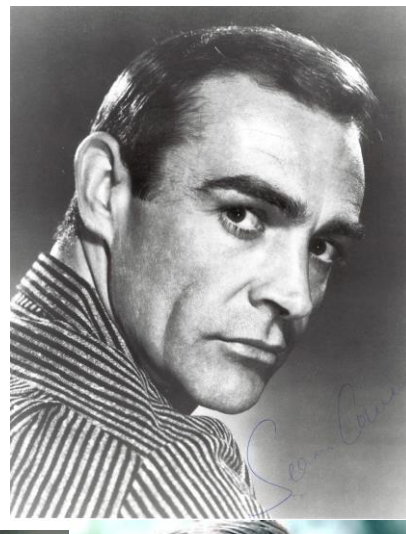
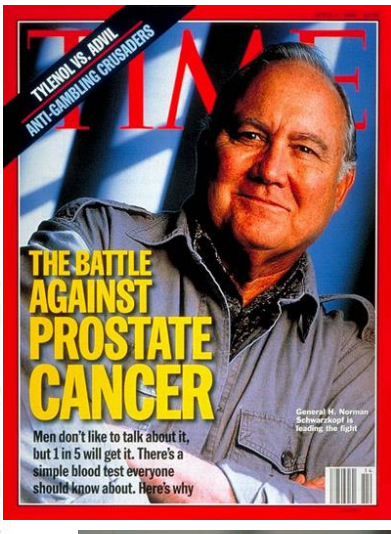
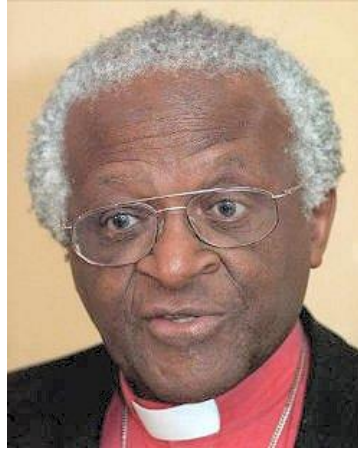
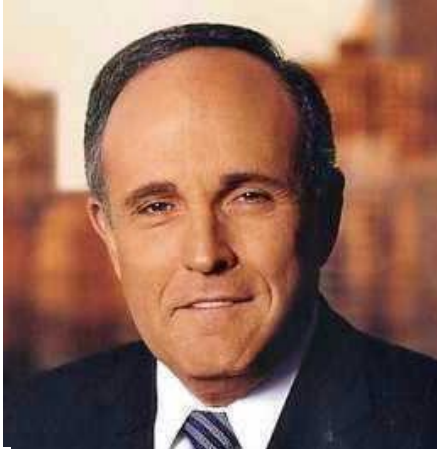


# PSA and prostate cancer: current concepts and future management strategies

Professor Abhay Rane OBE

# Cancer and urology

- The incidence of all cancers in general rises with increasing age
- 75% of urology patients are above the age of 70
- therefore the incidence of urology cancers is high, and is rising further with an increasing elderly population



# The strongest known risk factors for prostate cancer are increasing age, ethnic origin and family history

- Factors known to increase the risk of developing prostate cancer include:<sup>1-3</sup>
  - Age
    - Very low risk in men aged < 50 years, but after this risk increases with age
  - Family history
    - Men with  $\geq 1$  first-degree relative diagnosed with prostate cancer have an increased risk, especially if the relative was diagnosed aged < 60 years
  - Ethnic group
    - Men of West African or Caribbean origin have a higher risk of prostate cancer than white men
- Dietary and nutritional factors may have an impact on risk<sup>1-3</sup>
  - Foods containing lycopene and selenium may offer a protective effect

1. EAU, 2009.

2. Macmillan Cancer Support, 2007.

3. Cancer Research UK, 2009.

# Prostate cancer

## Clinical presentation

- Most present with signs / symptoms of BOO
- ~ 10% present with symptoms relating to metastases, ie. backache or path #
- Incidental diagnosis after TURP
- *No physical signs in majority of patients*

# Prostate cancer

## PSA or prostate specific antigen

- 240 amino acid single chain glycoprotein
- serine protease: liquefies the seminal coagulum that is formed after ejaculation
- half life of PSA is 2.2-3.2 days.
- *Upper limit of 'normal' reference range 4 ng/ml*

# Prostate cancer

- If PSA > 10, risk of cancer on biopsy ~60%
  - only 2% of patients with BPH have PSA >10
- If PSA between 4.1 and 10, risk of cancer on prostatic biopsy falls to ~20%.
- Overall, if PSA is greater than 4 ng/ml likelihood of prostate cancer is ~25-30%.

# Prostate cancer

- PSA is prostate specific
- Not cancer specific
- What can be done to improve its utility?



# Prostate cancer

## PSA Density

- Correction for the BPH contribution to the PSA value.
- Divide PSA value by the gland volume cc
- Values above 0.15: suspicious of malignancy

# Prostate cancer

- PSA Velocity

Over a year very suspicious if

- rise of more than 20%
- increase of 0.75 ng/dl

# Prostate cancer

## Age adjusted PSA

Values increase gradually with age

Upper limits of 'normal' :

- Age 40 - 49, 2.5 ug/ml
- Age 50 - 59, 3.5 ug/ml
- *Age 60 - 69, 4.5 ug/ml*
- Age 70 - 79, 6.5 ug/ml

# Prostate cancer

## ‘Free’ and ‘Bound’ PSA

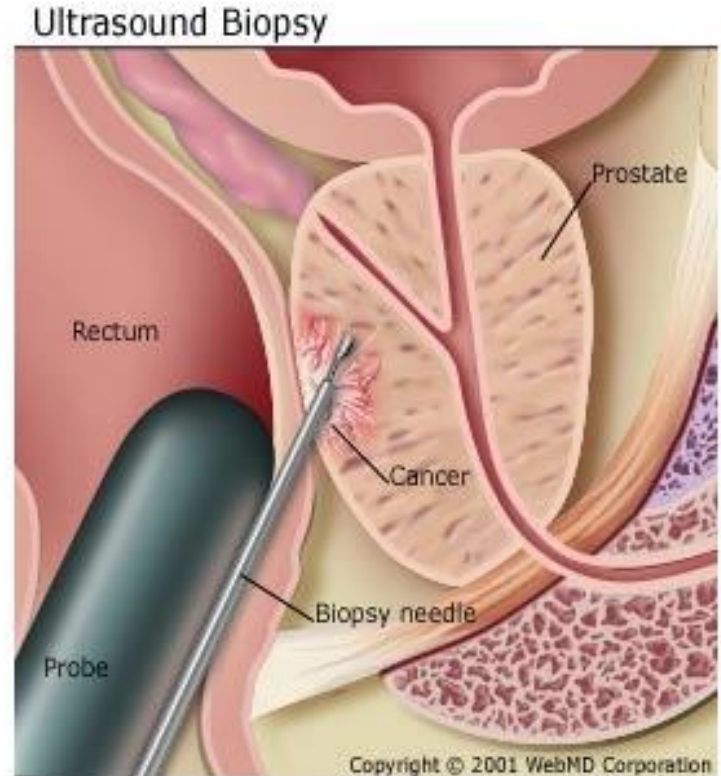
- In BPH, free PSA levels are generally increased
- ‘Free PSA is good PSA!’
- In prostate cancer, bound PSA levels are raised
- Best used to determine necessity for re biopsy if initial biopsy benign with an elevated PSA

# Digital rectal examination (DRE)

- simplest / safest means of detection
- palpable irregularity ~ 50% chance of being a carcinoma
- abnormal findings = biopsy of the prostate  
*(irrespective of serum PSA)*

# TRUS biopsies

- Risks
  - Septicaemia
    - 1-2%
  - Death
    - 0.03%
  - Haematuria
  - Haematospermia
  - Pain and discomfort
  - Anxiety of false negative biopsies
    - 10-15%



# Grading by Gleason scoring

- 5 different histological grades of tumour differentiation recognised
- For each tumour therefore, two grades are determined
- added together to provide a Gleason score ranging from 2 – 10
- ‘the higher the score, the worse the tumour’

# Screening for prostate cancer

- Value of screening asymptomatic men controversial





**Rx UNITED DRUGS**  
**KATTERMAN'S SAND POINT PHARMACY**

**PSA TESTS HERE !!!**

**CHOLESTEROL TESTS HERE !!!**

**Harry Potter**

# Criteria for screening

- Disease
  - Common in target population
  - Serious
  - Curable
- Screening test(s)
  - Sensitive and Specific
  - Acceptable to the target population
  - Identify significant disease

# Criteria for screening

- Treatment
  - Improve outcome
  - Clear proven benefit of early vs late treatment
  - Overall benefit should outweigh the overall physical or psychological harm
  - Adequate staffing and facilities for the diagnosis and treatment of abnormalities detected

# Screening prostate cancer?

## For

- Early diagnosis
- Reduced mortality
- Reduced morbidity
- Reduced metastatic disease
- Reassurance
- Reduced costs?

## Against

- Unnecessary biopsies
- Insignificant disease?
- Unnecessary treatment
- Treatment side effects
- Increased cost?
- Increased anxiety

# Prostate Cancer: Death Rate Shows a Small Drop. But Is It Treatment or Testing?

In the late 1980's, a blood test for prostate cancer came into widespread use. The test, the P.S.A., can find cancers when they are too small to feel and before they have spread. It is only now being evaluated in clinical trials to see if it reduces the risk of dying from the disease. Gina Kolata asked two experts to assess national data on prostate cancer.

**D**R. IAN M. THOMPSON JR., a urologist and professor of surgery at the University of Texas Health Science Center at San Antonio, looks at the data on P.S.A. screening and is encouraged.

Before the P.S.A. test came into use, the cancer's incidence was steady from year to year. That changed with increasing use of the P.S.A., for prostate specific antigen. The number of prostate cancer cases diagnosed rose from 143.3 per 100,000 in 1990 to a peak of 195.6 per 100,000 in 1992 and then fell to 155.3 per 100,000 in 1998, the most recent year for which data are available.

The pattern reflects the use of the test, which found men who had cancer and had never before had any kind of test sensitive enough to find it. The incidence fell as more and more men who had cancer all along were tested and their cancers found.

Before the blood test was introduced, Dr. Thompson said, doctors looked for the cancer by rectal exams, which he said was "not very good." The increasing incidence shows, he said, that the P.S.A. is doing what it is supposed to do — finding cancers early.

As for the mortality rates, Dr. Thompson said they were falling steadily and dropped by 16 percent from 1990 to 1998, going from 38.6 per 100,000 to 32.3 per 100,000. Treatment improved in that time, but Dr. Thompson said that alone was not enough to explain the drop in the death rate. Prostate cancers that have spread to other organs are less common, dropping in incidence by 60 percent from 1990 to 1998.

"Metastatic disease is falling so low that we've never seen those numbers before," he said. That, he says, is a tribute to early detection with the P.S.A. test.

"Yes, there are probably some



J. Michael Short for The New York Times

Dr. Ian Thompson Jr. says P.S.A. tests find prostate cancers early.

people who are treated unnecessarily," he said. "But all of medicine is that way. Is there a chance that when you have your appendix removed it will turn out to be normal? Yes." Dr. Thompson is 47 and has had a

P.S.A. test; it was normal. He intends to continue having the test and to be treated if cancer is found. The treatment, he said, does not worry him. It is a small price to pay for a potential cure.

**D**R. OTIS BRAWLEY, professor of medical oncology and epidemiology at the Winship Cancer Institute of Emory University, is concerned. National data, he said, make him wonder whether the P.S.A. test is saving many lives.

The test, Dr. Brawley said, has led to a huge increase in the number of prostate cancer diagnoses.

But if the P.S.A. was saving lives, the early diagnosis of prostate cancer should lead to a sharp downturn in its death rate. That has not happened, Dr. Brawley said. While the mortality rate has fallen, it did not fall precipitously and the introduction of better treatments clearly played a role.

Dr. Brawley said the data indicated that the test was finding tumors that would not be noticed and would cause no medical problems. But these tumors look exactly like dangerous ones.

"There are cancers that fulfill all the histological criteria for malignancy," Dr. Brawley said. "When a pathologist looks under the microscope, he says, 'Yes, this is cancer.'"



Marty Katz for The New York Times

Dr. Otis Brawley says screening for prostate cancer may not save lives.

But these tumors are not dangerous, and many that are dangerous may not be cured by early diagnosis and treatment.

"The concept that every cancer that can be found early can be cured

is a faulty concept," he said.

Yet, with no way of knowing which tumors are potentially lethal, doctors usually treat everyone with methods like surgery or radiation that can cause impotence and incontinence.

While the number of men with metastatic disease at the time of diagnosis has gone down, Dr. Brawley says the reason is not necessarily that the P.S.A. test is finding cancers when they can be cured.

Doctors, he said, operate and remove the prostate only when they find no evidence that cancer has spread. Those men are counted as having localized disease. But, he said, within two years, 40 percent of them have recurrences. The cancer had already metastasized, but the spread was not obvious when the original diagnosis was given. Before the test, most of those cancers would have been found after they had spread and counted as metastatic.

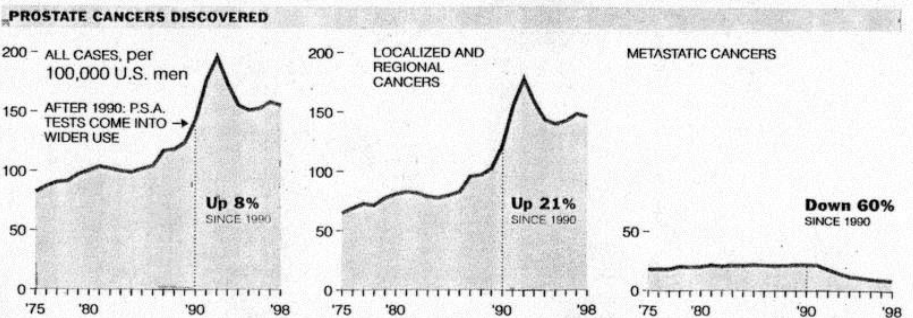
Dr. Brawley worries that some doctors are including P.S.A.'s in routine blood tests without discussing these issues.

"If a man understands that the test is unproven and still wants it, he should be allowed to get it and should not be criticized," Dr. Brawley said.

At 42, Dr. Brawley has not been tested and does not want to be. Once, a doctor ordered the test on a lab order sheet without telling him. "I asked her to scratch it off," he said.

## Weighing the Value of Prostate Antigen Tests

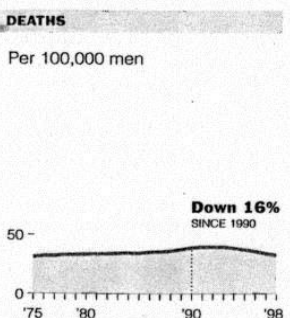
How supporters and critics view the data.



**SUPPORTERS OF THE P.S.A. TEST SAY:** Testing finds cancers. Rectal exams are ineffective at detecting all but late-stage disease, which is difficult to cure. Since the P.S.A., distant-stage cancers are declining.

**CRITICS OF THE TEST SAY:** Many tumors found by screening would not have caused medical problems. But they look like dangerous tumors, so they are treated anyway. The decline in late stage cancer may be because the P.S.A. finds cancers that seem to be early and are listed as such, but are in fact in late stages.

Sources: SEER Program, National Cancer Institute (cases); National Center for Health Statistics (deaths). All statistics are age-adjusted to a 2000 U.S. standard.



**SUPPORTERS SAY:** Deaths have dropped since the early 1990's.

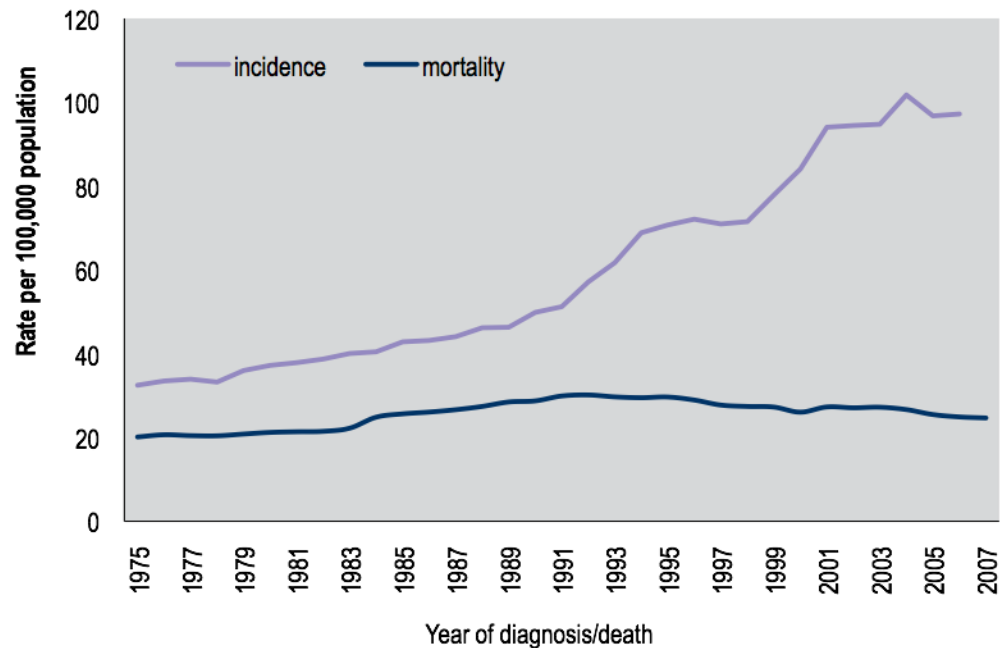
**CRITICS SAY:** Early detection should lead to a big drop in deaths, but they're up 4% since 1975.

The New York Times

# The huge increase in the incidence of prostate cancer is not reflected in prostate cancer mortality rates

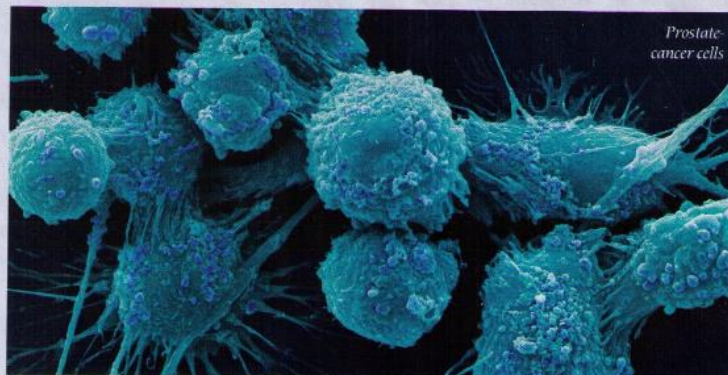
- Over the last 30 years, prostate cancer incidence rates have almost tripled from 33 per 100,000 in 1975 to 1,997 per 100,000 in 2006<sup>1</sup>
  - Much of the increase in incidence is due to increased detection through widespread use of the prostate-specific antigen (PSA) test

Age standardised (European) incidence and mortality rates of prostate cancer, GB 1975–2007<sup>1</sup>



1. Cancer Research UK, 2009.

# Health & Science



Prostate-cancer cells

## Skip the Screen. Experts say blood tests for prostate cancer don't save lives

By Alice Park

THE DOGMA IN CANCER CARE HAS ALWAYS been that preventing cancer is better than treating it. So routine screening for the early detection of the disease makes a lot of sense.

But a U.S. government group says that logic doesn't apply when it comes to the prostate-specific antigen (PSA) test for prostate cancer. Regular screening doesn't always save lives once you account for the high rate of false-positive results, and it increases men's risk of serious complications from biopsies and treatment of tumors that would never have killed them. So in new guidelines concluding that the harms of testing outweigh the benefits, the U.S. Preventive Services Task Force recommends that no men receive routine PSA screening at any age. The advice is based on a review of the research, including two large trials of the PSA test, which found no significant difference in survival rates between men who did and did not get screened, after 10 to 14 years of follow-up.

The idea of forgoing a cancer screen runs counter to everything patients and doctors have been taught about prevention, but the panel's advice stems from the understanding that not all cancers need to be treated. That's especially true of prostate tumors, which are generally slow-growing and often don't require aggressive intervention: 25% of men test positive for prostate cancer, but only 3% will die of it. Meanwhile, PSA testing can lead to medical interventions that unnecessarily raise the risk of infection, impotence, incontinence and even death.

It may take a while for doctors to accept the new advice, and critics are concerned that halting PSA tests will lead to a rise in more-advanced disease, which is harder to treat. The task force stressed, however, that patients with a family history of prostate cancer or other risk factors may still ask their doctor whether the PSA test makes sense for them, even if it's not part of their routine checkup.

### MEDICAL EVOLUTION

Health advice is based on research, but medical knowledge keeps advancing. That's why doctors' recommendations in these areas have changed over the years:

	MAMMOGRAPHY	HORMONE-REPLACEMENT THERAPY	LUNG CANCER
OLD SCIENCE	Many organizations advised women to start screening for breast cancer at age 40	Estrogen and progesterin protected post-menopausal women from heart disease	Chest X-rays can detect early lesions and get patients treated sooner
NEW SCIENCE	To avoid meningiomas, women should start screening at age 50	Hormones do not protect the heart and can increase the risk of breast cancer	X-rays don't help patients live longer even after they are treated

Sources: U.S. Preventive Services Task Force; *Journal of Clinical Oncology*; Federal Trade Commission

### BREAST CANCER

# 22%

Estimated drop in breast cancer risk in overweight women who lose 5% of their body weight. The benefit may be linked to hormone levels that fluctuate with weight

### DIET

## Pom, Not So Wonderful

If you're a fan of Pom Wonderful pomegranate juice, you probably got suckered into drinking it at least in part by the company's advertisements, which have claimed that the antioxidants in the crimson elixir can treat, prevent and reduce the risk of prostate cancer, heart disease and erectile dysfunction. That's a lot—too much, in fact—for any drink to do. A U.S. federal judge has ruled that Pom Wonderful used deceptive marketing in touting the beverage's benefits.

The judge's decision upheld most of the challenges included in a Federal Trade Commission complaint filed against the company in 2010 and ordered Pom to stop making misleading claims about the product's efficacy in fighting disease. The company says it will appeal parts of the decision.

—A.P.



Pom contains the juice of pomegranates, which are high in antioxidants

# Dilemma

- 50 year old male, completely asymptomatic, requests PSA test, because he has read about it in the newspapers or heard that his friend has had one done



# BAUS recommendations

- PSA test conducted in asymptomatic patients who request it
- appropriate counselling prior to test
- careful interpretation
- PSA only measured if appropriate to act on results

# NICE guidelines 2014

## Prostate cancer: diagnosis and treatment

Issued: January 2014

**NICE clinical guideline 175**

[guidance.nice.org.uk/cg175](http://guidance.nice.org.uk/cg175)

## Diagnosis

### Magnetic resonance imaging for rebiopsy

- Consider multiparametric MRI (using T2- and diffusion-weighted imaging) for men with a negative transrectal ultrasound 10–12 core biopsy to determine whether another biopsy is needed. **[new 2014]**

## Staging

- Consider multiparametric MRI, or CT if MRI is contraindicated, for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management. **[new 2014]**

# Active surveillance for CaP

At enrolment in active surveillance	Multiparametric MRI if not previously performed
Year 1 of active surveillance	Every 3–4 months: measure PSA <sup>2</sup> Throughout active surveillance: monitor PSA kinetics <sup>3</sup> Every 6–12 months: DRE <sup>4</sup> At 12 months: prostate rebiopsy
Years 2–4 of active surveillance	Every 3–6 months: measure PSA <sup>2</sup> Throughout active surveillance: monitor PSA kinetics <sup>3</sup> Every 6–12 months: DRE <sup>4</sup>
Year 5 and every year thereafter until active surveillance ends	Every 6 months: measure PSA <sup>2</sup> Throughout active surveillance: monitor

# Prostate health

- Lycopenes (from tomatoes)
  - precursors of vitamin A
  - cooked tomatoes have higher content
- Cruciferous vegetables
  - phyto oestrogens
- Soya bean produce
  - isoflavones → gut → phyto oestrogens
- Selenium
  - antioxidant / ?apoptotic

# Future?

- Focal therapy?
- Observation following template biopsies?
- Stereotactic hypofractionated accurate RT?
- Prostate cancer vaccine sipuleucel-T (Provenge) ... for advanced CaP

Thank you