PSA Screening 2013:
A Close Look at the USPSTF Report

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Introduction

- Widespread use of PSA begins in late 1980s
- Proportion of patients diagnosed with CaP due to symptoms of advanced disease reduced 50-70% between 1986 – 1999
- Screening in the past decade → downward stage migration
- Increase in incidence of early stage CaP could have contributed to a decline in CaP mortality

- PSA is a protein naturally made by the prostate
- Since the late 1980s, it has been used to identify patients which may have prostate cancer – it is important to know that prostate cancer rarely shows signs or symptoms until it has spread throughout the body
- From 1986-1999, we saw a 50-70% decrease in the number of patients diagnosed at a point where their cancer has already spread
- Catching cancers earlier in their course, with the use of PSA, may have led to a decline in death due to prostate cancer

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USPSTF Report

- 2012: USPSTF recommends against PSA screening: moderate certainty that benefits of screening do not outweigh the harms

- Based on ERPSC and PLCO screening trials

- Medians of 13 and 11 years of follow up

- "There is adequate evidence that the benefit of PSA screening and early treatment ranges from 0 to 1 prostate cancer death avoided per 1000 men screened"

- In 2012, the US Preventive Services Task Force recommended against PSA screening to detect prostate cancer, based on the results of two screening trials, stating that for every 1000 men screened, 0-1 prostate cancer related death is avoided

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- Lifetime risk (0 – 90 years) of death from CaP: 3%
- Lifetime risk of diagnosis of CaP: 17%
- Without accurate markers, screening → overdiagnosis and overtreatment
- Estimated overdiagnosis: 30-50%, directly proportional to age

- The lifetime risk of death due to prostate cancer (from age 0-90) is 3%; the lifetime risk of diagnosis of prostate cancer is 17% - this means that a certain number of people are being "overdiagnosed" – meaning that they are diagnosed with a disease that will not be likely to shorten their life span

Screening

- Screening can lead to false positives
- FP → unnecessary biopsy and treatment
- Adverse effects are a poor tradeoff if no benefit is seen in terms of years of life saved
- Costs of screening may not be justified if societal harm of diagnosis and treatment are greater than health benefits obtained

- Screening can lead to a "false positive" – a high PSA level (which can indicate prostate cancer) which leads to a patient having a prostate biopsy, leading to more treatment
- Screening may not be justified if it is not leading to benefits to society in terms of years of life saved

Population-Based Observations of Screening

- Population based observations before and after the onset of widespread PSA screening can provide a few clues as to screening benefits (Gann 1997)
- Since 1995 – 1997, age adjusted CaP mortality rates for black and white men age 50 – 84 in the US dropped below the rate in 1986, when PSA testing was rarely performed (Tarone et al 2000; Chu et al 2003)
- Between 1991 and 2001, the mortality rate for prostate cancer decreased by 27% (SEER Program)
- Why the decrease in mortality? It has been shown that the decrease in distant disease mortality was due to a decline in distant disease incidence, not to improved survival of patients with distant disease (Chu 2003)

- When populations are examined as a whole, clues can be gained as to the benefits of screening throughout that population
- Death rates for white and black men age 50-84 decreased in the 1990s with the use of PSA screening as compared to the 1980s, when PSA screening was rarely performed
- Overall death rates due to prostate cancer decreased by 27% in a period from 1991 – 2001
- Why did patients die of prostate cancer less often? Was it because patients with more advanced disease got better treatment, or because patients were diagnosed earlier in the course of their cancer? A study in 2003 answered this question, and the answer is that patients were being diagnosed before their cancer had spread

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Changes in Treatment Patterns

- US prostate cancer mortality decline 3.4% 1990-1995
- US prostate cancer mortality decline 15.3% 1995-1999
- Increased rate of surgical treatment for non-screening detected prostate cancer that began in the decade prior to the onset of widespread PSA testing (Mettlin et al 1994), owing to better QOL outcomes with the anatomic approach to radical prostatectomy (Walsh et al 1983)
- Other possible explanations:
  - Changing risk factors
  - Greater use of hormonal therapy
  (Etzioni et al 1999; Feuer et al 1999; Albertsen 2003)

- Why else could prostate cancer death rates have declined in the US in the 1990s?
  - Increased rate of surgery for prostate cancer which was detected without screening
  - Changing risk factors for development of prostate cancer
  - More frequent use of hormonal ablation therapy, an effective form of treatment for advanced prostate cancer

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How can we most accurately determine how screening affects disease specific outcomes?

Randomized trial!

- Randomized trials are necessary to accurately determine how screening affects survival specific to a disease (i.e. prostate cancer, colon cancer, heart disease, etc)

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Randomized Screening Trials

- 1988 Quebec prospective RCT
  - Endpoint: CaP specific mortality among 46,486 men aged 45 to 80
  - Men were invited or not invited for screening at a ratio of 2:1 in favor of screening
  - PSA 3.0, abnormal DRE (used only at first visit)
  - 62% reduction in disease specific mortality in the screened arm compared to those not screened
  - Problems:
    - Men were invited, but not all those invited were screened (24%)
    - Intention to treat analysis of those randomly assigned to screening or not showed a statistically insignificant relative risk of 1.08 associated with screening (Labrie et al, 2004)
    - Several biases noted

- In 1988, a trial was performed comparing screening vs. not screening in a group of over 46,000 men aged 45-80
- A 62% reduction in death due to prostate cancer was noted in the screened men
- A few minor faults of the study were noted

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Randomized Screening Trials

- ERSPC
- PLCO
- CaP specific mortality

ERSPC

- 182,000 men age 50-74
- 8.8 years median follow up
- Screening group: PSA every 4 years
- CaP incidence 8.2% screened vs. 4.8% control
- Rate ratio for CaP specific mortality in screened population: 0.80
- Absolute risk difference: 0.71 CaP deaths / 1000 men
- 20% corresponding relative risk reduction in mortality noted: NNS 1410, NNT 48
- 41% reduction of metastatic CaP in the screening group, and identification of higher percentage of patients with low risk disease
  - Gleason score 6-7: 72.2% and 27.8% in screened group vs. 54.8% and 45.2% in the control group

- The ERSPC (European Randomized Study of Screening for Prostate Cancer) includes 182,000 men followed for approximately 8 years
- It was found that to save one life from prostate cancer, 47 men would require treatment for a prostate cancer which would not shorten their lifespan
- Patients who were screened were found to have advanced prostate cancer far less often than those who did not undergo screening

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ERSPC

- After adjustment for non-compliance in the screening population and contamination in the control arm, the mortality benefit found in the ERSPC population can be as high as 30% – increasing the initial benefit by half (Roobol et al 2009)
- Relatively short median follow up time of 9 years
- NNS and NNT decrease to 503 and 18 respectively when data is extrapolated out to a modest 12 years of follow up (Loeb et al 2011)
- Data was gathered cumulatively from several European nations
- PSA cut-off value that triggered further work up was non-uniform
- Others used higher values than 3.0 and incorporated factors such as DRE and PSA kinetics to determine if further work up was necessary

- Some patients who were supposed to have screening did not, and others who were not supposed to have screening did; this underestimates the benefit of screening
- When mathematical models are used to look at the data after 12 years (rather than 8), only 17 men would need to be treated for prostate cancer to save one life
- Other factors such as levels of PSA which triggered further investigation were not standard throughout the facilities participating in the study

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ERSPC

Caveats

- Risk of over diagnosis was estimated to approach 50%
- Benefits of screening were restricted to core age group of 55 – 69
- High likelihood of over diagnosis and over treatment
- Unequal treatment decisions: high risk CaP more likely to receive radiotherapy (OR 1.43, p = 0.047), expectant management (OR 2.92, p = 0.007), or hormonal therapy (OR 1.11, p = 0.02) instead of radical prostatectomy
- Difference in treatment between arms unlikely to play a major role in interpretation of mortality results (Wolters et al 2010)

- The ERSPC did demonstrate a benefit with less patients dying of prostate cancer when they've been screened, however, over-diagnosis and over-treatment were noted

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ERSPC

- Relative reduction in deaths noted to be 21% after median 11 year follow up (Schroder 2012)
- Absolute reduction of 1.07 deaths per 1000 men
- USPSTF – "reduction in prostate cancer mortality 10-14 years after PSA screening is at most very small" (Moyer et al 2012)
- Big absolute reduction, modest absolute benefit?

- The ERSPC showed that 21% fewer patients will die of prostate cancer with the use of screening when followed to 11 years
- This large percentage translated into 1 death per 1000 men screened for prostate cancer
- Why the disparity?

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ERSPC

- Absolute benefit of screening depends on:

    Baseline disease specific mortality rate in the unscreened population

- ERSPC population: very low (0.5 deaths / 1000 person years), which translated into 1.07 lives saved per 1000 screened

- How is this relevant here?

- The actual, absolute benefit of screening for a disease depends on how likely people are to die from that disease when they have not been screened

- The population used in the European study had a death rate of 0.5/1000 person years, which translated into 1.07 lives saved per 1000 men screened

- Let's look at how this is relevant here

ERSPC

In population screening, when screening is continued until death from other causes or an age is reached where screening is no longer recommended, the <u>baseline disease specific mortality approaches the lifetime probability of CaP death</u>

- Populations are screened until they die of a cause other than the disease for which screening is performed, or an age is reached where screening is no longer recommended
- In this scenario, the chances that someone will die of prostate cancer approach the chance that the entire population, as a whole, has of dying of prostate cancer

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ERSPC

- ERSPC not only has short follow up – it's also a different population (European)
- US lifetime risk of CaP death based on 1990 death rates: 32 / 1000 men
- 21% reduction = 6.7 lives saved / 1000 screened
  - NNS decreases to 149
- Taking into account advances in treatment with 2006 mortality rates:
  - Lifetime risk of CaP death: 28 / 1000 men; 5.9 lives saved per 1000 screened, NNS 170

- The ERSPC study has short follow-up – meaning that patients have not been observed for a period of time long enough to see them dying of prostate cancer less often
- When US (rather than European) death rates are used in calculations, that 21% reduction in death from prostate cancer translates to 6.7 lives saved for every 1000 men screened – this means that to save one life, 149 men need to be screened
- When advances in prostate cancer treatment are considered, as are mortality rates from 2006, 5.9 lives are saved for every 1000 men, and 170 men need to be screened to save one life

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ERSPC

- Short follow up:
  - Distorts estimates of screening harm (especially overdiagnosis)
  - Overdiagnosis estimated to be 34 / 1000 men screened
    - This was the observed excess incidence in the screened group relative to the control group
    - This was combined with the 9 year estimate of 0.7 lives saved / 1000 men screened → NND of 48
    - Excess incidence over the short term inflates the estimate of overdiagnosis (58% of screen detected cases)
    - 11 years F/U (rather than 9) – NND revised down to 37

- A short follow-up (time that these patients are observed) means that harm from screening (patients treated that would not have died from their prostate cancer) is overestimated – this is because prostate cancer can take several years to spread
- The ERSPC estimated that 34/1000 men screened were overdiagnosed (diagnosed with a prostate cancer that would not shorten their lifespan)
- This was calculated by seeing how many patients were screened compared to those who weren't, and comparing their death rates, to arrive at a number of 48 men required to be diagnosed with prostate cancer to save one life
- Since follow up was not long enough to observe true death rates from prostate cancer, "overdiagnosed" patients were overestimated
- When follow-up was extended to 11 years, that number of men needing to be diagnosed with prostate cancer to save one life decreased to 37

ERSPC

- How can we better estimate the long term fraction of screening detected cases being overdiagnosed?
  - Trial based estimates: excess incidence in screened group is proxy for overdiagnosis
  - Two models have been performed estimating lead time associated with PSA screening and then deriving the fraction overdiagnosed as the fraction of screen-detected cases dying of other causes within their lead time (Kolata et al 2009, Ablin 2010)
  - Estimations: 23% and 28% overdiagnosis rates

- Clearly, the ERSPC is overestimating the fraction of prostate cancer cases detected by PSA screening which are overdiagnosed
- A more accurate method of estimating overdiagnosis, involving consideration for time and death from other causes, leads to estimates in the range of 23-28%, not over 50% as stated by the ERSPC
- These numbers are more accurate because they not only represent true overdiagnosis, they were estimated in the US setting, not the European one.

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ERSPC

- 16% of men will be diagnosed under current screening practices (Telesca et al 2008)
- Assuming all new cases are screen detected, with higher estimate of overdiagnosis, 44.8 patients / 1000 will be overdiagnosed
- So what is the long-term NND?

Overdiagnosed / lives saved

$$44.8 / 5.9 = 7.6 \text{ --- not 37!}$$

(Etzioni et al 2012)

- Under screening practices prior to the AUA statement of May 2013, 16% of men will be diagnosed with prostate cancer
- Using the overdiagnosis rates calculated on the previous slide, 44.8/1000 screened patients will be overdiagnosed
- The long term number of men needed to be diagnosed with prostate cancer to save one life is calculated from the number of those overdiagnosed (44.8) divided by how many lives are saved (5.9) – **this translates into 7.6 men needing to be diagnosed with prostate cancer in order to save one life**

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Goteborg

- Subset of ERSPC
- 20,000 men, age 50-64
- 1:1, screening with PSA q2 years vs. no screening
- Endpoint: cancer specific mortality
- 76% first time compliance rate

- The Goteborg trial was a subset of the patients enrolled in the ERSPC trial
- Patients had screening more often (every 2 years as opposed to every 4 in the ERSPC)
- A high number of patients participated in screening when asked (which increases accuracy of the data generated by the trial)

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Goteborg

- 1138 men diagnosed with CaP – 8.2% incidence (HR 1.64 95% CI 1.5-1.8)
- Screened patients diagnosed with lower stage disease and lower rates of metastases
- Rate ratio for death: 0.56 screened vs. not screened
- NNS, NNT – 293 and 12

- Patients who were screened for prostate cancer in the Goteborg subset had lower rates of spread of their prostate cancer; 293 men were needed to be screened, and 12 men needed to be treated, to save one life from prostate cancer

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Goteborg

- Better outcomes with screening compared to ERSPC and PLCO trials
- Why?
  - Younger patient population
  - Shorter interval of screening (2 rather than 4 years)
  - Lower rate of PSA testing before entry (3% vs. 44% PLCO)
  - Lower rate of contamination of control group
  - Longer follow up (14 years)
- 44% relative risk reduction in death!

- The Goteborg subset showed a greater benefit to screening than the ERSPC and PLCO trials (we will discuss PLCO in a moment)
- This is because patients were younger, had screening more often, had longer follow up, and obeyed instructions as to screening and not being screened more often than the patients in the other trials
- The use of PSA screening in this study resulted in a 44% reduction in the risk of death from prostate cancer

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PLCO

- US based multi-institutional RCT (10 institutions)
- 76,693 men
- 7 years follow up reported (1993 – 2001)
- Annual PSA x 6 years, DRE every 4 years vs. usual care
- Patient characteristics between screened and non-screened identical
- CaP / 10000 person years – 116 in screening group, 95 in control group.
- CaP specific mortality: 2.0/10000 screened, 1.7 unscreened
- Rates of low stage disease similar between groups

- The PLCO (Prostate, Lung, Colon, and Ovarian Cancer Screening Trial) is a US based randomized trial looking at almost 77,000 men
- The patients being screened have similar characteristics to those not being screened, including their rates of prostate cancer and death due to prostate cancer

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PLCO

Problems with the trial

- 44% of patients in the control group had at least one PSA prior to entry
- By 6th year, 52% of control population had been screened
- This introduces serious contamination – the control population is not only less likely to have CaP, but less likely to have higher stage or life threatening disease

- The PLCO trial had a major problem – the patients who were not supposed to be receiving screening sought out screening on their own
- By the 6th year of the study, 52% of the patients who were not supposed to receive screening had indeed been screened
- This means that these patients will be less likely to have prostate cancer and also that they are less likely to have more aggressive or life threatening prostate cancer

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PLCO

- Studies looking at the control arm saw rates of routine PSA screening of 33% at year 0; year 5: 55% (Roobol 2009)
- These parameters of the trial will tend to show RR outcomes showing no difference between arms
- Some patients initially enrolled already had a baseline PSA – some cancers detectable on initial screening may have been removed from the randomized population
- PSA of 4 – lower cut-off may have led to detection of more low risk cancers (which are associated with better survival data)
- Follow up of 7 years – not sufficient with the natural history of CaP

- When most of the control group has been screened, you end up comparing screened patients to screened patients, which leads to little to no difference being shown among the two patient groups – this does not help in determining the benefits of PSA screening
- Some patients who were not supposed to be screened already had a PSA level checked before they entered the study – some of these patients may have had cancers detected and were removed from the study, which alters the results for the reasons noted above
- Following patients for only 7 years does not aid in the determination of the benefits of screening, because prostate cancer can take many years to progress

PLCO

- Re-analysis by Crawford et al (2011) done with consideration of existing comorbidities
  - Significant decrease in risk of CaP specific mortality (22 vs. 38 deaths, adjusted HR 0.56; 95% CI [0.33-0.95], p=0.03) in men with no or minimal comorbidity randomized to intervention vs. usual care
  - Additional NNT to prevent one prostate cancer death at 10 years: 5
  - Suggests that selective use of PSA screening can reduce CaP specific mortality with minimal overtreatment

- The PLCO data was reanalyzed with consideration made for other diseases that the patients had
- Death rates due to prostate cancer (and not their other diseases) significantly declined with screening
- In fact, this reanalyzation demonstrated that only 5 men would require treatment for prostate cancer to save one life
- **This suggests that selective use of PSA screening can decrease death rates from prostate cancer with minimal overtreatment risks**

PLCO

- Modeling to replicate the trial showed that extremely low power exists (range, 9-25% across 3 models at 13 yrs) to infer a difference between the control and intervention groups even under a clinically significant benefit of screening (Gulati et al 2012)
  - Due to:
    - Control arm contamination
    - Lower than expected frequency of CaP deaths in the trial population (Pinksy et al 2010)
- The study:
  "does not provide actionable information regarding screening benefit or lack thereof" and *"instead provides important evidence of the equivalence of more intensive (annual) vs. less intensive (biennial) screening"*

  (Etzioni et al 2012)

- Statistical modeling to replicate the PLCO trial data showed that the trial had minimal ability to show a difference between screening and no screening
- The study:
  "does not provide actionable information regarding screening benefit or lack thereof" and *"instead provides important evidence of the equivalence of more intensive (annual) vs. less intensive (biennial) screening" (Etzioni et al 2012)*

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How are we doing compared to other cancers?

- ERSPC and Goteborg data compare favorably to breast and colon cancer

- Breast cancer: NNS with mammography of 377 women age 60-69 and 1339 for women 50-59 after 11-20 years of follow up (Nelson et al 2009)

- Colon cancer: FOBT NNS after 10 years of follow up? 1173

    Flexible sigmoidoscopy? 489 (11 year follow up)

- **In perspective, PSA testing is low compared to mammograms or FOBT or sigmoidoscopy**

- How does PSA screening for prostate cancer compare to screening for breast cancer and colon cancer?

- Compared to the 170 men who need to be screened to save one life from prostate cancer:
    - 1339 women age 50-59 and 377 women age 60-69 must be screened to save one life from breast cancer
    - 489 – 1173 patients need to be screened to save one life from colon cancer

- **In perspective, PSA testing a very effective screening test when compared to tests used for other common cancers**

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How are RCTs limited for screening policy use?

- Screening policy needs information about *long-term* benefits and harms – interventions are conducted over an individual's healthy lifetime

- Most trials provide short-term rather than long-term outcomes

- Results can be highly influenced by the trial population and compliance

- Any inferences about screening are limited to the strategy tested

- Identification and comparison of alternative policies is not possible

- Randomized controlled trials are excellent in many aspects, but examining screening policy is not one of them.

- Screening policy needs information about long-term benefits and harms which happen over a patient's healthy lifetime

- These trials, for the most part, provide short-term, not-long-term results

- The population itself, by not following instructions in the trial (i.e. getting a PSA screening done when they were not supposed to) can affect results

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Future Directions of Screening

- **PSA: perhaps not enough specificity/sensitivity, but clearly one of the best screening markers available**
- **Age 50, PSA <1.5 – risk of CaP in 7-8 years is <5%**
- **PSA 2.5? Risk increases to 20% PSA 4.0? Risk 40%**
- **Risk-based screening with baseline PSAs**
- **Urinary/serum markers**
- **Imaging**

- PSA may not be a perfect screening test, but it is clearly one of the best available
- Age-related PSA levels and lifetime prostate cancer risks can be used to alter screening schedules
- Urinary and serum tests are being investigated for detection of prostate cancer, as are imaging modalities such as MRI

Conclusions

- Published screening trial results do not accurately reflect the outcomes of a US population
- Possible directions for screening:
  - Age/risk based
  - Imaging
  - Markers
  - Conservative criteria for older patients
  - Adaptive screening (changing interval based on current PSA)
- The benefits and harms of PSA screening as assessed by USPSTF are based on an incomplete picture
- Limited-duration screening trials: interpret with caution for diseases with long natural histories

- The ERSPC and PLCO trials do not accurately reflect the outcomes of a US population
- Screening may take multiple different directions in the future
- The benefits and harms of PSA screening as assessed by the USPSTF are based on an incomplete picture of population characteristics, patients receiving screening when they have agreed not to, and limited durations not capable of fully studying the natural course of prostate cancer

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