Making sense of SNPs: Women's understanding and experiences of receiving a personalized profile of their breast cancer risks

Authors

•Mary-Anne Young[1-2], •Laura Elenor Forrest[2-3], •Victoria-Mae Rasmussen[2], •Paul James[2-3], •Gillian Mitchell[2-3], •Sarah Dilys Sawyer[2,4], •Katrina Reeve[2], and •Nina Hallowell[5]

1. The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, Australia; 2. Parkville Familial Cancer Centre, *Peter MacCallum Cancer Centre, Australia; 3. Sir Peter MacCallum Department of Oncology, University of Melbourne, Australia; 4. Department of Pathology, The University of Melbourne, Victoria, Australia; 5. Ethox Centre, Nuffield Department of Population Health, University of Oxford, UK*

Corresponding author

Mary-Anne Young

Garvan Institute of Medical Research, 370 Victoria St, Darlinghurst, NSW 2010 AUSTRALIA

Phone: +61 2 9355 5822

Fax: +61 2 9359 8033

Email: maryanne.young@genome.one

Running title

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ABSTRACT

Genome wide association studies have identified a number of common genetic variants - single nucleotide polymorphisms (SNPs) – that combine to increase breast cancer risk. SNP profiling may enhance the accuracy of risk assessment and provides a personalized risk estimate. SNP testing for breast cancer risks may supplement other genetic tests in the future, however, before it can be implemented in the clinic we need to know how it will be perceived and received. Semi-structured qualitative interviews were conducted with 39 women who had previously had a breast cancer diagnosis and undergone *BRCA1/2* testing, participated in the Variants in Practice (ViP) study and received personalized risk (SNP) profiles. Interviews explored their understanding and experiences of receiving this SNP information. Women reported feeling positive about receiving their personalized risk profile, because it: provided an explanation for their previous diagnosis of cancer, vindicated previous risk management decisions and clarified their own and other family members' risks. A small group was initially shocked to learn of the increased risk of a second primary breast cancer. This study suggests that the provision of personalized risk information about breast cancer generated by SNP profiling is understood and well received. However, a model of genetic counseling that incorporates monogenic and polygenic genetic information will need to be developed prior to clinical implementation.

Key words: SNPs, polygenic risk, genetic testing, familial breast cancer risk, qualitative interviews

INTRODUCTION

Recent genome-wide association studies have identified a large number of common genomic variants - single nucleotide polymorphisms (SNPs) –associated with a modest increase in breast cancer risk (Ghoussaini et al., 2012; Michailidou et al., 2015; Michailidou et al., 2013; Sehrawat et al., 2011). These SNP associations can be combined to produce a personalized risk profile of relative- and absolute lifetime risks of developing breast cancer - a polygenic risk score (PRS) (Mavaddat et al., 2015). SNPs may explain up to 28% of familial breast cancers (Michailidou et al., 2013). The implementation of personalized polygenic risk profiling in the familial cancer clinic (FCC) could revolutionize the care of women with a family history of breast cancer. However, before this occurs we need to establish the ethical, legal and social implications of personalized genetic testing (Chowdhury et al., 2013; Dent et al., 2013; Goldstein, 2009; Hall et al., 2014; Offit, 2008).

SNP risk information may differ from other types of genetic information, i.e., monogenic risk information, as it provides a definitive risk figure with less variability. Advocates of SNP profiling suggest that this information may positively influence risk management (Susmita Chowdhury et al., 2013). However, it has been argued that receiving personalized genetic risk estimates may lead to feelings of fatalism, which could lead to poor uptake of health promoting behaviors (McClure, 2002), although this has been dismissed in a recent systematic review (Collins, Wright, & Marteau, 2011). Others suggest that informing individuals that they are at moderate (genetic) risk of disease may be falsely reassuring and negatively impact health behaviors (Chapman & Bilton, 2004; McClure, 2002).

Empirical research examining responses to personalized genetic risk profiling is limited. Most studies have focused on those seeking direct to consumer testing or moderate risk patients (Anderson et al., 2014; Collins et al., 2011; Egglestone, Morris, & O'Brien, 2013; Leventhal et al., 2013). One study has been undertaken in high-risk populations, which used hypothetical scenarios thereby limiting the generalizability of results (Howe et al., 2014). To our knowledge there are no data reporting the psychosocial impact of receiving personalized genetic profiles for breast cancer risks. The study presented below focused on women who had a previous diagnosis of breast cancer, undergone *BRCA1/2* testing through a clinical genetics service, received a negative result and participated in the Variants in Practice Study (ViP) (see Box 1). No other genetic testing had been performed for other high or moderate risk genes that could contribute to risk to family members. A subset of women were invited to participate in a sub-study of ViP where they were informed of their personalized breast cancer risk (i.e., SNP profile) and participated in a semi-structured interview after receiving their SNP results. This paper examines women's understandings and experiences of receiving this information.

METHODS

Recruitment

Ethics approval was obtained from the Peter MacCallum Cancer Centre's Human Research Ethics Committee [11/PMCC/43]. Participants were identified for recruitment from the ViP study as their PRS scores were calculated. Eligible participants: had a previous breast cancer diagnosis, undergone genetic counselling through the Familial Cancer Centre at Peter MacCallum Cancer Centre and *BRCA1/2* testing and received a

negative result, were in the top quartile of the polygenic risk distribution (i.e., SNP profile consistent with a relative breast cancer risk >1.5), consented to receive their SNP profile results in the FCC, fluent English speakers and >18 years. Potential participants were sent a study invitation plus an opt-out card. A researcher telephoned respondents to arrange an appointment in the familial cancer centre (FCC) and a semi-structured interview.

Feeding back SNP results

Participants attended the FCC where they met a geneticist (PJ) or genetic counselor (MAY). The time spent with participants was between 30-60 minutes duration. The development of a model of genetic counselling for the delivery of the SNP profile results was informed by the literature and refined in an ongoing manner by the clinical expertise of investigators PJ and MAY. The protocol for delivering the results included reviewing the research objectives and the participant's former contact with the FCC, including reminding participants that other rare high or moderate risk genes could explain their family history of cancer. Participants were given information about the personalized nature of SNP inheritance, the impact on individual's risk and the fact that this SNP information does not reveal family members' risks. Personal relative risks were explained using a visual tool (personalised report) comparing the interviewee's relative risks to other known risk factors for breast cancer, such as, alcohol and having BMI $\geq$ 30 (see Fig 1). The clinical implications of being in the top quartile of the polygenic risk distribution were discussed (e.g., the fact that this increased their risks of breast cancer, including increased risks of a second primary breast cancer and that these genetic variants are not associated with ovarian cancer). Nearly all participants

requested a copy of their personal risk profile and all received a letter summarizing the information discussed following their consultation.

Fig 1 about here

Data collection and analysis

Interviews continued until data saturation was reached. Fourteen in-person and 25 telephone interviews (semi-structured) of 30-60 minutes duration were conducted during May 2013 and March 2014 by investigators SS and LF. Interviews were informed by a topic guide based on the literature and the research questions. These explored: recollections of learning about familial breast cancer risk, understanding of SNP profiling, the impact of genetic counseling and personalized risk profile on risk perception, risk management and family communication. Interviews were audio-taped, transcribed and pseudonyms allocated. The data were analyzed using the method of constant comparison using an inductive approach, which allows for systematic identification, comparison and coding of themes as they emerge within and across interviews (Strauss & Corbin, 1990). Members of the research team (MAY, NH, SS and LF) coded the transcripts to triangulate data analysis and achieve greater analytical rigor. Coding disputes were settled by group discussion and analytical justification. Overarching key themes were identified that illustrate participants' understanding of SNPs and perception of their polygenic breast cancer risk. This paper presents findings describing participants' understanding of the inheritance of polygenic information and perceived utility of personalized genetic profiling.

RESULTS

Participants

Sixty-five ViP participants were invited to participate. Thirty-nine (60%) were interviewed, the remainder, declined (n=19), had died (n=1) or dropped out (n=6). Interviewees were aged between 38-83 years. The interviews took place within 4 weeks of women receiving their personalized breast cancer risk profile. As per the ViP inclusion criteria, all women had a former diagnosis of breast cancer and received a negative clinical BRCA1/2 result. The majority (87%) had children and three-quarters had daughters. Thirty-one percent had undergone a bilateral risk-reducing mastectomy as part of their initial breast cancer treatment or at a later date. (see Table 1)

Table 1 about here

Perceptions of inheritance: Understanding genetic transmission

All the women demonstrated knowledge of the broad concepts related to polygenic risk information. Most women accepted the explanation they were given about SNPs' contribution to cancer risks and described their risks as determined by the combination of different genetic variations.

Louisa: 'There's these little variations that are not just whole gene mutations that are very minor but the more you have of them, that they specifically relate to breast cancer, the greater your risk.'

Almost all women recalled being told that SNPs are inherited maternally and paternally and are passed down in a random fashion. The inheritance of SNPs was described using a blending metaphor; like height, one's breast cancer risk profile was seen as involving the (genetic) contribution of mothers **and** fathers.

Helen: 'Well he just explained that it came from both sides of my family, both my father and my mother and it was like being born short or you know certain eye colour, it's just their genetic mix it's just produced this unfortunate side effect. So it was different to the BRAC 1 and 2 where it only came from one parent. It came from both.'

Some women also described the transmission of SNPs using a dilution metaphor in which cancer risks were described as lessening as SNPs were passed down the

generations, as Ruth commented: "*By the time it gets to the grandchildren the genetic aspect will be so watered down as to be less relevant*". Their use of blending and dilution metaphors suggests that women understood that SNP profiling provides individuals with a more personalized risk estimate. As Mary observed: "*From my understanding my mum probably won't have the same risk as me because it is the combination of her mum and dads genes*".

Thus, there was evidence that women were aware other family members' risks could not be inferred from their test results. For example, Daisy reflected that her daughter had inherited a different complement of SNPs, and therefore, has different risks from Daisy.

Daisy: 'He also explained that the risk to my daughter is about half my risk probably 'cos she's got her father's genes in her as well. So she's only got 50% of my genetic make-up in her. So that's good cos her father's family has no cancer in it whatsoever. So that means her risk is not nearly as strong, which should be good. And equally down the line her daughter wouldn't be very susceptible to it, any more than the average person.'

Women also explained that their children's breast cancer risks might be increased or decreased, depending upon which maternal and paternal variants they had inherited, but that they would not be as great as those resulting from *BRCA* mutations. The latter information was viewed positively, and many women expressed a great deal of relief that their children's risk may not be as high as theirs.

Perceptions of SNP testing: The utility of personalized profiling

Most women said they appreciated receiving SNP profile information as this provided them with an etiological explanation for their earlier diagnosis.

Ruth: 'Like I breastfed my kids, so you know I would have breastfed for like three years of the time, didn't smoke, didn't drink alcohol. You know, somewhat overweight but not horrifically …so there weren't any of the commonly known environmental factors that would have caused it, but it is still good to know that it's nothing you did.'

Some said they had just wanted an explanation for their cancer, while others, like Helen, were comforted by the idea that their cancer had involved genetic not just behavioral factors, as this absolved her of the responsibility for getting ill.

Helen: 'I think I had some explanation so it was good to know that the blame [for cancer] wasn't with me so to speak like it was out of my control, like it wasn't something that I'd done to help cause my cancer, you can't control everything. So it was good to have an answer.'

Others said they had always suspected that genetic factors had caused their cancer, but felt that this etiological explanation had been had been ruled out when they received an inconclusive *BRCA1* and *BRCA2* result. For these women receiving SNP information confirmed what they always suspected, and they described this as empowering.

Grace: 'So actually having information I find is empowering. I may not be able to control anything but I find having information is empowering. It just allows me to be aware. But it doesn't make me anxious.'

Finally, learning that risk is dependent on a combination of maternal and paternal SNPs was described as emotionally satisfying because it relieved women of the (sole) responsibility for transmitting risk to their children, as Betty said about the paternal contribution to risk: "*That again just makes it better because if [husband] has anything then that sort of increases the risk for the girls as well, so not just from me but from him*". Others commented that this not only affected them, but also their mothers.

Luna: 'my mother did tell me once that her regret was that she felt that she was passing on something to me and my daughters and it was all her fault, you know? And I thought, "Oh, bless her heart, what a nice thing if she'd known that really she wasn't completely responsible for this.'

Perceptions of personalized risks: responses to receiving a personalized profile

For a small group of women receiving their risk profile was described as "confronting" or shocking.

Elizabeth: 'I found it confronting that's all yep. So on the one hand I'm saying oh yeah well you know that's half expected because of family history and yet when you're actually told it, it is confronting.'

Some said they initially felt anxious after learning that they were at an increased risk of developing a second primary breast cancer. Victoria described how she felt at first: " *…it did shake me, I went home and certainly thought about the prospect of a second breast cancer, probably for the first time*". While these women had viewed themselves as at higher risk following their cancer diagnosis, receiving their SNP profile confirmed their suspicions and made risk feel more real.

Jenny :'You tend to think with cancer that after 8 years you're in remission and it [risk profile] made me realize that perhaps I'm never in remission and that I could get …another breast cancer primary at any stage.'

However, nearly all women went on to say that they had found the information useful and informative. Many women talked about their future cancer risks. They commented that they were less worried because their profile established that they had a moderately increased risk of cancer, compared with carriers of *BRCA1* and *2* mutations.

Alex: 'I've got a higher risk but the risk is moderate compared to BRCA1 or BRCA2 and we talked about my risk for ovarian cancer and I feel satisfied that that's not something I'm going to worry about now.'

They also understood the SNP variants are only related to risks of breast cancer, which for many was described as a relief. As Betty said upon being told that she was not at increased risk of ovarian cancer: *"I just feel like a weight's been lifted off my shoulders … I was worried about ovarian cancer but I'm not now. I feel really happy about that*".

Receiving their risk profile also affected some women's views of previous risk management decisions. Over one third of the women had undergone risk-reducing mastectomy and many of these women said they felt that their earlier decision to

undergo risk-reducing mastectomy, either at the time of their initial surgery or after completing treatment was validated.

Betty: 'I feel really happy. And I feel not vindicated, it's not's the right word, but I feel like I made the right choice back when (daughter) was a baby and even though, even niggling at the time I thought am I just being over cautious, have I gone through all this just for no reason. But I'm really happy that in actual fact it could've been quite a different story had I not done that.'

DISCUSSION

This is the first study to report high-risk individuals' understanding and experiences of receiving personalized genetic risk information for breast cancer based upon SNP profiling. Our data suggest that women were overwhelmingly positive about receiving personalized breast cancer risk profiles. Almost all the women said they were happy to receive this information because it provided an explanation for their earlier diagnosis and also clarified their future risks of developing breast cancer. Almost all the women also understood that the information they had been given pertained only to their personal risks of breast cancer. They also understood that unlike monogenic risk information their personalized risk information did not inform risk for family members.

The ease with which interviewees appeared to accept the implications of personalized genetic testing may be due to the fact that the explanation of the inheritance of SNPs resonated with preexisting lay understandings of inheritance. According to Richards (1998), lay understanding of inheritance is based on a bilateral kinship model, in which genetic variants are passed down from both parents in a random fashion combining to produce certain traits in their offspring. Richards (1998) observes that lay accounts include: the blending of maternal and paternal traits, the apparent dilution or

disappearance of traits as they are passed down and incorporates environmental influences.

Previous studies have described receiving *BRCA1/2* test results as stressful or distressing in the short-term (Claes et al., 2004; Lodder et al., 2001; van Roosmalen et al., 2004). While a small number of women in this study said they had felt anxious immediately after receiving their SNP results, specifically the confirmation of their increased risk of a second primary cancer. However, the majority said that on reflection they were relieved to receive their risk profiles and to learn that these genetic variants do not put them at increased risk of ovarian cancer and have few implications for other family members. As these women were interviewed within four weeks of receiving this information we can speculate that the different responses to receiving risk information in these different studies may be due to the fact that the risks identified by SNP risk profiles are much lower than those potentially revealed by *BRCA1/2* testing and, perhaps more importantly, less able to inform risk for other family members.

Indeed, the fact that SNPs are inherited through the maternal and paternal line was regarded by interviewees as important as they understood the personalized nature of the risk information and it alleviated them from bearing the sole responsibility for transferring genetic risks to their children. This contrasts with the feelings of guilt for passing on mutations that are frequently described by individuals undergoing genetic testing for monogenic conditions such as BRCA1/2 and HNPCC (Fisher et al., 2014; Hallowell et al; van Oostrom et al., 2007). It is also possible the lower relative risk

inferred by their SNP profile also contributed to the alleviation of feelings of responsibility.

Practice implications

Receiving genetic test results for mutations in high-risk cancer genes has been shown to enhance understanding of cancer risks and increase perceived personal control (Taber et al., 2015). Our study suggests there may be similar benefits for women who receive high-risk personalized breast cancer risk SNP profiles. However, implementing SNP testing in the clinic will present challenges for genetic health professionals. To date, the practice of cancer genetic counseling has focused on monogenic disorders and changes to genetic counseling practice will be required if genetic counselors are to provide monogenic **and** polygenic genetic information. While genetic counseling for common polygenic disorders (e.g., Type 2 Diabetes and psychiatric illness) is now available (Austin & Peay, 2006; Waxler et al., 2012), a model of genetic counseling that combines monogenic and polygenic risk information is yet to be developed.

Study limitations

A major limitation of this study is that these findings cannot be generalised beyond this sample, however, they point to some fruitful areas of future investigation. Moreover, we only recruited women who had agreed to receive their risk profiles and this group may differ from those who decline testing. Indeed, investigating the views of those who decline risk profiling can be seen as an important research priority, if we are to implement SNP profiling in clinical practice. Second, we only included women with a high polygenic risk score, it is possible that this group may react differently to those

with a low risk score. Again, these differences should be explored in future research. Finally, all the participants had been diagnosed with breast cancer, previously attended a clinical genetic service and undergone *BRCA1/2* testing and as such, had prior medical and genetic knowledge, and this may have affected their responses, specifically their prior cancer risk perceptions and understanding of the mode of genetic transmission. Indeed, it is possible that genetic testing naïve individuals may understand this type of information very differently.

CONCLUSION

We have known for a number of years that breast cancer risk is affected by SNPs. While clinical SNP profiling has not been implemented to date it is not unrealistic to speculate that, given the growth of whole genome sequencing, some form of SNP testing may become part of clinical assessment of breast cancer risks in the future. Therefore, we need to know how this information could be delivered and how it will be received so that the implementation of this technology may proceed effectively. Our study suggests that SNP profiling for breast cancer risk is well received and that personalized risk profiles may not be as difficult to explain as anticipated, at least when offered to women who have a personal history of breast cancer, and who have previously had BRCA1/2 genetic testing and counseling. However, while we acknowledge that personalized genetic risk profiling does not appear to provoke anxiety and is regarded as acceptable by the women in this study, the real challenge will come when it is offered to women who do not have a personal nor a family history of breast cancer, and no previous experience of breast cancer genetic testing. In conclusion, offering SNP profiling within the clinic is the first step in the translation of this technology, the next is to evaluate

more thoroughly its impact on patients' risk perception, health behavior, psychological and clinical outcomes.

CONFLICT OF INTEREST

Mary-Anne Young declares that she has no conflict of interest.
Laura Elenor Forrest declares that she has no conflict of interest.
Victoria-Mae Rasmussen declares that she has no conflict of interest.
Paul James declares that he has no conflict of interest.
Gillian Mitchell declares that she has no conflict of interest.
Sarah Dilys Sawyer declares that she has no conflict of interest.
Katrina Reeve declares that she has no conflict of interest.
Nina Hallowell declares that she has no conflict of interest.

HUMAN STUDIES AND INFORMED CONSENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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