2019

THE NIGHTINGALE CENTRE

ANNUAL SCIENTIFIC REPORT

prevent breast cancer

NHS
Manchester University
NHS Foundation Trust

CONTENTS

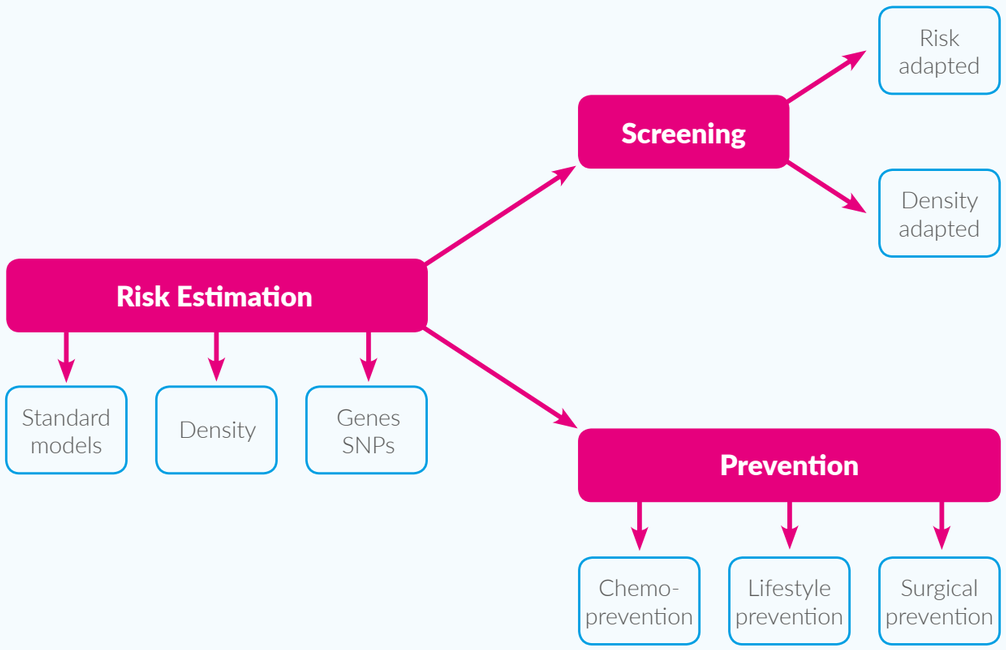
INTRODUCTION TO SCIENTIFIC REPORT

The aim of our annual report is to present the advances made over the past year towards prediction, early detection and prevention of breast cancer by investigators associated with Prevent Breast Cancer. We are hugely fortunate in having a talented group of clinical and non-clinical investigators who between them have published 42 original publications and 10 review articles related to risk, early diagnosis and prevention during 2018. This report presents a summary of our publications and the clinical implications of those recent advances, and explains our current direction of research.

An outline of our research programme at the Prevent Breast Cancer Research Unit in Manchester is shown in figure 1. The starting point in the diagram is "Risk Estimation". This is because predicting who is at risk of developing breast cancer is the first step towards determining which individuals need targeted strategies for screening and early detection, as well as prevention strategies to reduce that risk.

FIGURE 1

Outline of the Prevent Breast Cancer Risk Estimation, Screening and Prevention Programme.

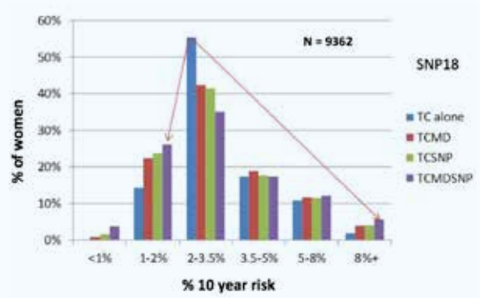


Over the last few years our research has demonstrated that the standard methods of predicting an individuals personal risk of breast cancer (based on family history and lifestyle and hormones) can be made much more precise by adding two additional factors: mammographic density and genetic testing. These improvements have enabled us to initiate pilot studies to improve the NHS breast screening programme so that it is based on individual risk of breast cancer rather than on a one-size-fits-all 3 yearly screening interval for the over 50's. Improvements in our ability to reduce breast cancer risk through preventive drugs (referred to as "chemoprevention" in Figure 1), lifestyle changes and preventive surgery can also be more focussed by more precise risk estimation. Please note that the term "chemoprevention" is widely used in medical literature to refer to the use of hormones or drugs (usually taken by mouth) to prevent cancer, but has nothing to do with chemotherapy drugs.

Our clinical investigators are located at the Prevent Breast Cancer Research Unit in the Nightingale Centre at Wythenshawe Hospital, while other investigators feed in to the prevention programme from the Manchester Cancer Research Centre at The Christie and departments on the main University site. In addition we have several national and international research collaborations, principally with Professor Jack Cuzick in London and Professor Doug Easton in Cambridge.

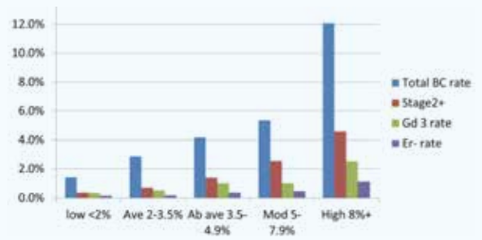
One of the more important publications this year is from Elke van Veen, a Dutch PhD student supervised by Gareth Evans. The publication in the JAMA Oncology journal (van Veen et al) was of the effect on risk distribution of breast cancer by combining standard risk factors, mammographic density and breast risk related single nucleotide polymorphisms (SNPs) after longer term follow up in the PROCAS (Prediction of Cancer at Screening) study (Figure 2). Combining the three groups of risk factors increased the accuracy of distinguishing between high and low risk women. Perhaps more importantly, Elke found that poorest prognosis tumours were associated with women at the highest risk. Tumours that did arise in women at low risk tended to be of be good prognosis. More recently an unpublished study using 143 SNPs (instead of the original 18 SNPs) showed an even better definition of risk with fewer women in intermediate groups. An overview of these results was given as an invited plenary lecture at the San Antonio Breast Cancer Symposium by Gareth Evans in December 2018.

FIGURE 2A



Data from the Prediction of Cancer at Screening (PROCAS) Study showing the change in proportion of women in 10 year risk groups as more risk factors are added to determine risks. For example, when the Tyrer-Cuzick (TC) model alone is used approximately 2% of women are estimated to be at 8% or more 10 year risk whereas this figure increases to 6% when mammographic density (MG) and 18 SNPs are added (TCMDSNP). Also more women are found in the low risk groups (</= 2% 10 year risk).

FIGURE 2B



More stage 2, grade 3 and ER-ve cancers are seen as risk increases. The blue bars are the total risk in each group.

IMPROVING RISK ESTIMATION

Accurate prediction of risk for individual women, improved screening and early diagnosis tailored to risk, reduction of risk through preventive therapy and lifestyle changes and, if necessary, by surgery, or all part of our strategy. The following sections outline that strategy by recording our published research papers over the last year in 2018, as well as ongoing projects involving both clinical and laboratory based research.

STANDARD RISK MODELS

Models to predict breast cancer risk in the past were mainly based on family history alone (eg CLAUS, BRCAPRD, BOADICEA). Then the Gail model and later the Tyrer-Cuzick model added additional important factors such as age of menarche and first pregnancy and weight, giving a more precise indication of risk (Table 1). Since its introduction in 2004 we have used the Tyrer-Cuzick model developed by our close collaborator, Jack Cuzick, head of the Wolfson Prevention Centre, London. The table indicates that the BOADICEA model, widely used by geneticists does not include hormonal/lifestyle factors. However this has recently changed. A paper published in January 2019 indicates that the BOADICEA model has now been improved to align with Tyrer-Cuzick and now not only are hormonal/lifestyle factors included but also mammographic density and SNPs making it similar to the Tyrer-Cuzick model.

	RR at extremes	Gail	Claus	BRCAPRO/Ford	TC	BOADICEA
Prediction						
Amir et al validation study ratio		0.48	0.56	0.49	0.81	Not assessed
95% CI		0.37 to 0.64	0.43 to 0.75	0.37 to 0.65	0.62 to 1.08	Not assessed
Personal Information						
Age (20-70)	30	Yes	Yes	Yes	Yes	Yes
BMI	2	No	No	No	Yes	No
Alcohol intake (0-4 units) daily	1.24	No	No	No	No	No
Hormonal/reproductive factors						
Age at menarche	2	Yes	No	No	Yes	No
Age at first live birth	3	Yes	No	No	Yes	No
Age at menopause	4	No	No	No	Yes	No
HRT use	2	No	No	No	Yes	No
OCP use	1.24	No	No	No	No	No
Breastfeeding	0.8	No	No	No	No	No
Plasma oestrogen	5	No	No	No	No	No
Personal breast disease						
Breast biposies	2	Yes	No	No	Yes	No
Atypical ductal hyperplasia	3	Yes	No	No	Yes	No
Lobular carcinoma	4	No	No	No	Yes	No
Breast density	6	No	No	No	No	No
Family history						
First-degree relatives	3	Yes	Yes	Yes	Yes	Yes
Second-degree relatives	1.5	Yes	Yes	Yes	Yes	Yes
Third-degree relatives		No	No	No	No	Yes
Age of onset of breast cancer	3	No	Yes	Yes	Yes	Yes
Bilateral breast cancer	3	No	No	Yes	Yes	Yes
Ovarian cancer	1.5	No	No	Yes	Yes	Yes
Male breast cancer	3-5	No	No	Yes	No	Yes

BMI, body mass index, CI, confidence interval, OCP, oral contraceptive pill
a Expected over observed cancer ratio (all models assessed underestimated cancer occurance)
Adapted with permission from Evans and Howell Biomed Centre 2007

Table 1. Risk factors used in models available for risk prediction (Evans et al 2016). Both the BOADICEA and Tyrer-Cuzick model now include mammographic density and SNPs.

MAMMOGRAPHIC DENSITY

Mammographic density (MD) is one of the strongest risk factors for breast cancer. Women with very dense breasts have 4-6 times the risk of women with the lowest density. MD has been shown to be a risk factor independent of standard risk factors and SNPs. The standard method of assessing MD is for a radiologist to score the density of breast tissue on the mammogram using a visual analogue scale (0 to 100% density). To incorporate MD with risk estimation into screening programmes either in the NHSBSP or in the Family history Risk and Prevention Clinic it would be preferable to use techniques which could automatically score MD and integrate those scores with the other risk factors.

In the PROCAS (Prediction of Cancer at Screening) study, Dr Sue Astley and colleagues estimated MD in over 60,000 women. They assessed density using a visual analogue scale (0-100% density) and compared this with automatic volumetric techniques such as Quantra and Volpara and a semi-automated area-based technique known as CUMULUS. A comparison of five methods on a matched case-control dataset from PROCAS was published in Breast Cancer Research (Astley et al). Results indicate that the visual method was superior to the others. Since Volpara was the best of the automated methods we decided to use this automatic volumetric technique for PROCAS II (Introducing real time risk estimation into the NHSBSP. See 'Current studies').

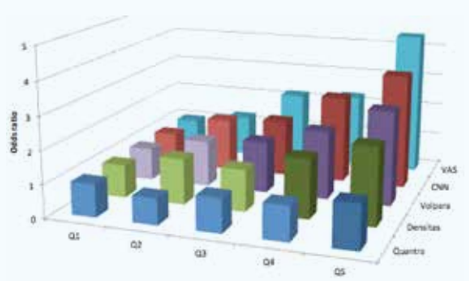
Further analysis of Volpara in two case control studies from PROCAS investigated thresholding Volpara density maps to improve performance (Wang et al).

In a separate paper, Stephen Duffy, Sue Astley and others assessed the Volpara volumetric techniques in women already at increased risk because of high density or a family history of breast cancer. All density measures showed an association with the presence of cancer. The strongest effect was seen using Volpara particularly for large and grade 3 cancers (Duffy et al). The fully automated measures can be added with little addition to human resource costs.

Sue Astley and her team have also assessed the value of deep convolutional neural networks to predict readers' estimates of mammographic density from raw and processed mammographic images. This study was given as an oral presentation at the Radiological Society of North America in Chicago in late November, and a full paper has been accepted for publication in the Journal of Medical Imaging.

The breast density measure was developed by Georgia Ionescu, one of Dr Astley's PhD students. The method uses artificial intelligence to learn density assessment from the average observer using over 30,000 mammograms from the PROCAS study. Its performance in predicting risk of breast cancer is comparable with reader assessments, with the advantage that it can be applied to give automatic readings (Figure 3). Unlike the majority of automated methods, it can be applied to processed (for presentation) mammograms.

FIGURE 3



Odds ratio of developing breast cancer by quintiles of percent density and method from over 30,000 women in the PROCAS Study. The visual analogue scale (VAS) produced by our radiologists showed the best separation (OR of highest to lowest quintile of density 4.48 (95% CI 2.79–7.18) and a method based on machine learning (CNN) (OR 4.16 (2.53 - 6.82)), with Volpara the best of the automated ; the volumetric technique, Volpara gave an OR of 2.87 (95% CI 1.77–4.64).

Elke van Veen assessed the breast cancer risk SNPs that have been linked to density. She assessed the 22 that have been reported as linked to MD and confirmed 9 as having a clear link in the same direction as previous reports. Only 3 appeared to have an interaction between their density prediction and breast cancer risk prediction meaning that very little adjustment is necessary for breast cancer risk prediction given that current SNP PRSs use 143-313 SNPs. Of the 13 SNPs without verification most have only been reported once and not been validated. These associations may well therefore be spurious.

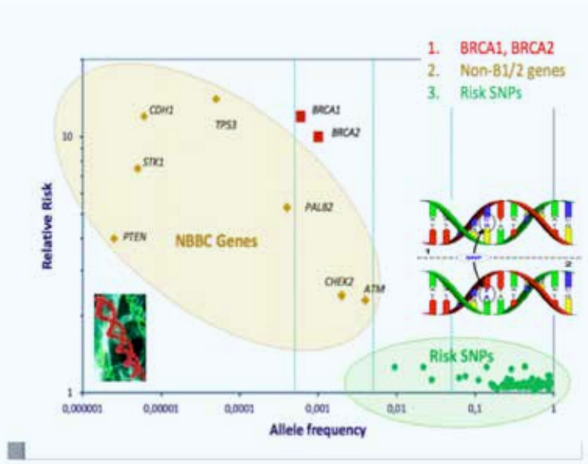
COMPUTER AIDED DETECTION

Computer Aided Detection (CAD) systems have been developed to aid radiologists' interpretation of screening mammograms. The impact of CAD is difficult to assess without a prospective randomised controlled trial involving large numbers of women without breast cancer, as previous research has shown that CAD systems can increase recall rates as well as sensitivity. Many studies have employed a methodology that assesses performance without CAD then allows the reader to immediately see the CAD prompts, recording their decision both before and after CAD. Ethan Du Crow (PhD student), Sue Astley and Johan Hulleman (Psychological Sciences) have shown, by tracking the eye movements of observers, that when observers know they will have CAD prompts they reduce their initial search of images. This leads to an overestimation of the benefits of CAD, depending on assessment methodology. The work will be presented by Ethan at SPIE Medical Imaging in February 2019.

GENETIC PREDICTORS OF RISK

The BRCA1 and BRCA2 genes were discovered in 1994 and 1995 respectively and since that time at least 7 other genes associated with breast cancer risk have been discovered (Figure 4). However, all of these genes together account for a relatively small part of breast cancer risk. In addition to these major gene mutations we now know that tiny DNA changes in other parts of our DNA can also increase or decrease breast cancer risk. These changes in single points along DNA (SNPs) which relate to breast cancer risk were first reported with us by our Cambridge collaborators (Easton et al 2007) and now over 300 have been reported by large consortia of investigators (including data from the PROCAS and FH-risk studies) since that time. SNPs are becoming of greater importance in risk prediction alongside the discovery of mutations in breast cancer related genes, and both are crucially important on an individual basis (Figure 4).

FIGURE 4

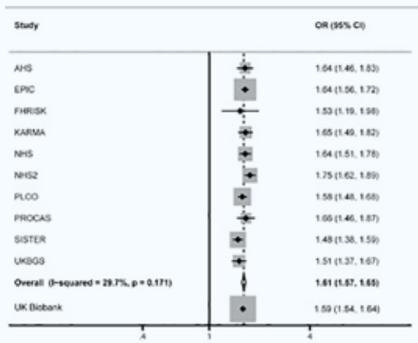


Risk of breast cancer in relation to the frequency of mutations in breast cancer genes (BRCA1/2 and 7 non BRCA1/2 genes) and breast cancer risk associated single nucleotide polymorphisms (SNPs).The inset shows a SNP change at a single point.

SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS)

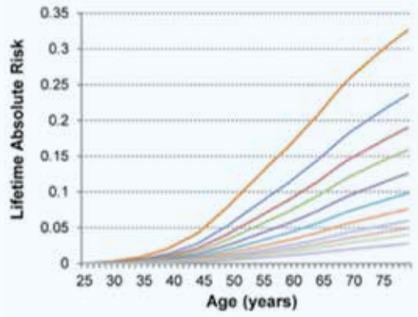
SNPs associated with breast cancer risk are discovered by comparing nucleotide changes in large numbers of women with breast cancer and similarly large numbers of control women without breast cancer. The results require worldwide collaborations organised as the Breast Cancer Associated Consortium (BCAC – including Prof Evans & Howell). In the initial studies in PROCAS in Manchester we used the first 18 SNPs to be reported and more recently 143 SNPs. However, this year BCAC reported on the value of 313 SNPs. In this analysis performed by the Cambridge group (Mavadatt et al), 94,075 breast cancer cases and 75,017 controls were divided into test and validation sets. In figure 5 we show the contribution of the PROCAS data for the confirmation set and in figure 5b how deciles of SNP score contribute to breast cancer risk with the highest score giving about a 1 in 3 lifetime risk and the lowest a less than 1 in 20 risk.

FIGURE 5A



The consortium of BCAC groups including PROCAS indication that each subgroup gave similar results so that combining them is valid.

FIGURE 5B



Deciles of risk associated with the 313 SNPs. Women with the highest SNP score have about a 1 in 3 lifetime risk whereas the lowest score less than 1 in 20 lifetime risk.

MUTATIONS IN BRCA1/2 AND OTHER BREAST CANCER RELATED GENES

Mutations in BRCA1 and BRCA2 may occur throughout the genes. A collaborative study by CIMBA investigators (Consortium of Investigators of Modifiers of BRACA1/2. G Evans) indicated that 1,650 unique BRCA1 and 1,731 unique BRCA 2 deleterious (disease associated) mutations have been identified around the world (Rebbeck et al). Knowledge of the population specific mutational spectrum in BRCA 1/2 may inform efficient strategies for genetic testing in individual populations.

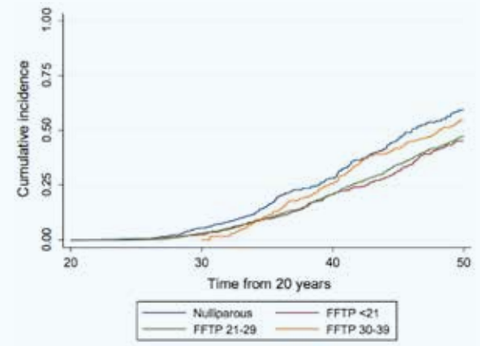
An individual may have a mutation in BRCA1/2 but not develop breast cancer. The variability in expression of the gene mutation is known as 'penetrance' and is important to try and predict in individuals for management purposes. Gareth Evans and the genetics teams in Manchester and Cambridge reported a new method for penetrance estimation using Bayesian calculations based on ratios of pre-symptomatic testing by 10 year age cohorts. They found that the overall cancer associated penetrance for BRCA1 by 68 years was 73%, and 60% for BRCA2. BRCA2 mutations outside the ovarian cancer region were associated with significantly greater breast cancer risk, in general agreement with other studies (Evans et al). Larger studies are required to confirm these findings and to extend the age range of penetrance estimation which in the future will include SNP based estimations. Penetrance estimation, if shown to be accurate, will help counselling for risk reducing breast surgery. Women with mutations with low penetrance may well elect to avoid surgery and rely on screening.

It is possible that the BRCA genes are 'silenced' rather than mutated. Many families with multiple breast and ovarian cancers which appear BRCA1/2 related are found not to have mutations in these genes. This suggests there may be a BRCA3 gene but this has not been discovered despite extensive searches. As one explanation, the Clinical Genetics Group at St Mary's have found that in 2 of 49 'BRCA-like' families testing negative there was inactivation of the BRCA1 gene by silencing of the gene promoter by methylation (Evans et al). This explained the cancers in these two families. This finding needs confirmation in other studies but is a likely explanation for some strong families testing negative for a BRCA1 mutation.

It is possible that BRCA1 promoter methylation may be an event which occurs in the foetus. In a collaborative study with Professor Per Lonning in Norway promoter methylation was positively associated with the development of ovarian cancer in the adult but was detectable in newborns and women of all ages (Lonning et al). Thus suggesting that BRCA1 methylation is, at least in some women, an embryonic event and may be tested for in the young.

We investigated whether the known risk factors for breast cancer affect BRCA1/2 penetrance. Three papers from our group and our collaborators assessed the effect of standard risk factors (age of first pregnancy, smoking, height & BMI) on penetrance of BRCA1 and BRCA2. Gareth Evans was the lead author on a study of 2,500 carriers of BRCA1/2 in Manchester which indicates that age of first pregnancy affects penetrance (as it does with incidence of other breast cancers). Figure 6 shows that age of first pregnancy affects penetrance. BRCA1/2 was associated with higher penetrance in carriers who were nulliparous or had a first full term pregnancy over the age of 29, approximately doubling the penetrance compared with women who had a first pregnancy below the age of 30. For example nulliparous women had a risk of breast cancer at 50 of 54.6% whereas women with a pregnancy below 21 had a risk to 50 of 33.2% (Evans et al).

FIGURE 6



Incidence of breast cancer in 1278 BRCA1 and 1146 BRCA2 mutation carriers in relation to nulliparity and age of first pregnancy (900 developed breast cancer before the age of 50).

In a collaborative study with the Canadian Hereditary Breast Cancer Clinical Study Group it was shown that, compared with non-smokers, smoking was associated with a 17% increased risk of breast and ovarian cancer in BRACA1/2 carriers (HR 1.17 95% CI 1.04-1.56) and was not affected by mutation type or by age of diagnosis. Women in the highest group of total pack years had an increased risk of breast cancer of 33% (HR 1.33, 95% CI 1.02-1.75) indicating smoking is a important risk factor in carriers as well as the general population (Ko et al).

We now know that there are SNPs for several traits including risk of breast cancer, height and BMI. In a collaborative study the CIMBA group assessed the effect of 586 SNPs for height and for BMI on penetrance of BRCA1/2 in 22,588 carriers. SNP for height was associated with a non-significant increased risk of breast cancer whereas BMI was associated with a significant decreased risk. The BMI SNPs are presumably associated with young age of BMI which is known to be associated with decreased risk of breast cancer in the general population. Later age of high BMI (gaining weight as one gets older) is associated with increased breast cancer risk (Qian et al).

The studies outlined in this section are important for the development of precise prediction of penetrance of BRCA1 and BRCA2 mutations for patient management. For example, a woman with a BRCA1/2 mutation associated with a very low penetrance may mean that risk reducing breast surgery is not indicated.

OTHER BRCA RELATED ISSUES

Some studies, including our own, have indicated that, surprisingly, family members who test negative for the familial BRCA2 mutation may have risks of breast cancer 2-5 fold higher than in the general population. Not all studies report this phenomenon and thus the finding is controversial. Because of this controversy the EMBRACE (Epidemiological Study of Familial Breast Cancer) group of investigators in the UK and Republic of Ireland studied 1,895 BRCA1/2 predictive test negative eligible relatives. This large study indicated no significant increase in breast or ovarian cancer in the relatives who tested negative for the family BRCA1/2 mutation (Girardi et al). This finding is important for management of women negative for the family mutation: previous reports of increased risk may be related to small numbers or case selection.

Although women who test negative for the family BRCA1/2 mutation may have a low incidence of cancer we found that it may be worthwhile to test for other gene mutations in this group. In a collaborative study with a group in Norway we showed that 5 of 49 women who tested negative but who nevertheless developed breast cancer had other mutations in BRCA1 or in ATM, MSHG or MUTYH genes (Dominguez-Valentine et al). Thus it may be worth testing women testing negative in BRCA+ families for mutations in other genes if they develop breast cancer.

One problem with genetic testing is the finding of alterations in the gene DNA sequence, the importance of which is unknown. These VUS (variants of unknown significance) pose difficulties for geneticists when giving advice to 'genetic' families. This problem is highlighted in a paper from our group where a variant was thought to be pathogenic but was not on further investigation (Smith et al, Evans et al). If VUS are wrongly thought to cause cancer this may wrongly induce women to be advised to undergo intensive screening or risk-reducing surgery.

Another collaborative study with Cambridge assessed whole genome testing in women with the misfortune to develop 2-3 different cancers testing negative for standard individual tumour genes. On further testing of a panel of genes the study demonstrated that up to 1 in 3 of patients had mutations in other genes on panel testing (Whitworth et al, Innes et al). In another study with Cambridge and other centres we assessed the importance of gene changes in families with multiple stomach cancers and breast cancer. This syndrome can be caused by mutations in the CDHI gene. In 22 families without pathogenic variants the group found other mutations to account for this syndrome including PALB2, MSH2, ATR/NBN and RECQL5 (Fewings et al.) which may impact on management within particular families.

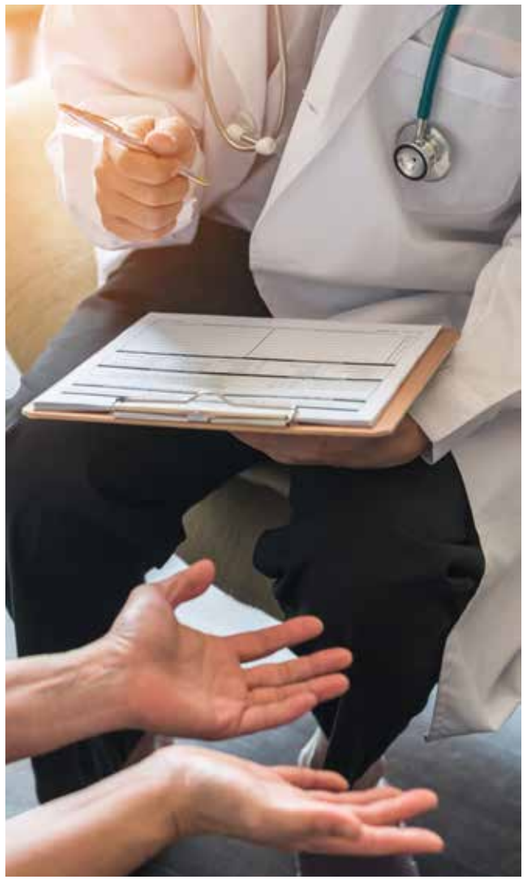
We also assessed the incidence of breast cancer in individuals with mutations in the neurofibromatosis type 1 (NF1) gene. These studies indicated that breast cancer was increased in women with certain variants of NF1 mutation. Breast cancer was only related to 45(64.3%) of the 70 different mutations found in the NF1 gene (Frayling et al). We reviewed all studies of the relationship of NF1 with breast cancer. This indicated standardised incidence ratios of breast cancer risk between 4 and 11 times greater. This suggests a need for screening for breast cancer in NF1 cases. However cases tend to occur in younger women and as NF1 is associated with sensitivity to ionising radiation this means we need to set up studies of MRI screening rather than mammography in this group of women (Howell SJ at al).

Population-based BRCA1/BRCA2 founder-mutation testing has been demonstrated as cost effective compared with family history based testing in Ashkenazi Jewish women. However, only 1 of the 3 Ashkenazi Jewish BRCA1/BRCA2 founder mutations (185delAG [c.68_69delAG]), 5382insC[c.5266dupC]), and 6174delT[c.5946delT]) is found in the Sephardi Jewish population (185delAG[c.68_69delAG]), and the overall prevalence of BRCA mutations in the Sephardi Jewish population is accordingly lower (0.7% compared with 2.5% in the Ashkenazi Jewish population). Cost-effectiveness analyses of BRCA testing have not previously been performed at these lower BRCA prevalence levels seen in the Sephardi Jewish population. We reported that population screening of Sephardi Jewish women was cost-effective. Population testing resulted in gain in life expectancy of 12 months (quality-adjusted life-year 1⁄4 1.00). Population-based BRCA1 testing is highly cost effective compared with clinical criteria driven approach in Sephardi Jewish women. This supports changing the paradigm to population-based BRCA testing in the Jewish population, regardless of Ashkenazi/Sephardi ancestry.

Although the current clinical significance of some of the findings outlined in the studies reported above may not be clear it is likely that several will lead to more precise genetic testing in women with and without breast cancers in the future.

RISK-ADAPTED AND DENSITY-ADAPTED BREAST SCREENING

The PROCAS study indicated that it was possible to determine risk in the context of the NHS Breast Screening Programme (NHSBSP). We were able to use data from a two page questionnaire to produce an estimate of standard risk factors (in the Tyrer-Cuzick model) and to collect information on mammographic density and SNPs. Combining the three methods (which provide non-overlapping information) we were able to give more precise risks to women and the question is whether these data could be used to introduce screening based on risk. Currently, in the PROCAS study we are assessing the feasibility of performing risk feedback in real time (i.e. feeding back information soon after the mammogram). These data can then be used to vary screening intervals based on risk rather than the 3 yearly interval currently used for all women in the NHSBSP.



The feasibility of the risk-based approach was discussed in two papers by Linda Rainey, a postdoctoral investigator based in Nijmegen in Holland. Linda investigated the views of women undergoing screening and clinicians at the Prevent Breast Cancer Research Unit in Manchester, the Karolinska Institute in Stockholm, and in Holland. Dr Rainey performed a literature review and in depth interviews with professionals in the three countries. Although there were considerable reservations in the literature and amongst professionals it was generally considered that such an approach should be tested in a randomised trial (Rainey et al).

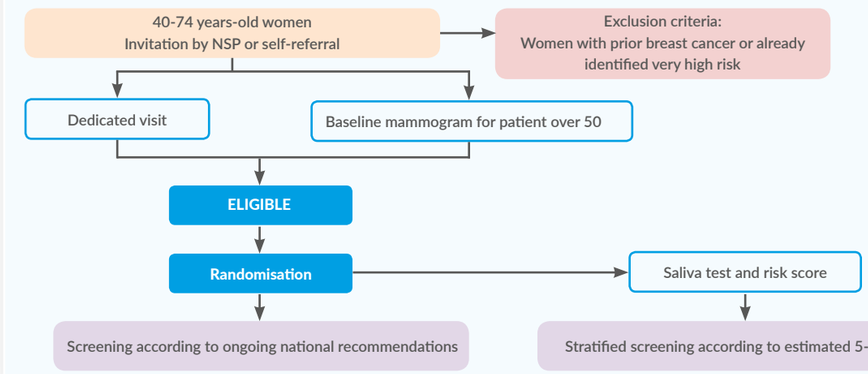
Screening may also be organised on the basis of MD. This is particularly important in women with high breast density for not only are they at high risk of breast cancer, the pick up rate of cancers is reduced because of the problem of MD masking tumours.

INITIATION OF A CLINICAL TRIAL OF RISK-ADAPTED AND DENSITY-ADAPTED SCREENING

A clinical trial called MyPebs (My Personal Breast Screening) has been initiated in several European countries as a result of a €12 million EU grant. The study will begin early in 2019 in France, Italy, Belgium, Israel and in Manchester, Cambridge and Leeds in the UK. It is headed by Dr Suzette Delalogue, a medical oncologist based in Paris. The overall aim of the study is to compare risk and density adapted screening with standard screening in each country (Figure 7A). The format of the test arm is shown in Figure 7 (but also varies by country eg 3 years screening in the UK). The aim is to define risk by T-C, MD & SNPs and to increase screening in women at higher risk and to reduce or eliminate screening in women at low risk. Additional measures in each group will be given in women with high MD including additional MRI and ultrasound (Figure 7B).

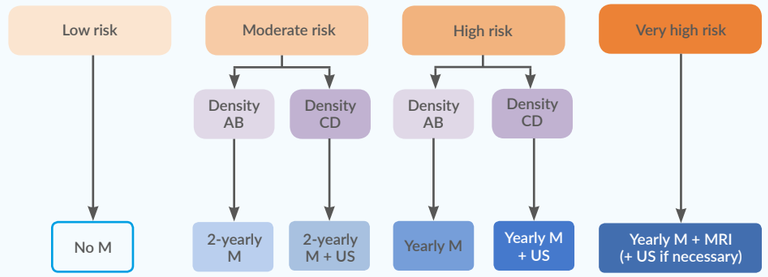
This is a highly important study to test the clinical and monetary value of risk adapted screening and will, hopefully, inform whether changes is indicated in national breast screening programmes.

FIGURE 7A MY-PEBS' CLINICAL TRIAL STRUCTURE



MyPebs is a randomised trial of standard screening in each country compared with risk adapted screening.

FIGURE 7B STRATIFIED STRATEGY BASED ON: AGE, QUESTIONNAIRE, BREAST DENSITY (IF BASELINE MMG, OTHERWISE, MAXIMUM RISK APPLIED), SNPS



The outline randomisation of the intervention arm. Risk will be assessed by T-C, MD and SNPs and screening intervals will depend on this score. Women with high density breasts will receive additional screening using ultrasound and MRI.

Yearly update of risk factors

R = estimated risk of developing a breast cancer ER BC = Oestrogen receptor negative breast cancer (most agressive breast cancer subtype) M = mammogram US = ultra sound MRI = Magnetic resonance imaging

STUDIES IN ASIAN POPULATIONS

Additional studies in Asian populations are important with respect to targeting this often underrepresented group for screening and to investigate whether there are differences in this population which may affect clinical management for preventive approaches.

The differences between breast cancer risk factors in white British/Irish and Asian women attending screening in the UK are not well documented. Between 2009-15 ethnicity and traditional breast cancer risk factors were self-identified by a screening cohort from Greater Manchester. Eight hundred and seventy-nine Asian women and 51,779 unaffected white British/Irish women aged 46-73 years were recruited (The PROCAS study). Asian women were at lower predicted breast cancer risk from hormonal and reproductive risk factors than white British/Irish women (mean 10 year risk 2.6% vs 3.1%, difference 0.4%, 95%CI 0.3-0.5%). White British/Irish women were more likely to have had a younger age at menarche, be overweight or obese, taller, used hormone replacement therapy and not to have had children. However, despite being less overweight, Asian women had gained more weight from age 20 years and were less likely to undertake moderate physical activity. Asian women also had a slightly higher mammographic density. Asian age-standardised incidence was 3.2 (95%CI 1.6-5.2, 18 cancers) per thousand women/year vs 4.5 (95%CI 4.2-4.8, 1076 cancers) for white British/Irish women (Evans et al). Thus Asian women attending screening in Greater Manchester are likely to have a lower risk of breast cancer than white British/Irish women, but they undertake less physical activity and have more adult weight gain.

Germline mutations in the BRCA1 and BRCA2 genes have significant clinical implications for both risk-reducing and early surveillance management in Asian populations. With Joanne Ngow and her colleagues in Singapore we assessed how effective the Manchester Score was in this Southeast Asian population The score was 93% sensitive for predicting mutations in this group and is thus just as effective tool in Asia as in the Manchester population (Ngow et al).

With Dr Taib and his colleagues in Kuala Lumpur we assessed the incidence of contralateral risk reducing mastectomy (CRRM) in the middle income Malay population. The study indicated that the risk of contralateral beast cancer is very low in this Southeast Asian setting. Any recommendations or practice of CRRM should be reviewed with caution and patients must be counseled appropriately (See et al).

It is clearly important to continue to investigate differences between Asian and other populations since they may affect our management of this group in our clinics and trials.

IN-SITU CARCINOMA OF THE BREAST

Inhibiting the progression from in-situ to invasive carcinoma is an important target for prevention and is a particular interest of Prevent Breast Cancer researchers Tony Maxwell (from the radiological viewpoint) and Cliona Kirwan and Charles Streuli (from the biological viewpoint). In order to determine factors related to progression to invasion Tony Maxwell and his colleagues in the Sloane Project (a national group of UK investigators interested in in-situ disease) studied a group of 89 women who did not have their in-situ carcinoma removed surgically and received no other treatment. At long term follow up 33% of the women developed invasive breast cancer. They found that high grade DCIS, mammographic microcalcification, young age and lack of endocrine therapy were risk factors for DCIS progression to invasive cancer. Surgical excision of high grade DCIS remains the treatment of choice. Given the uncertain long-term natural history of non-high grade DCIS, the option of active surveillance of women with this condition should be offered within a clinical trial.

PREVENTION OF BREAST CANCER

There are currently three major methods we use for prevention of breast cancer. One is the use of preventive drugs given for a five year period, the second is lifestyle change and the third is surgical resection of breast tissue (risk reducing surgery).

PREVENTIVE DRUGS ("CHEMOPREVENTION")

Manchester has been a major centre for recruitment of the IBIS I and II trials (IBIS – International Breast Intervention Studies) of tamoxifen and anastrozole for breast cancer prevention in women at high risk of the disease. When taken for 5 years tamoxifen reduces risk by 40% for up to 20 years. Anastrozole reduces risk by 50% but the duration of this effect is not known. NICE (2013 and 2017) have now accepted both drugs and another called raloxifene for use for prevention within the NHS. NICE concluded that anastrozole was the most cost effective preventive treatment, resulting in an overall cost saving to the NHS.

Raloxifene, unlike tamoxifen, does not stimulate the uterus but is ineffective in premenopausal women. In view of the potential benefit of reduced side effects in premenopausal women we performed a 2-year randomised collaborative study of no preventive treatment compared with raloxifene combined with and goserelin, a drug which stops the ovaries producing oestrogen (The RAZOR trial, Howell A et al). The study indicated that the treatment was feasible but was not well tolerated and we concluded that tamoxifen without ovarian suppression (the current standard prevention for premenopausal women) should still be used .

We also further investigated the reason for drop out of women in the IBIS-II trials (anastrozole v placebo primary prevention and anastrozole v tamoxifen DCIS). In the primary prevention trial, 3864 postmenopausal women were randomised to either placebo or anastrozole and 2980 with DCIS to anastrozole v tamoxifen . In the prevention trial adherence to anastrozole, was 65.7% and to placebo was 65.9% over the five years and figures were similar for the DCIS study (Figure 8). Dropouts were higher in the first 1.5 years of therapy. The importance of this study is that there were no significant differences in drop-out rates between anastrozole and either placebo or tamoxifen indicating that the issues for stopping therapy are complex and probably largely unrelated to side effects. (Sestak et al)

FIGURE 8A

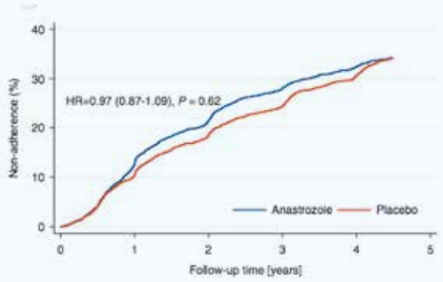


FIGURE 8C

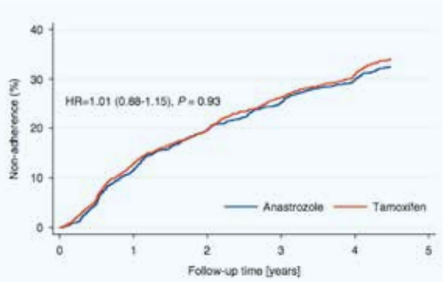


FIGURE 8B

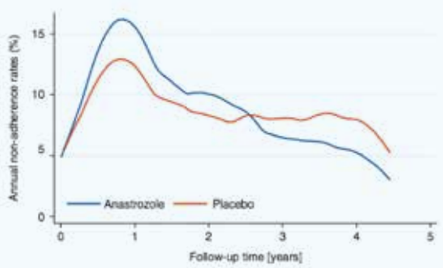
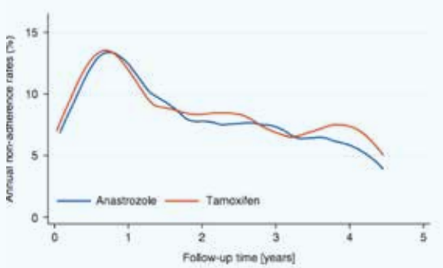


FIGURE 8D

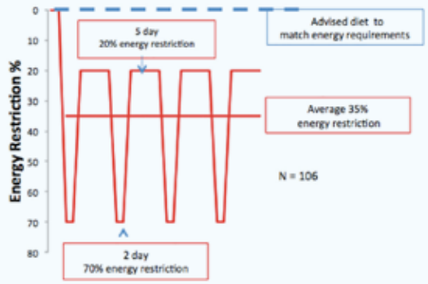


Kaplan–Meier plots for non-adherence and annual non-adherence rates (%) according to treatment arm for the IBIS-II prevention (A, B) and DCIS (C, D) studies. Kaplan–Meier curves were calculated and tested for equality using log-rank test. All statistical tests were two- sided. IBIS, International Breast cancer Intervention Study; HR, hazard ratio; CI, confidence interval.

LIFESTYLE PREVENTION

We estimate that maintained weight reduction of greater than 5%, exercise and moderation in alcohol intake might prevent up to 25% of breast cancers indicating the importance of breast cancer prevention focussed on lifestyle factors as part of our preventative approaches. Michelle Harvie and her team previously demonstrated in a randomised trial that energy restriction for 2 days per week (Intermittent energy restriction [IER]) was more effective than continuous energy restriction and thus we largely advocate the two day diet approach. Further analyses of calorie intake in women choosing IER gave an indication of the reason for the superiority of the two day approach and is shown in figure 9. After 2 days of 70% energy restriction women are told they can eat as much as they wish of a Mediterranean type diet for the further five days. However, it is clear from this diagram that after the 2 day restriction women eat approximately 20% less than expected giving an overall energy restriction on the diet of 35% compared with the expected 25% (Harvey et al). In our current studies we use the 2 day diet but women may use continuous dieting if they prefer.

FIGURE 9A



Changes in energy restriction after initiation of the 2 day diet. Greater restriction than expected is seen because on average women eat less on unrestricted days.

FIGURE 9B

	TAM-Prev population n = 137	Women age 35-44 in England (HSE 2012)
Overweight (including obese)	59.2%	55.6%
Obese BMI ≥ 30	23.8%	24.6%
<150 min mod exercise/week	37%	34%
Alcohol > 14 units/ weel	45%	19%
Smoker	9.0%	19.0%
Fibre g/day	17.5 (5.3)	17.0 (6.0)
Saturated fat g/day	26.1 (10.3)	22.1 (9.7)
Added sugar g/day	37.2 (22.0-59.0)[a]	36.1 (21.1-51.1)[a]

Comparison of the diets of women in the family history clinic with the general population of women of the same age. Surprisingly, there is little difference indicating no spontaneous alteration of diet by women who know they have a higher breast cancer risk.

Louise Gorman (nee Donnelly) performed semi-structured interviews in 13 women aged 39–62 years, who followed a 4-month intermittent energy restriction (2 days of low energy/low carbohydrate, 5 days of healthy eating). Nine of the 13 women successfully lost >5% of their total body weight. Data were analysed using thematic analysis. Many participants found intermittent dieting preferable to previous experiences of continuous dieting. The findings provide some insight into the ways in which intermittent dieting is successful, and why it could be considered a viable alternative to continuous energy restriction for weight loss (Donnelly et al).

Mary Pegington, a senior research dietician in the Prevent Breast Cancer team, made a telling observation when she examined lifestyle factors in a premenopausal group of women in our clinic who volunteered to join a trial of tamoxifen. Our hypothesis was that these women might naturally have a healthy lifestyle because of the high risk of breast cancer. However, this was not the case. Compared with the general population of women aged 35-44 in England they had exactly the same incidence of overweight and obesity and similar low exercise levels as the standard population and consumed greater amounts of alcohol (Figure 9. Pegington et al)

In addition to the established association between general obesity and breast cancer risk, central obesity and circulating fasting insulin and glucose have been linked to the development of this common malignancy. Findings from previous studies, however, have been inconsistent, and the nature of the associations is unclear. The Breast Cancer Associated Consortium conducted a Mendelian randomization analysis to evaluate the association of breast cancer risk, using genetic instruments, with fasting insulin, fasting glucose, 2-h glucose, body mass index (BMI) and BMI-adjusted waist-hip-ratio (WHRadj BMI). We first confirmed the association of these instruments with type 2 diabetes risk in a large diabetes genome-wide association study consortium. We then investigated their associations with breast cancer risk using individual-level data obtained from 98 842 cases and 83 464 controls of European descent in the Breast Cancer Association Consortium (Shu et al). We confirmed the previously reported inverse association of genetically predicted BMI with breast cancer risk, and showed a positive association of genetically predicted fasting insulin and 2-h glucose and an inverse association of WHRadj BMI with breast cancer risk. Our study suggests that genetically determined obesity and glucose/ insulin-related traits have an important role in the aetiology of breast cancer.

Excess body adiposity is associated with increased risk of pancreatic cancer, and in animal models excess intra-pancreatic fat is a driver of pancreatic carcinogenesis. Within a programme to evaluate pancreatic fat and PC risk in humans, we verified that MR-quantified pancreatic fat fraction (PFF) was ‘fit for purpose’ as an imaging biomarker (Coe et al).

Our current drive is to introduce healthy lifestyles into the NHSBSP and into the Family History Risk and Prevention Clinic – using grants from Prevent Breast Cancer.

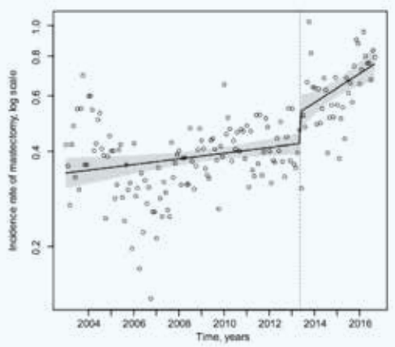
RISK REDUCING SURGERY

It is well known that Angelina Jolie disclosed in an open editorial in The New York times entitled 'My Medical Choice' that she had learned that she was a BRCA1 mutation carrier and had undergone risk reducing breast surgery. Gareth Evans and our team reported that the publicity surrounding Angelina's decision increased the numbers threefold of women at high risk in the clinic who wished to discuss surgery (Evans et al 2014) and later a similar increase in the number of risk reducing operations performed (Evans et al 2015). Using a large representative health insurance database (Market-Scan ®Truman Health Analytics) Prof Evans together with colleagues from Amgen in the USA have now demonstrated a marked increase in risk reducing surgery in the USA as seen in other countries. Monthly rates of surgery increased from 0.2% per month before Angelina Jolie's article to the remarkable figure of 0.9% each month after May 2013 (Figure 10. Leide et al).

We have shown increase in numbers in our clinic of high risk women is not a function of the worried well wishing to be reassured but a true increase in women at very high risk feeling empowered to go ahead with surgery. We believe that Angelina Jolie has performed a great service to women at very high risk of breast cancer by her courageous editorial.

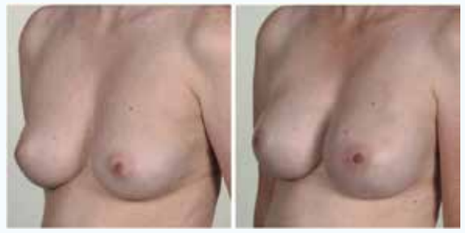
A formal protocol for risk reducing surgery as an approach to prevention was introduced into our clinical service in 1996. Most women elect to have implants inserted after surgical removal of breast tissue. In the past this was performed by a two-stage operation of insertion of an expander under the pectoral muscle and later replacement of the expander with an implant in a two stage procedure. Our surgeons and others have developed a one stage procedure which involves covering the implant with an acellular dermal matrix (Strattice and Atria) to fix the reconstruction in position, give a more natural appearance and aid vascularisation and regeneration which in turn reduce future complications and revision surgery rates. Initially this was used at the lower pole of the reconstruction covering the implant not covered by pectoralis major. More recently full coverage of the implant has been used negating the need to raise the pectoralis major muscle (Highton et al), with a faster recovery, reduced donor site morbidity and quicker return to normal activities. Higher Surgical Trainee Benjamin Baker and Consultants Mr James Harvey and Mr John Murphy from the Nightingale Centre performed a prospective study to determine which method was optimal in terms of pain, patient reported outcome and safety of the two approaches. Early post-operative pain and quality of life were not different between the two procedures indicating that the complete coverage technique was safe (Figure 10. Baker et al).

FIGURE 10A



Change in the rate of risk reducing surgery in a health insurance plan in the USA before and after Angelina Jolie's article in the New York Times.

FIGURE 10B



Before and after results of risk reducing surgery in a woman who had a one stage breast reconstruction using implant and pre-pectoral acellular dermal matrices (Strattice).

MECHANISTIC STUDIES

Understanding the potential mechanisms of the development of breast cancer from normal epithelial cells in the breast to cancer cells is important for developing new approaches to preventive therapies. We are fortunate in Manchester in having breast biology labs at the University with Charles Streuli and his colleagues and at the Manchester Cancer Research Centre Breast Biology Laboratory under Robert Clarke.

HORMONES AND THE DEVELOPMENT OF BREAST CANCER

The Clarke lab is particularly focussed on the importance of the breast stem cell as a target for treatment. In a recent review Denis Alferez and other lab members summarised the action of steroid hormones on breast stem cells. They highlighted the importance of progesterone which stimulates differentiated progesterone receptor positive cells to release cytokines which, in turn, stimulate stem cell proliferation. They emphasised the importance of this pathway and indicated that our current trials are not designed to inhibit this pathway. One approach to prevention of this pathway is to block the progesterone receptor with antiprogestins and another is to block the stimulatory effect on the stem cell of the progesterone-induced protein RANK Ligand using the osteoporosis drug, denosumab. Both of these approaches are in clinical trials in Manchester thus exploring news avenues for prevention (Alferez et al. See 'Current Study Reports').

BIOLOGICAL CLOCKS AND BREAST CANCER

Charles Streuli and his colleagues have also made the very interesting observation that biological clocks found in virtually all body cells, including the breast, are disordered during the development of breast cancer. The amplitude of the clocks is reduced in tumour cells compared with normal epithelial cells (Fig 11) and increased in breast fibroblasts. It appears that in normal and malignant epithelial cells the amplitude of the clocks is decreased by tissue stiffness. The lab has previously shown as part of a Prevent Breast Cancer grant that the potential reason that breast density is associated with increased risk is because of the associated increase in stiffness in dense tissues (Williams et al, Broadberry et al) The lab is pursuing whether clock changes are a cause or consequence of malignancy. It may be possible to develop new therapeutics to reverse clock abnormalities if they are a direct cause of breast cancer.

CONTROL OF STEM CELL PROLIFERATION

The Streuli lab is also interested in the control of proliferation of the breast stem cell since this is the likely target of breast carcinogenesis. In a study of mouse mammary stem cells his group demonstrated that proliferation was controlled via extracellular integrins binding to the cell surface. After integrin binding they demonstrated, for the first time, activation of the RAC/1 signalling pathway which, in turn, stimulates the wnt/beta catenin pathway. Another finding which could lead to new therapeutic approaches (Olabi et al).

FIGURE 11

The amplitude (A) of biological clock activity is reduced in mammary tumour cells (C) compared with normal mammary epithelial cells (B) from the same patient.

THE CHEMICAL CAUSES OF BREAST CANCER

The human population is widely exposed to the chemicals benzophenone-3 (BP-3), octylmethoxycinnamate (OMC), 4-methylbenzilidenecamphor (4-MBC) and homosalate from their use in consumer goods. Their oestrogenic activity and presence in human milk suggest a potential to influence breast cancer development. In a study with Lester Barr as the clinician and Philippa Darbre from Reading as the principle scientist, high-performance liquid chromatography- tandem mass spectrometry was used to measure concentrations of these chemicals in human breast tissue from three locations across the breast from 40 women undergoing mastectomy for primary breast cancer. They investigated whether there was any link between chemical concentration of the potential carcinogens and whether a tumour was present in that region. For the lateral region, more BP-3 was measured when a tumour was present (P = .007) and for OMC the P value was .061. For seven (of 40) women with measurable 4-MBC, six of seven had measurable 4-MBC at the site of the tumour only (Barr et al). This study cannot identify either the source of the chemicals or whether the chemicals entered the breast tissue by dermal absorption or through physiological transport mechanisms (blood, lymphatics). However, these results are suggestive that levels of these chemical may be higher at tumour sites and thus, potentially associated with the development of breast cancer.

SUMMARY OF REVIEWS WRITTEN BY MEMBERS OF THE TEAM

Sestak I, Evans DG, Cuzick J. Epidemiology risk factors and strategies. In Breast Surgery: A companion to Specialist Surgical Practice. 6th Ed Dixon MJ. Elsevier, Philadelphia 2018 pp63-73

Breast cancer is by far the most common cancer in women worldwide, with an estimated 1.67 million new cancers diagnosed in 2012. In the United Kingdom, where the age-standardised incidence and mortality is one of the highest in the world, the annual incidence among women aged 50 and over is 3.2 per 1000, and the disease is the commonest cause of death among women aged 40–50, accounting for about a fifth of all deaths in this age group. Over the last 30 years the annual number of new breast cancer cases in women has almost doubled. There are about 12 000 deaths each year, although the number of deaths has declined over the past 5 years. Breast cancer survival rates vary by age at diagnosis, with those diagnosed in their 50s and 60s having higher survival rates than either younger or older patients. There has been a trend in improvement of breast cancer mortality, due to better early detection and better therapeutic strategies, but both breast cancer incidence and mortality have remained high. Here, we review risk factors and prevention strategies for breast cancer.

Howell A, Harvie M, Howell S, Donnelly LS, Evans DG. The prevention of breast cancer in Cancer Prevention and Screening: Concepts, Principles and Controversies Eds Eeles R, Berg C, Tobias J. Wiley, 2018; ISBN1118990870, 978111899087

It is now feasible to prevent a proportion of breast cancers using preventive therapy (chemoprevention), lifestyle change and risk reducing breast and ovarian surgery. In order to offer these approaches to appropriate women it is important to have in place measures to identify women at moderate and high risk of breast cancer and to offer options to reduce risk. Here we summarise available methods for predicting risk, how this may be applied on a population basis and how preventive measures may be offered appropriately.

Personalized prevention in high risk individuals: Managing hormones and beyond. Evans DG, Howell SJ, Howell A. Breast. 2018 Jun;39:139-147. doi: 10.1016/jbreast.2018.03.009.

Increasing numbers of women are being identified at 'high-risk' of breast cancer, defined by The National Institute of Health and Care Excellence (NICE) as a 10-year risk of ≥8%. Classically, women have been so identified through family history based risk algorithms or genetic testing of high-risk genes. Recent research has shown that assessment of mammographic density and single nucleotide polymorphisms (SNPs), when combined with established risk factors, trebles the number of women reaching the high risk threshold. The options for risk reduction in such women include endocrine chemoprevention (preventive therapy using oral anti-oestrogen medication) with the selective oestrogen receptor modulators tamoxifen and raloxifene or the aromatase inhibitors anastrozole or exemestane. NICE recommends offering anastrozole to postmenopausal women at high-risk of breast cancer as cost effectiveness analysis showed this to be cost saving to the National Health Service. Overall uptake of preventive anti-oestrogen therapy has been disappointingly low but this may improve with the improved efficacy of aromatase inhibitors, particularly the lack of toxicity to the endometrium and thrombogenic risks. Novel approaches to chemoprevention under investigation include lower dose and topical tamoxifen, denosumab, anti-progestins and metformin. Although oophorectomy is usually only recommended to women at increased risk of ovarian cancer it has been shown in numerous studies to reduce breast cancer risks in the general population and in those with mutations in BRCA1/2. However, recent evidence from studies that have confined analysis to true prospective follow up have cast doubt on the efficacy of oophorectomy to reduce breast cancer risk in BRCA1 mutation carriers, at least in the short-term.

Opportunities and priorities for breast surgical research. Cutress RI, McIntosh SA, Potter S, Goyal A, Kirwan CC, Harvey J, Francis A, Carmichael AR, Vidya R, Vaidya JS, Fairbrother P, Benson JR, Reed MWR; Association of Breast Surgery Surgical Gap Analysis Working Group. Lancet Oncol. 2018 Oct;19(10):e521-e533. doi: 10.1016/S1470-2045(18)30511-4.

The 2013 Breast Cancer Campaign gap analysis established breast cancer research priorities without a specific focus on surgical research or the role of surgeons on breast cancer research. This Review aims to identify opportunities and priorities for research in breast surgery to complement the 2013 gap analysis. To identify these goals, research-active breast surgeons met and identified areas for breast surgery research that mapped to the patient pathway. Areas included diagnosis, neoadjuvant treatment, surgery, adjuvant therapy, and attention to special groups (eg, those receiving risk-reducing surgery). Section leads were identified based on research interests, with invited input from experts in specific areas, supported by consultation with members of the Association of Breast Surgery and Independent Cancer Patients' Voice groups. The document was iteratively modified until participants were satisfied that key priorities for surgical research were clear. Key research gaps included issues surrounding overdiagnosis and treatment; optimising treatment options and their selection for neoadjuvant therapies and subsequent surgery; reducing rates of re-operations for breast-conserving surgery; generating evidence for clinical effectiveness and cost-effectiveness of breast reconstruction, and mechanisms for assessing novel interventions; establishing optimal axillary management, especially post-neoadjuvant treatment; and defining and standardising indications for risk-reducing surgery. Strategies for resolving these knowledge gaps were then proposed. Surgeons are ideally placed for a central role in breast cancer research and it was highlighted that a culture of engagement and participation in research to benefit patients and health-care systems should be fostered. Development of infrastructure and surgical research capacity, together with appropriate allocation of research funding, is needed to successfully address the key clinical and translational research gaps that are highlighted in this Review within the next two decades.

Psychosocial issues of a population approach to high genetic risk identification: Behavioural, emotional and informed choice issues.

French DP, Howell A, Evans DG.
Breast. 2018 Feb;37:148-153. doi: 10.1016/j.breast.2017.11.008.

To allow women at high genetic risk of breast cancer to benefit from prevention or early prevention strategies, a screening programme is required to identify them. The present review considers the likelihood of key outcomes that would arise from such a programme, in relation to behavioural, emotional and informed choice outcomes. The likelihood of outcomes in each category is considered in relation to the limited direct evidence and relevant indirect evidence, given the dearth of studies that have directly studied the effects of communication of personal genetic risk of breast cancer. Overall, there is promise that such a programme would have several behavioural benefits, such as good uptake of increased screening in women at high risk but little effect on screening in women at low risk. The available evidence suggests that major adverse effects on emotional outcomes are unlikely. There is very limited evidence in this developing area on the extent to which decisions of women offered breast cancer risk estimation will be fully informed choices. Recommendations are made for increasing benefits and reducing harms of population-wide breast cancer risk estimation in light of current evidence. Key research gaps are identified.

The Role of Steroid Hormones in Breast and Effects on Cancer Stem Cells. Alferez DG, Simões BM, Howell SJ, Clarke RB. Curr Stem Cell Rep. 2018;4(1):81-94. doi: 10.1007/s40778-018-0114-z.

This review discusses how the steroid hormones, oestrogen and progesterone, as well as treatments that target steroid receptors, can regulate cancer stem cell (CSC) activity. The CSC theory proposes a hierarchical organization in tumours where at its apex lies a subpopulation of cancer cells endowed with self-renewal and differentiation capacity. In breast cancer, CSCs have been suggested to play a key role in tumour maintenance, disease progression, and the formation of metastases. In preclinical models of breast cancer, only a few CSCs are required to sustain tumour re-growth, especially after conventional anti-endocrine treatments. CSCs include therapy-resistant clones that survive standard of care treatments like chemotherapy, irradiation, and hormonal therapy. The relevance of hormones for both normal mammary gland and breast cancer development is well described, but it was only recently that the activities of hormones on CSCs have been investigated, opening new directions for future breast cancer treatments and CSCs.

Genetic counselling and testing of susceptibility genes for therapeutic decision-making in breast cancer-an European consensus statement and expert recommendations.

Singer CF, Balmaña J, Bürki N, Delaloge S, Filieri ME, Gerdes AM, Grindedal EM, Han S, Johansson O, Kaufman B, Krajc M, Loman N, Olah E, Paluch-Shimon S, Plavetic ND, Pohlodek K, Rhiem K, Teixeira M, Evans DG.
Eur J Cancer. 2019 Jan;106:54-60. doi: 10.1016/j.ejca.2018.10.007.

An international panel of experts representing 17 European countries and Israel convened to discuss current needs and future developments in BRCA testing and counselling and to issue consensus recommendations. The experts agreed that, with the increasing availability of high-throughput testing platforms and the registration of poly-ADP-ribose-polymerase inhibitors, the need for genetic counselling and testing will rapidly increase in the near future. Consequently, the already existing shortage of genetic counsellors is expected to worsen and to compromise the quality of care particularly in individuals and families with suspected or proven hereditary breast or ovarian cancer. Increasing educational efforts within the breast cancer caregiver community may alleviate this limitation by enabling all involved specialities to perform genetic counselling. In the therapeutic setting, for patients with a clinical suspicion of genetic susceptibility and if the results may have an immediate impact on the therapeutic strategy, the majority voted that BRCA1/2 testing should be performed after histological diagnosis of breast cancer, regardless of oestrogen receptor and human epidermal growth factor receptor 2 (HER2) status. Experts also agreed that, in the predictive and therapeutic setting, genetic testing should be limited to individuals with a personal or family history suggestive of a BRCA1/2 pathogenic variant and should also include high-risk actionable genes beyond BRCA1/2. Of high-risk actionable genes, all pathological variants (i.e. class IV and V) should be reported; class III variants of unknown significance, should be reported provided that the current lack of clinical utility of the variant is expressly stated. Genetic counselling should always address the possibility that already tested individuals might be re-contacted in case new information on a particular variant results in a re-classification.

European Breast Cancer Council manifesto 2018: Genetic risk prediction testing in breast cancer.

Rutgers E, Balmana J, Beishon M, Benn K, Evans DG, Mansel R, Pharoah P, Perry Skinner V, Stoppa-Lyonnet D, Travado L, Wyld L.
Eur J Cancer. 2019 Jan;106:45-53.

European Breast Cancer Council manifesto and supporting article on genetic risk prediction testing in breast cancer, presented at the 11th European Breast Cancer Conference in Barcelona, Spain. Predictive genetic testing for breast cancer and other diseases is a crucial area of research and ongoing clinical implementation. The complexity of the biology and algorithms needed to interpret data is increasing and is placing pressure on health services already hard pressed to provide services such as high-quality genetic counselling. The market for DTC tests is also growing rapidly amid a fragmented regulatory picture in Europe under which there are fundamental questions about whether such tests even fall within legal definitions of health services. The nature of the Internet means that people can easily circumvent any European and national restrictions on DTC testing in any case. To maximise benefits and minimise possible harms, the EBCC considers that the breast cancer community in Europe must lead in implementing the call to action in this manifesto.

Systematic review of the empirical investigation of resources to support decision-making regarding BRCA1 and BRCA2 genetic testing in women with breast cancer.

Grimmett C, Pickett K, Shepherd J, Welch K, Recio-Saucedo A, Streit E, Seers H, Armstrong A, Cutress RI, Evans DG, Copson E, Meiser B, Eccles D, Foster C.
Patient Educ Couns. 2018 May;101(5):779-788. doi: 10.1016/j.pec.2017.11.016.

This study identified existing resources developed and/or evaluated empirically in the published literature designed to support women with breast cancer making decisions regarding genetic testing for BRCA1/2 mutations. A systematic review of seven electronic databases was performed. Studies were included if they described or evaluated resources that were designed to support women with breast cancer in making a decision to have genetic counselling or testing for familial breast cancer. Outcome and process evaluations, using any type of study design, as well as articles reporting the development of decision aids, were eligible for inclusion. A total of nine publications, describing six resources were identified. Resources were effective at increasing knowledge or understanding of hereditary breast cancer. Satisfaction with resources was high. There was no evidence that any resource increased distress, worry or decisional conflict. Few resources included active functionalities for example, values-based exercises, to support decision-making. Tailored resources supporting decision-making may be helpful and valued by patients and increase knowledge of hereditary breast cancer, without causing additional distress. Clinicians should provide supportive written information to patients where it is available. However, there is a need for robustly developed decision tools to support decision-making around genetic testing in women with breast cancer

Boosting care and knowledge about hereditary cancer: European Reference Network on Genetic Tumour Risk Syndromes.

Vos JR, Giepmans L, Röhl C, Geverink N, Hoogerbrugge N; ERN GENTURIS (incl Evans G).
Fam Cancer. 2018 Oct 9. doi: 10.1007/s10689-018-0110-6.

Approximately 27-36 million patients in Europe have one of the ~5.000-8.000 known rare diseases. These patients often do not receive the care they need or they have a substantial delay from diagnosis to treatment. In March 2017, twenty-four European Reference Networks (ERNs) were launched with the aim to improve the care for these patients through cross border healthcare, in a way that the medical knowledge and expertise travels across the borders, rather than the patients. It is expected that through the ERNs, European patients with a rare disease get access to expert care more often and more quickly, and that research and guideline development will be accelerated resulting in improved diagnostics and therapies. The ERN on Genetic Tumour Risk Syndromes (ERN GENTURIS) aims to improve the identification, genetic diagnostics, prevention of cancer, and treatment of European patients with a genetic predisposition for cancer. The ERN GENTURIS focuses on syndromes such as hereditary breast cancer, hereditary colorectal cancer and polyposis, neurofibromatosis and more rare syndromes e.g. PTEN Hamartoma Tumour Syndrome, Li Fraumeni Syndrome and hereditary diffuse gastric cancer

SUMMARY OF CURRENT CLINICAL STUDIES IN THE PREVENT BREAST CANCER RESEARCH UNIT

A pilot prevention study of the effects of the anti-progestin Ulipristal Acetate (UA) on surrogate markers of breast cancer risk.

PI Sacha Howell

In this single arm phase II study the anti-progestin tablet ulipristal acetate is given to women at moderate to high risk of breast cancer for 3 months. Before treatment starts MRI scan and vaccum assisted biopsy (VAB) is performed, both being repeated in the last week of treatment. Recruitment is almost complete and preliminary results demonstrate that the primary endpoint has been met, with significant reduction in normal breast proliferation. The proportion of luminal progenitor cells, thought to be the cell of origin of most breast cancers, was reduced with treatment. This suggests that anti-progestins may be effective in the chemoprevention of breast cancers, including the triple negative subtype which is not prevented by anti-estrogens.

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, International Phase 3 Study to determine the Preventive Effect of Denosumab on Breast Cancer in Women carrying a BRCA1 Germline Mutation.

PIs Sacha Howell and Gareth Evans

Preclinical data show that the luminal progenitor subpopulation in BRCA1 carriers becomes insensitive to progesterone signaling, but retains sensitivity to downstream signals such as RANKL. In a large multinational collaborative study the RANKL inhibitor denosumab is to be tested against placebo in a population of more than 2,500 BRCA1 mutation carriers. Manchester is the only UK site and the study is due to open in 2019. If successful this will be the first preventive drug therapy shown to be effective in this very high risk group, in whom the only successful approach to prevention to date has been prophylactic mastectomy.

Biomarkers of breast cancer prevention

PI Sacha Howell

This study opened to recruitment in December 2018 and seeks to identify the molecular mechanisms of resistance to commonly used preventive agents. Women commencing tamoxifen (n=30) or anastrozole (n=40) will have a VAB before and after 3 months of therapy. The molecular changes in the normal breast tissue will be subjected to supervised analysis based on whether or not a response in breast density was seen on the 1 year mammogram. At the same time, through a Prevent Breast Cancer grant we are developing culture systems that can maintain the structural integrity and signalling of normal breast tissue outside of the body (in vitro). If the effects of tamoxifen in patients can be recapitulated in vitro we will be able to use such a model to develop novel preventive approaches in future.

Introduction of breast cancer prevention with tamoxifen and raloxifene for women at increased risk of breast cancer.

PI Gareth Evans

The overall aims of the study are to: (a) determine the uptake of tamoxifen and raloxifene for prevention in eligible women from the Family History Clinic (FHC) at the Prevent Breast Cancer Research Unit, and moderate and high risk women from the NHS Breast Screening Programme (NHS BSP) identified through the PROCAS (Predicting Risk of Cancer at Screening) study, and (b) determine whether it is possible to predict who is likely to benefit from preventive therapy.

Efficacy of diet and exercise weight loss programmes amongst overweight women attending a Family History Clinic at high risk of breast cancer.

Harvie M, Howell A, French D, Gorman L, Evans DG

Ongoing trial to reduce breast cancer risk for women at high risk as an alternative to preventive therapy.

Biomedical Research Centre Manchester, Risk and Early Detection programme. NIHR programme grant of £28.5million over 5 years.

Professor Gareth Evans leads the Cancer Prevention Early Detection (PED) theme and is overall lead for the 3 cancer themes out of a total of 7 themes. Many of the Prevent Breast Cancer PIs are prominent in the theme including Sacha Howell, Tony Howell, Michelle Harvie, Tony Maxwell and Sue Astley.

MyPeBS (My Personal Breast Screening),

Delalogue S, Sirven A, French D, Evans DG, et al (7 EU countries-18 partners)

Randomized Comparison Of Risk-Stratified versus Standard Breast Cancer Screening In European Women Aged 40-74. EU Horizon 2020 grant of Euro 12.4M over 5 years.

Developing and piloting a Single Nucleotide Polymorphism Polygenic risk Score for real time risk feedback for women attending their first mammogram in the NHS Breast Screening Programme.

Evans DG (PI), Newman W

Prevent Breast Cancer grant to test feasibility of offering SNP testing within the NHS screening programme.

How feasible and acceptable is it to recommend to women at low risk of breast cancer that they delay further screening?

PI David French

The aim is to assess the feasibility of recommending to women identified as being at low risk at the first routine screen in the NHS BSP that they delay attending further screening. Women attending their first routine screening appointment who opted for risk estimation would receive this recommendation if their overall risk of breast cancer is <1.5% and risk of oestrogen negative breast cancer is 0.5% over 10 years. (These women may continue to attend BSP at 3-yearly intervals if they so wish).

NATIONAL AND INTERNATIONAL PRESENTATIONS

Risk modelling in breast cancer and Manifesto round table

Gareth Evans

European Breast Cancer Conference March 2018 Barcelona.

Energy restriction for the treatment and prevention of breast cancer

Tony Howell

European Breast Cancer Conference March 2018 Barcelona.

Personalised Breast Cancer Prevention in the NHS

Tony Howell

PHG Foundation St Catherine's College October 2018 Cambridge.

Risk stratification in breast cancer use of common variants; Ready for use?

Gareth Evans

San Antonio Breast Cancer Symposium. Dec 2018.

AI in Mammographic Screening

Sue Astley

Grand challenges in Artificial Intelligence in Clinical Radiology and Clinical Oncology. Clinical Oncology. The Royal College of Radiologists in partnership with Health Data Research UK, The Engineering and Physical Research Council and The Turing Institute.

Wednesday 16 May 2018. The Wellcome Collection, London.

Intermittent Fasting : Is it doable and does it do you good?

Michelle Harvie

Clinical trials of intermittent energy restriction weight control & weight related diseases conference 1st International Conference on Fasting, Dietary Restriction, Longevity and Disease USC Longevity Institute, Los Angeles, November 9th/ 10th 2018.

Intermittent Energy Restriction: Translating theory into practice: Supporting patients

Michele Harvie

International Fasting Summit November 9th 2018, Los Angeles Midtown at USC Los Angeles, California.

Intermittent diets: The latest fad or here to stay?

Michelle Harvie

British Dietetic Association Specialist Obesity Services: What? How? Who? When? Obesity prevention & treatment str: BDA Obesity Specialist Group Birmingham 28th November 2018.

Lifestyle Lessons

Michelle Harvie

Eisai First Thoughts Meeting Royal College of Physicians, London February 28th 2018.

Breast Stem cells: a research or a philosophical question?

Rob Clarke

Basel Breast Centre Meeting, April 10th, Basel, Switzerland.

Comparative biology of normal and high risk normal breast tissue

Rob Clarke

3rd Annual ENBDC Think Tank, 13th December, University of Bilbao, Spain.

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