University Hospital of South Manchester
NHS Foundation Trust

Genesis Breast Cancer Prevention Centre

Research Overview

March 2014

genesis
preventing breast cancer

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Contents

Foreword

Welcome to this year's annual Research Overview from the Genesis Breast Cancer Prevention Centre in Manchester. We are proud to be at the forefront of research into breast cancer prediction, prevention, screening and early diagnosis strategies as we work with others around the globe to remove the threat of this disease.

The purpose of this Research Overview is to tell you what progress has been made during 2013 as step by step we move forward towards achieving our goal of preventing breast cancer for the next generation. Our Principal Investigators and research team are well known around the world in their fields, and much of the work which we do is collaborative in nature working with other centres and with other charities all acknowledged within these pages.

A particular strength of our work here in the Prevention Centre is that we are working with thousands of women volunteers with a direct interest in the outcome, and as a result improved clinical outcomes are always at the top of our priorities.

We are hosts to the largest Family History Clinic in the UK and are working alongside a large NHS Screening Centre with government funding to improve patient outcomes from the NHS screening programme. The majority of our work however relies on funding from

the charity Genesis Breast Cancer Prevention and its dedicated team of supporters, volunteers and community fundraising groups without whom this research would simply not happen. I hope you find these pages interesting, and thank you for your support!

Lester Barr
Chairman of Genesis Breast Cancer Prevention

This year's Overview is dedicated to Geoff Swarbrick, our Honorary Treasurer and good friend, who died in 2013 and is greatly missed.

Overview of 2013

By Professor Tony Howell, Research Director


Professor Tony Howell

This has been another good year for research within the Genesis Centre. It has also been a good year for awareness of risk, screening and prevention in general , as the new NICE Clinical Guidelines for Familial Breast Cancer were published in June.

Gareth Evans was the Clinical Lead on the guideline group and thus Genesis was well represented[1]. The Guidelines gave us an important update for management of women in the Family History Clinic, and the main points are shown in Table 1, right. Gareth Evans produced a very useful brief summary which was published in the BMJ[2].

During 2013 most of the Genesis Principal Investigators took part in an extensive overview of the areas where we still need to make progress with respect to breast cancer prevention and treatment called the 'Gap Analysis' organised by our sister organisation, Breast Cancer Campaign[3 4].

This followed a similar Gap Analysis in 2007. We were able to highlight the advances made since that time and also the considerable way to go in our aims to eliminate the modern scourge of breast cancer. The main gaps for risk, screening and prevention are shown in Table 2, right. Genesis has programmes in most of these areas which are incorporated into its recent five year plan Presented to the Board of Trustees in 2013.

Our research at Genesis and with our collaborators focuses on risk prediction (Gareth Evans), screening (Sue Astley and Tony Maxwell), preventive therapy (Tony Howell), lifestyle change (Michelle Harvie),

Table 1

Main NICE Guidelines for the management of familial breast cancer

- Offer patients individually tailored information, including information about sources of support.
- Refer to specialist clinic if >/=17% lifetime risk of breast cancer
- Offer genetic testing in affected person if probability of carrying a BRCA1/2 gene is 10% or more or 20% or more if the family member is unaffected
- All women with >/=17% lifetime risk to be offered annual mammographic screening from age 40-49 and if >30% probability of being a BRCA1/2 gene carrier until 59.
- Offer MRI and mammographic screening annually from 30-49 for gene carriers and >30% chance of having a a BRCA1/2 mutation. Annual mammographic screening should continue until age 69 for carriers.
- Offer tamoxifen or raloxifene for women at >1 in 3 lifetime (high) risk and consider both if >1 in 6 (moderate) lifetime risk.
- Discuss risks and benefits of risk reducing breast and/or ovarian surgery to women at high risk.

Evans DG et al. BMJ 2013

Table 2

'Gap analysis': major gaps identified with respect to risk prediction screening and prevention as key indicators for future research.

Risk
Identify exact causes of breast cancer
Discover remaining genes which indicate risk
Research the influence of epigenetics on risk
Better predictors of risk based on all risk factors

Screening
New more cost effective diagnostic methods eg tomosynthesis
NHS Screeening interval based on risk

Prevention
Offer all women at risk tamoxifen or raloxifene
Introduce aromatase inhibitors
Predict non-responders
Introduce new agents especially for ER-ve tumours
Offer all women at risk lifestyle change

Eccles SA et al. Breast Cancer Research 2013, 15:R92

Figure 1

Prominent findings at the Genesis Centre and with our collaborators in 2013

NICE
Guidelines tamoxifen & raloxifene

BRCA1/2 PENETRANCE
'predictable'

Genesis Risk Predictor
'probably the best'

SNP
Predicts Mammographic density

FHO1 study
Final report Screening from age 40-49 Improves survival

IBIS-II TRIAL
Anastrozole highly effective for prevention

TAM/Prev
Study indicates uptake of tamoxifen

Risk Reducing Surgery
Improves survival

Laboratory Studies
New insights for prevention

2 Day Diet
published February 2013

Tops best seller list

Over 250,000 copies sold worldwide

Two new books published 2013/2014

surgical prevention (Lester Barr) and laboratory studies (Tony Howell, Nigel Bundred and Cliona Kirwan). As last year we have highlighted a 'top ten' of the advances in relation to the Centre for 2013 (*Figure 1, above*). With colleagues in Cambridge we are moving towards being able not only to predict whether a woman with a BRCA1/2 mutation will develop breast cancer (penetrance), but also, if she has the misfortune to develop breast cancer, when in her lifetime the tumour will develop[5,6]. Clearly, when confirmed by further studies, this knowledge will be very important for the management of these women with respect to screening and risk-reducing surgery and will result in a new level of refined management which will help women with difficult treatment decisions.

The records of the women under follow-up in the FHC are of vital importance to our research. This year Gareth Evans with Sarah Ingham demonstrated, in over 8,000 women from the FHC, that the Genesis 'Manual method' of risk prediction is probably one of the most accurate available[7,8]. These women are also part of the, so called, 'FH Risk Study' designed to assess if the addition of mammographic density and estimation of over 70 single nucleotide polymorphisms (SNPs) will improve prediction of breast cancer risk.

This approach is also the basis of the PROCAS study (Predicting of Risk of Cancer at Screening) which has now recruited nearly 53,000 women. Both FH Risk and PROCAS will be analysed this year and the results will appear in next years' Annual Report. We hope that we will be able to move towards the level of risk prediction which is becoming established for BRCA1/2 carriers. We are absolutely indebted to the exceptional management by Paula Stavrinos and her excellent team on these projects.

Our screening programme includes the estimation of mammographic density since we know that the more 'dense'

the breast, the greater the breast cancer risk. Our expert radiologists, led by Mary Wilson and with an able band of radiographers, have performed the herculean task of estimating density visually in over 60,000 women in the PROCAS and FHRisk studies.

Sue Astley and her colleagues have now established a methodology to deal with the variations which occur between readers which will be used in the PROCAS and FHRisk analyses[20,21]. Several trials of screening are in progress (eg FH02, Tomosynthesis) but this year we have the final report of FH01 trial which was a multicentre study of screening of women at increased risk, age 40-49 (the Genesis Centre was the largest single centre recruiter to the study)[25]. The study predicts that screening of this group of women by mammography may reduce mortality by as much as 40% and reinforces the policy of the Genesis Centre where we have been screening women between these ages for many years.

This has been a good year for preventive therapy research. The IBIS-II trial of anastrozole versus placebo was presented at The San Antonio Breast Cancer Symposium and simultaneously published in the Lancet in December. It indicated a reduction of 50% in the risk of breast cancer with five years treatment[30].

Tony Howell is a Principal Investigator of the study and, with Gareth Evans, recruited the Manchester patients which were excellently managed during the five years of treatment by Research Sisters Rosemary Greenhalgh and Jenny Affen.

We have also completed recruitment to our study of tamoxifen uptake in premenopausal women managed by the 'team' but especially Research Nurse Julia Wiseman. Louise Donnelly performed in-depth interviews to assess reasons for taking or not taking tamoxifen. The two major reasons were the thought of side effects and experience of tamoxifen in the family.

It has also been a good year for our lifestyle studies. Over the year, three books for the general public on the 2 Day Diet have been published by Michelle Harvie and Tony Howell with all proceeds going to the Genesis Charity.[32-34] The books are based on the results of a randomised trial of the 2 Day Diet versus a standard diet performed by Michelle Harvie and her team[31].

These studies are not easy and it is a great tribute to the whole team on the remarkable result which indicates that intermittent energy restriction is superior to continuous restriction. The value of the intermittent approach has been widely publicised with great public uptake and we hope there will be benefits not only for women at risk of breast cancer but for public health in general.

Risk-reducing breast surgery was introduced into the FHC/Genesis Centre in the mid 1990's. We now have sufficient long term follow up to determine the effects of surgery on overall mortality and our papers published during the year indicate that mortality is reduced by surgery.

The continuing success of the programme is in no small measure due to the excellence of our surgeons and breast care nurses over the years and their efforts to continue to improve surgical practice and patient management.

New drugs to prevent breast cancer will come from the laboratory in Manchester. We are fortunate to have the Manchester Breast Centre led by Gareth Evans and consisting of seventeen principal investigators with major interests in the breast and breast cancer. Results from our associated laboratory colleagues have helped understand the mechanisms of risk produced by mammographic density, alcohol and smoking[23,49,50].

We are particularly interested in the stem cell and its interaction with the breast stroma as potential targets for anti-cancer therapy and also for prevention and it is from these studies that new preventive agents will arise[44-47].

Finally we are absolutely indebted to Lester Barr (Chairman of Genesis), the Board members and their administrative team for providing a bedrock of funding and support for the FHC and the

The Family History Clinic

The Family History Clinic (FHC) within the Genesis Breast Cancer Prevention Centre provides an NHS referral service for the management of women at increased risk of breast cancer

Most referrals come from Greater Manchester GPs and breast surgeons. The services offered are risk estimation and counselling, mammographic screening, preventive therapy, lifestyle change and risk-reducing surgery.

There are two clinics per week (ably organised by Jayne Beasley and her colleagues), monthly Multidisciplinary Team meetings and three times a year clinics for women who have had risk-reducing surgery. Most women are seen annually by Sisters Rosemary Greenhalgh and Jenny Affen to check their breast health and to refer for mammography.

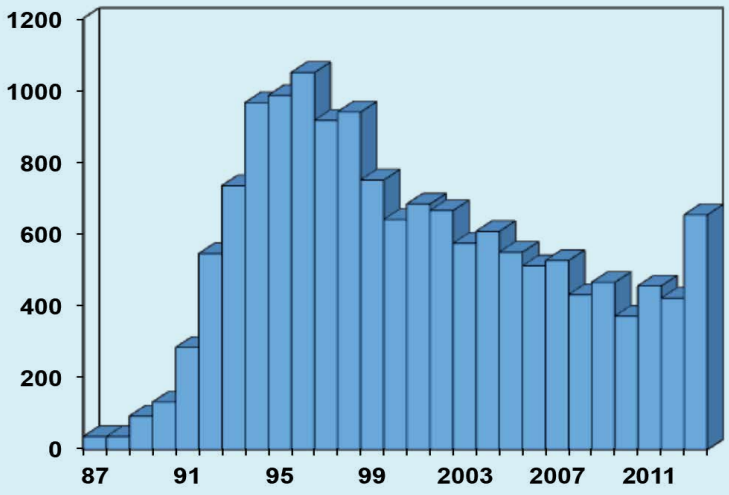
The FHC was set up in 1987. We have seen over 10,000 referrals to the NHS service and large numbers of these women have volunteered to help with our research, particularly entering trials of the value of screening, preventive agents and lifestyle, many of which are outlined below. We would like to especially thank all the women who give up their time to help in this way

After setting up the clinic in 1987, there were large numbers of referrals in the 1990's which we assume was a result of filling an unmet need amongst women at increased risk (*Figure 2, above*). There is a marked rise in referrals this year after the publicity surrounding Angelina Jolie who carries a mutation in the BRCA1 gene and had risk-reducing breast surgery. At Genesis we were given the great opportunity to comment on BBC Breakfast Television and also on BBC Newsnight on the day the story broke and helped put risk-reducing surgery into perspective especially indicating the alternatives to risk-reducing surgery.

The new NICE guidelines are important for our management. These have been particularly helpful especially that they now recommend to the preventive agents, tamoxifen and raloxifene, may be offered to women at high risk and considered by women at moderate risk of breast cancer. (*A summary of the guidelines is shown in Table 1 on page 4.*)[1]

Figure 2

Referral pattern to the Genesis Family History Clinic



The high level of referrals in the 1990s is probably related to an unmet need at that time. The rise in 2013 is almost certainly related to the highly publicised decision of Angelina Jolie (She carries a BRCA1 mutation) to have risk reducing breast surgery and indicates the influence that public figures can have on referral patterns in the NHS

Risk Prediction for BRCA1 and BRCA2 carriers

The discovery of mutations in the BRCA1 and BRCA2 genes in the 1990's revolutionised our management of women with a family history of breast cancer

BRAC1/2 is the paradigm for risk prediction and the stimulus for our PROCAS study where we hope to be able to predict the breast cancer risk in non-carriers with similar accuracy.

More new insights into BRCA1/2 biology and prediction have been discovered during 2013 by ourselves and in collaborations with colleagues around the world.

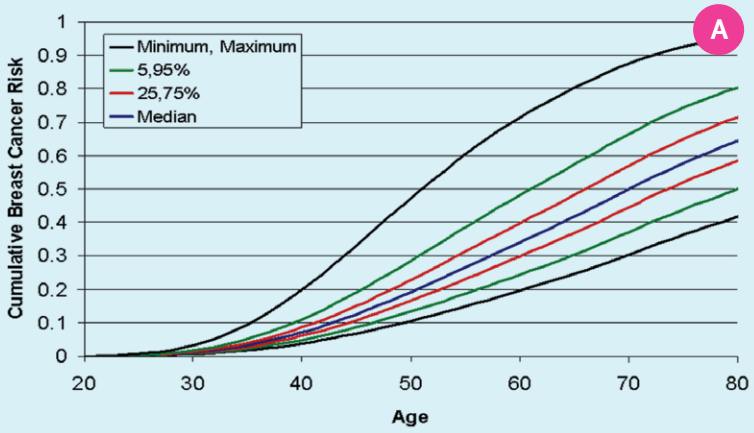
Collaborations are helped by the numbers of women identified with BRCA1 and BRCA2 in the Northwest, the largest series in this country (415 BRCA1 and 378 BRCA2 families). We reported that life expectancy of women with BRCA1 and BRCA2 mutations in our series was 62 and 68 years respectively[5].

There is evidence from modelling studies that these figures are likely to increase considerably on further follow up because of the judicious use of breast and ovarian surgery and more intensive screening, particularly using MRI combined with mammography

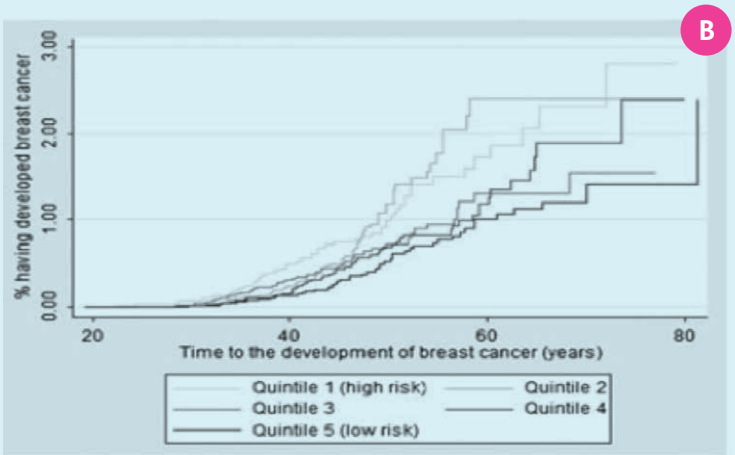
It is important to have accurate figures for the chance of developing breast cancer, ovarian cancer and contralateral breast cancer in order to counsel women with mutations wisely. Figures for these parameters were published by our collaborative group (EMBRACE[6]).

Figure 3

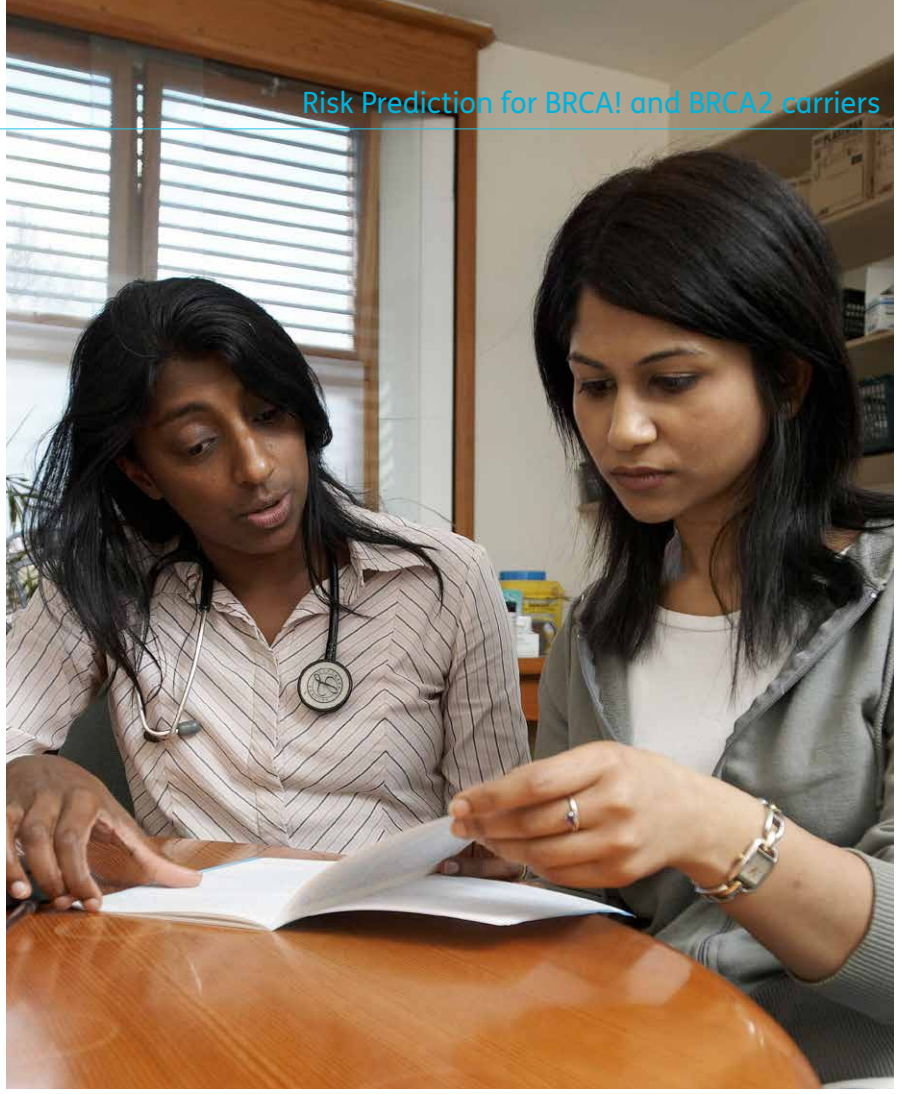
Prediction of the outcome of women with BRCA2 mutations using breast cancer associated single nucleotide polymorphisms



Risk of developing breast cancer varies according to the SNP pattern (6 & Antonis A et al Cancer Res 70:9742, 2010).



In women who develop BRCA2 related breast cancer the SNP pattern also gives an indication of the time of onset of the cancer[8].



The average cumulative risks by age 70 years for BRCA1 carriers were estimated to be 60% for breast cancer, 59% for ovarian cancer, and 83% for contralateral breast cancer. For BRCA2 carriers, the corresponding risks were 55% for breast cancer, 16.5% for ovarian cancer, and 62% for contralateral breast cancer.

We contributed the greatest number of carriers to the nationally organised EMBRACE study but even so our penetrance figures are higher for BRCA2 than the overall group (57.7% for BRCA1 and 72.3% for BRCA2 by age 70 years) possibly related to our longer follow up[6].

Importantly from the point of individual genetic counselling it was possible in BRCA2 to show carriers in the highest tertile of risk, defined by the joint genotype distribution of seven single nucleotide polymorphisms associated with breast cancer risk, were at about 70% chance of developing a tumour compared with 20% chance in the bottom tertile (see *Figure 3, on previous page, 8*)[6].

In another collaborative study it was shown that similar separations could be made for women with BRCA1 mutations. Also we demonstrated that SNPs could predict the timing of onset of tumours in BRCA1 carriers. These data, when confirmed, are highly important for the management of mutation carriers and the need for and timing of risk-reducing surgery[7,8].

Rather surprisingly, we demonstrated in BRCA2 families that women who test negative for the gene still have a moderately increased risk of breast cancer, particularly where there are a large number with cancers in the family. We demonstrated that the increased risk was associated with a greater number of higher risk polymorphisms (SNPs) shown to be associated with breast cancer. Our work can help with counselling women from BRCA2 families who have tested negative, and impacts on how individual breast cancer risk is related back to these women[9,10].

Women who have a strong family history and are going for BRCA1 and BRCA2 testing are often young and the decision to be tested can be mixed with decisions concerning childbirth and passing on the gene mutation to their children[11].

Since this area is underexplored, Louise Donnelly performed semi-structured interviews with 25 women aged 18-45 who had received a positive result for a BRCA1 or BRCA2 gene mutation while childless.

This study explored the views of female BRCA carriers and indicated that further research should explore the views of couples, and include samples with greater ethnic and social diversity. The study highlighted the need for reproductive decision-making to be addressed at the time of pre-test genetic counselling[11].

Other observations in BRCA1/2 carriers are reported in references [12-17].

(*For all references, see pages 24-27*).

Risk prediction in the Family History Clinic and NHS Breast Screening Programme

It would transform our approach to the elimination of breast cancer if we could predict risk in the general population of women as accurately as we do for BRCA1 and BRCA2 gene carriers

Those at high risk would need intensive surveillance whereas surveillance may be limited or omitted altogether for those at very low or no risk.

In 2002 we compared various current risk prediction models (eg Gail, Claus, Tyrer-Cuzick, Manual) used to estimate lifetime risk of breast cancer in the Family History Clinic (Amir E et al 2003).

The best predictor was the so called "Manual Model' which we used in the FHC closely followed by the (now widely used) Tyrer-Cuzick model devised by Jack Cuzick, one of the Genesis Centre International Advisory Board (*Table 3, right*).

The Manual Model depends on the Claus Tables for familial risk modified to include the 'so called' hormonal risk factors such as age of menarche and age of first pregnancy.

The numbers of cancers in our original study was only 52 in 1933 women with a mean follow up of 5.27 years. We have now updated this study to 8,824 women attending the family history evaluation and screening programme at the Genesis Prevention Centre.

Their mean follow up was 9.7 years: 406 incident breast cancers occurred, and 385.1 were predicted (E/0 = 0.96, 95% CI 0.86-1.06) using the Manual Model.

Table 3

	Observed (O)	Expected (E)	E/O	95% CI
Gail	64	44.3	0.69	0.54 to 0.90
Claus	64	48.5	0.76	0.59 to 0.99
BRCAPRO	64	42.3	0.66	0.52 to 0.86
Tyrer-Cuzick	64	69.6	1.09	0.85 to 1.41
Manual (3150) (2003)	64	77.9	1.22	0.95 to 1.58
Manual (8824) (2013)	406	385.1	94.9	0.84 to 1.06

It is important to predict risk of breast cancer as accurately as possible. Here we summarise an early paper which indicates that the Tyrer-Cizick and Manual Models we use predict more accurately than others (Amir E et al J Med Genet 40:807, 2003). A more recent study in the FHC in larger numbers of women and more cancers also indicates very good prediction of risk using the "Genesis' Manual Model[7]

Predictions were close to that of observed cancers in all risk categories and in all age groups, including women in their forties. We conclude that the Manual Model for risk prediction with use of adjusted Claus tables and curves with modest adjustment for hormonal and reproductive factors was a well-calibrated approach to breast cancer risk estimation in a UK family history clinic[18].

The problem remains that using the Manual and Tyrer-Cuzick models we can give a high risk woman an accurate risk of, say, 1 in 3 lifetime risk of developing breast cancer.

This is accurate but we cannot tell her whether she is the one who will develop breast cancer or one of the two who will not. This dilemma underlies the need to explore additional risk factors to attempt to improve prediction.

This is the basis of an NIHR programme where we are assessing whether the addition of mammographic density and single nucleotide polymorphism

measurement to the standard models will improve prediction in the FHC (FHRisk) and in the National Breast Screening Programme (Predicting the Risk Of Cancer At Screening - PROCAS). The analyses from these programmes will be performed this year (2014).

The analyses depend upon the numbers of cancers which have occurred during follow up. Over 400 cancers have occurred in women in FH-Risk and over 600 in PROCAS, which is sufficient for analysis.

We know that BRCA1/2 carriers have an increased risk of ovarian cancer and we asked the question whether there is increased risk in women with a family history of breast cancer but who are BRCA1/2 mutation test negative[19].

This study, on a large number of women (8003) in or previously seen in our clinic, indicates the importance of the continuity and records of the Genesis FHC and is a tribute to the clinic and research staff.

We determined whether any women had developed ovarian cancer during the period of follow up. Importantly there was no significant increase in the incidence of ovarian cancer in the women at risk.

Thus risk of ovarian cancer is confined to the small population of at risk women who also have mutations in the BRCA1 or BRCA2 genes[19].

Predicting the Risk of Cancer at Screening (PROCAS)

The PROCAS study, led by Professor Gareth Evans, aims to determine whether it is feasible to accurately predict each woman's personal breast cancer risk when they attend routine breast screening

All women aged between 47 and 73 who attend for routine breast screening mammograms as part of the NHS Breast Screening Programme in Greater Manchester are invited over a three year recruitment period to join the study.

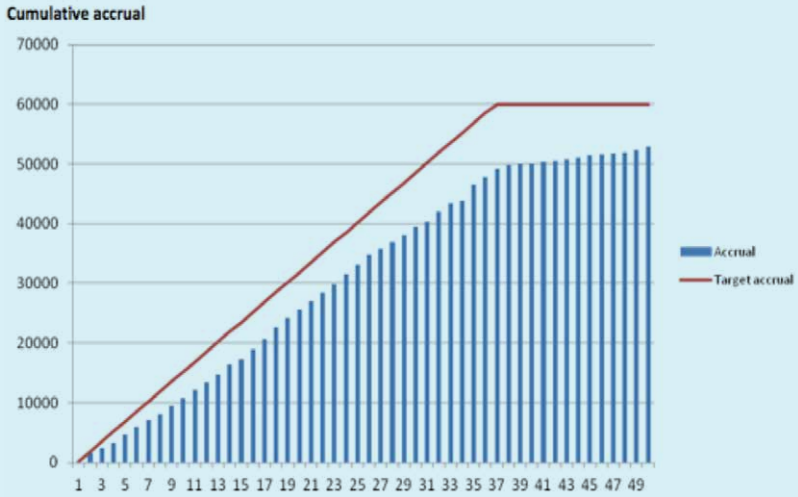
The study is run from The Genesis Prevention Centre by Paula Stavrinos and her team. Data are being collected on the following breast cancer risk factors: mammographic breast density (the amount of dense tissue in the breast), lifestyle factors, reproductive factors and family history.

Together these factors are used to give an overall risk score for each woman. In addition, 10,000 women have been being invited to provide a saliva DNA sample which will undergo genetic testing for over 70 single nucleotide polymorphisms [SNPs] associated with breast cancer risk.

PROCAS is the first study to investigate the use of these genetic tests on women who undergo routine screening. All women are given the choice of finding out their personal risk of breast cancer and so far 95% of women participating in the study have indicated a desire to know their risk at time of consent to the study.

Figure 4

Recruitment figures for PROCAS



After three years' recruitment we only accepted women on the programme who were having their first ever mammogram

Any women who have chosen to know their risk and are high-risk are offered a consultation with Tony Howell or Gareth Evans. Women are given advice on ways of reducing their risk and, if appropriate, may be offered more frequent screening and preventive measures.

To date 443 high risk women have been seen, and 158 have been referred for more frequent screening (18-monthly screening, as opposed to three-yearly).

Of these women, three have had breast cancer detected on their extra mammogram. This means that for these three women, their cancer was detected potentially up to 18 months sooner than it would have been had they not joined the PROCAS study.

If the PROCAS study can demonstrate that it is feasible to accurately predict and feedback breast cancer risk to women attending routine breast screening, then this process of personalised risk prediction could be incorporated into the NHS screening process. In the longer term there may also

be the potential for women's mammographic screening interval to be altered based on personal breast cancer risk (i.e. women at increased risk receiving more frequent screening).

As a result of PROCAS, the University Hospital of South Manchester now has the largest number of participants recruited into a research study in the UK.

To date (November 2013), nearly 53,000 women have agreed to take part in PROCAS (*Figure 4, previous page, 12*) and about 10,000 saliva samples have been collected.

It is a great credit to the PROCAS team and the participants who gave up their weekends when these samples were collected.

Genesis has funded SNP research, which is being carried out within the PROCAS study. For the last 5-10 years the family history population has been the focus of prediction studies; however as the PROCAS study is being run within the national breast screening programme, we are now including women from the general population in our prediction research.

The study is funded by the National Institute for Health Research, with additional support from Genesis for special data capture software, the DNA kits to test women's saliva samples and the extraction of DNA from the samples.

Mammographic Density

We have published three studies this year concerning the highly important topic of mammographic density: the assessment of inter-observer variability in density assessment, the association of SNPs with density, and an evaluation of potentially why density is associated with risk of breast cancer

Mammographic density is the radio-dense 'white' part of the x-ray mammogram which represents the glandular and fibrous parts of the breast. The remainder is fat and appears darker. Others have shown that women with very dense breasts have up to five times the risk of breast cancer compared with those with predominantly fatty mammograms. A major part of the PROCAS and FHRisk projects is to ask whether mammographic density can be incorporated into standard risk models.

We are comparing automatic methods for volume density assessment with visual methods in these studies. Our long-suffering radiologists and radiographers (please see acknowledgements inside the back cover) have double read density as a continuous visual analogue assessment in over 60,000 mammograms. Inevitably there will be discrepancies between readers and so we have published a method of correcting for observer bias[20, 21].

Existing literature on inter-observer reliability focuses on quantifying the disagreement between observers. In this paper, we introduce a method to correct for inter-observer disagreement (or observer bias), where observers are assigning scores on a continuous scale. To do this, we propose a two-stage approach. In the first stage, we standardise the distributions of observer scores to account for each observer's subjective interpretation of the continuous scale. In the second stage, we correct for case-mix differences between observers by exploiting pairwise information where two observers have read the same entity on a case. We illustrate the use of our procedure on clinicians' visual assessments of breast density (a risk factor for breast cancer). After applying our procedure, 229 out of 1398 women who were originally classified as high density were re-classified as non-high density, and 382 out of 12,348 women were re-classified from non-high to high density[20, 21].

Mammographic density has a 60% genetic component, much of which remains unidentified. Genome-wide association studies have identified a number of breast cancer susceptibility loci. We investigated whether mammographic density estimated in 3489 women in the PROCAS study is associated with 17 known breast cancer susceptibility loci. Significant association was identified between the minor allele of an intronic variant in ZNF365 (rs10995190) and mammographic density in the whole PROCAS population (n=3469, p=8.59x10-5), and in post-menopausal women (n=2555, p=4.26x10-5), but not in pre-menopausal women (n=914, p=0.51). This SNP has been identified by others. We need to find other SNPs so that potentially we may be able to replace density by SNPs in our risk algorithms in the future[22].

The biological processes underlying the associations between risk of breast cancer and mammographic density remain largely unknown. We re-interrogated genome-wide transcriptional profiling data obtained from low-density (LD) mammary fibroblasts (N=6 patients) and high-density (HD) mammary fibroblasts (N=7 patients), derived from a series of thirteen female patients. We focused on the genes that were increased by >1.5-fold ($p < 0.05$) and performed gene-set enrichment analysis (GSEA), using the Molecular Signatures Database (MSigDB). Our results indicate that HD fibroblasts show up-regulation and/or hyper-activation of several key cellular processes, including the stress response, inflammation, stem-ness and signal transduction. The transcriptional profiles of HD fibroblasts also showed striking similarities to human tumor fibroblasts including breast cancer. Thus, this unbiased informatics analysis of high breast density provides a novel framework for additional experimental exploration and new hypothesis-driven breast cancer research, with a focus on cancer prevention and personalized medicine[23].

Screening

One of our Principal Investigators Cliona Kirwan has published a useful clinical commentary in the BMJ during this last year, discussing the problem of potential overdiagnosis within the NHS screening programme.

Her paper helps to quantify its effects and minimise its impact on patient care[24] .

Although there have been encouraging recent studies showing a the benefit from annual mammography in women aged 40-49 years of age who have an elevated breast cancer risk due to family history[25], there are few data concerning efficacy in women aged <40 years of age (Duffy).

A prospective study (FH02) has been developed and lead from the Genesis Centre to assess the efficacy of mammography screening in women aged 35-39 years of age with a lifetime breast cancer risk of ≥17 % who are not receiving MRI screening. Retrospective analyses from five centres with robust recall systems identified 47 breast cancers (12 of which were in situ) with an interval cancer rate of 15/47 (32%).

Invasive tumour size, lymph node status and current vital status were all significantly better than in two control groups of unscreened women (including those with a family history) recruited to the POSH study. Further evaluation of the prospective arm of FH02 is required to assess the potential added value of digital mammography and the cancer incidence rates in moderate and high risk women in order to inform cost effectiveness analyses. These figures are the

basis for the FHO2 trial led by Gareth Evans. To date 2820 women have entered the study (825 from Manchester) and we expect to get a result by 2016[26].

Tony Maxwell and others investigated the effect of false positive breast screening examination results on subsequent attendance in the UK National Health Service Breast Screening Programme. 253,017 previously screened women who were invited for rescreening were studied. Attendance rates of women who had received a normal result at the last (index) screen were compared with those of women who had received a false positive result.

The findings suggest that most women who undergo the breast screening assessment process retain confidence in breast screening. Needle sampling and open biopsy should be used judiciously in the assessment of screen-detected abnormalities in view of the reduced re-attendance that results from their use after incident screening examinations[27].

Gareth Evans was involved in studies to assess the value screening for ovarian cancer (OC) by annual transvaginal ultrasonography and serum CA125. A recent publication of these studies indicates the difficulties of population ovarian screening[28].

Preventative therapy

It has been an important year for chemoprevention – or the better term of 'Preventive Therapy'

We produced a commentary[29] on the Lancet paper which reported an overview of all trials published on tamoxifen and raloxifene and other, so called, Selective Oestrogen Receptor Modulators (SERMS).

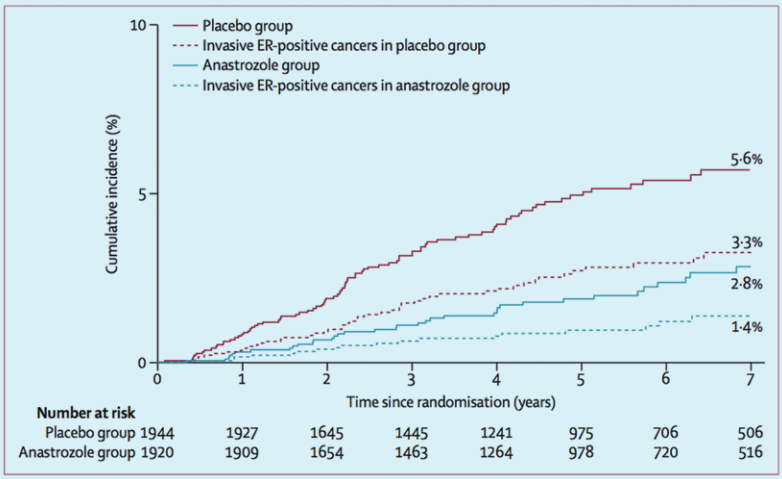
It was demonstrated that this type of drug reduced the risk of breast cancer by approximately 40% if given for five years or more. These results were reflected in the recommendations from the NICE overview of management in Family History and Genetics Clinics that tamoxifen may be prescribed for prevention in pre and postmenopausal women and tamoxifen or raloxifene for postmenopausal women.

More recently we published the results of the IBIS-II trial of the aromatase inhibitor, anastrozole, in the Lancet[30]. We assessed the efficacy of anastrozole in postmenopausal women who do not have breast cancer, but are at high risk of developing the disease. IBIS II is an international randomised placebo-controlled trial of 1mg/day oral anastrozole vs. matching placebo for five years which was conducted in 3864 postmenopausal women at increased risk of breast cancer.

The primary endpoint was the incidence of breast cancer (including ductal carcinoma in-situ (DCIS). 1920 women were randomly assigned to receive anastrozole and 1944 women to receive matching placebo. After a median follow up of 5·0 years, 125 breast cancers were recorded (40 anastrozole vs. 85 placebo). A 53% reduction (95% CI (32-68%), P<0·0001) was seen in the anastrozole arm (*Figure 5, above*).

Figure 5

Results of the IBIC-II trial of anastrozole versus placebo



There was a 50% reduction in invasive cancers (solid lines) and a greater reduction in ER+ve cancers (dotted lines). Note the left hand scale: about 30 women need to be treated to prevent one breast cancer.

Fractures were non-significantly higher (164 (8·5%) vs. 149 (7·7%), P=0·3) and musculoskeletal events were significantly higher in the anastrozole arm (1226 vs. 1124, RR=1·10 (1·05-1·16)) but were very common in both arms (63·9% vs. 57·8%).

Vasomotor symptoms were also increased with anastrozole (RR=1·15 (1·08-1·22)). Cancers at other sites were significantly decreased (40 vs. 70, RR=0·58 (0·39-0·85)). Thus anastrozole is an effective agent for reducing breast cancer incidence in postmenopausal women at high risk and may be superior to tamoxifen and raloxifene (*Figure 6, overleaf, page 17*)[30].

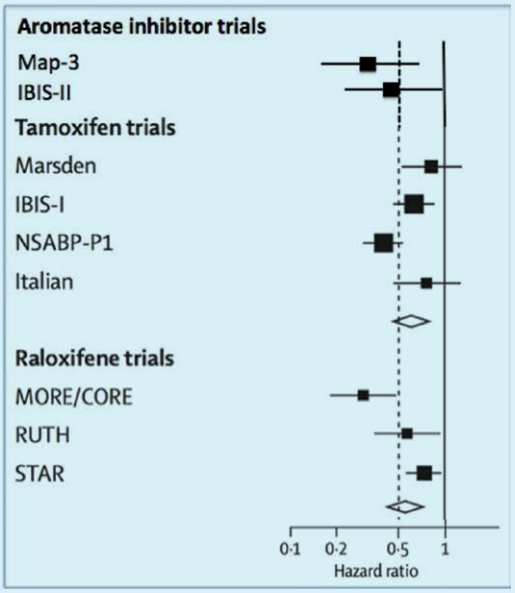
Anastrozole was generally well tolerated and side effects associated with oestrogen deprivation were only slightly higher than for placebo. It is now important to make anastrozole available within the NHS through the NICE process as additions to the already available tamoxifen and raloxifene.

Lifestyle prevention

The 2 Day Diet was developed after we demonstrated that weight gain in middle aged women resulted in an increase in the risk of breast cancer and that weight reduction reduced the risk (Harvie et al CEBP 2005;14(3):656-61)

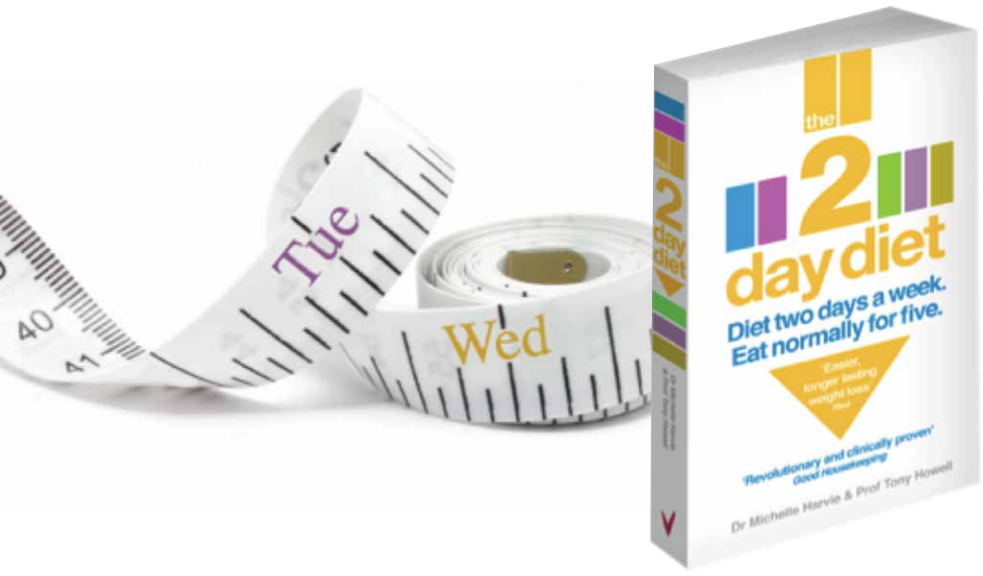
Figure 6

Results of all randomised trials of breast cancer prevention using aromatase inhibitors, tamoxifen and raloxifene.



Compared with the pooled results of the tamoxifen and raloxifene trials, the aromatase inhibitors appear more effective. All trials had a placebo control with the exception of the STAR trial which was a comparison of tamoxifen and raloxifene: raloxifen was 25% less active, in this study, than tamoxifen.

Cuzick et al, Lancet 2013



Since continuous dieting often has limited success Michelle Harvie devised the 2 Day Diet, based on previous animal experiments by others, with the underlying hypothesis that dieting for just two days per week would be easier and more effective than continuous dieting.

In a randomised trial comparing the two approaches, we demonstrated that this was the case: over a three month period 58% of women were able to stick to the 2 Day Diet whereas only 40% maintained a daily diet, a figure commonly seen on most daily diets[31].

On the 2 Day Diet energy was restricted by 50-70% over the 2 day period, mainly by reducing the intake of carbohydrate, but women were allowed as much protein and healthy mono and polyunsaturated fat as they wished. The control group were advised to have 25% restricted healthy Mediterranean diet.

The 2 Day dieters were advised they could eat unrestricted amounts of a healthy Mediterranean diet over the subsequent five days. Perhaps the most extraordinary finding was that during the 5 days of Mediterranean diet the 2 Day Dieters naturally reduced their calorie intake by an average of 23%. This markedly reduced intake for 2 days has a carry-over effect where women do not wish to eat as much for the rest of the week.

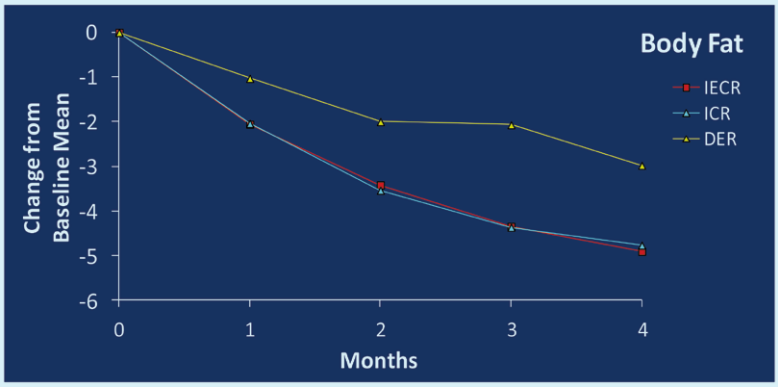
The 2 Day Diet resulted in the consumption of 700 fewer calories/week. This may be the reason why the 2 day dieters lost nearly twice as much fat over three months (3.7kg) compared with the continuous dieters (2.0kg). This was associated with a 14% greater reduction of insulin, which in turn, should reduce cancer risk.

The preliminary results of the randomised trial were published in the British Journal of Nutrition in October 2013[31]. However during the period in between we were asked to write a book on the Two Day Diet by the Ebury Press (now a part of the Penguin-Random House Group). Michelle Harvie (against her better judgement as it reduced our research output) did the lion's share of the writing. The first Two Day Diet Book was published in February 2013 and quickly rose to the top of the non-fiction best seller list and stayed in the top ten for 26 weeks[32].

This was followed by publication of the Two Day Diet Cookbook in April[33] and, in January 2014, The Two Day Diet 'Quick & Easy' edition was published[33,34]. These books have engendered a high degree of interest and we see this as a useful public health message.

In addition, Michelle has been asked to talk at conferences in the UK and also accepted a prestigious invitation to present at the American Society for Clinical Oncology (ASCO). Many questions remain, especially with the long term efficacy and safety of this approach, but the 2 Day Diet at least offers an alternative to the difficulties of trying to adhere to daily low calorie diets.

Figure 7



Significantly greater weight loss of body fat with the 2 day (intermittent) low energy/low carbohydrate diet (IECR) and the 2 day unrestricted ad lib diet (ICR) compared to the daily 25% energy restricted diet

(DER (P<0.01)[31]

Surgical prevention

Most risk-reducing surgery is performed on our patients with BRCA1 and BRCA2 mutations because of the high risk on breast and ovarian cancer

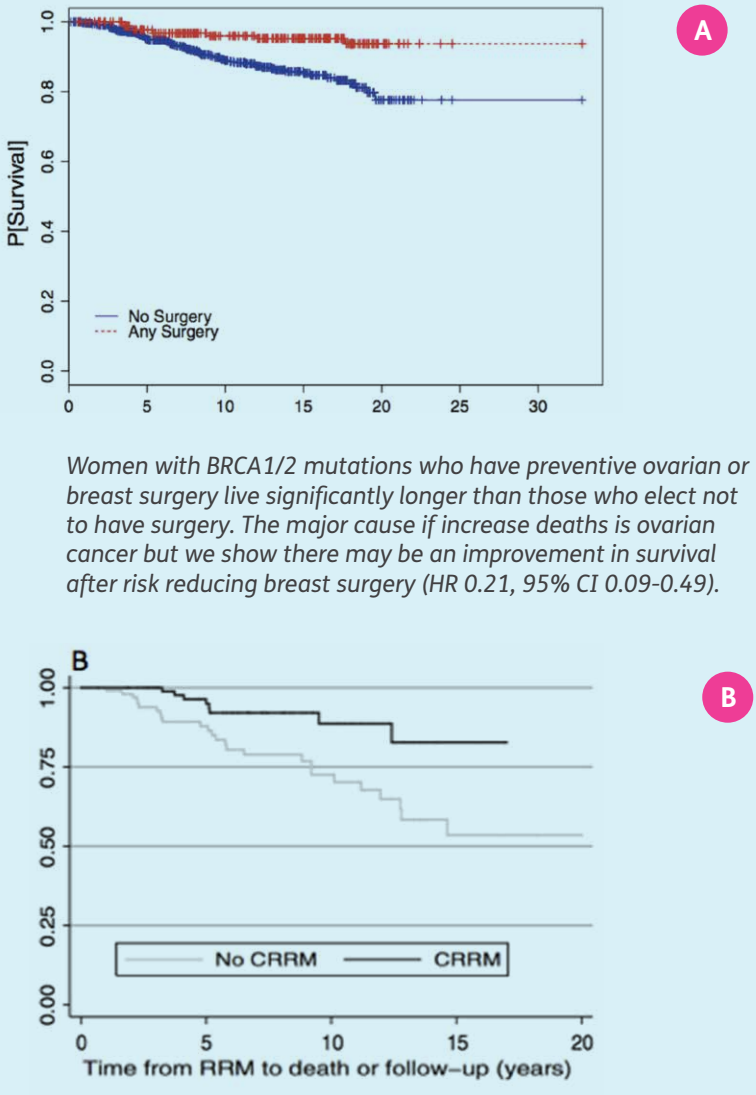
At Genesis approximately one half of women at very high risk elect to have risk-reducing breast surgery and the other half wish to rely on increased screening with a combination of MRI and mammography. Also women with mutations and breast cancer have a very high risk of developing a new breast cancer in the contralateral breast.

Both groups of women have a markedly reduced incidence of breast cancer after surgery but there are few data concerning the effect of surgery on overall survival. Our recent studies indicate that there is, indeed, a survival advantage to surgery in high risk women (*Figure 8, see right*)[36].

We studied 346 BRCA1 and 345 BRCA2 carriers without breast or ovarian cancer. 105 BRCA1 carriers and 122 BRCA2 carriers developed breast cancer during follow-up. The hazard of death was statistically significantly lower (P < 0.001) following risk-reducing surgery (RRS) compared with no surgery[36].

Women who had any form of RRS had increased survival compared to those who did not have RRS; a further increase in survival was seen among women who had both types of surgery. However, formal evidence for a survival advantage from bilateral mastectomy alone requires further research, particularly longer term follow up in our series[36]. We also studied the effect on survival in carriers with breast cancer who did (105) or did not elect (593) to have contralateral mastectomy. The 10-year overall survival was 89% in women electing to have a contralateral mastectomy compared to 71 % in the no surgery group (p < 0.001). The survival advantage remained after matching for oophorectomy, gene, grade and

Figure 8



Women with BRCA1/2 mutations who have preventive ovarian or breast surgery live significantly longer than those who elect not to have surgery. The major cause if increase deaths is ovarian cancer but we show there may be an improvement in survival after risk reducing breast surgery (HR 0.21, 95% CI 0.09-0.49).

Contralateral risk reducing mastectomy in women with BRCA1/2 associated breast cancer. Rather unexpectedly, surgery appears to improve overall survival (p=0.008)(References)

stage: HR 0.37 (0.17-0.80, p = 0.008). This finding needs confirmation in a larger series but if this is the case contralateral surgery should form part of the counselling procedure at diagnosis of the primary tumour [37,38].

Although risk-reducing mastectomy (RRM) has proven to be the most effective method to reduce the risk of breast cancer in high-risk women and may improve overall survival there is marked variation in the uptake of surgery internationally.

We were part of a questionnaire study performed to compare the attitudes towards RRM among physicians in France, Germany, the Netherlands and the United Kingdom (UK) amongst 1196 general practitioners (GPs) and 927 breast surgeons (BS) using a mailed questionnaire.

Only 30% of the French and 27% of the German GPs were of the opinion that RRM should be an option for an unaffected female BRCA1/2 mutation carrier, as compared to 85% and 92% of the GPs in the Netherlands and UK, respectively. Similarly, 78% of the French and 66% of the German BS reported a positive attitude towards RRM as compared to 100% and 97% of the BS in the Netherlands and UK, respectively.

These results demonstrated marked international variation in attitudes towards RRM among physicians and might reflect different national policies adopted to prevent breast cancer in women at risk [39,40].

Optimal surgical technique is vital for our patients who elect to have RRM. In our studies to improve technique we have demonstrated that there is not an increase in postoperative pain between women who elect for immediate compared with delayed reconstruction [41], evaluating the practical use of acellular dermal matrices [42] and their costs [43].

Laboratory studies

Members of the Genesis Centre (NJB, CC, DGRE, MH &AH) work closely with colleagues in the CRUK Manchester Institute and Breakthrough Unit on the Christie Hospital Campus, including Rob Clarke, Gillian Farnie, Michael Lisanti and Federica Sotgia

We are all principal investigators (n=17 in total) of the overarching Manchester Breast Centre led by Gareth Evans. Our collaborative experiments are designed to understand more clearly the causes of breast cancer and how we might develop agents to treat and prevent breast cancer.

We are particularly interested in inhibiting the stem cell which generates tumours and how the stem cell interacts with and is stimulated by the stroma (*which consists predominantly of fibroblasts, immune cells and adipocytes, Figure 9, right*).

In summary (*see Figure 10, below*) the major laboratory findings in 2013 are that:

1. The stromal derived inflammatory cytokine interleukin 8 stimulates the stem cell and can be inhibited agents such as repartaxin[44,45]

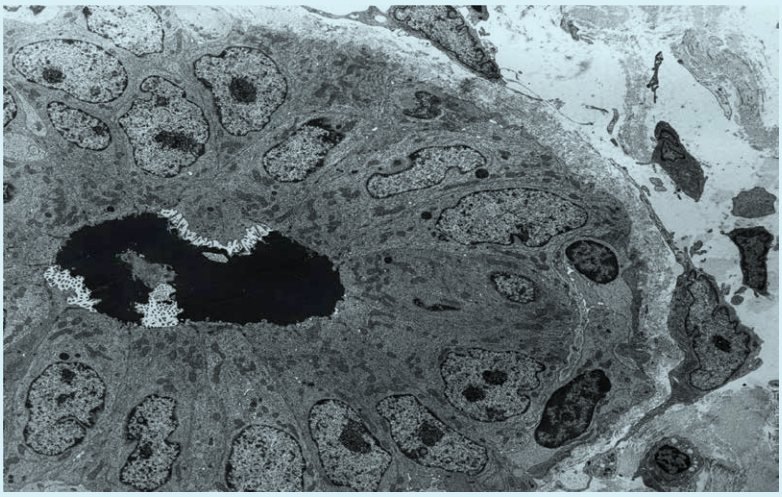
2. Alcohol and smoking may cause breast cancer by first affecting the stroma[49,50]

3. We have a greater understanding of the control of growth of in-situ carcinoma[46-48]

4. Inhibiting epithelial interactions with agents such as metformin and N-acetyl cysteine can block this interaction[51-53].

Further details of these exciting findings may be found in the individual papers published by the group. They indicate the strong future possibility of finding new agents to treat and prevent breast cancer.

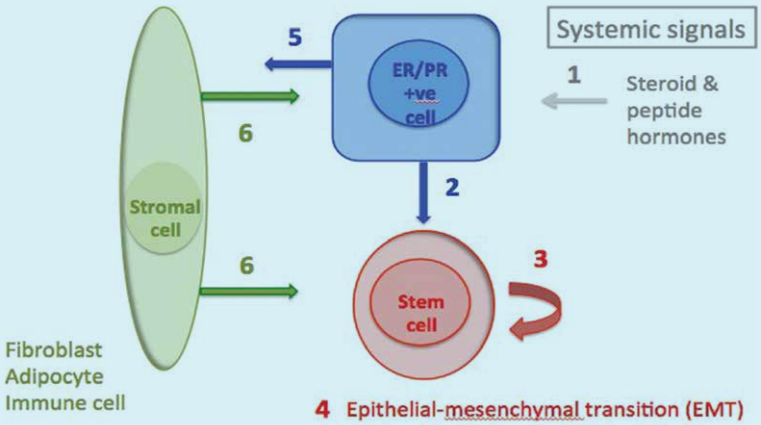
Figure 9



Contralateral risk reducing mastectomy in women with BRCA1/2 associated breast cancer. Rather unexpectedly, surgery appears to improve overall survival (p=0.008) (References)

Figure 10

Potential targets for breast cancer treatment and prevention



1. The oestrogen receptor is the major target as seen by the positive effects of targeting this receptor with anti-oestrogens and (indirectly) aromatase inhibitors. New approaches are being developed to target the progesterone receptor for prevention. 2. These agents inhibit the interaction between the ER+ve cell and the stem cell. Our studies indicate that Notch inhibotors block this interaction[46]. 3,4. Direct inhiboitos of the stem cell[3] and its change to a motile cell by an epithelial-mensenchymal transition. Tumour cells are known to activat the stroma[5] and, in turn the stormo stimultes tumourr cells[6]. We have shown that this interaction may be how alcohol causes breast cancer[48]. The interaction can be inhibited by drugs such reparaxin[45], metformin[50] and N-acetyl cysteine[52] which may be used ultimately to prevent breast cancer.

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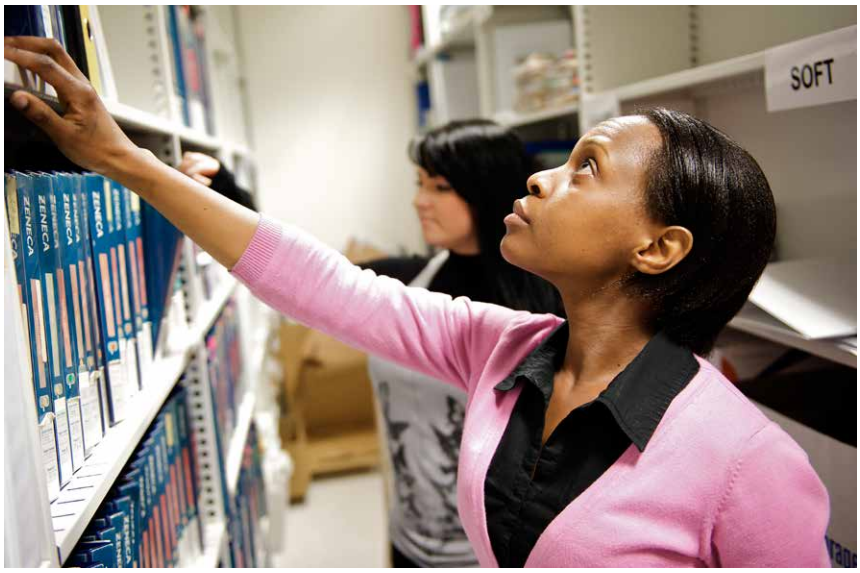

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Published March 2014

Produced by the Genesis Breast Cancer Prevention Appeal
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We are extremely grateful to all our supporters and fundraisers and to the charitable trusts that have contributed to particular projects within this overview.