should be done are not being supported. Ironically some studies that have been completed demonstrate that the utility of PSA is a legitimate question.

It is important to note that all major medical organizations that have a process for developing screening recommendations have recognized the fact that PSA screening is a legitimate question.

The American Urologic Association in it 2009 PSA Screening Best Practice statement says "Given the uncertainty that PSA testing results in more benefit than harm, a thoughtful and broad approach to PSA is critical. Patients need to be informed of the risks and benefits of testing before it is undertaken. The risks of overdetection and overtreatment should be included in this discussion. "

The European Association of Urology has made a statement that recommends against mass screening and recommends for informed decision making within the physician-patient relationship. They state "Men should obtain information on the risks and potential benefits of screening and make an individual decision" (European Urology 56(2), 2009).

The American Cancer Society screening statements since 1997 have been largely consistent with the above statements. The current ACS statement is "men should have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer, after receiving information about the uncertainties, risks, and potential benefits associated with prostate cancer screening."

The three organizations above made these comments after incorporating the interim results of two large clinical studies published in spring 2009. The Prostate, Lung, Colon, and Ovarian Cancer Screening Trial (PLCO) is a large Federaly funded study. The prostate portion is 73,000 men randomized

European Association of Urology

- Recommends against mass screening.
- Recommends for informed decision making within the physician-patient relationship.

"Men should obtain information on the risks and potential benefits of screening and make an individual decision"

European Urology 56(2), 2009

The American Cancer Society 2010 Prostate Cancer Screening Guideline

"Men should have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer, after receiving information about the uncertainties, risks, and potential benefits associated with prostate cancer screening."

to screening or usual care. The European Randomized Study of Screening for Prostate Cancer (ERSPC) is a conglomerate of eight clinical studies comprising more than 150,000 men in six countries.

Simply finding cancer is not proof that a screening test saves lives. Indeed two cancer screening tests have been widely implemented and then withdrawn after it was realized that they found disease, but also caused more harm than good. Urine testing for a chemical, called VMA, was advocated for a childhood tumor called neuroblastoma in the 1980's and ultimately found to increase the number of children receiving major surgeries without a change in cancer specific mortality. Chest Xray screening for lung cancer was advocated from 1960 to 1975. Several randomized studies ultimately showed it did not save lives and actually increased the number lung biopsies. Since the mid 1970's, medicine has not had an accepted screening test for lung cancer.

The problem in prostate cancer screening is there are scientifically proven to be two kinds of prostate cancer and we hope there is a third.

- There is cancer that can be diagnosed and need not be cured but can. Some epidemiologists estimate that 60% or more of all diagnosed prostate cancers over the past twenty years in the U.S. did not need treatment as they were of no threat to health.
- There is cancer that can be diagnosed and needs to be cured but cannot. These are our patients who die of the disease. They represent 20 to 30% of men diagnosed with the disease in the U.S through screening.
- The unanswered question is "Are there prostate cancers that need to be diagnosed and cured, that can be diagnosed and cured?"

There is much evidence that there is a type of prostate cancer that does not need to be cured. This type of prostate cancer is commonly found through screening. We desperately need to find a test to determine the cancers that need to be watched and those that need to be aggressively treated. Gleason score is a very crude method that is clearly useful but needs improvement.

The Prostate Cancer Prevention Trial (PCPT) was an 18,000 man study that began in 1992. Half of all men received placebo for seven years. Their median age was 62 at the start of the trial and 69 at the end. A total of 28% of men median age 69 were diagnosed with prostate cancer. Half because of an abnormal screening test during the seven years and half after a biopsy done after eight normal screens done over seven years. PSA screening missed as much disease as it found.

In this population who are the most thoroughly screened cohort in the U.S. there was definite overdiagnosis (the diagnosis of those who did not need treatment) as it is estimated that 3% of this population will die of the disease. Ninety plus percent of the men diagnosed with prostate cancer had volumes of disease and Gleason grades that would normally be treated in the U.S.

The PCPT and several other studies have shown us that screening misses a lot of prostate cancer. If one screens 10,000 male volunteers over the age fifty, we would have 7.6% or 760 with a PSA greater than 4.0 ng/ml. Of these 760 men 190 will have a positive biopsy and 36 with have high grade disease. We now know that among those with a normal PSA (less than 4.0) 1386 would have cancer and 208 would have high grade disease. PSA screening as done over the past twenty years misses more cancer than it finds and misses morehigh grade cancer than it finds.

I will conclude by noting that the scientific process has shown us many of the shortcomings of prostate cancer screening. The scientific process has also not been fully respected by some advocates for prostate cancer and men's health has suffered for it.

QUESTION

- Pretend you are a 50 year old male and a preventive pill exists:
  - If you take the pill it will definitely double your risk of prostate cancer diagnosis from 10% lifetime to 20% lifetime.
  - It you take it, it may decrease your lifetime risk of prostate cancer death by 20% from 3% to 2.4%
- Would you take this pill?

PSA Testing

William J Catalona MD
Northwestern University

Financial Disclosures

- Beckman Coulter, Inc. – manufacturer of PSA assays (research support and honoraria for consultation and speaking)
- deCODE genetics – DNA based reference laboratory for multiple genetic risk factors (research collaboration)

Prostate Cancer

- Most common non-skin cancer in US men
- Most are detected through PSA screening of men without symptoms with the objectives of earlier disease detection, thereby improving outcomes

William Catalona, MD

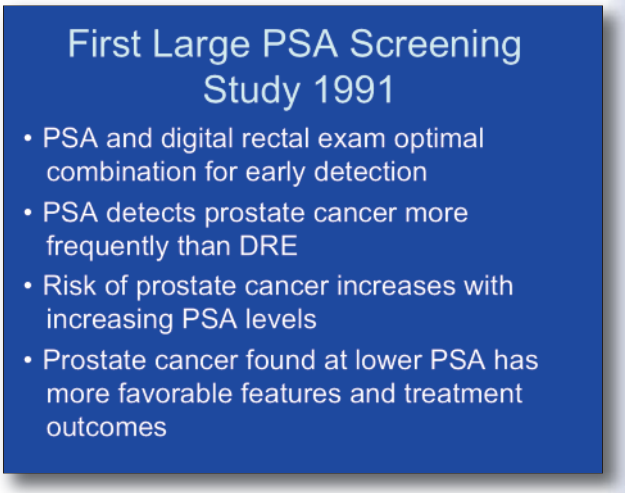
I. Introduction

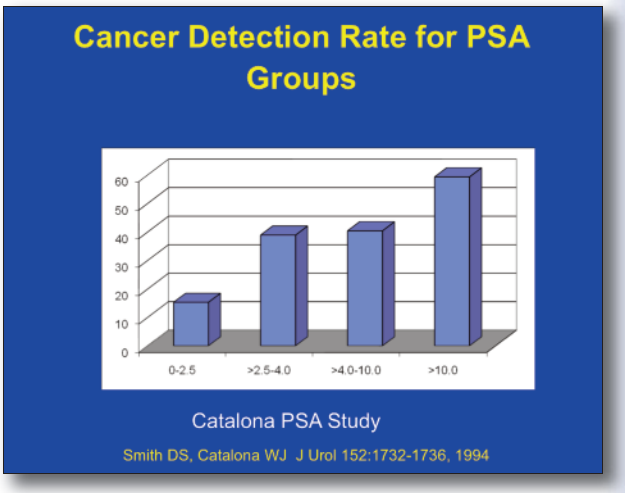
William Catalona, MD

I am for prostate cancer screening, and I will present the other side of the issue. Most men with prostate cancer are detected through PSA screening, and the objectives of prostate cancer screening are to detect cancer earlier than it would be detected if you waited for symptoms and to allow for improved outcomes because the cancer was detected earlier.

II. First Large PSA Screening Study

The first large PSA screening study was published by my research group in 1991 in the New England Journal of Medicine, and it showed that PSA and the digital rectal exam together make up the optimal combination for screening detection. PSA is the better of the two tests and detects more prostate cancer than the digital rectal exam. As a man's PSA level increases, his risk of having prostate cancer increases, and men who are diagnosed with prostate cancer at lower PSA levels have more favorable tumor features than men with higher PSA levels and better treatment outcomes.

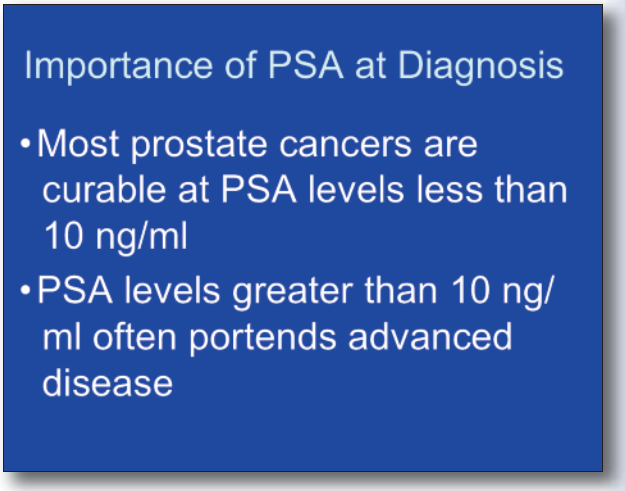




III. Importance of PSA at Diagnosis

These studies have also shown that most prostate cancers that are detected with a PSA of less than 10 are curable, and prostate cancers that are detected with a PSA of higher than 10 are more likely to have advanced disease at the time of diagnosis.

When we did the screening study, we enrolled 36,000 men, and the study went on for 12 years. When the study ended, we looked at the median PSA value for each age group. If we looked at the probably of being diagnosed with prostate cancer



Median PSA in Men Enrolled in PSA Study 1989-2001 (n = 36,000)

Age Group	Median PSA (ng/ml)
40s	0.7
50s	0.9
60s	1.3
70s	1.7

as a function of a man's PSA in relation to the median for his age group, if his PSA was lower than the median, his risk was not zero but it was very, very low. If it was higher than the median value, his risk was higher than the general population of his age group. The higher the PSA was in relation to the median, the greater the likelihood that he would be diagnosed with prostate cancer and the greater the likelihood that the prostate cancer detected would be an aggressive prostate cancer.

Age-Group-Specific Median PSA

- Risk for cancer is low for men below the median
- Risk for cancer is higher for men above median
- Risk for aggressive cancer also increases

Loeb S, et al. Urology. 2006;67:316-20

PSA Derivatives Improve Accuracy

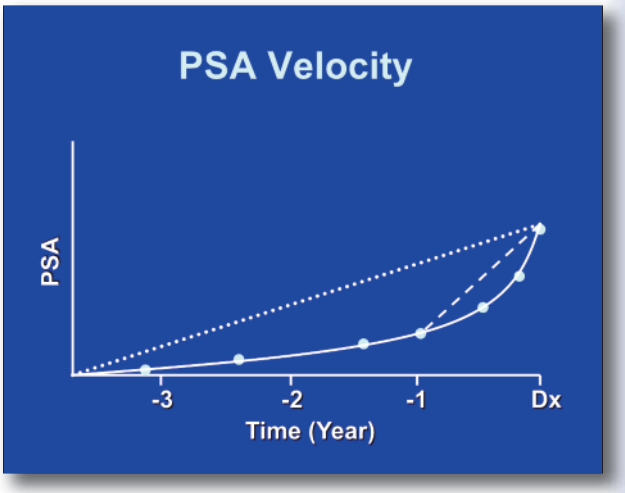
- PSA velocity
- PSA density
- Percent free PSA
- *Pro-PSA (future)*

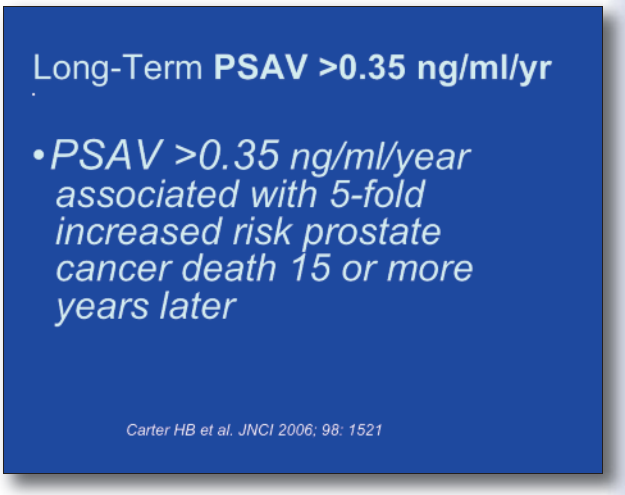
IV. PSA Derivatives Improve Accuracy

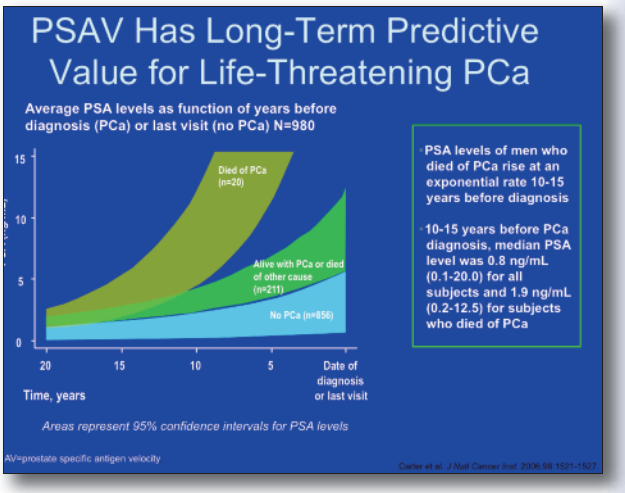
The PSA is not a perfect test and it does need improvement, but it's the best thing that we currently have. There are ways to improve the accuracy of PSA, which include measuring how rapidly it rises over time, which is called PSA velocity, measuring how big the prostate is in relation to the PSA level in the blood, which is called PSA density, and measuring the percentage of PSA that is free floating in the blood stream, which is called percent free PSA. There is also a new test that is under review by the U.S. FDA called the Pro-PSA that is

approved in Europe and is commercially available there. It is more accurate than PSA and preferentially detects the more aggressive forms of prostate cancer.

A PSA velocity of greater than 0.35 mg/ml/year is associated with a five-fold increased risk of prostate cancer death 15 or more years later. The PSA velocity test has long-term predictive value for life-threatening prostate cancer.







No screening test is perfect

- False positives (inflammation and benign enlargement)
- False negatives (some aggressive cancers do not produce much PSA)
- Diagnosis and treatment of some tumors that would not have caused harm

V. Overview

No screening test is perfect. There are false positives. Men who have inflammation in their prostates or a benignly enlarged prostate can have high PSAs, and these can cause false alarms that are sometimes very upsetting. False negatives also occur, and there are some very aggressive cancers that do not produce much PSA. In screening for cancer and trying to detect cancer earlier, you are going to diagnose and treat some tumors that would not have caused harm during the patient's lifetime. That goes with the territory.

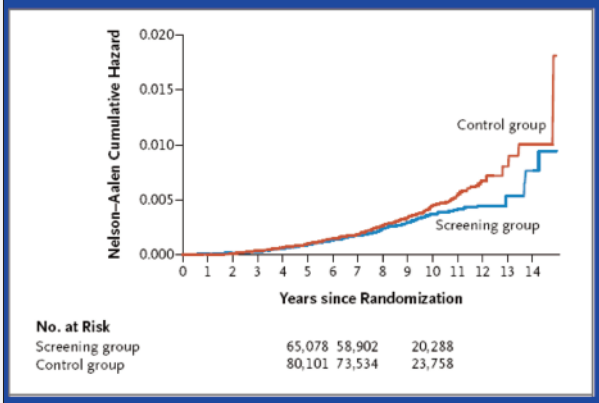
Screening and prostate cancer mortality in a randomized European study (ERSPC)

- At a median f/u 9 years
- PCa mortality = 20% lower in screening arm-27% lower for men who were actually screened
- 1410 men need to be screened and 48 cases treated to prevent 1 PCa death
- Conclusion: Screening reduces PCa death rate with a high risk for over-diagnosis

Schroder FH et al NEJM 360:1320, 2009

VI. ERSPC

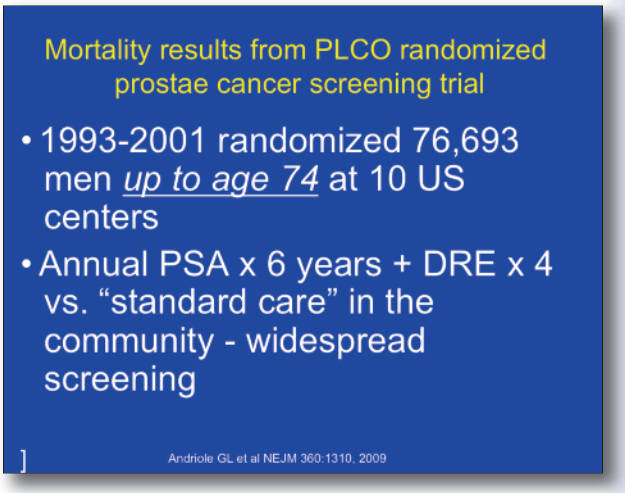
At a median follow up of nine years in the randomized European study (ERSPC), the prostate cancer mortality was 27% lower for men who were actually screened. The calculations of number needed to treat and number needed to screen, which were that 1,410 men needed to be screened and 48 cases treated to prevent one prostate cancer death are very dependent on the follow up. With greater follow up and greater differences in survival, the numbers have come down dramatically. Based on this European trial, screening reduces the prostate cancer death rate but carries with it a high risk for over diagnosis.

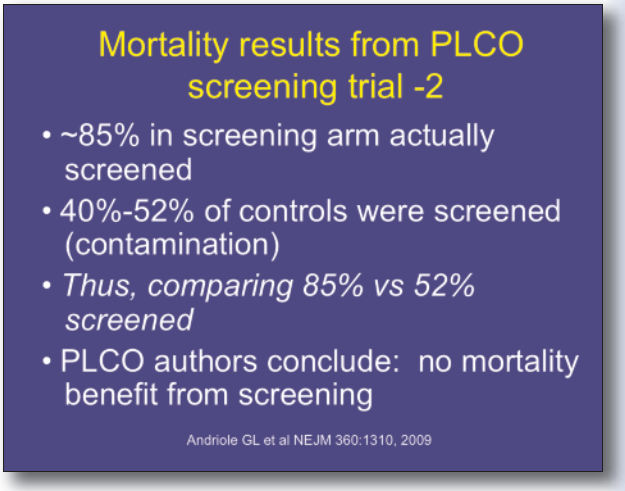


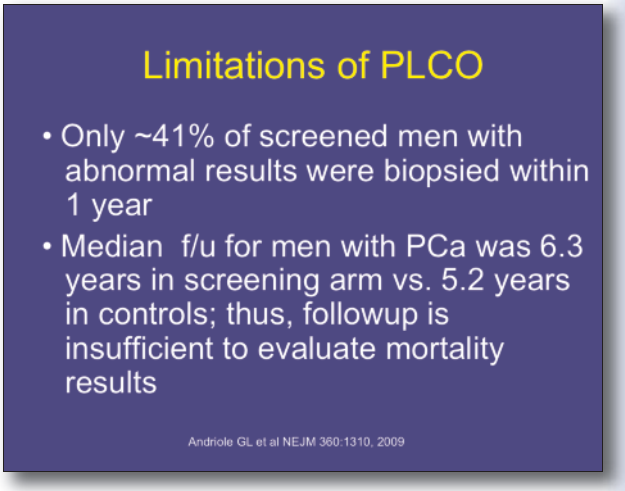
VII. PLCO

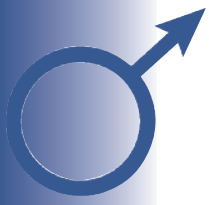
Another study, PLCO, is stated to be a study that found no difference, but the study was so flawed that it is impossible to interpret. Part of the reason is that 85% of the men in the screening arm were screened, but 40% of the men were screened before they even got into the study. In addition, during the study 40 to 50% of the men were screened. They weren't really comparing screening with non-screening. They were comparing screening in 85% versus screening in 52%.

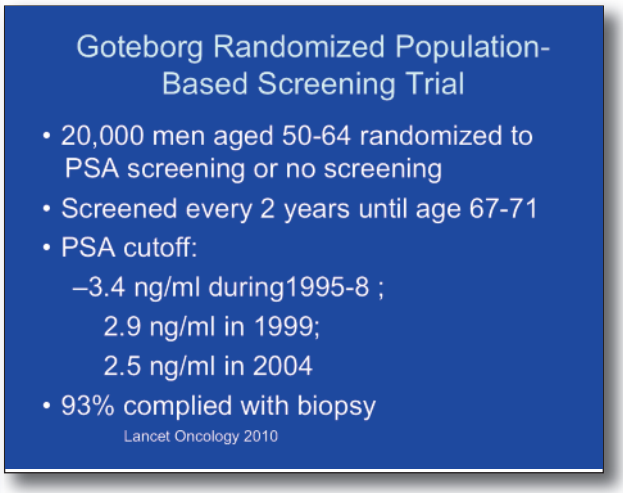
Not only that, but of the men who had an abnormal PSA or an abnormal rectal exam, less than half of them underwent a biopsy within a year. The median follow up for the whole study was 9 years, but for the men with prostate cancer, the median follow up was only 6.3 to 5.2 years. The curves don't begin to separate until nine years. There is no way one can expect to see a mortality difference.

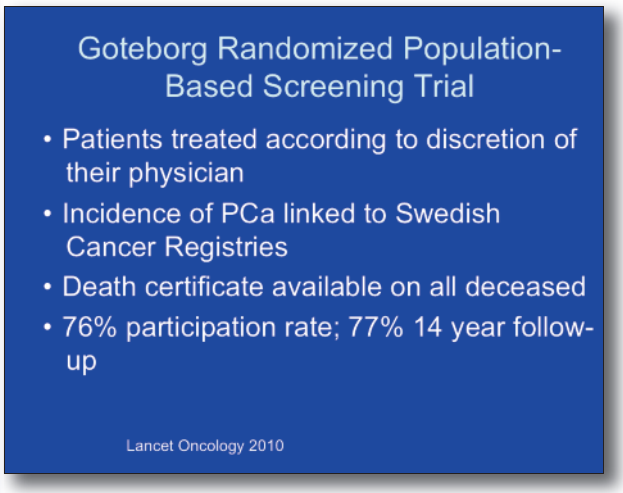


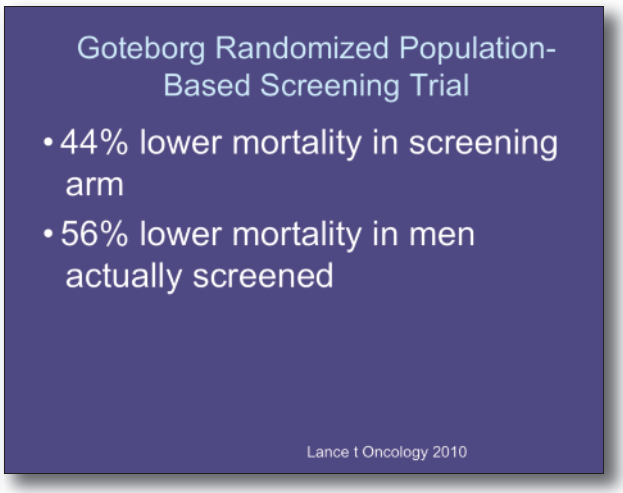










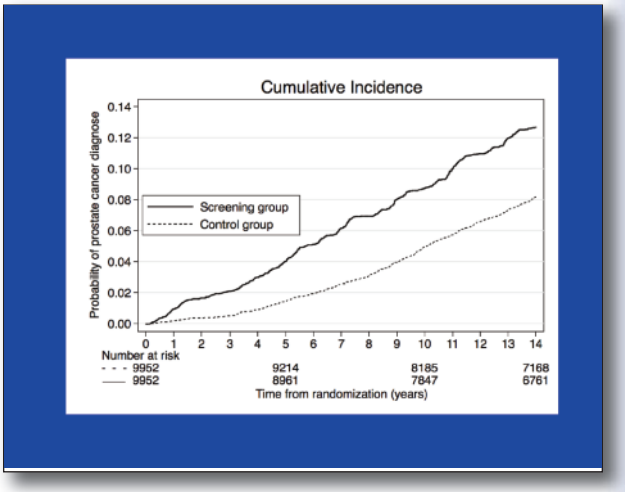


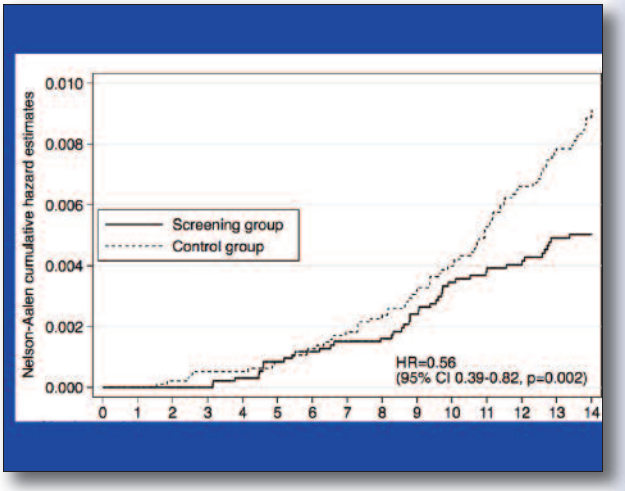
VIII. Goteborg Randomized Population-Based Screening Trial

The Goteborg study was a population-based study, and the men tended to be younger. They were screened more frequently, and they used lower PSA cut-offs. When the men had an abnormal screening test, 93% complied with an immediate biopsy.

The patients were treated according to the discretion of their physicians, and they had death certificates on the great majority of patients. Their outcomes were also linked to the Swedish cancer registries, which are more accurate than the registries in the United States.

They found that the life-saving mortality benefit was not 20%, but it was 44%. If you looked at the men who were actually screened, the mortality benefit was 66%. The prostate cancer death rate was cut in half. The study had 14 years of follow up, and by 14 years you see a tremendous life-saving benefit associated with prostate cancer screening. The curves are still diverging. At 14 years of follow up, the number needed to screen came down from 1,400 to 293, and the number needed to treat came down from 48 to 12. The PSA is as effective as mammography for breast cancer screening.





Goteborg Randomized Population-Based Screening Trial

To prevent 1 PCa death:

ERSPC : NNS = 1410; NNT = 48

Goteborg:

- Number needed to screen = 293
- Number needed to treat = 12

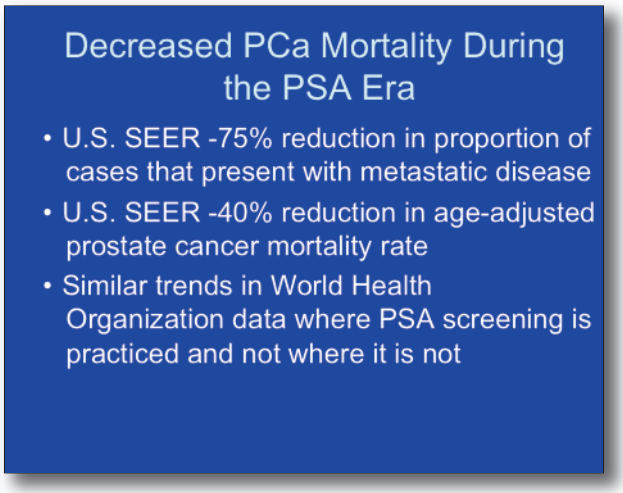
Breast Ca: NNS = 377-1339; NNT = 12

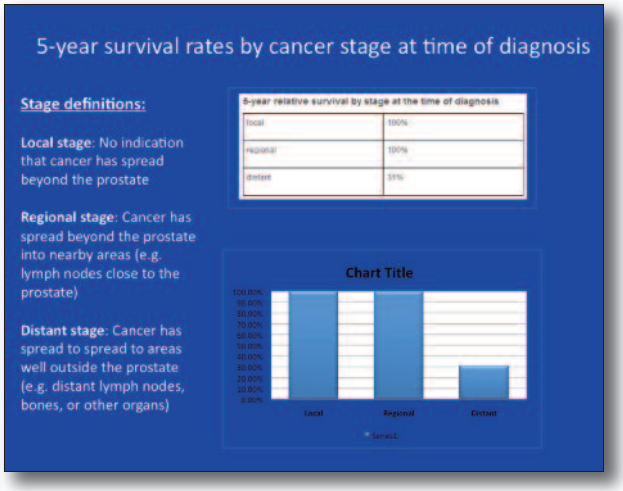
- Mortality benefit 14% younger, 32% older

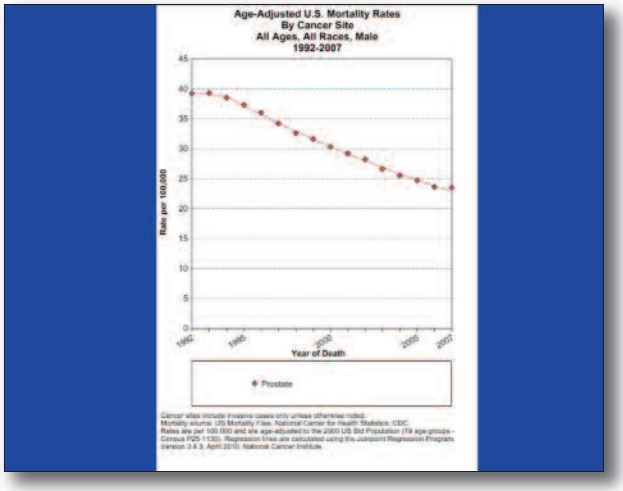
Colorectal Ca: NNS 489-1173

- Mortality benefit 13%-33%

Lancet Oncology 2010



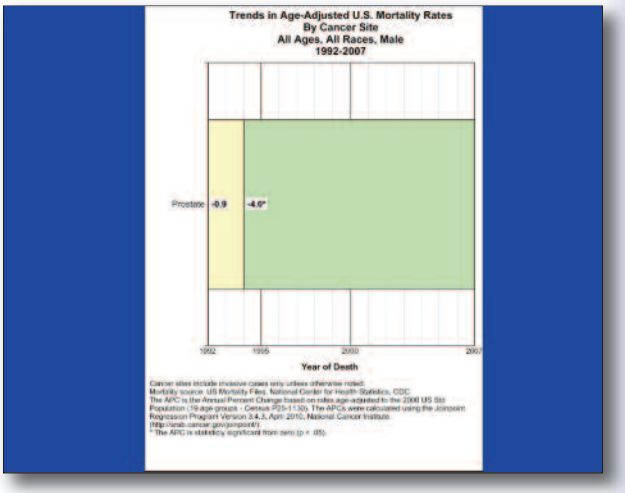




IX. Decreased Prostate Cancer Mortality During the PSA Era

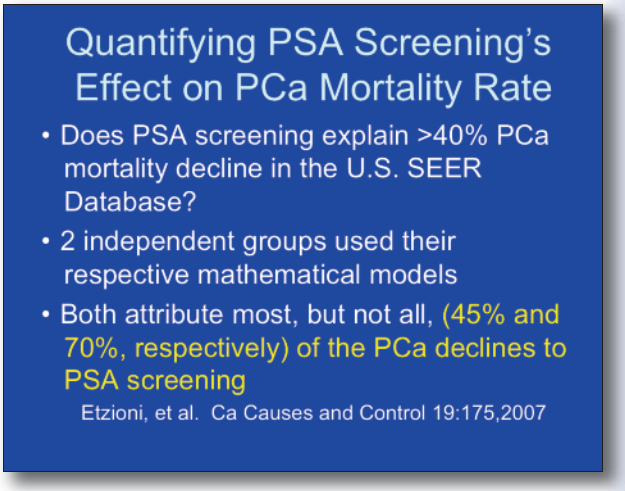
In the United States in the PSA era, since 1991, there has been a 75% decrease in the percentage of men who present with advanced metastatic prostate cancer at the time of diagnosis. There has also been a 40% reduction in the prostate cancer death rate in the United States, which is the same thing that was seen in the Swedish population. There are similar trends in the World Health Organization data.

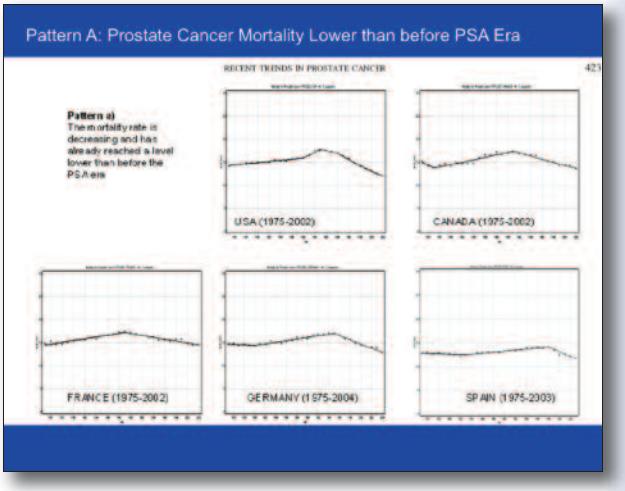
The five-year survival rate for men who present with localized prostate cancer is 100%. For those who present with regional prostate cancer, it is 100%, and for those who present with metastases from prostate cancer, it is 31%. The clear issue is detecting prostate cancer before it metastasizes. From 1992 to 2007 the prostate cancer death rate in the U.S. decreased from less than 40 down to 22 deaths per 100,000, which is greater than a 40% reduction.

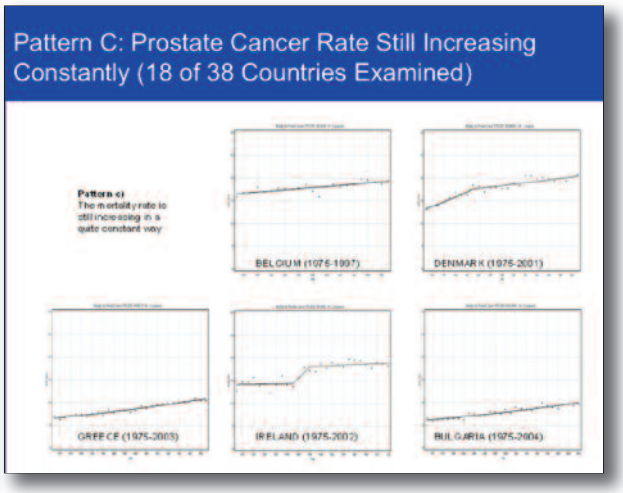


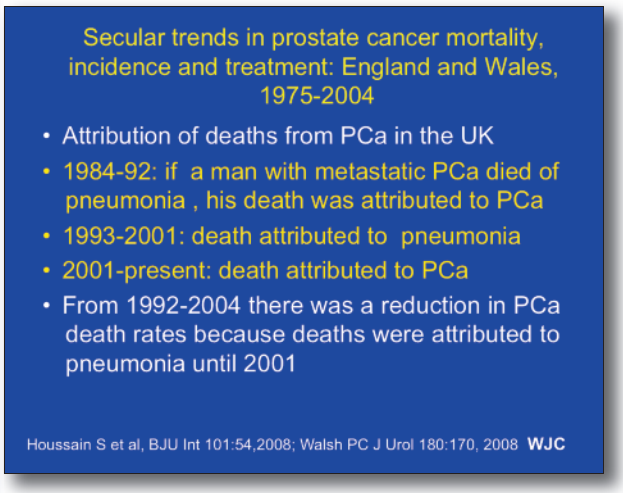
X. Quantifying PSA Screening's Effect on Prostate Cancer Mortality Rate

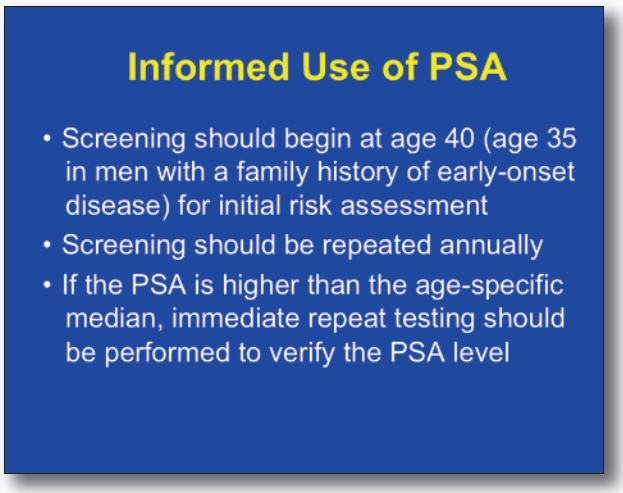
Does PSA screening explain the greater than 40% prostate cancer mortality decline in the U.S. SEER database? Two independent groups used their respective mathematical models to look at this, and both of them suggested that from 45% to 70% of the reduction in the prostate cancer death rates was due to PSA screening.











XI. Informed Use of PSA

Screening should begin at age 40 (age 35 in men with a family history of early-onset disease) for initial risk assessment. Screening should be repeated annually, and if the PSA is higher than the age-specific median, immediate repeat testing should be performed to verify the PSA level. To evaluate possible confounding from benign prostatic hypertrophy, PSA density should be estimated and the percent of free PSA should be measured. To help rule out prostatitis, a repeat PSA should be performed within a few weeks. If the PSA elevation is confirmed, a biopsy should be performed, or PSA should be monitored at three to six-month intervals to monitor the PSA velocity. If the PSA velocity is convincingly greater than approximately 0.35 ng/ml/year, a biopsy should be performed. Finally, a biopsy should be performed or strongly considered for all men with a PSA greater than 2.5 ng/ml. If you are a healthy man aged 40 to 69 who does not want to die of prostate cancer, there is conclusive evidence that PSA testing can save your life.

Informed PSA Testing

- To evaluate possible confounding from BPH, PSA density should be estimated (cutoff > ~0.1) and the % free PSA should be measured (cutoff <~10%)
- To help rule out prostatitis, repeat PSA should be performed within a few weeks

Informed PSA Testing

- If the PSA is elevated, a biopsy should be performed, or,
- PSA should be monitored at 3-6 month intervals to monitor the PSA velocity (> ~0.35 ng/ml/year)

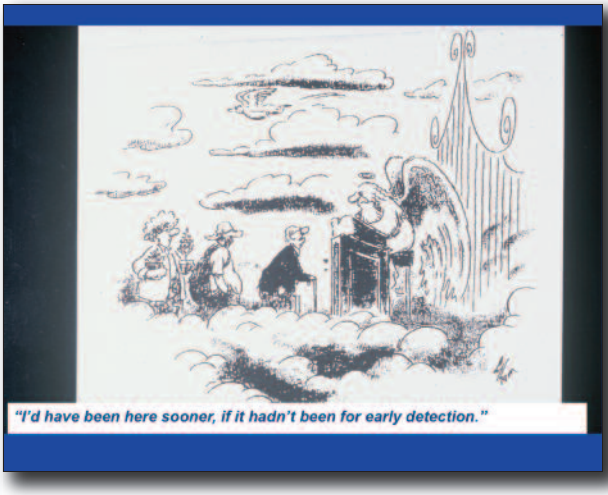
Informed PSA Testing

- If the PSA velocity is convincingly >~0.35 ng/ml/year, biopsy should be performed
- Biopsy also should be performed or strongly considered for all men with a PSA > 2.5 ng/ml

Take Home Message

- If you don't wear a seat belt or go to the dentist or doctor for a checkup, and you are not concerned about dying of prostate cancer, *do not undergo PSA testing*
- On the other hand, if you are a healthy man aged ~ 40 to 69 who does not want to die of prostate cancer, *there is conclusive evidence that PSA testing can save your life*.

Modified from Patrick C. Walsh, M.D.



"I'd have been here sooner, if it hadn't been for early detection."

Rebuttal

Otis Brawley, MD

Note that the decline in prostate cancer mortality started in 1992, and Dr. Catalona's very good article was published in 1991 to start PSA screening. Yet when we talk about the trials, we can't look at five or six-year survival. We need to look at ten or twelve-year survival. To say that the mortality decline in the United States is due to PSA screening but that we have to look at the trials long term doesn't jive together. We do need to look at the trials long term, but there is another possible reason for the decline in mortality in the United States. It is a problem that is seen in the European screening studies—advances in treatment once diagnosed whether diagnosed through screening, symptoms or other things.

An important element about the Goteborg trial and the European randomized study is that the European randomized study was actually eight trials in different areas of Europe. One was in Goteborg, and the men in the Goteborg trial who were born between 1930 and 1939, which was over 7%, are included in the European study. They are one of the eight parts. Six of the eight parts of the European study have an important difference from the American trial, which is that the men in the control arm still don't know they are in the do-not-screen arm. They were randomized without ever being informed, and they are being watched through death registries. What that creates is in the six arms of the European trial you have men who are being screened and if diagnosed get treated in one of the specialized centers for treatment of prostate cancer. If you are in the control arm and you happen to get diagnosed with prostate cancer, you get the treatment that is normally given in Europe, which is very passive and not nearly up to the U.S. standards of treatment. That is one reason why the mortality rises are continuing in the parts of Europe that do the old style passive treatment. Finally, in terms of survival data, in schools of public health we teach our graduate students not to look at survival. It's like counting people who didn't have cancer in the five-year survival statistic. Mostly importantly with regard to screening is what the three organizations all said. There is a debate, and men need to make an informed decision about screening. That philosophy carries over to making a treatment decision as well.

William Catalona, MD

There have been improvements in treatment. Radiation has improved, and surgery has improved. When the statistical teams analyzed to what extent early detections or PSA testing affects the mortality rates, the results came out 40 to 70%. The PSA has contributed greatly to the reduction in prostate cancer mortality rates.

As far as the Goteborg study being part of the European randomized study, it was an independent study and started before the European randomized study. It can stand on its own two feet and is actually better than the other parts of the European randomized study. The results are robust and fully stand on their own.

Virgil Simons

When you look at the number necessary to screen, 293 on one side and 1,410 on the other, and the number necessary to treat, what do these things mean?

William Catalona, MD

I don't think number needed to screen data is that important. I think number needed to treat is, however, important. The number needed to treat of 12 from the Goteborg study means, for example, if we treat 12 men with localized disease, one of the twelve's, and we don't know which one, life will be saved. The other 11 get treatment that is not necessary either because they did not need to be cured or unfortunately the treatment that we currently have cannot cure them. They either died from prostate cancer or never would have died from prostate cancer. We desperately need to do studies to get better answers.

Participant

The number needed to treat may be 12, but for example, maybe the number needed to treat to prevent someone from suffering from metastatic disease and being treated with hormonal therapy, radiation therapy or secondary therapy would come into that. If one is screened for prostate cancer and the cancer is detected early, it might prevent you from actually having to die from prostate cancer. It might prevent you from developing metastatic prostate cancer and having you and your family go through the inconveniences of having advanced cancer. A number needed to treat of 12 is considered very acceptable. The other statistic that often bothers me is they say that one in six men are diagnosed with prostate cancer, but only one in thirty die of it. Why is that? Maybe a lot of the other 24 were diagnosed early and cured by surgery and radiation therapy.

Virgil Simons

All of the recommendations suggest that a man should have an informed conversation with his healthcare professional. Right now we have something like 37 million men who are uninsured in the United States, and we have seen that less than half of men go to the healthcare system to be checked compared to women. How do we address these issues from a public health standpoint?

Otis Brawley, MD

This is one of the reasons why the American Cancer Society was a supporter of health care reform, and we need to reform not just how we pay for health care and who has health insurance to get health care paid, but we also need to reform our entire approach to health care to include preventive services and counseling about blood pressure, diet, weight and other things. We currently have a third-world health care system.

William Catalona, MD

One of my real fears is that PSA testing, which is now paid for by Medicare and Medicaid, will be removed with health care reform. Realistically, the only way you can decrease health care cost is to decrease the amount of health care delivered. They could never get away with that for breast cancer.

Participant

The American Cancer Society is out there sucking a lot of money off of the American public. From a prostate cancer research standpoint on a scale of one to ten, where are we? You have really painted a very bleak picture.

Otis Brawley, MD

First off, the American Cancer Society is the largest private funder of cancer research in the United States. Eighty percent of our money is spent on young investigators, but because these people are early in their careers it is sometimes hard to figure out if they are a prostate cancer researcher, a breast cancer researcher, or a colon cancer researcher. We have some estimates that prostate cancer is the number two cancer that we support among cancers. Breast cancer is number one.

Sometimes it is difficult and wrong to play disease Olympics—how much money is for prostate cancer versus breast cancer? For instance, Lupron was developed for prostate cancer in the 1980s, but by 1990 it had been FDA approved not just for prostate cancer but also for pre-menopausal breast cancer and for treatment of precocious puberty in children. There are other examples of this type of thing, and I don't know when money stops being called, for instance, breast cancer research money and starts being called prostate money. We need to support all research and all leads.

Participant

With respect to the statistics that you have shown us, most of them seem to be based on the financial cost to the society of screening. If that is the case, is there any medically adverse effect from screening?

Otis Brawley, MD

None of my data is based on cost. The adverse side effects of screening include men who have abnormal PSAs and end up stuck in their jobs because they have been offered a new great job but they have to change health insurance. There is also a paper to show that there is a higher suicide rate amongst men who are obsessed with their PSA level. We also know for a fact that at least half of all Americans who are treated for localized disease and consequently have all of the side effects of treatment for localized disease be it impotence, incontinence, bowel pain, and other things do not need to be treated. The problem is that right now I can't tell you which half.

Virgil Simons

We have to be our own advocates. We have to understand what our expectations are for the quality of life that we want to have and what our expectations are for the quality of life we want our family to have. Will this treatment ultimately provide benefit for me?

The Prostate Net