Principles of cancer screening

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Abstract

Screening in healthcare is the process of identifying individuals in a given population who either have an early stage asymptomatic disease or are at a higher risk of developing a disease that then can be managed at an early stage. It can be used for a variety of health conditions. Screening for cancers started in the mid-20th century with the introduction of screening for cervical cancers, and has since been extended to a number of other cancers. In this article we present an overview of the principles of cancer screening that underpin all these screening programmes with a brief overview of the current cancer screening programmes in the UK.

Keywords Cancer screening programmes; QALY; screening biases; screening criteria; screening test

Introduction

The World Health Organization (WHO) defines screening as 'presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures, which can be applied rapidly to the target population'.[1]

Screening was used for preclinical conditions as early as the start of 20th century, when the US Army used screening to exclude subjects with psychological disorders from being recruited.[2] The benefits of screening were also recognized in the UK as early as the 1950s after the introduction of Mass Miniature Radiography (MMR) for the identification of tuberculosis that was an intractable problem in Glasgow and Liverpool after the Second World War.

The first ever cancer screening test was developed by Dr George Papanicolaou in 1943, and was based on detecting cytological abnormalities of the uterine cervix by collecting and staining vaginal cells to diagnose cervical cancer, the most common cancer affecting women in Western Europe. The test is called Pap smear and in its refined form is still used for cervical screening in many parts of the world, including the USA. Subsequently, cervical screening was introduced in the UK in the 1960s. In 1968 Dr JMG Wilson, a senior medical officer in the Ministry of Health in the UK and Mr G Jungner, a Swedish Biochemist wrote a crucial paper for the WHO that elaborated various principles of screening setting the criteria for any screening programme.[1]

More screening programmes, such as breast cancer screening, were started in the USA and in the UK in early 1970s and 80s, but their framework remained weak. The National Screening Committee (NSC) was introduced in the UK in 1996, and has played a pivotal role in managing screening programmes in the four countries of the UK and continues to monitor the evidence to recommend commencement, modification or stoppage of any screening programme. Public Health England (PHE) sets standards and defines key performance indicators for various national screening programmes in England.

The UK NSC has set out recommendations on various public health issues that have led to 11 different screening programmes in the UK. Of these, there are only three screening programmes (cervical, breast and bowel) that deal with cancers and pre-cancerous conditions. The remainder focus on prenatal and neonatal screening of infective and inherited metabolic disorders, while others deals with acquired conditions such as diabetic retinopathy and abdominal aortic aneurysm.

Criteria for selection of screening

The criteria for selection for a screening programme were first described by Wilson and Jungner for the WHO in 1968. Since then the UK NSC has elaborated on these criteria, but the principles remain the same (Criteria for screening programme, UK NSC).[3]

- Knowledge of the disease:
  - The condition screened should be an important public health issue.
  - The natural course of the disease should be clearly defined and well understood.
  - There should be a latent period for the disease with development in to the declared disease.
- Knowledge of the test:
  - Test should be simple, safe, precise and validated.
  - The distribution of test values and suitable cut off levels should be defined and agreed.
  - Acceptable to the population.
  - Agreed policy should be in place for further diagnostic investigation and choices available to the individuals with positive screening test.
- Intervention:
  - There should be an effective intervention for the disease.
  - All options should be considered and exhausted to ensure that no more cost effective intervention could be introduced to manage the disease or the current intervention/s increased within the resource available.
  - Evidence to support that intervention at the pre-symptomatic phase detected through screening should lead to better outcome compared to usual care.
  - Evidence based policies to guide whom to offer intervention and what intervention is appropriate.
- Screening programme:
  - High quality randomized controlled trials to support that screening programme is effective in reducing the morbidity and mortality.

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- The clinical, social and ethical acceptability of the programme to the public and health professional should be evidence based.
- The benefit gained from screening programme should outweigh any harms (over-diagnosis, over-treatment, false positives, false reassurance, uncertain findings and complications).
- Agreed plan on quality assurance standards, monitoring and managing the screening programme.
- In order to assist participants to make informed decisions, there should be evidence-based information on the purpose and potential.

Performance characteristics of a screening test

The common performance characteristics used for a screening tool are:

- **Sensitivity** – the effectiveness of a test to determine a disease in those who have the disease (true positive).
- **Specificity** – the ability of the test to identify correctly those who don't have the disease (true negative).
- **Positive predictive value (PPV)** – proportion of subject who have the disease in whom the test gave a positive result.
- **Negative predictive value (NPV)** – proportion of subject who are free from the disease in whom the test gave a negative result.

Table 1 helps to understand how the parameters are measured. They all are represented in percentage terms and are calculated as follows:

$$\text{Sensitivity} = a/(a+c) \times 100 = 75\%$$

$$\text{Specificity} = d/(b+d) \times 100 = 56\%$$

$$\text{Positive predictive value} = a/(a+b) \times 100 = 30\%$$

$$\text{Negative predictive value} = d/(c+d) \times 100 = 90\%$$

An ideal screening test should have a sensitivity and specificity of 100%, but unfortunately no such test exists. Generally speaking, with increasing sensitivity of a test, the rate of false positives increases too, making the test less reliable in differentiating between the diseased and non-diseased. On the other hand, a high specificity gives low false positive rate but increases false negativity, again making the test less useful. To overcome this problem, in some cases it may be prudent to alter the threshold of a particular screening test for it to be positive, to reduce its sensitivity and thus have better specificity.

Receiver operating characteristics (ROC) curve: this is a fundamental tool to evaluate a diagnostic test by plotting true positive rates against false positive rates for different cut off points of the test. The area under the ROC curve (AUROC) is an indicator of the usefulness of the test. The graph in Figure 1 shows various examples of AUROC. An area of one represents a perfect test and an area of 0.5 or less is a failed test. Utility of a test by AUROC are 0.9–1.0 (excellent), 0.8–0.9 (good), 0.7–0.8 (fair), 0.6–0.7 (poor) and <0.6 is not useful for the purposes of screening. It is worth remembering that while sensitivity and specificity are the characteristics of the test and hence not influenced by the disease prevalence, the PPV and NPV are affected by how common the disease is, in a given population.

Effectiveness and evaluation of a cancer screening programme

The effectiveness of a screening programme is measured by its ability to reduce morbidity and mortality from the disease being screened.

The most definitive measure of efficacy of a screening programme is the difference between disease-specific mortality between those diagnosed by screening versus those diagnosed when presenting with symptoms. The optimal means of measuring efficacy of a screening programme is by conducting well-designed randomized controlled trials (RCT), meta-analyses, or good case control/case cohort studies, to minimize confounding factors. The latter are not as good as RCT or meta-analysis as the study groups may not be comparable and be affected by various biases. However, biases are not limited to any one type of study in the context screening and apply to most of them being inherent to the principles of any screening programmes. The four common confounding biases are:

- self-selection bias
- lead time bias
- length time bias
- over-diagnosis bias.

Self-selection bias: this is a major confounding factor in any screening programme due to the difference in health seeking behaviour between the educated and affluent of the society and those who are deprived and less health conscious. This means that the healthier section of the society is more likely to participate in the screening process. For example, breast screening uptake rate in the UK varies from 63% to over 79% and is generally better in wealthier parts of the country.[4,5] The better outcome in the healthier group with a higher uptake of screening would appear to be related to screening alone, whereas other factors such as healthier life style (food, exercise, better compliance) could also have significant impact on the outcome of the disease.[5]

Performance characteristics of a screening test

		Disease	No disease	Total
Test result	Positive	True positive (a) 15	False positive (b) 35	Total positive ($a + b$) 50
	Negative	False negative (c) 5	True negative (d) 45	Total negative ($c + d$) 50
	Total	Total number of true disease ($a + c$) 20	Total number of true no disease or normal ($b + d$) 80	Total number of population screened 100

Table 1

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