Has your name, address or telephone number changed?

If your name or address is different from that on the newsletter envelope, please detach and return this reply slip in an envelope (no stamp needed) addressed to:

Breakthrough Generations Study Team
FREEPOST NAT 21013
Institute of Cancer Research
Sutton SM2 5BR

(BLOCK CAPITALS PLEASE)

Title First name(s)

Surname(s)

Address

Postcode

Telephone number

Your date of birth (Day) / (Month) / (Year)

Your study number

(Six-digit number next to your address on envelope containing this newsletter)

For more information about Breakthrough Breast Cancer

Breakthrough Breast Cancer, who fund the Generations Study, is a charity dedicated to improving and saving lives through finding the causes of breast cancer, enabling early detection, ensuring precise diagnosis, discovering new and better treatments and improving medical services.

If you would like to know more about Breakthrough, please complete the other side of this slip and return it to the address below, or visit breakthrough.org.uk Please note that you will be giving your details to Breakthrough Breast Cancer, not the Generations Study Team.

Breakthrough Breast Cancer
FREEPOST LON 8816
London
WC1V 7BR

First PhD awarded from study research

Junior scientists who wish to make a career in medical research these days need first to undertake training and earn a PhD degree.

Danielle Morris, who joined the study team with these ambitions four years ago, has now, we are very pleased to say, achieved this qualification, and has therefore become Dr Morris. Danielle said, "I have enormously enjoyed working on the Generations Study, and I have learned a great deal. I would like to thank my colleagues here who have taught me so much, and also to thank the study participants, many of whom I have met personally."

At the end of last year Danielle moved back to her hometown of Leicester, where she started a new post in medical research at the University of Leicester.

She continued, "I loved working at the Institute of Cancer Research. I think the Breakthrough Generations Study is already a fantastic study and will only get stronger as time goes on. I'm a study member too, so hopefully I'll still hear about all the new research via the newsletter."

Danielle has also recently become engaged, so we would like to wish Danielle all the best both for her new job and for her forthcoming marriage.

Kim Sibley

We are very sad to report that a valued member of our staff, Kim Sibley, who had worked on the Generations Study for many years, died of cancer in the Royal Marsden Hospital on 28 August 2011.

Kim was originally a participant in the study and then helped as a volunteer. She later joined the staff, and worked here until a few days before her death – even when ill she was determined to come in when she could, to make her contribution.

She was a very kind person, full of spirit and determination, who took pride in all that she did, and especially took pride in her two daughters, Fiona and Lauren. Many of you will have spoken to her over the years if you have been in touch with the Study Team by phone. We will miss her greatly, as a colleague and as a friend. Her death is a sad and very personal reminder of why we are carrying out the Generations Study.

Online communications

As an alternative to the paper version, we will be offering for the next follow-up round the option to complete your questionnaire online. This will help to save on mailing costs, which could then be used for other aspects of the research, and also to reduce the use of natural resources. If you would like to complete future questionnaires online, or to receive future newsletters via email, please register to do so at **bgs.icr.ac.uk**

We do appreciate, however, that there are many of you who would prefer to communicate by post, in which case you don't need to do anything and we will continue to write to you.

We are grateful for the commitment and funding provided by the sponsors of the study, Breakthrough Breast Cancer **(www.breakthrough.org.uk)** and The Institute of Cancer Research **(www.icr.ac.uk)**.

Finally

Thank you again for your continuing support of the Generations Study. We are very grateful for the contributions of all of you, which make the study possible.

With best wishes,
The Breakthrough Generations Study Team

Issue No.6
Summer 2012

GENERATIONS

THE NEWSLETTER OF THE BREAKTHROUGH GENERATIONS STUDY

Welcome

Dear study member,

The past year has been an exciting one for the Generations Study. Analysis of the study questionnaires and blood samples that you have sent has progressed greatly and we are pleased to include details of some of the results in this newsletter.

Several of the papers published from the study this year have investigated the causes of factors that are associated with risk of breast cancer, while others have examined the genetics of the disease. The investigation of risk factors is important because it can lead to information on ways that women can lower their risk of breast cancer and also lower the risk for their daughters.

The study samples have been used during the year to contribute to the discovery of new genes associated with breast cancer risk. Such discoveries can help us not only to predict a woman's risk of breast cancer, but also to develop more personalised treatments for patients.

We also include in this newsletter some happy, and unfortunately also some sad, news about the Generations research team here at the Institute of Cancer Research.

The number of participants in the study has continued to grow over the past year with many hundreds of mothers and daughters joining the study from the invitation in last year's newsletter. The information from the mother-daughter pairs will be particularly useful for investigating breast cancer risk.

Thank you for your continued participation in the study. Without you the research could not continue. We wish you well for the next year and look forward to telling you about further progress in a year's time.

With best wishes,

Professor Anthony Swerdlow

Professor Alan Ashworth

Study progress and next steps

Just over 113,000 participants have joined the Generations Study. We have now sent most of you your first (2½ year) follow-up questionnaire, but for those who joined most recently, we will write to you as you reach 2½ years from joining. We would be most grateful if you would return your questionnaire if you haven't already done so, because the results of the study depend on completion of the follow-up questionnaires by as many of the study members as possible.

Those of you who have been in the study the longest will now have received your second follow-up questionnaire. We are currently asking for email addresses in this questionnaire in order to facilitate an online option for the next questionnaire. Postal versions will still be available, but for those who wish to complete their questionnaires online, they will be able to do so in the next follow-up round.

Three generations in the Generations Study

Judith, Sarah and Caroline

Judith Cooper and Caroline and Sarah Holmes are a grandmother, mother and daughter from Horsham, West Sussex, who have all joined the Generations Study. Both Judith and Caroline have had breast cancer.

Caroline said "Breast cancer, as all cancer, is scary. As far as I know I am the first person in our family to develop breast cancer – my Mum had it after me. We are not over weight, don't smoke and eat reasonably healthily. I thought we were doing all the right things but we got it anyway. I was lucky that the cancer was found at an early stage and so far it has not returned. I would prefer never to have been ill but I feel very lucky to still be alive."

Judith said "I was due to have knee surgery the day my breast surgeon scheduled to operate. She said that cancer took precedence, so the knee op was delayed about 6 months. Fortunately, my breast cancer was caught early. With my daughter and I both developing breast cancer in a short period, it's good to be able to support each other, and be able to talk frankly. It helps too, that we live only a few minutes walk from each other."

"I am very concerned about finding the causes. It would be so good if the possible legacy of it was removed from my grandchildren, as it could hang over them like the sword of Damocles! So finding the generational link is important. I also pray that the cancer stops here, and that Sarah and her little sister can look forward to a healthy future."

CONTINUED ON PAGE TWO

You can download copies of this newsletter, and other information, from our website: www.breakthroughgenerations.org.uk

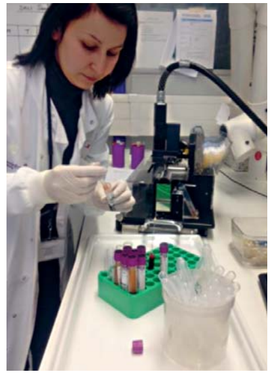
How your blood sample is processed

The blood sample you provided for the study is already being used to identify genetic and hormonal factors that may be associated with breast cancer risk. We describe here how the samples are processed and later in this newsletter explain some of the results from the blood sample analyses.

When your blood samples arrive at the Generations Study laboratory in London they are spun at a very high speed to separate the blood into its different parts. The cells that contain DNA and the plasma (the fluid that surrounds the cells) are then divided into very small portions for storage in long thin tubes known as "straws". Keeping them in such small portions (about 30 from the blood samples of each woman taking part in the study) ensures that in the future they can be used for as many analyses as possible.

The straws are then placed into colour-coded triangular tubes. These are stored overnight in a low-temperature freezer set at - 80°C, which freezes the samples rapidly. The samples are then transferred for long-term storage into tanks containing liquid nitrogen, which keeps the samples at -180°C. To give you an idea of how cold this is, the lowest natural temperature ever recorded on earth was -89.2°C at a Russian research station in Antarctica. Each individual's samples are divided up and stored in three different tanks to ensure that they remain secure.

A sophisticated computer system keeps track of precisely where each sample is stored in the liquid nitrogen tanks so that they can easily be retrieved for analysis. The cells that have been stored are used to extract DNA for genetic analyses, while the plasma, which is stored separately, can be tested to determine levels of female hormones such as oestrogens, and of other hormones such as those involved in growth.



Processing blood samples as they arrive at the laboratory

Hormones are undoubtedly important to women's risk of breast cancer and other female cancers, and we will return to discuss them in future newsletters, but in this newsletter we wanted to highlight, in the articles below, some aspects of the genetics of breast cancer.

Since each person's DNA has about 23,000 genes, the task to find out which genes have an impact on breast cancer risk is a complicated one. However, in recent years enormous progress has been made.

Three generations in the Generations Study

CONTINUED FROM PAGE ONE

Sarah said "My Mum's diagnosis was a bit of a shock as until then she had always been the strong and healthy one in our family. Thankfully the cancer wasn't that advanced and my Mum made a good recovery. She's always been amazing at carrying on with life in whatever circumstance."

"Grandma has recovered well too and we are all moving on and enjoying life as a cancer free family. I am also getting married in the summer so I am looking forward to that too."

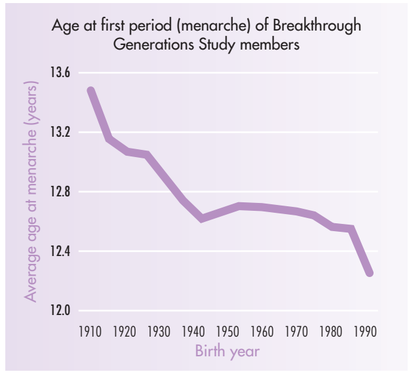
"Since my Mum and my Grandma have both had breast cancer, I think that it is hugely important to try to determine the causes of any kind of cancer as it causes such chaos in the lives of people that are affected by it. I am also very interested in finding out the results of the study in order to learn if there are any ways my sister and I can reduce the risk of getting cancer when we are older."

Families, genes and breast cancer

It has been known for 150 years that breast cancer sometimes runs in families, but only recently have advances in laboratory methods made it possible to find out how particular genes contribute to these risks.

It has turned out that many genes are involved in breast cancer risk, but there is a sharp contrast between the small number of rare genes that have very large effects, but only occur in a few families (you may have heard of the BRCA1 and BRCA2 genes), and a much larger number of more common genes that many women have, but whose effect individually is very small.

The article on the right describes the discovery of a new gene that is in the latter category, and which was found by a collaboration using Generations Study blood samples and samples from other studies. As we explained in a previous Newsletter (No. 4), international collaborations of this type can sometimes make discoveries more powerfully and more rapidly than individual studies separately. Finding all of the genes that have an impact on breast cancer risk is going to be a complicated task and will take many years. The search for those genes, so that women can be given clearer information on their personal risks, is a task that will therefore continue using your samples and those from other studies for many years to come.



Two pieces in the puzzle

Using samples from the Breakthrough Generations Study and other studies, a new gene has been found that is associated with breast cancer risk and another gene has been found to be associated with the most common type of breast cancer.

The first genetic findings have been made using blood samples from the Breakthrough Generations Study. Based on these samples and ones from other smaller studies in the UK and US, a new gene associated with breast cancer risk has been discovered. Although this gene has only a small effect on risk, it adds to information found previously about other genes that also have small effects individually. It is probably the combined effect of these multiple genes, each small in itself, that add to give a woman's breast cancer risk.

We believe there are more genes of this kind yet to be discovered. However, it is also important to find out if the genes that are already known affect risk of breast cancer in general, or only affect particular types of the tumour. In a second collaboration, involving blood samples from more than 46,000 breast cancer patients, including many from the Generations Study, it was shown that another gene was associated particularly with risk of the oestrogen-positive type of breast cancer.

Dr Julia Wilson, Head of Research at Breakthrough Breast Cancer, said, "This research provides two pieces in the puzzle of how genes affect our risk of developing breast cancer."

Journal of the National Cancer Institute 2011;103:425 – 35
Human Molecular Genetics 2011; 20:4693 – 706

Changing lifestyles and changing age at puberty

The Generations Study questionnaires will be used to investigate exactly how age at puberty affects breast cancer risk, but also we have been publishing research on how age at puberty has changed between the generations.

As we said in previous newsletters (Nos. 4 and 5), a woman's age at puberty, and her age at menopause, are related to her risk of breast cancer. We are now using the information you sent to us to investigate this in more detail, but in the meanwhile we have been publishing papers on the factors that affect age at puberty and age at menopause.

In a new paper we found that the age at first period (menarche) decreased by about a year when comparing Generations Study members born at the beginning of the 20th century and those born in the 1940s. Although there was little change between most generations born after the Second World War, the age decreased again for the youngest Generations Study members, born in the late 1980s and early 1990s. Interestingly, although in Victorian times, and also for the oldest members of the Generations Study, women from better-off families started their periods earlier than women who were poorer, the opposite is now true for the youngest study members – poorer girls now have their menarche younger than better-off ones.

While we don't know all of the reasons behind this, the decrease in age at menarche over time is important because the age at which a girl starts her periods can influence her chances of developing breast cancer later in life.

Since we have found that body weight is linked to the age at which a girl starts her periods (those who are heavier tend to start their periods earlier), and exercise also matters (those who exercise more tend to start their periods later), it is possible that diet and exercise changes in society are responsible for the trends in age at puberty.

Incidence of breast cancer has risen progressively over a long time in the UK and the latest statistics show nearly 48,000 women were diagnosed with the disease in 2008. This change has probably come about through a combination of factors, each of which individually makes a small difference, and one of which is likely to be the decreasing age at puberty.

Paediatric and Perinatal Epidemiology 2011;25:394 – 400

Using the Generations Study questionnaires for research on breast screening

It has become clear as the Generations Study has progressed that as well as being a powerful way to investigate the causes of breast cancer, the information in the study questionnaires could also be very valuable for research on breast screening and how it can be improved.

In the questionnaire you completed when you joined the study, you gave information about your past breast screening and where it took place. In order to be able to study screening better, we now plan to gain further screening information from medical records, for those study members who have already sent their signed consent for us to obtain their recorded information. If you do not wish us to do this in your case, however, please let us know and we will not include your records in this aspect of the study.

Please send me information on Breakthrough Breast Cancer

(BLOCK CAPITALS PLEASE)

First name(s)

Surname(s)

Address

Postcode

If you are happy to receive emails or telephone calls from Breakthrough Breast Cancer, please provide your email address and/or telephone number:

Email

Telephone number