Prostate Cancer Screening – Where are we?

Prof. Bob Steele

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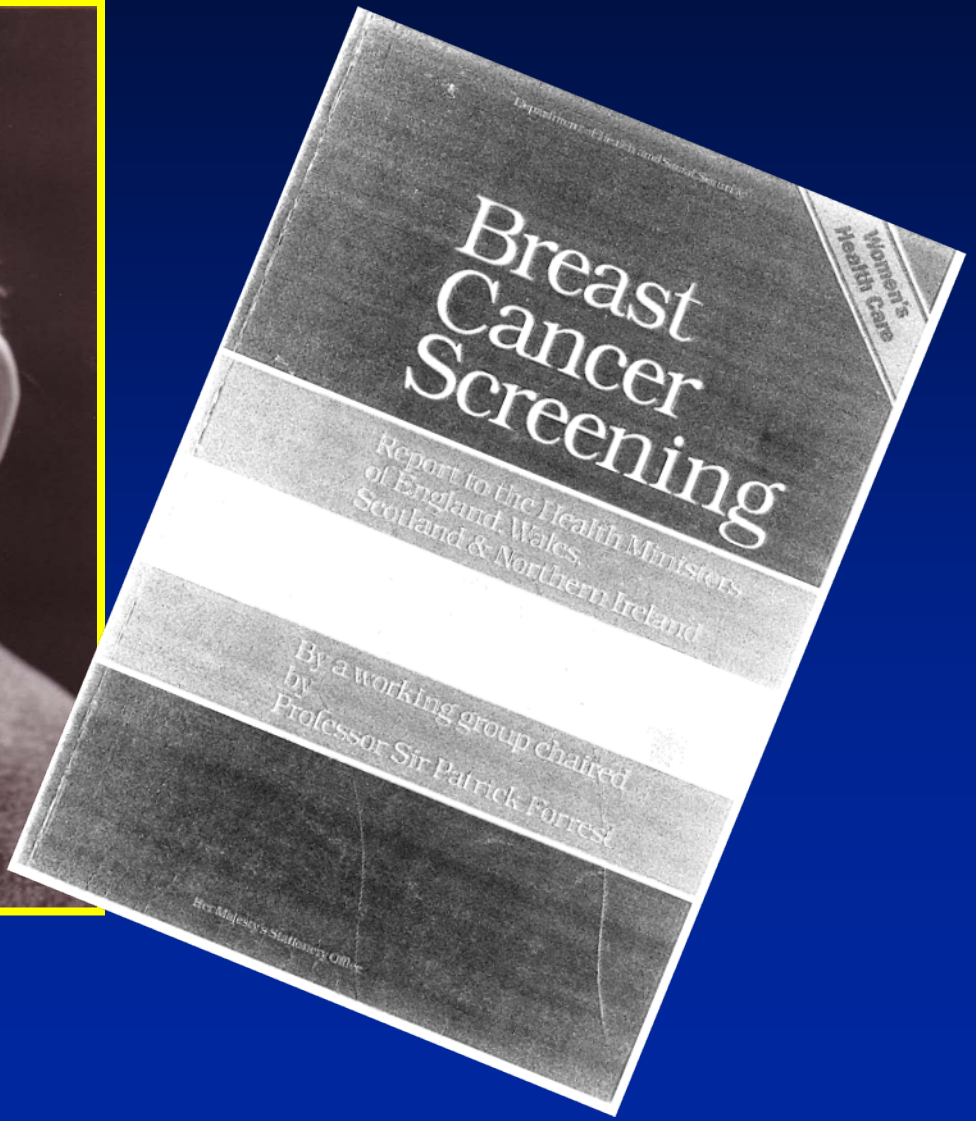
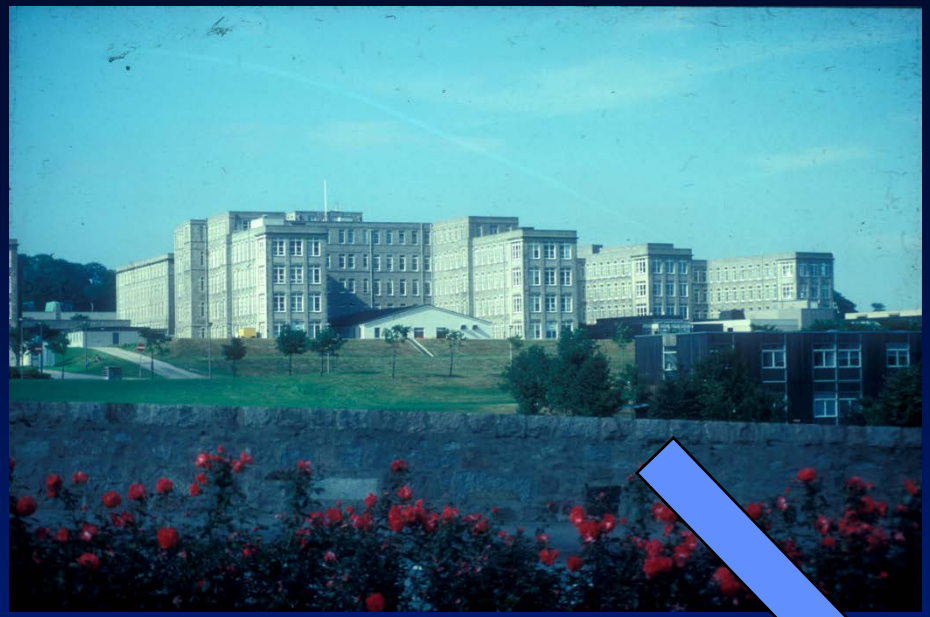

Women's Health Care
Breast Cancer Screening
Report to the Health Ministers of England, Wales, Scotland & Northern Ireland
By a working group chaired by Professor Sir Patrick Forrest
Her Majesty's Stationery Office



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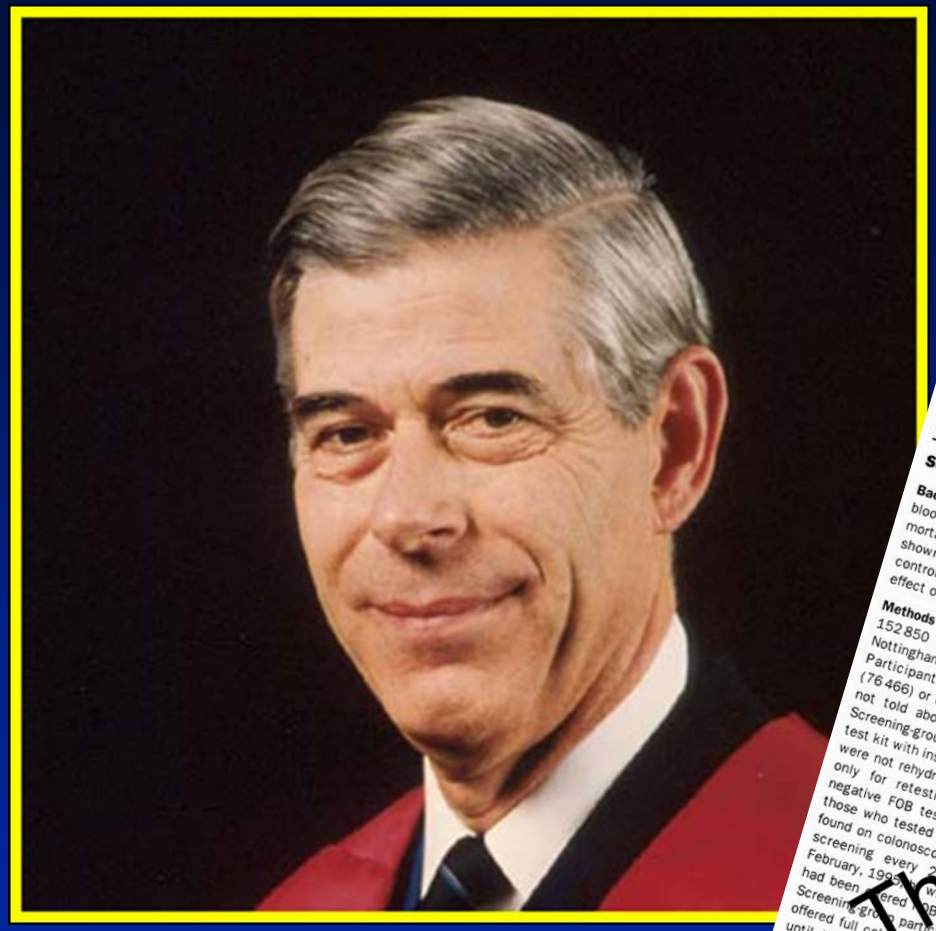


THE LANCET

Randomised controlled trial of faecal-occult-blood screening for colorectal cancer

Jack D Hardcastle, Jocelyn O Chamberlain, Michael H E Robinson, Susan M Mos... Sellars, Jamar, Tom W Balfour, Peter D James, Christine M Mangham

Summary

Background There is growing evidence that faecal-occult-blood (FOB) screening may reduce colorectal cancer (CRC) mortality, but this reduction in CRC mortality has not been shown in an unselected population-based randomised controlled trial. The aim of this study was to assess the effect of FOB screening on CRC mortality in such a setting.

Methods Between February, 1981, and January, 1... 152 850 people aged 45–74 years who lived ... Nottingham area of the UK were recruited to ... Participants were randomly allocated ... (76 466) or no screening (controls; 76 384). ... Screening-group participants were sent ... test kit with instructions from their ... were not rehydrated and diet ... only for retesting borderline ... negative FOB tests at the first screening, together with those who tested positive but in whom no neoplasia was found on colonoscopy. ... screening every 2 ... February, 1995. ... had been ... Screening ... offered full colonoscopy. All participants were followed up until June, 1995. The primary outcome measure was CRC mortality.

... people died from CRC in the screening group compared with 420 in the ... CRC mortality in the screening group (odds ratio=0·85 [95% CI ... 0·98], p=0·026).

Interpretation Our findings together with evidence from ... suggest that consideration should be given to a national programme of FOB screening to reduce CRC mortality in the general population.

Lancet 1996; **348**: 1472–77

See Commentary page 1463

Introduction

Colorectal cancer (CRC) is the second commonest cause of death from malignant disease in England and Wales, and resulted in about 16 000 deaths in 1993.[1] Although there have been advances in the management of symptomatic CRC, there has been little overall reduction in CRC mortality during the past 30 years. Tumour stage is an important determinant of outcome; 24–28% of patients have metastatic disease at presentation and the tumour is confined to the bowel wall in only 6–10% (Dukes' stage A).[2-4] Early diagnosis before the development of symptoms may be an effective way of reducing CRC mortality.

Tumours diagnosed as a result of screening by faecal-occult-blood (FOB) testing are known to include a higher proportion at a less advanced stage than those presenting

The "Nottingham" Study

Screening

The detection of disease in *asymptomatic* people in order to improve the outcome of the disease in question or to prevent it.

Which cancers do we screen for?

- Cervical
- Breast
- Bowel

Cancer in the UK

	Deaths /yr	New Cases/yr	5yr survival
Lung	34,859	42,026	6%
Bowel	15,708	40,695	58%
Breast	11,633	49,961	79%
Prostate	10,721	40,975	61%
Pancreas	7,901	8,463	2%
Oesophagus	7,610	8,477	8%
Stomach	4,960	7,266	12%
Bladder	4,907	10,695	65%

UK National Screening Committee

- Advises ministers and NHS
  - Introducing, continuing, modifying and withdrawing screening programmes
- Meets 3 times a year
  - New recommendations and updates existing ones
  - Supported by FMCH and ARG
- Keeps abreast of new evidence

Screening in the UK

Each UK health department responsible for setting screening policy, taking account of advice from UK NSC

Why is the work of UK NSC important?

Screening is Popular

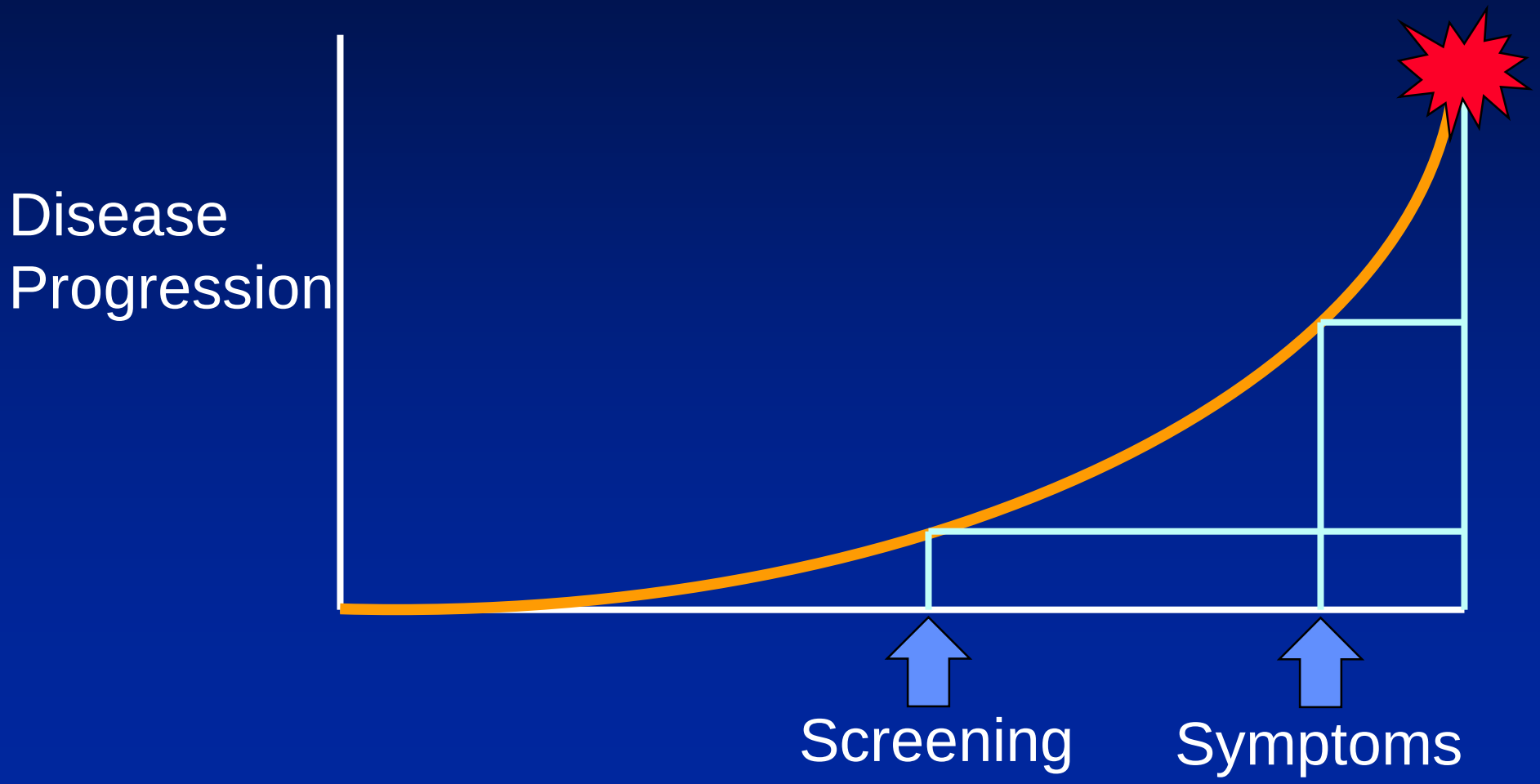
- *Most* people have a negative test 
- A *few* people have a false positive test 
- A *few* people are cured 
- A *few* people are harmed by investigation or treatment 

Advising on Screening Policy

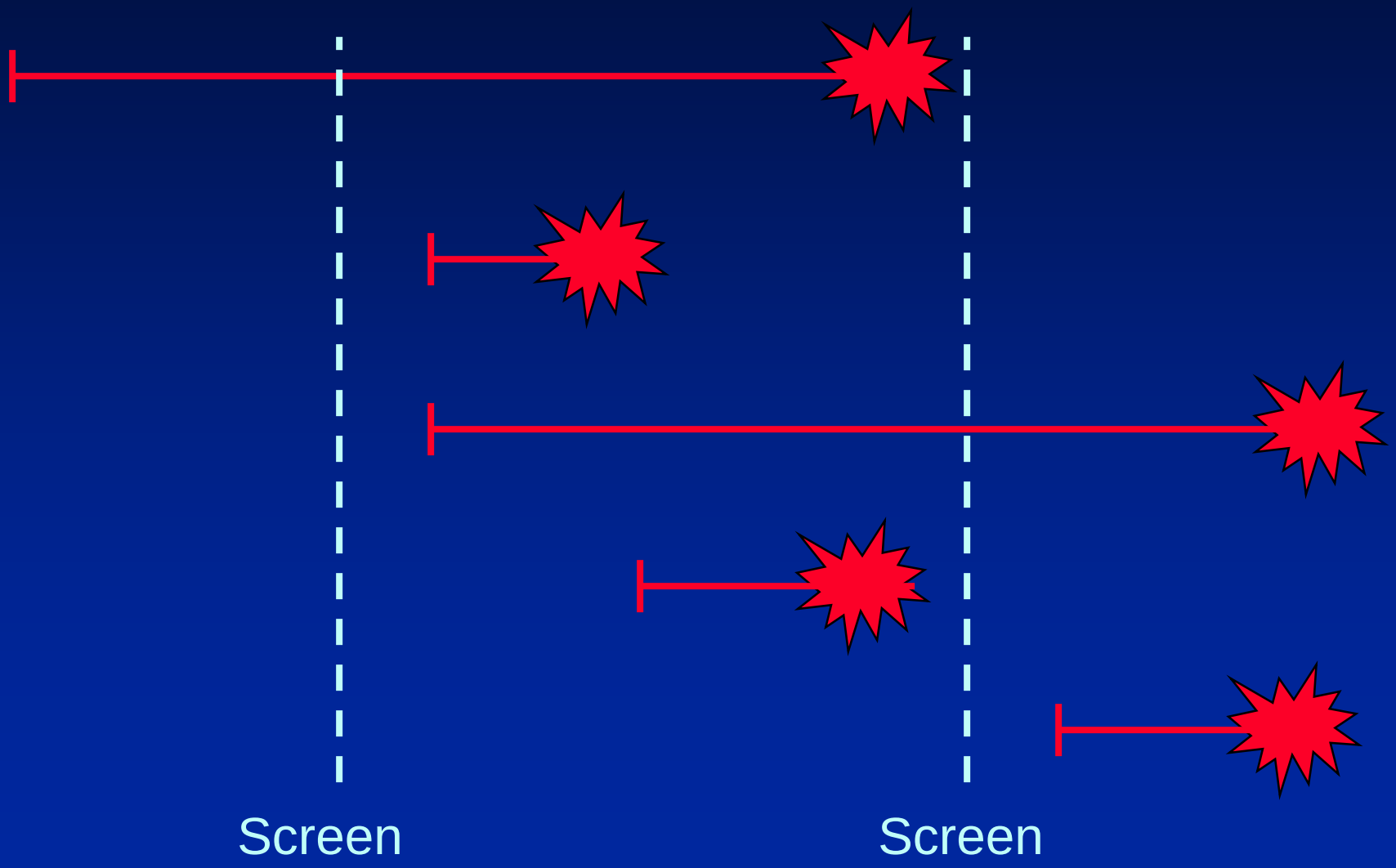
- Starting screening
- *Stopping screening starting*
- Changing screening
- Stopping screening

We have to careful with the interpretation of screening data

Lead-time Bias



Length Bias



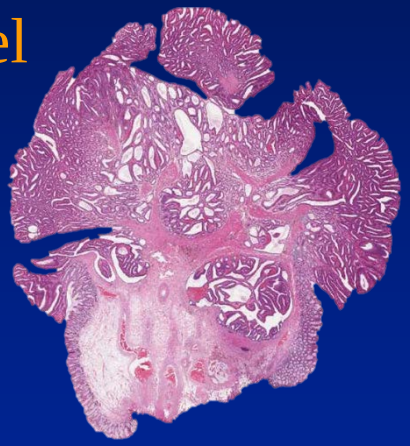
Selection Bias

Individuals accepting screening tend to be health conscious

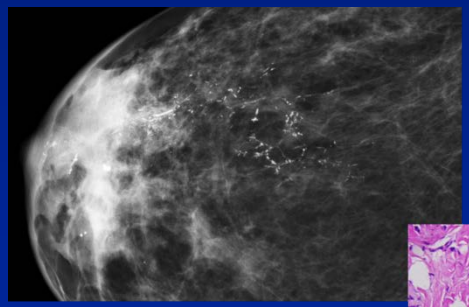
Overdiagnosis Bias

Screening detects disease that is not destined to cause death

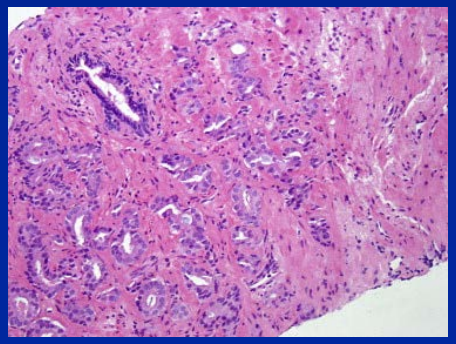
Bowel

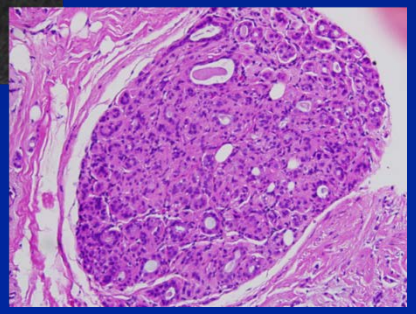


Breast



Prostate





Screening RCTs

Population

No screening offered

Screening Offered

(including those who choose not to participate and those developing interval disease)

Compare numbers of deaths or adverse outcomes from disease

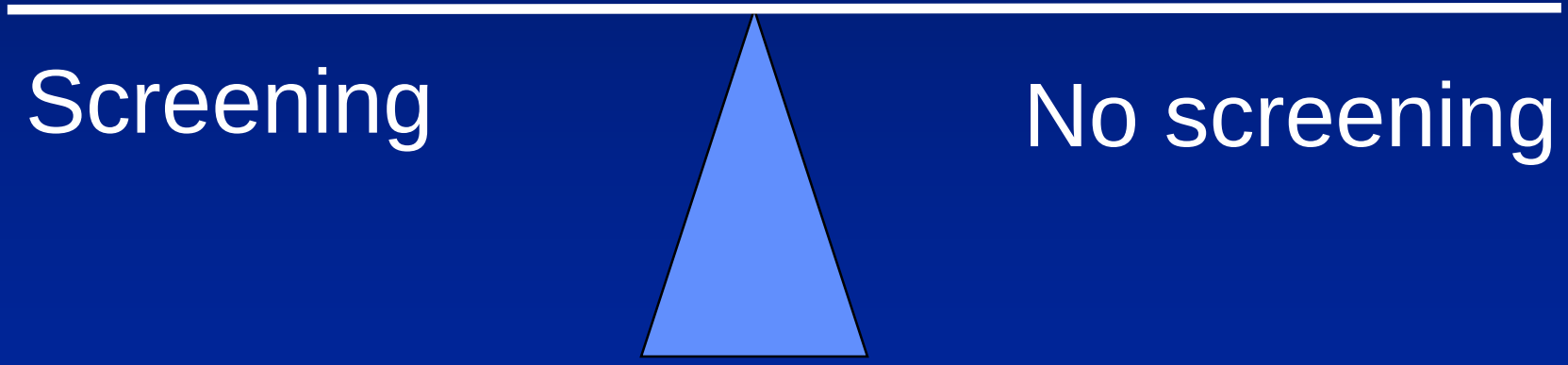
Criteria for Screening

- Effective treatment
- Treatment at early stage better
- Diagnostic and treatment facilities available
- Suitable test
  - Sensitive
  - Specific
  - Acceptable
- Economically viable
- *Benefit outweighs harm*

Modified from Wilson and Jungner, 1968

Cost
Harm

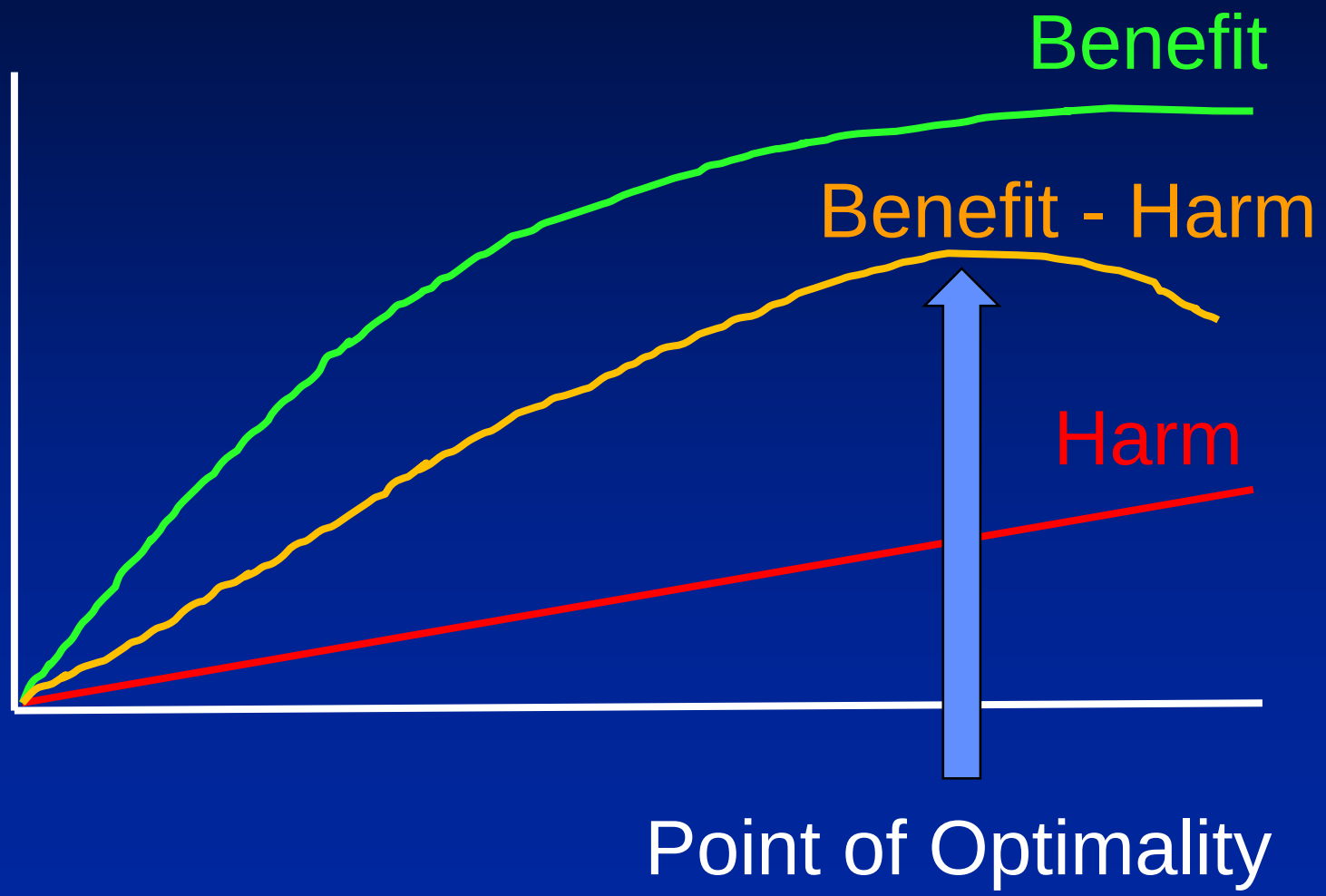
Cost and harm of treating disease not detected



Screening

No screening

Benefit-Harm



How can screening cause harm?

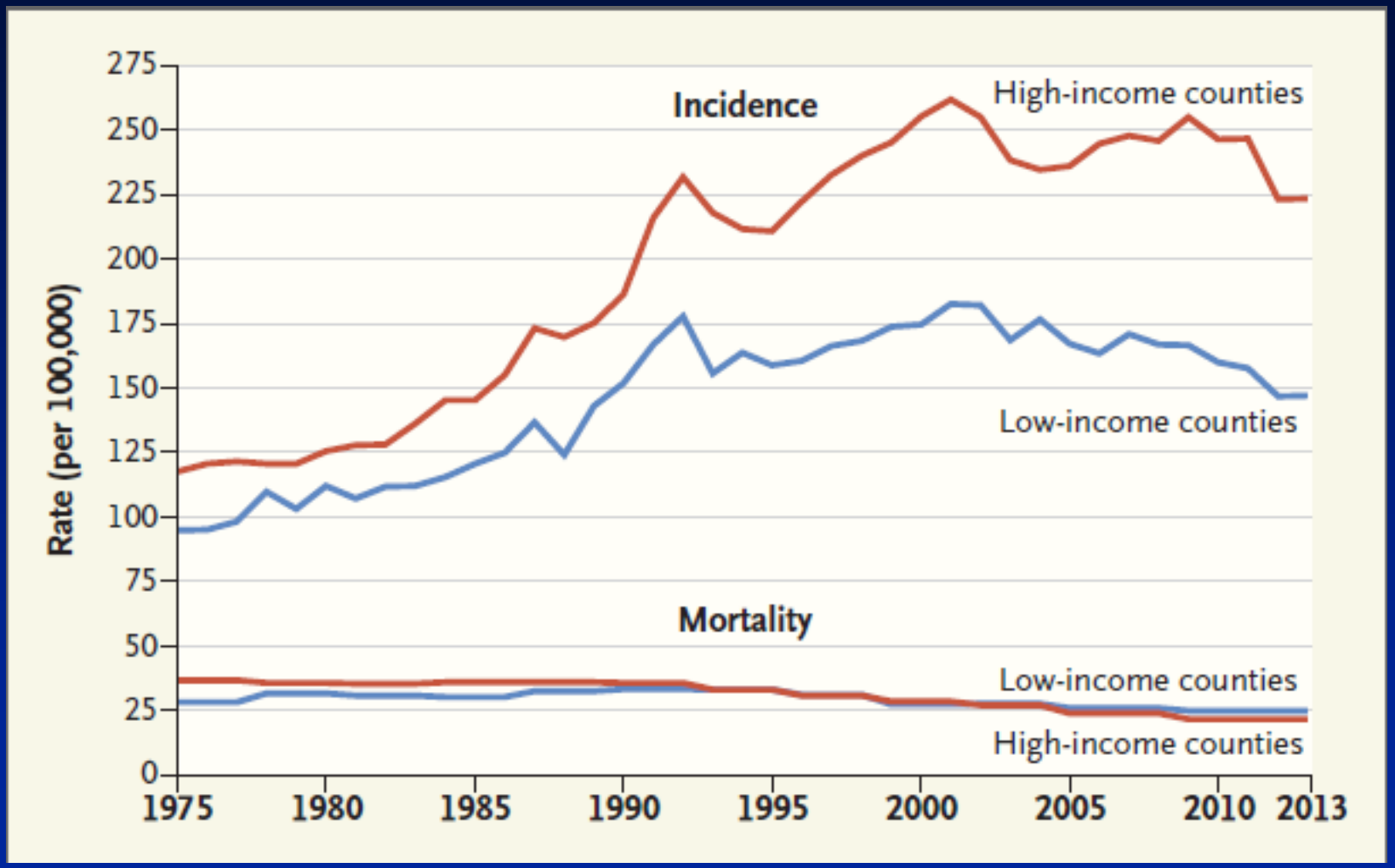
- Over-diagnosis
- Complications of diagnostic tests
- Complications of treatment
- Certificate of health
- Psychological distress
- Use of NHS resource

Prostate Cancer


ker Report
Male
Specimen type
Received date
PSA
Reference Range
0.0 – 4.0
Results
9.9 (High)
Lab Test
Prostate-specific antigen (PSA)

Incidence and Mortality

Prostate Cancer



Welsh and Fisher NEJM 2017; 376: 2208

Two RCTs of Screening

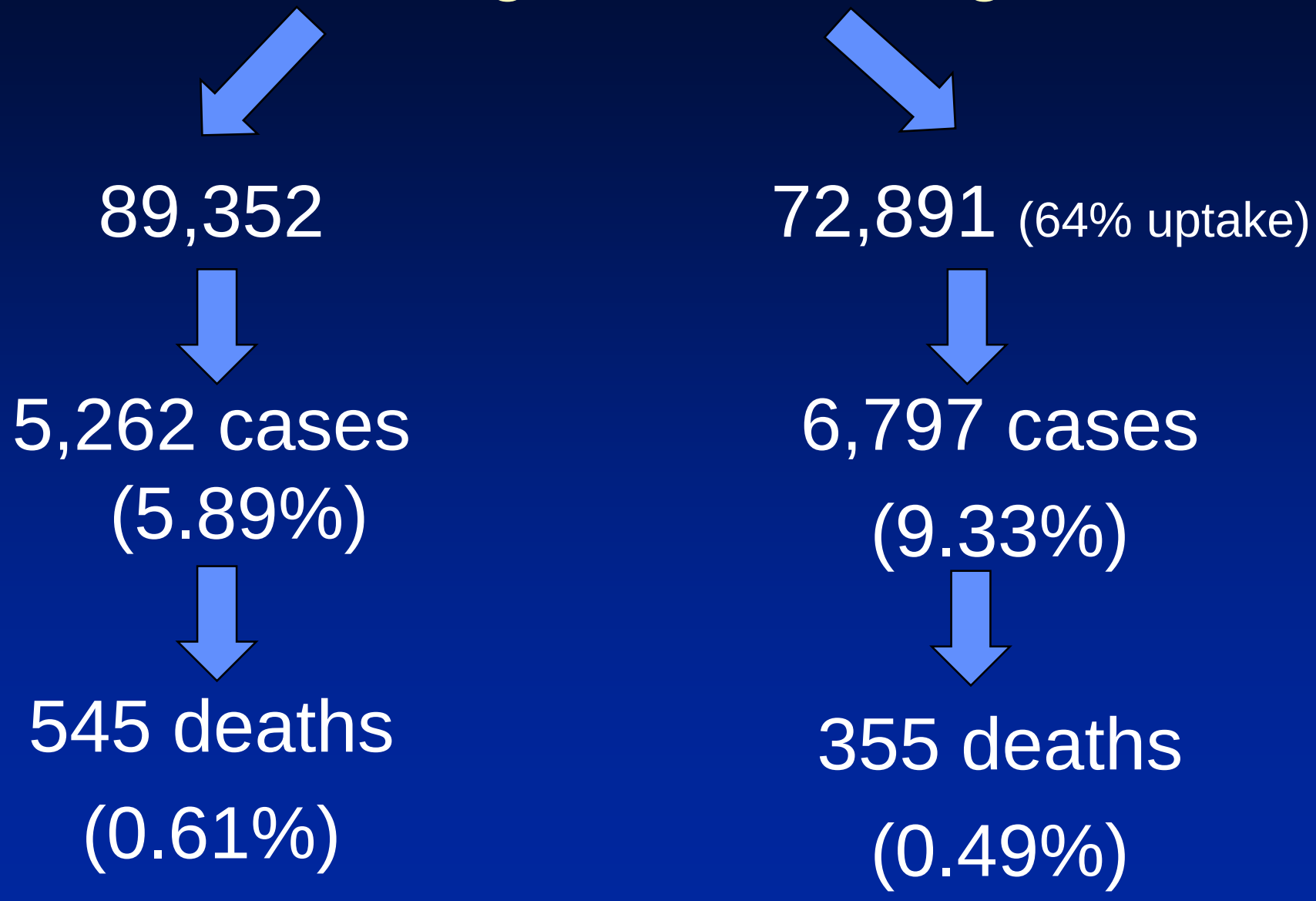
- United States (PLCO)
  - No benefit (but PSA testing in 50% of control group)
- Europe (ERSPC)
  - Disease- specific survival benefit

ERSPC Trial

- 162,388 men randomised
  - PSA screening vs no screening
- Screening → 21% reduction in Prostate Cancer deaths at 13 years

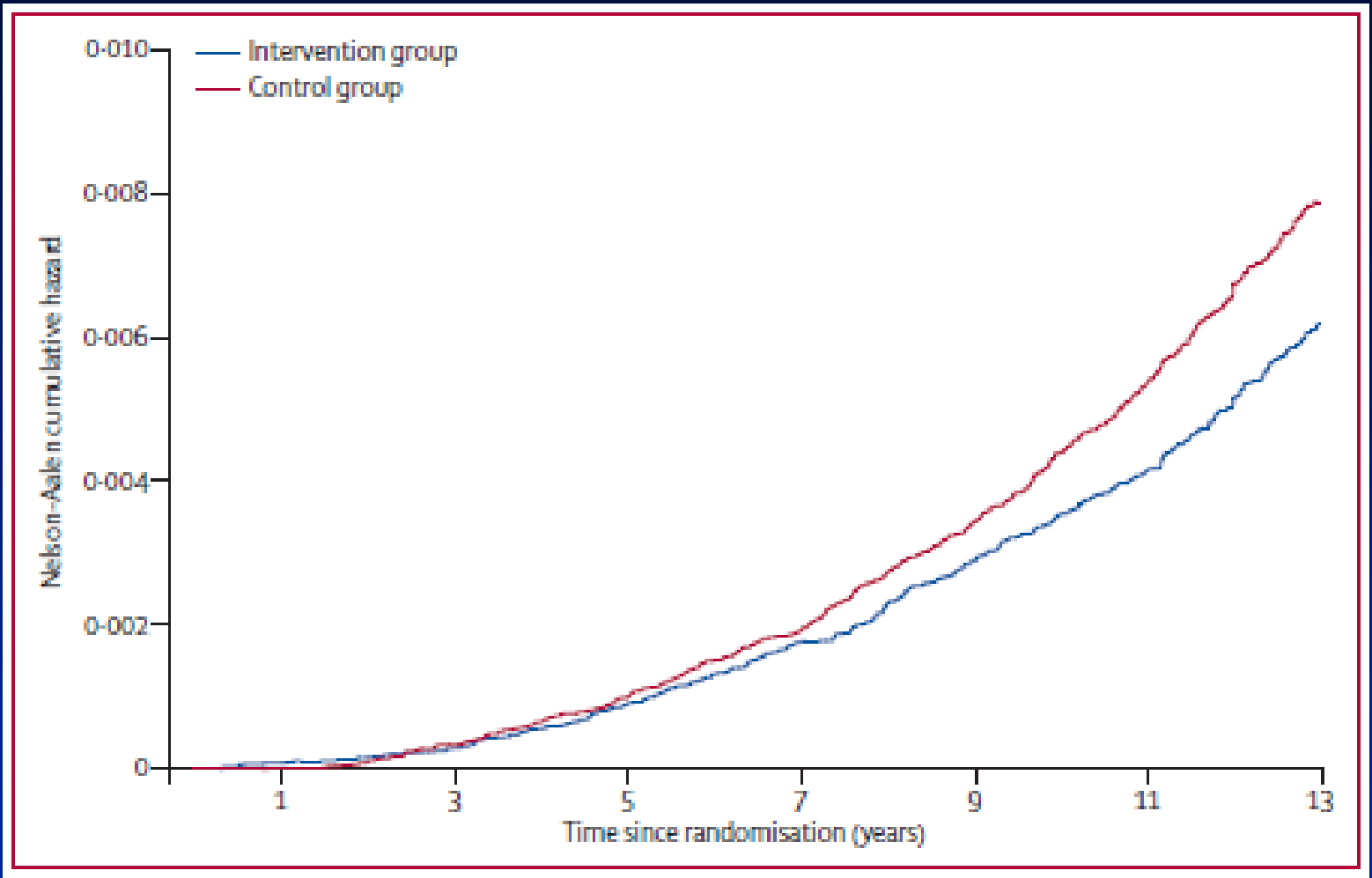
Presenting Evidence

- Relative risk reduction
  - 2/100 ⇨ 1/100
  - 2% ⇨ 1% = 50% RRR
- Absolute risk reduction
  - 2/100 ⇨ 1/100
  - 2% ⇨ 1% = 1% ARR


No Screening
Screening
89,352
72,891 (64% uptake)
5,262 cases
(5.89%)
6,797 cases
(9.33%)
545 deaths
(0.61%)
355 deaths
(0.49%)

ERSPC Trial

- 21% *Relative* reduction in risk of dying
- 0.12% *Absolute* reduction in risk of dying
- One death prevented per 27 *additional* cases detected


Intervention group
Control group
0·010
0·008
0·006
0·004
0·002
0
Nelson-Aalen cumulative hazard
1
3
5
7
9
11
13
Time since randomisation (years)

Harm

- Biopsy induced infection 10%

- Side effects of treatment
  - Incontinence
  - Impotence
  - Chronic diarrhoea

87%

Need to treat 28 men to prevent one PC death

Current Strategy

- Prostate Cancer Screening Programme not recommended
- Prostate Cancer Risk Management Programme (PCRMP)
- Any man can consult GP to discuss or request PSA testing
- PCRMP material supplied to GPs and patients

Summary Information for GPs

Public Health England

NHS

Advising well men aged 50 and over about the PSA test for prostate cancer: information for GPs

This Prostate Cancer Risk Management Programme (PCRMP) sheet helps GPs give clear and balanced information to asymptomatic men who ask about prostate specific antigen (PSA) testing. The PSA test is available free to any well man aged 50 and over who requests it.

GPs should use their clinical judgement to manage symptomatic men and those aged under 50 who are considered to have higher risk for prostate cancer.

Prostate cancer

Each year in the UK about 47,000 men are diagnosed with prostate cancer and about 11,000 die from the disease. The most common age of diagnosis is 65 to 69.

Men are at higher risk if they:

- have a family history of prostate cancer
- are of black ethnic origin – lifetime risk 1 in 4 compared to 1 in 8 for white men
- are overweight or obese (specifically for advanced prostate cancers)

Slow-growing tumours are common and may not cause any symptoms or shorten life. Some tested men may therefore face unnecessary anxiety, medical tests and treatments with side-effects.

PSA test

The test aims to detect localised prostate cancer when treatment can be offered that may cure cancer or extend life. It is not usually recommended for asymptomatic men with less than 10 years' life expectancy.

Evidence suggests PSA screening could reduce prostate-cancer related mortality by 21%.

About 3 in 4 men with a raised PSA level (>3ng/ml) will not have cancer. The PSA test can also miss about 15% of cancers.

Before a PSA test men should not have:

- an active urinary infection
- ejaculated in previous 48 hours
- exercised vigorously in previous 48 hours
- had a prostate biopsy in previous 6 weeks

When taking blood:

- ensure specimen will reach laboratory in time for serum to be separated within 16 hours
- send samples to laboratories taking part in UK National External Quality Assessment Service

Digital rectal examination (DRE)

DRE allows assessment of the prostate for signs of prostate cancer (a hard gland, sometimes with palpable nodules) or benign enlargement (smooth, firm, enlarged gland). A gland that feels normal does not exclude a tumour.

Biopsy

A biopsy can diagnose prostate cancer at an early stage when a cure may be possible.

About 2 out of 5 men describe biopsy as painful. The most common complications (3 out of 10 men) are bleeding and infections. Most men experience blood in urine and sperm after biopsy.

Some prostate cancers will be missed at biopsy (up to 1 in 5 men). If the biopsy is negative, follow-up and additional biopsies may be needed.

Management and treatment

Some men may benefit from treatment for localised prostate cancer. There is no clear evidence as to the best treatment option for localised prostate cancer.

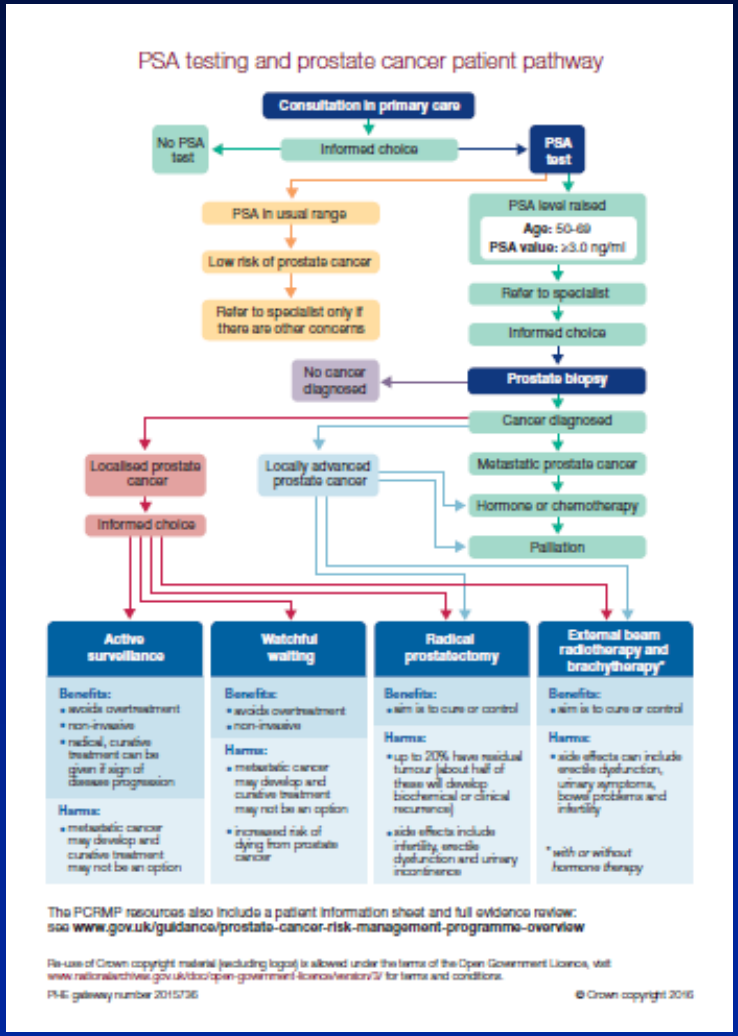
The main treatment options are:

- active surveillance
- watchful waiting
- radical prostatectomy (open, laparoscopic or robotically assisted laparoscopic)
- external beam radiotherapy (EBRT)
- brachytherapy (low and high dose rate)

There are important quality of life differences between each option. The options available depend on the stage of disease, the man's age and general health.

Active surveillance involves repeat PSA testing and biopsies. Surgery and radiotherapy may offer the possibility of a cure but can have significant side-effects.

See patient information sheet for summary of the potential benefits and harms of PSA testing.



The PCRMP resources also include a patient information sheet and full evidence review: see **www.gov.uk/guidance/prostate-cancer-risk-management-programme-overview**

PHE gateway number 2015736

Patient Information

Public Health England

NHS

PSA testing and prostate cancer: advice for well men aged 50 and over

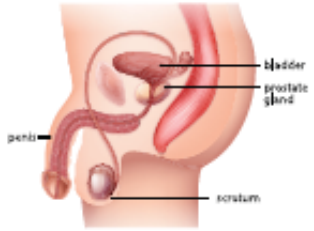
The prostate specific antigen (PSA) test may help find out if you are more likely to have prostate cancer. It is not perfect and will not find all prostate cancers.

Having a PSA test has potential harms and potential benefits.

This information should help you decide if you want to have the test or not. It is your decision. Before making your decision you may want to talk to your GP, practice nurse and your partner, family member or a friend.

Prostate cancer

The prostate gland lies just below your bladder. It helps produce healthy sperm. Problems with the prostate gland can affect how you urinate and your sexual function.



Prostate cancer is caused when some cells in the prostate start to grow out of control. Slow-growing cancers are common. They may not cause any symptoms or shorten your life.

Prostate cancer is the second most common cause of cancer deaths in UK men. Each year about 47,000 men are diagnosed with prostate cancer and about 11,000 die from the disease. Prostate cancer is rare in men under 50. The most common age of diagnosis is between 65 and 69.

Symptoms

Most early prostate cancers do not have any symptoms. If there are symptoms, many are the same as those caused by an enlarged prostate that is not cancerous.

Symptoms can include problems urinating, pain when ejaculating, pain or stiffness in the lower body, extreme tiredness and loss of appetite.

Risk

You are at higher risk of prostate cancer if you:

- have a family history of prostate cancer
- are of black ethnic origin – the lifetime risk is 1 in 4 compared to 1 in 8 for white men
- are overweight or obese

There is no clear evidence to recommend PSA testing more for high risk men than low risk men.

PSA test

The PSA blood test measures the level of PSA in your blood. A raised PSA level can mean you have prostate cancer. But it can also mean you have a condition that is not cancer, such as enlargement of the prostate or a urinary infection.

Test results and follow-up

If you have a raised PSA level you might need further tests, including a biopsy. This involves taking small samples of your prostate through your back passage and checking them for cancer.

If you have prostate cancer, your specialist will discuss options. Men with slow-growing cancers may be offered active surveillance. This involves repeat PSA tests to monitor the cancer, with treatment offered if the cancer starts to progress.

Possible treatments include surgery, radiotherapy and hormone therapy. Side effects of treatment can include problems with erections, loss of fertility and incontinence.

Find out more at www.nhs.uk/psa

Potential benefits and risks of PSA testing

	Having the PSA test	Not having the PSA test
Health	If you have the PSA test and follow-on treatment you are less likely to die of prostate cancer than men who do not have the test. Having an abnormal PSA test result means you may be offered further tests and treatments, which may harm your health.	If you do not have the PSA test you are more likely to die of prostate cancer than men who do have the PSA test. You are also more likely to experience the complications of advanced incurable prostate cancer.
Test results	The PSA test may reassure you if the result is normal. But it can miss cancer and provide false reassurance. If you have prostate cancer, you are more likely to be diagnosed and treated early. But an abnormal test result may also lead to unnecessary worry and medical tests when there is no cancer. The test cannot tell the difference between fast-growing cancers and slow-growing cancers that may not cause symptoms or shorten your life.	If you do not have the PSA test you may avoid unnecessary worry and tests after an abnormal result when there is either no cancer or a slow-growing cancer. If you have prostate cancer, you are less likely to be diagnosed and treated early.
Accuracy	About 75 out of every 100 men who have an abnormal PSA test result do not have prostate cancer. This is called a false positive result. About 15 out of every 100 men who have a normal PSA test result do have prostate cancer. This is called a false negative result.	If you do not have a PSA test, you will not get a false positive or a false negative result but the chance of early detection may be missed.
Follow-up	About 17 out of every 100 men who are tested have an abnormal test result. About 82 out of every 100 men who have an abnormal result will have a biopsy. Some men have problems or complications after a biopsy for prostate cancer. The most common complications are bleeding and infections.	If you do not have a PSA test, it is unlikely you will need to have a biopsy unless you get symptoms of prostate cancer, at which stage the cancer might be more advanced.
Treatment	If you are diagnosed with prostate cancer, you will need to decide about treatment. Potential treatments can include surgery, radiotherapy and hormone therapy. Side effects of treatments for prostate cancer can include problems with erections, loss of fertility and incontinence.	If you choose not to have a PSA test, it is unlikely you will need treatment for prostate cancer, unless you get symptoms. This means you are less likely to have any complications from treatments.

ProtecT Study

- PSA-detected early prostate cancer
- Three-way randomisation
  - Active monitoring
  - Conformal RT + NA androgen suppression
  - Radical Prostatectomy

Active Monitoring

- PSA measured every 3 months (Year 1) and every 6 months thereafter

- 50% rise in 12 months
  - Repeat within 9 weeks
  - If persistently raised – radical treatment offered

ProtecT Study Results

- No difference in prostate cancer deaths at 10 years
- *But* – higher rates of metastatic disease in the active monitoring group.

ProtecT Study @ 10 years

	Surgery n=533	Radiotherapy n=545	Monitoring n=545
Deaths	5	4	8
Recurrence	13	16	33

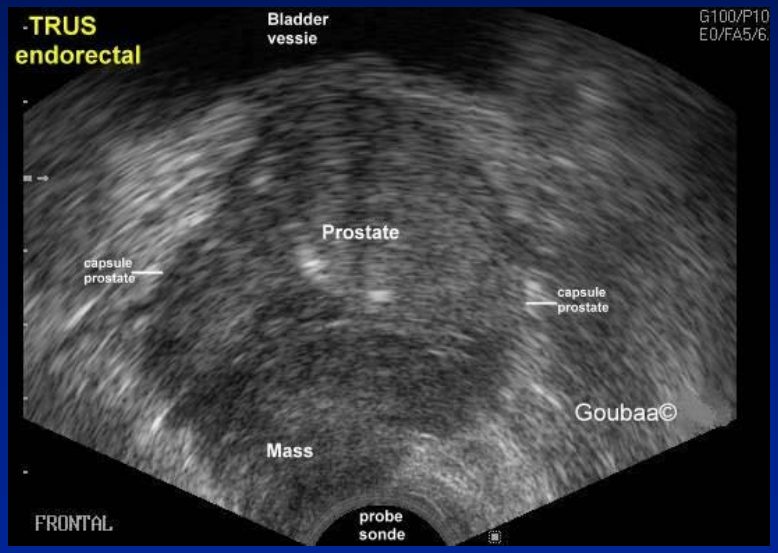
CAP Trial

- Cluster RCT of PSA Testing
- Random assignment of primary care centres
  - Standard Care (no routine PSA testing)
  - ProtecT (written invitation to PSA testing to 228,966 men in 337 practices)

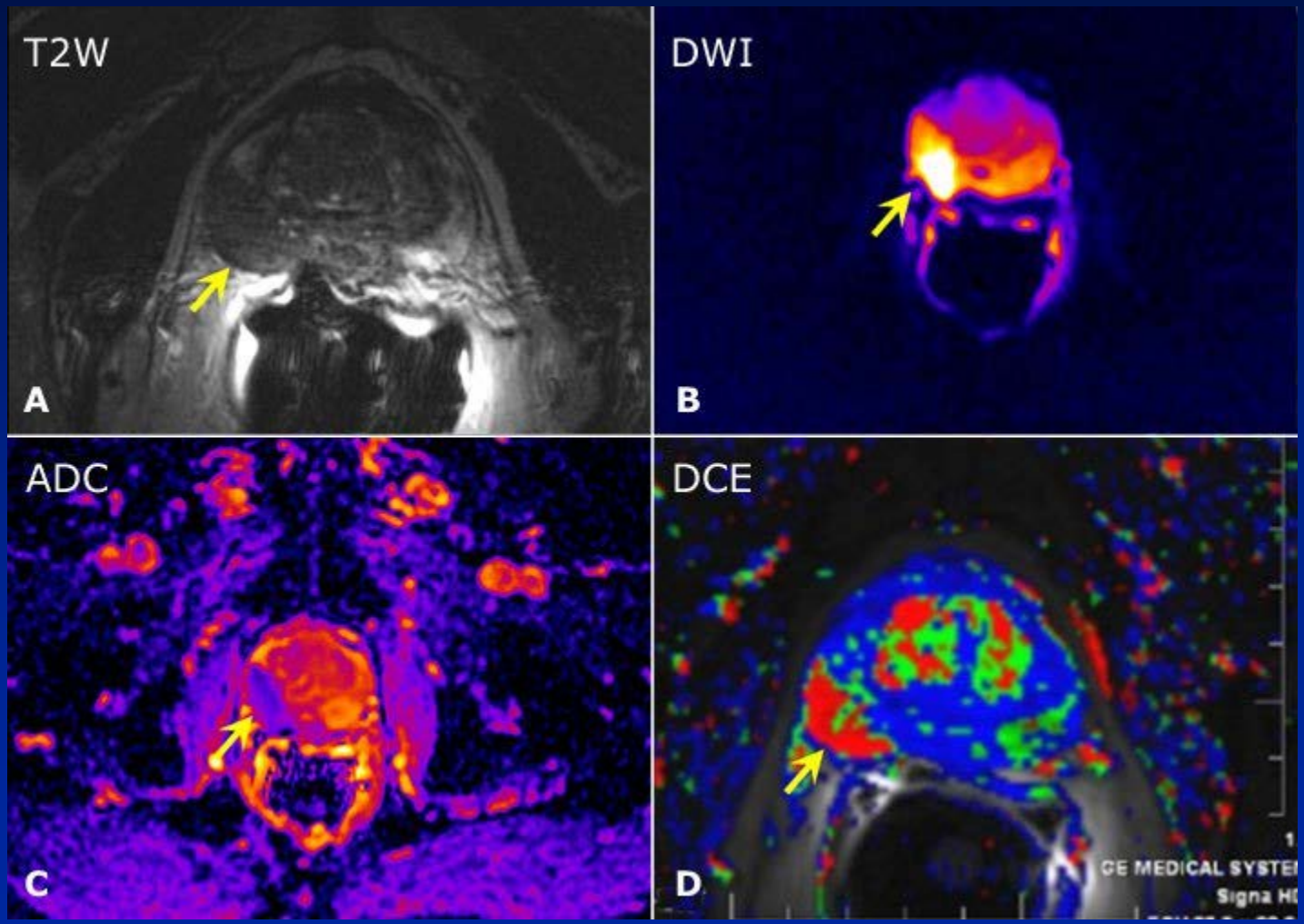
Challenge

To identify only those cancers that are destined to cause premature death

Biopsying the Prostate (TRUS)



MP-MRI



PROMIS Study

- Use of MP-MRI Scan directed biopsy
- Better than TRUS in detecting “clinically significant” cancer
- Implications for screening not yet clear

“All screening programmes do harm. Some do good as well and, of these, some do more good than harm at reasonable cost. It is the responsibility of policy-makers, public health practitioners, managers and clinicians to ensure that only programmes that do more good than harm at reasonable cost are implemented and, when they are implemented, that they are managed in such a way as to achieve a level of quality which will ensure that the balance of good and harm demonstrated in research is reproduced in real life.”

Muir Gray, 2007