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The path to individualised breast cancer screening

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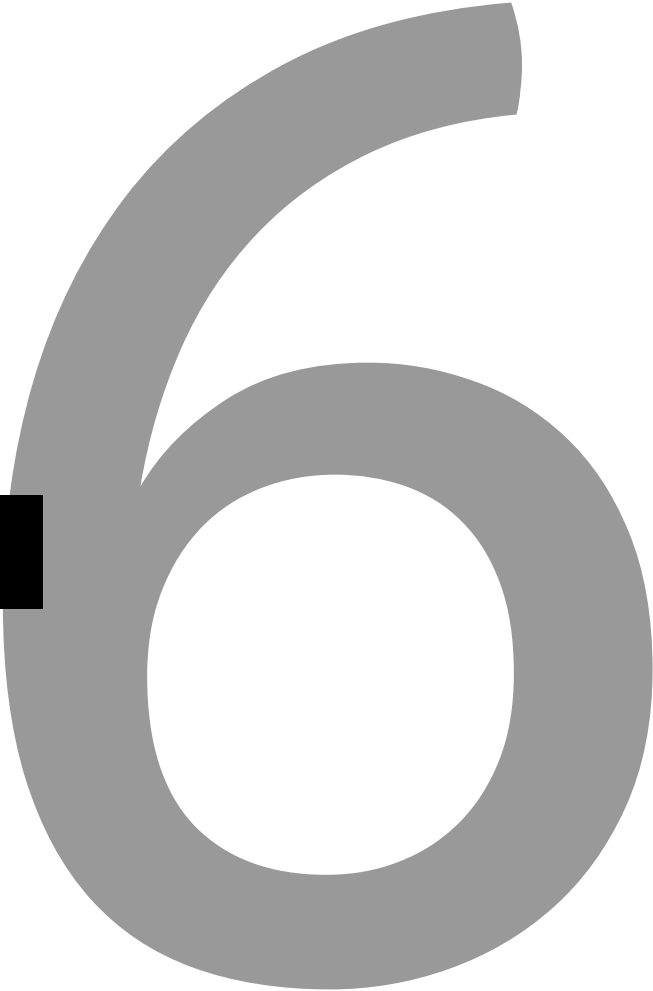
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CHAPTER 6



Comprehensive breast cancer risk prediction for women from non-*BRCA1/2* breast cancer families – an observational pilot study in one Dutch medical centre

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This chapter is a draft of a Dutch pilot study that will be published in a full manuscript together with data from France and Germany.

Abstract

Introduction: Our aim was to determine the clinical and emotional impact of using and communicating Comprehensive Risk Prediction (CRP) compared to standard family history-based risk prediction (FHRP).

Methods: In this observational pilot study, we included 38 unaffected first-degree female relatives of women affected with breast cancer, who underwent breast cancer counselling in 2019/2020 and tested negative for pathogenic variants in *BRCA1/2*, *PALB2*, *CHEK2*, and *ATM*. During that consultation, the counslee had received a single risk score for their healthy relatives based on FHRP (clinical advice). Individual FHRP and CRP were (re-)calculated by using the CanRisk web tool. CRP included family history, the PRS₃₁₃, and lifestyle/hormonal factors. CRP results were communicated to the participants via web consultation on individual basis. To assess the psychosocial impact, participants were asked to fill in questionnaires before and after risk communication.

Results: Based on their individual CRP, ten participants changed to a lower, and eight to a higher risk category compared to FHRP. Notably, two sisters who had been given the same FHRP-based moderate risk category, changed respectively to a higher and lower risk category after CRP, mainly due to the PRS₃₁₃. Moreover, individual FHRP re-calculated with CanRisk differed from the risk category and corresponding clinical management given during the first genetic consultation of the affected family member for 13 out of 38 participants. Participants were overall positive about receiving their CRP, explanation during the web-consultation and method of communication (online versus hospital visit)

Conclusion: In this pilot-sample, 47% of healthy relatives shifted to another risk category and received a different screening advice based on their CRP as compared to their FHRP. The dissimilarity between the initial clinical advice and CanRisk-based FHRP emphasizes the need for standardised tools and protocols.

Introduction

Women with a first-degree relative affected with breast cancer have a twofold increased risk of developing the disease themselves¹. Over half of the familial risk of breast cancer has been clarified genetically, with rare pathogenic mutations in moderate- and high-risk genes, such as *BRCA1* and *BRCA2*, accounting for ~25%, and common low risk variants associated with breast cancer for a further ~36%^{2,3}. Summarized in a Polygenic Risk Score (PRS), these common low risk variants are useful to stratify women into different risk categories³⁻⁸. Breast cancer surveillance for unaffected women from breast cancer families is currently guided by risk assessment based on family history and DNA testing results of five breast cancer genes (i.e. *BRCA1/2*, *PALB2*, *CHEK2*, *ATM*). We have shown previously that addition of the polygenic risk score (PRS) to this routine changed screening recommendations for a substantial proportion of the women according to breast screening guidelines^{5,9}. Because secondary prevention by mammogram to reduce the burden of the disease has several disadvantages as well, including overdiagnosis¹⁰, it would be optimal to target those women most likely to benefit from screening by their individual breast cancer risk.

Individual breast cancer lifetime risks can be calculated by various risk prediction algorithms¹¹, such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)¹². BOADICEA calculates cumulative breast cancer risk based on family history, mammographic density, lifestyle/hormonal and genetic risk factors, including the most predictive PRS, based on 313 variants (PRS₃₁₃)^{3,12}. This model has been externally prospectively validated¹³⁻¹⁶, is implemented in the user friendly CanRisk online tool¹⁷, and has received CE-marking. Although it seems ready for implementation into breast cancer prevention programs, Comprehensive Risk Prediction (CRP) is currently not used in clinical management.

At this moment, genetic testing is mainly offered to women affected by breast cancer and is mainly restricted to the high penetrant genes *BRCA1*, *BRCA2*, *PALB2* and the moderate risk genes *CHEK2* and *ATM*. With the possibility for individualised risk prediction (CRP), a new group of unaffected relatives of breast cancer patients become eligible for counselling. Because we know that counselling can be a cause for a wide range of psychosocial problems¹⁸, we should be cautious with this new form of risk prediction. With the current study, we aim to determine the clinical and emotional impact of CRP by measuring how often these unaffected women shift in risk category compared to standard family history-based risk prediction, as well as the psychosocial impact of CRP by measuring cancer worries of counselees after having been given their individual CRP score.

Methods

This study is known as the IBR-study (Individualised Breast cancer Risk prediction study), a pilot observational cohort study at the Leiden University Medical Center (LUMC) which has been approved by the medical ethical committee (NL68501.058.18). The IBR-study is still ongoing in close collaboration with the BRIDGES (Breast cancer Risk after Diagnostic GENE Sequencing) study¹⁹. The aim of the BRIDGES study is to build a knowledge base that will allow identification of women at high-risk of breast cancer, in particular through comprehensive evaluation of DNA variants in known and suspected breast cancer genes²⁰

Study cohort

The cohort consist of unaffected female relatives from counselees affected with breast cancer. These women were included in 2019/2020 via the outpatient clinic of the Department of Clinical Genetics at the LUMC in Leiden, the Netherlands. After a counselee with breast cancer had tested negative for (likely) pathogenic variants in the breast cancer genes *BRCA1*, *BRCA2*, *PALB2*, *CHEK2* and *ATM*, her unaffected first-degree female relatives aged 35-60 years, were invited to participate in the study via an appendix to the family letter. The family letter is part of the diagnostic routine in counselling, in which the healthy relative receives a family history-based clinical management advice for breast screening (henceforth termed “clinical advice”). Women interested to participate in the study were asked to enrol in the Hereditary Breast and Ovarian cancer study in the Netherlands (HEBON)²¹, during which they gave informed consent. The HEBON study (initiated in 1999) is an ongoing nationwide cohort study with members from breast cancer families, which arranges prospective follow up through record-linkage with the nationwide cancer and pathology registries. Informed consent for the IBR study was received from 45 participants. An overview of our study flow scheme is shown in Figure 1.

Comprehensive risk prediction

CRP was calculated with the CanRisk webtool in which BOADICEA is implemented. Participants received a saliva sample package at home to collect DNA. Breast cancer genes were tested by a multigene panel of which 5 genes were analysed (*BRCA1*, *BRCA2*, *PALB2*, *ATM* and *CHEK2*). The 313 common low risk variants³ were genotyped by a slightly modified panel of 340 variants (27 backup variants). Participants were asked to fill in the HEBON questionnaire, including questions about lifestyle/hormonal factors. Four different calculations were performed in the CanRisk webtool.

- FHRP: Family history-based risk prediction including pedigree based family history, and gene panel results of the index and participant
- Non-Genetic Risk Factors (NGRF): FHRP including hormonal/lifestyle risk factors
- PRS₃₁₃: FHRP including PRS₃₁₃

- CRP: Full model, i.e. FHRP, NGRF, and the PRS₃₁₃.

For all four types of calculations, we have reported the 5-year, 10-year and lifetime risk (between age 20 and age 80) for developing breast cancer. Hormonal/lifestyle risk factors included age at menarche, age at menopause, number of children, age at first life birth if applicable, Body Mass Index, height, oral contraception use, and alcohol use.

Risk communication

A web consult was scheduled with the investigators (IMML) or (CJvA) and the participant to communicate the individual breast cancer lifetime risk (CRP) including 10-year risk and corresponding clinical management advice, in comparison with the previous reported risk and corresponding clinical management advice given in the family letter (clinical advice). When a participant shifted to a higher risk category, clinical management was advised as recommended in that risk category. When a participant shifted to a lower risk category, the clinical management advice did not change relative to the clinical advice received in the family letter.

Psychosocial questionnaires

To assess the psychosocial impact, participants were asked to fill in questionnaires before and after communication of the individual breast cancer risk score. Approximately three months before the web consult (T1) participants were asked to fill in two online questionnaires: the Psychosocial Aspects of Hereditary Cancer questionnaire (PAHC)²², including the Distress thermometer (DT)²³ and the Cancer Worry Scale (CWS)²⁴ questionnaire. Two months after the web consult (T2), the participant received again the PAHC including the DT and CWS questionnaire. Six months after the web consult (T3), participants were asked to fill in a questionnaire about the uptake of the clinical management advice and experience with counselling.

Descriptive analyses

Summary statistics are shown for all four types of calculations. For all risk calculations, the corresponding risk category was determined based on the Dutch breast cancer screening guideline (Table 1)²⁵. The number of individuals who shift to another risk category based on their CRP as compared to family history-based risk prediction (FHRP) was determined. Furthermore, FHRP calculated by CanRisk was compared with the clinical management advice given during counselling of the index (clinical advice).

The psychosocial impact of comprehensive risk prediction (CRP) for unaffected relatives of affected counselees at T1 and T2 will be analysed in the context of the BRIDGES study and will be published by Bredart et al. (*manuscript in preparation*).

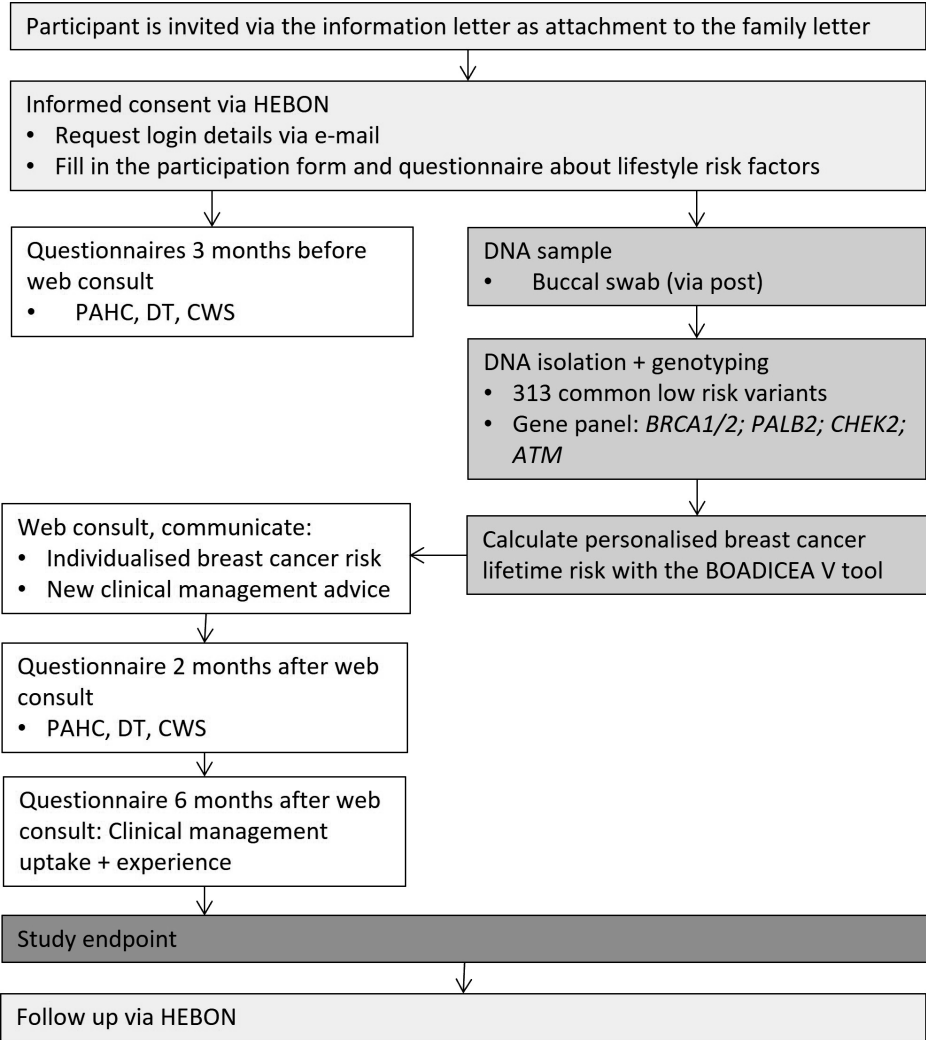


Figure 1. Flow scheme of the IBR study

Abbreviations: CWS, Cancer Worry Scale; DT, Distress Thermometer; PAHC, psychosocial aspects of Hereditary Cancer.

Table 1: Breast cancer screening recommendation in the Netherlands based on lifetime risk of developing breast cancer²⁵.

| | Low (RR<2) | Moderate (RR: 2-3) | High (RR: >3) |
|------------------------|----------------------|--|--|
| Lifetime risk | <20% | 20-30% | >30% |
| Start screening | 50yr | 40yr | 35yr |
| Mammography | Population screening | <50yr annual >50yr population screening | <60yr annual >60yr population screening |
| MRI | - | - | - |

Results

In total, 45 participants were included in the IBR-study for whom we were able to perform the CRP using the *CanRisk* tool for 38 of these participants (Figure 2). The mean age at inclusion was 45 years with an age range from 35 to 59. All included participants derived from 32 families; 6 families had 2 participants included and the remaining families 1 participant.

The mean difference in lifetime risk of including risk factors, PRS₃₁₃ or both (full model) to FHRP was respectively 2.5%, 4.5% and 5.0% (Table 2). For 18, 24 and 24 participants the risk difference was negative (lower) and for 20, 14, and 14 participants the risk difference was positive (higher). The absolute difference in risk was larger by including their PRS₃₁₃ compared to their risk factors, but the largest when both were included (Figure 3).

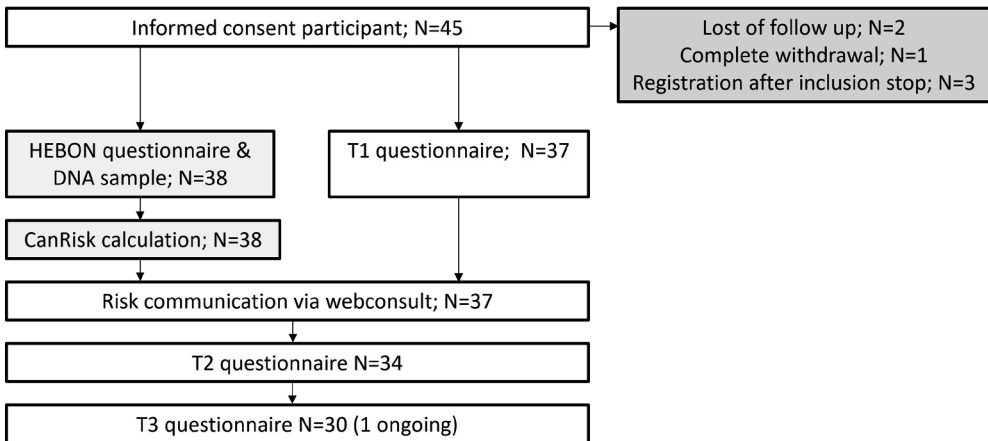


Figure 2. Inclusion of participants in the IBR study

Of the 45 included participants, we were able to calculate breast cancer lifetime risks for 38 of the participants. These risks were only communicated to the participants if they filled in the first psychosocial questionnaires (N=37). For one participant the risk communication was less than two months ago, therefore she has not received the third questionnaire yet.

Abbreviations: N, Number; T, Timepoint.

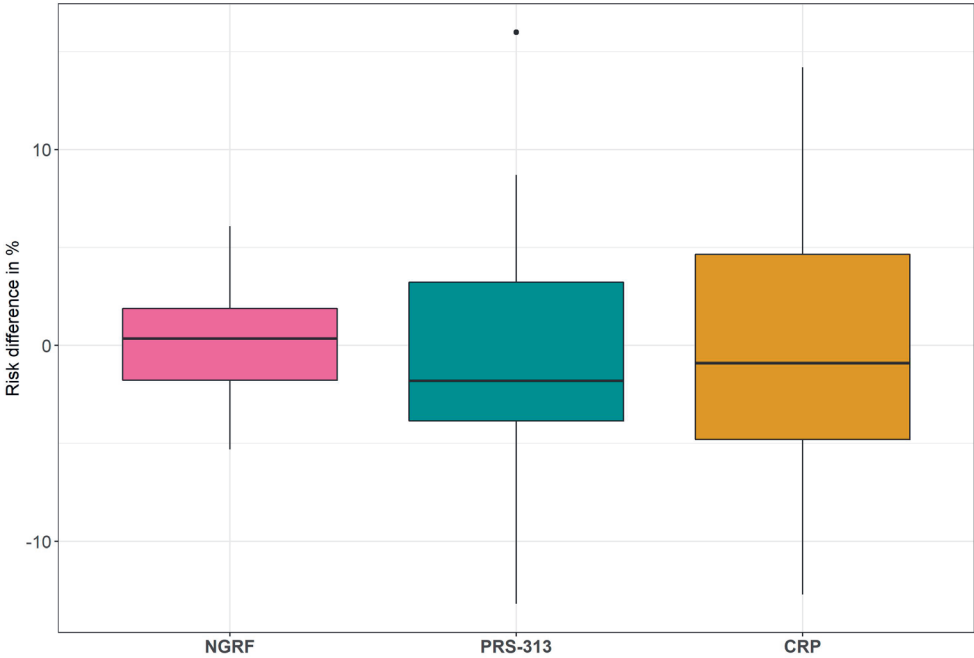


Figure 3: Difference in breast cancer lifetime risk calculated by CanRisk

Boxplot of difference in breast cancer lifetime risk compared to FHRP after a) including hormonal/lifestyle risk factors (purple), b) including the individual PRS₃₁₃ (green), and c) after including both (orange).

Abbreviation: CRP: Comprehensive Risk Prediction (Full model, i.e. FHRP, NGRF, and the PRS₃₁₃); FHRP, Family History-based Risk Prediction; NGRF, Non-Genetic Risk Factors; PRS, Polygenic Risk Score

Table 2. Difference in lifetime risk compared to FHRP based on 38 participants

| | Mean | Lowest | Highest |
|--------------------------|------|--------|---------|
| NGRF | 2.5% | 0.1% | 6.1% |
| PRS₃₁₃ | 4.5% | 0.1% | 16% |
| CRP | 5.0% | 0.1% | 14.2% |

Abbreviation: CRP, Comprehensive Risk Prediction (Full model, i.e. FHRP, NGRF, and the PRS₃₁₃); FHRP, Family History-based Risk Prediction; NGRF, Non-Genetic Risk Factors; PRS, Polygenic Risk Score

FHRP calculated by CanRisk versus clinical advice

For 13 out of 38 (34%) of the participants, the risk category based on family history only calculated with *CanRisk* was not consistent with the risk category and corresponding clinical advice given during the genetic consultation of the affected family member. For 12 participants the clinical advice category was higher and for 1 participant it was lower (Table 3).

Table 3. Family -based breast cancer lifetime risk estimated in the clinic versus estimation by CanRisk for 38 healthy women

| | | FHRP calculated by CanRisk | | |
|-----------------|----------|----------------------------|----------|------|
| | | Low | Moderate | High |
| Clinical advice | Low | 7 | - | - |
| | Moderate | 6 | 17 | 1 |
| | High | - | 6 | 1 |

Abbreviation: FHRP, Family History based Risk Prediction

CRP versus FHRP calculated by CanRisk

Based on full CRP including both risk factors and PRS₃₁₃, 10 participants changed to a lower and eight participants to a higher risk category, compared to FHRP calculated by CanRisk (Table 4). Interestingly, two sisters with the same moderate risk category based on their family history, changed respectively to a higher and lower risk category based on their CRP, which was mainly due to their difference in the PRS₃₁₃ (Table 5).

Experiences with CRP

Participants were overall positive about the individual breast cancer risk prediction, explanation during the web-consultation and method of communication (online versus hospital visit) (Figure 4).

Table 4: Family-based risk prediction in CanRisk vs comprehensive risk prediction in CanRisk for 38 healthy women

| | | CRP calculated by CanRisk | | |
|----------------------------|----------|---------------------------|----------|------|
| | | Low | Moderate | High |
| FHRP calculated by CanRisk | Low | 10 | 2 | 1 |
| | Moderate | 9 | 9 | 5 |
| | High | - | 1 | 1 |

Abbreviations: CRP, Comprehensive Risk Prediction (Full model, i.e. FHRP, NGRF, and the PRS₃₁₃); FHRP, Family History-based Risk Prediction; NGRF, Non-Genetic Risk Factors; PRS, Polygenic Risk Score.

Table 5: Breast cancer lifetime risk scores for 12/38 participants with a family member included

| Family | Individual | Relation | Clinical advice | Lifetime risk percentage | | | |
|--------|------------|-------------------------------------|-----------------|--------------------------|------|--------------------|------|
| | | | | FHRP | NGRF | PRS ₃₁₃ | CRP |
| 1 | 1 | 2 nd degree (aunt/niece) | Moderate | 20.8 | 22.7 | 20.7 | 22.6 |
| | 2 | | | 19.4 | 18.4 | 19.9 | 18.8 |
| 2 | 1 | 1 st degree (sisters) | Moderate | 20.2 | 26.0 | 20.0 | 25.8 |
| | 2 | | | 20.2 | 21.7 | 26.3 | 28.2 |
| 3 | 1 | 1 st degree (sisters) | Low | 16.1 | 14.3 | 15.7 | 13.9 |
| | 2 | | | 16.2 | 13.6 | 13.7 | 11.4 |
| 4 | 1 | 1 st degree (sisters) | High | 24.1 | 22.6 | 32.8 | 31.1 |
| | 2 | | | 24.3 | 24.9 | 16.9 | 17.3 |
| 5 | 1 | 1 st degree (sisters) | Moderate | 13.7 | 13.1 | 9.8 | 9.3 |
| | 2 | | | 13.6 | 10.9 | 15.9 | 12.7 |
| 6 | 1 | 1 st degree (sisters) | Moderate | 24.5 | 22.8 | 27.2 | 25.4 |
| | 2 | | | 24.7 | 19.4 | 22.8 | 17.7 |

^aSmall risk differences between sisters are due to birth year difference. Abbreviations: CRP, Comprehensive Risk Prediction (Full model, i.e. FHRP, NGRF, and the PRS₃₁₃); FHRP, Family History-based Risk Prediction; NGRF, Non-Genetic Risk Factors; PRS, Polygenic Risk Score

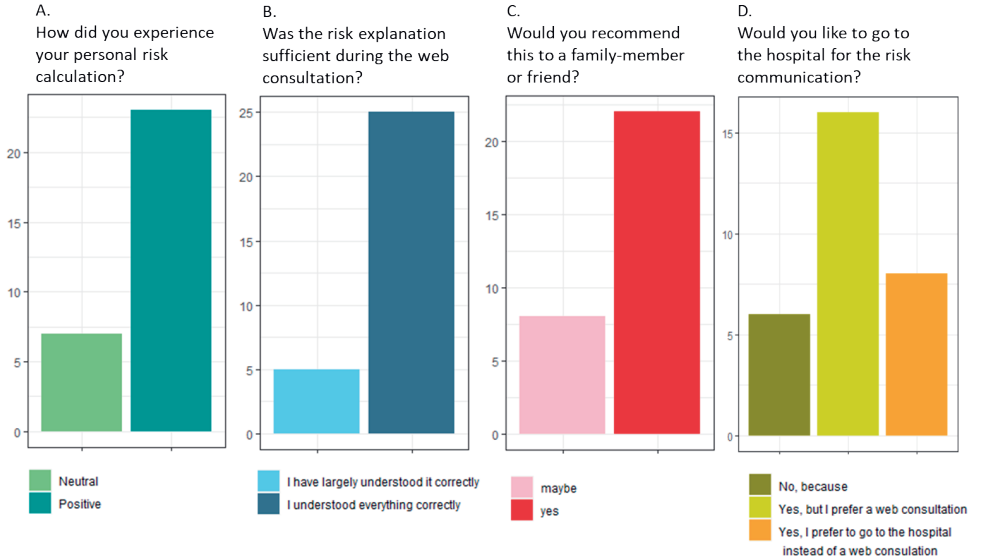


Figure 4: Experience of participants with their individual breast cancer risk prediction and communication via a web consultation

Discussion

This small single-centre pilot study illustrates the potential clinical impact of using CRP in the clinic for healthy relatives of counselees affected with breast cancer. In our study, 18 out of 38 women (47%) shifted to another risk category and received another screening advice based on their CRP calculated by the CanRisk tool as compared to the current standard risk prediction including only family history. Although these small numbers are not statistically significant, this is substantially higher than found in our previous analyses of high-risk research families⁵ and clinic-based moderate-risk families⁹. The difference in percentage may be caused by including only unaffected women in comparison to a mixed group of cases and healthy relatives⁵ or cases only⁹. However, the number of included participants in our pilot study was too low to draw conclusions from this comparison.

The risk category based on family history only calculated with CanRisk was not always consistent with the clinical advice given during the genetic consultation of the affected family member. Although they are both based on family history only, the risk category was different for 34% of the participants. The main reason for this dissimilarity is probably the lack of uniformity of risk prediction in the clinic. Different risk prediction models²⁶ (e.g. BOADICEA, Tyrer-Cuzick, Claus) are used in clinical genetic services in the Netherlands for breast cancer risk prediction to guide clinical management for healthy relatives from breast cancer families. Furthermore, clinical management will sometimes be chosen based on clinical view, for example if the predicted lifetime risk is close to a risk category cut of point (i.e. 20% or 30%, Table 1). It would improve consistency if a single risk prediction algorithm is used in the clinic, such as CanRisk.

Psychosocial correlates and details on counselees' and clinical geneticist's perception of CRP from the larger multicenter study of BRIDGES will be presented by Tüchler et al. and Brédart et al. (*manuscripts in preparation*).

To conclude, we have used CRP in clinical practice on individual level and shown that CRP can shift a substantial proportion of counselees from gene-panel negative breast cancer families to another risk category with consequences for clinical management advice. Furthermore, the dissimilarity between clinical advice based on 'family history only' or based on the CanRisk-calculation emphasizes the need for standardized tools, protocols and training for clinicians.

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