1. Title page

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~~"Another piece of the pie":~~ Influence of lived experience on risk perception among women who received a ~~personalized~~ breast cancer polygenic risk score: "Another piece of the pie"~~risk assessment~~

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Running head

Role of lived experience in breast cancer risk perceptions and assessment

2. Abstract

Polygenic risk scores (PRS) are personalized assessments of disease risk based on the cumulative effect of common low-risk genetic variants. PRS have been shown to accurately predict women's breast cancer risk, and are likely to be incorporated into personalized breast cancer risk-management programs. However, there are few studies investigating the individual impact of receiving a clinically meaningful breast cancer PRS. Existing studies have not demonstrated significant changes in perceived risk or risk management behaviors after receipt of polygenic risk information. The aim of this qualitative study was to explore how women with a family history of breast cancer construct breast cancer risk perceptions after receipt of a breast cancer PRS. Unaffected women with a family history of breast cancer who had not previously received genetic counselling regarding their breast cancer risk were invited to participate in this study. In-depth, semi-structured interviews were conducted with 20 women who attended a familial cancer clinic in the Australian states of Victoria and Tasmania. Data were analyzed using an inductive thematic approach. Women's lived experience played a significant role in the construction and maintenance of their breast cancer risk perception. Women's pre-existing risk perceptions were informed by their family history and ~~understanding of~~their knowledge that breast cancer ~~as~~ is a multifactorial disease. Knowing that breast cancer is a multifactorial disease enabled most women to integrate genetic information with their pre-existing notions of risk. Women reported that the information they received was consistent with their existing notions of personal risk and screening advice. Therefore, the PRS did not lead to a change in perceived risk or risk management behaviors for most women. The results of this study provide

insight into how polygenic risk information is integrated with pre-existing notions of risk, which will inform its implementation into clinical practice.

Keywords

Polygenic risk score; Breast cancer; Risk perception; Qualitative; Lived experience; Genetic counseling; Health behavior

3. Contribution

What is known about this topic:

The clinical utility of breast cancer polygenic risk scores (PRS) is increasing, and translation of breast cancer PRS into clinical practice is currently underway in Australia. However, there is little data regarding how women undiagnosed with breast cancer understand and make meaning of PRS.

- ~~Lived experience has a strong influence on breast cancer risk perceptions.~~
- ~~Breast cancer risk perceptions are multifactorial and influence screening behaviors.~~

What this paper adds to the topic

Women undiagnosed with breast cancer have well-formed perceptions of breast cancer risk, largely informed by their lived experience and empathic knowledge of breast cancer. Polygenic risk information is well understood by these women, easily incorporated into their existing risk perceptions and may reinforce positive health behaviors.

- ~~Polygenic risk scores can be integrated into women's breast cancer risk perceptions.~~

- ~~Polygenic risk scores can have a positive impact on screening behaviors.~~

4. Main text

Introduction

Polygenic risk refers to the combinatorial effect of multiple common low-risk variants, also known as single nucleotide polymorphisms (SNPs). To date over 100 SNPs have been associated with breast cancer risk, which together account for 18% of hereditary breast cancer, comparable to the risk attributable to rare moderate- and high-risk penetrance genes (International Agency for Research on Cancer, 2012; Michailidou et al., 2017). When combined to produce a polygenic risk score (PRS), SNPs can provide clinically meaningful reclassification of breast cancer risk among non-*BRCA1/2* carriers and predict breast cancer risk independent of other known biological risk factors among women with and without a family history of breast cancer (Evans et al., 2017; Kurian et al., 2016; Sawyer et al., 2012).

SNP testing shows great promise for providing personalized breast cancer risk assessments, which in turn could lead to targeted screening advice and more cost-effective screening programs (Feld et al., 2018; van Veen et al., 2018). However, a recent systematic review reported that substantial changes in perceived risk, cancer screening or lifestyle behaviors have not been observed after SNP testing for colorectal cancer, prostate cancer or melanoma (Yanes et al., 2018). Fewer studies have investigated the impact of SNP testing for breast cancer risk, with the majority of these based on hypothetical testing scenarios. Participants in one study raised the potential for anxiety after receiving a high-risk breast cancer PRS (Henneman et al., 2011). On the other hand, there are also concerns that a “low-risk” assessment may be falsely reassuring, and information about low or moderate genetic risk may have

a negative impact on health behaviors (Beery & Williams, 2007; Hallowell et al., 2002; McClure, 2002).

Two studies where a PRS was provided to women regarding their breast cancer risk reported little negative psychosocial impact and a good understanding of polygenic risk information. In this setting, women viewed the information from the PRS (Sawyer et al., 2012) as providing an explanation for their breast cancer diagnosis and described the PRS as confirming their perceptions of personal risk (Forrest et al., 2019; Young et al., 2018). However, all of the women included in these previous studies had been diagnosed with breast cancer, undergone genetic testing of *BRCA1/2* and received a high-risk PRS. Thus, the findings of these existing~~se findings~~ studies may not be transferable to the broader population of women who will be offered a PRS to inform their risk and risk-management strategies in future.

The lack of consistent evidence for changes in perceived risk or behavior after SNP testing could be due to a number of factors, including the variable clinical utility of the SNP tests used in studies and differences in cohort characteristics. However, the complex nature of perceived risk and the significant role of lived experience in constructing risk perceptions is also likely a factor (Austin, 2010; Sivell et al., 2008; Tracy et al., 2008; Walter et al., 2004). Research has shown that risk perceptions informed by lived experience can be resistant to change, and objective risk information may be rejected if it is incongruent with pre-existing notions of risk (Senay & Kaphingst, 2009; Smerecnik et al., 2009).

The impact of polygenic risk information on perceived risk of breast cancer has not been explored, particularly among women without a diagnosis of breast cancer and those who have not received genetic counselling. While SNP-based risk assessments are not yet routinely available in familial cancer genetic clinics, they are

currently offered by private genetic testing companies and have been incorporated into a widely used breast cancer risk assessment algorithm (Lee et al., 2019). There is also a large international trial of the feasibility of risk-stratified breast screening using PRS (National Library of Medicine (U.S.), 2018). Given the current re-shaping of how genetic testing is offered in the oncology setting to manage the increased demand for oncogenetic information (Wright et al., 2019), there is impetus to determine how women understand and react to personalized SNP-based risk assessments and develop models for integration into clinical practice. The aim of this study was to explore women's experience of receiving a PRS, and understand how the PRS impacts their breast cancer risk perceptions and health behaviors.

Materials and methods

A qualitative phenomenological approach was used in this study to explore the experiences of women receiving a PRS from their perspective and understand the meaning they derived from the experience (Starks & Trinidad, 2007). Ethical approval to conduct the study was provided by the Human Research Ethics Committee at the Peter MacCallum Cancer Centre, Melbourne, Victoria (HREC/16/PMCC/2) and the Tasmania Health and Medical Human Research Ethics Committee (H0016395).

Setting and participants

Participants were recruited from the Variants in Practice Psychosocial Study (ViPPS), a large mixed-methods study investigating the psychosocial impact of SNP testing for breast cancer. The ViPPS procedures have been described in detail elsewhere (Yanes et al., 2017). In summary, the ViP cohort includes women diagnosed with breast cancer who do not carry a pathogenic variant in a moderate- or high-risk breast cancer gene, and their female relatives. SNP testing was

performed in all participants to produce an individual PRS, and 400 individuals with a high or low PRS were invited to receive their PRS under the ViPPS research protocol. The PRS was calculated based on 62 SNPs, an updated version of a previously validated 22 SNP panel (Sawyer et al., 2012). Risk groups were determined by quartile, with the top quartile classified "high PRS" (RR>1.2) and bottom quartile "low PRS" (RR<0.64). Results were reported as a relative risk and reported as a research result, with limited utility for changing medical management as PRS do not yet have clinical accreditation in Australia.

Women who opted to receive their PRS attended a genetic counseling~~n~~ appointment with a genetic counselor, clinical geneticist or oncologist with genetics training at one of the participating family cancer clinics in the Australian states of Victoria and Tasmania. At the appointment, they received their individual PRS ~~in the context of other~~and a personalized breast cancer risk assessment based on genetic, family history and environmental risk factors~~ using a personalized results report~~. Topics covered during the PRS genetic counseling appointment included their lifetime risk of breast cancer, breast cancer risk management, lifestyle factors associated with cancer risk and implications of the personalized risk assessment for the family. The limitations of the PRS as a research result were also discussed.

Previous studies have already explored the experiences of women with breast cancer who have had *BRCA1/2* genetic counseling and testing prior to receiving their PRS. Therefore, in order to build on existing knowledge, unaffected women who had not had genetic counseling or testing prior to participation in this study were invited to participate in this qualitative study.

Recruitment

Potential participants for this study were identified from the ViPPS participant database. Women were eligible to participate in this study if they met the following criteria: (i) unaffected by breast cancer; (ii) had not ~~previously~~ attended genetic counseling for breast cancer risk prior to their PRS appointment; and (iii) had received their PRS. The women were contacted by phone ~~approximately~~ one to two weeks following their PRS appointment to confirm eligibility, obtain verbal informed consent and schedule an interview. Interviews were conducted as close to two weeks after the PRS disclosure appointment as possible. The average time from appointment to interview was 17 days (range 9-24 days, SD 4.2). The average length of the interviews was 45 minutes (range 22-81 minutes, SD 13.5). Women who met the eligibility criteria were recruited consecutively and were unselected on the basis of personal characteristics. Women who received both low and high PRS were recruited, so as to provide a full description of the study phenomenon and maximize the transferability of the findings (Guba, 1981). All participants provided verbal informed consent, which was audio recorded at the commencement of the interview.

Data collection

In-depth, semi-structured ~~telephone~~ interviews were conducted between June 2017 and August 2018 by AW, a genetic counsellor not involved in returning PRS to participants. Interviews were done by telephone, due to distance and for the convenience of participants. A criticism of telephone interviews is that they cannot capture visual cues, which may limit the depth of the interview and make building rapport more difficult. However, it is also argued that the anonymity of a telephone interview may enable some participants to be more open in their responses

(Minichiello et al., 1995). The study team did not observe a negative impact from conducting interviews by telephone in this setting. Interviews were informed by a topic guide, in which emerging themes in earlier interviews became the focus of targeted questioning in subsequent interviews. The following topics were explored: women's experiences of breast cancer in their family, the experience of receiving their PRS, thoughts regarding breast cancer risk and breast cancer risk management. Interviews were audio-recorded with participants' consent and transcribed verbatim. Transcripts were de-identified by assigning pseudonyms and removing all other identifying information.

Data analysis

The inductive analysis was conducted according to the thematic analysis method outlined by Braun and Clarke (2006). AW read all interviews and checked them against the audio recording to familiarize herself with the data and ensure accuracy. Initial codes were generated by reading transcripts and applying descriptive codes to pieces of text. Initial codes were collated into preliminary themes, which were reviewed and further refined until a set of discrete and internally consistent themes was developed, and relationships between themes were defined. Coding and analysis were iterative and performed concurrently with data collection, to enable the identification of new lines of enquiry and aid in determining the point of data saturation, at which point recruitment ceased. Analytical rigor was achieved by multiple research team members coding interviews to confirm themes (authors AW, MAY and SS). NVivo qualitative research software (QSR International, 2017) was used to organize and analyze the data. Quotes are presented using pseudonyms, with the age and PRS of participants.

Results

Twenty-four women were invited to participate in the study, 20 of whom were interviewed. The demographic characteristics of the interviewees are summarized in Table 1. Among the remainder one was not contactable, one previously had genetic counseling and *BRCA* genetic testing and two were not available for interview within the prescribed timeframe.

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Lived experience of cancer and salience

Women had a broad range of experiences of breast cancer. One woman was the primary carer for her daughter who had died of breast cancer. In contrast a young woman's mother was diagnosed with breast cancer prior to her birth. Most women had an active role in supporting a first-degree relative through a diagnosis of breast cancer.

I've attended a lot of her doctor's appointments and then she has her Herceptin every 21 days, so I sort of go along to that a lot. So yeah sort of yeah been there for a lot of it with her. Lauren, 40, High PRS

Women's proximity to the cancers in their family influenced the personal impact of the cancer diagnosis. The impact seemed more significant for women who had been closely involved in the care of their affected relatives compared to women who were more distant to relatives with cancer in their family.

I was still sort of young when my auntie got diagnosed, it was still – and she lived [overseas] so didn't really get to really see her or really, yeah, just fully understand what that was all about. But then, yeah, when mum was diagnosed it was pretty terrible and pretty horrible watching her go through chemo. Jacque, 28, Low PRS

Other aspects of witnessing the diagnosis and treatment of cancer, including the recency of the diagnoses, age at diagnosis, prognosis, treatment, and survival influenced the impact of the cancer diagnosis on women and their attitudes to cancer.

I guess it was the first exposure to cancer for our family and, you know, the first exposure to the treatments which, you know, are pretty horrendous to go through. So the whole process was, you know, disturbing, mostly for my sister but, you know, also for the rest of the family as well. Tracey, 50, High PRS

Overall, women described the family experience of breast cancer as being internalized and becoming part of the family narrative, regardless of whether or not they were present at the time of diagnosis and treatment. This lived experience of breast cancer also awakened an awareness of personal breast cancer risk for most women.

A multifactorial model of cancer etiology

It was clear from women's accounts that they strongly endorsed a multifactorial model of cancer etiology, both before and after receiving their PRS. Women discussed a number of modifiable risk factors they considered relevant to their risk in addition to their family history, including diet, exercise, weight and alcohol consumption.

Obviously there's environmental or lifestyle factors, you know, but I don't smoke anymore and I'm not on the pill and, you know, we try to live – eat healthy and keep a reasonable sort of exercise regime most of the time. Samantha, 47, High PRS

Age was another risk factor raised by women, which often influenced whether they currently felt at risk. Older women described feeling at risk because of their

awareness of increasing risk with age, whereas younger women saw it as more of a future problem not requiring current intervention.

Does that mean, because I've reached that magical age of seventy or whatever age they thought it was, that I'm therefore not going to? Well that's not true, because I do know one of my friend's mother's got it, she was ninety! Mary, 77, Low PRS

Not really, just sort of self-exams as regularly as I can, but yeah, that's – I mean you can't really do much more at my age yet. Jacque, 28, Low PRS

The role of chance, or "bad luck", was frequently raised by women as a component of breast cancer risk. This led many women to see their breast cancer risk as one of many risks in daily life and something to be controlled to the best of their ability.

I've known 86-year old people that have smoked all their life and never had a speck of cancer. They had a stroke, but they never had a cancer, you know, so it's just, you know, the luck of the draw. Christine, 54, High PRS

Women also discussed the role of genetics in breast cancer development, with many being aware that a relative had undergone previous *BRCA1/2* testing. After receiving their PRS women described being more aware of the role of other genetic factors in breast cancer development.

I think just that, you know, initially there was only the two breast cancer genes that they thought were relevant, but now it's opened up a whole range of other things. I guess, you know, it's similar with other types of illnesses that have a genetic link. *Suzanne*, 47, Low PRS

Construction of breast cancer risk perceptions

Women had gone through a process of appraising and interpreting their family history well before receiving their PRS, considering the results of prior genetic testing

in the family, family size, the number of affected and unaffected relatives and the age of breast cancer diagnoses in the family.

We don't have the BRCA gene, and we come from a big family, my mum's one of 11. In all of those family members, there's boys and girls, but no one else. Well, my nan had breast cancer, my mum's mum, but it was when she was about 75, you know it was old age and it wasn't, from memory, aggressive. Davina, 33, High PRS

Some women also used non-genetic factors to explain the history of cancer in the family, including other health issues, lifestyle and environmental exposures. As a result of this, some breast cancer diagnoses in the family were seen as less relevant when thinking about their own breast cancer risk.

...because I suppose my mum's sister had breast cancer, but I think I might not have been that aware of what she died of because she was an outrageously heavy smoker, she had a lot of stress in her life. Nancy, 68, Low PRS

Women in this study described a sense of vulnerability to breast cancer, and a spectrum of perceived risk was observed, strongly influenced by lived experience. For one woman, a traumatic experience with her healthy mother's late diagnosis of breast cancer and eventual death, combined with a strong family history of cancer, led her to believe that a cancer diagnosis was inevitable.

I think subconsciously am I preparing for it? I think I am in a way because I do live with the, with the fear I suppose you could say that, of not if but when. Donna, 52, High PRS

However, most women perceived their breast cancer risk to be moderately increased based on their family history. These lay risk assessments were largely consistent

with women's actual breast cancer risk (i.e. the risk as assessed by the clinical team).

Probably a bit higher than average because my sister has had breast cancer. But I never felt that it was you know, you know how you hear of some women who would have a voluntary mastectomy as a preventative measure I was never in that space. Davina, 33, High PRS

Women who reported a higher than average perceived risk and attributed the family history to a genetic cause also reported a greater number of affected relatives and breast cancer diagnoses across multiple generations.

No, not until – well, yeah, definitely not until my sister had it. And my aunt and my grandmother were much older, so – but, you know, the more instances of it in the family, the more you start to think, you know, it's something that you need to at least be conscious of and need to manage proactively. Tracey, 50, High PRS

Women who described their breast cancer risk as average had fewer women diagnosed with cancer in their family. They were also aware that a *BRCA1/2* gene mutation had not been identified in their family and raised their own healthy behaviors as contributing to their personal risk assessment.

I just thought it was just average because my sister didn't have the gene, the BRCA1 and BRCA2. She doesn't have them so I just thought well it's not – I just thought well it's not genetic so my risk is just the average person. Kirstie, 37, High PRS

For a small number of women, the intensity of a current experience of breast cancer, or the more salient risk of recurrence for a relative, meant they had not yet considered the impact of the diagnosis for their own breast cancer risk.

I don't know, we were just so much more focused on the fact that [sister] had been diagnosed. Yeah, I didn't take it on-board for myself. Nancy, 68, Low PRS

In addition, the two women whose daughters were diagnosed with breast cancer had not considered the prospect of their daughters' diagnoses increasing their own risk.

It actually didn't occur to me that I could possibly have it because [Daughter] having it didn't seem, from my mind say, "well, you have an increased likelihood." Mary, 77, Low PRS

Accepting and integrating genetic information

The majority of women in this study reported that the PRS they received was consistent with their existing perceptions of breast cancer risk. Rather than causing them to re-evaluate their risk, the PRS merely confirmed what they already felt and was easily accepted and integrated into their understanding of breast cancer and risk.

I think it's just reinforced our view that – and my view in particular - that because of the family exposure to it, we're already high risk, so it's just reinforced that view. Tracey, 50, High PRS

Women who perceived themselves at low risk and received a low PRS were happy to have their perceptions confirmed and accepted their result, but often emphasized that breast cancer was a multifactorial disease and a low genetic risk did not equate with no risk.

No, I did, yeah, believe it was the, you know, the risk was low so that's still the same. I'll still do testing and, you know, mammograms and things just like anybody because I know it [risk] doesn't just go away. Jane, 47, Low PRS

A minority of women reported that the PRS had changed how they thought about their breast cancer risk, with some feeling that their risk was now slightly lower or higher than before. The two women who reported a decrease in their perceived risk again made a point of emphasizing the multifactorial nature of breast cancer development, and that they still felt at risk of breast cancer, albeit to a slightly lesser extent.

I feel as though I now am at low risk, but as I said I will still continue to monitor the situation really carefully. I'll continue to have my annual mammogram, because I know that other factors can influence cancer. Anne, 70, Low PRS

One participant expressed disbelief at her low-risk result given her strong family history of cancer, reconciling the discord between her high perceived risk and low PRS by emphasizing that her genetic profile was only one factor in breast cancer development.

I'm delighted by the fact that I am at a lower percentage risk but it's only, and as was explained to me clearly and concisely, it really is only one part of the whole pie when it comes to understanding the risk. So yeah, I'm just as likely as anyone else really. So I feel that I still am at risk. Nicole, 42, Low PRS

The remaining women, who were mostly young and had not yet commenced formal screening, stated that they had not previously considered their breast cancer risk in much detail and described becoming more aware of their risk through receiving their PRS.

Well it's made me think about it. I hadn't really thought too hard about it before beyond not having the BRCA gene. Heather, 30, High PRS

When considering how the PRS fitted with their family history, some women reflected on the reliability of genetic and family history risk assessment. For many women, the concordance between their PRS and their family history meant that *"one just reinforces the other"*. Some women felt that the personalized nature of the genetic information made it a more reliable or trustworthy assessment of their risk, with some recognizing that a high PRS could occur with no family history of breast cancer.

I mean genetic testing seems pretty great because I'm sure that there are instances where people's family history doesn't obviously point to someone's own genetic coding...because I'm sure that people can die before they develop cancers and then, if you don't know that that would have happened, then your genes don't accord with that history because that history never played out. Mikaela, 26, High PRS

Many women also considered genetic factors as more important than modifiable risk factors, because one's genetic makeup can't be changed or controlled.

I guess if you're genetically predisposed to something, you can't change that factor so I guess that's probably got more – more power in the equation than maybe the other elements. Samantha, 47, High PRS

However, two women suggested that a family history-based risk assessment might be more salient to a lay person than the genetic information, reflecting the significant impact of lived experience on risk perceptions.

More family history than genetic. Even though I'm medical, genetics would come into it, you'd think about that. If I was a layman it would all purely be family history. So, if you think layman's terms, my family history sucks, and my chances are high. Christine, 54, High PRS

Coping and control

Women's self-reported risk management strategies were proportionate to their risk, and reflected their accurate risk assessments and multifactorial understanding of cancer development. Strategies they employed prior to receiving their PRS included both screening (with some having increased screening based on family history) and limiting exposure to lifestyle risk factors.

You check your boobs and go for your mammogram and I don't smoke, I don't drink to excess. We eat fresh fruit, fresh veg, not a whole lot of processed foods. We don't eat a lot of takeaway food. We walk almost every day because we've got [pet dog]*.*

Lisa, 47 High PRS

After receiving their PRS, most women reported no plans to change their risk management strategies. However, some discussed that receiving the PRS may increase their motivation to keep up with their screening recommendations and healthy lifestyle behaviors.

I don't know that there's anything much I could do. I mean I guess I could go teetotal but I'm not much of a drinker so it wouldn't make a great deal of difference. I exercise, I eat healthily, I'm not overweight, there's not a lot you can do. Valerie, 66 High PRS

One participant did report plans to improve her lifestyle after receiving her PRS, as the discussion had changed her prior perception (based on her healthy mother's diagnosis of breast cancer) that lifestyle factors had little impact on breast cancer risk.

I sort of look at mum and she don't drink, she don't smoke, she eats healthy, she walks a lot you know, but she still got it. So I thought is it worth me making some

changes, but then in that appointment they said that can lower the risk by making them changes, regardless of you know what your genetics and what your DNA and all say, you can still make changes to lower the risk. Lauren, 40, High PRS

Women who received a low PRS, or whose perceived risk decreased after receiving their results, continued to raise the importance of screening and maintaining a healthy lifestyle because of the multifactorial nature of breast cancer and the role of chance in breast cancer development.

I don't know why, but in my head it's these determinants, and I don't know why but I think there's going to be a multiple of them. So every time I get a negative to something, that's one, it lowers my overall risk. So right now I believe my overall risk has slightly lowered in my own head, but I can't rely on that to not still do the program of precaution that I do. Karen, Low 54, PRS

For one woman, the role of age and chance in breast cancer development overrode other risk factors and she described having made an educated decision about the risks associated with her lifestyle and had no plans to change. However, she was still very committed to breast screening to ensure an early diagnosis.

If I'm going to get it, I'm going to get it, or I'm not - I drink, I'm a bit overweight and I like to have a durry [cigarette]*, so yes again it could be a different type of cancer, not necessarily be breast cancer. But you run the gauntlet, you take the chance.*

Christine, 54, High PRS

This acknowledgement of the inherent uncertainty in breast cancer risk was common among women, with screening and other risk management strategies discussed as a way to cope with and feel in control of one's breast cancer risk. Women gained reassurance from a sense that "I'm doing everything I can do".

I think in the back of your mind you're always fairly conscious that, well, it could be you, do you know what I mean? But by having the mammogram, it's like everything, you can only do what you can do to the best of your ability. Ellen, 62, High PRS

Discussion

The results of this study demonstrate that a lived experience of breast cancer in the family was women's primary source of knowledge about breast cancer and played a key role in determining their beliefs around cancer development, diagnosis and treatment. Women also described the contribution of this experiential knowledge to their perceptions of their own breast cancer risk. This sense of vulnerability to breast cancer among women with a family history and the key role of experiential knowledge in shaping perceived risk has been reported in other studies (Andersen et al., 2003; Hailey et al., 2000; Sivell et al., 2008).

A dynamic model of processing familial risk proposed by Walter et al. (2004) fits well with the accounts of women in this study. The first construct in this model is salience, or an acknowledgement that the disease 'runs in the family'. The second construct is the personalizing process, by which individuals apply their personal models of disease causation to their family history, to produce the third construct, the personal sense of vulnerability (or perceived risk). The perceived risk resulting from this model of risk construction is a multifaceted and dynamic construct, which can change with new experiences and knowledge (Austin, 2010; Walter et al., 2004). This perceived risk in turn impacts on the behaviors individuals undertake to control the risk (Walter et al., 2004).

Women's lived experience of breast cancer provided them with both objective knowledge and experiential knowledge about the disease, both of which played a role in determining how salient the family history was to personal risk. Objective

factors, such as the number of affected relatives, biological relationships, ages and disease course also played a part. For example, women ~~tended not to see a daughter's diagnosis as relevant to their own risk, whereas those with sisters or mothers diagnosed did.~~ linked a greater number of affected relatives, young age at diagnosis and closer biological relationship with higher familial breast cancer risk. However, women's subjective, experiential knowledge was also critical in shaping risk perceptions, beliefs about screening and screening behaviors, as observed in other studies of breast cancer and melanoma risk (Kasparian et al., 2009; Tracy et al., 2008; Turner-Cobb et al., 2006).

The relationship between experiential knowledge and risk perceptions was further explored in a study of women with a family history of hereditary breast/ovarian cancer by d'Agincourt-Canning (2005). This study identified four distinct types of empathic knowledge, or knowledge derived from close association with others who experience a phenomenon, and posited that the type of empathic knowledge (tangible, recent, distant and accidental) influenced the extent of the personal impact of the family history and women's subsequent perceptions of their breast cancer risk. These different types of empathic knowledge, with the exception of accidental knowledge, were observed among the participants of this study and influenced women risk perceptions, consistent with the findings of d'Agincourt-Canning (2005).

Many of the women in this study described tangible knowledge of breast cancer, or knowledge from close personal experiences with people diagnosed with cancer, having cared for or supported a relative through a breast cancer diagnosis. These experiences were clearly impactful for women, demonstrated by the highly emotive language used to describe them. These experiences also led many women to see breast cancer as a threat to themselves, as has been demonstrated in other studies

reporting increased perceived risk, as well as increased cancer anxiety and intrusive thoughts among women with close personal experiences of breast cancer (Andersen et al., 2003; Hailey et al., 2000).

The findings of this study support recent knowledge (based on a recent diagnosis of breast cancer) as a unique component of tangible knowing, as it had a different impact on the women and their families (d'Agincourt-Canning, 2005). Women described their first experience of breast cancer in a relative as particularly difficult, as they had no prior experiential knowledge to draw on. Women were also less likely to consider the impact of a very recent diagnosis of breast cancer on their own risk and focus on the more salient treatment-associated risks, and risk of death, for their affected relative.

In contrast, distant knowledge is acquired through family discussion rather than personally witnessing a breast cancer diagnosis in a relative (d'Agincourt-Canning, 2005). In this study, distant knowledge was observed among women who were removed from the breast cancer diagnoses in their family by time or physical distance. This shielded women somewhat from the significant emotional impact described by women with tangible knowledge, and they described the experiences of breast cancer in their family more objectively (d'Agincourt-Canning, 2005). However, this distant knowing still influenced women’s perceptions of cancer and cancer treatment and led women to see the family history as salient to their own risk. Many women with distant knowledge believed their risk of breast cancer was increased because of their family history, although typically to a lesser extent than women with tangible knowledge. Women with distant knowledge also expressed less distress regarding their personal risk of breast cancer than women with tangible or recent knowledge.

Having become aware of the potential for their family history to impact their own risk, women then went through a process of appraising and interpreting their family history, consistent with Walter's model (Walter et al., 2004). Here, women's endorsement of a multifactorial model of breast cancer development, which included not only family history and genetic factors, but environmental and lifestyle factors, chance and age, played a significant role. Endorsement of a multifactorial model of disease causation has been observed among individuals at risk of a variety of diseases, as well as the general public (Gordon et al., 2012; Paalosalo-Harris & Skirton, 2017), emphasizing the importance of this multifactorial model to lay understandings of cancer risk.

A multifactorial model of cancer etiology enables the personalization of risk by variable emphasis of different risk factors within the family history (Austin, 2010; Sivell et al., 2008; Walter et al., 2004). For example, as observed in this study, a cancer diagnosis may be seen as less relevant to personal risk if it occurs in an older relative, or someone who is very unhealthy. Of note is the observation that women's self-reported risk perceptions, both before and after receiving their PRS, were generally consistent with their actual risk, based on a clinical assessment. This accuracy of perceived risk has been reported in other studies of breast cancer risk, and accurate risk perceptions have in turn been associated with appropriate levels of cancer worry and screening (Fehniger et al., 2014; Tracy et al., 2008). Women's understanding of the multifactorial nature of breast cancer development, and this constructivist model of perceived risk, also provides a mechanism by which new external information, such as a new diagnosis in the family or the PRS, can be incorporated into existing risk perceptions.

While women accepted the PRS they received as part of their study participation, women's breast cancer risk perceptions largely did not change after receiving their PRS. This is consistent with other studies of cancer risk perceptions after genetic counseling and testing in a range of settings, including SNP testing for colorectal or prostate cancer risk (E. K. Bancroft et al., 2015; Graves et al., 2013; Senay & Kaphingst, 2009). The ease with which women accepted the genetic information and incorporated it into their pre-existing risk perceptions may be explained by the accuracy of women's pre-existing risk perceptions and the congruence of the genetic information provided with risk perceptions. Understanding and endorsing a multifactorial model of breast cancer risk also helped women to reconcile their PRS with their family history in cases where the two were not congruent, which also facilitated acceptance of the genetic information.

However, the multifactorial model of cancer development also facilitated one participant's disbelief at her result, as it enabled greater weighting of non-genetic factors to maintain her perceived high risk of breast cancer based on her strong family history. Subjective perceptions of risk based on experiential knowledge being resistant to change is well described, with persistence of inaccurate or exaggerated perceptions observed even after genetic counseling and testing (d'Agincourt-Canning, 2005; Senay & Kaphingst, 2009; Smerecnik et al., 2009). While not observed in this study, difficulty incorporating objective risk information into risk perceptions can also be exacerbated by low numeracy and difficulties with understanding probability or relative risk (Bodemer et al., 2014; Reyna et al., 2009).

Many of the women in this study viewed the genetic information as more certain than other types of risk information, or placed greater weight on genetic estimates of risk than estimates based on their family history alone, which was also reported in a

previous study of women's attitudes to SNP testing (Henneman et al., 2011). It has been suggested that overemphasis of the utility of personalized genetic risk estimates could lead to fatalistic beliefs and reduced engagement in health behaviors (Anderson et al., 2017; Elizabeth K. Bancroft et al., 2014; McClure, 2002). However, while women in this study trusted and valued the genetic information they received, they understood that their genetic result was only a component of their risk and treated it accordingly.

An emphasis on the role of chance or bad luck in disease causation, as observed in this study, has also been linked with fatalistic beliefs and reduced engagement in health behaviors (Anderson et al., 2017; Steptoe & Wardle, 2001). However, for the women in this study, emphasis on the contribution of chance to cancer development provided motivation to screen, so as to avoid death from breast cancer. Engagement in risk management behaviors is recognized to promote a sense of personal control and help people to live with their disease risk (Bennett et al., 2010; Walter et al., 2004). The high motivation to screen among women in this study is encouraging, as it suggests that clinical SNP testing can be provided safely, without leading to an inappropriate increase or decrease in breast screening behaviors.

Concerns have been raised that receiving genetic information indicating a lower risk of disease may lead to a false sense of reassurance and reduced motivation to engage in health behaviors (Elizabeth K. Bancroft et al., 2014; Beery & Williams, 2007; Hallowell et al., 2002; McClure, 2002). These concerns were not realized in this study or other studies regarding SNP testing for breast cancer and prostate cancer (Elizabeth K. Bancroft et al., 2014; Henneman et al., 2011). In contrast, participants in studies of SNP testing have described exclusion from screening on the basis of low genetic risk as potentially anxiety-causing or discriminatory,

particularly for those exposed to public messaging promoting cancer screening (Henneman et al., 2011; Smit et al., 2015). Women in this study were not recommended to reduce screening on the basis of their PRS, however further research exploring the acceptability of targeted screening programs involving reduced screening on the basis of genetic profile is required.

As in other studies of SNP testing, few women in this study reported an intention to change lifestyle risk factors after receiving their PRS (Leventhal et al., 2013; Nusbaum et al., 2013). A likely explanation here is that women reported leading a healthy lifestyle prior to their appointment, although some suggested that receiving their results may provide extra motivation to maintain healthy behaviors. In addition, previous ~~Regardless of the results of SNP testing,~~ studies have reported improvements in lifestyle ~~behaviors have been reported~~ after genetic counseling for polygenic colorectal cancer and melanoma risk, regardless of the results of SNP testing (Nusbaum et al., 2013; Smit et al., 2017). It is possible that, in this and other studies, the detailed discussion of lifestyle factors, their impact on risk, and discussion of strategies to reduce lifestyle risk factors provided by genetic counseling~~This suggests that genetic counselling~~, rather than genetic testing itself, may prompt behavior change for some individuals~~.~~. This appeared to be the case for at least one participant in this study who reported that genetic counseling changed her prior belief that lifestyle factors had little impact on breast cancer risk. The impact of SNP testing on lifestyle behaviors may ~~also~~ be more significant among patients without a family history in a primary care setting, who may have less prior awareness of the contributors to cancer risk (Graves et al., 2013).

Field Code Changed

Strengths and limitations

A strength of this study is that it extends existing literature by focusing on unaffected women with a family history of breast cancer receiving both high and low risk PRS, who have also not previously received genetic counseling. Participants were diverse with regard to age, education, employment, parity, geographic location and cancer family history, which aids in the transferability of the findings of this study to other settings. However, all participants were Australian-born and spoke English, and future studies should aim to capture more diverse views in order to better represent the multicultural Australian population. In addition, due to the research nature of the PRS, risk management was not changed based on the PRS and this limits the extent to which behavior change based on the PRS can be assessed. Participants~~the women participating~~ in this study were also very engaged with breast cancer research and interested in personal breast cancer risk information, which may limit ~~limits~~ the transferability of study findings to the general population.

Practice implications

The findings of this study indicate that polygenic risk information is valued and well understood by women and, along with the increasing clinical utility of PRS for risk stratification and personalized risk management, provide supporting evidence for the ~~provide important data regarding women's acceptance and understanding of a breast cancer PRS to support~~ translation of polygenic risk information into clinical practice. These findings also reinforce the pivotal role of lived experience in construction of perceived risk and may provide a useful framework for genetic counse~~l~~lors and other health professionals providing PRS in a clinical setting. Further research is recommended to assess the behavioral impact of PRS when used to directly inform breast screening, particularly the acceptability of reduced screening

on the basis of a reduced breast cancer risk given women in this study demonstrated high motivation to screen even after receiving a low PRS. Research to ~~determine~~ investigate whether women in the general population understand and respond similarly to a personalized SNP-based risk assessment, as well as~~, as well as research investigating~~ how best to integrate the PRS with current clinical practice~~, particularly given the current trend towards mainstreaming oncogenetic testing~~ is also recommended.

Conclusions

The results of this study reinforce the significant impact of lived experience and empathic knowledge on breast cancer risk perceptions and provide insight into how women with a family history interpret their family history and other risk factors to construct personal risk perceptions. The sophistication of women's lay risk assessments emphasizes the importance of acknowledging the lived experience and expertise of women and supports the use of existing frameworks for understanding perceived risk. These frameworks may also help clinicians to identify factors contributing to inaccurate or problematic risk perceptions and develop tools and strategies to facilitate integration of polygenic ~~genetic~~ risk information into risk perception and engagement in appropriate risk management strategies.

5. Author contributions

This study was designed by AW, MAY, SS, BM, TY and MB, with substantial conceptual and resource contributions from PJ and DT. Data were collected by AW, and analyzed by AW, MAY and SS. BM, MB and TY also contributed to data interpretation. AW drafted and revised the manuscript, which was critically reviewed for intellectual content by all authors. Authors AW and MAY confirm that they had full

access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors gave final approval of this version to be published and agree to be accountable for all aspects of the work.

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7. Compliance with ethical standards

Conflict of interest

Amanda M. Willis, Sian K. Smith, Bettina Meiser, Paul A. James, Mandy L. Ballinger, David M. Thomas, Tatiane Yanes and Mary-Anne Young declare that that they have no conflicts 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. Informed consent was obtained from all patients for being included in the study.

Animal Studies

No non-human animal studies were carried out by the authors for this article.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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9. Tables

Table 1: Interviewees' demographic characteristics (n=20)

	N
Age	
25-34	4
35-44	3
45-54	8
55-64	1
>65	4
Polygenic risk score	
High	12
Low	8
Education level	
High school	1
Certificate/diploma	6
University	13
Employment	
Employed	14
Unemployed	1
Homemaker	1
Retired	4
Marital status	
Never married	4
Married/de facto	15
Separated/divorced	1
Children	
0	5
1	3
2	11
>3	1
Daughters	
Yes	11
No	9