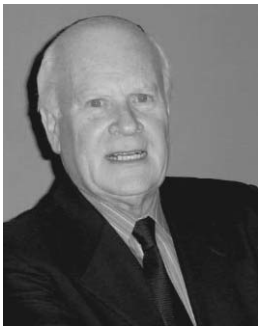
BREAST CANCER SCREENING

SHOULD ROUTINE SCREENING BY MAMMOGRAPHY BE REPLACED BY A MORE SELECTIVE SERVICE OF RISK ASSESSMENT/RISK MANAGEMENT?



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INTRODUCTION

The majority of lay people could be forgiven for believing that one of the mainstays in the fight against cancer is "early detection". In the vanguard of this campaign, the NHS screening programme for breast cancer (NHSBSP) by mammography has been lauded as a triumph. If nothing else the introduction of this programme has improved the service for the diagnosis and treatment of all women with breast cancer of any age and any stage. However we cannot remain complacent and continue uncritically with a service based on a limited number of trials that are more than 20 years out of date. Our understanding of breast cancer has moved on since then and as a result our attitude to screening is worthy of a fresh look.

THE ILLUSIONS AND DELUSIONS OF "EARLY DETECTION"

Let us start by considering two separate but related issues; firstly biases of screening that give a false impression of benefit and secondly the over-detection of cancer "look-alikes" that if left undetected might never threaten a patient's life. The *survival* from cancer is measured from the time of detection until recurrence and death. If a frame shift in the chronology of the disease due to screening occurs, then survival is automatically extended even if the ultimate outcome is the same; this is called lead-time bias. Next, bearing in mind that the interval between screens is anything from one to three years, it is inevitable that the fast growing tumours with a bad prognosis will appear during the intervals whilst the slow growing tumours with a good prognosis will sit around until found by mammography; this is called length bias. There is also another subtle bias that can be described as the "self selection" bias. In that women who accept invitations for screening might be demographically different to those who ignore the invitation. The only way to account for these biases is to consider all the clinical trials of screening versus no screening and look for the pooled results described in terms of *mortality* ie the number of women dying in the screened group compared with those dying in the control group rather than case survival. The results are then described as relative risk reduction (RRR) or hazard ratios (HR). There is in fact a modest advantage to screening looked upon in those terms, (RRR 15% or HR 0.85) as described in the recent publication in the BMJ; "Breast screening: the facts—or maybe not" by Peter C Gøtzsche and his colleagues from the influential and *independent*, Nordic Cochrane Centre.[1]

In this paper they describe a synthesis of all the papers that describe both the benefits and harms of screening using absolute benefits (ie number needed to screen) rather than RRR, that makes it easier for women to comprehend and conclude as follows. If 2000 women are screened regularly for 10 years, one will benefit from the screening, as she will avoid dying from breast cancer. (The independent United States Preventive Services Task Force derived a similar number in 2004.[2]) However even the figures 1:2,000 might be an over-estimate. Remember these data were derived from the trials that were mostly started in the 1970s and reported in the late 1980s. Since then improvements in treatment, such as the adoption of tamoxifen and adjuvant chemotherapy, have narrowed the window of opportunity and we have witnessed a drop in mortality of 30%-40% both in the age group that are invited for screening (>50) as well as for the younger woman. So perhaps the correct number might be 1:3,000. (See table 1).

Absolute value screening 10,000 women for 10 years assuming two estimates of relative risk reduction and assuming that unscreened symptomatic women receive the best of modern therapy.

Whatever the number, that one woman who benefits from a decade of screening has a life of infinite worth and if screening were as non-toxic as wearing a seat belt there would be no case to answer. However there is a downside and that is the problem of the over-diagnosis of "pseudo-cancers". [3, 4, 5,] It is deduced by the Cochrane report that for every life saved 10 healthy women will, as a consequence, become cancer patients and will be treated unnecessarily. These women will have either a part of their breast

TABLE 1

10,000 women aged 50 screened for 10 years	25% Relative risk reduction[6] (HR 0.75)	15% Relative risk reduction[1] (HR 0.85)
Cancer incidence (2 per 1,000/year)	200	200
Cancer deaths without screening at median follow up 5 years[9]	20	20
Cancer deaths with screening (20 X HR)	15	17
Absolute benefit	5	3

or the whole breast removed, and they will often receive radiotherapy and sometimes chemotherapy.

AN EXPLANATION FOR, AND THE NATURE OF, THE OVER-DIAGNOSED CANCERS

Screening for breast cancer is now adopted as an unequivocal good by most of the members of the EU. Invitations for screening promote this activity by being economical with the truth.[6] One of the uncomfortable truths concerns the over-diagnosis of both in-situ and invasive breast cancers in screening populations.[3,4,5] Over-diagnosis of breast cancer doesn't mean false positive rates but the detection and treatment of cancers that left undetected would never threaten a woman's life and with which she would live, in blissful unawareness, until she died naturally of old age. We had always assumed that there was an over-diagnosis of duct carcinoma in-situ (DCIS), some of which had the potential of progressing to an invasive and life-threatening phenotype. However, there is now clear evidence that anything between 10% and 50% of invasive cancers detected and treated radically as a result of screening, would never threaten life.[1, 3,4,5] As a result the overall mastectomy rate rises after any country implements screening in contrast to the message in the NHSBSP leaflet, "breast cancer the facts" that implies that screening saves breasts. It doesn't. I would therefore like to argue that some of these screen detected "cancers" if left unperturbed, would not progress to a disease with lethal potential. In other words there are latent conditions, which under certain conditions might progress, remain stable or even regress. Other biological processes behave in a similar way. Wound healing starts with the knife and ends when it needs to, although rarely wound healing carries on too long and leaves an ugly keloid scar. Virchow, the father of modern pathology, himself once described cancer as the wound that never heals. Prolonged latency followed by catastrophe should not be all that surprising.

IS THERE A REASONABLE WAY OF MODERNISING THE NHS SCREENING PROGRAMME THAT ENHANCES THE BENEFIT AND REDUCES THE HARM?

Since 1997 when I resigned from the NHSBS committee I have publicly expressed my concerns on the issue of informed choice for women invited for screening. I take no particular pleasure in the fact that NHS has at last accepted the point and agreed to rewrite the letters of invitation.

My concern is that they will repeat the mistakes of the past if we leave this task to those with a conflict of interest. Furthermore it's not for me to prejudge what level of benefit and what level of harm might influence the average woman to accept the invitation. For this reason I think there are two related areas of research. First, the development of an information pack that includes decision aids. This could be used in a person preference study where well women might be offered sliding scales of benefits and harms to find the point at which screening is judged acceptable. These data might then inform the next area of research on more efficient ways of using scarce resources in the NHS such as risk assessment/risk management.

The beauty of a risk assessment/risk management approach is that it provides a platform for the management of all women in an attempt to reduce all causes of mortality as well as mortality from breast cancer where mammographic screening is only one component of an integrated programme. The first step is to set up a facility nationwide for risk assessment using one of the modern computer programmes. Women would then be *offered*, not *compelled* to accept this service. Initially a practice nurse could administer this questionnaire but it would be quite easy to transfer this to a web- based programme for the computer literate members of the community. From the read-out an initial triage could be agreed. Those at the most extreme end of the risk spectrum could be invited to a clinical genetics consultation. At the other extreme those with a low risk might be reassured and given lifestyle advise on diet, alcohol, tobacco and exercise that might not only impact on the risk of breast cancer but also on the more important risks of cardio-vascular disease.[7] Those in between could then be invited to a special clinic for the second step. At this clinic women of say 45 or older would be invited to have a mammogram. Those with radiological abnormality at this stage would be investigated in the accepted way. In addition those who were pre-menopausal might be offered prevention with tamoxifen and those who were post-menopausal could be offered entry into the IBIS II trial, a study comparing tamoxifen with arimidex for the chemo-prophylaxis of breast cancer. A recent paper in JNCI supports the validity of this approach.[8]

CONCLUSION

To carry on regardless is no longer acceptable, neither is political spin the answer. Women are now getting smarter. However the changes I have in mind are not nihilistic but constructive. The NHSBSP has indirectly lead to the provision of the best specialist services for the diagnosis and treatment of symptomatic breast cancer in the world, riding on the back of the screening units. The centralisation of care has lead to the rapid recruitment into RCTs for the treatment of cancer that is the major contributor to the dramatic fall in breast cancer mortality in the UK over the last two decades. If we can now add to this the prevention of the disease and a risk adjusted screening programme then everyone is a winner.

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MEDICAL TESTING

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HEALTH AND SOCIETY

There are several trends in the way in which people of all cultures are dealing with health. We now live in a global village crammed full of information – national boundaries are no hindrance to the power of the internet. The ongoing revolution in mobile phones without reliance on a creaking telecommunications infrastructure means that people in some of the world's remotest places can connect to remarkable health information websites. In an increasingly politically centrist Europe there is tremendous interest in being seen to do something to improve the speed and accuracy of medical diagnosis. The policies of most political parties are becoming extremely difficult to differentiate, and therefore doing something to improve health and the clarity of diagnosis is a natural vote winner.

The integrity of conventional religious structures and families is declining due to greater mobility, divorce, single parenthood and the break-up of traditional caring patterns for older people. This means that when a life-threatening illness strikes, patients have fewer psychological crutches to lean on today than in the more structured society of 20 years ago. Better psychosocial care is therefore needed alongside the technology-based service doctors are traditionally trained to provide. Offering patients more informed choice may well cause uncertainty and psychological confusion. Speeding up the pathway to achieve the correct diagnosis helps to reduce much of the uncertainty in many illnesses.

RISK ASSESSMENT AND PREVENTION

The public perception of cancer risk is heavily swayed by interesting but negligible risk factors. These are fanned by good media stories and the desire to find scapegoats for our unhealthy lifestyle. Cellphones, radiation from power lines, plastic films for food packaging and stress figure large in public surveys on causes of cancer, even though their risks are so low as to be nearly impossible to measure. Public education is the key to the future.

Over the next 20 years, novel programmes of individual risk assessment will be established. From the newly sequenced human genome we will learn about the complex interplay of our genes and the environment. Tailored prevention programmes will be available. New screening technology coupled with drugs and vaccines that prevent disease will come into routine use. All this requires novel approaches to diagnostics.

Cancer preventive drugs and hormones are already available for certain high-risk situations: tamoxifen for breast cancer and the COX-2 inhibitors for familial polyposis, which if untreated will inevitably lead to colon cancer. These drugs were developed and marketed for indications other than cancer prevention. The identification of effective biomarkers of cancer risk is essential if novel drug discovery programmes are to be created. The ability to prevent cancer will dramatically increase the number of people who will need to attend clinics regularly.

THE NEW DIAGNOSTICS

Diseases present with a myriad of symptoms depending on the site, size, severity and pattern of their development. Doctors are trained to analyse symptoms and then after clinical examination to utilise a series of medical tests to make a firm diagnosis. Although some symptoms alarm patients more than others there is tremendous variability in the speed at which any illness can be precisely diagnosed. With cancer a lump can be biopsied, but many deep-seated tumours present late, long after they have already spread. Most patients have actually been harbouring the cancer for several years before it becomes apparent. In psychiatry there is much more diagnostic difficulty as there is a huge spectrum of abnormalities with many blurred boundaries. Schizophrenia, bipolar disorders and severe depression may all be present in the same patient and there are no effective diagnostics other than the psychiatrist's skills.

The two drivers for improvement in medical diagnosis are imaging and biomarkers. The last decade has seen a massive rise in the use

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of computed tomography (CT) and magnetic resonance imaging (MRI) scans to outline in beautiful detail the anatomy of disease and surrounding normal structures. Positron emission tomography, in which a molecule is labelled with a radioactive marker, allows us to examine the living biochemistry of the body. The future of imaging will be the coupling of high-definition structural information to real-time functional change. This will allow the precise effects of drug or other treatment to be monitored in three dimensions. It is also likely that the telecom revolution will produce new devices for examining the function of interior compartments of the body without causing distress to the patient.

Biomarkers are biochemical changes produced by the presence of disease. They may be synthesised directly by a cancer, for example prostate specific antigen (PSA), or represent a complex change in an organ system, for example abnormal liver function tests caused by hepatitis. As we understand more about the molecular abnormalities that lead to disease through the science of genomics and proteomics, novel biomarkers will be identified. These will not only enable us to diagnose cancer at an earlier stage but also to predict the likely natural history of an illness in an individual. This information will become essential for planning optimal care. It is likely that a cancer screening kit for the four major cancers (lung, breast, colorectal and prostate) will be on sale within the next decade in pharmacies, fitness centres and health food shops, so increasing consumerism. There will be a rise in cancer screening and prevention clinics in the private sector, almost certainly attached to the 'cancer hotels' of the future.

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THE $1,000 GENOME

The cost of sequencing an entire human genome is currently around $100,000. This figure is likely to reduce dramatically over the next five years with many predicting a price tag of below $1,000. Looking further forward it is likely that continuous monitoring for potentially dangerous mutations will be possible. Up-market car engines have systems to measure performance against baseline, sending a signal to the driver if a problem arises. Implanted devices to identify genomic change and signal abnormalities to a home computer may well allow the detection of disease long before any symptoms. Such pre-patients will require appropriate counselling and intervention probably with newly developed drugs. It will be essential to carry out careful outcome research on such new diagnostic and screening techniques to validate their benefits.

THE FUTURE OF DIAGNOSTICS

- New diagnostic tests are introduced by enthusiasts and enter routine practice
- Specific diagnostics will accompany new therapies
- Pathologists will move away from morphological diagnostics into molecular assays
- There will remain a global shortage of pathologists
- Imaging and pathology will merge into a single discipline
- Computer based decision support systems will enhance clinical judgement
- Future patients will interact with such systems from home

IN DISCUSSION THE FOLLOWING POINTS WERE MADE:

In response to a question regarding the inherent dangers attributable to the increasing extent of radiation of the human body arising from CT scans the reply indicated that too much mindless imaging is going on. Imaging using ionising radiation should only be used as a last resort, but now it is the first resort. Why bother to conduct examinations when you have CT scans? However one in ten CT scans reveal abnormalities and these should only be undertaken therefore where a problem arises and should not form part of a routine screening programme. Over-diagnosis also occurs as a result in a population where tumours are common but we live with them as they do not need treatment. This is the core to the argument that everyone in this room has something in their body that under the microscope looks like cancer. This is the inevitable consequence of living to a mature age, although realisation of the implications are difficult for many to accept. The public who have fear of but a lack of the relevant scientific knowledge about cancer, receive confusing mixed messages from the experts who do not speak with one voice. The public also generally lack understanding of risk, especially the implications of false positives and false negatives arising from testing, for example. This gives rise to the demand to "do something" in response which has huge implications for the NHS resulting in ever-expanding costs which results in unsustainable budgetary growth, and something has to give. £55 million a year is the cost of screening all women, much of it futile, and a cost saving of £25 million could be achieved for use in treating their preventable death from other more threatening diseases. An example of heart disease was treated by a statin on the basis of a test algorithm that saved the NHS money. Point of care testing undertaken by police with electronic tools for monitoring alcohol are a good example which could be extended to genetic testing to determine whether genes are switched on or off. However anything other than the length and quality of life is a surrogate and the unnecessary use of testing fails to address this issue.

Are we spending enough NHS/Research Council money on non-invasive testing? The main financial resources underpinning novel testing methods are located in the biopharmaceutical industry rather than in government funded sources primarily concerned with delivery of clinical treatment. The NHS is very good at collecting data but the will appears to be lacking, for reasons unknown, to apply sufficient time and resources to interpret the outcomes and apply the results to medical testing and clinical care in order to maximise the available knowledge and potential benefits. Screening using cervical cytology, for example, is "intermediate technology" that is inherently subject to human error, and which has now been replaced by tests that provide yes/no answers unaffected by human error. We must learn from these experiences and develop improved methods, but unfortunately those involved with intermediate technologies won't let go! We need better testing, not more testing. Translational research on patients rather than more animal research is the way forward to drive new diagnostics. The pharmaceutical industry realises that drugs increasingly require tailoring to the individual patient, as a result both industry and the NHS are gradually moving to a new paradigm.