

Issues of consent and feedback in a genetic epidemiological study of women with breast cancer

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Women (N=21) who had had breast cancer and had been enrolled in a large genetic breast cancer epidemiological study were interviewed about their experience of participation in the study, their attitudes to the confidentiality of data, and the feedback of personal and general research results. Collection of family history information seemed more salient in indicating the genetic nature of the study than the enrolment information sheet. There were no concerns about confidentiality.

While participants would have welcomed general feedback about the results of the study and were critical that this had not been provided, the feedback of personal information proved complicated and, sometimes, difficult. It is suggested that individual feedback of genetic test information in epidemiological studies should be undertaken only when there are specific reasons.

A growing number of population based genetic studies have been set up, or are planned, to explore the roles of gene mutations and polymorphisms in disease. Such studies raise questions about participants' consent, confidentiality of information, and the feedback of findings, which have been widely discussed.¹⁻⁴ As Knoppers⁵ comments, the communication of results has long been a sensitive issue in large scale human genetic studies for both aggregate and personal results, not least because results may become available long after the initial participation. Indeed, this has led some data banks, such as the DeCode Icelandic project, to use unidirectional encryption.⁶ We are, however, unaware of reports of participants' experiences of involvement in such studies and their views on these issues. We provide such a report from participants in the UK Anglian Breast Cancer Study (ABC).⁷ This study offered participants the possibility of receiving personal results but no aggregate results were initially given. In our interview study we also explored participants' attitudes to the confidentiality, and to the wider use, of the data and DNA that they had contributed to the ABC study.

PARTICIPANTS

The Anglian Breast Cancer Study

This is a study of all incident cases of breast cancer in the area served by the Anglian cancer registry occurring in women under the age of 65 years, combined with a retrospective collection of breast cancer cases diagnosed under the age of 55 between 1991 and 1996. It aims to describe the prevalence of BRCA1 and BRCA2 mutations and various lifestyle and socio-demographic factors, and family histories of participants. Patients are invited to complete an epidemiological and lifestyle questionnaire and a family history. A blood sample is taken by their general practitioner (GP). A BRCA1 and BRCA2 mutation analysis is being carried out on participants' DNA. At the time of our research 1484 women had been enrolled in the ABC study at the time of our research. Women are identified through the Anglian Regional Cancer Registry and, after first checking with their GP, they are approached by letter and provide written consent for the study before they receive questionnaires and blood is drawn.

The information sheet provided for potential participants states that the study was designed to find out more about the causes of breast cancer, using the comparison of family medical history, and blood samples and that the blood sample

would be used "to look for any differences which can give us clues to genes which might increase breast cancer risk. This may take several years, and, since most cases of breast cancer are probably not the result of genetic differences, we expect most samples to be entirely normal If we do find something, it may indicate that members of your family might have an increased risk of developing breast cancer . . . you can indicate whether or not you would like to be informed if we find something. The results will not be given to anyone else without your consent." The consent form also states that the blood sample will be used to "test for genes which may confer an increased risk of breast cancer and possibly other cancers" in the participant's family.

Of those enrolled in the study 93% indicated that they wished to be informed if something is found. If a BRCA1 or BRCA2 mutation is found, a woman requesting feedback receives a letter saying that something of interest to her and her family has been found and she is offered an appointment at the regional genetics centre. All offered it took up this invitation, although one woman only did so after she had received a phone call from the research nurse repeating the written invitation. Counselling was provided by a cancer geneticist. If the woman agrees, a second blood sample is drawn for a clinical mutation test. At this point the laboratory is made aware of the mutation that has been found by the research team. Results are given at a second counselling session which occurred up to six months after the first session. At the time of our study, 16 women had received letters to say something had been found, and all had been tested in the clinic. In two cases, when retested, no mutation was found. One of these was further complicated because the proband's sister was also enrolled in the ABC study. She did not receive a letter but her sister told her about hers and she attended the regional centre with her sister and also had blood taken for a mutation test. No BRCA1/2 mutation was found in either sister.

METHODS

Interview study

We have carried out semistructured interviews (face to face or by phone) with three groups of ABC participants: group A, who had requested personal feedback and received recall letters (N = 9) (this included the two sisters where the mutation was not confirmed on clinical retesting); group B, who

Table 1

	Number approached			Number interviewed	Mean age years	Range
	Sent	Returned	Declined			
Group A	16	10	1*	9	47.4	39 to 56
Group B	12	11	2	9	52.8	48 to 62
Group C	10	8	5	3	42.6	32 to 61

*The woman who returned the form but declined to take part in our study was one of the women for whom the mutation found in the ABC study was not confirmed by clinical retesting.

requested feedback but for whom, as yet at least, no mutation has been found ($N = 9$), and group C, who did not want feedback. We had intended to interview 10 women for group C. But, perhaps not surprisingly, the women approached were reluctant to take part in our study and we decided it was not ethical to continue the recruitment process, having interviewed three women. The groups B and C were selected at random from women enrolled in the ABC study in the last two years. We also interviewed the cancer geneticist who saw the group A women in the clinic (see table 1).

RESULTS

Most of those we interviewed understood that the ABC study was about genetics and inheritance of breast cancer, although this was expressed in a wide variety of ways. "I guessed it was to do with genetics. They didn't say that but I thought they would check the genes". "It's the gene factor". "I guessed it was something to do with hereditary (*sic*), a genetic thing". "Because of the family history I knew it was genetics". Many could not remember what the information sheet said, or recall seeing it at all, but the fact that they had filled in a form about their family history of cancer was highly salient and this was often specifically mentioned. Many were familiar with stories in the media about inherited breast cancer.

The most common reasons given for taking part in the ABC study was to help others and the importance of cancer research. Many mentioned their own family and the potential help the study might give to their sisters or daughters. One woman hoped the study would tell her "where her cancer really came from", while another saw the study as a (potential) opportunity to have a genetic test which had been denied to her sister because she did not have the necessary family history of breast cancer to qualify for a test in a National Health Service (NHS) clinic. Women also found the questions on lifestyle relevant and interesting. For a minority of women this aspect of the study was predominant in their perceptions of the research.

Those who had not requested feedback (group C) shared the same general wish to help others by taking part in the research but all three of them had particular reasons for not wishing to face the issues that receiving feedback might raise. Two were young (aged 35 and 31) and both had young children. In one case the woman's first child died in infancy and she was diagnosed with breast cancer a few months after her second child was born. The other woman said she had found the collection of the family history information very upsetting and in the end had not completed the form for the study. The third woman was very involved in the impending birth of a grandchild and was worried about the possible impact any adverse information might have on her daughter.

Completing the family history form had had a significant effect for a minority of women who, in making enquiries amongst their family, had become aware of cases of cancer they had not known of previously, or it had simply brought home to them that cancer ran in their family. Despite the relevance many saw for the ABC study for their own families, all the women we interviewed said they would have been content

to join the study even if they knew there would be no individual feedback to participants.

None of those we interviewed had any concerns about confidentiality in relation to the ABC study. We asked if they knew how they had been selected for the study. None did; most simply assumed the researchers would have been told by their GPs or the cancer clinic of their breast cancer. Such possible passing on of information did not cause any concerns. In fact, the sample had been identified through the regional cancer registry but this was not stated in the information given at recruitment. The existence of such a registry was unknown to all but one of the interviewees, who include two nurses and a GP's secretary. The woman who knew of the registry had a close relative who worked in cancer research.

Women were asked how they would feel if their blood sample was passed to other medical researchers for work on other diseases "such as heart disease or mental illness". All said they would be quite happy for this to be done. They were further asked what they would feel about their samples going to a commercial company or a drug company for research. Most were also content with this though a couple were a little hesitant. One had concerns over patenting and said she would only agree if it was for a drug that would be available to everyone. She said she thought that cancer research should be done by the government, not private companies.

As mentioned already, the majority of women in the ABC study opted to receive personal feedback if anything was found. Their reasons varied from very specific concerns about inherited breast cancer to do with themselves or family members, to a more general sense of wanting to have whatever information the study produced. But, importantly, all said they would have joined the study even if no individual feedback had been offered.

Half the women interviewed suggested spontaneously that they would have liked to hear more about the progress of the research and all the others, when asked, said they felt there ought to have been some general feedback about the outcomes of the study for all participants. This included those who did not want personal feedback. The women wanted to know the aggregate results of the research and thought this could have been done by letter or through a leaflet. A minority felt very strongly about this and implied that it was a fair return for the contribution they had made to the research. Apart from this lack of information about the results of the study, the interviewees said they felt sufficiently informed about the ABC study. Only one woman (who was in the group who did not request feedback) had taken up the invitation given in the information sheet to phone a research nurse for further details.

Providing genetic counselling for those who were given feedback created the unusual situation in which the genetic counsellor (a cancer geneticist) already had information about the mutation the researchers had found. In the first cases seen, women were counselled on the assumption that the clinical retest would almost certainly confirm what the researchers had found. Most of these sessions were taken up in discussing the implications for the woman and her family of the mutation she was thought likely to be found to carry.

Women were very appreciative of the explanations given and the time spent by the counsellor with them. They left the clinic assuming they would go back to hear that the retest was positive. Sometimes their wait was lengthy (up to six months). One said she was “on tenterhooks waiting, though I knew it would be positive”.

After seeing the two women where clinical retest failed to find a mutation, the counsellor changed what he said to be more circumspect and there was much less discussion of implications of a positive test result. However, none of the women seen after this change were particularly surprised when the positive test result of the clinical retest was given. The way the need for retesting was generally understood by the women was that a faulty gene had been identified by the study but it could be “anybody’s”, so a retest was needed to see if a particular individual carried it.

Several women were shocked at their risk of a second breast cancer or of ovarian cancer, which was described in the counselling. This was something they had not previously considered.

“It was a bit of a shock . . . I didn’t know if you had this gene you had a higher percentage chance of it coming back”.

“I was not upset. I was surprised by the connection between breast and ovarian cancer”.

The implication for family members of the information women were given during the counselling was not always easy for them to accept. A few of the women seemed to find it particularly difficult to tell family members about the test result and its implications. Precise comparisons are very difficult here, but our impression was that, for some, this was more difficult or was less likely to happen than would be the case for the general population of women at risk who are tested for BRCA1 or 2 mutations in the clinic.

One woman said that after she had left the clinic she “had felt dirty” and that she was “spreading it to hundreds of people”. Another, who had not told her daughters about the study said that telling her daughters was going to be the most difficult part of her involvement in the research.

As the result of receiving a positive clinical test result, women took a number of clinical decisions, including having a prophylactic mastectomy and oophorectomy, as well as starting various forms of screening. One woman, who had been hoping to stop taking Tamoxifen five years after her diagnosis, as this had given her unpleasant side effects, realised this might not be appropriate after a positive test result.

Perhaps not surprisingly, the two women who were least satisfied with their involvement in the ABC research were the two sisters who received negative test results in the clinic. They both said they accepted that genetic research is complicated and there is much more to learn but they both felt they had been given feedback prematurely: “they should have waited until they were sure”. They resented the distance (60 miles) they had to travel to the clinic and the time they had spent, “to learn nothing”. They had told the clinic that if anything more emerged in relation to their samples that they should be told by letter. Another woman, whose research result was not confirmed by clinical retesting, declined to take part in our study.

COMMENT

In discussing these interviews we should be mindful of two limitations. Our sample is a small one, and necessarily so in the case of those who received individual feedback. We are struck, however, by the consistency of many of the attitudes

across those women to whom we spoke. The second point is that all the women we interviewed have had breast cancer and so had a strong interest in that disease and research related to it. Clearly we should be very cautious in generalising our findings to studies that involve a general population which has not been diagnosed with a serious disease. Our study is relevant, however, to other population genetic studies such as the Medical Research Council (MRC) funded DNA collections of those with inherited cancer and their relatives.

Our interviews suggest that those who have had breast cancer are pleased to take part in genetic epidemiological research and do not perceive any particular issues related to confidentiality. Furthermore, participants said they were content for their blood samples to be used for other medical research. Most, but not all women, included commercial or drug company research in this. Without further evidence, however, it should not be assumed that a general population sample, rather than women who have had cancer, would share these attitudes.

The question of individual feedback is more complicated. When the ABC study was set up the relevant local research ethics committees insisted that participants were offered the possibility of feedback on an individual basis and the multicentre medical research ethics committee (MREC) took the same view for a similar study of families at risk of inherited ovarian cancer. In taking this view the committee endorsed the widely accepted principle that if researchers uncover information relevant to the health of participants, this should be given to them so that they can make informed choices about their care.⁸ Ninety three per cent of the women participants in the ABC study chose to receive individual feedback. A very small proportion of these were found to have a BRCA1 or 2 mutation. Those who received this information had, with clinical information and advice, taken various actions themselves—for example, prophylactic surgery—and in some cases had passed information to relatives who themselves were taking action—for example, seeking predictive testing. We should also note that the ABC study revealed mutations in some women whose family was not known to have a history of breast cancer. Thus these mutations would not have been found by the usual clinical strategy of offering predictive testing to those whose family history suggests a high risk of a gene mutation being present.

Giving individual feedback also raised some difficulties, however, as our study illustrates. Most obviously, because the methods and standards for mutation detection differ in research and the clinical context, there are the difficulties caused for those who are first told that the researchers have significant information for them and their families but then after counselling and clinical retesting are informed that a mutation cannot be found. This left the women somewhat frustrated, believing that they may carry an inherited risk but associated with a gene(s) yet to be discovered. The failure to verify clinically a mutation apparently identified in research is likely to be a rare event. Not only will it be unsettling for those directly involved, however, but it complicates genetic counselling for all those receiving feedback. We found that participation in a genetic epidemiology study might influence attitudes to family genetic risk. In providing a family history, participants may seek information from other family members and they and other members may become aware of a potentially significant pattern of disease in the family. We also found that a motive for participation in the ABC study was that the study might provide helpful information about inherited risk for themselves and family members. This will only be true, however, for those very few individuals who have a mutation identified. This suggests there could be participants who may be disappointed by this aspect of their participation in the population study, though this was not expressed by the small group of women we interviewed.

Women in the ABC study who were found to have BRCA1/2 mutations were given a predictive genetic test without following the usual clinical protocol of pretest counselling. They were invited to attend the genetic clinic with a letter which stated that something of significance to them and their families had been found in the research. As we have seen, this left the cancer geneticist with a complex counselling task before blood was drawn for the genetic test. Effectively, these participants gave potential agreement to have a genetic predictive test when they consented to take part in the research study. It is unclear, however, whether they really understood this and therefore whether they may be said to have given informed consent for this. Not all had discussed their participation in the study with their family so when a positive result occurred, it raised particular difficulties in communication with those family members who were revealed as now "at risk".

A further point concerns the generalisation of these considerations to population studies. Two aspects of the ABC study simplify the question of individual feedback to participants. The ABC study involves a population of women all of whom have had breast cancer, they are a group with obvious interests in knowing whether they carry an inherited predisposition to breast cancer. Furthermore, the inherited subset of breast cancer cases has been widely discussed in the media and may be relatively well understood by the public. Several of the women were shocked, however, by the knowledge that they also have a risk of ovarian cancer. This has implications for studies of other inherited cancer syndromes where there are risks of more than one kind of cancer—for example, colorectal and uterine cancer in human non polyposis colorectal cancer [HNPCC]). Healthy individuals who may be unaware of any particular inherited disease risk are likely to react rather differently to revelations of genetic risk that might be fed back to them in a research study. We should also note that in a study like the ABC one, the great majority of women will receive no individual feedback because they are not mutation carriers. There may be issues of false expectations.

Germline mutations of BRCA1 and 2 are associated with a Mendelian disease and disease risks are relatively well understood. Advice for those in affected families can be grounded in research evidence. Similar arguments are unlikely to apply to genetic polymorphisms associated with common conditions, or low penetrance Mendelian diseases, where risks are less well understood. It is such genetic polymorphisms which will be sought in population studies such as the proposed MRC/Wellcome Trust Biobank UK.⁹

These considerations lead us to conclude that, unless there are some very clear and specific reasons, individual feedback should not be offered at recruitment in genetic epidemiology studies. Wherever possible, the data in such studies should be anonymised. Such a procedure has the additional advantage of avoiding the possibility of having unknown untoward future obligations to reveal information.⁹

On the other hand, our research suggests participants would welcome regular information about the progress of research and what may have been achieved—perhaps in the

form of a newsletter and a website that participants can consult. As a result of our study, a leaflet giving general feedback about the ABC study has been prepared and will be sent to all participants in the study. As part of such information, as well as at enrolment, participants should receive details of appropriate clinical services where they may obtain advice and information about any inherited condition that may be of concern to them or members of their family. This suggestion is in accordance with national⁸ and international ethicolegal standards.⁹

As a final point, we would suggest that this study demonstrates the value of empirical evidence for informing bioethics debates. It shows—for example, that the importance and salience of issues for research participants may not be the same as for all those who contribute to these debates from a more theoretical standpoint.

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REFERENCES

- 1 **Human Genetics Commission**. *Whose hands on your genes?* London: Human Genetics Commission, 2000. Also at www.hgc.gov.uk
- 2 **Human Genetics Commission**. *Inside information. Balancing interests in the use of personal genetic information*. London: Human Genetics Information, 2002. Also at www.hgc.gov.uk
- 3 **Martin P**, Kaye J. *The use of biological sample collections and personal medical information in human genetic research*. London: Wellcome Trust, 1996.
- 4 **Chadwick R**, Berg K. Solidarity and equity: new ethical framework for genetic databases. *Nat Rev Genet* 2001;2:318–21.
- 5 **Knoppers B**. Of populations, genetics and banks. *Genetic Law Monitor* 2000;Jan/Feb:3–6.
- 6 **Gulcher JR**, Kristjánsson K, Gurdbjartsson H, et al. Protection of privacy by third party encryption in genetic research in Iceland. *Eur J Hum Genet* 2000;8:739–42.
- 7 **Anglian Breast Cancer Study Group**. Prevalence and penetrance of BRCA1 and BRCA2 in a population based series of breast cancer cases. *Br J Cancer* 2000;83:1301–8.
- 8 **Medical Research Council**. *Human tissue and biological samples for use in research. Operational and ethical guidelines*. London: Medical Research Council, 2001. Also at www.mrc.ac.uk
- 9 **Wellcome Trust/Medical Research Council**. *Public perceptions of the collection of human biological samples*. London: Wellcome Trust/Medical Research Council, 2000. Also at www.wellcome.ac.uk and www.mrc.ac.uk