

## Welcome

Dear study member,

It is some time since we last sent you a newsletter from the Generations Study. The study has continued very well, but I must apologise that various changes, described below, have resulted in a delay in preparing and sending this newsletter to you.

One change has been that our funders since the cohort started, Breakthrough Breast Cancer, have merged with another breast cancer charity, Breast Cancer Campaign, to form the UK's largest breast cancer charity, Breast Cancer Now, who are now our funders. One consequence is that we have altered the name of the study to simply "The Generations Study", since Breakthrough no longer exists. This does not affect in any way how the study works, or how we hold your personal data which have not been, and will not be, passed on to the funding charity.

A second change is that although the study team has been very stable since the study started in 2003, a 40-year study cannot continue with exactly the same staff forever. Professor Alan Ashworth, who was the joint leader of the study when it started, has now left to work in the United States. His input was vital to the study's creation, and we are continuing scientific collaboration with him. However, the other scientists working on the study have been here for many years and continue to work on the research – we introduce one of them to you in this Newsletter.

The last few years have also seen a large number of scientific papers published from the study: there are now more than 100 in total. This Newsletter includes a description of the results of some of them.

Finally, may I wish you all the very best for the coming year and indeed for the coming decades. The Generations Study has come a long way, and is fulfilling the potential that we hoped for when we started it 15 years ago. Thank you again for your help that has made this possible.

With best wishes,



Anthony Swerdlow, Professor of Epidemiology  
The Institute of Cancer Research

## Lauren Wright: study statistician



**Lauren Wright is a medical statistician working on the Generations Study at The Institute of Cancer Research in Sutton. Lauren was born and raised in County Durham. She studied mathematics at York University and statistical epidemiology at Leeds University.**

Her interests outside of work are competitive ballroom and Latin dancing, reading historical fiction, and going for country walks. It was the shock of suddenly losing her grandmother to stage 4 lung cancer that inspired Lauren to combine her passion for mathematics, science, and helping others, to pursue a career in cancer research. In 2014, Lauren joined the Generations Study team as a medical statistician.

As a statistician Lauren carries out analyses using the information from the study questionnaires and blood samples, looking particularly for links between lifestyle factors and breast cancer risk. These analyses involve several team members, so that Lauren's day is spent working with others, and has continual opportunities to learn from other, more-experienced, statisticians and epidemiologists, and also to learn how to write scientific papers. She has recently published a paper examining whether there is a link between complications of pregnancy and subsequent breast cancer risk.

She found that women who suffered pre-eclampsia during pregnancy had a one third lower risk of developing breast cancer before the menopause than women who had no pre-eclampsia history. This may be

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linked to altered hormone levels. However, she found no evidence that another pregnancy complication, hyperemesis gravidarum (severe vomiting in pregnancy), was related to breast cancer risk. The aspect of her work that Lauren values the most is knowing that the Generations Study and her research can make a real difference to people's lives.

Lauren explains: "I hope that the work we do now will contribute to reducing breast cancer rates in the future, as we could understand better the reasons why breast cancer develops. By following women's lifestyles and health over many years, we have an incredible opportunity to uncover as-yet-unknown risk factors and to enable women to reduce their risks and those of future generations."

This research would not be possible without our participants filling in questionnaires and sending samples to the Study staff.

"I am always very aware, as I work with the data, of the time that you have all contributed. It is your continuing dedication to provide exceptionally detailed responses to the questionnaires that gives us such high quality data to work with."

## Findings from the Study

The research outputs from the questionnaires and samples that you have contributed to the Generations Study have been growing rapidly since we last wrote to you. There are now more than 100 scientific papers published from the Study, and we are pleased to describe here some recent highlights.

### Assessing family history more accurately

Family history is an important risk factor for breast cancer, with about one case in ten occurring in a woman whose mother, sister or daughter has already had breast cancer. However, for predicting risk, it is incomplete to consider only the number of breast cancers in a woman's family: the size of family matters too. Women with many sisters might be expected, on average, to have a sister with breast cancer more often than women with only one sister. Similarly, the younger a woman's relatives are, the less likely, on average, that they will have had breast cancer.

Therefore, using the very detailed family history information that you gave in the Generations Study questionnaires we developed a more accurate method to assess family history risks, taking into account both the number of breast cancer cases in a woman's first degree relatives and the number of female relatives she has and their ages. We hope that this new method can be added to existing factors to offer women a more accurate prediction of their risk of developing breast cancer, and

hence to allow them to make more informed decisions about managing and reducing their risk.

### Smoking and breast cancer risk

Smoking cigarettes is known to increase the risk of around 14 different types of cancer, most notably lung cancer. It has been uncertain whether the same could apply, to a lesser extent, to breast cancer. A number of plausible biological reasons have been suggested, but to date studies have been inconsistent as to whether there is a link.

We recently analysed information provided by Generations Study participants and found that smoking was indeed associated with an increased breast cancer risk within the cohort. Those who had smoked at some point in their life had a 14% greater chance of developing breast cancer than women who had never smoked, and this risk was even greater - by 24% - for women who had started smoking before age 17. These risks may particularly apply to women already at an increased risk of breast cancer due to their family history of the disease; our results showed that female smokers with a family history of breast cancer were around 35% more likely to develop the disease than a woman with a family history who had never smoked.

There are already very strong health reasons not to smoke, and these findings add to evidence that there may be a further reason, especially among those who are young.

## Questionnaires

**Although we have not been able to send you a newsletter for a while now, we have nevertheless been making good progress with the Study.**

We continue to send out follow-up questionnaires to you every three years or so, to keep up to date on changes in study members' lives and health, because it is the pattern of women's lives over the years, not just at one moment, that affects breast cancer risk.

There are now more than 113,000 women who have joined the Study. Nearly all of you have been study members for long enough to have sent back your first and second follow-up questionnaires, and three quarters have now received the third questionnaire. Those of you who joined the very earliest, 15 years ago, have recently been sent your fourth follow-up questionnaire. It can be completed online, which would save on costs that can then be spent on the research. If you have already sent us your email address, or if you register now on the study website (<https://bgs.icr.ac.uk>), then when your questionnaire is due, we will send you an email notification for you to complete it. If we don't have your email address, we will still send you a paper questionnaire to complete.

Thank you for the time and effort you have all put into the questionnaires - they are a vital part of the Study's success.

# Study members: Helen Lavis and Jayne Hawksley



**Helen Lavis and Jayne Hawksley are twin sisters who both joined the study in 2007. Helen had had breast cancer in 2006. Jayne has twin daughters, but she and her daughters are well. Breast cancer is of course a concern.**

Jayne tells us about their family and growing up together: "Our mother didn't know that she was having twins, 60 years ago until we appeared. This must have been a tremendous shock! I also had quite a surprise when at the age of 44 I was told that I was expecting twins, they are now 16 years old and beautiful identical girls. Helen and I are identical too and it still amuses both of us to be mistaken for the other even now.

My sister and I were very close growing up: we had an older brother who was away at boarding school. We had quite a strict upbringing which probably made us closer. We chose quite different career paths, I went into fashion buying and Helen had a successful career as a podiatrist. As well as the twin girls I have two boys who are now 26 and 28 years old, so I have had a fulfilling life with both a career and motherhood.

When Helen told me that she had been diagnosed with breast cancer I was terrified for her and for the journey that she had to

go on. Having lost both parents and sadly our brother in a car accident I couldn't contemplate losing her and so I tried as hard as I could to support her during her operations and treatment. It was such a difficult time as we lived far apart and I had a young family to raise. I felt hopelessly inadequate at times when I saw how poorly Helen was especially during the chemotherapy. I knew that Helen needed me so much during this time and I remember my feelings of guilt if I was out enjoying family time. Many, many times I asked myself why you and not me?"

Helen says: "I'm the eldest identical twin by 10 minutes – I wonder if that made the difference! At the time of my chemotherapy Jayne had her work cut out with her twin girls



*As well as a twin sister, Jayne also has identical twin daughters.*

who were only four years old, it must have been tough for her when she knew that I was feeling paranoid about being left alone during the treatment and I know that she did her best to be supportive. When you are a twin you know what the other is thinking and feeling.

I don't have any children, and I never wanted breast cancer to dominate the lives of my sister and nieces. We discussed genetic testing but I left the decision up to her and we didn't go along that route. The treatment is not pleasant but you need to get on with it as quickly as possible putting all your energy into getting better. I want to feel free and not worry about my sister and her twins. Let's hope a cure is found soon.

Post cancer I am a different person. I look ahead to the future and even think about lovely things I want to do a year down the line. I fill my life with as much fun and joy as possible. I am aware of my limitations due to some post op pain but listen to my body when I need a rest. I take more time to enjoy life with my partner and always go to sleep feeling content with my lot. I am positive about the future and I don't dwell on the past. Jayne and I have just celebrated our 60th birthdays together – thank goodness we didn't choose the same dress to wear – it can often happen!"

Jayne says of the future: "My hopes for the future are that my beautiful sister Helen lives a long, happy and healthy life; she survived and fought bravely. I hope that my children are not touched by cancer, but if they are I think that as each year passes the medical advances will be of huge benefit to them." And finally, Helen and Jayne's advice from the experience: "Go for it, if you can, for as long as you can."

We, from the Generations Study Team, totally agree.

# More findings from the Study

## *Sex hormones and mammographic density*

Breast cancer is a hormonal disease. It has been known since George Beatson's pioneering operation in Glasgow in 1895 that removal of the ovaries (oophorectomy) can reduce the risk of breast cancer recurrence, and the 100-fold difference in risk of breast cancer between women and men reflects, at least in part, the very different sex hormone levels between the sexes. Another important factor affecting breast cancer risk is the structure of a woman's breasts – in particular how 'dense' they appear when an x-ray of the breast (a mammogram) is done.

Although it is clear that a woman's levels of sex hormones and her breast density are related to her risk of breast cancer, it is important to know also whether these factors influence a woman's risk independently (separately) or not and therefore what their effect is together. Using information from Generations Study participants, we examined the separate and combined impacts of these two factors on an individual's risk. From our analysis it appears that these effects are in fact independent, with women who had the highest levels of both sex hormones and breast density being seven times more likely to develop breast cancer after the menopause than those with the lowest. This knowledge is important in understanding the causes of breast cancer and in helping to identify women with an increased risk, who might benefit from more regular screening or preventative measures, to reduce their risk and diagnose breast cancer early if it does occur.

## *Unravelling the genetic causes of breast cancer*

In recent years there has been enormous progress in worldwide research to find the genetic changes that put a woman at raised risk of breast cancer, and the samples you contributed to the Generations Study have been an important part of this international effort. Over 170 genetic changes called single nucleotide polymorphisms ("SNPs", pronounced snips) have now been discovered that affect the risk of breast cancer, and blood samples from the Generations Study have been used in the discovery of the great majority of them. 2017 was a particularly successful year: in one paper alone, which included Generations samples, 65 new SNPs for breast cancer overall were found, and in another 10 SNPs affecting risk of oestrogen receptor negative breast cancer were discovered.

Each SNP on its own has a small effect, but together their effect is considerable. Their discovery will enable much more precise assessment of women's genetic risk than has previously been possible. We and our collaborators are working to combine the information from these SNPs with information about other factors that affect breast cancer risk, to provide methods to enable better personalised prediction of breast cancer risk for individual women according to their personal circumstances, lifestyle and genetic make-up.

## Our sponsors

**We are grateful for the commitment and funding provided by the sponsors of the study, Breast Cancer Now and The Institute of Cancer Research.**

As noted in the letter on the front of this Newsletter, the charity Breakthrough Breast Cancer, which had sponsored the Generations Study since its inception, merged in 2015 with Breast Cancer Campaign to form Breast Cancer Now. Breast Cancer Now are very committed to the Study and continue to fund it. They are the largest breast cancer charity in the UK and fund a wide range of breast cancer research. You can find out more about them at [breastcancer.org](http://breastcancer.org)

This change in the funder does not affect what happens to your data or samples. Your identity and your personal information are kept securely and confidentially by the Study team at the Institute of Cancer Research, and have not been, and will not be, released to the funding charity.

**breast cancer  
now**

**ICR** The Institute of  
Cancer Research

## Can we email you instead?

To minimise costs, we send newsletters electronically to study participants for whom we hold an email address, unless you contact us to say that you don't want this. We will still continue to send newsletters by mail to those for whom we don't have an email address.

If you received this newsletter on paper but would be willing to receive it electronically in future (or received it electronically but would prefer paper) please let us know.

## Thank you

Thank you again for continuing to take part in the Generations Study. Without the contributions from all of you, the study would not be possible.

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# Has your name, address or telephone number changed?

If your name or address is different from that on the newsletter envelope, please update it at <https://bgs.icr.ac.uk/cod/cod.php> or detach and return this reply slip in an envelope addressed to:

**Generations Study Team  
Institute of Cancer Research  
15 Cotswold Road  
Sutton  
SM2 5NG**

(Please fill in BLOCK CAPITALS)

Title

First name(s)

Surname(s)

Address

Postcode

Telephone number

Email address

Your date of birth      Day / Month / Year

Your study number

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

