Prevent Breast Cancer

Making a Difference

prevent breast cancer

Contents

Prevent Breast Cancer is a research charity supporting projects related to the prediction, early diagnosis and prevention of breast cancer.

We first registered as a charity in 1997 and have since then awarded £4.9 million in grants to clinical and laboratory breast cancer prevention research. In addition, we raised £2 million towards the building of the world's first purpose-built breast cancer prevention centre, The Nightingale Centre, which opened in 2007. We have also contributed a further £3.64 million towards the running of the centre and to educating the public on breast awareness and prevention.

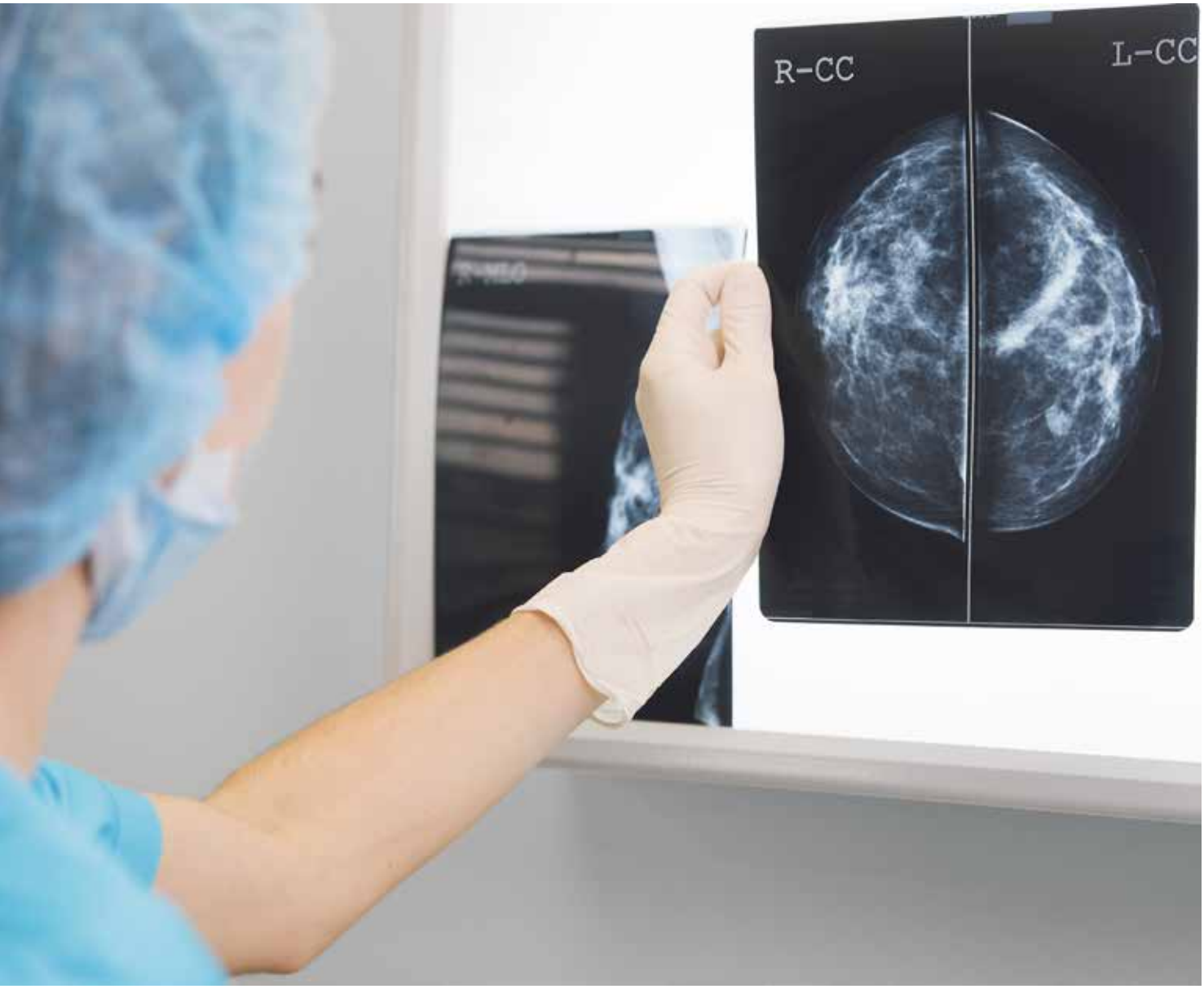
We have made a huge difference since 1997 and our research has contributed to understanding the many factors that cause breast cancer, the strategies that can be used to prevent the disease and how the screening process can be revolutionised.

WE PREDICT
WE PREVENT
WE PROTECT

1. What causes breast cancer?

Unlike other cancers, breast cancer is not caused by only one thing. Rather, it seems to be caused by the combination of several risk factors working together. In medical language, the cause is 'multifactorial'.

It has been accepted for many years that breast cancer is partly genetic and partly caused by non-genetic risk factors, strongly linked to lifestyle. Globally, it is the most common cancer in women and is becoming increasingly common in developing countries as the women there adopt a Western lifestyle. Breast cancer is the most intensely researched of all cancers and we now have a good understanding of the various possible causes of breast cancer.



1a. The genetic causes of breast cancer

The search for breast cancer genes started with families where breast cancer had struck multiple times across several generations: so-called 'hereditary breast cancer'. This led to the discovery of the breast cancer genes BRCA1 and BRCA2 in 1990 and 1995.

At first, it looked as if such cancer-causing genes only occurred in a small number of women and were linked to 2-4% of all breast cancers. However, as a result of subsequent gene research carried out by researchers throughout the world, including Prevent Breast Cancer's researchers, it is now clear that a much larger percentage of breast cancers are linked to inherited genes. In addition to the high-risk hereditary BRCA genes, we have also identified several other genes that also increase risk and tiny gene variations called SNPs (single nucleotide polymorphisms, pronounced 'snips') which increase risk even when there is no family history.

What percentage of breast cancers are caused by inherited genes?

Our current best estimate is that around 25% of breast cancers are caused by genetic factors. This is illustrated in **Figure 1**: 8% of breast cancers may be caused by an inherited single gene mutation such as BRCA1, BRCA2, ATM, CHEK2, PALB2, PTEN, TP53, CDH1, STK11, BARD1, RAD51C, RAD51D. An estimated 12% of breast cancers are caused by small gene variants known as SNPs and 5% of breast cancers seem to be related to an inherited genetic component that research has not yet been able to identify.

Thus, 25% of all breast cancer seems to have a genetic component while 75% appears to be caused by non-genetic risk factors often linked to Western diet and lifestyle. This 25/75 split, however, is not a strict dividing line because there is much crossover between the genetic and the non-genetic components. For example, the risk of breast cancer in someone carrying a mutation can be hugely influenced by changing lifestyle. Similarly, a person's susceptibility to potentially harmful lifestyle factors is often related to their genetic makeup. Indeed, it may be that most breast cancers are caused by a combination of the genes you are born with and the environment and lifestyle into which you are born.

How common are BRCA1 and BRCA2 gene mutations?

BRCA1 and BRCA2 are the most common breast cancer genes. Around 1 in 450 of the general population in the UK are carrying a faulty BRCA1 or BRCA2 gene. However, the risk is much higher within the Jewish community as around 1 in 40 women of Ashkenazi Jewish descent and 1 in 140 women of Sephardi Jewish descent will carry a faulty gene.

Women who carry a BRCA1 or BRCA2 faulty gene have a high risk of developing breast cancer - between 60% and 80% depending on which of the faulty genes they have, combined with other factors, such as SNPs and lifestyle habits. In addition, they also have a risk of ovarian cancer varying from 11% to 50%.

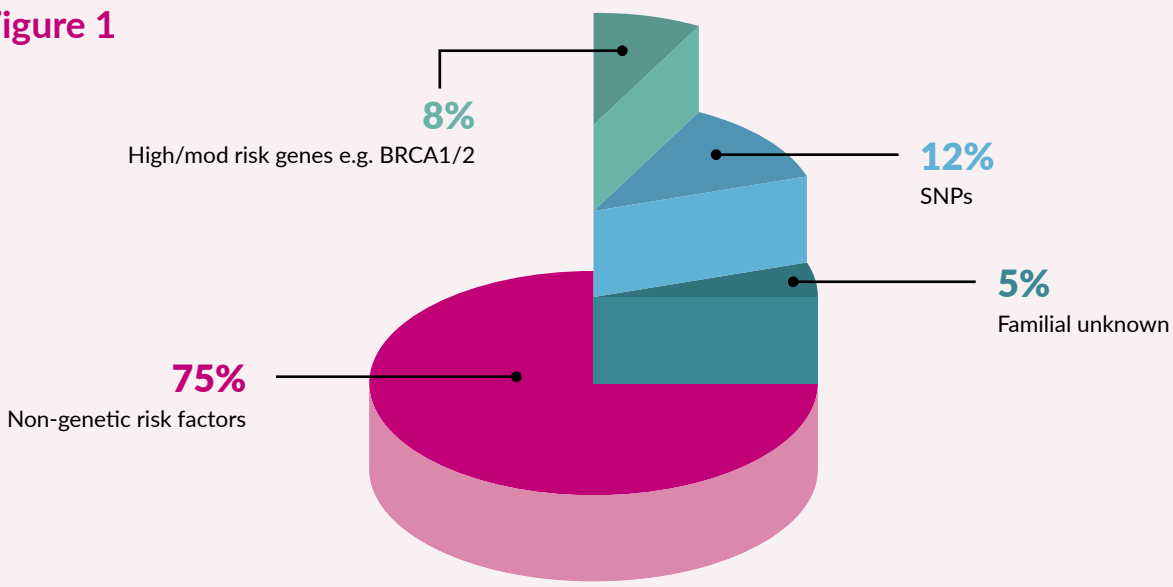
What about men?

Men can get breast cancer too, but it affects only around 1 in 1000 men in the general population. However, when a man does develop breast cancer, in 20% of instances they are found to have a faulty gene.

BRCA1 and BRCA2 are inherited by men as well as women, and men are often "silent carriers". Men who have a faulty gene also have a higher chance of developing breast cancer: as many as 1 in 20 men carrying BRCA2 and 1 in 100 carrying BRCA1 will get male breast cancer.

Men with BRCA2 gene mutations also have a higher chance of developing prostate cancer: as many as 1 in 3 during their lifetime. Thus, the men in the family tree of someone with a known BRCA mutation should also have a test, partly for their benefit and partly so that they know whether they could pass it silently on to their children.

Figure 1

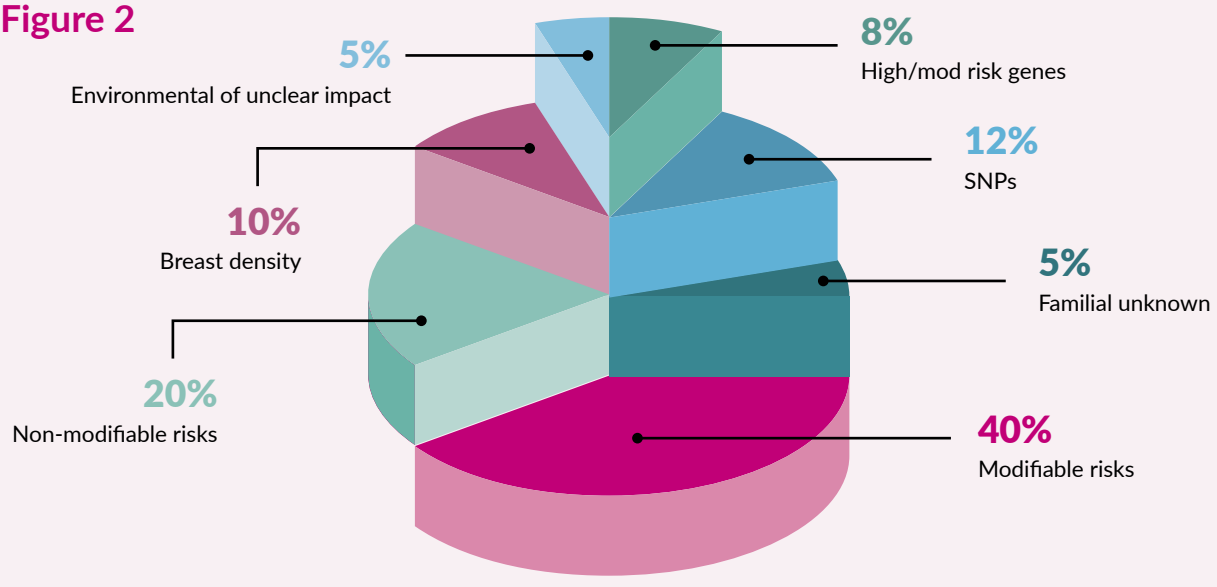


1b. The non-genetic causes of breast cancer

These are often listed in two main categories: modifiable and non-modifiable. The modifiable category mainly consists of factors that are characteristic of a Western lifestyle and can therefore be changed by individuals who want to lower their risk. The non-modifiable category relates to things over which an individual has no control.

There are two additional categories of non-genetic risk factors that cause breast cancer: breast density and environmental factors of unclear impact. Our current best estimate of how this all looks in terms of relative importance is shown in **Figure 2**.

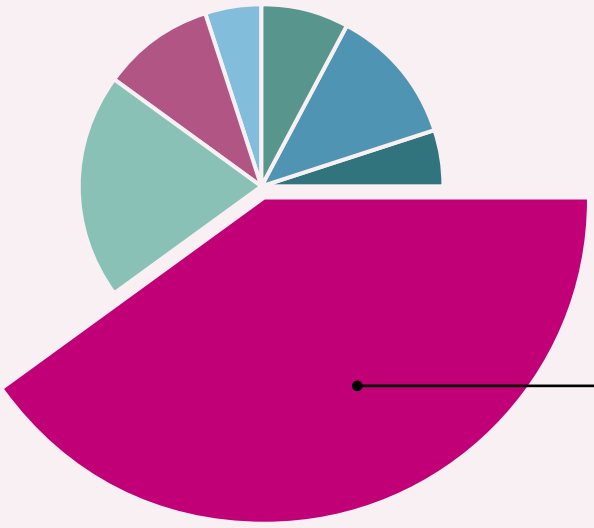
Figure 2



The effect of a Western diet, with its ultra-processed foods high in both fat and sugar content, high levels of alcohol intake and a lack of physical activity, combined with inevitable weight gain, have a major impact on breast cancer risk. In fact, studies have shown that you reduce your risk of breast cancer by about a third if you can lose 5% of your body weight and maintain a healthy BMI through diet and exercise (Evans et al 2016). This is even true for women carrying a faulty breast cancer gene. The next big drivers of breast cancer risk are also related to a Western lifestyle: having children at an older age, having fewer children and choosing not to breastfeed. Reversing these trends would reduce the number of breast cancers in Western countries by half (The Collaborative Group on Hormonal Factors in Breast Cancer, 2002). However, this is not practical, so scientists are looking for ways to mimic the hormonal effects of an early first childbirth and having multiple children as a potential preventive therapy. We have listed early first childbirth and number of babies (parity) in the non-modifiable section, but the counselling process for young BRCA gene carriers discusses the possibility of deciding to start a family at a young age. Breastfeeding is an effective preventative method for everyone, but this is a personal choice and there may be reasons why breastfeeding is not possible.

Smoking also registers as a risk but, interestingly, it seems to apply only to women who start smoking as adolescents and around the time of menarche, when the breast tissue is first developing.

Figure 3



40%
Modifiable risks

Weight gain
Poor diet
Alcohol
Exercise
Smoking
Breast feeding
HRT
Pill

There are several hormonal factors, such as taking the oral contraceptive pill and hormone replacement therapy (HRT), which increase risk. Thankfully, taking the contraceptive pill increases risk by only a very small amount and can therefore be ignored as a risk factor for women under 30. However, women with a faulty BRCA gene are advised against taking the contraceptive pill to avoid adding additional risk. Oestrogen only HRT appears safe, but all forms of combined HRT carry an extra risk of breast cancer while you are taking it. We would therefore advise that women take HRT for 5 years or less. Once a woman stops taking HRT, her risk will decrease again.

The non-modifiable risk factors are listed in **Figure 4**. Interestingly, these are also typical of Western societies. For example, early menarche, being taller and late menopause are likely to be caused by better nutrition. Having your first child when you are older is common because women tend to stay in education longer and have better work opportunities. Similarly, contraception is readily available. Adding these factors to the modifiable risk factors mentioned in the previous section accounts for the increased breast cancer incidence in Western countries over the last few decades. It also accounts for the increased incidence in developing countries as they adopt more Western lifestyle habits. Changing these non-modifiable factors is not feasible, but knowing how important they are allows us to add them to an algorithm (computer programme) which can calculate an individual's risk of getting the disease alongside the other lifestyle factors (Tyrer et al 2004).

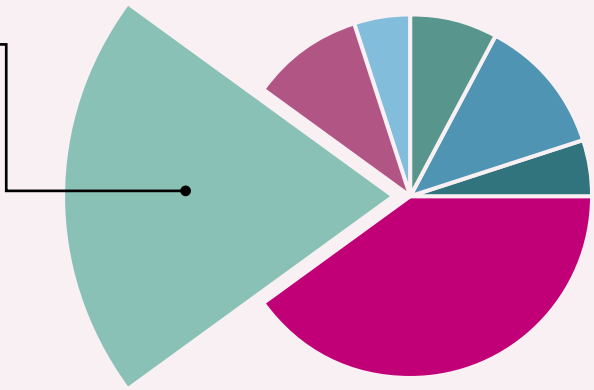
The fact that Western populations are ageing also contributes to the number of breast cancers diagnosed, but this is not an age-adjusted factor. However, the ageing process increases the occurrence of random gene mutations within our cells, so ageing is included in our list of non-modifiable risk factors.

A rare, non-modifiable risk factor is the treatment for cancers in childhood and early adulthood, particularly the treatment for Hodgkin's lymphoma. Young women who have undergone this treatment are eligible for NHS breast screening from a younger age.

Figure 4

20%
Non-modifiable risks

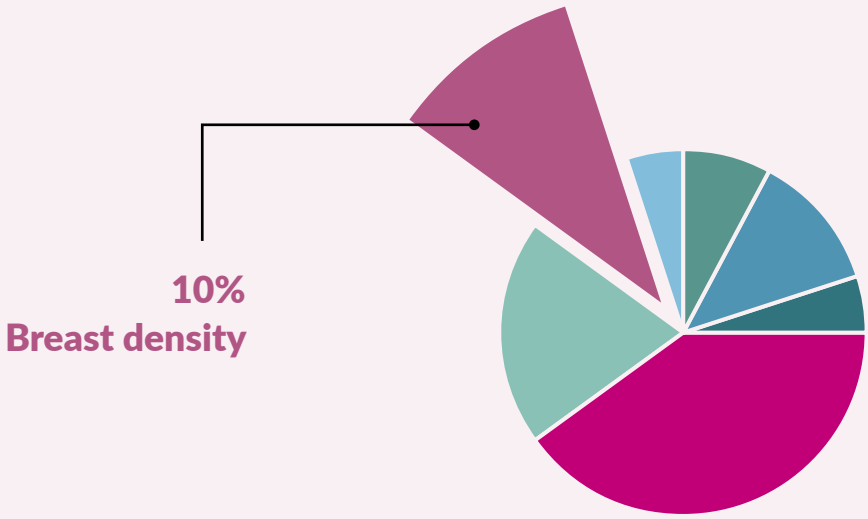
Early menarche
Late menopause
Height
Age 1st childbirth & parity
Cancer treatment when young
Ageing population



Breast density is another non-modifiable risk factor and much current research is investigating the link between breast density and cancer. Breast density refers to the density of breast tissue seen on a mammogram; denser tissue shows as white areas and makes spotting small cancers much harder. Although high breast density is not caused by any known specific genes, it seems to have a genetic component because families often have similar breast density. We can therefore assume that high breast density is caused by both a genetic component and a non-genetic component acquired during adult life, possibly reflecting exposure to hormonal influences. One study has suggested it may be more common in urban dwellers compared to those living in the countryside (Perry et al 2008).

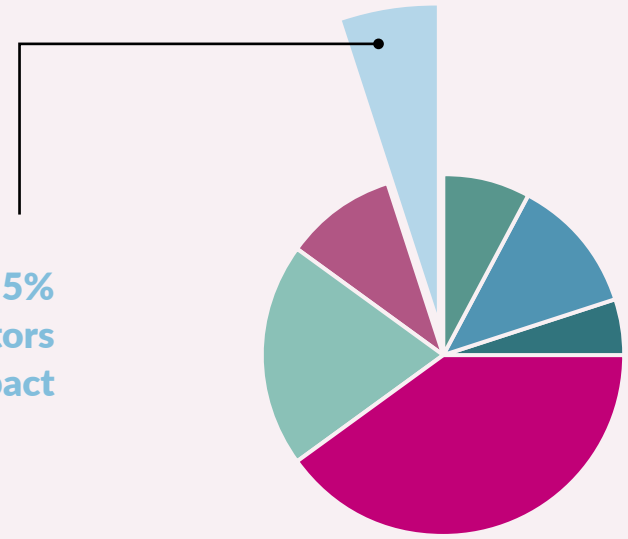
Interestingly, breast density is a strong predictor of risk that is independent of the 25% genetic risk and of all the modifiable and non-modifiable risk factors. It therefore registers as its own slice of risk, as shown on Figure 5. By investigating why some women have high breast density, we can discover new ways of preventing breast cancer.

Figure 5



The final slice of pie in the risk chart is environmental factors of unclear impact as shown on **Figure 6**. Included in this category are the artificial chemicals in our environment. In the modern world, we are surrounded by hundreds of chemicals used in plastics, cosmetics, pesticides, food preservatives and so on, and trace amounts can be found in human tissue, including breast and breast milk. Many of these chemicals are known to have mild oestrogen properties, and this is a theoretical concern because of the role of oestrogen in breast cancer. They are known as 'endocrine disrupters' or 'oestrogen mimics'. In laboratory tests using animals and cancer cell experiments, many of these chemicals can mimic oestrogen in producing potentially harmful cell changes. However, the impact of these chemicals, if any, is unclear. This is because, so far, all the incriminating evidence is either theoretical or circumstantial. As of yet, we have no direct evidence proving a causal link, in contrast to all the other known risk factors in the pie chart. The circumstantial evidence, placing these chemicals 'at the scene of the crime', is certainly worrying and researchers are continuing to look for evidence.

Figure 6



5%
Environmental Factors of unclear impact








Air pollution also comes under the heading of environmental chemical exposure, and there is some direct evidence from geographical location studies that prolonged exposure to higher levels of pollution over many years increases breast cancer risk, as does industrial exposure to solvents.

There is evidence that environmental radiation exposure causes increased cancer risk. For example, multiple X-rays and CT scans used to manage scoliosis of the spine has been shown to increase breast cancer rates later in life. However, the potential risk of X-rays must be balanced against the potential benefits. In theory, the X-ray dosage to the breasts from mammography could trigger one extra breast cancer for around every 50,000 women having routine breast screening with the NHS. Because early detection through screening saves lives, using mammographs in breast screening is 200 times more beneficial than the risk it represents.

Environmental radiation from the atmosphere or radon in the ground is also a theoretical risk. Studies of flight crew exposed to relatively high levels of cosmic radiation have more breast cancer cases than might otherwise be expected, but the effect may be related to lifestyle factors, thus making it difficult to prove this link. There is, however, good evidence that women who work night shifts have an increased breast cancer risk, probably due to disturbed circadian rhythm, which in turn disturbs hormonal patterns.

There are two challenges for researchers investigating environmental chemicals as a risk factor for breast cancer. Firstly, it is necessary to demonstrate a clear causal link between chemicals and breast cancer, for example through epidemiological studies and clinical trials. Secondly, it is necessary to show that this risk is modifiable and caused by certain chemicals in products that could be avoided, rather than in the environment around us.

2. How can we Prevent Breast Cancer?

The obvious place to start in our vision to prevent breast cancer is to address all the causes and risk factors one by one. However, as you can see, there is no one easy way to do this because of these multiple risk factors all working together. Each risk factor must be addressed one by one and in combination.

As well as considering and addressing the different risk factors, another important prevention strategy is promoting early diagnosis through breast screening. Screening can detect precancerous cells (cells that show abnormal changes but have not yet developed into cancer cells) and small breast cancers at stage 1 that have not yet become life-threatening. We now have the technology to predict which women are at a particularly high risk of developing the disease, so by offering regular screening to this group we can promote early detection and prevent breast cancer.

Another prevention strategy is to predict who is at high risk of developing breast cancer and offer them preventative drugs to reduce their risk. In the UK, there are already three preventative drugs (each a daily tablet) approved by NICE and available for high-risk women. There are also others in the pipeline.

Prevent Breast Cancer's research strategy involves four main areas of research working in parallel. We call these our four pillars of research:

- Gene research (gene mutations and SNPs)
- Screening and early detection (breast density research, screening techniques, risk prediction models)
- Lifestyle and environmental risk factors (diet, exercise, hormones, environmental chemicals),
- Preventative drugs (clinical and lab research using non-animal models.

3. What has Prevent Breast Cancer achieved so far?

Prevent Breast Cancer is a nationwide charity collaborating with researchers and institutions throughout the UK, including the University of Cambridge, the University of Southampton, UCL and Queen Mary's, as well as groups overseas in Oregon, Stanford, Toronto and across Europe.

Our researchers are part of the Manchester Breast Centre, a partnership for breast cancer research based at several sites across the city, including the Prevent Breast Cancer Research Unit at Wythenshawe Hospital, the Christie Cancer Centre, the Manchester Cancer Research Centre, the Manchester Centre for Genomic Medicine, and the University of Manchester Division of Cancer Sciences. The Manchester Breast Centre has become one of the world's leading research centres for breast cancer prevention. Most of our research is collaborative and we often co-fund prevention research with Cancer Research UK, Breast Cancer Now and the University of Manchester.

Single gene mutations

The UK's first Family History Clinic was set up in The Nightingale Centre in Manchester by Professor Tony Howell in 1988. Since then, our Family History Clinic team has been a major contributor to the discovery of multiple high-risk cancer-predisposing mutations in BRCA1, BRCA2 and other genes linked to breast cancer. These discoveries were made through index case identification and lab research carried out by the clinic, which remains the largest Family History Clinic in the UK. Our team has produced multiple papers on the clinical management of familial breast cancer and the outcome of prevention strategies, such as surgery and preventative drugs. Our laboratory team has published various papers on genetic variants and the genetics of oestrogen positive, triple negative and lobular breast cancer. Professor Gareth Evans, one of our Directors of Research, was chair of the National Institute for Clinical Excellence which produced the guidelines for addressing family history and breast cancer.

SNPs

One of the largest clinical studies in the world of breast cancer was called PROCAS (Predicting Risk of Breast Cancer at Screening), and was headed by our research team in Manchester under the leadership of Professor Gareth Evans. Since 2010, Prevent Breast Cancer has invested considerable funds into this area of research. The PROCAS 1 study recruited 57,900 women who had their breast cancer risk assessed when they attended their breast screening appointment, which included an analysis of SNPs for 10,000 of these women. Our team has been instrumental over several years in creating risk-predicting algorithms based on SNPs profile and calculated from over 300 individual known SNPs. The study demonstrated that women without a family history of breast cancer could be divided into distinct risk categories, from high risk to low risk, by assessing their mammogram, their lifestyle questionnaire, and their SNPs. The PROCAS 2 Study followed, and 3000 women were recruited to assess how feasible it would be for women to alter their lifestyles or take preventative drugs based on their risk profile.

This led to a further study called BC-Predict, which studied the feasibility of risk adapted screening (explained later on). This research has now led to the development of a new, clinically available test called a "Polygenic Risk Score", which gives someone a risk estimate based on their SNPs. Interestingly, this test is not only valuable for women without a family history, but also for carriers of the BRCA faulty genes, because it can modify their risk (certain SNPs might mean that the increased risk from the BRCA gene is lowered).

Familial cancers with unknown gene

The hunt for undiscovered genes in familial breast cancers continues, with our research team in Manchester at the forefront. It looks likely that no more highly penetrant genes will be found (i.e., there is no BRCA3). However, our team and others have found that a mutation can lie hidden within the BRCA area, situated in a non-coding piece of DNA. An epigenetic mechanism silences the gene, which is known as 'epigenetic gene silencing', meaning that the tumour-supressing gene is not functioning properly, which causes increased cancer risk. We are still investigating the existence of other gene-silencing mutations and trying to identify the remaining undiscovered genes which are likely to be less penetrant (weaker) than those already known to us. This is the subject of one of our current PhD research projects.

Modifiable risk factors

Since we were founded, one of our major focuses has been on the relationship between diet and lifestyle and breast cancer risk. For many years, we have been funding Dr Michelle Harvie, the only UK dietitian working full time on spearheading research into this area. In collaboration with groups in the US, Dr Harvie has proven that diet and weight gain have a huge impact on breast cancer risk. A diet of calorific and highly processed foods, high levels of alcohol consumption, weight gain and low levels of physical exercise have been confirmed as the largest piece of the pie in the breast cancer risk pie chart. Dr Harvie has also shown that reversing some of these factors reduces breast cancer risk, and she formulated the 2-Day Diet programme and co-authored a book about the diet with Professor Tony Howell, published in 2013. Since then, Dr Harvie and her team have produced multiple peer-reviewed publications. They have also produced online resources to help women lose weight, as well as educational materials for schools and colleges to disseminate her work and encourage a healthy lifestyle.

Non-modifiable risk factors

Unfortunately, non-modifiable risk factors do not provide any potential for developing risk-reduction strategies. For that reason, our research in this area has focused on using these factors to predict someone's level of risk. For many years, Professor Tony Howell has been working collaboratively with Professor Jack Cuzick to refine risk assessment tools in breast cancer: the Tyrer-Cuzick score and the Manchester Score. These are now widely used in clinical practice. In addition, Professor Howell collaborated with Professor Cuzick in running the largest ever breast cancer prevention trials, known as IBIS-I (International Breast Cancer Intervention Study) and IBIS-II. The IBIS-I trial demonstrated that tamoxifen given to women as a preventative breast cancer drug reduced the incidence of breast cancer by 40%. IBIS-II demonstrated an even bigger risk reduction of around 50% with the drug anastrozole. The Family History Clinic in Manchester was one of the biggest contributors to both studies. The Tyrer-Cuzick and Manchester Scores have been refined now to include breast density measurements and the two scores are used in the clinic to determine which individuals might benefit from preventative tamoxifen or anastrozole in line with the results of the trials.

Another example of a non-modifiable risk is cancer treatment in children and young adults that involves radiotherapy to the chest area. Dr Sacha Howell and Professor John Radford (The University of Manchester) have found that young women treated for Hodgkin lymphoma in their teens and twenties go on to have a lifetime risk of breast cancer equivalent to carrying a BRCA gene mutation (around 50% by aged 50), so these women are now eligible for MR and mammogram screening starting 8 years after their treatment.

Breast density

It has been a surprising discovery in recent years to learn how big an impact breast density, or mammographic density, has on breast cancer risk. The reason for this is something of a mystery. Breast density seems to have both genetic and acquired, non-genetic influences, and yet it stands out as its own separate 'piece of pie' in the pie chart of breast cancer risk factors. Because of this, Prevent Breast Cancer has commissioned Professor Rob Clarke and Professor Bill Newman's research into the biology of breast density. Areas of both high and low breast density have been microdissected from human breast tissue samples and then analysed using different techniques, such as

electron microscopy. Research has revealed that the dense areas are not caused by an increased number of breast ducts or greater amounts of connective tissue around the ducts, but rather how molecules, such as collagen and elastin, fit together.

This causes the tissue to become stiffer in nature, which in turn influences the behaviour of the cells around them. Cells show altered signalling pathways and more DNA damage. This work is continuing as we need to know more about what causes high breast density and how it might be lowered. Another of our researchers, Professor Cliona Kirwan, is investigating a possible link between clotting factors and wound healing with breast density.

Environmental of unclear impact

Hundreds of artificial chemicals can be found in human tissue, but so far, the evidence linking them to breast cancer is either theoretical (many are oestrogen mimics) or circumstantial (they can be found in human breast tissue and breast milk). For this reason, Prevent Breast Cancer has funded three studies to look for a direct link. The first investigated parabens (preservative chemicals that have oestrogenic properties), and the second investigated aluminium compounds (the key ingredient in underarm anti-perspirants together with parabens). The third investigated chemical ultraviolet (UV) filters (used in sun cream). These studies tested breast tissue from 40 mastectomies from women with breast cancer, taking samples from the axilla, lateral, mid and medial regions. Parabens and aluminium were found throughout the breast, but they were not concentrated in the axilla (armpit) or lateral regions. Furthermore, they were also found in 7 of the 40 women who had never used underarm deodorants or antiperspirants. The study did not demonstrate a link between underarm cosmetics and breast cancer. Three UV filters were also found in the specimens in similar distribution to the aluminium and parabens, including in the women who did not use cosmetics. Overall, there was no link between a high concentration of these chemicals and the position of the cancer in the breast. The conclusion of these three studies was that avoiding cosmetic products that contain parabens, aluminium or UV filters is not a protection from breast cancer. However, more research is still needed to investigate the link between chemicals and breast cancer.

Screening

A big focus of our recent research is the concept of 'risk-adapted screening'. At present, the NHS offers a "one size fits all" approach of a mammogram every 3 years offered to women between 50 and 70 years of age. However, we now know how to predict an individual woman's risk of breast cancer by analysing her modifiable and non-modifiable risk factors, her breast density, and her gene tests for both cancer-causing mutations and SNPs (polygenic risk score). Some women are at such a high risk that they should be screened every year. Some women have such a low risk that screening every 5 years or 10 years may be enough.

In addition, our team have also been researching the use of artificial intelligence and computer algorithms to analyse mammograms and breast density. Our team are one of four centres conducting a study called the BRAID Trial, investigating the new technologies of automated breast ultrasound (ABUS), contrast-enhanced spectral mammography (CESM), or abbreviated breast MRI (AB-MRI) in women with high breast density. Combining these new technologies with risk-adapted screening will have a significant impact and our ambition is to see these new technologies and risk-adapted screening adopted across the UK.

Screening For Younger Women

At present, there is no population screening available for women under 50 in the UK. As a result, there is no opportunity to detect early-stage breast cancers that occur within this age group.

The 'prediction' techniques described above also work for younger women, and could therefore identify many, if not most, of the women who are destined to develop breast cancer in their thirties or forties. This could be particularly important for the early detection of 'triple negative' breast cancer. This type of breast cancer is more in this younger age group and in women of African and South Asian ancestry. It could also help early detection of lobular breast cancer and cancers in women with a high breast density, which are harder to spot in a mammogram. We believe that the NHS screening programme should start at a much earlier age, and start with risk prediction. Those at a high risk could then be screened between 30 and 50 years of age. The next step is to investigate how the NHS could deliver this cost effectively, something that our team is currently working on. One example is the BCAN-RAY trial, headed by one of our scientific directors, Dr Sacha Howell, and funded by The Christie and CRUK. The trial is investigating how to detect high risk women without family history through testing for SNPs and breast density.

Preventative drugs

One of the biggest recent clinical achievements in breast cancer has been the large international research study called the ATAC trial. This multi-centre trial's Principal Investigator was one of our directors of research, Professor Tony Howell. This demonstrated that the drug anastrozole not only reduced breast cancer recurrence, but also prevented breast cancer developing in the opposite breast. This formed the basis for the National Institute for Clinical Excellence in the UK accepting anastrozole as a preventative drug for high-risk postmenopausal women (with no diagnosis of cancer), and tamoxifen for premenopausal women.

Prevent Breast Cancer has recently funded a project taking place in the labs of Professor Rob Clarke. The project is testing new preventative drugs using a pioneering technique called 'patient-derived mammospheres', where human breast tissue models are used as an alternative to animal testing. This is happening in the lab, alongside a multi-centre clinical research study called the Antiprogestin Prevention Study. This study has just been completed with Dr Sacha Howell as Principal Investigator, and the results will soon be published.

4. What are the next steps?

Our strategy for the next 5 years is to continue building on our four pillars of our research:

Gene Research
(gene mutations and SNPs)

Screening and Early Detection
(breast density research, screening techniques, risk prediction models)

Lifestyle and Environmental Risk Factors
(diet, exercise, hormones, environmental chemicals)

Risk Reducing Drugs
(clinical and lab research using non-animal models)

There is no single easy route to preventing breast cancer, and we believe that this multipronged approach is the correct one. Our Trustees and Scientific Advisory Board are aiming to fund a balanced portfolio of research projects across these four pillars and include both clinical research and lab-based research. We remain confident that the ever-swelling tsunami of breast cancer diagnoses can be slowed down and one day stopped completely in its tracks through prediction and prevention.

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1a. The genetic causes of breast cancer

Figure 1

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Figure 3

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