Double trouble: exploring risk factors to better predict contralateral breast cancer

Kramer, I.

CHAPTER 5

Preferences for graphical presentation of probabilities in a contralateral breast cancer risk prediction model: an exploratory interview study among breast cancer survivors

Submitted for publication

Iris Kramer
Josephine M.N. Lopes Cardozo
Daniele Giardiello
Hester S.A. Oldenburg
Maartje J. Hooning
Ellen G. Engelhardt*
Marjanka K. Schmidt*

*authors contributed equally

Abstract

Objective

As a first step towards the development of a patient-friendly interface to facilitate clinical implementation of a newly developed contralateral breast cancer (CBC) prediction model to support decision making about contralateral prophylactic mastectomy (CPM), we investigated among breast cancer survivors': (1) preferences for and understanding of graphical presentation of probabilities, (2) which factors are associated with their trust in the risk estimates, and (3) which factors play a role in decision about CPM.

Methods

Semi-structured interviews were conducted with 19 breast cancer survivors. Two researchers independently coded the interview transcripts to identify themes. Discrepancies were resolved using consensus.

Results

Almost all participants (17/19) found a graphical display of added value, but preferences varied regarding which graphical display format was most clear. The majority of participants (13/19) had moderate to good understanding of all display formats and 14/19 highly trusted the probabilities. Participants (11/19) wished to receive information about epistemic uncertainty (e.g., confidence interval), but only four participants had good understanding of the graphical display format containing this information. High probability of developing CBC and fear of future breast cancer were the factors most frequently mentioned as relevant for decision-making about CPM.

Conclusion

No single graphical display format was preferred by all participants. Incorporating multiple display formats into the CBC tool seems to be the best option to meet the needs of a wide range of women considering CPM. Since women wish to receive information about uncertainty associated with the risk estimates, effective ways to graphically communicate this are needed.

Introduction

Active involvement of patients in decisions regarding their health care is widely advocated and shared decision-making is the preferred style in clinical practice nowadays[1,2]. Providing patients and clinicians with personalized probabilities of outcomes can help them when weighing the pros and cons of treatment options. Prediction models including patient-friendly presentation of probabilities can play a key role in clear risk communication, and thereby, support effective *well-informed* and *shared* decision-making. This is particularly important in the context of medical decisions when from a clinical perspective there is no best choice (i.e., preference-sensitive treatment decisions).

A preference-sensitive medical decision where risk communication can play a major role is the context of contralateral prophylactic mastectomy (CPM) for breast cancer patients who are worried about developing breast cancer again in their other (contralateral) breast. Even though the incidence of contralateral breast cancer (CBC) is low in the general breast cancer population (~0.4% per year)[3-5], an increasing number of patients with unilateral breast cancer opt for a CPM, even when they are at low risk[5,6]. One of the most important reasons why patients opt for CPM is the fear of getting breast cancer again[7]. CPM significantly reduces the risk of CBC, but the procedure is drastic, irreversible and can negatively impact women's long-term quality of life[8]. Accurate individualized information about the actual CBC risk is lacking, and e.g., in the Netherlands, CPM is mainly indicated for breast cancer patients carrying a *BRCA1/2* mutation[9], since these women experience high 10-year CBC risks of ~10-20%[10,11].

To support physicians' and patients' decisions about CPM, we recently developed and validated a CBC risk prediction model (PredictCBC) which provides 5- and 10-year individualized probabilities of developing CBC[4]. To make a prediction model useful in clinical practice, the model should be incorporated into a decision support tool, which is not yet available in current practice. Such a tool can help to better identify women at high risk of CBC who may benefit from a CPM, while the estimates can also be used to reassure patients who are at low risk of developing CBC.

It is, however, challenging to effectively communicate probabilistic information. Only a small proportion of people have skills that correspond to minimum statistical literacy in health[12,13]. Literature showed that graphics, e.g., pictographs and bar charts, can improve patients' understanding of probabilistic information[14]. Moreover, patients appear to have a more accurate understanding of risk if probabilistic information is presented as absolute risks (e.g., 10%) rather than verbal labels (e.g., 'a high chance'), and particularly when the information is tailored[14-16]. Whether absolute risks should include a range representing epistemic uncertainty (e.g., 5-15%) is still under debate[17-19]. Conveying the randomness of future outcomes (i.e., aleatory uncertainty) to patients seems to be done more easily by clinicians, and patients generally do not seem to struggle with this as much as they do with epistemic uncertainty[18]. Currently, little is

known about how this can best be communicated[17-19].

Even though many prediction models have been and continue to be developed, very few have been implemented in clinical practice. One of the reasons for this is that they often lack patient-friendly interfaces to facilitate their use during doctor-patient consultations. Moreover, most research on risk communication is performed among healthy participants (e.g., students)[14], and not among patients. For successful implementation of a decision tool, it is important to test the interface within the target end-users. As a first step towards development of a CBC prediction tool that can help clinicians to communicate probabilities to patients, the main aim of this exploratory interview study was to get insights into breast cancer survivors' (i.e., potential end-users) preferences for the graphical presentation of the probabilities, including the epistemic uncertainty, provided by the model. Secondary aims were to evaluate which factors are associated with participants' level of trust in the risk estimates provided, participants' understanding of different graphical display formats, and which factors (in particular probabilities) would play a role in participants' decision on whether to undergo a CPM.

Methods

Design

Study population

Female breast cancer survivors aged ≥18 years were eligible to participate if their invasive breast cancer diagnosis was at least one year prior to the interview (range 2-38 years) and they did not have bilateral breast cancer at primary diagnosis. We chose to exclude women with bilateral breast cancer at primary diagnosis, as these women were no longer at risk of developing CBC during follow-up, and therefore, did not have to consider the prophylactic removal of the contralateral breast. Breast cancer survivors were recruited between March and May 2020 via three different networks; 1) a patient advisory group from the Dutch Breast Cancer Research Group (BOOG), 2) the Dutch Breast Cancer Society, and 3) a breast cancer panel from the Antoni van Leeuwenhoek hospital (AVL; a Dutch cancer hospital). From the applications, we tried to select a heterogeneous sample of participants, i.e., patients with low and high risk of developing CBC (e.g., *BRCA1/2* carriers and Hodgkin lymphoma survivors), a wide age range, and both women who did and those who did not undergo a CPM. We selected a heterogeneous sample to capture the diversity of the population of breast cancer survivors. We did not put any restriction on time since primary breast cancer diagnosis, as women diagnosed long ago have had more time to process and reflect on their breast cancer (treatment) trajectory and can provide input on what is important in the long-term. The Netherlands Cancer Institute-AVL review board approved the study protocol.

Contralateral risk prediction model (PredictCBC)

The PredictCBC risk prediction model quantifies the probability of developing a CBC during follow-up[4]. The model provides individualized estimates of 5- and 10-year CBC probabilities based on patient, primary tumor and treatment (received for the primary tumor) characteristics, and *BRCA1/2* germline mutation status. The PredictCBC model shows an area under the curve (AUC) of 0.63 (95% prediction interval at 5 years, 0.52-0.74; at 10 years, 0.53-0.72)[4].

Graphical display formats

We created five different display formats of the 10-year CBC probability based on formats described in the literature and discussions with experts (Figure 1). All display formats were based on an example patient who had a probability of developing CBC within 10 years after the primary diagnosis of 4% (average risk in the general breast cancer population[3-5]). The probability was visualized using I) text only, II) horizontal bar chart, III) pictograph including graphical representation of randomness, IV) pictograph including epistemic uncertainty by showing the confidence interval around the point estimate, as was described by Raphael et al[17], and V) vertical bar chart including reference lines depicting average risk of the general breast cancer population and *BRCA1/2* mutation carriers. All graphical display formats also included textual explanation of the probabilities, both positively and negatively framed (Figure 1).

Procedures and measures

Interviews

We carried out semi-structured interviews using a video connection (due to the COVID-19 outbreak) after participants electronically provided informed consent. The interviews (Supplementary Information A) were conducted by a research clinician (JMNLC) and took on average 45 minutes (range 34-66 min). The research protocol was developed by two researchers (IK and EGE) based on available literature regarding risk communication principles and input from clinicians. We did not include a patient representative in the development phase as the main aim of this study was to get the perspective of a diverse sample of patients. The interviewer used display format I (Figure 1) to explain the purpose of the model and which factors were included to quantify the probability of developing CBC. The participants were then asked to indicate how much trust they had in the probability provided on a 6-point Likert-type scale, ranging from *no trust at all* to *full trust*, and were asked to elaborate on their answer. Next, participants were shown each of the graphical display formats (display formats II-V, Figure 1) and asked to describe in their own words what the display format depicted (*"Could you explain in your own words what the chances are for this (example) patient to develop breast cancer in the other (tumor-free) breast?"*). Participants were encouraged to verbalize which aspects they liked and which aspects they disliked,

reasons for their preferences, and any changes they would make to improve the display format. Finally, to evaluate which factors, and in particular probabilities, would play a role in participants' decision to undergo a CPM, participants were asked (using an open-ended question) to indicate which factors would play an important role in their decision on whether to undergo a CPM.

Questionnaire

After the interview, all participants completed an electronic questionnaire assessing background information, such as age, educational level, genetic testing, and subjective numeracy (i.e., their ability to use mathematics in everyday life) (Supplementary Information B). We used the Ability subscale from the Subjective Numeracy Scale developed by Fagerlin et al.[20], rated on 6-point Likert-type scales ranging from *not at all good* to *extremely good*. Finally, to better understand whether probabilities play a role in decision-making we asked participants to indicate at what minimum level of risk to develop CBC they would choose to undergo CPM.

Coding and analyses

The interviews were transcribed verbatim. To identify and score the themes that came up during the interviews, an initial codebook was developed by two researchers (IK and EGE) based on three interviews. All interviews were then independently coded by the same two researchers. Items that were coded included factors associated with participants' level of trust, understanding of the graphical display formats, wishes regarding adjustments to display formats, and factors influencing CPM decision. Understanding of the graphical display formats of the participants was scored as 'good', 'moderate', or 'bad' based on the impression of the two researchers (IK and EGE). To score understanding, we looked at whether participants could correctly explain the probabilities visualized in the display formats in their own words *and* if they understood the different aspects of the display format (e.g., for display format V (Figure 1) if they understood the reference lines for *BRCA1/2* carriers and the general breast cancer population). All transcripts were double coded. Discrepancies in coding were resolved through consensus and new codes were added to the initial codebook as encountered. Finally, the two researchers grouped the categories into overarching domains for presentation purposes. All findings and codes were shared and discussed in the project team.

Results

We included breast cancer survivors until we achieved saturation (N=19). Table 1 shows the characteristics of the breast cancer survivors who were interviewed. Mean age was 50 years (range 25-72) at primary breast cancer diagnosis and 59 years (range 34-76) at date of interview. Thirteen of the 19 participants were highly educated, and in general, participants had high confidence in their ability to perform mathematical tasks. Twelve participants underwent breast conserving surgery for their primary breast cancer and three participants had undergone a CPM. The participants who had undergone a CPM were younger than 45 years at primary breast cancer diagnosis, and two of them had been diagnosed with Hodgkin's disease prior to their breast cancer diagnosis, for which they received (mantle field) radiation therapy (i.e., radiation was delivered to a large area including the breasts). The participants without CPM (N=16) indicated that removal of the other breast was not discussed as an option during consultations on their primary breast cancer.

Table 1. Characteristics of participating breast cancer survivors (N=19)

	Number of participants (%)[a]
Personal characteristics	
Mean age in years at interview (range)	59 (34-76)
Education	
Low	2 (11)
Intermediate	4 (21)
High	13 (68)
Breast cancer risk gene testing result at clinical genetic center[b]	
Not tested	5 (26)
Positive	1[c] (5)
Negative	12 (63)
Unknown whether testing has been performed	1 (5)
Non-breast cancer diagnosis prior to primary breast cancer diagnosis[d]	7 (37)
Subjective numeracy[e] (1=not at all good, 6=extremely good), median (range)	
How good are you at working with fractions?	3 (1-6)
How good are you at working with percentages?	5 (1-6)
How good are you at calculating a 15% tip?	5 (1-6)
How good are you at figuring out how much a trouser will cost if it is 25% off?	6 (3-6)
Primary breast cancer and treatment characteristics	
Mean age in years at breast cancer diagnosis (range)	50 (29-72)
TNM stage[f]	
I	4 (21)
II	7 (37)
III	8 (42)
Surgery	
Mastectomy	7 (37)
Breast conserving surgery	12 (63)
Radiotherapy	13 (68)
Chemotherapy	12 (63)
Endocrine therapy	6 (32)
Trastuzumab	3 (16)

[a] May not total 100% because of rounding
[b] The participants were asked to indicate if they were tested for any germline mutation (*BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, etc.)
[c] *BRCA2* carrier
[d] Hodgkin's lymphoma (N=2), basal cell carcinoma (N=2), cervical cancer and anal cancer (N=1), endometrial carcinoma in situ (N=1), oral cancer (N=1)

[e] We used the Ability subscale from the Subjective Numeracy Scale proposed by Fagerlin et al.[20]. In these questions, participants were asked to assess their perceived numerical ability in different contexts. Higher scores denote greater belief in own ability to use mathematics in everyday life

[f] TNM staging source: Brierley JD, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. 8th ed. West-Sussex: Wiley-Blackwell; 2017:272

Preferences for model layout and inclusion of information on uncertainty

During the interview, the participants were able to give their opinion on the visualization of probability in the different display formats. Five participants felt that, in all display formats shown, there was too much emphasis on the group of women who do develop a CBC. They mentioned they would have preferred more emphasis on the group of women who do not develop CBC, as a reassuring message, for example by using a more pronounced/vibrant color for that group. One participant said:

> *"Well, especially in this case, it is of course 96% [chance] to remain free of cancer, and that is quite a positive message. But, by making it very light gray, [the positive message] falls away and highlights especially those cases that do develop [breast cancer in the other breast]."*

In display format III and IV, CBC probabilities were visualized using pictographs (Figure 1). Six participants liked the fact that in display format III the female icons were randomly scattered throughout the array. Conversely, five participants preferred a sequential arrangement of the icons (display format IV), mainly because they found the random arrangement messier and more confusing. Some participants indicated that it would help to explicitly mention that the icons are randomly distributed because of chance. The confusion that arose from the random arrangement is illustrated by this quote:

> *"Well, let's see. Yeah, well, I wonder why, uh, those 4 women are … those green women. Why is one on the 3rd row and the other on the 5th row and the other on the 7th row and the other on the last row? I wonder what's the reason or, ...? [interviewer explains why icons are randomly distributed and checks if participant understands this] Well, I would add [to the display format] that… what the meaning is of the place where those women are put. Otherwise, I would think maybe, maybe uh uh, well maybe one is in the 3rd year [of follow-up] and the other in the 5th year [of follow-up] and the other, well… I want to give it a meaning right away and that [the meaning I give it] would not be that it is just randomness. So, it gets it [a wrong interpretation] then... And when you say that they are placed like that to show that it is random, you think, oh yes…"*

Of the 19 participants, 11 thought it was important to show the epistemic uncertainty, as was visualized in display format IV where a confidence interval was shown around the point estimate (Figure 1). However, nine participants mentioned that they did not like the way the confidence interval was currently visualized. They found only coloring in part of the female icons step by step confusing. For example, some participants mentioned *"It is not about getting cancer in your legs, as it looks now".* Six patients mentioned that they would have preferred a fading color to indicate the confidence interval of the icons rather than only coloring in part of the female icons step by step.

In display format V (Figure 1), the CBC probability was visualized using a bar chart including reference lines showing the average CBC risk in the general breast cancer population and in *BRCA1/2* mutation carriers. Fourteen participants mentioned they did not value the reference lines for *BRCA1/2* mutation carriers, since they felt this information was not of added value and/or the dotted lines made the graphical display messier. Ten participants found that the reference line for the general breast cancer population was not of added value either. One participant said:

> *"I think this [display format] contains too much information. It says, 'general breast cancer population', but this lady is not general. She wants to know what her personal risk is. So it should state 'your risk is...'. And if she is not a BRCA1 or BRCA2 mutation carrier… I would not mention it. This [information] is not useful for her."*

Finally, participants were asked to select the display format they most liked. Seventeen of the 19 participants indicated that a graphical display of the probabilities was of added value. Participants had varying preferences and not one graphical display format was clearly preferred. However, 10 participants preferred a bar chart, specifically when oriented vertically.

Trust in risk estimation

Median score on trust in the probability provided by the CBC model was 5 (SD=0.99) based on a 6-point Likert-type scale ranging from *no trust at all* to *full trust* (Figure 2). Eleven participants mentioned that having trust in science in general and/or trusting that the scientific foundation of the predictions is sound were important factors that increase their trust in the model probability (Table 2). The majority of participants mentioned that they would not be able to give a score of six as it is impossible to have 100% certainty; there is always the possibility that you are the unlucky person who does develop a CBC. Five participants had the perception that not all relevant factors were included in the prediction model, which made them score low on trust in the probability (Table 2). Factors they missed in the current model included information on *CHEK2* c.1100del mutation, detailed information about adjuvant treatment (e.g., which type of chemotherapy), number of positive lymph nodes, and the MammaPrint (70-gene signature).

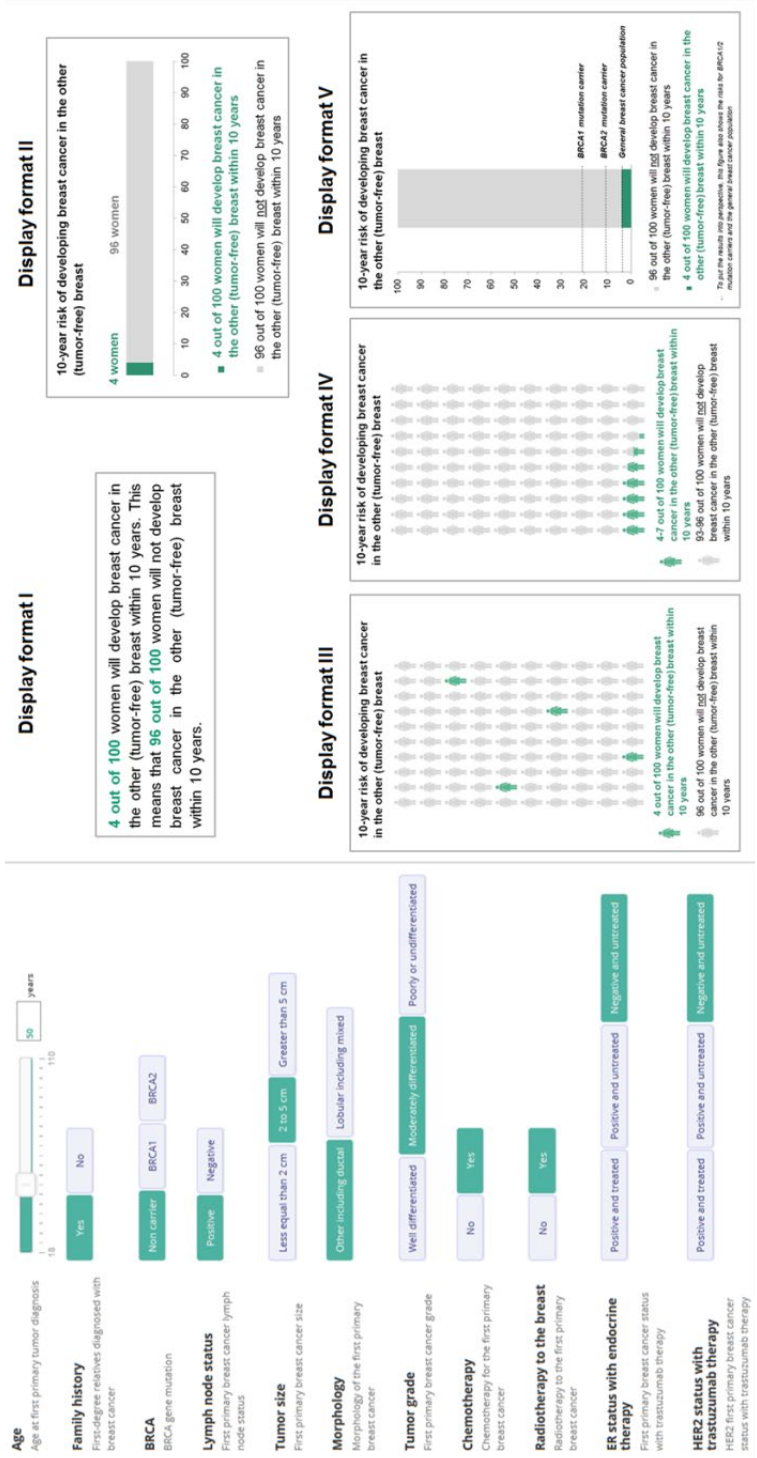


Figure 1. Overview of the display formats of the contralateral risk prediction model (PredictCBC) shown during the interview[a]
Display format 1 – text only
Display format 2 – horizontal bar chart
Display format 3 – pictograph including graphical representation of randomness
Display format 4 – pictograph including epistemic uncertainty by showing the confidence interval around the point estimate as was similar to Raphael et al.[17]
Display format 5 – vertical bar chart including reference lines depicting average risk of the general breast cancer population and *BRCA1* and *BRCA2* mutation carriers
[a] For the purpose of this study, our CBC risk prediction model was implemented in an online tool using the Evidencio platform (https://www.evidencio.com/home)

Table 2. Factors mentioned by the participating breast cancer survivors that influence trust in probabilities provided by the contralateral risk prediction model (PredictCBC)

Mentioned factors[a]	Frequency[b]	Example quotations
Factors that increase trust in the probability shown		
Trust in science and/or scientific foundation of prediction	11	"If I would have known that this [calculation of probability] is based on a very large dataset… Yes, then I would have more trust."
Perception that all relevant factors are included in risk prediction model	3	
Factors that decrease trust in the probability shown		"I cannot fully trust it, but I think that is true for many cancer patients. There will never be complete trust."
You can never be 100% sure/you could always be the unlucky person that experiences the outcome	13	
Perception that not all relevant factors are included in the risk prediction model	5	"What I am actually missing here is [results from] the pathological examination. Because it seems to me that with the pathological examination you should also be able to make a certain prediction. So that makes this incomplete, right?"
Perception that included factors do not discriminate sufficiently between high and low risk	3	

[a] Factors were listed that were mentioned by at least two participants
[b] Rows do not add up to the number of participants (N=19) because some answers contained multiple factors

Understanding of the graphical display formats

We observed that the majority of participants had good understanding of display formats II (horizontal bar chart), III (pictograph including graphical representation of randomness), and V (vertical bar chart including reference lines depicting average risk for other populations) (Figure 3). We found that the participants generally seemed to have difficulty understanding display format IV (pictograph including epistemic uncertainty by showing the confidence interval around the point estimate). Out of the 19 participants, 14 scored moderate on understanding of display format IV and one had poor understanding (Figure 3).

Factors influencing CPM decision

Figure 4 shows factors mentioned by the participants that would influence their decision on whether to undergo a CPM and quotes to illustrate this. Almost all participants (N=18) mentioned that they would choose to have their other (tumor-free) breast removed if the probability of developing CBC was high. In the post-interview survey seven participants (out of 14 participants who answered this question) indicated that the 10-year probability of developing a CBC had to be minimally 10% for them to choose to undergo a CPM. Other factors that were repeatedly mentioned were the reduction of fear of future breast cancer, being a *BRCA1/2* mutation carrier, and the desire to achieve breast symmetry (if the breast of the primary breast cancer is removed).

An important factor for not opting to undergo a CPM was to avoid side-effects of prophylactic surgery (Figure 4). Some participants mentioned that they considered CPM unnecessary as long as they received follow-up check-ups for their primary breast cancer, including mammography of the other breast. Other factors were the negative impact on femininity or body image, or that a breast is a cherished part of the body and/or plays a role in sexuality.

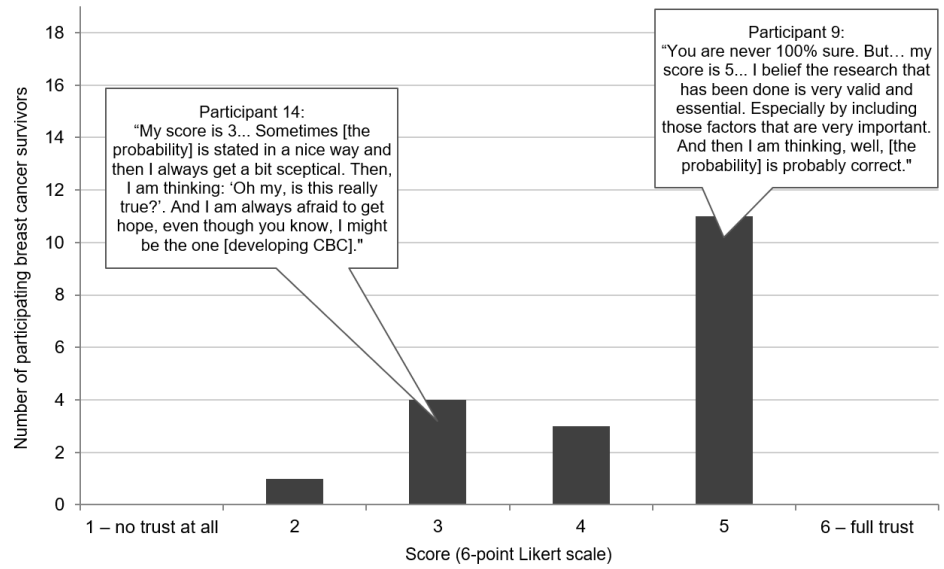
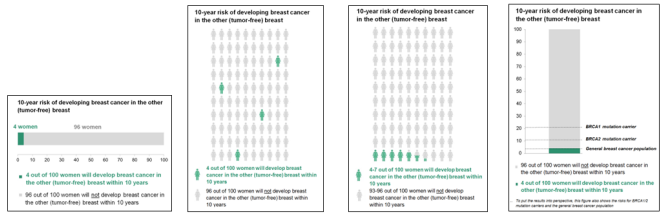


Figure 2. Trust in the probabilities provided by the contralateral risk prediction model (PredictCBC) indicated by the participating breast cancer survivors (N=19) on a 6-point Likert-type scale
Abbreviations: CBC = contralateral breast cancer



	Display format II	Display format III	Display format IV	Display format V
Subjective understanding	N participants (%)	N participants (%)	N participants (%)	N participants (%)
Good	13 (68)	15 (79)	4 (21)	11 (58)
Moderate	0 (0)	3 (16)	14 (74)	5 (26)
Bad	5 (26)	1 (5)	1 (5)	2 (11)
Not clear from answer	1 (5)	0 (0)	0 (0)	1 (5)

Figure 3. Rater's scoring of understanding of the different graphical display formats of the contralateral risk prediction model's (PredictCBC) 10-year probability of developing contralateral breast cancer
To score understanding, we looked at whether participants could correctly explain the probabilities visualized in the display formats in their own words *and* if they understood the different aspects of the display format (e.g., for display format V if they understood the reference lines for *BRCA1/2* carriers and the general breast cancer population)

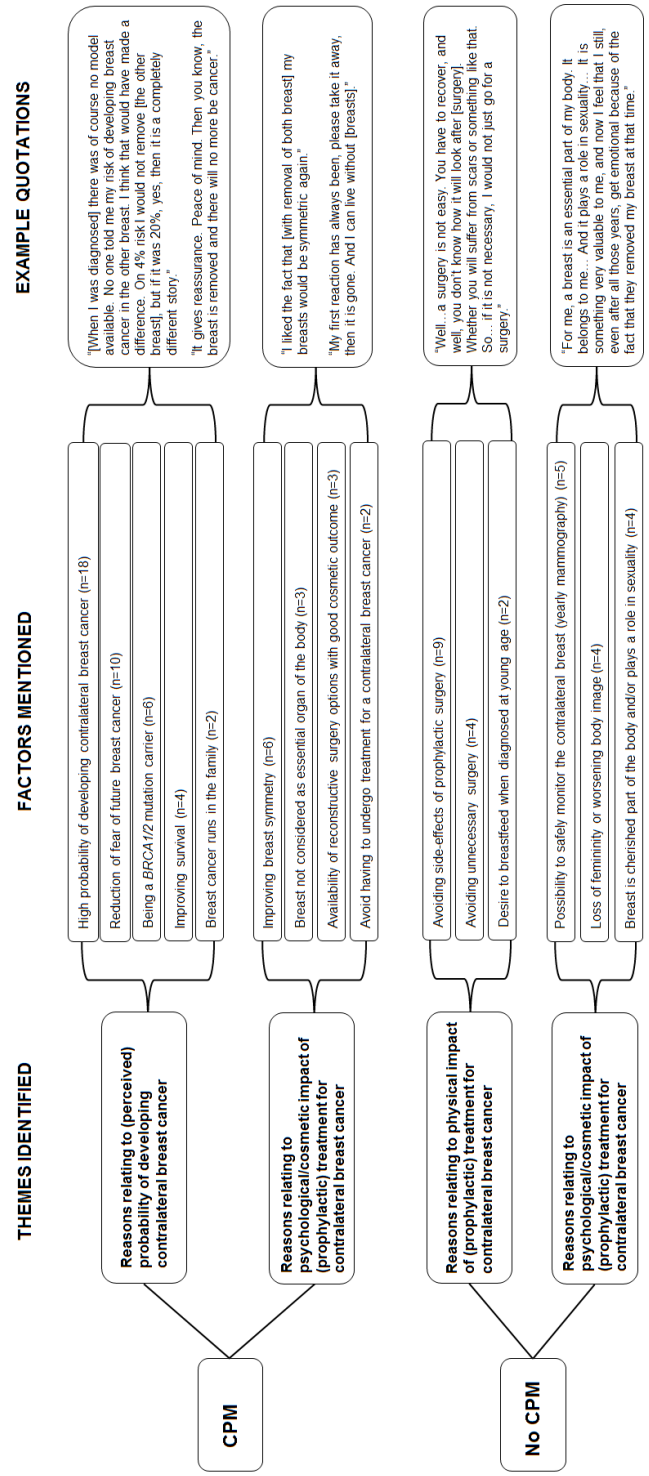


Figure 4. Important factors influencing the participating breast cancer survivors' decision to undergo a contralateral prophylactic mastectomy
Abbreviations: CPM = contralateral prophylactic mastectomy
Factors that were listed in this figure were mentioned by at least two participants. Rows do not add up to the number of participants (N=19) because some answers provided by participants contained multiple factors

Discussion

As a first step towards the development of a CBC prediction tool that can help clinicians to communicate probabilities to patients, the main aim of this exploratory interview study was to get insights into breast cancer survivors' (i.e., potential end-users) preferences for the graphical presentation of the probabilities, including the epistemic uncertainty, provided by the model. Participants in this study preferred graphics to show probabilities in a CBC risk prediction model, but they had varying preferences regarding the type of graphical representation. It is reassuring that participants had high levels of trust in the probabilities shown, which indicates that a CBC risk prediction model can be of added value in helping patients to make decisions. Moreover, probabilities seem to play an important role in decision-making about CPM, as we found that having a high probability of developing a CBC as well as fear of future breast cancer were the factors most frequently mentioned by participants' as relevant for their decision-making. Interestingly, the majority thought it was important to show the epistemic uncertainty associated with risk estimates. However, including the epistemic uncertainty also seems to have its drawback, as only four participants had good understanding of the graphical display format containing this information.

Our findings are in line with previous research showing that textual risk communication is better understood in combination with graphical formats[21-24]. In the literature, no consensus has been reached yet on the optimal graphical format for presenting a single probability. This is reflected in our study where participants had varying preferences, and no display format was a clear favorite. However, a substantial proportion of participants preferred a bar chart, specifically when oriented vertically. The preference for a vertical orientation is in line with some previous studies that showed that vertical graphs were processed slightly faster than horizontal graphs[25-27].

Some studies recommend pictographs as the optimal format to communicate probabilistic information to patients, especially for patients with low numeracy[23,28-30]. They argue that pictographs improve patients understanding of probabilities as they better represent the part-to-whole relationship[23] and they are easier to identify with than bar charts[31,32]. In our study, participants had slightly better understanding of the display format including a pictograph (display format III) compared with a bar chart (display format II). However, the improvement in understanding could potentially be explained by a learning curve, as participants become more familiar with the concept of risk prediction by viewing multiple display formats. Participants had varying preferences between a random and sequential arrangement of the cases in the pictograph. Randomly arranged pictographs have the benefit that they convey the difficult concept of randomness[32], so they are in a way more realistic, but they are generally perceived as more difficult to understand[30]. In our study, participants indicated that when using random arrangement, some additional information on the explanation of the randomness may be a solution to overcome confusion.

In the display format including a vertical bar chart (display format V), we also included reference lines depicting average risk of the general breast cancer population and *BRCA1/2* mutation carriers. The intent was to help patients put their risk in perspective. However, our results suggested that it would be better to leave out these reference lines, as the majority of the participants thought these were not of added value and made the display messier. Moreover, model understanding was slightly worse for display format V compared to display format II (horizontal bar chart) and III (pictograph including graphical representation of randomness). This is in line with the growing evidence that "less is more" in the field of decision-making[33]. For example, a recently published systematic review that evaluated the effect of different ways of communicating treatment risks and benefits to cancer patients, showed that limiting the amount of information in a graphical display improved patients' understanding[34].

In the literature, there is an ongoing debate about whether epistemic uncertainty should be communicated to patients, and if so, how this should be visualized by risk prediction models and in decision aids[17,18]. In current practice, epistemic uncertainty is rarely explicitly communicated[18,19]. In our study, more than half of the participants thought it is important to show epistemic uncertainty, since this information is "more true" and complete. However, the participants seemed to struggle with information about epistemic uncertainty, as understanding of the graphical display format containing the confidence interval was worse. Many participants pointed out they did not like the way the confidence interval was currently visualized (stepwise coloring in part of the female icons) and they recommended a fading color. This is in contrast with another study in the Dutch breast cancer survivor population[17], where the stepwise coloring came out as best format. Future studies should investigate the best way to communicate epistemic uncertainty to patients.

The results of our study indicate that the probability of developing CBC and fear of future breast cancer play an important role in participants' decision on whether to undergo a CPM. This is in line with a systematic review on patient reported and psychological factors influencing the decision on CPM[7]. Our finding highlights that at least some patients have a need for personalized CBC risks. Indeed, we are careful and hesitant in extrapolating our findings to *all* breast cancer patients since our study included a selected group of breast cancer survivors due to the invitation approach and our sampling to achieve a heterogeneous group of participants. The majority of the participants was highly educated, had high confidence in their ability to perform mathematical tasks, and some may have been more actively involved with research than the general breast cancer population. Another limitation is the potential learning curve that participants may have developed by viewing several display formats during the interview. In addition, since this was an exploratory interview study, future large-scale experimental studies are needed to investigate how to effectively design the interface

for a risk prediction tool that meets the diverse needs of end users, and to investigate differences in preferences between subgroups of women. The main strength of this study is that we performed the interviews within the target end-users, breast cancer survivors for whom decision-making about CPM is relevant at different time-points in their survivorship (time since primary breast cancer diagnosis ranged from 2-38 years). As a next step, healthcare professionals' preferences for the CBC model interface should also be investigated as they play a key role in implementation of the model in clinical practice.

In conclusion, our study provided valuable information on preferences for graphical presentation of probability and uncertainty in a CBC prediction model. Graphical components are important to explain probabilities, but there is no single best method for communication of probabilities to patients. Any tool intended for use with patients' needs to allow flexibility in display format (e.g., as done in the frequently used PREDICT prognostication tool [35]). Our study showed that participants valued information on epistemic uncertainty, but future studies are needed to investigate the best way to effectively communicate this type of information. As the probability of developing CBC plays an important role in the participants' decision to undergo a CPM, it is important to carefully design and test the risk prediction model interface prior to implementation. Finding better ways to communicate probabilities will result in better understanding and consequently improve the quality of health decisions and outcomes such as decision regret.

Article Information

Funding

This work was supported by a grant from Alpe d'HuZes/KWF Kankerbestrijding (Dutch Cancer Society) grant number A6C/6253 and by the PRECISION project (Cancer Research UK and KWF Kankerbestrijding ref. C38317/A24043).

Conflict of interest

The authors declare that there is no conflict of interest

Author's contributions

MKS and EGE designed the study; JMNLC conducted the interviews; IK and EGE coded the data; IK drafted the first version of the manuscript; all other authors contributed to the interpretation of the results and revisions of the manuscript. All authors approved the final manuscript.

Acknowledgements

We are very grateful to all the breast cancer survivors who participated in this study. We thank the patient advisory group from the Dutch Breast Cancer Research Group (BOOG), the Dutch Breast Cancer Patient Association, and the breast cancer patient panel from the Antoni van Leeuwenhoek hospital for their help with the recruitment of the breast cancer survivors. We thank Manon Verwijs for her help with the transcription of the interviews.

References

1 Naik, G., Ahmed, H. & Edwards, A. G. Communicating risk to patients and the public. *Br. J. Gen. Pract.* **62**, 213-216, doi:10.3399/bjgp12X636236 (2012).

2 Stiggelbout, A. M., Pieterse, A. H. & De Haes, J. C. Shared decision making: Concepts, evidence, and practice. *Patient Educ. Couns.* **98**, 1172-1179, doi:10.1016/j.pec.2015.06.022 (2015).

3 Giardiello, D. *et al.* Contralateral breast cancer risk in patients with ductal carcinoma in situ and invasive breast cancer. *NPJ Breast Cancer* **6**, 60, doi:10.1038/s41523-020-00202-8 (2020).

4 Giardiello, D. *et al.* Prediction and clinical utility of a contralateral breast cancer risk model. *Breast Cancer Res.* **21**, 144, doi:10.1186/s13058-019-1221-1 (2019).

5 Xiong, Z. *et al.* Patterns of Occurrence and Outcomes of Contralateral Breast Cancer: Analysis of SEER Data. *J Clin Med* **7**, doi:10.3390/jcm7060133 (2018).

6 Wong, S. M. *et al.* Growing Use of Contralateral Prophylactic Mastectomy Despite no Improvement in Long-term Survival for Invasive Breast Cancer. *Ann. Surg.* **265**, 581-589, doi:10.1097/sla.0000000000001698 (2017).

7 Ager, B., Butow, P., Jansen, J., Phillips, K. A. & Porter, D. Contralateral prophylactic mastectomy (CPM): A systematic review of patient reported factors and psychological predictors influencing choice and satisfaction. *Breast* **28**, 107-120, doi:10.1016/j.breast.2016.04.005 (2016).

8 Carbine, N. E., Lostumbo, L., Wallace, J. & Ko, H. Risk-reducing mastectomy for the prevention of primary breast cancer. *Cochrane Database Syst. Rev.* **4**, Cd002748, doi:10.1002/14651858.CD002748.pub4 (2018).

9 Nederland, N. B. O. (2018).

10 van den Broek, A. J. *et al.* Impact of Age at Primary Breast Cancer on Contralateral Breast Cancer Risk in BRCA1/2 Mutation Carriers. *J. Clin. Oncol.* **34**, 409-418, doi:10.1200/jco.2015.62.3942 (2016).

11 Kuchenbaecker, K. B. *et al.* Evaluation of Polygenic Risk Scores for Breast and Ovarian Cancer Risk Prediction in BRCA1 and BRCA2 Mutation Carriers. *J. Natl. Cancer Inst.* **109**, doi:10.1093/jnci/djw302 (2017).

12 Reyna, V. F. & Brainerd, C. J. The importance of mathematics in health and human judgment: Numeracy, risk communication, and medical decision making. *Learning and Individual Differences* **17**, 147-159 (2007).

13 Gigerenzer, G., Gaissmaier, W., Kurz-Milcke, E., Schwartz, L. M. & Woloshin, S. Helping Doctors and Patients Make Sense of Health Statistics. *Psychol. Sci. Public Interest* **8**, 53-96, doi:10.1111/j.1539-6053.2008.00033.x (2007).

14 Zipkin, D. A. *et al.* Evidence-based risk communication: a systematic review. *Ann. Intern. Med.* **161**, 270-280, doi:10.7326/m14-0295 (2014).

15 Trevena, L. J., Davey, H. M., Barratt, A., Butow, P. & Caldwell, P. A systematic review on communicating with patients about evidence. *J. Eval. Clin. Pract.* **12**, 13-23, doi:10.1111/j.1365-2753.2005.00596.x (2006).

16 Büchter, R. B., Fechtelpeter, D., Knelangen, M., Ehrlich, M. & Waltering, A. Words or numbers? Communicating risk of adverse effects in written consumer health information: a systematic review and meta-analysis. *BMC Med. Inform. Decis. Mak.* **14**, 76, doi:10.1186/1472-6947-14-76 (2014).

17 Raphael, D. B. *et al.* Risk communication in a patient decision aid for radiotherapy in breast cancer: How to deal with uncertainty? *Breast* **51**, 105-113, doi:10.1016/j.breast.2020.04.001 (2020).

18 Engelhardt, E. G. *et al.* Disclosing the Uncertainty Associated with Prognostic Estimates in Breast Cancer. *Med. Decis. Making* **37**, 179-192, doi:10.1177/0272989x16670639 (2017).

19 Han, P. K. J. *et al.* Uncertainty in health care: Towards a more systematic program of research. *Patient Educ. Couns.* **102**, 1756-1766, doi:10.1016/j.pec.2019.06.012 (2019).

20 Fagerlin, A. *et al.* Measuring numeracy without a math test: development of the Subjective Numeracy Scale. *Med. Decis. Making* **27**, 672-680, doi:10.1177/0272989x07304449 (2007).

21 Waters, E. A., Weinstein, N. D., Colditz, G. A. & Emmons, K. Formats for improving risk communication in medical tradeoff decisions. *J Health Commun* **11**, 167-182, doi:10.1080/10810730500526695 (2006).

22 Lipkus, I. M. Numeric, verbal, and visual formats of conveying health risks: suggested best practices and future recommendations. *Med. Decis. Making* **27**, 696-713, doi:10.1177/0272989x07307271 (2007).

23 Zikmund-Fisher, B. J. *et al.* Communicating side effect risks in a tamoxifen prophylaxis decision aid: the debiasing influence of pictographs. *Patient Educ. Couns.* **73**, 209-214, doi:10.1016/j.pec.2008.05.010 (2008).

24 Klein, K. A., Watson, L., Ash, J. S. & Eden, K. B. Evaluation of risk communication in a mammography patient decision aid. *Patient Educ. Couns.* **99**, 1240-1248, doi:10.1016/j.pec.2016.02.013 (2016).

25 McCaffery, K. J. *et al.* The influence of graphic display format on the interpretations of quantitative risk information among adults with lower education and literacy: a randomized experimental study. *Med. Decis. Making* **32**, 532-544, doi:10.1177/0272989x11424926 (2012).

26 Shah, P. & Hoeffner, J. Review of graph comprehension research: Implications for instruction. *Educ. Psychol. Rev.* **14**, 47-69 (2002).

27 Tversky, B. in *Spatial schemas and abstract thought.* 79-111.

28 Hawley, S. T. *et al.* The impact of the format of graphical presentation on health-related knowledge and treatment choices. *Patient Educ. Couns.* **73**, 448-455, doi:10.1016/j.pec.2008.07.023 (2008).

29 Franklin, L., Plaisant, C. & Shneiderman, B. An information-centric framework for designing patient-centered medical decision aids and risk communication. *AMIA Annu Symp Proc* **2013**, 456-465 (2013).

30 Ancker, J. S., Weber, E. U. & Kukafka, R. Effect of arrangement of stick figures on estimates of proportion in risk graphics. *Med. Decis. Making* **31**, 143-150, doi:10.1177/0272989x10369006 (2011).

31 Schapira, M. M., Nattinger, A. B. & McHorney, C. A. Frequency or probability? A qualitative study of risk communication formats used in health care. *Med. Decis. Making* **21**, 459-467, doi:10.1177/0272989x0102100604 (2001).

32 Ancker, J. S., Senathirajah, Y., Kukafka, R. & Starren, J. B. Design features of graphs in health risk communication: a systematic review. *J. Am. Med. Inform. Assoc.* **13**, 608-618, doi:10.1197/jamia.M2115 (2006).

33 Zikmund-Fisher, B. J., Fagerlin, A. & Ubel, P. A. A demonstration of ''less can be more'' in risk graphics. *Med. Decis. Making* **30**, 661-671, doi:10.1177/0272989x10364244 (2010).

34 van de Water, L. F. *et al.* Communicating treatment risks and benefits to cancer patients: a systematic review of communication methods. *Qual. Life Res.* **29**, 1747-1766, doi:10.1007/s11136-020-02503-8 (2020).

35 Predict: Breast Cancer. Version 2.2, Release 1.14. Available from: https://breast.predict.nhs.uk/tool.

Supplementary Information A - Interview protocol

Introduction

- **Word of welcome:** Thank you for participating in this study. Let me introduce myself. The interview will take about 45 minutes.
- **Explanation goal of the study:** Our research group focuses on women diagnosed with breast cancer. We would like to have a better estimate for every woman diagnosed with breast cancer what the probability is of developing a second breast cancer in the other (tumor-free) breast. We are currently developing a risk prediction model. In general, the probability of developing a second breast cancer in the other (tumor-free) breast is small. The purpose of this interview is to understand what patients think of our model and how we can improve the risk visualization, in order to make the model as clear as possible and patient-friendly. The results of this study may be published in scientific journals. From the text, you will not be identifiable. With your permission I will record the interview. Everything you say will be treated confidentially. After analyzing the information, we will delete the recording. Do you give consent for this?

Background

- Before we start with the questions related to the model, I would like to know how you are doing?
- I would like to ask a few more questions to get some background information.
    - How old were you when you were diagnosed with breast cancer? What is your current age?
    - At what stage was the primary breast cancer diagnosed?
    - What treatments did you receive when you were diagnosed with breast cancer? Did you receive:
        - Breast conserving surgery, mastectomy, or no surgery? Was this conform the doctor's advice?
        - Did you and your doctor discuss the possibility for preventive removal of the other (tumor-free) breast?
        - Did you receive chemotherapy?
        - Did you receive endocrine therapy?
        - Did you receive HER2-specific therapy?
        - Did you receive radiotherapy?
    - Was your primary breast cancer diagnosis the first time that you were diagnosed with cancer? If not, may I ask what diagnoses you have had previously?

Model introduction

- As I just explained, we developed a model to estimate the probability that a woman who has been diagnosed with breast cancer will develop breast cancer again in the other (tumor-free) breast. I will give some more information [shows display format I]. We developed a mathematical model with data from a large group of patients. In this example we use a fictitious patient with an average CBC risk. The model contains factors that influence the risk of a second breast cancer. For example, age at first breast cancer diagnosis, tumor characteristics of the primary tumor, and treatment. These factors can be entered for each patient, which will result in a certain risk estimate.

The end goal is that this model can be used by doctors to inform patients about the risk of developing breast cancer in the other (tumor-free) breast. For example, additional treatment may be provided, preventive removal of the other breast, or the model can be used to reassure women who are at very low risk of developing breast cancer in the other breast. The latter will be applicable to most women.

In this example (display format I), 4 out of 100 women, who have the same characteristics as this fictitious patient, will develop breast cancer in the other (tumor-free) breast within 10 years. This means that 96 out of 100 women do not develop breast cancer in the other (tumor-free) breast. Currently, the model is still under development and therefore, it is not used by doctors yet. First, we would like to investigate how we can improve the risk visualization, to make the risk information provided by the CBC prediction model as clear and patient-friendly as possible. Therefore, I would like to ask you some questions based on some examples of model visualizations.

Model trust

- [Show display format I and explain the information shown, and then show the 6-point Likert-type scale to rate trust] Could you indicate on this 6-point scale, ranging from *no trust at all* to *full trust*, how much trust you have in the risk estimates you just viewed?
- Could you elaborate on the score you have given? What could be said to improve your trust?

5

Different display formats of model

- As I just explained, we would like to investigate what type of risk visualization is most clear and patient-friendly. Therefore, I will show you different display formats of the model and ask a few questions.
- [show display format II-V, one by one, and repeatedly ask the following questions] Could you explain in your own words what the chances are for this (example) patient to develop breast cancer in the other (tumor-free) breast? Do you miss specific information?
- [show overview of display format I-V] You have just viewed five different display formats of the model. What display format do you prefer? And why?

Factors contralateral prophylactic mastectomy

- Finally, I would like to talk about important factors that influence patients' decision to opt for preventive removal of the other (tumor-free) breast. We ask you this question to get an idea about what information is important when making such a decision.
- [for patients without CPM] Imagine that you have the choice to have the other (tumor-free) breast removed preventively. What would be reasons to remove the other (tumor-free) breast? And what would be reasons for not removing the other (tumor-free) breast?
- [for patients with CPM] You have had your other (tumor-free) breast removed preventively. What were the reasons to remove the other breast preventively?

End interview

- These were all my questions. I would like to thank you for this interview. If you have any questions left, please contact me at any time.

Supplementary Information B – Questionnaire

Question 1. What is your current age: _____

Question 2. What is your highest level of education you have completed:

- ☐ Elementary school, primary school
- ☐ Pre-vocational secondary education
- ☐ Secondary vocational education, senior general secondary education, pre-university education
- ☐ University of applied sciences (i.e., higher professional education) or university
- ☐ Other, namely _____

With the following questions we want to get insight into whether you or someone in your family has undergone genetic testing. Genetic testing can be used to find out whether someone has an increased risk of developing cancer due to a genetic predisposition. Genetic predisposition does not automatically mean that someone will get cancer.

Question 3. Have you or someone in your family undergone genetic testing?

- ☐ No (as far as I know)
- ☐ I do not know
- ☐ I would rather not answer this
- ☐ Yes, please tick what is applicable below:
  - ☐ I have undergone genetic testing
  - ☐ Son(s) and/or daughter(s)
  - ☐ Father and/or mother
  - ☐ Brother(s) and/or sister(s)
  - ☐ Uncle(s) and/or aunt(s)
  - ☐ Cousin(s)
  - ☐ Grandfather(s) and/or grandmother(s)

Question 4. Has a genetic mutation been found in yourself or someone in your family?

- ☐ Yes
- ☐ No
- ☐ I do not know

Question 5. Please indicate in the table below in whom a genetic mutation has been found and which mutation was found.

A genetic mutation has been found by:			CDKN2A mutation	APC mutation	*BRCA 1* mutation	*BRCA 2* mutation	*P53* mutation	*CHEK 2* mutation	*PALB 2* mutation	*Other, namely:*	I do not know
			Which genetic mutation has been found?								
Myself	☐ Yes	☐ No	☐	☐	☐	☐	☐	☐	☐	☐	☐

If a genetic mutation has been found in someone in your family, please indicate below in which family member the mutation has been found and which genetic mutation was found.

Family member	CDKN2A mutation	APC mutation	*BRCA 1* mutation	*BRCA 2* mutation	*P53* mutation	*CHEK 2* mutation	*PALB 2* mutation	*Other, namely:*	I do not know
Example: sister	☐	☐	☐	☒	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐

Question 6. For each of the following questions, please check the box that best reflects how good you are at doing the following things[1]:

a. How good are you at working with fractions?

1	2	3	4	5	6
O	O	O	O	O	O
Not at all good					**Extremely good**

b. How good are you at working with percentages?

1	2	3	4	5	6
O	O	O	O	O	O
Not at all good					**Extremely good**

c. How good are you at calculating a 15% tip?

1	2	3	4	5	6
O	O	O	O	O	O
Not at all good					**Extremely good**

d. How good are you at figuring out how much a trouser will cost if it is 25% off?

1	2	3	4	5	6
O	O	O	O	O	O
Not at all good					**Extremely good**

Question 7. At what level of probability of developing breast cancer in the other (tumor-free) breast would you choose to have the other (tumor-free) breast removed preventively?

- **1-2 out of 100 women** will develop breast cancer in the other (tumor-free) breast within 10 years
- **3-5 out of 100 women** will develop breast cancer in the other (tumor-free) breast within 10 years
- **5-10 out of 100 women** will develop breast cancer in the other (tumor-free) breast within 10 years
- **More than 10 out of 100 women** will develop breast cancer in the other (tumor-free) breast within 10 years

Supplemental References

1 Fagerlin, A. *et al.* Measuring numeracy without a math test: development of the Subjective Numeracy Scale. *Med. Decis. Making* **27**, 672-680, doi:10.1177/0272989x07304449 (2007).

5