

Genesis Breast Cancer Prevention Centre

Research Overview

February 2011



Foreword

The Genesis Breast Cancer Prevention Centre opened in July 2007. The building combines a prevention centre, a screening centre, and a national education centre, and its construction was made possible through a partnership between the Genesis Appeal and the University Hospital of South Manchester NHS Foundation Trust.

The Prevention Centre provides an NHS service for the care of women in the Northwest at increased risk of breast cancer and a major focus for research into prevention of the disease. The adjacent Nightingale Breast Centre offers a comprehensive diagnostic service, with a strong emphasis on supporting research and

education. Breast cancer is the most common cancer in women and its incidence is increasing worldwide as more countries become Westernised in lifestyle. Although the results of treatment of breast cancer are improving there is an urgent need to determine ways of preventing the disease. We believe that Thomas Adam, a 17th Century physician, was right when he said, 'Prevention is better than healing because it saves the labour of being sick'.

The major thrust of our prevention research is to focus on predicting women who will develop breast cancer more precisely, and then to target new preventative approaches we discover to this population. Our programme of research

is run from the Genesis Prevention Centre, but with strong collaborations with the adjacent Nightingale Centre, the Central Manchester and Christie Hospital NHS Trusts under the umbrella of the Manchester Academic Health Sciences Centre (MAHSC), and our national and international collaborators.

Our aim is to reduce the burden of breast cancer. This overview summarises our research published during 2010 towards fulfilling that goal. We also present outlines of studies completed this year, but still being analysed: we will give the full results of these next year when we report on our 2011 publications.



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Research Strategy of the Genesis Prevention Centre

- to predict women at risk accurately and to target them with appropriate screening and prevention measures in order to reduce the incidence of breast cancer.
- to evaluate models that predict breast cancer risk in order to adapt the NHS National Breast Screening Programme in a way that recognises those women that need increased screening.
- to identify biomarkers of high breast cancer risk and thus identify women who will benefit from preventative interventions.
- to develop preventive approaches which are easy to administer, are assessed by biomarker change and are cost effective.
- to assess biomarkers of effectiveness of the commonly used breast cancer drug tamoxifen in order to target its use more effectively.
- to investigate new lifestyle approaches for prevention of breast cancer and to develop biomarkers of their effectiveness in reducing risk of breast cancer.

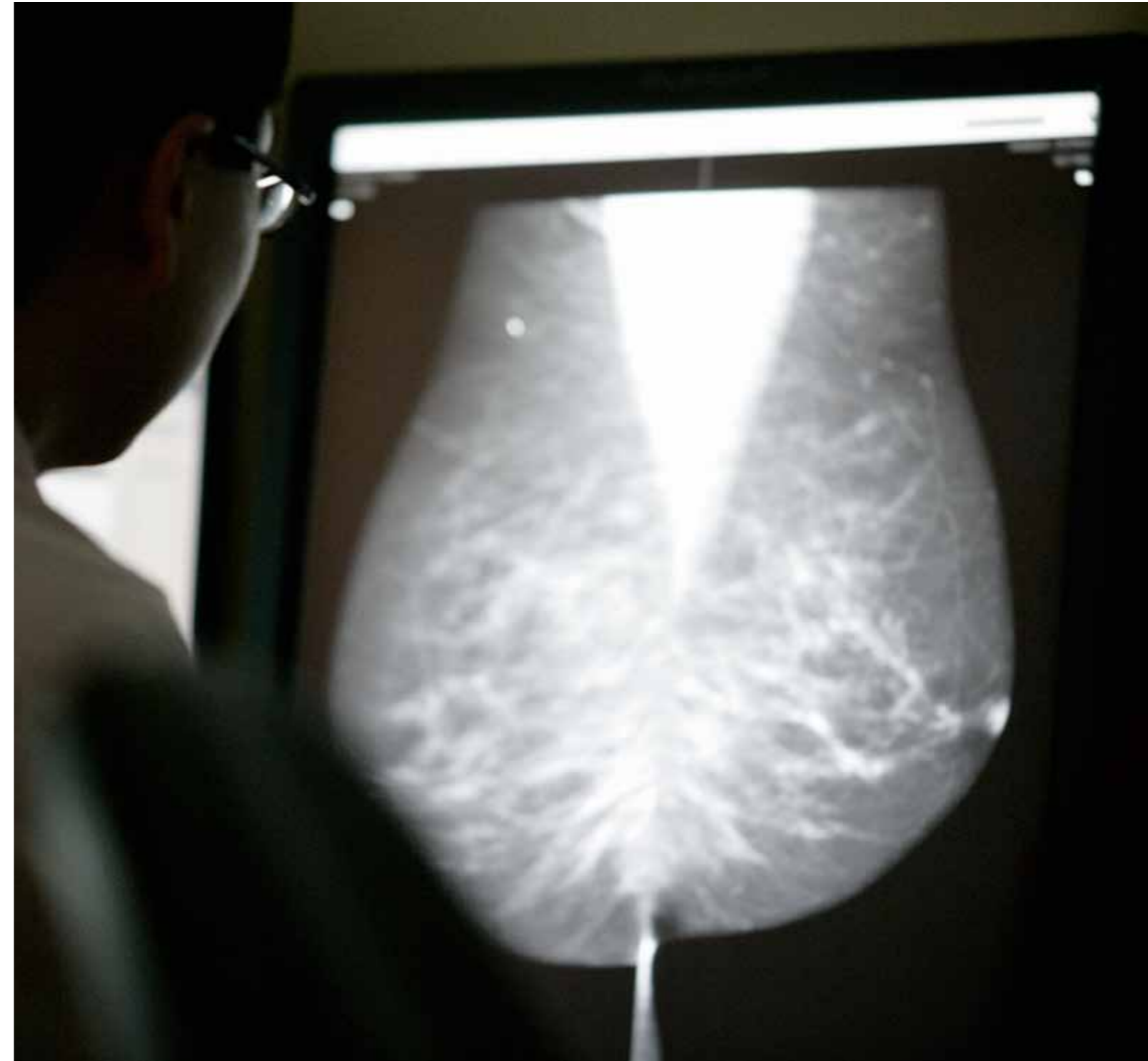


Progress during 2010

We have made some progress towards achieving our strategy during 2010.

Specifically we have:

- **Initiated a new multicentre mammographic screening trial** for women aged between 35 - 39 at high risk (FH02 Trial) in order to determine the effectiveness of early detection in this age group. As lead centre, we have already entered 542 women in Manchester to the trial.
- **Helped produce a consensus document** outlining international priorities on Preventive Therapy for Breast Cancer as a result of the 2010 St Gallen Cancer Prevention Conference.
- **Entered the first 16,000 (of 60,000) women into the Prediction Of Cancer At Screening (PROCAS) study** attending the NHS Breast Screening Programme in order to assess improvement of risk prediction by combining biomarkers of risk.
- **Set up a Genesis pump-primed study** to determine the uptake of tamoxifen and to predict premenopausal women most likely to benefit. (Tam Prev Study). This study has now been fully funded by NIHR.
- **Entered the first women into the 'FH-Risk' programme** to improve risk prediction and targeted screening in high risk women in the Family History Clinic.
- **Hosted the first national conference on 'Addressing Health Inequalities in Breast Screening'** at the Centre in order to help improve screening uptake in under-screened populations.
- **Gained an honour:** **Michelle Harvie** received the National Award for best published paper by the Association for the Study of Obesity for her work on intermittent dietary approaches to prevention.
- **Professor Gareth Evans**, through work at the centre, has been made an NIHR senior investigator with Professor Nigel Bundred amongst only 200 nationally.
- **Professor Bundred** has been awarded a Royal College of Surgeons Fellowship for researcher Kate Williams to study stem cell kill in DCIS.
- **Completed recruitment into three of our current lifestyle studies (B-AHEAD, BRIDE and Intermittent)** with the aim of defining how best to administer this approach and producing biomarkers of their effectiveness on the breast. The results of these studies will be reported next year in a report of 2011 publications.
- **With our collaborators**, published 37 research papers linked to our strategic goals.



Prevention Centre Research

1. Prediction

These papers describe our attempts to predict as accurately as possible which groups of women and which individuals are likely to develop breast cancer. We want to develop gene testing and other methods for predicting who is susceptible to breast cancer. This will allow us to target screening and early diagnosis specifically at women at most risk. A major focus of this work is the increased risk seen in women who carry within their genes a number of genetic variants known as single nucleotide polymorphisms (SNP's).

We have previously reported a comparison of several types of breast cancer risk prediction models (Amir et al J Med Genet 40: 807, 2003). Some of these use family history only, whereas others use family history and other risk factors such as age of first birth, menarche and menopause.

We demonstrated that for our UK practice the optimal model was one devised by our collaborators, Jack Cuzick and Stephen Duffy (the Tyrer-Cuzick model).

However we recently re-reviewed all models and have emphasized the need for further improvements in their accuracy (see reference 1).

This need has led to the development of the PROCAS study in the Prevention Centre.

Prediction of Risk in the NHS National Breast Screening Programme

A £1.6m programme grant from the National Institute of Health Research (NIHR) is enabling the group to improve risk prediction. We plan to improve the prediction of breast cancers which will arise in 60,000 women undergoing mammographic screening in the National Health Service Breast Screening Programme (NHSBSP) in Manchester. The aim is to improve prediction by combining the standard risk factors with additional factors known to predict risk such as mammographic density and the newly discovered risk genes (Single Nucleotide Polymorphisms-SNPs).

We have been involved in providing cases for Genome Wide Association Studies (GWAS) based in Cambridge (Easton et al 2007; see reference 2) in order to detect new additional SNPs. GWAS detect single changes (polymorphisms) in one of the thousands of nucleotides in the

genetic code, which can alter the activity of the protein the gene makes. This paper adds to the number of single nucleotide polymorphisms (SNPs) associated with breast cancer risk (now about 30).

These SNPs will be incorporated into our new approach to risk modelling in the PROCAS study. Over 16,000 women in Manchester have agreed to enter the PROCAS study to date and we expect to recruit the remaining 44,000 over the next two years under the guidance of Paula Stavrinou who is in overall administrative charge of this highly complex project.

Prediction of risk in the Family History Clinic

We have performed preliminary studies to determine whether SNPs predict altered susceptibility to breast cancer in women with a strong family history attending our clinic (reference 3). A cohort of unrelated individuals with breast cancer due to the presence of either BRCA1 (121) or BRCA2 mutations



(109) and individuals with familial breast cancer not due to BRCA1/2 mutations (n=722) were genotyped using Taqman SNP Genotyping Assays. Allele frequencies were compared with an ethnically and gender-matched group (436). A synonymous variant (Ser51) in TOX3 (previously TNRC9) was associated with an increased risk of breast cancer (OR=1.82, $p < 0.001$) in BRCA2 mutation carriers.

The associations for FGFR2 (OR=1.20, $p=0.046$), TOX3 (OR=1.5, $p < 0.001$), MAP3K1 (OR=1.26 $p=0.03$), CASP8 (OR=0.73 $p=0.02$) and the chromosome 8-associated SNP (OR=1.31, $p=0.004$) were replicated in individuals without BRCA1/2 mutations. In addition, homozygote carriers of MAP3K1 variants were shown to have a significantly lower Manchester Score (mean 13.8-17.6, $p=0.003$), whereas individuals carrying one or two copies of the FGFR2 variant had a higher Manchester Score (mean 17.5-17.9, $p=0.01$). This study

confirms that susceptibility variants in FGFR2, TOX3 and MAP3K1 and on chromosome 8q are all associated with increased risk of cancer in individuals with a family history of breast cancer, whereas CASP8 is protective in this context.

The level of risk is dependent on the strength of the family history and the presence of a BRCA1/2 mutation and contributes to the understanding of the use of these variants in clinical risk prediction. We have performed additional studies of this type in the context of the Family History Clinic and have tested a number of other potentially useful gene alterations (see references 4 to 9) some of which may be useful for risk prediction in our new models.

Prediction of the probability of BRCA1 or BRCA2 mutations in families

Tests for mutations in the BRCA1 and 2 genes are regularly performed in clinical practice. The NHS has a threshold for

allowing testing in the clinic of a 20% probability of a mutation being present. We have devised a simple way of determining this probability in the clinic known as the Manchester Scoring System (Evans et al J Med Genet. 41:474, 2004).

The scoring system is now used by many centres across the world. We have now reported that this prediction is improved by adding pathology and hormone receptor information of the tumours from individuals with breast cancer in high risk families (see references 10 & 11).

We have also reported the probability of women under 30 with breast cancer and those with two primary cancers carrying a mutation (see references 12 & 13) and the chance of men with a mutation actually developing breast cancer (see reference 14).

Further gene interactions identified by collaborative research have been published in 2010 (see references 15-18).

Publications concerning Prediction 2010

1. Assessing women at high risk of breast cancer: a review of risk assessment models. Amir E, Freedman OC, Seruga B, Evans DG. *Journal of the National Cancer Institute* 102:680-91.2010

** This is a timely review of the models we use to predict risk of breast cancer. It emphasizes the deficiencies of our current models and the need for the Genesis strategy to improve them.*

2. Genome-wide association study identifies five new breast cancer susceptibility loci. Turnbull C, Evans DG et al. *Nat Genet* 42: 504-7, 2010

** A single change (polymorphism) in one of the thousands of nucleotides in a gene can alter the activity of the protein the gene makes. This paper adds to the number of single nucleotide polymorphisms (SNPs) associated with breast cancer risk. At Genesis we are investigating combining information on the breast SNPs (Assessed from DNA samples and measured in Bill Newman's laboratory at St Mary's) with standard risk factors and mammographic density to improve risk estimation in the general population of screened women (PROCAS1 study).*

3. Breast cancer susceptibility variants alter risks in familial disease. Latif A, Hadfield KD, Roberts SA, Shenton A, Lalloo F, Black GC, Howell A, Evans DG, Newman WG. *J Med Genet* 47:126-31, 2010.

** This and the next two papers begin to explore how the SNPs modify risk in women with a family history of breast and ovarian*

cancer. This information and the SNP assays will be important in our study to define the extent of risk more precisely in women attending the Family History Clinic at the Genesis Prevention Centre.

4. Breast cancer susceptibility variants alter risk in familial ovarian cancer. Latif A, McBurney HJ, Roberts SA, Lalloo F, Howell A, Evans DG, Newman WG. *Fam Cancer* 9: 503-6, 2010.

5. RASSF1A polymorphism in familial breast cancer. Bergqvist J, Latif A, Roberts SA, Hadfield KD, Lalloo F, Howell A, Evans DG, Newman WG. *Fam Cancer* 9:263-5, 2010.

6. Common variants associated with breast cancer in genome-wide association studies are modifiers of breast cancer risk in BRCA1 and BRCA2 mutation carriers. Wang X, Evans DG et al *Hum Mol Genet* 19:2886-9, 2010.

** Women who carry mutations in the BRCA1 and BRCA2 genes are at very high risk of breast cancer. However the gene faults do not always result in breast cancer. This and the next three papers address how changes in other genes can affect the expression (penetrance) of BRCA1/2 and become an important additional test when counselling risks in gene carriers in the future.*

7. Association of the Variants CASP8 D302H and CASP10 V410I with Breast and Ovarian Cancer Risk in BRCA1 and BRCA2 Mutation Carriers. Engel C, Versmold B, Wappenschmidt B, Simard J, Easton DF, Peock S, Cook M, Oliver C, Frost D, Mayes R, Evans DG,



Cancer Epidemiol Biomarkers Prev. 19:2859-2868, 2010.

8. A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. Antoniou AC, Evans DG et al *Nat Genet.* 42: 885-92, 2010.

9. Pooled analysis indicates that the GSTT1 deletion, GSTM1 deletion, and GSTP1 Ile105Val polymorphisms do not modify breast cancer risk in BRCA1 and BRCA2 mutation carriers. Spurdle AB, Evans DG et al *Breast Cancer Res Treat.* 122:281-5, 2010.

10. Addition of pathology and biomarker information significantly improves the performance of the Manchester scoring system for BRCA1 and BRCA2 testing. Evans DG, Lalloo F, Cramer A, Jones EA, Knox F, Amir E, Howell A. *J Med Genet.* 46: 811-7, 2010.

11. Development of a scoring system to screen for BRCA1/2 mutations. Evans GR, Lalloo F. *Methods Mol Biol;* 653:237-47, 2010.

** The Manchester scoring system was introduced to decide when a gene test is indicated. This is set at a 20% chance of there being a mutation in the family. This*

study shows that the accuracy of this prediction is improved by considering pathology and hormone receptor status of tumours detected in the family.

12. Long-term outcomes of breast cancer in women aged 30 years or younger, based on family history, pathology and BRCA1/BRCA2/TP53 status. Evans DG, Moran A, Hartley R, Dawson J, Bulman B, Knox F, Howell A, Lalloo F. *Br J Cancer* 102:1091-8, 2010.

** This paper updates our previous report concerning the proportion of women who develop breast cancer under age 30 who carry faults in the BRCA1/2 genes. We show that women with one or more affected relatives are likely to have faults whereas this is highly unlikely when there is no family history. This knowledge is important when counselling young women to consider a gene test or not.*

13. BRCA1, BRCA2 and CHEK2 c.1100 delC mutations in patients with double primaries of the breasts and/or ovaries. Evans DG, Ahmed M, Bayliss S, Howard E, Lalloo F, Wallace AJ. *Med Genet.* 47: 561-566, 2010.
** This study demonstrates that two primary cancers in families with a number of cancers increase the likelihood of a positive gene test for BRCA1/2.*

14. Risk of breast cancer in male BRCA2 carriers. Evans DG, Susnerwala I, Dawson J, Woodward E, Maher ER, Lalloo F. *J Med Genet.* 47:710-1, 2010.
** Male breast cancer is associated with mutations in the BRCA2 gene. Here we show that about 8% of*

male carriers will develop breast cancer.

15. Evidence for SMAD3 as a modifier of breast cancer risk in BRCA2 mutation carriers. Walker L ...Evans DG. *Breast Cancer Res;*12:R102, 2010.

16. Common genetic variants and modification of penetrance of BRCA2-associated breast cancer. Gaudet MM. ...Evans DG....*PLoS Genet.* 6:e1001183, 2010.

17. Common Breast Cancer Susceptibility Alleles and the Risk of Breast Cancer for BRCA1 and BRCA2 Mutation Carriers: Implications for Risk Prediction. Antoniou AC ...Evans DG....*Cancer Res;* 70(23): 9742-9754, 2010.

18. Mutation and association analysis of GEN1 in breast cancer susceptibility. Turnbull C, ..., Gareth Evans D... *Breast Cancer Res Treat* 124(1):283-8, 2010.

Late entries

36. Wilson JR, Bateman AC, Hanson H, An Q, Evans G, Rahman N, Jones JL, Eccles DM. A novel HER2-positive breast cancer phenotype arising from germline TP53 mutations. *J Med Genet* 47:771-4, 2010.

37. Ramus SJ, ...Evans DG, et al. Genetic Variation at 9p22.2 and Ovarian Cancer Risk for BRCA1 and BRCA2 Mutation Carriers. *J Natl Cancer Inst.* 2010 Dec 17. [Epub ahead of print]

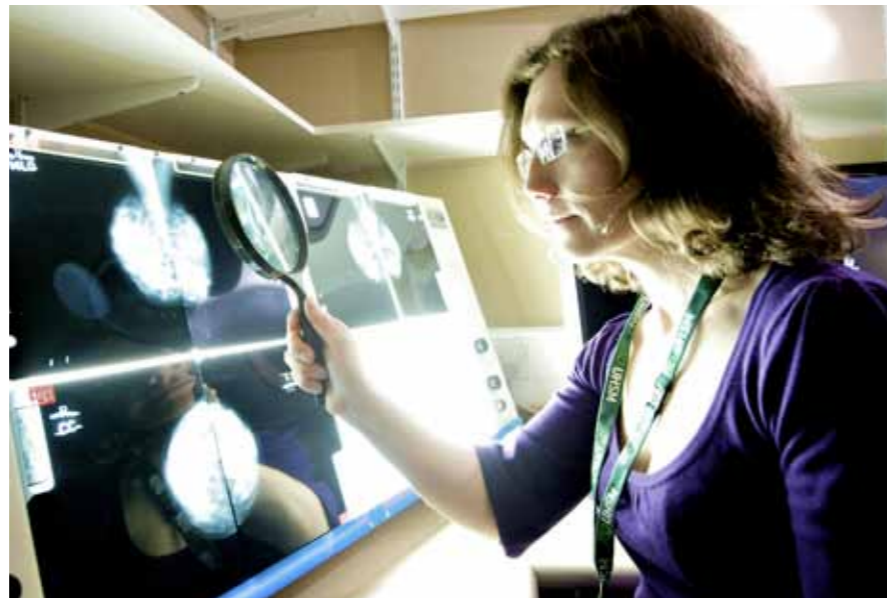
Prevention Centre Research

2. Early Detection and Screening

Screening and early diagnosis are important components of our prevention strategy. We are enthusiastic supporters of the NHS breast screening programme. We have also published the successful outcomes of screening a younger population when a family history of breast cancer is present. The NHS screening programme has its limitations and has well publicised critics. The future of screening will be smarter, much more targeted, and thus more effective, and these papers describe the steps we are taking towards this goal.

Women under surveillance by annual mammography in the Family History Clinic had smaller tumours, fewer involving lymph nodes and a better survival compared with women of the same age diagnosed in the symptomatic clinic in the adjacent Nightingale (clinical) Centre. The eight year survival was 79% in screened women and 60% in unscreened women (Maurice et al 2006).

This study was performed on a subset of the women who attended the Family History Clinic between 1987 and 2005. Now we have analysed all 7475 women referred between the start of the clinic in 1987 and 2008. This study confirmed the generally favourable nature of the tumours detected (80% <2cm 65% node -ve. See reference 19). Women are also offered Clinical Breast Examination by our nurses who detected a small number of tumour not seen by mammography. Our data informed the NICE Guidelines for women at increased



risk but it was important to obtain additional data from a multicentre study. We were involved in setting up the multicentre FHO1 screening trial which has reported very recently (see reference 20). 6710 women were entered from 78 centres and had annual mammographic screening.

The proportion of women with small tumours and negative nodes was almost identical to our single centre series. The results of screening were

compared with controls in a previous trial (The Age Trial) and also with unscreened women from another Family History Clinic in Holland.

The results were virtually identical to those seen in our FHC with estimated improvement in survival in the screened population of 20% ($p < 0.001$) thus, also suggesting, that screening of women at increased risk in the context of Family History Clinic context is effective.

Publications concerning Early Detection and Screening 2010

19. Surveillance of women at increased risk of breast cancer: mode of tumour detection and outcome. Maurice A, Evans DG, Affen J, Greenhalgh R, Duffy SW, Howell A. Submitted
* Dr Andrew Maurice, GP Research Fellow in the Genesis Family History Clinic, has summarised the outcome of more than 7,500 at risk women we have seen in the Genesis Family History Clinic. Our 1-2 yearly mammographic screening picks up most tumours when small and without axillary lymph node involvement. Some tumours are only picked up by the breast examinations performed by our Research Sisters, Rosemary Greenhalgh and Jenny Affen. We have demonstrated an improvement in survival compared with unscreened women.

20. Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study. FH01 collaborative teams. Lancet Oncol ;11:1127-34, 2010.

* This multicentre study (with the Prevention Centre as the biggest contributor) shows the same improvement in size and node status as found in our clinic and with a similar predicted improvement in survival compared with unscreened populations.

3. Prevention in Clinical Practice

We were involved in the development of a consensus statement concerning the present status of breast cancer prevention research as a result of the International meeting at St Gallen, Switzerland in March 2010. The consensus highlighted our successes but indicated the magnitude of the task ahead. Drugs such as Tamoxifen, aromatase inhibitors and raloxifene can lower cancer risk but have side effects; but already what we have learned is useful in clinical practice.

Publications concerning Clinical Practice 2010

21. Preventive Therapy for Breast Cancer: An International Consensus Statement Jack Cuzick Florian Otto, Banu Arun, Powel H. Brown, Monica Castiglione, Andrea DeCensi, Barbara Dunn, John Forbes, Christine Friedenreich, Agnes Glaus, Anthony Howell, Gunter von Minckwitz, Victor Vogel, Heinz Zwierzina. Lancet Oncology in press

* International experts in prevention met in St Gallen, Switzerland earlier this year to discuss the present state and future of breast cancer prevention research.

22. Uptake of breast cancer prevention and screening trials. Evans DG, Harvie M, Bundred N, Howell A. J Med Genet. 47(12):853-5. 2010.

* We have summarized the proportion of women asked who enter our trials. Uptake is excellent in screening trials but less so in primary prevention studies. We are currently testing improved methods of explanation for our studies including specially prepared decision aids to be studied first in the Tam Prev trial of tamoxifen in premenopausal women beginning early in 2011.

Prevention Centre Research

4. Preventive Therapy

One of our goals is to develop drug treatments – tablets, injections, vaccines – that could block the development of cancer changes in those identified as being at high risk. These papers describe our work towards that goal. Anti-oestrogen drugs are effective in reducing breast cancer risk, but have significant side effects. We are learning how to minimise those effects, and at the same time how to target the drugs at those women who obtain maximum benefit.

The most studied preventive therapies for women at risk are anti-oestrogens. We were one of the major contributors to the IBIS-I prevention trial which compared tamoxifen with placebo (Cuzick et al 2008). This trial showed about a 40% reduction in cancer risk by tamoxifen. Interestingly the beneficial effects of five years of therapy increase with further follow up to ten years (Cuzick et al 2008).

We were also involved in the ATAC trial which demonstrated reduced relapse after surgery using the aromatase inhibitor anastrozole compared with tamoxifen (see reference 23) Women taking anastrozole had a 60% reduction in contralateral breast cancer, a result which led us to set up the IBIS II prevention trial which will complete recruitment in 2011.

The ATAC trial has provided a great deal of information concerning anastrozole useful for management of patients in IBIS-II trial including management of bone issues and gynaecological issues (see

references 24,25). Surprisingly tamoxifen and anastrozole appear to be equally active in women who are obese and this requires further investigation in the context of the IBIS II prevention trial (see reference 27).

We are now starting a Genesis funded programme of offering tamoxifen for prevention for premenopausal women at increased risk in the Family History Clinic TAM-Prev study). We will closely examine which women are most likely to benefit from preventative tamoxifen therapy.

We recently demonstrated that women who are good metabolisers of tamoxifen (see reference 28) and those who have a reduction of more than 10% in mammographic density on tamoxifen (see reference 29) are the most likely to benefit. We will now need to determine whether these and other measurements are valuable predictors of tamoxifen benefit for women in our clinic.

In another recent study we demonstrated that the anti-

inflammatory agent celecoxib had no effect on the growth of carcinoma in-situ in women which, amongst other evidence, makes it unlikely that this drug will be a useful preventive agent (See reference 30).



Publications concerning Preventive Therapy 2010

23. 10-year Analysis of the ATAC Trial Comparing Anastrozole to Tamoxifen in Early Breast Cancer Jack Cuzick, Ivana Sestak, Michael Baum, Aman Buzdar, Anthony Howell, Mitch Dowsett, John F Forbes on behalf of the ATAC/LATTE investigators Lancet Oncology 11: 1135-1141, 2010. **The ATAC trial compares tamoxifen and anastrozole in women after surgery for breast cancer. The trial provides important efficacy and toxicity information about for use of the drugs as preventives therapy in the IBIS-I (tamoxifen v placebo) and IBIS-II (anastrozole v placebo) prevention trials in progress in the Genesis Prevention Centre.*

24. Long-term effects of anastrozole on bone mineral density: 7-year results from the ATAC trial. Eastell R, Adams J, Clack G, Howell A, Cuzick J, Mackey J, Beckmann MW, Coleman RE. Ann Oncol. 2010 [epub ahead of print]. ** This study shows that the reduction in bone density on anastrozole is reversed when treatment is completed at five years.*

25. The ATAC adjuvant breast-cancer trial: six-year results of the endometrial subprotocol. Duffy S, Jackson TL, Lansdown M, Phillips K, Wells M, Clack G, Bianco AR; ATAC Trialists' Group Howell A. J Obstet Gynaecol. 30:596-604, 2010. ** Here we report that anastrozole has very little endometrial toxicity.*

26. Effect of body mass index on recurrences in tamoxifen and anastrozole treated women: an exploratory analysis from the ATAC trial. Sestak I, Distler W, Forbes JF, Dowsett M, Howell A, Cuzick JJ Clin Oncol 28: 3411-5, 2010. ** Anastrozole appears less effective in women with a high body mass index. Thus for prevention we may consider calorie restriction in addition to anastrozole.*

27. Insights into the place of fulvestrant for the treatment of advanced endocrine responsive breast cancer. Howell A, Bergh J. J Clin Oncol 28: 4548-50, 2010. ** This review indicates that the pure anti-oestrogen fulvestrant at the appropriate dose may be the most active endocrine therapy. If an oral form can be formulated it would be a useful preventive agent.*

28. Comprehensive CYP2D6 genotype and adherence affect outcome in breast cancer patients treated with tamoxifen monotherapy. Thompson AM, Johnson A, Quinlan P, Hillman G, Fontecha M, Bray SE, Purdie CA, Jordan LB, Ferraldeschi R, Latif A, Hadfield KD, Clarke RB, Ashcroft L, Evans DG, Howell A, Nikoloff M, Lawrence J, Newman WG. Breast Cancer Res Treat. [Epub ahead of print]. ** This study shows a reduction in tamoxifen metabolism impairs its activity. We are now exploring the importance of tamoxifen metabolism in the prevention setting.*

29. Change in Mammographic Density as a Predictor of Risk Reduction for Tamoxifen: Results from a case-control study within the Randomized IBIS-1 Breast Cancer Prevention Trial Jack Cuzick, Jane Warwick, Elizabeth Pinney, Stephen W Duffy, Simon Cawthorn, Anthony Howell, John F Forbes, Ruth ML Warren Journal of the National Cancer Institute – in press.

** Mammographic density slowly declines with age. However in this study we show that this decline is accelerated in about half the women given preventative tamoxifen and, it appears, that these are the group who have a reduction in tumour incidence.*

30. Cyclooxygenase-2 inhibition does not improve the reduction in ductal carcinoma in situ proliferation with aromatase inhibitor therapy: results of the ERISAC randomized placebo-controlled trial. Bundred NJ, Cramer A, Morris J, Renshaw L, Cheung KL, Flint P, Johnson R, Young O, Landberg G, Grassby S, Turner L, Baildam A, Barr L, Dixon JM. Clin Cancer Res 16: 1605-12, 2010.

** The Cox-2 inhibitor, celecoxib, is not effective biologically in the preoperative setting and casts further doubt on its efficacy as a preventive agent.*

Prevention Centre Research

5. Lifestyle Prevention

A significant component in the rising incidence of breast cancer across the world is the adoption of a Western lifestyle – diet, lack of exercise, use of hormonal medication, alcohol consumption, and changes in the pattern of childbirth and breast-feeding. These publications describe our search for diet and exercise interventions that are practical, acceptable, and that really do lower breast cancer risk. A particular interest is the role of intermittent rather than continuous diets to lower risk. We are also studying diet and exercise as a means of preventing breast cancer re-occurrence in those who have had the diagnosis once before.

Recent expert reports have highlighted the role of lifestyle factors, particularly excess weight, high calorie diets and lack of exercise, rather than specific dietary components in increasing the risk of breast cancer (WCRF 2008).

These potentially modifiable factors are thought to account for up to 30% of breast cancer cases. We were one of the first groups to report the potential benefits of weight control on breast cancer risk. In a study of 34,000 women we demonstrated that overweight women who lost more than 5% of their body weight were at 25-40% less risk of breast cancer compared with women who continued to gain weight (Harvie et al Cancer Epidemiol Biomarkers Prev.14:656, 2005).

We went on to review the literature of animal and human studies on calorie restriction for breast cancer prevention (Howell et al Recent Results Cancer Res. 181:97, 2009). Some reports

indicated that intermittent calorie restriction (short spells of strict dieting interspersed with normal intake) was as or more effective than continuous (daily) calorie restriction and possibly better tolerated. We therefore performed a randomised trial to test this hypothesis.

Randomised trial of intermittent v continuous energy restriction

We performed a randomised trial of intermittent (IER) vs continuous calorie restriction (CER). 107 women at increased risk of breast cancer were asked to restrict calorie intake by 25%. One group were randomised to an intermittent restriction (IER ~ 650 kcal for two days/week) and the other group to a continuous calorie restriction (CER) (~ 1500 kcal seven days/week).

The women were studied for six months, and we assessed by anthropometry changes in weight and blood markers of breast cancer risk. We found IER

and CER to be equally effective for weight loss and changes in risk biomarkers. We conclude IER is as effective as CER with regard to weight loss, insulin sensitivity and other health biomarkers, and may be offered as an alternative equivalent to CER for weight loss and reducing disease risk (see reference 31).

The above study demonstrated that intermittent restriction was feasible but not better tolerated than the daily approach. However many women seemed to prefer the intermittent diet. We hypothesised that, if we could make the two days of energy restriction more tolerable, it might prove an easier approach for women and more applicable to breast cancer prevention in general.

We have recently completed recruitment of 114 women at increased breast cancer risk to a three arm study, two arms of which are testing potentially more acceptable two day regimens (low carbohydrate,

Publications concerning Lifestyle Prevention 2010

31. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. Harvie MN, Pegington M, Mattson MP, Frystyk J, Dillon B, Evans G, Cuzick J, Jebb SA, Martin B, Cutler RG, Son TG, Maudsley S, Carlson OD, Egan JM, Flyvbjerg A, Howell A. *Int J Obes (Lond)*. 2010 Oct 5. [Epub ahead of print].

** This randomized trial performed in the Unit indicates that calorie restriction for two days is at least as effective as continuous restriction. The two day regimen is an important additional dietary choice for women at risk.*

32. Increase in Serum Total IGF-I and Maintenance of Free IGF-I Following Intentional Weight Loss in Pre-menopausal Women at Increased Risk of Breast Cancer Harvie M, Renehan AG, Frystyk J, Flyvbjerg A, Mercer T Malik R, Adams J, Cuzick J, Howell A. *The Open Obesity Journal* pp.63-70 (8). ** The mechanism of risk reduction with weight loss is not known but often believed to be linked to reduction in circulating levels of cancer promoting growth factors. Increased serum total IGF-1 levels, and maintenance of free IGF-1 with weight loss in this study does not suggest intentional weight loss with diet and exercise mediates reduced risk through the circulating IGF-axis.*

33. Adherence to a diet and exercise weight loss intervention amongst women at increased risk of breast cancer. Harvie M, Cohen H, Mason C, Mercer T, Malik R Adams J Evans DGR, Hopwood P, Cuzick J, Howell A. *The Open Obesity Journal* pp.71-80 (10) 2010. Target weight loss (5%) was achieved by 55% of the intervention group at the end of the 12 month but maintained by fewer women at 54 months (21%). Weight loss is achievable within our high risk women but not more so than in previous studies in the general population. Further studies are required to better understand factors which can promote compliance in women at increased risk of breast cancer.

high protein). The third arm is our standard daily continuous Mediterranean type diet. If successful we plan to test introducing the successful diet arm for high risk women identified in the NHSBSP, and also to prevent weight gain for women receiving treatment after a diagnosis of breast cancer.

Lifestyle is also important for reducing the chances of recurrence for women who have been diagnosed with the disease. In order to determine the optimal and most cost effective method for delivering diet and exercise advice we have set up and completed recruitment to the trial "Breast - Activity & Healthy Eating After Diagnosis".

The randomised B-AHEAD trial compared three approaches; telephone advice, community based supervised diet and exercise, or a simple leaflet

given after diagnosis of breast cancer. Recruitment to this study has been very successful (n=400) with over 40% of women agreeing to enter soon after completion of surgery.

This study will help inform us the best ways to deliver lifestyle interventions for high risk women in the future. Lifestyle is important for preventing cancer risk but may also reduce chances of recurrence for women who have been diagnosed with the disease.

Determining markers of breast cancer risk reduction with energy restriction

A major difficulty of energy studies is to know whether weight loss and maintenance after loss is having beneficial effects on our target of interest, the breast. We are undertaking a series of studies to examine

the effects of energy restriction in the breast in collaboration with scientists at the Paterson Institute (Dr Rob Clarke and Catherine Spence).

We have conducted a study, Breast Risk Reduction Intermittent Diet Evaluation (BRRIDE) which is examining the effects of 1 month of the intermittent diet on gene expression in the breast compared with peripheral blood white cells, and metabolomic markers in serum and urine of energy restriction, in collaboration with Prof Roy Goodacre and Dr Rick Dunn at the Manchester Centre for Integrative Systems Biology. We have now completed recruitment of 24 women at increased risk of breast cancer to this study. The results of this study will be available by June 2011.

Prevention Centre Research

6. Risk Reducing Surgery

Many women who carry a high risk cancer predisposing gene mutation will opt for risk-reducing surgery. This may involve mastectomy, removal of ovaries to protect against ovarian cancer, or both. One day these operations will become unnecessary when the Genesis goal of cancer prevention through other means is realised. Until then high quality surgery and breast reconstruction is vital, and these publications describe our experience.

We recently published a review of the Manchester experience of risk reducing breast and ovarian surgery for women carrying, or suspected of carrying a high risk gene mutation.

Women are more likely to undergo surgery the higher the risk but often take considerable time over the decision for treatment (Evans et al *Cancer Epidemiol Biomarkers Prev*. 18:2318, 2009).

Also we collaborated in a multicentre study which indicated that surgery is associated with improved survival (see reference 34). In some women occult cancers may be found at the time of surgery (Ref 35).

Publications concerning Risk Reducing Surgery 2010

34. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. Domchek SM, Friebel TM, Singer CF, Evans DG et al *JAMA*. 304:967-75, 2010.

** This multicentre study indicates that risk reducing surgery is associated with a survival advantage which we have also reported from within our centre.*

35. Occult ovarian cancers identified at risk-reducing salpingo-oophorectomy in a prospective cohort of BRCA1/2 mutation carriers. Domchek SM, ... Evans DG et al *Breast Cancer Res Treat*. 124:195-203, 2010.

Publications prior to 2010

- Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme. Amir E, Evans DG, Shenton A, Lalloo F, Moran A, Boggis C, Wilson M, Howell A. *J Med Genet* 40:807-14, 2003
- Genome-wide association study identifies novel breast cancer susceptibility loci. Easton DF, ... Evans DG et al *Nature* 447:1087-93, 2007.
- A new scoring system for the chances of identifying a BRCA1/2 mutation outperforms existing models including BRCAPRO. Evans DG, Eccles DM, Rahman N, Young K, Bulman M, Amir E, Shenton A, Howell A, Lalloo F. *J Med Genet* ;41:474-80, 2004.



- Screening younger women with a family history of breast cancer--does early detection improve outcome? Maurice A, Evans DG, Shenton A, Ashcroft L, Baildam A, Barr L, Byrne G, Bundred N, Boggis C, Wilson M, Duffy SW, Howell A. *Eur J Cancer* 42:1385-90, 2006.

- Long-term results of tamoxifen prophylaxis for breast cancer--96-month follow-up of the randomized IBIS-I trial. Cuzick J, Forbes JF, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A; International Breast Cancer Intervention Study I Investigators. *J Natl Cancer Inst* 99:272-82, 2007.

- The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Wiseman M. *Proc Nutr Soc* ;67:253-6, 2008.

- Association of gain and loss of weight before and after menopause with risk of postmenopausal breast cancer in the Iowa women's health study. Harvie M, Howell A, Vierkant RA, Kumar N, Cerhan JR, Kelemen LE, Folsom AR, Sellers TA. *Cancer Epidemiol Biomarkers Prev* 14:656-61, 2005.

- Energy restriction for breast cancer prevention. Howell A, Chapman M, Harvie M. *Recent Results Cancer Res* 181:97-111, 2009.
- Uptake of risk-reducing surgery in unaffected women at high risk of breast and ovarian cancer is risk, age, and time dependent. Evans DG, Lalloo F, Ashcroft L, Shenton A, Clancy T, Baildam AD, Brain A, Hopwood P, Howell A. *Cancer Epidemiol Biomarkers Prev* 18:2318-24, 2009.

Addressing Health Inequalities

Minority ethnic communities at present constitute around 10% of the UK population. Their number is increasing year by year and in some inner city areas they constitute around 50% of the population. Their screening uptake has been consistently low and, due to lack of awareness, they present with more advanced stage breast cancers. Our aim is to promote early detection and breast screening in minority ethnic communities. We are using multi-pronged approaches to achieve the above objectives. These include:

- Steer, support and undertake various research projects dealing with minority ethnic issues (with the help of our steering group).
- Raise awareness amongst these communities by Genesis fundraising events and by recruiting volunteers and ambassadors.
- Set up minority ethnic patient and carer information and support groups.
- Organise conferences and meetings to listen to our patient and public stakeholders and colleagues and disseminate findings from our research work.

Asian Women's Health Awareness Conference - 1 October 2010

'Addressing Health Inequalities in Breast Cancer Screening - A Partnership Approach'

A national conference focussing on health inequalities within the NHS Breast Screening Programme was held in October 2010 at the Genesis Prevention Centre. The conference focussed on the lack of uptake in breast

cancer screening across the South Asian population in the UK. Key note speakers presented the results of research that Genesis and other organisations had commissioned to investigate the socioeconomic disparity between the uptake of breast screening amongst ethnic groups compared to the general population. Members of the public from within the Asian community were invited to attend an interactive workshop. The solutions outlined following this session included:

- Improving breast health awareness by reaching out to the appropriate opinion leaders, community organisations and lay leaders.
- Refining literature in terms of quality and availability; different forms of literature; and using social media and networking sites.
- Utilising the Asian media.
- Educating South Asian health professionals - over 40% of health professionals in the NHS are from an ethnic minority. These members of NHS staff can

act as opinion leaders, and help lift the taboo of cancer, self-checking and screening within South Asian communities.

Prof Anil Jain, chair of the conference, said: "From what we've learned, the lack of breast screening awareness is not confined to just first generation UK Asians; the second generation is lagging behind significantly as well.

Neither generation realises that, with changing lifestyles, breast cancer cases are increasing among Asian women living both in the Indian sub-continent and also in the UK.

There actually seems to be more awareness of breast cancer in South Asian metropolitan areas than in UK Asian communities and this is due to more targeted charity campaigns and influential role models. The irony lies in the fact that, although the UK has an arguably better and more established breast screening programme than in South Asia, it's simply not being utilised to its full extent by ethnic minority groups."

The Family History Clinic

The Genesis Prevention Centre runs one of the largest Family History Clinics in Europe for women concerned about a family history of breast cancer. Each year the clinic sees between 300 - 600 new referrals of women at risk and over 2,000 women for follow-up.

Since the clinic opened we have seen over 8,300 referrals. Many of these women have volunteered to take part in our research programme, and their contributions are greatly appreciated.

Dr Andrew Maurice has published the outcome of the highest risk women we have seen (see reference 19). Our 1-2 yearly mammographic screening picked up most tumours when small and without lymph node involvement.

Some tumours were only picked up by breast examination performed by our Research Sisters. The multicentre FH01 Trial was recently published in Lancet Oncology and confirms the improvement in size and node status found in our clinic. An important finding of the study was a predicted improvement in survival compared with unscreened populations of approximately 20%.

The NICE Family History Guideline Committee (chaired by Prof Gareth Evans) recommended that all women with proven mutations in the



breast cancer genes, BRCA1, BRCA2 and TP53, should have annual MRI scans. This recommendation has been adopted across the UK. The radiologists listed below deliver a high quality screening service and MRI support to our clinical studies and high risk women.

Since 1996 we have offered a surgical service for risk reducing mastectomy. The surgeons listed below provide 'state-of-the-art' breast surgery and reconstruction techniques. Mrs Anne Brain instituted the service with Mr Baildam and we wish her well after her recent retirement and great service to the centre. All women enter the programme by strict

protocol, are discussed at the RRM multidisciplinary team meeting and are offered annual follow up by a team of surgeons, psychologist, oncologist, geneticists and specialist nurses.

We are particularly thankful to our excellent office staff Jayne Beesly, Christine Taylor and Jean Edney who recently retired after 18 years of service to the clinic. We are also tremendously grateful to our Research Nurses Rosemary Greenhalgh and Jenny Affen who have given great service for over 15 years.

Lead Investigators

in the Genesis Breast Cancer Prevention Centre

Professor Nigel Bundred

Clinical Lead for Research for the Greater Manchester and Cheshire Cancer



Research Network (GMCCRN); Principle Investigator on National Institute for Health Research Programme Grant entitled 'Individualising breast cancer treatment to improve survival and minimise complications'; member of Editorial Board of Endocrine Related Cancer and The Breast journals. NIHR Senior Investigator.

Professor Gareth Evans

Chairman of the NICE Committee on services for women at increased risk



of breast cancer, Principle investigator NIHR Programme Grants, NIHR Senior Investigator, Vice-Chairman Scientific Committee of Breast Cancer Campaign, Ex officio Chairman of the Cancer Genetics Group, Director Manchester Breast Centre, Member of the NIHR breast CSG committee, Chairman of the ICG on familial breast and ovarian cancer.

Michelle Harvie

Member of Breast Cancer Campaign (BCC) Scientific Committee;



reviewing grants and organising BCC National Conference. Part of BCC Research Gap Analysis 2007.

Member Committee for Manchester and Cheshire Cancer Prevention Network

Member of World Cancer Research Fund (WCRF) grant reviewing committee. Expert advisor for the breast cancer charities; Breast Cancer Care, Breast Cancer Campaign and Breakthrough Breast Cancer guiding their policy and advice sheets for breast cancer prevention and patients after diagnosis.

BDA representative on national Research Forum for Allied Health Professions; promotes research among Allied Health Professions.

BDA representative on Rehabilitation Workforce Project Cancer Action Team; to develop evidence based guidelines for dietary management of cancer patients.

Member of WCRF/AICR protocol development group for cancer survivors as part of WCRF/AICR Continuous Update Project.

Professor Tony Howell

Research Director of the Genesis Breast Cancer Prevention Centre.



Co-Chairman of the IBIS - II trial.

Vice Chairman of the Steering Committees of the FH01 and FH02 screening trials.

Co-Chairman of Manchester and Cheshire Cancer Prevention Network.

Director of the Breakthrough Breast Cancer Research Unit.

Past Chairman of the Manchester Breast Centre and of the ATAC Trial.

Member of the Board of the International Society for Cancer Prevention.

Member of the Editorial Board of Cancer Prevention Research.

Genesis Prevention Teams

Programme to predict risk in the NHSBSP and in the Family History Clinic population (PROCAS)

Paula Stavrinos (Director), Sarah Sahin (data manager) Sarah Dawe, Jill Fox (administrators), Sarah Ingham (Genetic epidemiologist), Iain Buchan, Wendy Watson, Fiona Harrison, Barbara Bulman (Blood tests), Bill Newman (SNPs).

Mammographic Density and Screening group programme

Mary Wilson, Barbara Eckersley, Ursula Beetles, Caroline Boggis, Sue Astley, Alan Hufton, Jenny Diffey, Ruth Warren, Jamie Sargent, Yit Lim, Anil Jain, Nicky Barr, Sally Bundred, Emma Hurley.

Preventive therapy and biomarker programme

Louise Donnelly, Rosemary Greenhalgh, Jenny Affen, Julia Wiseman, Victoria Adinca.

Lifestyle change and biomarker programme

Mary Pegington, Debbie McMullen, Karen McKinley, Clare Wright, Ellen Mitchell, Thobekile Mthethwa.

Genesis staff team and volunteers

Nikki Hoffman, Judi Hibbert, Angela Wrobel, Lynda Ellis, Tooba Farooq, Gill Kay, Jane McLaughlin, Saima Rashid, Michelle Cohen.

Breast Surgeons

Nigel Bundred, Lester Barr, Andrew Baildam, Ashu Gandhi, Ged Byrne, Richard Johnson, Asaid Zeiton, Janet Walls, Maria Bramley, Mr Chittalia, Simon Ellenbogen, A Sharif, Vanessa Pope, Zahida Saad, Duncan Matheson.

Medical Oncologists

Sacha Howell, Tony Howell, Ann Armstrong, Andrew Wardley.

Breast Research Nurses and team

Sue Grassby, Thobekile Mthethwa, Kathryn Fellows, Lesley Howard, Annie Duffy, Charlotte Stockton, Kirsty Ewing, Nisha Patel, Georgina Pennington-Smith, Angela Ashton.

Breast Care Specialist Nurses

Lesley Thomson, Maria Noblet, Fiona O'Regan, Julie Orford, Evelyn Poynter, Nicola Robinson-Grieg, Claire Liu.

Radiographers

Rita Borgen, Liz Lord, Jill Johnson, Val Reece, Pam Coates.

Laboratory

Rob Clarke, Cath Spence, Roy Goodacre, Helen Sumner.

Family History Clinic service

Rosemary Greenhalgh, Jenny Affen, Jayne Beesley, Christine Taylor, Andrew Maurice, Tara Clancy, Fiona Laloo, Gareth Evans, Tony Howell.

Risk reducing surgery service

Andrew Baildam, Judith Rogers, Stuart Wilson, Victoria Rose, Lester Barr, Gary Ross.

National and International collaborators

Mark Mattson (NIH, Baltimore), Jan Frystyjk (Aarhus, Denmark), Jack Cuzick, Jane Warwick, Stephen Duffy, Ruth Warren, Jane Wardle (London).

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Genesis Scientific Advisory Board

Gareth Evans (Chair), John Winstanley, Andrew Renehan, Tom Warnes.

Genesis Trustees

Lester Barr (chair), Andrew Baildam, Mary Wilson, Nicky Barr, Pam Glass, Geoff Swarbrick, Jaci Dick, David Gaster, John McGrail, Charles Levine.

International Advisors

Rowan Chhlebowski (Los Angeles), Anne McTiernan (Seattle), Peter Boyle (Lyon), Jack Cuzick (London), John Forbes (Newcastle Australia).

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For further information, please contact us on 0161 291 4400 or via our website
www.genesisuk.org

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