Screening. When Is It Useful, When Is It Not?
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Screening is one of the most powerful tools in public health, but only for a limited number of diseases at present. This lecture lays out why this is, concentrating on the major diseases screened in adults in the UK as illustrative examples. What follows are notes about the lecture rather than a full transcript.

Two strong strands of medicine have existed for many centuries. Curative medicine historically depended on people with symptoms coming forward for diagnosis. Alongside that there is a long tradition of preventing disease through diet, sanitation and exercise among other things. Screening lies between these two; it starts with people who have no symptoms and identifies those with very early disease or a major risk factor for subsequent disease.

Many diseases have a much better outlook if identified early. This includes most cancers including the major cancers in the UK; breast, prostate, lung and bowel cancer which I have talked about in more detail in previous lectures. It also includes many genetic diseases which if identified early can be treated. Additionally, there are some major predisposing factors for disease such as high cholesterol or high blood pressure which if identified can be treated to prevent subsequent disease. In principle screening is a tool that should be considered for all these kinds of indications. If we consider the major cancers, breast cancer, prostate cancer, lung cancer and bowel cancer, all have much better outlooks if diagnosed early (stage 1) than late (stage 4). For two of them, breast cancer and bowel cancer, there are established screening programs which diagnose any disease and for the other two there are not. This illustrates the fact that just being an important disease is not enough to be sensible to have screening.

For most diseases, with existing technology screening is currently not a good idea. To be an exception where screening may help several criteria need to be met. It must be a serious disease or the screening is not worthwhile. We have to be able to diagnose it reliably and safely or there is a high chance of missing cases or over treating. We must be able to prevent or treat it effectively and safely relative to the risk; a disease you cannot treat is usually not worth diagnosing at scale. It must be reasonably common to justify a national programme and there must be a sufficiently long time from diagnosable disease to serious disease that you can intervene early enough.

For the diagnostic step the practical question for screening is what is the risk of a false positive test or false negative test. A false positive result means you will have a procedure or treatment which you do not need. False-negative results means you being incorrectly reassured. How likely a false positive or false negative depends on two things; how good the test itself is, and how common the condition is. Relatively few medical tests are completely accurate. This is measured by their sensitivity, which is the percentage of true positives the test detects, and the specificity which is the percentage of true negatives the test detects. Very few biological diagnostic tests have both 100% sensitivity and 100% specificity. In general, there is a trade-off between sensitivity and specificity so if you make the test more sensitive it becomes less specific. What is more important depends on whether missing a true case or not diagnosing a false positive is the bigger problem in the clinical context.

Whilst the sensitivity and specificity of the test are relatively intuitive, less widely understood is the importance of prior probability in how accurate a test will be. This is most well-known through Bayesian statistics, first demonstrated by the Rev Thomas Bayes in the 18th century. This is the mathematical proof that if you ask a silly question, you get a silly answer. If the disease is highly unlikely before the test, it is still unlikely even if the test is positive unless the test is 100% specific. In screening, pre-test possibilities are very important; as important as how accurate the test is. If you do screening with an imperfect test in a population with a very low prevalence of the disease you will get a very high proportion of false positives.

False positives matter because many treatments and even some diagnostic tests, can do harm. All of medicine is a risk of treatment versus risk of no treatment judgement. If you treat someone with no possibility of benefit from treatment because it is a false positive, you only get the risk of treatment. In addition to the actual risks of treatment, it leads to the medicalisation of otherwise healthy people. As a minimum it turns a previously healthy person into a medical case to be followed up. It often causes worry and sometimes overtreatment, and in a few cases stigma. A screening programme which throws up very large numbers of false positives is therefore potentially very problematic.

Whether screening is a good idea for a disease is not static. Tests are improving the whole time and with better specificity, sensitivity, safety or cost of a test it may become more sensible. Improvements in the effectiveness and safety of prevention or early treatment also change the risk benefit analysis. If the treatment becomes very easy, safe, widely available and cheap then some degree of overdiagnosis can be tolerated. The epidemiology of the disease may also change, becoming more common (making screening more attractive) or less common. Screening also throws up important philosophical questions, for example should we screen for presymptomatic Alzheimer's disease given that we do not currently have an effective treatment to change its progression?

The key to most screening is risk stratification. The higher the pre-test probability the more accurate the screening will be and the more useful for someone to know about. The greater the disease risk, the greater the justification of side effects of treatment. Currently screening is largely stratified by age, gender and in some cases ethnicity. The diseases that are common in a 70-year-old woman are different to those which are common in a 30-year-old woman, or 70-year-old man.

The current UK national screening programme screens at various points along the life course. These are based on an assessment of the risks and benefits of screening at different ages. Some of the tests are antenatal to pick up major foetal abnormalities. Some are shortly before birth to pick up genetic abnormalities where treatment prevents lifelong ill-health. There is a national screening programme in adults which is for major diseases, three of which we will consider below. There is specific test screening in high risk groups such as people with diabetes. Finally, there is the group of health checks and other important opportunistic GP screens for diseases such as diabetes and high cholesterol which are not screening in the classical sense.

It is often said that screening prevents disease. Actually, many screening programmes in adults are to prevent progression of disease. There are four general national screening programmes in adults; cervical screening, breast screening, bowel cancer screening and aortic aneurysm. We will consider the first three, all of which are for important cancers.

Cervical screening is done to pick up the commonest cancer of young women and is undertaken in women aged 25 through 64. It has led to substantial reduction in cervical cancer, 30 to 40% in UK data, and new tests from last year are likely to improve accuracy further. Unlike most cancers, risk

of cervical cancer decreases with age and the precancerous cells are usually easily diagnosable some years before cancer presents. By picking up cells with very early changes which could progress to cancer it allows very minor treatment, at the risk of a certain amount of overtreatment. If we waited for certainty about the cancer cells later in time, some cancer would have gone on to progress and need much more invasive or extensive treatment. Both the test and the epidemiology are changing. Vaccination for HPV is going to lead to a significant reduction in cervical cancer. A move over to HPV DNA testing will reduce overtreatment. Cervical cancer screening is however likely to be highly effective in reducing the risk of this cancer of young women for many years.

Breast cancer screening has also been demonstrated to be effective. Women are screened between 50 and 70 every three years and over a thousand lives are saved a year. Large trials relatively consistently demonstrate a 20% reduction in breast cancer mortality. It will lead to a certain amount of extra procedures, mainly biopsies, but the overall benefits for breast screening in the correct age group are clear. There is an ongoing trial to see whether younger and older women should be screened. Women with a very strong family history of young onset (younger than 40) breast cancer may need more intensive screening.

Bowel cancer screening has also been demonstrated in clinical trials to reduce cancer deaths. This can either be based on tests on the stool, or a bowel scope looking into the bowel. Both of these methods have large randomised trials demonstrating that they reduce colorectal cancer deaths. When people are invited to take part in bowel, breast or cervical cancer screening they should do so; these are highly evidence-based screening programmes were benefit exceeds risk.

To illustrate why screening is however often not useful it is worth considering prostate cancer. This undoubtedly is common, being the most important cancer of men, and has a significant overall mortality because of the large numbers. However, the current test for it is a blood test PSA, and very large systematic reviews of trials found no difference between those screened and those not screened using PSA in terms of mortality. What screening does do however is lead to a very large number of men having quite unpleasant biopsies, and in some cases operations, whilst the overall impact on survival is zero. This is an example of a screening programme which in theory should be very attractive, but because of the relatively limited diagnostic test is worse than having no screening programme at all.

There are several other diseases where screening would clearly be useful if we have better tests. These include lung cancer, pancreatic cancer, ovarian cancer and oesophageal cancer. All of these have very high mortality, usually identified in late disease.

Where is screening adults likely to go? We are steadily improving our ability to risk-stratify to help target screening to people who most need it. Genomics is an example of a risk tool which is improving and there are already some well-known genetic changes such as BRCA 1 & 2 mutations which are strongly associated with some cancers. Secondly, changes in diagnostics, in particular artificial intelligence, are likely to help with radiology and histology. Liquid biopsy technology where blood tests can pick up diseases and in particular cancers early are being developed. All the time diagnostic tests and treatments are being improved. It is likely therefore that screening will look quite different in adults in the decades ahead.

Antenatal screening is routinely offered for Down's syndrome and other major chromosomal conditions. Not all women wish to know. For those who do the combined test of a blood test and an ultrasound of the neck of the foetus at week 10 to 14, you can tell whether a woman is high enough risk to consider the next stage of testing which is amniocentesis or chorionic villus sampling; both are very accurate tests but they come with a small risk of miscarriage.

Five days after birth, newborns are also screened for nine genetic diseases. These include cystic fibrosis and several metabolic diseases. Early identification allows for early treatment which significantly improves the life chances of the baby.

Screening for infectious diseases throws up a number of additional challenges. There is a logic to identify people with infectious diseases and treating or isolating them before they pass it on. Screening, (as opposed to mass testing) is easier to do where people have a chronic disease and remain infected and infectious for long periods. Historically, examples include tuberculosis, syphilis, trachoma and sleeping sickness. In infectious disease screening there is the concept of active versus passive screening. Active screening is where you go and find cases. For passive screening we wait until they come to you with relevant symptoms. This is rather different from the way noncommunicable disease screening is conceptualised. For example, there used to be extensive tuberculosis active screening in the UK, but since the disease is much rarer this is not necessary except in very high-risk groups such as those who are rough sleeping.

Screening is a very useful tool but under a restricted set of circumstances. We already have several very good screening programs. It is likely these will improve with improved diagnostic techniques and better treatments over the next decades.