Preventive Medicine and Medical Screening

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Preventive Medicine

- Prevention was defined by Last as:

"Actions aimed at eradicating, eliminating, or minimizing the impact of disease or disability, or if none of these is feasible, retarding the progress of disease and disability".

Spectrum of health and disease with the main strategies for prevention at each level

	Stages			Outcomes		
Intervention strategies	**Health**	**Asymptomatic**	**Symptomatic**	**Disability**	**Recovery**	**Death**
Levels of prevention	**Primary** →	**Secondary and Quaternary** →		**Tertiary**		

Medical Screening

What is screening

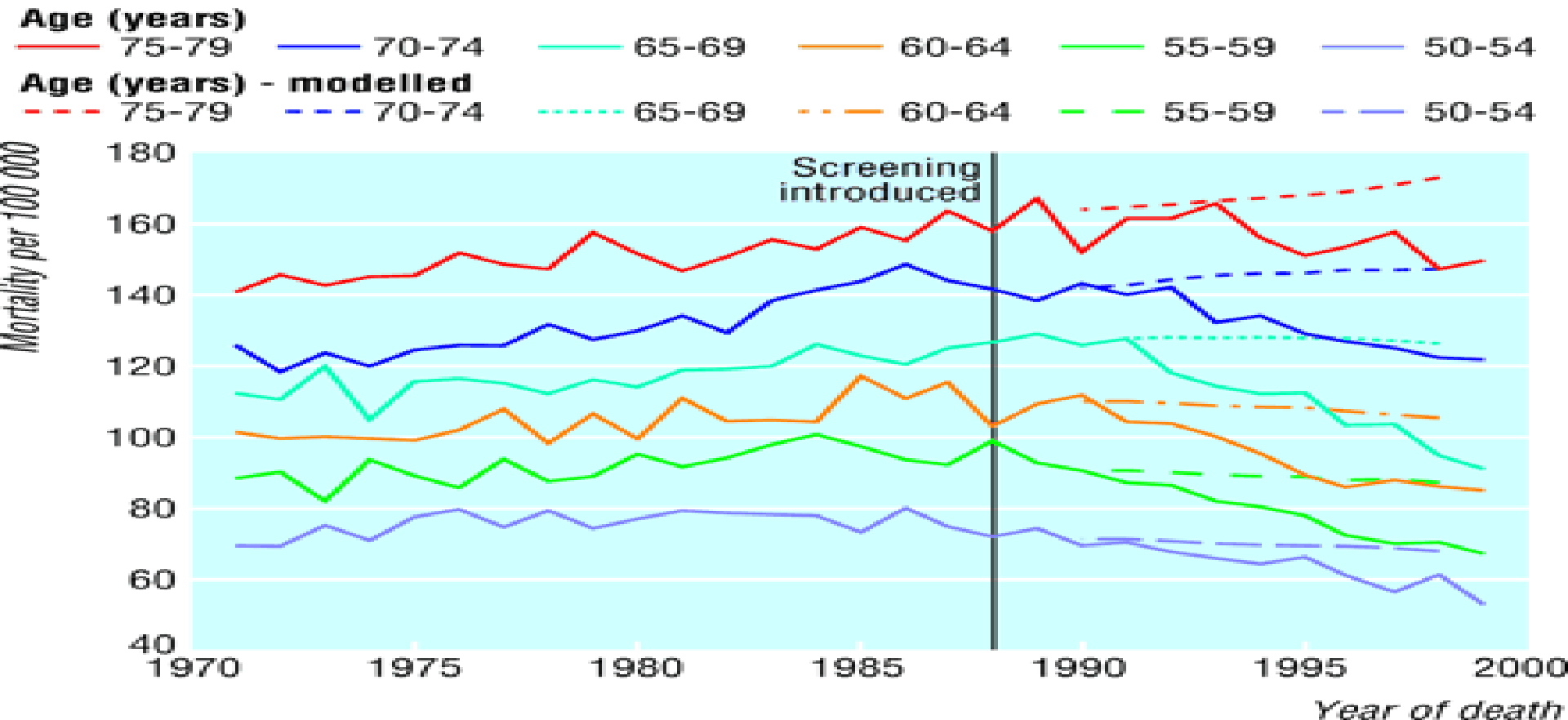
"The systematic application of a test or enquiry, to identify individuals at sufficient risk of specific disorder to benefit from further investigation or direct preventive action, among persons who have not sought medical attention on account of symptoms of that disorder." Wald,2004

Aims of screening

- Better prognosis/outcomes for individuals
- Protection of public from communicable diseases
- Rational allocation of resources
- Research (understanding natural history of disease)

Example of successful medical screening

- Mortality from breast cancer by year of death for selected age groups, England and Wales, 1971-99



Opportunistic screening (case finding):

- Do screening for someone when he/she comes into contact with the health system for another reason
- Check the lipid profile for your overweight or obese patients when they come to your clinic
- Refer women within age criteria for cervical or breast cancer screening

Screening versus diagnosis

- Early detection: symptoms and signs
- It is essential to work in both directions in parallel way:
- Start your screening programs

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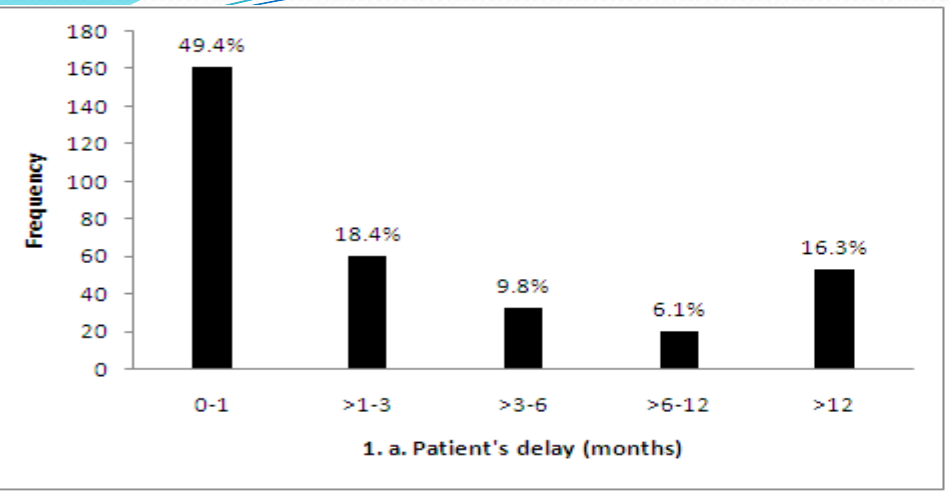
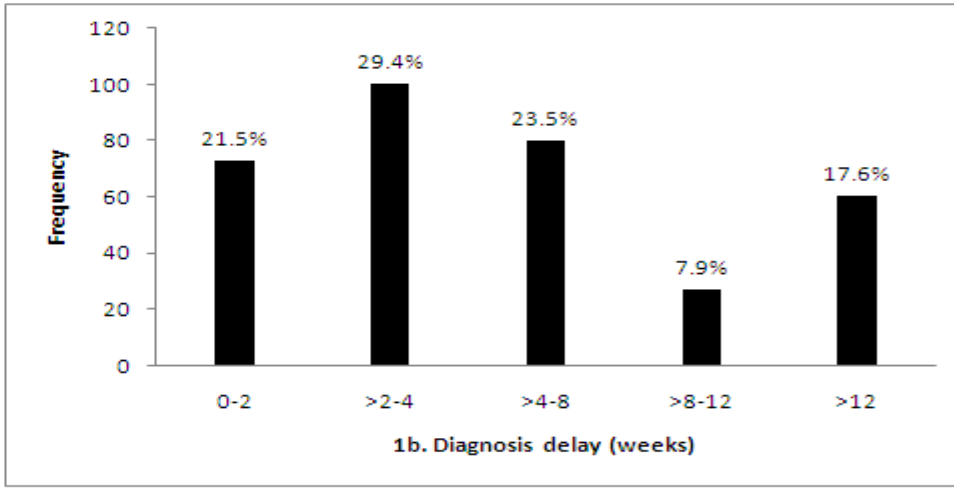
- Invest in early detection at GPs and selected specialties & general population levels awareness.

Delay in presentation, diagnosis and treatment for Breast cancer patients in Jordan





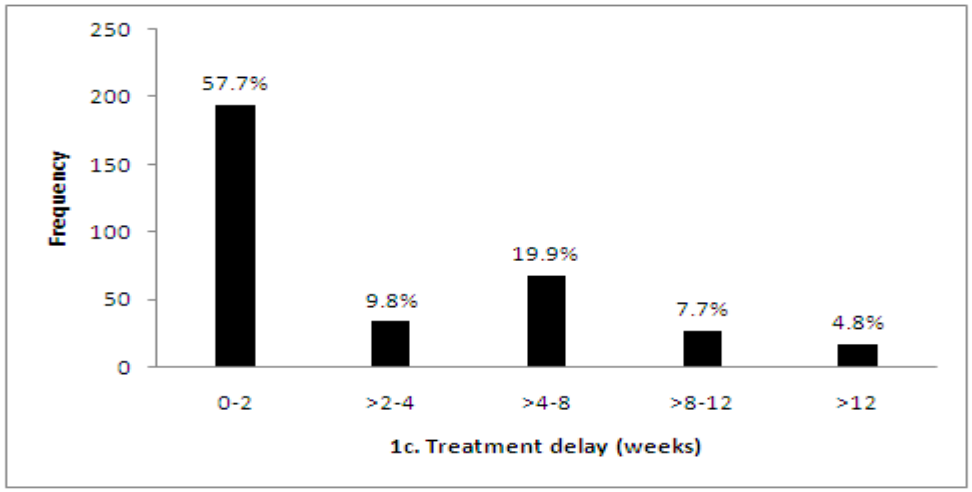
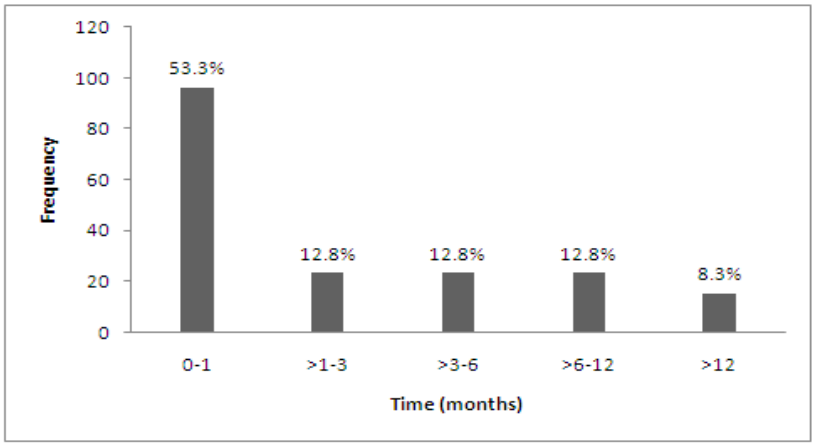


Figure 1: Proportion of participants by patient's delay, diagnosis delay, and treatment delay

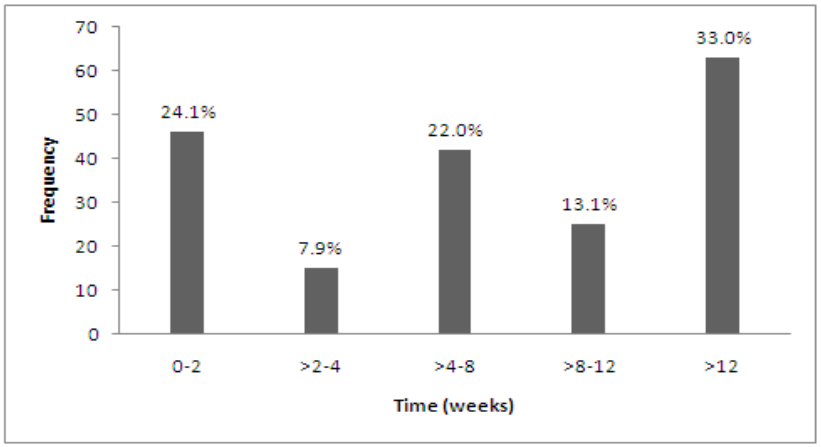
Abu-Helalah, M., Alshraideh, A. H., Al-Hanaqtah, M. T., Da'na, M. D., Al-Omari, A., & Mubaidin, R. (2016). Delay in presentation, diagnosis, and treatment for breast cancer patients in Jordan. *The breast journal*, *22*(2), 213-217.

Delay in presentation, diagnosis and treatment for colorecrtal cancer patients in Jordan

Fig1. Proportion of participants by patient's delay, diagnosis delay and treatment delay



(a)



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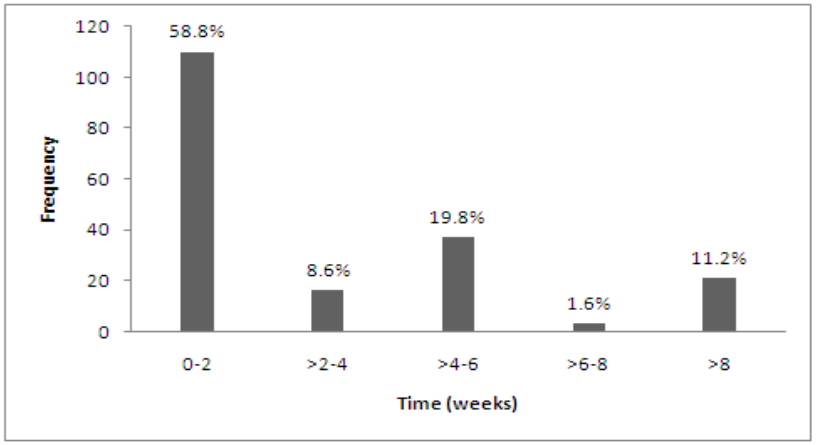

(c)

Abu-Helalah, M. A., Alshraideh, H. A., Da'na, M., Al-Hanaqtah, M. T., Abuseif, A., Arqoob, K., & Ajaj, A. (2016). Delay in presentation, diagnosis and treatment for colorectal cancer patients in Jordan. *Journal of gastrointestinal cancer*, *47*(1), 36-46.

Criteria for screening

1. The disease/condition is an important health problem:

- Well-defined disorder
- Known epidemiology
- Well-understood natural history
- Prevalence of undiagnosed cases

Shall we screen only for common illnesses?

- For serious diseases, even if it is not highly prevalent.
  e.g. Neonatal screening for inborn errors of metabolism.

Phenylketonuria screened for in the UK.

Incidence 1:12000 live births.

If undetected, it would lead to severe mental retardation and growth retardation. While detected cases could be treated simply by dietary restriction of phenlylalanine.

If undetected leads to severe mental and growth retardation.

Early Detected cases easily treated by dietary restriction of PKU.

Congenital hypothyroidism screening in Jordan

2. Presence of presymptomatic or early stage

- **Is there an evidence from a randomised controlled trial that an earlier intervention would work?**
- Detecting the disorder at this stage should help in getting better outcomes when compared with the situation without screening.
- Randomised controlled clinical trials could be needed to evaluate the impact of treatment on those detected from screening programmes as they could be different from those seeking medical attention for their conditions.

- Screening for a disease or a risk factor

It is recommended to screen for diseases, while risk factors are bad screening tools

Diabetes test	Normal	Prediabetes	Diabetes
Hemoglobin A_{1C}, %	< 5.7	5.7–6.4	≥ 6.5
Fasting blood glucose, mg/dL	< 100	100–125	> 125
Oral glucose tolerance, mg/dL	< 140	140–199	> 199

Trial	Design	Subjects	*N*; duration (years)	Control group	Active treatments	% change in diabetes risk
Principal diabetes prevention trials that evaluated metformin						
DPP (US) [19]	RCT	IGT and high–normal glucose	3234; 3	Placebo plus standard lifestyle advice	Metformin plus standard lifestyle advice	−31
					Intensive lifestyle intervention	−58
DPP Outcome Study (US) [69]	O	Epidemiological follow-up to DPP	2766; 5.7	Placebo plus intensive lifestyle advice	Metformin 1700 mg/day + intensive lifestyle advice	−13
					Intensive lifestyle advice	+5
IDPP (India) [20, 65]	RCT	IGT	531; 2.5	Standard lifestyle advice	Metformin plus standard lifestyle advice	−26
					Metformin plus intensive lifestyle intervention	−28
					Intensive lifestyle intervention	−29
Wenying et al. (China) [68]	NR	IGT	321; 3	Standard lifestyle advice	Metformin	−88
					Acarbose	−87
					Intensive lifestyle intervention	−43
Li et al. (China) [66]	RCT	IGT	70; 1	Placebo	Metformin	−66[a]
Iqbal Hydrie et al. (Pakistan) [67]	RCT	IGT	317; 1.5	Standard lifestyle advice	Metformin	−76.5
					Intensive lifestyle intervention	−71
CANOE (Canada) [64]	RCT	IGT	207; 3.9	Placebo	Metformin 500 mg plus rosiglitazone 2 mg twice daily	−66
Principal diabetes prevention trials that did not evaluate metformin						
Diabetes Prevention Study (Finland) [70]	RCT	IGT	522; 3.2	Standard lifestyle advice	Intensive, multifactorial lifestyle intervention	−58
Da Qing study (China) [71]	RBS	IGT	577; 6	Standard lifestyle advice	Diet, exercise, or both together	−31 to −46
STOP-NIDDM (International[b]) [72, 73]	RCT	IGT	1429; 3.3	Placebo	Acarbose	−25
XENDOS (Sween) [74]	RCT	IGT and obesity	694; 4[c]	Placebo	Orlistat	−45
DREAM (21 countries[d]) [75, 76]	RCT	IGT ± IFG	5269; 3	Placebo	Rosiglitazone	–62[e]
				Placebo	Ramipril	–9[f] (NS)
IDPP–2 (India) [77]	NR[f]	IGT	407; 3	Placebo + lifestyle intervention	Pioglitazone + lifestyle intervention	+8 (NS)
SOS study (Sweden) [78]	RCT	Obese, non-diabetic	3429; 10	No surgery[g]	Bariatric surgery	–83

ORIGINAL ARTICLE

A randomized double-blind crossover trial to investigate the efficacy of screening for adult hypothyroidism

M Abu-Helalah, M R Law, J P Bestwick, J P Monson and N J Wald

J Med Screen 2010;**17**:164–169
DOI: 10.1258/jms.2010.010057

Objective To assess the value of population screening for adult hypothyroidism.
Setting Healthy people attending for a general health assessment.
Methods A thyroid-stimulating hormone (TSH) measurement was performed on people attending for a general health assessment (women aged 50–79 [35–49 with a family history of thyroid disease] and men aged 65–79). Those with TSH levels above 4.0 mU/L were invited to join a randomized double-blind crossover trial of thyroxine and placebo, each given in random order for four months. On entry a second blood sample was collected for a TSH measurement after the end of the trial to determine whether this would help select individuals for thyroxine treatment. The daily thyroxine dose started at 50 μg and if necessary was increased to achieve a TSH level of 0.6–2.0 mU/L.
Results There were 341 (8%) people with a TSH level above 4.0 mU/L, 110 met eligibility criteria (64 agreed to participate), and 56 (49 women, 7 men) completed the trial. Among the 15 individuals with a repeat TSH measurement above 4.5 mU/L, 11 reported feeling better on thyroxine than placebo and none reported feeling better on placebo ($P = 0.001$; four felt no different), indicating that in this group 73% benefitted (i.e. 11/15; 95% CI 45–92%). The main symptoms relieved were tiredness and loss of memory. There was no indication of harm. In the 41 individuals with a repeat serum TSH of 4.5 mU/L or less: 10 reported feeling better on thyroxine than placebo and 16 better on placebo ($P = 0.42$, 15 felt no different). Thus about 8% of men and women in the specified age groups had a TSH above 4.0 mU/L, and of these about a quarter had a repeat TSH above 4.5 mU/L, of whom about half would benefit from thyroxine treatment.
Conclusion The results indicate that screening for hypothyroidism would be worthwhile. Approximately 1% of people screened would have a better quality of life. Pilot screening programmes for adult hypothyroidism are justified.

See end of article for authors' affiliations

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What do you aim to achieve from your screening programme?

- Mortality
- Morbidity
- Quality of life and psychological wellbeing

Screening test:

- Safe
- Inexpensive
- Acceptable
- Reliable
- Valid
- No or minimal adverse effects: pain or any possible adverse effects should be considered in addition to convenience and duration of the test.

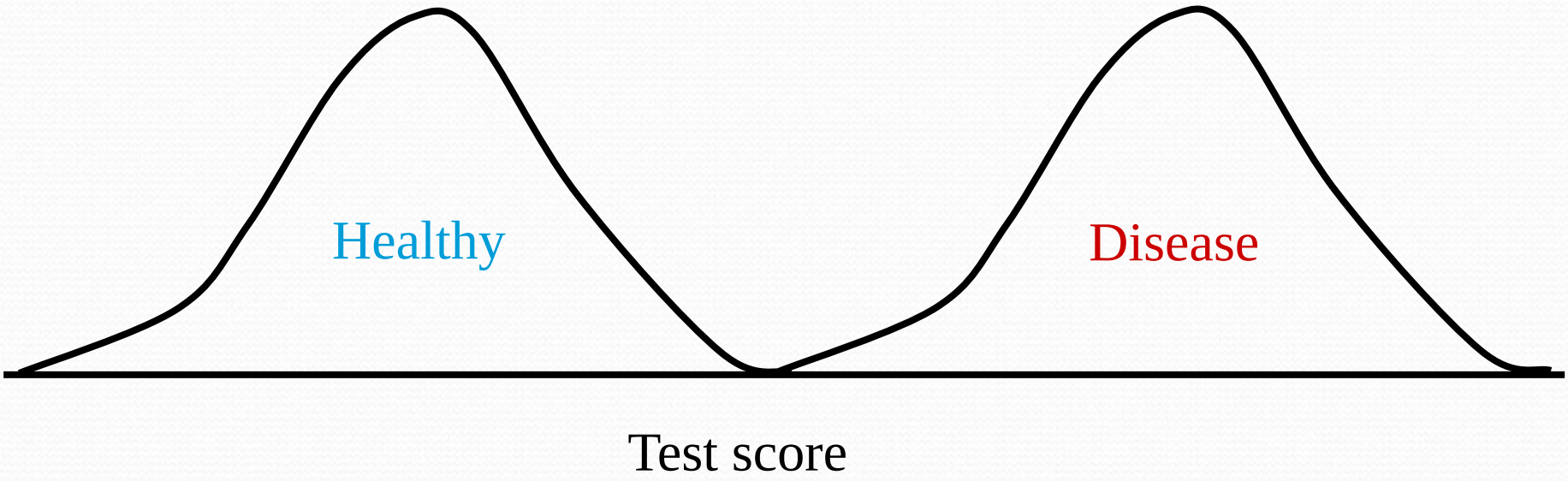
Screening test validity

- **The validity of a screening test can be evaluated through its detection rate (sensitivity) and specificity.**

  A. Detection rate (sensitivity) evaluates the ability of a screening tool to detect the disorder or problem. It represents the proportion of diseased individuals who have a positive screening test.

  B. Specificity is the ability of a screening tool to label people without the targeted condition as "unaffected" (for diseases, healthy people as non-diseased).

An ideal laboratory test would detect all people who have a disease and at the same time identify as normal all those who do not have the disease



False positive rate (1-specificity)

- More meaningful and practical than specificity because it shows the expected rate of those who would be falsely labelled as diseased or screen positive and might offered further investigations.
- It helps in estimation the magnitude of the economic (further investigations) and other harmful effect such as psychological distress associated such outcomes.

Validity of a test

How well a test performs can be assessed based on the values in the following 2x2 table

	Disease present	**Disease absent**
Test positive or Surveillance Detection positive	**True Positives TP** **a**	**False positives FP** **b**
Test negative or Surveillance Detection negative	**c** **False negatives FN**	**d** **True negative TN**

	Disease present	Disease absent
Test positive or Surveillance Detection positive	True Positives TP a	False positives FP b
Test negative or Surveillance Detection negative	c False negatives FN	d True negative TN

$$\text{Sensitivity} = \frac{\text{Diseased people with a positive test}}{\text{All diseased people}} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

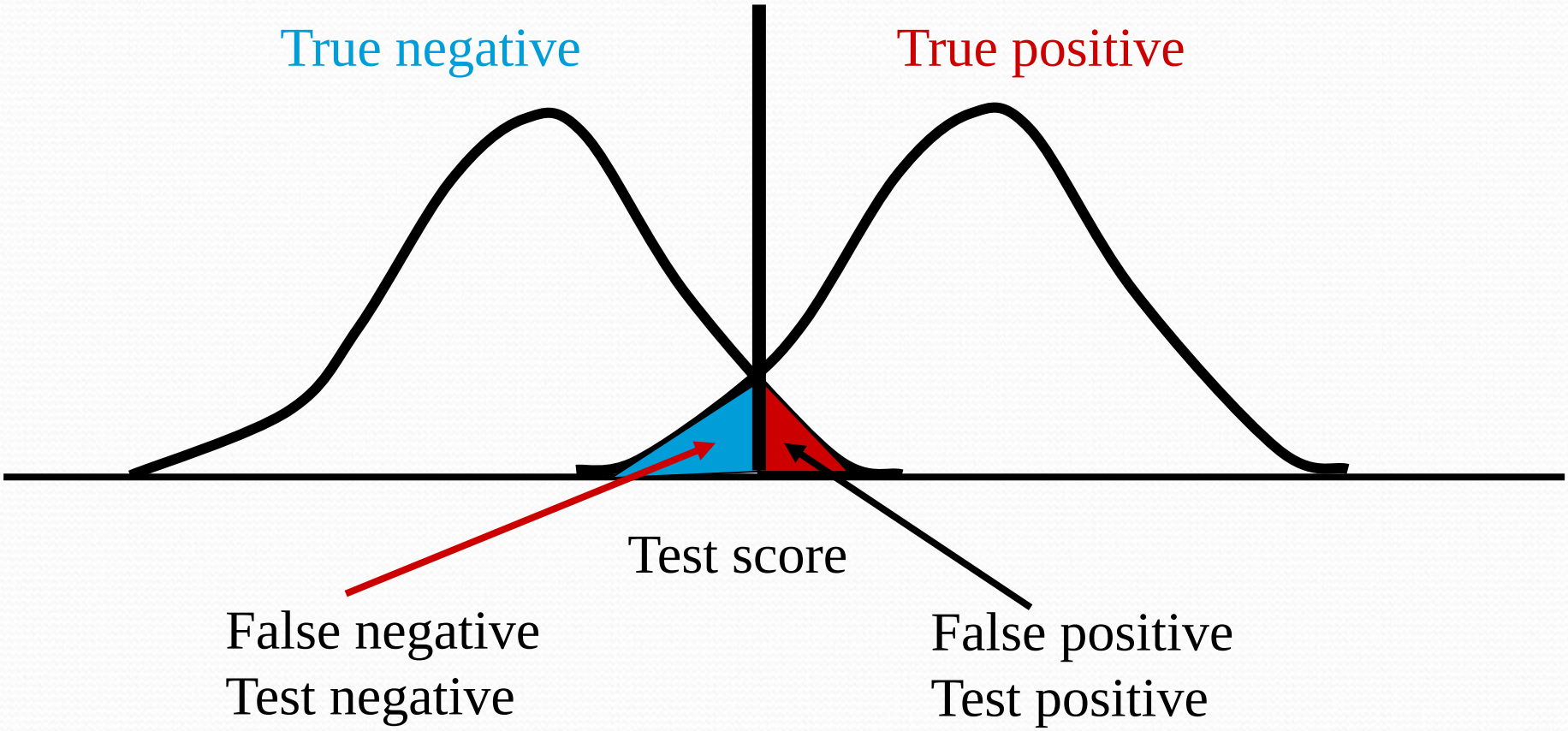
$$\textbf{\textit{Specificity}} = \frac{\textbf{\textit{Well people with a negaitive test}}}{\textbf{\textit{All well people}}} = \frac{\textbf{\textit{TN}}}{\textbf{\textit{TN} + \textit{FP}}}$$

False positive rate= FP/FP+TN

Test based on continuous data

- Hematocrit
- Blood glucose
- Optical density testing

the values between normal/disease overlap



False positive rate

- The proportion of unaffected individuals with positive test results.

- False positive rate= $\frac{b}{b+d}$ =1-specificty

Predictive values

- Positive predictive value= all true positives/all positives(all true and all false) ×100
- How likely it is that a positive test result indicates the presence of the disease.
- It is the percentage of all people who test positive and who really have the disease
- Negative predictive value= True negatives/all negatives ×100
- It is the percentage of all people who test negative who really do not have the disease

	Disease present	Disease absent
Test positive or Surveillance Detection positive	True Positives TP a	False positives FP b
Test negative or Surveillance Detection negative	c False negatives FN	d True negative TN

$$prevalence = \frac{Diseased\ people}{All\ \ people} = \frac{TP + FN}{TP + FN + FP + TN}$$

$$predictive\ value\ \ positive = \frac{Diseased\ people\ with\ a\ positive\ test}{All\ \ people\ with\ a\ \ positive\ test} = \frac{TP}{TP + FP}$$

$$predictive\ value\ \ negative = \frac{Well\ people\ with\ a\ \ negative\ test}{All\ \ \ people\ with\ a\ negative\ test} = \frac{TN}{TN + FN}$$

Screening test validity: Outcomes of screening tests

	Disease present	Disease absent	All
Positive screening test	***a*** **(true positive)**	***b*** **(false positive)**	***a + b***
Negative screening test	***c*** **(false negative)**	***d*** **(true negative)**	***c + d***
All	***a + c***	***b + d***	***a + b + c + d***

Detection rate	proportion of affected individuals with positive test results	$\frac{a}{a+c}$
Specificity	Proportion of unaffected individuals with negative test result	$\frac{d}{b+d}$
False positive rate	proportion of unaffected individuals with positive test results	$\frac{b}{b+d}$ =(1-specificity)
Positive predictive value	Probability of the disease being present given a positive test	$\frac{a}{a+b}$
Negative predictive value	probability of no disease being present given a negative test result	$\frac{d}{c+d}$

		Patients with bowel cancer (as confirmed on colonoscopy)		
		Positive	***Negative***	
Fecal occult blood screen test outcome	***Positive***	**True Positive (TP) = 20**	**False Positive (FP) = 180**	**→ Positive predictive value = TP / (TP + FP) = 20 / (20 + 180) = 20 / 200 = 10%**
	Negative	**False Negative (FN) = 10**	**True Negative (TN) = 1820**	**→ Negative predictive value = TN / (FN + TN) = 1820 / (10 + 1820) = 1820 / 1830 ≈ 99.5%**
		↓ Sensitivity = TP / (TP + FN) = 20 / (20 + 10) = 20 / 30 ≈ 66.67%	**↓ Specificity = TN / (FP + TN) = 1820 / (180 + 1820) = 1820 / 2000 = 91%**	

Example of validity assessment

	G-FOBT	FIT
Sensitivity	50.00% (6.76–93.24)	75.00% (19.41–99.37)
Specificity	77.87% (72.24–82.83)	90.12% (85.76–93.50)
Positive likelihood ratio	2.26 (0.83–6.18)	7.59 (3.86–14.94)
Negative likelihood ratio	0.64 (0.24–1.71)	0.28 (0.05–1.52)
Positive predictive value	3.45% (0.42–11.91)	10.71% (2.27–28.23)
Negative predictive value	98.99% (96.42–99.88)	99.56% (97.59–99.99)

False positive rates: 1-Specificity
More un-necessary colonoscopes and more cost for the program

Reliability of screening test

- Reliability means that the same results should be obtained by different observer or the same observer at different occasions.
- In practice, it is hard to achieve 100% reliability
- Guidelines should be in place on decisions when two observers have different opinions.

Agreed plan on further investigation, diagnosis and treatment:

- Where to refer your positive subjects
- What is the diagnostic tests
- Who will pay for the investigations and treatments
- Diagnostic tools, screening intervals and treatment
- Facilities required for such steps should also be available or easily installed and equally accessed by the screened population

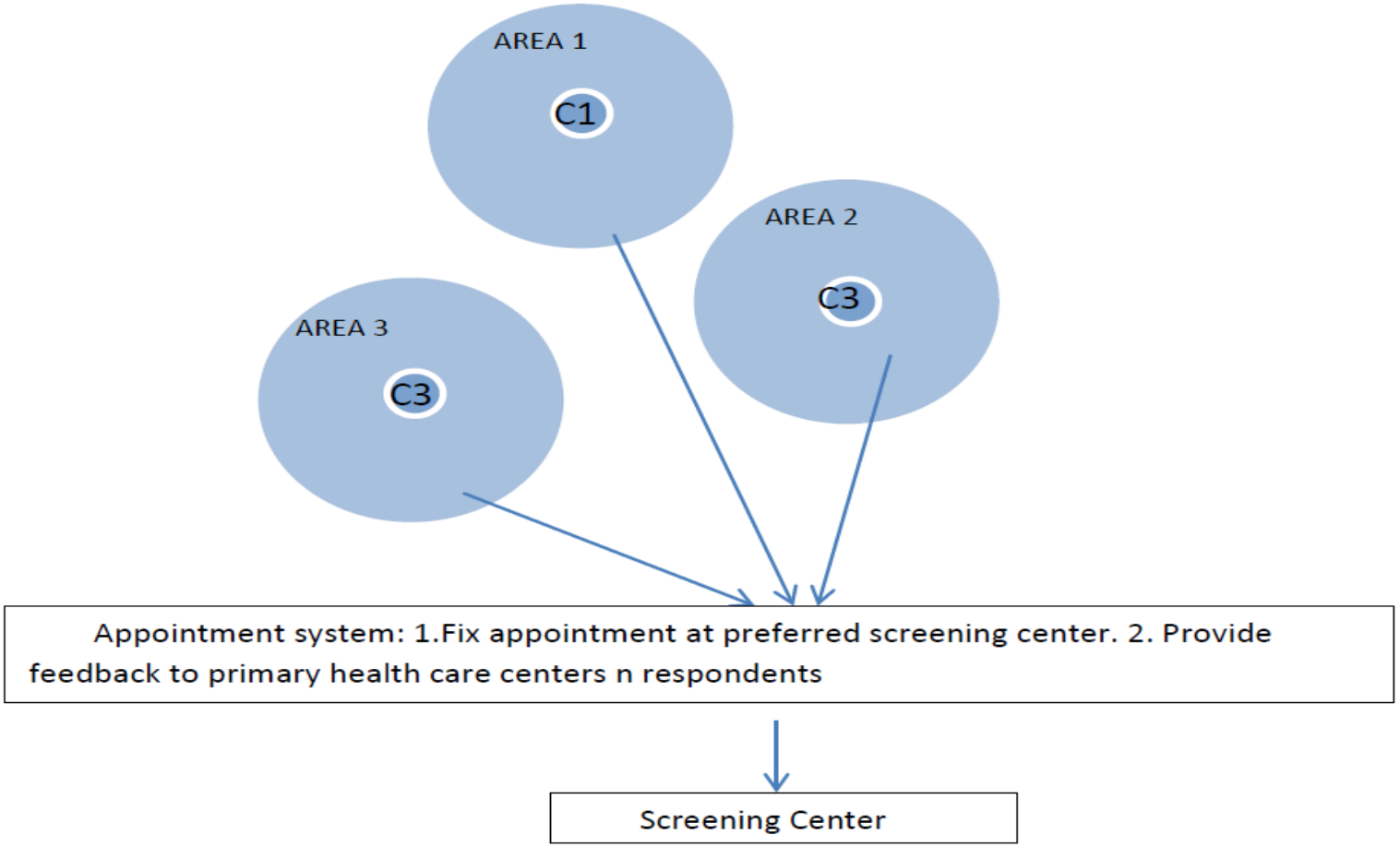
Systematic application

- This means that the test is offered routinely to the target group based on agreed criteria.

Do it in a systematic way!

- **Regular systematic national screening programs** for breast and colorectal cancers **should replace the current scattered campaigns and activities in many countries in the region.**

- Work should start with pilot systematic screening projects in representative area in the country of interest.



Obtain data from Ministry of Interior on residents in Areas 1,2,3 who fulfills screening criteria

Send letters through Health Centers C1,C2,C3

Send reminders through Health Centers C1,C2,C3 for non-respondents

Ask practice manager or health counselor to call non-respondents from the two calls and arrange for GP visit if needed.

Obtain data from the screening centers for respondents to screening calls.

Simplify your program

Is it too difficult to have a national systematic regular screening program for breast cancer in country "x" where the number of women aged 40-70 is 1,000,000?

In this country: it is recommended to screen women aged 40-69 once every two years

Notice: Screening interval depends on mean sojourn time and should not be fixed to be on annual basis unless there is clinical evidence for that

Cut it down so it will be simple

Practical example: In country X, there are 1000000 women aged 40-70 who are eligible for screening

100000 Women aged 40-70

To be screened annually 500000

75% response rate: 375000

300 working days/ 6 days work 1250

if there are 12 main districts in your country

25 centers in the whole country **2 mammograms per center** 50 mammograms

1250/50 25 subjects Per machine per day 7 working hours, means 4 subjects per hour In the UK, 6-8 patients per hour per machine.

If we have only 5 centers in Amman, 3 centers in Irbid, 2 centers in Zarqa, 2 centers in Karak and one center in the remaining governorates

we need 50 machines in 25 centers for 1 million women across Jordan

This number is already available and can be provided at the public sector

Breast self-examination and death from breast cancer: analysis

AK Hackshaw*[,1] and EA Paul[1]

[1]*Barts & The London School of Medicine & Dentistry, Wolfson Institute of Environmental & Preventive Medicine, Queen Mary, U Charterhouse Square, London EC1M 6BQ, UK*

Breast self-examination (BSE) is widely recommended for breast cancer prevention. Following recent controversy mammography, it may be seen as an alternative. We present a meta-analysis of the effect of regular BSE on breas From a search of the medical literature, 20 observational studies and three clinical trials were identified that reporte death rates or rates of advanced breast cancer (a marker of death) according to BSE practice. A lower risk of mo breast cancer was only found in studies of women with breast cancer who reported practising BSE before di pooled relative risk 0.64, 95% CI 0.56–0.73; advanced cancer, pooled relative risk 0.60, 95% CI 0.46–0.80). The r due to bias and confounding. There was no difference in death rate in studies on women who detected thei examination (pooled relative risk 0.90, 95% CI 0.72–1.12). None of the trials of BSE training (in which most practising it regularly) showed lower mortality in the BSE group (pooled relative risk 1.01, 95% CI 0.92–1.12). T BSE is associated with considerably more women seeking medical advice and having biopsies. Regular BSE is not a of reducing breast cancer mortality.

British Journal of Cancer (2003) **88,** 1047–1053. doi:10.1038/sj.bjc.6600847 www.bjcancer.com

Keywords: breast self-examination; breast cancer; mortality; meta-analysis

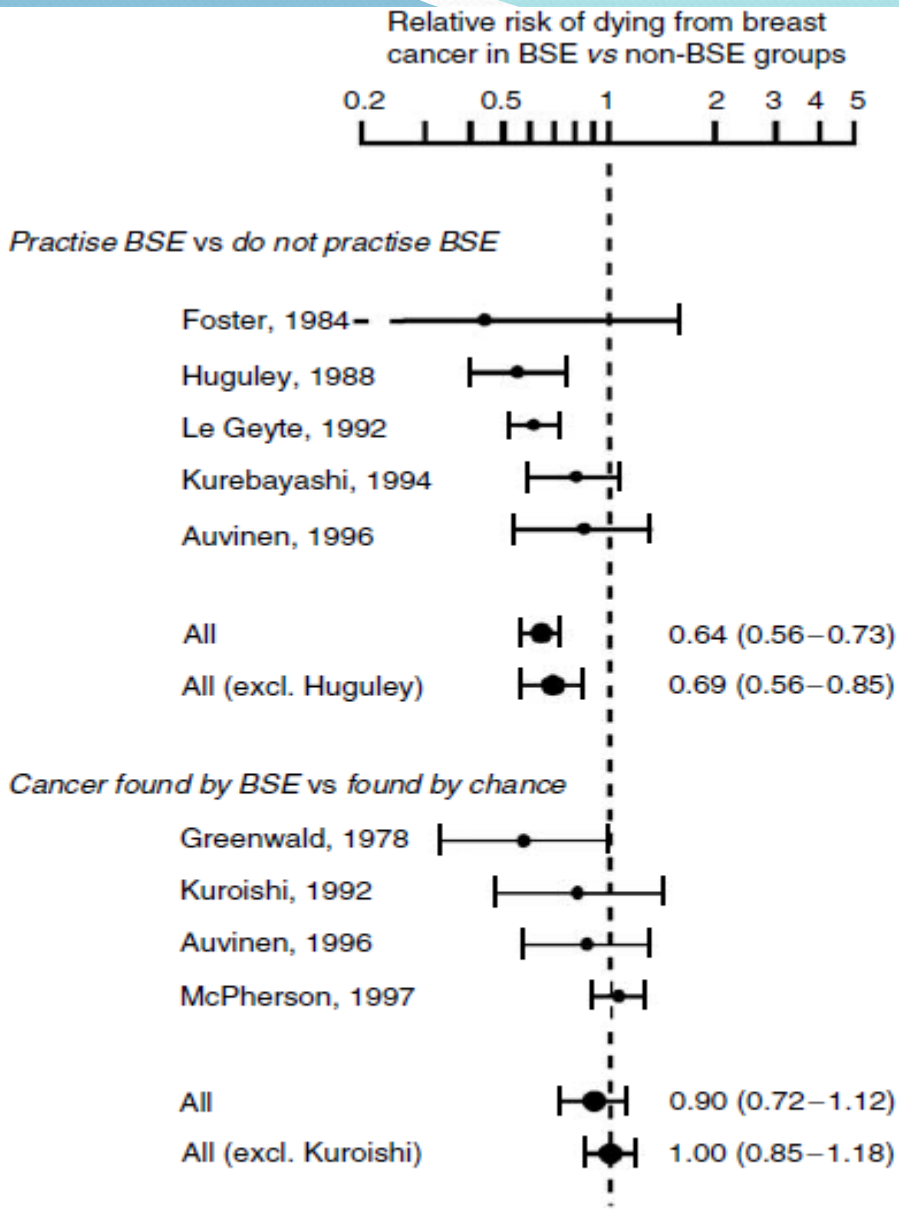
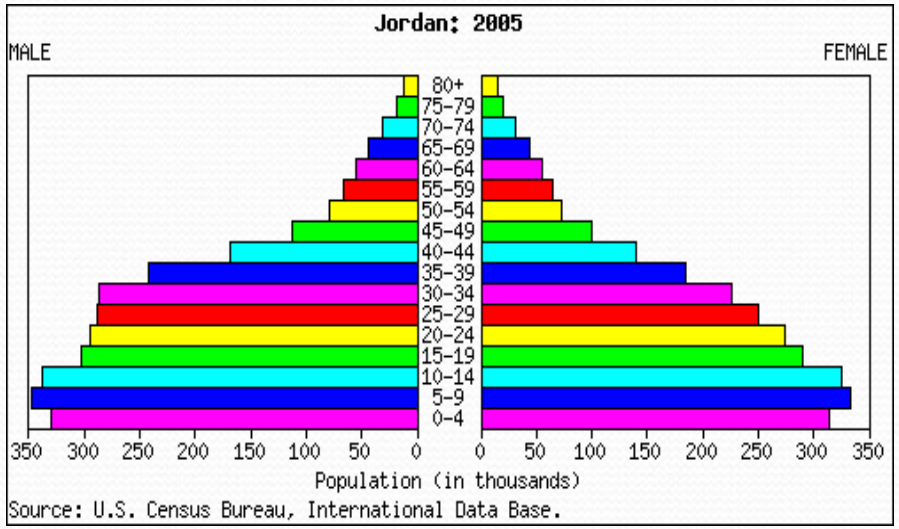
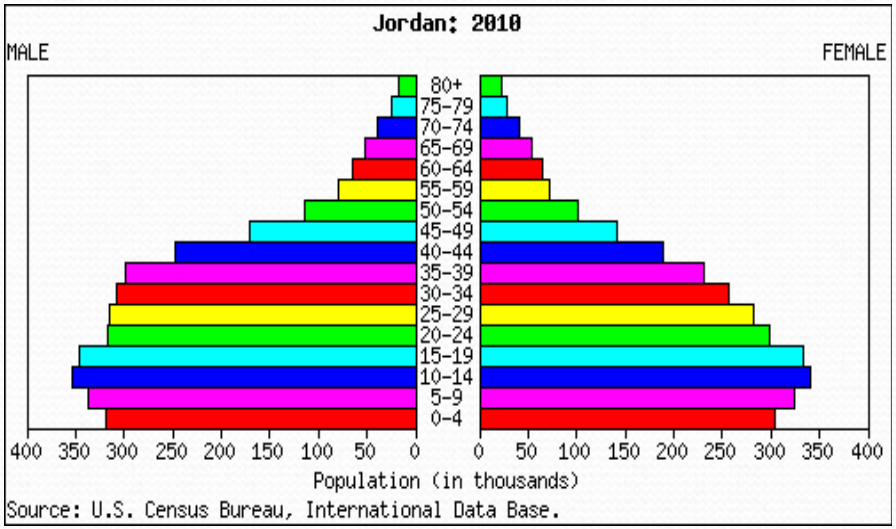
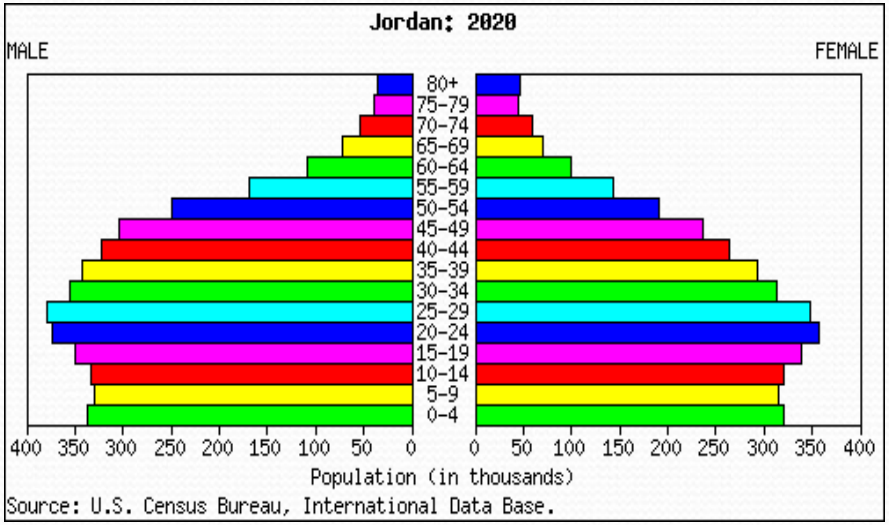


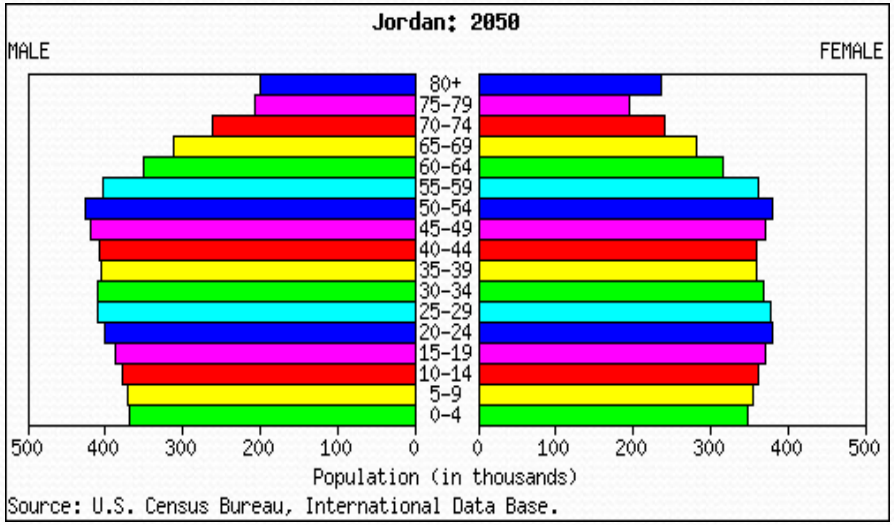
Figure 1 Observational studies of women with breast cancer, comparing the breast cancer death rates between the BSE and non-BSE groups. A test for heterogeneity between the studies yielded a *P*-value of 0.41 for those studies based on women who practise BSE and a *P*-value of 0.26 for those based on finding cancer by BSE.

Population pyramids- Jordan









Test it before you generalize it

- Start with pilot program
- Assess response rate
- Is my program cost-effective
- What is my cost-effective screening criteria
- Quality of all involved steps (single versus double reader mammography screening, FIT versus Haemoccult test)
- Compare respondents with non-respondents
- Assess success rates
- Look for determinants of success and failure
- Is there a specific group who needs different intervention?

Importance of Pilot Projects

1. Health economics evaluation
2. Setting age cut-off based on local data
3. Improve performance at national level by learning from experience at pilot phase
4. Comprehensive assessment of the screening program helpline, waiting time, film quality, guidelines such as double readers, false positive rate, false negative rate, diagnosis process, psychological counseling, treatment, prognosis, economic evaluation, how can we make it better at the national level.
5. Assessment of barriers to screening
6. Quality assessment of staff

Acceptability of programme to the public and health care staff.

- Screening test, diagnostic test and therapeutic options should be ethically and socially accepted by the general public and the health care professionals.

Economic evaluation:

- Implementing screening programmes should be more economically effective than the existing system.
- Cost of all steps related to the screening programme should be assessed and compared with outcomes of the screening and with other services.
- **Each country should has its own studies and data**
- What is cost effective in the UK might not be cost effective in Jordan or India
- In breast cancer screening: age range for screening plays a key role in the cost-effectiveness of the program
- UK (Screening aged 50-70 Every three years, then in few years ago aged 40-49 at high risk)
- Sweden (age 40-70) annually

EUROPEAN JOURNAL OF PUBLIC HEALTH 1997, 7: 68-76

MAMMOGRAPHIC SCREENING

Economic evaluation of a mammography-based breast cancer screening programme in Spain

ROBERTO GARUZ, TARSICIO FORCÉN, JUAN CABASÉS, FERNANDO ANTOÑANZAS, CRISTINA TRINXET, JOAN ROVIRA, FRANCISCO ANTÓN *

The aim of the study was to perform a cost-effectiveness analysis of a breast cancer (BC) mammography screening programme, compared to a do-nothing alternative, in Spain. Screening consisted of a biennial mammography performed on all women 50–65 years old. A marginal analysis including women 45–49 years old was also performed. With the aid of a decision tree model, the numbers of BC cases diagnosed through screening, BC cases missed by screening and false-positive BC cases were calculated. Costs were calculated by feeding local data into Markovian models and the cost-effectiveness ratio calculation was performed in a computer spread sheet. A sensitivity analysis was also conducted. Results were presented in ECUs of 1993. The cost-effectiveness ratio per avoided death is 115,500 ECUs and per saved life year 7,300 ECUs. Including women 45–49 years old in the programme raises this ratio to 229,000 and 9,400 ECUs respectively. The sensitivity analysis showed the efficacy of mammography, compliance of the programme and screening costs to be the more sensitive variables.

Key words: breast cancer, screening, economic analysis, cost-effectiveness analysis

Bias related to medical screening

- Lead time bias: screened cases are detected at an earlier stage than that in which treatment would be worthwhile.

  Does treatment work better at this stage?
- Length time bias: cases detected through screening are slowly progressive and may not harm the patient in lifetime
- Selection bias: respondents are different from decliners

Volunteer bias:

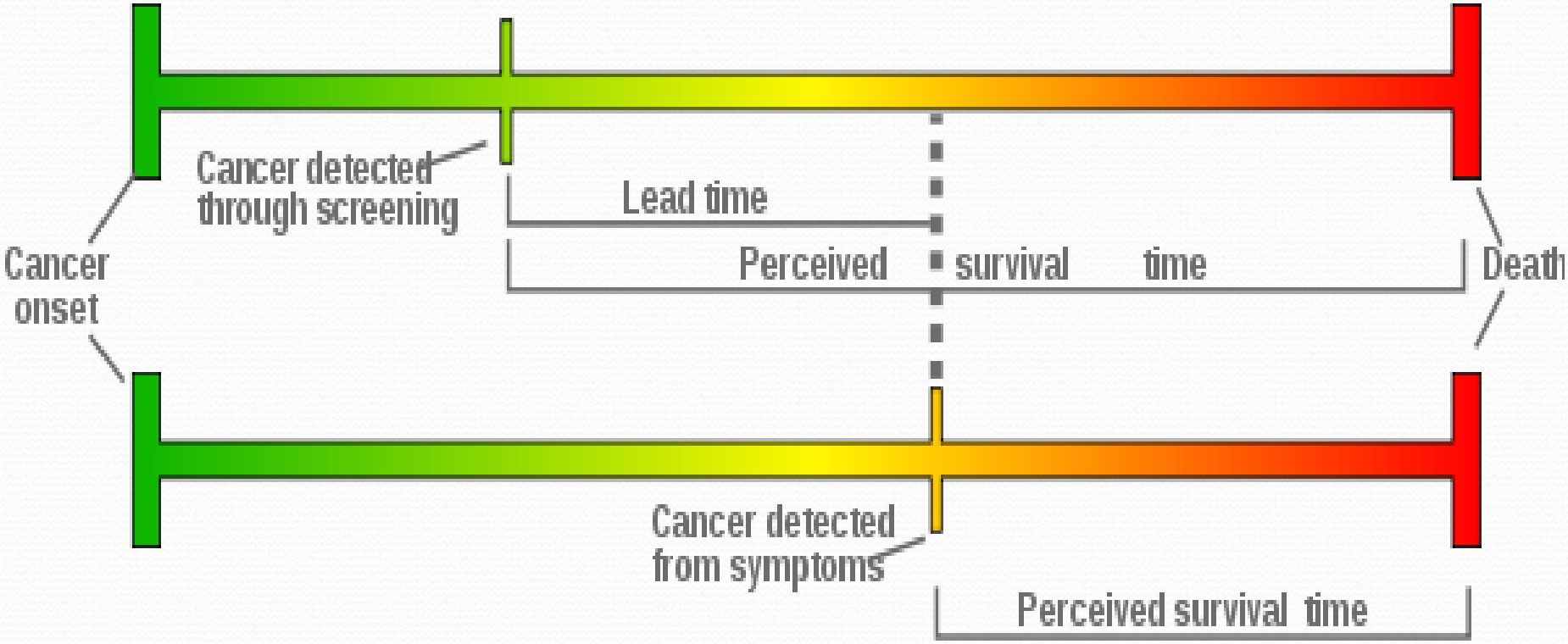
- They tend to be of higher socioeconomic class
- More health-conscious
- Comply better with prescribed advice
- Therefore, better results for a screening programme of volunteers compared with disease outcomes for non-voluntees may be relate to factors associated with the “volunteerism” rather than benefits of treatment following diagnosis.

- Therefore it is essential to analyse data on participants and ensure that all target group have the same access and received the same message

Lead time bias

- Lead time: period between when the disease is detected by screening and when it would have become symptomatic and been diagnosed in the usual way.

- Prolongation between diagnosis and death
- There is no difference in outcomes between patients detected through screening and patients who is treated when the condition manifest clinically
- Screening simply makes the condition evident at an earlier stage without actually affecting its course. (appears to lead to longer survival because of earlier detection)
- If left with no screening the disease will be diagnosed at age of 50 and die at age of 54
- If screened disease will be diagnosed at age of 47 and die at the age of 54


Cancer detected through screening
Lead time
Cancer onset
Perceived survival time
Death
Cancer detected from symptoms
Perceived survival time

Lead time bias in Prostate cancer

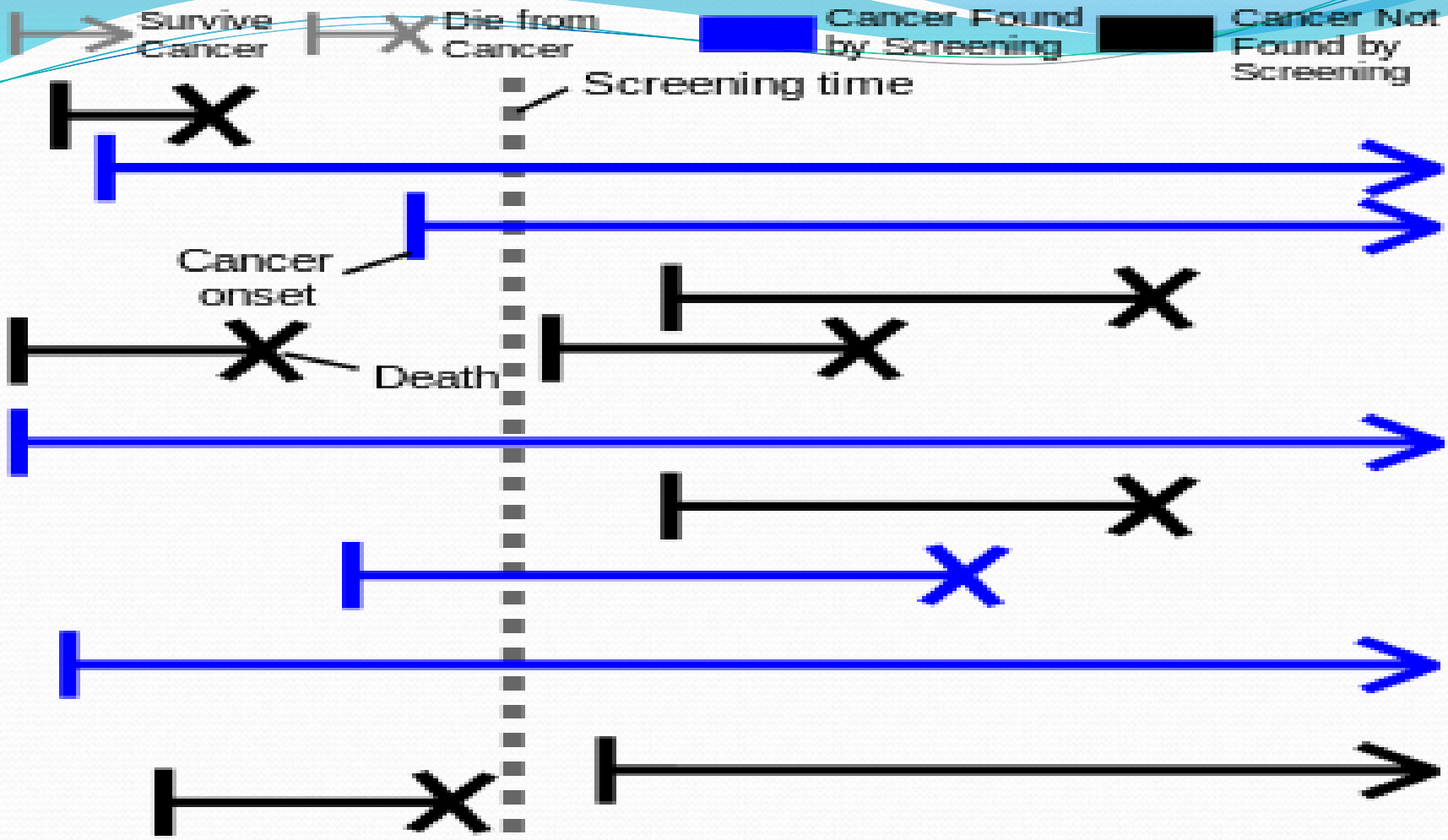
- **Lead Times and Over detection Due to Prostate-Specific Antigen Screening: Estimates From the European Randomized Study of Screening for Prostate Cancer**
- Gerrit Draisma Rob Boer Suzie J. Otto Ingrid W. van der CruijsenRonald A. M. Damhuis Fritz H. Schröder Harry J. de Koning
- *JNCI: Journal of the National Cancer Institute*, Volume 95, Issue 12, 18 June 2003, Pages 868–878, https://doi.org/10.1093/jnci/95.12.868

Length time bias

- It is a form of selection bias.
- When we screen for disease were more likely to detect cases where the disease is progressing slowly
- Over-presentation of slowly progressing disease among cases detected by screening.
- Screening will detect more slowly growing tumours, while rapidly growing tumours are more likely to develop and to proceed to clinical presentation within the interval between two consecutive screening examinations.

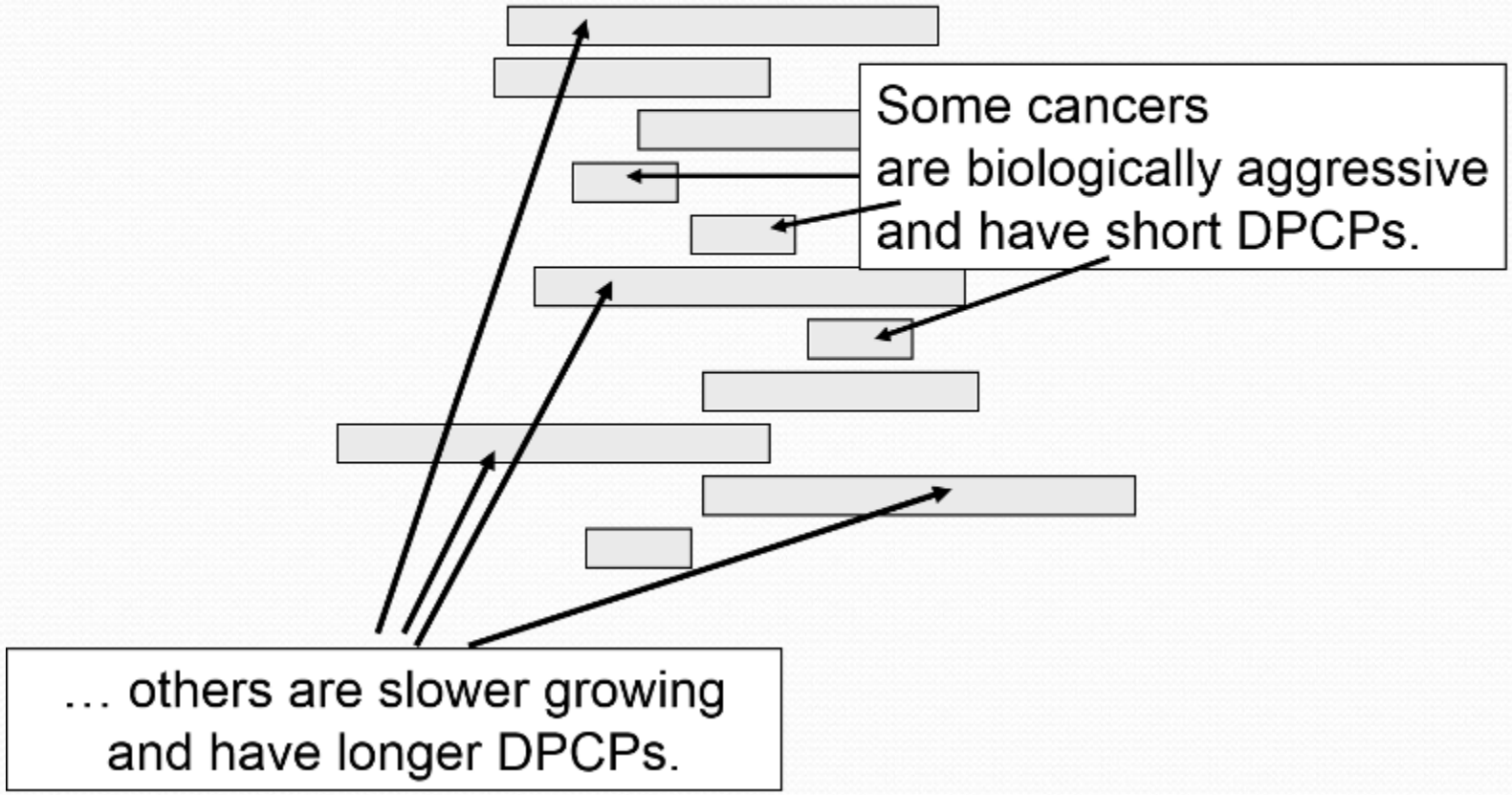
Length time bias

- Faster-growing tumors generally have a shorter asymptomatic phase than slower-growing tumours, and so are less likely to be detected. However, faster-growing tumors are also often associated with a poorer prognosis. Slower-growing tumors are hence likely to be over-represented in screening tests. This can mean screening tests are erroneously associated with improved survival, even if they have no actual effect on prognosis.



	Death from Cancer	Survive Cancer	% Surviving Cancer
Cancer Discovered Through Screening	1	4	80%
Not detected through Screening	7	5	41.7%

Prostate Cancers With Varying DPCPs



DPCPs: detectable preclinical phase

Challenges

- Validity of the screening test
- Healthy people need further tests
- Anxiety caused
- Health care resources

Pilot basis

- What is my next step?

Quality Assurance

- Quality assurance means that the assessment of the service provided and applying modifications when necessary.
- This includes various steps such as recruitment, registration, waiting time, test procedures, results handling and follow up or referral for treatment procedures.
- Clinical audit

My programme is already in place

- Continuous monitoring and regular evaluation

Thank you!