Chances and changes : psychological impact of genetic counselling and DNA testing for breast cancer.

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Chances and Changes

Psychological impact of genetic counselling and DNA testing for breast cancer, focusing on women who receive an uninformative result.

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Voor Ton en Ria

CONTENT

1

General introduction

1. Introduction

Cancer. The very word evokes feelings of anxiety or vivid memories of loss experiences in most of us, as it is one of the primary causes of mortality. Among women in industrialised countries breast cancer is the most common cancer with about 12.500 new diagnoses in 2005 in the Netherlands alone.[1] This means that the cumulative lifetime risk of developing breast cancer for a Dutch woman is about 12%. In some families breast cancer seems to occur even more frequently or women fall ill at a relatively young age. Such families may have a genetic susceptibility towards breast cancer.

To learn more about the likelihood of this susceptibility actually being present, members of such families may request genetic counselling. In the Netherlands, counselling for cancer susceptibility is provided in eight university hospitals and at the Netherlands Cancer Institute. Based on the family pedigree, individualised estimates about the family's risk status can be made. This personalised risk estimate determines whether further medical options are available. For example, whether DNA testing is indicated, and which risk-management options would be appropriate.

The main purpose of this thesis is to provide more insight into some effects of genetic counselling and DNA testing for breast cancer. We address effects on: (a) risk perception; (b) psychological distress; and (c) intentions for risk-management behaviour. Regarding the effects of DNA testing, special attention will be paid to women who receive a so-called uninformative DNA-test result. In this introduction, I first provide some background information on the practice of genetic counselling and DNA testing, and on options for managing cancer risks. Subsequently, the associations between these options, and risk perception and psychological distress are introduced. The last paragraphs of this introduction address the study design and the thesis' outline.

1.1. Genetic counselling

Depending on the number of family members that have developed breast or ovarian cancer either before or after the age of 50, a referral for genetic counselling regarding breast cancer can be made.[2;3] In a first (and sometimes only) consultation at the department of clinical genetics a standard counselling protocol is applied. This implies that a counsellor, usually a clinical geneticist or a genetic counsellor, records the family medical history and provides general information about the hereditary transmission and implications of high-risk mutations in genes, such as BRCA1 and BRCA2 (BRCA=Breast CAncer). Usually, the counsellor also initiates an investigation to confirm medical information for a personalised risk estimate. An interim estimation of the cumulative familial

lifetime risk of developing breast cancer is usually provided in the first consultation. Four risk categories can be distinguished[4]: (1) general population risk, i.e. around 10% (nowadays in fact 12%[1]); (2) slightly increased risk, i.e. 10-20%; (3) moderately increased risk, i.e. 20-30%; and (4) highly increased risk, i.e. 30% or over. Based on this estimation, or on an update if applicable, further medical options are discussed. These are (a) additional DNA testing directed at obtaining more specific knowledge about the personalised risk status, and/or (b) risk-management choices. Figure 1 provides a simplified flowchart of the steps in genetic counselling and DNA testing with respect to the options and limitations in acquiring knowledge about counsellees' familial risk status.

If a BRCA1 or BRCA2 mutation has been detected previously in a family member, the estimation of the probability of having inherited that specific mutation is relatively straightforward. This is because first-degree relatives of a mutation carrier have an average 50% probability of having inherited the mutation. However, if no BRCA1 or BRCA2 mutation was detected within the family previously, both a personal breast-cancer risk estimation,[3;5] and an estimation of the probability of finding a BRCA1/2 mutation with DNA testing (e.g. Myriad tables) must be based on the familial medical history. In addition, if the probability of detecting a mutation is equal to or exceeds approximately 10%, DNA testing is offered to acquire possibly more specific information about his or her personal or familial cancer risks[3;6] (see Figure 1).

1.2. DNA-test results

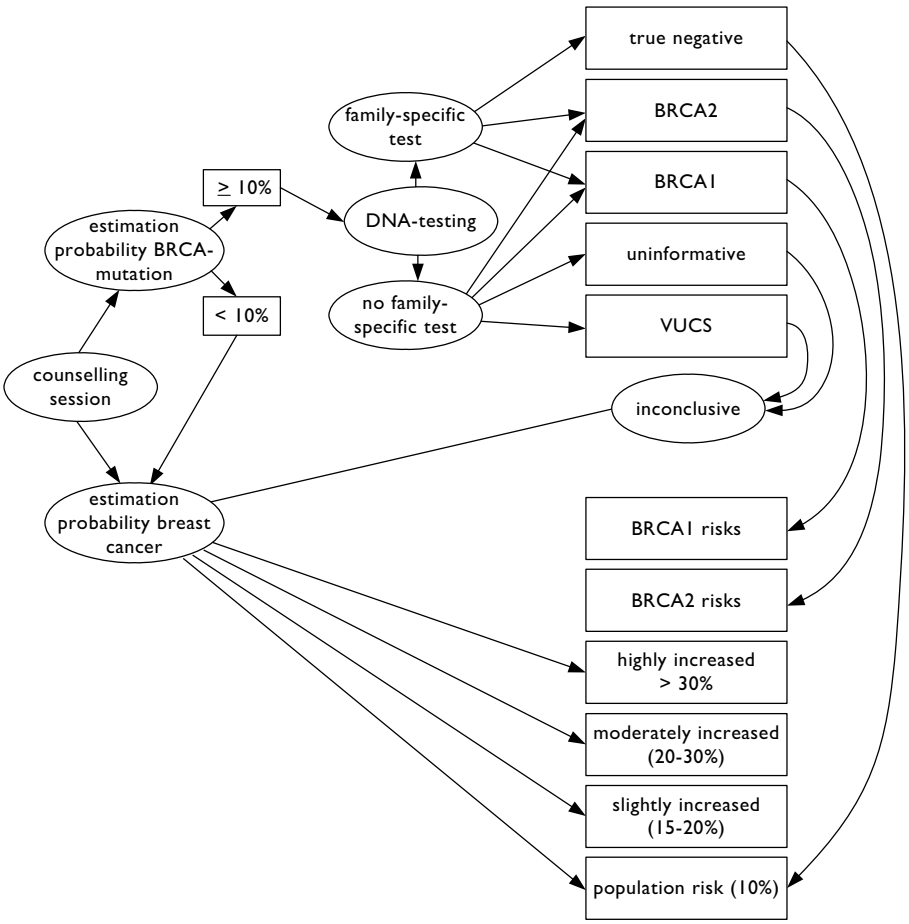
As is depicted in Figure 1, BRCA testing can yield five different types of results: A positive result, that is a new or family-specific (1) BRCA1 or (2) BRCA2 mutation; (3) a true negative result, that is a negative result for a family-specific BRCA1 or BRCA2 mutation; (4) an uninformative test result, that is a negative result in the absence of a family-specific BRCA1 or BRCA2 mutation, and (5) a positive result for which it is unknown whether it concerns a pathogenic mutation or an innocent variant, a so-called variant of uncertain clinical significance (VUCS). The first three possible results are conclusive results, as they provide information about the risk status of the individual concerned beyond the pedigree-based risk assessment. The remaining types of results can both be considered inconclusive, as strictly, they provide no additional information beyond the pedigree-based risk assessment.

In the literature no consistent terminology is applied to an inconclusive DNA-test result. For example, a negative result in the absence of a family-specific mutation is often designated as 'negative', 'uninformative', or 'inconclusive'.

Throughout the text in this thesis a negative result in the absence of a family-specific mutation will be designated as 'uninformative'. A VUCS result will refer

to those women who have inherited a variant of uncertain clinical significance. Finally, both kinds of results will be called inconclusive. In the next paragraph we will elaborate on the types of DNA-test results.

Figure 1. Counselling model



1.2.1. A *conclusive* DNA-test result

Only about 7% of all breast cancers can be attributed to a high-risk predisposition.[7] Relatives within the mendelian line of hereditary transmission of an identified mutation carrier can apply for a family-specific DNA test. The interpretation of the result is relatively unambiguous. Test candidates can learn whether they have inherited the BRCA mutation running in their family or whether they have not. It is estimated that having a BRCA1 mutation is associated with a risk of developing a primary breast cancer before the age of 70, ranging from 65%[8] to 85%[9], and with a risk for developing ovarian cancer before the age of 70, ranging from 39%[8] to 69%[10]. BRCA2 mutations are associated with an estimated risk ranging from 45%[8] to 84%[11] of developing a primary breast cancer before the age of 70, and estimations for developing ovarian cancer before the age of 70 range from 11%[8] to 27%[11]. For women with a previous diagnosis of breast cancer a BRCA mutation is associated with a risk up to 60% for a second primary breast cancer.[9;12] However, if a family-specific test is negative, applicants' lifetime risk approaches population risk. This is often designated as a true negative result (see Figure 1).

Nowadays, most DNA test applicants do not come from families in which a BRCA mutation has been detected previously. To maximise the likelihood of detecting a new BRCA1/2 mutation in these families, usually the first individual tested is someone who has been affected with breast- or ovarian cancer already. This individual is often called the index patient. If a BRCA1 or BRCA2 mutation is found in this index patient, relatives may request a family-specific BRCA test. In such cases conclusive DNA testing has become available.

1.2.2. An *inconclusive* DNA-test result

The majority of test applicants receive a negative result. A negative test result in the absence of a known BRCA1/2 mutation in the family is often designated as uninformative. This is because genetic susceptibility cannot be ruled out due to limitations of the current genetic technology, and due to the possibility of deleterious mutations in as yet not identified genes. Regarding the latter, it is estimated that the known BRCA1/2 mutations only account for 20 to 25% of familial aggregation.[13] If an index patient receives an uninformative test, unaffected relatives usually have no access to an additional test for themselves, because this is ineffective. Hence, an uninformative DNA-test result of an index patient also refers to unaffected counsellees. Blood samples of women who receive an uninformative result are usually conserved because of the possibility that in the future new mutations on the BRCA1/2 genes or a BRCA3 gene will be discovered for these families.[14]

A last possible finding from BRCA testing, which is found in approximately 12.5% of all full sequence BRCA tests, is a 'missense mutation' or a 'variant'.[15] This means that the sequence of the BRCA1 or BRCA2 gene differs from wildtype, but it is unknown whether these variants are associated with an increased cancer risk or not. For this reason they are designated as 'Variants of Uncertain Clinical Significance' (VUCS). It is estimated that 32% of all detected BRCA1 variants, and 53% of all detected BRCA2 variants are of uncertain clinical significance (Breast cancer Information Core, http://research.nhgri.nih.gov/bic/). From a clinical point of view, women who receive an uninformative result may be comparable in several respects to women with a VUCS result. For example, for both results, clinical management recommendations are based on the pedigree-risk estimation. Furthermore, additional testing of unaffected relatives is not routinely offered.[16]

Two contradicting hypotheses about the impact of an uninformative DNA test for breast cancer susceptibility have been posed. First, concern was expressed about the possible psychological harm following from the uncertainty associated with either an uninformative or a VUCS result. This 'uncertainty is harmful' hypothesis is described in section 3.3. The second hypothesis displays concern about possible negative behavioural effects due to a lack of under-standing, or the 'false reassurance hypothesis'. This hypothesis is introduced in more detail in section 2.4.

1.3. Risk-management options

Traditionally, genetic counselling has distinguished itself from other medical disciplines in that it is characterised by a 'personal service model', rather than a 'public health model'. The principle of free choice, or non-directiveness, has been central to the definition of counselling goals, and has been viewed as a safeguard against eugenics. The focus is on communicating information so that individuals can make their own 'informed' decisions, in line with their personal values. However, it has been argued that due to the emerging prophylactic options and the associated possibility of 'saving life', the ethos of non-directiveness gradually changes.[17] In line with this, offering risk-management options to women at elevated risk for breast cancer is an important purpose of genetic counselling. Risk-management options for prevention and early detection of breast and/or ovarian cancer are intensive surveillance or prophylactic surgery of breasts and/or ovaries.

1.3.1. Surveillance

Genetic counselling practice is much more prescriptive regarding surveillance options than for prophylactic surgery. Usually, quite firm recommendations for breast surveillance are being made. Those recommendations are based on the risk estimations, deducted from either a conclusive DNA test, or from the family-based pedigree, and are shown in Table 1.

Women without a prior breast cancer diagnosis can opt for more intensive clinical breast surveillance than women from the general population, provided that their estimated lifetime risk for breast cancer equals or exceeds 20%.[3] Regular breast screening implies mammography screening, breast examination by a physician, monthly breast self-examination and magnetic resonance imaging (MRI screening). MRI screening is often proposed as an useful alternative or additional technique to mammography screening, especially in younger women. This is because the sensitivity of mammography screening in younger women is relatively low,[18] and because of evidence that especially these younger women, and also BRCA-mutation carriers in general, seem to be particularly vulnerable towards tumour induction by mammography radiation.[19] In addition to the option of breast surveillance, some women may be eligible for surveillance of their ovaries. Ovary screening is offered to BRCA-mutation carriers, but also to other women at risk, provided that cases of ovarian cancer are present in their family history.

As a part of this thesis we have studied the intentions of women to undergo mammography screening after having received either a conclusive or an uninformative DNA test (Chapter 6).

1.3.2. Prophylactic surgery

Women with a very high lifetime risk of developing breast or ovarian cancer, usually BRCA1/2-mutation carriers, can opt for preventive surgery that removes the breasts (i.e., prophylactic mastectomy), or preventive surgery that removes the ovaries (i.e., prophylactic oophorectomy). The latter is preferably performed after menopause.[3] Evidence suggests that these kinds of surgery are very effective in reducing the risk of developing cancer. The residual risk of developing breast cancer after bilateral prophylactic mastectomy is estimated to be less than 5% in unaffected BRCA-mutation carriers.[20-22] In addition, the residual risk for contralateral breast cancer for women who have had breast cancer is about 9%.[23] Finally, prophylactic oophorectomy reduces the risk of breast cancer by approximately 50% and the risk of ovarian cancer by almost 95%.[24;25]

Table 1. Clinical risk-management options associated with breast cancer risk (based on CBO guidelines[3])

Risk status	mammography screening		MRI screening	palpation		prophylactic mastectomy	prophylactic oophorectomy
	every yr	every two yrs	every yr	twice a yr	every yr	offer	offer
Population risk		≥50 yr <75yr					
Slightly increased		≥50 yr <75yr					
Moderately increased	≥35 yr <50 yr	≥50 yr <75yr			≥35 yr <50 yr		
Highly increased	≥35 yr <60yr [c]	≥60 yr <75yr		≥35 yr <50yr	≥50 yr		
BRCA1/2 risks [b]	≥30 yr	not sufficient	≥25 yr	≥25 yr	not sufficient	yes	≥40 yr [d]

[a] population-screening programme.
[b] both identified BRCA1/2 carriers and women with a 50% probability of being carriers.
[c] surveillance, combined with MRI screening may be offered from 25 years depending on the age at diagnosis of family members.
[d] Prophylactic oophorectomy may be offered earlier based on the family history.

Despite the considerable reduction of the risk of breast cancer, prophylactic mastectomy remains controversial, because it is a mutilating, irreversible procedure. Furthermore, it is estimated that almost two-thirds of women suffer from at least one complication following surgery.[26] However, on-going studies regarding the psychological implications of prophylactic mastectomy suggest that women may significantly benefit from prophylactic surgery.[27] The major advantage found is a significant reduction in breast cancer related anxiety.[28-31]

The topic of prophylactic mastectomy is touched upon in Chapter 2, Chapter 6 and Chapter 7. In Chapter 3, the process of decision making regarding prophylactic mastectomy was studied more thoroughly.

1.4. Effects of genetic counselling and DNA testing

Much research has been directed at evaluating the benefits of genetic counselling and DNA testing for individuals at risk of developing familial breast cancer. The research questions in those studies are closely associated with the aims of genetic counselling. In accordance with the principle of non-directiveness, definitions of genetic counselling often put an emphasis on fulfilling the counsellee's needs.[32] Indeed, counsellors mentioned meeting counsellee's wishes as the main goal of genetic counselling.[33]

In a similar vein, several studies evaluating the effects of genetic counselling have focused on counsellee satisfaction,[34] and Berkenstadt et al.[35] proposed a measure of increased 'perceived personal control' as an effect of genetic counselling. However, the needs and expectations of counsellees vary to a great extent.[36;37] Some will primarily seek counselling for the acquisition of knowledge, whereas others want decision making support. Chapter 2 of this thesis focuses upon clusters of motives for seeking counselling, and whether clinical or socio-demographic characteristics predict the counsellee's motives.

As mentioned before, frequently studied outcomes of genetic counselling are: (1) risk perception, (2) psychological distress, and (3) decision making. A reason why these outcome variables have been popular is that the goal of genetic counselling has been defined as "facilitating clients' ability to use genetic information in a personally meaningful way that minimises psychological distress and increases personal control".[38] Risk perception has been examined extensively, simply because counsellees should comprehend the risk message. The application of the other outcome variables is based upon the assumption that genetic counselling and genetic testing will help counsellees only if the information enhances psychological well-being, and/or if it is translated into effective risk-management behaviours, provided that these options exist.[39]

Notably, risk perception and psychological distress have been frequently addressed in different parts of the counselling and DNA testing process. For

example, the concept of risk perception, and especially the accuracy of this perception, has been mainly studied with regard to the counsellee's personal risk estimation during the first consultation, when the results of DNA testing are not yet available.[40;41] In contrast to this, the concept of psychological distress has been studied in particular in the context of DNA testing.[42] In line with the literature, in this thesis 'genetic counselling' refers to the first counselling session, in which DNA testing is not (yet) applied.

Another characteristic of studies assessing the impact of genetic counselling and DNA testing is that several groups of counsellees are underreported. For example, the majority of studies on DNA testing focuses on women who receive a conclusive DNA-test result (i.e., BRCA-mutation carrier, or true negative). There is a paucity of data on the impact of DNA testing on women who receive uninformative results, or women who receive a VUCS result. One of the primary goals of this thesis is to report on women with an uninformative result (Chapters 4-6). In addition, some preliminary data about women with a VUCS result will be provided in Chapter 5. Another group of counsellees commonly not addressed consists of women who already have had breast or ovarian cancer. In this thesis explicit attention is paid to both counsellees with and without a personal history of breast cancer (designated as 'affected' versus 'unaffected' women). In the following sections I elaborate on the primary outcome measures that have been applied to genetic counselling and DNA testing for breast cancer.

2. Risk perception

In most social psychological theories aimed at predicting human behaviours with regard to health, perceived risk plays a central role in determining intentions and behaviours.[43-46] For example, according to the Precaution Adoption Process model,[46] individuals not only need to be aware of certain threats, but they also have to feel personally vulnerable to them, before they will act to protect themselves.

In theories on risk perception, the probability that a harmful event will occur is not the only determinant of perceived risk. The severity of the potential harm also plays an important role.[43;45] This entails a personal evaluation of how serious it would be if that particular negative event would happen to you personally. Although such beliefs can be affect-laden, risk perception has been viewed traditionally as a cognitive appraisal of hazards.[47]

In most studies within the field of genetic counselling a rather narrow definition of risk perception is used; it refers solely to individuals' estimation of the probability that a certain negative event might occur. This is usually interpreted as the accurate recall of that specific probability.

2.1. Risk perception associated with genetic counselling and DNA testing

Although aimed at reducing uncertainty, genetic counselling and DNA testing for breast cancer will never generate complete certainty. Even if DNA testing has proven the presence of a BRCA1/2 mutation, it remains uncertain whether and if so, when breast or ovarian cancer will eventually occur. Likewise, if DNA testing has ruled out the presence of a BRCA1/2 mutation, the risk of a sporadic cancer is still present. In addition to this, many different risks with varying probabilities are involved, for example the risk of having inherited a BRCA1/2 mutation, the lifetime risk of developing breast or ovarian cancer and the chance of surviving cancer. The communication of such complex risks has been a central goal of genetic counselling.

Therefore, comprehension of these risk messages is considered an important indicator of the effectiveness of genetic counselling. In this line of reasoning, the risk estimates based for example on the Claus or the Gail models are viewed as the real, or objective risks, whereas the individuals' estimation of the same risk is defined as the subjective, or perceived risk. It was hypothesised that inaccurate risk perceptions could have detrimental behavioural and psychological consequences. Women underestimating their breast cancer risk would possibly lack motivation to adhere to mammography screening guidelines, whereas overestimators perhaps would suffer from unnecessary anxiety and might seek for unjustified options to manage their risk. Hence, from an educational view on genetic counselling, counsellees ideally perceive a risk that fully matches the objective risk estimate after counselling. Therefore, concern was raised by the persistent finding that this compatibility was hard to achieve.

2.2. Accuracy of risk perception after genetic counselling

Although most studies report that accuracy improves after genetic counselling,[48-52] recall of the correct risk estimate remains relatively poor.[41] Level of accuracy after counselling varies between studies, and range from 31%[52] to 81%.[49] This variation is, in part explained by the different criteria by which a response is designated as correct or incorrect. Furthermore, the majority of studies report that women in general overestimate their risk of developing breast cancer, especially those studies that use a numerical response scale instead of a verbal scale.[53] Chapters 3 and 4 of this thesis deal with perceived risk after an initial counselling session.

As mentioned before, few studies reported how women who have had breast cancer perceive their risk of developing a second breast cancer. In a meta-analysis of Braithwaite et al.[40] that analysed twelve studies about perceived risk before

and after counselling, only one study included both affected and unaffected women.[54] In addition to this, very few data are available about risk perception after DNA testing is completed, and most of these data exclusively concern women receiving conclusive results.[55]

2.3. Risk perception after a *conclusive* DNA-test result

Most unaffected women who receive a conclusive result, and thus a low or a high risk estimate, adapt their perceived risk accordingly. Those with a true negative result reported a very much lower perceived risk than women in whom a mutation was detected.[55;56] For example, Watson et al.[55] reported that one year after counselling 95% of the women who received a true negative result correctly reported that their risk was the same or lower than that of the average woman. With regard to the women who were identified as carrying a BRCA1/2 mutation, 71% thought that they had a risk of 85% of developing breast cancer.

2.4. Risk perception after an uninformative DNA-test result or the 'false reassurance hypothesis'

According to the 'false reassurance hypothesis' women with an uninformative result would interpret this incorrectly as a true negative result. Put differently, women would perhaps incorrectly feel so reassured that they do not see a proper reason to comply with screening recommendations any longer. Although scarce data are available about this 'false reassurance hypothesis', findings from both qualitative studies,[57;58] and quantitative studies[59;60] suggest that women may indeed misunderstand their uninformative result. For example, Bish et al.[59] observed that affected women reported a decreased risk perception after disclosure of an uninformative result. It should be noted that despite this decrease, intentions to have mammograms did not change. Chapter 6 of this thesis addresses the 'false reassurance hypothesis'.

3. Breast cancer worry and cancer-specific distress

Besides risk perception, cancer distress or worry are often assessed as important parameters of the impact of genetic counselling and DNA testing. Worry can be defined as a cognitive component of anxiety, concerned with future negative events where there is uncertainty about the outcome.[61;62] Measures of cancer worry involve straightforward questions about, for instance, the amount of worry and the extent to which this worry interferes with daily functioning.[63] Various

studies observed a positive relationship between the estimation of the probability of occurrence, and worries about breast cancer.[52;64;65] For example, women with a family history of breast cancer usually know that they are at higher risk and express a higher level of worry than those not at risk.[66;67] Several other studies failed to find a correlation at all.[68;69] That the relation may be complex was shown by Van Dooren et al.[70]. These authors reported higher levels of cancer worry in women overestimating their cancer risk, whereas for under-estimators no relationship to worry could be found. Moreover, a measure of risk perception that focuses on the feeling about the magnitude of the risk[71] may be more indicative of distress than a more knowledge-based risk perception measure with a numerical response scale.[70] In general, studies which did find positive associations between cancer worry and risk perception observed intermediate correlations, ranging from .30-.40.[72]

Among the most popular measures of psychological impact is the notion of cancer-specific distress.[73] This is frequently measured by inspecting the amount of intrusion and avoidance associated with cancer or cancer-related events. Intrusion is characterised by penetrating thoughts, images and emotions, whereas avoidance is defined by conscious attempts to inhibit thoughts and feelings.[74] An example of intrusion is "I thought about it when I did not mean to" (Impact of Event Scale[74]). The assumption is that providing information about future health threats has similar psychological consequences as in the cases of traumatic events. Measures of general distress, such as general levels of anxiety and depression may tap more severe, pathological, and relatively stable levels of anxiety, whereas cancer-specific distress may be less associated with stable personality traits, and pathology. This is because these measures are specific and perhaps also more sensitive to the potential source of stress.[75] In concordance with this, cancer distress and cancer worries were more sensitive to effects of genetic counselling and testing than measures of general distress.[76]

3.1. Cancer worry and cancer-specific distress associated with genetic counselling and DNA testing

Cancer worry and cancer distress have been viewed as useful variables to measure the potential benefits of genetic counselling and DNA testing, for two different reasons. The first is because changes in cancer worry and cancer distress probably reflect important elements of the psychological impact of genetic counselling and DNA testing. The second reason is that worries might facilitate or hamper behavioural changes, such as compliance with mammography screening recommendations. We will discuss associations between worry and behaviours in section 4.2 of this introduction.

When genetic counselling, and in particular DNA testing became available, positive expectations about the potential benefits for counsellees were tempered by concerns about the possibility of psychological harm. Several of the early studies in this field described the levels of psychological distress of unaffected women who applied for genetic counselling for breast cancer. Those initial studies supported the concerns regarding the psychological vulnerability of at-risk women.[77;78] For example, Kash et al.[77] reported that within their sample of women at risk for familial breast cancer, 27% reported levels of psychological distress that were above standardised cut-off points, indicating a serious need for psychological counselling. However, in a later study, Coyne et al.[79] reinterpreted several of the latter studies. They compared the findings regarding the levels of clinically significant distress with the levels of population-based and medical samples. Their conclusion was that the actual amount of psychological distress associated with genetic counselling is, in fact, relatively low.

Indeed, to date, a more reassuring view has emerged. Several recent reviews suggest that the psychological impact of genetic counselling is limited, and the level of clinically relevant anxiety of women identified as having a high risk hardly seems to differ from women from the general population.[40;41] In a meta-analysis, Braithwaite et al.[40] concluded from 11 studies that cancer-specific distress did not increase as a result of genetic counselling. Moreover, several studies reported decreasing levels of distress after counselling.[54;80] Chapter 4 of this thesis presents some data about the effects of an initial counselling session on cancer worries.

3.2. Cancer worry after a conclusive DNA-test result

In addition to the reassuring findings for genetic counselling, similar observations were made for the effects of conclusive DNA testing.[31] In a review of Broadstock et al.[42] about DNA testing for various conditions it was concluded that a positive DNA test for various diseases was rarely predictive of distress more than one month after testing, with non-carriers showing a more rapid decrease in distress than carriers. Indeed, several studies only report a short-lived increase immediately after DNA test disclosure for women who receive a positive result.[55;81] In a study of Van Roosmalen et al.[81] the negative impact of a positive result was greater for women who had been diagnosed with breast cancer previously, especially among those who were diagnosed more recently. In the longer term, the overall pattern for women without a prior diagnosis of breast cancer is that the distress levels of carriers remain relatively stable, whereas those of women with a true negative result decrease.[55;56]

3.3. Cancer worry after an inconclusive DNA-test result or the 'uncertainty is harmful' hypothesis

It has been suggested that women with an inconclusive test result (uninformative result and/or VUCS-result) may suffer from continuing uncertainty.[82-84] These concerns are based on the assumption that individuals who decide for DNA testing expect or wish for clear-cut results, either positive or negative. This assumption was supported by a study of Press et al.[85] in which women were least interested in a DNA test with a low negative predictive value. Lerman et al.[86] added support to the hypothesis that uncertainty may be harmful. They reported that women who declined conclusive BRCA testing, and thus remained uncertain about their risk status, exhibited even worse psychological well-being than those who learned that they definitely carried a BRCA mutation.

Another study that compared the psychological impact of an inconclusive or an uncertain result with that of a conclusive or a certain result was that of Cioffi.[87] She offered subjects diagnostic testing for a fictional condition to demonstrate biases in responding to uncertain health information. Her results suggest that: (1) inconclusive information about being well may be as distressing as a clear-cut diagnosis of being ill; and (2) inconclusive information about being well may be more distressing than inconclusive information about being ill. These results can perhaps be applied to the domain of DNA testing for breast cancer. In this perspective a VUCS result can be designated as an uncertain diagnosis of disease, and an uninformative result may be an uncertain diagnosis of being well.

In line with the first hypothesis (i.e. uncertainty about being well is equally as distressing as a clear-cut diagnosis of illness) Schwartz et al.[56] observed comparable levels of distress among women with an uninformative result and those with a positive BRCA result. However, it should be noted that both groups of women reported decreasing levels of psychological distress, and thus did not provide support for the view of increasing levels of anxiety.[56] Indeed, the few data that are available do not provide strong evidence for the 'uncertainty is harmful' hypothesis.[59] Chapter 7 of this thesis addresses the course of distress and worry of women receiving an uninformative result.

4. The effects of cancer worry and risk perception on mammography screening

Some psychological models with regard to screening behaviours allocate a special role to risk perception and cancer worry. For risk perception, it is hypothesised that individuals should be cognitively aware of a certain risk before they are motivated to take action. Hence, a higher level of perceived risk would predict a higher level of adherence to screening guidelines. There have been many studies

supporting this hypothesis. A higher level of perceived risk is indeed associated with a higher level of mammography uptake, although effect sizes reported in meta-analytical reviews are rather small.[53;88]

If we apply this to the 'false reassurance hypothesis' for women with an uninformative result, these data would support the proposal that women who incorrectly interpret their result as a true negative result may lack motivation to adhere to screening guidelines. Put differently, their perceived vulnerability would perhaps be too low to stimulate them to seek protection. Chapter 6 will report on intentions for mammography screening for women with an uninformative result.

Different hypotheses can be derived from theoretical frameworks about the effect of fear, or in this case cancer worry, on mammography screening. In fact, three different kinds of relationships have been proposed. First, some suggest that worry serves as a barrier for protective health behaviour.[78] In this view, worry prompts denial of vulnerability and avoidance of thinking about breast cancer. Secondly, some studies propose a curvilinear relation,[89;90] in which low levels of anxiety may reflect too much indifference to opt for screening, whereas too high levels may evoke denial, and thus withdrawal from screening. A third hypothesis suggests that worry merely facilitates mammography screening by making the individual willing to cope with health threats, thus assuming a linear relation.[91] Up to now, evidence is not fully conclusive about the relationship between worry and mammography screening. Most evidence about this relationship for women at risk for familial cancer is cross-sectional, which is problematic because it obscures the causality of the relationship. For example, some studies suggest that for women with a family history of breast cancer, levels of cancer worry may be elevated by actually undergoing mammography screening.[92] In spite of limitations in assessing the causal relations, most studies to date suggest that cancer worry does not impede mammography screening.[72;93]

5. The effects of cancer worry and risk perception on decision making with regard to prophylactic mastectomy

The large majority of women who opt for prophylactic mastectomy base their decision upon a DNA test that proves that they are carrier of a BRCA1 or BRCA2 mutation.[94] Several women have described prophylactic mastectomy as "the price to pay for peace of mind". As this freedom from anxiety is mentioned as the major benefit of the procedure, it is not surprising that among high-risk women, those who wish to undergo prophylactic surgery report higher levels of breast cancer-related distress.[29;64;95;96]

With regard to risk perception, the relationship is obscure. Women who intended to have prophylactic surgery had a longer awareness about cancer

heredity within their family,[96] and they felt more vulnerable to developing breast cancer.[29;64;97] However, other studies did not find a relationship between perceived risk, or overestimation, and uptake for prophylactic mastectomy.[55;98] The latter may be due to a 'ceiling effect'. That is, the higher the risk, the harder it is to overestimate it. Likewise, the risk measures may be relatively insensitive due to a restriction in range of the perceived likelihood in women who have learned that they have an exceptionally high risk of developing breast cancer.

Apart from perceived risk and cancer worry, other factors seem to be associated with decision making in favour of prophylactic mastectomy. For example, womens' decision making might be influenced by personal disease experiences. Women who choose for prophylactic mastectomy tend to have a history of more investigatory tests.[95] In addition, it seems that women with a previous history of breast cancer favour prophylactic mastectomy somewhat more frequently.[81;99] This may be especially the case for women in a so-called rapid testing procedure, in which they learn that they carry a BRCA mutation almost immediately after being diagnosed with breast cancer. Schwartz et al.[100] found that 52% of these women opted for bilateral mastectomy. In Chapter 4 we address how cancer worry, risk perception and a previous breast cancer history influences intentions for prophylactic mastectomy.

6. Outline of the study and this thesis

This thesis reflects upon the results from the 'Chances & Choices' project, which was financially supported by the Dutch Cancer Society (RUL 98-1740). The research proposal was entitled "Risk perception and informed decision making of women at risk for familial breast cancer, who receive inconclusive DNA-test results". As the title suggests, the aim of this research project was to gain insight into the psychological effects on women who receive an uninformative test result. At the start of the project in 1998, virtually nothing was known about the psychological impact of such a result. And although the scientific interest in psychosocial outcomes of genetic counselling has been overwhelming since the project was initiated, up to now data about the impact of DNA testing on this large group of women have remained relatively scarce.

The scope of the study was more extensive than solely the implications of an uninformative DNA test. One of the aims was, for example, to determine the extent to which genetic counselling for breast cancer generally contributes to a more accurate risk perception. As a consequence, this thesis will have a somewhat broader focus. The Chapters are arranged in line with the chronological order of the study design. Although both the official and the popular title of the project perhaps promise clear-cut data on actual decision making for women who receive an inconclusive result, unfortunately the follow-up period of seven

months after DNA test disclosure proved to be too short for this purpose. We had to rely on behavioural intentions instead of the actual uptake of annual mammography screening. Only for BRCA-mutation carriers do we touch upon the actual percentage of women who had prophylactic mastectomy within the period under study.

6.1. Chances & Choices: study procedure

In November 1998 we started to approach all eligible women who made an appointment for breast cancer counselling at the Department of Clinical Genetics in the Leiden University Medical Center. In addition, from January 2000 women who made an appointment at the Department of Clinical Genetics in the Erasmus Medical Center were also approached. In both centres the last participants were included in June 2002. Figure 2 depicts the design of the study. A baseline questionnaire was sent to all women who wished to participate at T_1. In addition, all study participants received a second questionnaire by mail at T_2. Almost all women who had a single appointment, and all women who had more than one appointment, received a summary letter after their last consultation. If applicable, this letter included results from DNA testing, and the implications of these results. One month after the summary letter was sent, another questionnaire was mailed to all participants at T_3. Finally, six months after T_3, a last questionnaire was mailed at T_4.

In addition to the questionnaire, a selected number of respondents was invited for interviews. Initial face-to-face interviews were conducted after the initial consultation (T_2). At T_3 and T_4 a percentage of the women who participated in the first face-to-face interview at T_2 were contacted by telephone for follow-up interviews. Results from these telephone interviews, which focus on opinions regarding prophylactic surgery, are not included in this thesis.

6.2. Outline of this thesis

The chapters in this thesis reflect different phases in the process of genetic counselling and DNA testing for breast cancer susceptibility. The scope of the first part (Chapters 2-4) addresses the first consultation at the department of clinical genetics. The second part (Chapters 5-7) focuses on the effects of DNA testing.

Chapter 2 describes counsellees' motives for applying for genetic counselling (T_1). First of all, we assessed clusters of motives to enhance counselling adapted to the specific needs of counsellees. Secondly, we investigated whether medical and socio-demographic characteristics of counsellees would help predict

their motives. For example, we assessed whether women with a personal history of breast cancer have other reasons than those who were unaffected.

Chapter 3 presents results from face-to-face interviews (T_2). A selection of respondents were invited for these face-to-face interviews after the initial consultation. One of our purposes was to address the concept of an 'accurate' risk perception in a qualitative manner.

Chapter 4 addresses several related research questions by comparing the baseline responses with those after the first consultation (T_1-T_2). First, we assessed whether women's baseline risk perceptions and cancer worries would be affected by the initial consultation. Secondly, we investigated whether these effects were modified by whether women had a personal history of breast cancer or not. Finally, we tried to determine which, if any, of the factors in our model predict intentions regarding undergoing prophylactic mastectomy after the initial counselling session.

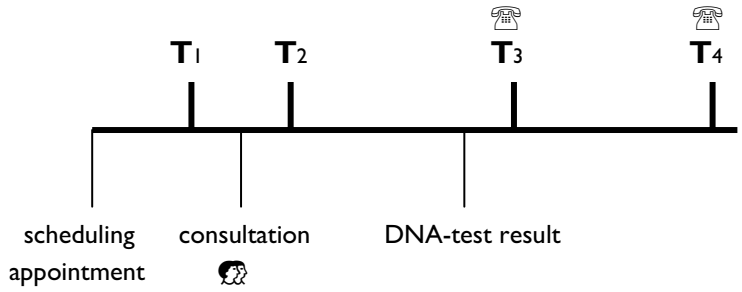
In **Chapter 5** we explored the psychological impact on counsellees of a variant of uncertain clinical significance (T_2-T_3). A relatively small group of women who received such a result was compared with the three other groups of test applicants regarding pre and post disclosure levels of psychological distress and perceived risk. In addition, self-reported comprehension after DNA test disclosure was assessed.

In **Chapter 6** the 'false reassurance hypothesis' with regard to women who receive an uninformative result is addressed. Data are presented about whether women who receive an uninformative result report that they are no longer at risk for having a deleterious mutation (T_2-T_3). In addition, potential changes in intentions for mammography screening were assessed for all groups of test applicants. A first aim of this was to check whether the motivation to adhere to screening would be adversely affected by an uninformative result. A second aim was to detect potential suboptimal screening intentions for women who learn that they carry a BRCA mutation.

In **Chapter 7** we focus on the course of worry and distress of women with uninformative result, as compared to test applicants who receive conclusive results, until seven months after disclosure (T_2-T_4). In this Chapter we tried to gain more insight into the heterogeneity within the group of women with an uninformative result. We inspected the effects of two medical characteristics: (1) a personal history of breast cancer, and (2) pedigree-based familial breast cancer risk.

Finally, **Chapter 8** concludes the thesis with a summary and general discussion.

Figure 2. Study design 'chances and choices'



T_1 tot T_4 refer to the moments a questionnaire was sent.
refers to a face-to-face interview immediately after the first consultation.
refers to telephone interviews at T_3 and T_4.

2

What do women really want to know?

Motives for attending familial breast cancer clinics

What do women really want to know? Motives for attending familial breast cancer clinics.
Van Asperen CJ, Van Dijk S, Zoeteweij MW, Timmermans DR, De Bock GH, Meijers-Heijboer EJ, Niermeijer MF, Breuning MH, Kievit J, Otten W.
Journal of Medical Genetics 39:2002; 410-414

ABSTRACT

Background

An ever-increasing number of women from breast cancer families visit familial cancer clinics for genetic counselling. For this reason, it is important that the geneticists efficiently recognise the informational needs of the counsellee. Essential information is needed for the counsellee to make a conscious choice. The aim of this study was firstly to identify subgroups of counsellees with a specific cluster of informational demands and secondly, to see whether particular sociodemographic and/or medical characteristics had any influence upon the different motives for genetic counselling.

Methods

Women with a personal or familial history of breast cancer received a questionnaire prior to their first appointment for genetic counselling. A total of 539 women were asked to participate in the study, 322 (60%) returned the first questionnaire. Information was gathered about medical and sociodemographic characteristics and details about their motives for attending. Logistic multivariate regression analysis was applied to predict the endorsement of motives, as dependent variables, using several medical and sociodemographic characteristics, as independent variables.

Results

Every woman has her own unique combination of multiple motives when seeking advice. Clear-cut clusters of motives are lacking. Four medical and sociodemographic characteristics influenced the motives for attending genetic counselling as follows: a previous history of breast cancer, a BRCA-mutation in the family, having children, and the age of the counsellee.

Discussion

Medical and sociodemographic characteristics of the counsellee might determine a special interest for genetic counselling. Some parts of information given to the counsellee should be emphasized, when taking these characteristics of the counsellee in mind. Communication during genetic counselling process could in that way be more tailored to suit.

INTRODUCTION

Genetic counselling is a highly specialised service in medical care. The service is expensive and its task is comprehensive, including "starting a communication process which deals with the human problems associated with the risk of occurrence of a genetic disorder in a family".[32] For a breast cancer service, this process is an attempt to assist the counsellee in understanding the medical facts, the mode of inheritance, the risk of getting breast and/or ovarian cancer (again), and the implications for daily life. Options for dealing with the risk are discussed and counsellees, depending on their own cumulative risk of getting breast cancer, are presented with a choice of surveillance of their breasts, DNA testing, or prophylactic mastectomy, either with or without oophorectomy.

An ever increasing number of women from breast cancer families visit familial cancer clinics for genetic counselling. Because of the comprehensive task of genetic counselling and the increasing numbers of appointments, it is important that the geneticist optimally and efficiently recognises the informational needs that are essential to the counsellee.[101] For the counsellee, it is important that she should receive all the information to make a conscious choice. One possible approach is to assess the specific motives for women to attend a familial breast cancer clinic. In this respect, different sets of motives may require different sets of information. Several studies have examined individual motives for attending familial breast cancer clinics and much insight has been gleaned into the most common ones.[37;102-107] Motives often encountered for attending these clinics included: "to find out my risk", "knowledge of my family history", "to find out the risk to other family members", "to reduce my worry", "to find out about genetic testing", and "to get information about preventive methods". Some of these studies[102;103;108] simply focused on a single aspect of genetic counselling, namely DNA testing, but did not include any of the other options counsellees are confronted with, such as breast surveillance or prophylactic mastectomy. Most of these previous studies have focused exclusively on healthy women.[37;109-111] To our knowledge, only one study has included women with a previous history of breast cancer.[105] To the best of our knowledge, no other study has ever compared the motives of affected and unaffected women who have attended a familial breast cancer clinic.

Recently, a comprehensive study[37] examined the motives for attending familial breast cancer clinics and showed that women who endorsed different motives also differed in demographic, medical, and psychological factors. For example, those women who were mainly interested in establishing the risk for family members were generally older than women who had other motives. However, one restriction of this study was that women had to choose just one out of 10 motives, so that mutually exclusive groups could be established. The authors admitted that women might have had multiple motives and that there might have

been a general pattern of combined motives. Development of a methodology that would allow women to register multiple reasons would provide more insight into this issue.

The broad population of women from breast cancer families who seek genetic counselling is composed of women both with and without a history of breast cancer from families with and without an identified mutation. For these reasons, the present study includes this whole population of women. It could well be that these two medical factors, that is, a history of breast cancer and a BRCA mutation in the family, could influence the type of motives that induce women to seek counselling. Another factor, which may influence motives for seeking advice not yet addressed in published reports, is whether the counsellees had children. The current study has attempted to assess the impact of these three factors, in association with sociodemographic factors such as age and educational level, that prompts women to visit a family cancer clinic. For the very reason that some factors are related, like having children, age, and a history of breast cancer, we have examined the individual effect of each factor.

The primary goal of this study is to examine whether motives mentioned for seeking genetic counselling are mutually related, in order to identify subgroups of counsellees with a specific cluster of informational demands. Secondly, we studied whether sociodemographic and medical characteristics influence the different motives for genetic counselling.

PATIENTS AND METHODS

Patients

Data were collected as part of an continuing study on risk perception and decision making of women at risk for familial breast cancer at the Departments of Clinical Genetics in Leiden and Rotterdam ("Chances and Choices" study). The medical ethics committees of both the Leiden University Medical Center and the Rotterdam University Hospital approved the study protocol. Eligible women had a personal or familial history of breast cancer and were attending the clinic for genetic counselling.

Referrals were based on current guidelines.[2] Additional criteria for participation were fluency in the Dutch language, being older than 18 years, and not at a terminal stage of cancer. From November 1998 (Leiden) and from January 2000 (Rotterdam) until December 2000, all new counsellees referred for familial breast cancer were informed about this study by letter. Women gave their written informed consent and received a first questionnaire, a few days to a few weeks before their first appointment with a clinical geneticist. In total, four questionnaires were collected but the data presented in this study were collected only from the first questionnaire. A total of 539 women were asked to participate in

the study and 322 (60%) returned the first questionnaire. Of those who returned their questionnaire, 244 (76%) were eventually seen at the Department of Clinical Genetics at Leiden and 78 (24%) women at the Department of Clinical Genetics at Rotterdam.

Both departments generally used the same protocol for genetic counselling. This included consultation with either a 410 clinical geneticist or genetic nurse. All available management options for the counsellee and her relatives were routinely discussed, a family history was taken, a risk estimation was made, and information about surveillance was given, if applicable. DNA testing was offered if there was a probability of mutation detection of about 10% or more. The choice between prophylactic mastectomy and surveillance, as options for potential BRCA1 or BRCA2 mutation carriers, was discussed.

Measurement

Medical and sociodemographic characteristics

Information was collected on personal history of breast cancer, age, educational level, and having had children. Furthermore, the marital status of the counsellee and whether a BRCA1 or BRCA2 mutation had already been detected in the family was registered. Mutation status was self-reported.

Motives for attending familial breast cancer clinics

Counsellees were asked to tick all-important motives from a list of 12. This list was based on previous research on Huntington's disease and familial breast cancer and clinical experience of the team (clinical geneticist, psychologist, oncologist).[37;102-107;112;113]

Statistical analysis

The SPSS 10.0 statistical package for Windows was used to analyse the data. For the description of the medical and sociodemographic characteristics of the counsellees, frequencies, means, and standard deviations were used. In order to investigate if the motives mentioned for seeking genetic counselling were mutually related, women could select the most important motives from a list of 12. Firstly, the number of motives was counted by summing all motives selected, which ranged from 0 to 12. Secondly, the kind of motives for each number of motives that were selected were also assessed. Thus, theoretically, for the number of 0 and 12 motives, only one combination could be identified (that is, 0 motives selected or all 12 motives selected); for the number of 1motive selected, 12 separate motives could be identified; for the number of 2 motives, 66 pairs of different motives could be distinguished; for the number of 3 motives, 220 different triplets of motives could be differentiated, and so on. To check whether a possible variety of chosen motives was uncommon or not, the most common number of motives (three) were examined in closer detail. Logistic multivariate

regression analysis was applied to predict the endorsement of motives, as dependent variables, and by several medical and sociodemographic characteristics, as independent variables. In the analyses, only motives selected by more than 5% of the counsellees were used. Some characteristics were dichotomous by themselves, such as "having breast cancer, yes or no". Others like "age" and "education" were dichotomised so that all predictor variables would have the same number of categories in order to give equal weight to all predictors and to ease the interpretation of the odds ratio.

A complete overview of all characteristics and their dichotomisation follows: "breast cancer" (no = 0, yes = 1); "age" (age 41 years and younger = 0, age above 41 years = 1); "mutation known in family" (no = 0, yes = 1); "having children" (no = 0, yes = 1); education (higher technical or vocational training or a university degree; under this level = 0, conform = 1); "married or cohabiting" (no = 0, yes = 1). The two participating centres in this study were categorised as Leiden = 0, Rotterdam = 1.

Presentation is limited to relevant and/or significant odds ratios, starting with the most frequent predictors. Relevant odds ratios have values smaller than 0.5 or larger than 2. Significant odds ratios have P values < .05. In order to balance the relevance versus the significance of the results, both pieces of information are presented.

RESULTS

Description of participants

The majority of the counsellees (70%) were unaffected by breast cancer (Table 1). The mean age of the whole group of women was 41 years (SD 11.24 years, range 18-72 years). In 12% of the counsellees, a mutation had already been detected in the family, before their first visit to a family cancer clinic. Most women had child-ren (71%) and were either married or living together (78%). The educational level was high; almost half of the women had higher technical or vocational training or a university degree. Three-quarters of the counsellees were seen at the Depart-ment of Clinical Genetics in Leiden. There were no differences between the counsellees of the two participating centres, except for the percentage of women with a known mutation in the family, which was higher in Rotterdam (28%) than in Leiden (9%). For this reason "Centres" was included as one of the variables in the multivariate logistic regression analyses.

Description of motives

Table 2 describes the selected motives. From the possible 12 motives, the mean number selected was 3.8 motives (SD 1.54 motives, range 1-9 motives). Two motives were important for the majority of counsellees: "I want to know if

Table 1. Medical history and sociodemographic characteristics of counsellees (N = 322)

	All counsellees	
	N	%
Breast cancer in history	96	30
Mutation already detected in family	37	12
Having children	230	71
Education		
Higher technical or vocational training or a Universtity degree	153	48
Married or cohabiting	251	78
Centre		
Leiden	244	76
Rotterdam	78	24
Age		
≤ 41 years	158	49
> 41 years	164	51

cancer in my family is hereditary" (74%) and "I want to get more certainty about my own risk of getting cancer" (69%). Fivemotives were chosen by a third to a half of the participants, namely motives concerning children's risk of getting cancer, physician's advice to make an appointment, breast surveillance, DNA test, and breast cancer worry. Motives concerning future planning and raising a family were chosen by less than 5% of the counsellees.

Combinations of motives

Table 3 provides an overview of the possible combinations of motives chosen by the 322 counsellees. The majority of women had chosen an individual combination of three or four motives. Overall, the selected number of motives by the participating women could be divided into 186 different combinations. For example, 13 counsellees had chosen one motive. These 13 motives consisted of eight different motives. Nine motives were selected by two counsellees and both had chosen a different combination. To examine in more detail whether only unique combinations of motives could be differentiated, we focused on the 102 counsellees who had chosen the most common number, that is three motives. In this case, a total of 47 triplets could be discerned (that is, about two women per

Table 2. Motives of counsellees for attending a family breast cancer clinic (N = 322)

Motive*	**N**	%
I want to know if cancer in my family is hereditary	238	74
I want to get more certainty about my own risk of getting breast cancer	223	69
I want to get more certainty about the risk of getting cancer for my children	150	47
Because my physician advised me to make an appointment	122	38
I want to get surveillance of my breasts	111	35
I want a DNA test	122	38
I am worried about getting cancer (again)	106	33
I want to help scientific research	46	14
I am thinking about prophylactic mastectomy	39	12
Because a family member asked me to make an appointment	24	8
I want to raise a family	13	4
I want to plan my future	8	3

triplet). The triplet consisting of the three most selected motives (Table 2) was chosen by 10 counsellees only. These results show that no clusters of motives could be identified.*

Predicting motives

Having a medical history of breast cancer was a significant predictor for five motives (Table 4). Affected women less frequently endorsed the two motives regarding their own risk of getting breast cancer and regarding breast surveillance. However, they selected more often the motives regarding the risk of their children getting breast cancer, worry about getting cancer again, and helping scientific research.

If a BRCA1 or BRCA2 mutation had already been detected in the family of a counsellee, these women were less often interested in the genetics of breast cancer in their family. They selected more often the motive "because a family-

* Each kappa for pairs of motives was less than .17, which is generally classified as poor.

Table 3. Number of motives chosen by counsellees and number of combinations of these motives

Number of motives	Number of counsellees		Number of combinations
	N	%	
1	13	4	8
2	39	12	18
3	102	32	47
4	73	23	29
5	48	15	37
6	27	8	27
7	14	4	14
8	4	1	4
9	2	1	2
10	0	0	0
11	0	0	0
12	0	0	0
Sum	**322**	**100**	**186**

member asked me to make an appointment for genetic counselling". This group of women from BRCA1 or BRCA2 families endorsed motives concerning the risk of getting breast cancer for their children and helping scientific research. These women chose less often the motive of prophylactic mastectomy.

Age was also a predictor of five motives. Younger women were more often interested in motives regarding their own risk of breast cancer and prophylactic mastectomy. They were also more interested in the motive regarding cancer worry. Older women were more willing to help scientific research and were interested in the risk of their children getting cancer.

Having had children was a very strong predictor for the motive of the counsellee's children getting breast cancer and also for the motive of prophylactic mastectomy. Women with a lower level of education were more often asked by a family member to make an appointment for genetic counselling. Married women or women living together less frequently endorsed the motive to help scientific research. In the Leiden Centre, more women were interested in the motive concerning breast surveillance, in the Rotterdam Centre more women chose the motive of prophylactic mastectomy.

Two motives could not be predicted, namely the motive "Because my physician asked me to make an appointment" and "I want a DNA test".

Table 4. Multivariate analysis to assess unique contribution of counsellee's medical and sociodemographic characteristics as predictors for motives

Motives	**Medical and sociodemographic characteristics**						
	Previous history of breast cancer	Mutation already detected in family	Education	Age	Married or living together	Children	Centre
I want to know if cancer in my family is hereditary	1.22	0.13***	0.78	1.68	1.10	0.66	1.77
I want to get more certainty about my own risk of getting breast cancer	0.09***	1.36	1.05	0.49*	0.53	0.90	1.14
I want to get more certainty about the risk of getting cancer for my children	3.43***	2.22	0.73	1.91*	0.76	29.34***	0.59
Because my physicians advised me to make an appointment	0.80	0.62	1.23	1.35	1.23	0.81	0.60
I want to get surveillance of my breasts	0.40**	0.85	0.81	0.77	1.27	0.64	0.48*
I want a DNA test	0.90	1.59	1.18	1.36	1.42	1.23	1.23
I am worried about getting cancer (again)	4.68***	1.00	1.08	0.50*	1.00	0.68	0.89
I want to help scientific research	2.96**	2.13	0.63	2.24*	0.40*	0.91	0.87
I am thinking about prophylactic mastectomy	1.15	0.15	1.23	0.33**	1.79	2.15	2.12
Because a family member asked me to make an appointment	1.3	4.07**	0.47	1.53	0.77	1.00	1.00

White cell: relevant odds ratio Exp (B) <0.5 or > 2. *Grey cell*: odds ratio Exp (B) between 0.5 and 2. *Light grey cell*: significant odds ratio only

* P < .05, ** P < .01, *** P < .001

DISCUSSION

The principal results of this study were two-fold. Firstly, based on a population of women seeking advice at two familial breast cancer clinics, we conclude that women have their own unique combination of motives when seeking advice. Secondly, although clear cut clusters of motives were not detectable, some medical and sociodemographic characteristics could be used to focus on the informational needs and demands of the counsellee.

The present study clearly shows that two motives are the most chosen. As could be expected, most women want to be informed about the genetic nature of breast cancer and their own risk. In addition, our results indicate that an average woman had about four motives for seeking medical advice at the familial cancer clinic. These additional motives illustrate the restrictive nature of the method of Brain et al,[37] which exclusively assigned women to just one motive.

Counsellees with a personal history of breast cancer are a special group and represent 30% of the women in this study. The data confirm the results of a French study[105] that reported that such women attended the clinic mainly for their offsprings' sake. These women with a history of breast cancer wanted to be informed about their children's risk of getting breast cancer and were less concerned about their own risk. From the present study,we conclude that this group of women was also worried about their own cancer recurrence risk. A higher risk for a contralateral tumour is one of the characteristics of hereditary cancer.[114] This could explain why women with a personal history of breast cancer were more worried than those who had no previous history.

If a BRCA1 or BRCA2 mutation had already been detected in the family of a counsellee, these women were less often interested in the genetic nature of the breast cancer in their families, since this had already been proven. One could argue that women from BRCA families seriously consider a prophylactic mastectomy as one of the options. However, it appeared that these women, with a 25% or 50% risk of having a BRCA1 or BRCA2 mutation, less often endorsed the motive of prophylactic mastectomy. A possible explanation is that these women will only start to think about surgical intervention when they actually receive their own DNA-test result and not at the beginning of the genetic counselling process, when the present data were collected.

Younger women were especially interested in their own risk of getting breast cancer and options for prophylactic mastectomy; furthermore they were also worried about recurrence of cancer. As published earlier,[115] serious psychological morbidity may not be prevalent in the general population of younger women at increased risk of breast cancer. However, many of these women may have breast cancer worries that have the potential to compromise their quality of life. It is understandable that younger women would be more worried about the consequences of breast cancer, which could compromise the goals they wanted to

Younger women were especially interested in their own risk of getting breast cancer and options for prophylactic mastectomy; furthermore they were also worried about recurrence of cancer. As published earlier,[115] serious psychological morbidity may not be prevalent in the general population of younger women at increased risk of breast cancer. However, many of these women may have breast cancer worries that have the potential to compromise their quality of life. It is understandable that younger women would be more worried about the consequences of breast cancer, which could compromise the goals they wanted to attain. Having had children clearly is a predictor for enquiring about the children's risk of getting cancer. These women more often endorsed the motive of prophylactic mastectomy. Parenthood was found to be an important predictor of surgical intervention in the Rotterdam centre.[94] It is understandable that parenthood would give women a strong feeling of responsibility. They want to survive to bring up their children, even if a mutilating and irreversible intervention is needed for their future health.

One limitation of our study could be related to the list of preselected motives that we have compiled for the counsellees. Such a list could induce the counsellee to select more than one main topic and this would partially explain the multiple reasons for attending a familial cancer clinic. In addition, our list may not completely represent all the motives that our counsellees considered relevant. Furthermore, a methodology that would allow women to indicate the extent to which a specific motive applied to them might be more sensitive in the detection of clusters of motives than the dichotomous measure used in the present study.

One fundamental question, which needs to be addressed, is whether women's motives for attending a familial breast cancer clinic for genetic counselling correctly identify their informational needs. These motives have often been formed before their first consultation. However, women's informational demands could also be influenced by the information they receive during the genetic counselling process. For example, they may learn about new possibilities, for example, prophylactic mastectomy, or they may realise the restrictions of a DNA test. The issue would then be whether women's precounselling motives should completely guide the communication during the genetic consultation or whether a specific programme of information should be communicated irrespective of women's motives. This in turn raises the question of the content of that specific programme of information. Should information about all aspects of familial breast cancer be communicated so that counsellees can make an informed choice? A possible drawback of this could be that a fully comprehensive programme of information would confuse and frighten the counsellee to such an extent that she would be unable to come to terms with the situation.

However, we can conclude that most women would like to be informed about the genetics of breast cancer and their own risk. Some medical and

sociodemographic characteristics of the counsellee might determine a special interest. Four specific characteristics appear important to understand these reasons for additional information: having a history of breast cancer, having a BRCAmutation in the family, having children, and the age of the counsellee.
These medical and sociodemographic characteristics should be considered, as specific areas of the information can be dealt with more thoroughly. For example, if a young breast cancer patient applies for genetic counselling, one should pay extra attention to her feelings and emotions concerning her chance of getting breast cancer again. Similarly, the topic of prophylactic mastectomy can be talked through more extensively for younger women with children. Having a BRCA mutation in the family seems to bring on a kind of step by step approach by the counsellee. They start up the process of genetic counselling, are waiting for the test result, and will continue this process by taking a decision about surveillance or prophylactic surgery. In this manner, communication during the genetic counselling process could be more tailored to suit the individual person.

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3

Feeling at risk; how women interpret their familial breast cancer risk

Feeling at risk; how women interpret their familial breast cancer risk.
Van Dijk S, Otten W, Van Asperen CJ, Timmermans DRM, Tibben A, Zoeteweij MW, Silberg S, Breuning MH, Kievit J.
American Journal of Medical Genetics Part A 131A: 2004; 42-49

ABSTRACT

Introduction

Women's inaccuracy in recalling their breast cancer risk, even immediately after genetic counselling, has received much attention. However, scarce data are available about how women describe their risk in their own words and about what the risk information actually means to them. The present study aims to address these questions and to asess whether these are congruent with the objective risk.

Patients and methods

Face-to-face interviews were conducted with 123 women immediately after their (initial) counselling session. N-Vivo software was used to describe the data.

Results

The level of accuracy of recall depended strongly on the leniency of the criterion applied. For example the level of verbal accuracy ranged from 25.8% (an exact match with the verbal label) to 98.4% (a more global awareness of having a high versus a low risk). In assessing the significance of personal risk information, we identified a wide variety of risk beliefs, and stress and coping responses. In general, women associated their risk with the medical options, e.g. breast screening, that were available for them given their risk status.

Discussion

The results indicate that the accuracy of recall might be a limited outcome measure for the effectiveness of genetic counselling. First, this is because the level of accuracy of recall depends on how rigorously accuracy is defined. Secondly, because the probability of occurrence is just one of the elements comprising perceived risk, accuracy might rather apply to the distress, and to risk-management behaviours that are elicited by the risk information. These beliefs that women hold about their risk status, and concomitant levels of stress should play a prominent role in genetic counselling.

INTRODUCTION

Risk communication is an essential component of genetic counselling for hereditary breast cancer. Women with a relatively low risk can be reassured, whereas women who are eligible for risk-management options should be able to make informed decisions. The general assumption is that genetic counselling should correct women's perception of risk if necessary, thus subsequently, levels of distress may be adapted, and appropriate behavioural options can be chosen. However, many women show an inaccurate recall of their personal risk, even after genetic counselling[41] and as a consequence, may experience inappropriate levels of distress and may wish to choose risk-management options that are not available to them.

The present study aims to address the content and the meaning of perceived breast cancer risk, and to see whether this is congruent with the objective risk in a qualitative design, which allows women to describe their breast cancer risk in their own words. Little is known about how women verbalize their risk, because generally a questionnaire is used, which measures perceived risk by asking women to tick off the appropriate number or label of a limited range of fixed answers. In limiting responses, implicit assumptions about how women generally remember risks are being made. However, women differ in their preference for using various risk formats.[116] Moreover, it has been demonstrated that people tend to use rather broad categories to translate detailed risk information.[117-119]

There is not only a lack of knowledge about how women at risk of familial breast cancer verbalize their risk, but also about what the risk information actually means to them. It has been shown that people's appraisal of the risk is multidimensional.[120] The present study not only examines how women describe their risk, but also which cognitions, emotions and beliefs are associated with the risk information in genetic counselling for breast cancer.

METHOD

Procedure

In the period from November 1998 until June 2002, we invited all eligible women who had an appointment at the Department of Clinical Genetics in Leiden, to take part in a large longitudinal study. This was to assess their perception of risk and decision making after genetic counselling for hereditary breast cancer. Ethical approval was obtained for the integrated study from the hospital's research ethics committee. Of the 850 women we approached for the integrated study, 660 (response rate 77.6%) provided informed consent. All participants met the inclusion criteria of being at least 18 years old, and of not having received genetic counselling elsewhere. As we wished to understand and elaborate on the themes

brought to the fore by women themselves, we also wanted to interview women personally, besides using a questionnaire design. Therefore, at the beginning of the study, we invited a convenience sample of 114 of all participants for a face-to-face interview, immediately after their first consultation. Of the 114 women we approached, one woman chose to withdraw from the interview because she considered it too emotionally draining. All interviews were done at the hospital, except for nine home-interviews. Two interviewers conducted the interviews.
In addition to the afore-mentioned group, ten women from proven BRCA families (who did not know whether they were BRCA carriers themselves, and who had also consented to take part in the study) were interviewed by three psychologists from our department. Within the period in which data collection was taking place, women from proven BRCA-families were offered a consultation with a psychologist immediately after the first counselling session as standard procedure. We wanted to include women from BRCA-families to obtain a representative sample of women applying for counselling. In order not to burden these women with an extra interview, the consulting psychologist interviewed these women during the consultation. We analysed 123 interviews.

Information provided during counselling
Referrals for genetic counselling for breast cancer were based on current national guidelines.[2;121] These guidelines specify how many first or second grade family members should have developed breast cancer either before or after the age of 50, as a prerequisite of referral to a cancer clinic. In the first consultation, a clinical geneticist counseled the women, applying a standard counselling protocol, and recorded their family medical history. General risk information was provided about the population risk (i.e., 10%). If sufficient medical information was available, a familial lifetime risk of developing breast cancer was estimated.[5] Usually, the probability of harboring a gene mutation was estimated. Genetic testing was offered if there was a probability of mutation detection of about 10% or more.[6;15] General information was given about the hereditary transmission of BRCA1 and BRCA2 (i.e., 50% chance of transmission of a gene mutation) and about the lifetime risk of developing breast cancer for gene carriers (i.e., 60-80%). General information about ovarian cancer risk was also provided. If indicated, breast and/or ovary surveillance was offered. If supplementary medical information had to be collected for risk estimation, or if genetic testing was applied, further consultations were scheduled.

For each standard topic, the geneticist could tick a checklist on whether the item was covered in the session. In addition, if personal risk information was provided in the first consultation, the geneticist could fill in whether verbal or numerical risk information was provided, as well as the exact content of this information. Finally counsellors evaluated the counsellee on six 5-point scale ratings, whether the counsellor thought that the counsellee: (1) had understood

the information; (2) was well-informed already; (3) asked questions; (4) was anxious; (5) was open to receiving information; and (6) had taken the initiative for referral herself. For one women no checklist was completed. We obtained information about the objective risk from her medical record.

Interview structure

Data were collected using open-ended, semi-structured interviews covering several topics. Concerning risk perception, we first asked the women what they had learned about their personal risk of developing breast cancer (*"What did you learn about your risk of developing breast cancer (again)?"*). In addition, we asked them what the chance of developing breast cancer meant to them (*"What does the risk of developing breast cancer (again) mean to you personally?"*). Answers to the questions were written verbatim by the interviewer in an interview protocol booklet, and if permission was obtained, interviews were tape-recorded. We transcribed 15% of the tapes at random to see whether the interview booklet text matched the recorded text. Two reviewers independently checked both the transciptions of the taped interviews and the interview booklets and coded every text fragment that could potentially contain relevant information. As this was highly satisfactory because no single fragment was missed, we used the interview booklets for our analyses.

Data analysis

The SPSS 11.5 statistical package was used to analyse data. Frequencies were used to describe the study population. We conducted chi-squares to compare participants who were interviewed with participants who were not. With chi-squares and t-tests we tested whether providing additional risk information (numerical risk figures) was related to patient characteristics or the counsellors' evaluation of the patient.

Two reviewers compared the responses about personal risk with the information provided in the checklist, to estimate the level of accuracy of recall, if women were provided with personal risk information. When women chose to describe their risk numerically, we assessed the numerical accuracy; whereas when participants described their risk in verbal terms, the verbal accuracy was checked. To estimate how accurate women's responses were, we first checked whether participants used the same numbers (e.g. 16%, or, less than 30%), and/or the same words (that is; population risk, slightly raised, moderately raised, and highly raised), as recorded in the checklist. To assess whether women had a correct sense of the magnitude of their personal risk, we classified the other verbal answers as low or high. We used this dichotomy in line with the findings of Parsons and Atkinson.[118] They showed that patients translated their risk figure into a broad, high or low category. In cases of discrepancy, the judgments were discussed together with a third reviewer to reach consensus.

For the question about what the risk of breast cancer means to women, we conducted a grounded theory approach in several stages. N-Vivo software was used to describe the data.

In the first stage all 123 interview booklets were read by three reviewers to identify all emergent themes, which were condensed after discussion into a subset of 20 more general themes for a coding scheme. Three reviewers each coded 10 randomly selected interview booklets to rate whether the coding system was sufficient and appropriate to capture the information. After discussing the findings, the coding scheme was adapted again. At this stage it appeared that our pattern of categorizations seemed to match the stress model of Lazarus and Folkman[122] rather well. In this interactional model, it is proposed that people appraise various features of the threat and explore ways to respond to such a threat. A discrepancy between the demands of the threat and the ability to manage it causes stress and generates the subsequent execution of coping responses. We decided to use this stress model as a general framework to describe our data. We differentiated between "risk appraisal", "emotion-focused coping", "problem-focused coping" and "stress" (see Table 3). After redefining the specific coding system, all reviewers coded all interview booklets, again with agreement over categorization achieved by discussion. Data related to each theme were retrieved and representative quotes were selected to illustrate important themes in the data. All data were entered into SPSS.

Regarding our study population, which comprised both affected and unaffected women, we hypothesised that the significance of personal risk might be different for both groups of women. Similarly, we wanted to check whether women with a relatively low objective risk would mention different themes than those women with a moderately or highly increased risk. Finally, we compared the classifications in the coding system. For example, we assessed whether women who mention a specific coping response would also mention a typical stress response more frequently. However, for many classifications the number of women who mentioned these were too small. We conducted 2x2 chi-squares, corrected for continuity under the condition that no cell should have an expected frequency of less than one.

RESULTS

Participants

The mean age of the interviewees was 40.7 years (range 19-71 years; SD 11.9 years; see Table 1). The majority were married or co-habiting (81.3%) and had one or more children (60.2 %). Almost half of the women had high school or university level education (40.7%). More than one-third of the women had had

breast cancer (38.2%). A small minority of the women was from a known HBOC-family (9.8%).

Table 1. Sociodemographic and medical variables of the study population (N = 123)

	N†	%
Sociodemographic		
Age		
< 30 years	29	23.6
30-39 years	26	21.1
40-49 years	35	28.5
50+ years	33	26.8
Marital status		
Married or cohabiting	100	81.3
Not married or cohabiting	23	18.7
Children		
Yes	74	60.2
No	49	39.8
Educational level		
High school or university	48	40.7
Less than high school	70	59.3
Medical		
Breast cancer history		
Yes	76	38.2
No	47	61.8
Objective risk		
10% (population risk)	6	5.8
10-15%	8	7.8
15-30%	32	31.1
> 30%	57	55.3
BRCA detected in family		
Yes	12	9.8
No	111	90.2

† Because not all women were provided with an objective risk, and not all sociodemographic information could be concluded from questionnaires, some categories do not add up to 123.

A personal estimation of the familial risk for breast cancer could be provided for 103 women. Four risk categories were distinguished; (a) general population risk, i.e., around 10%, N = 6; (b) slightly raised, i.e., 10-15%, N = 8; (c) moderately raised, i.e., 15-30%, N = 32; and (d) highly raised, i.e., 30% or more, N = 57. According to the checklist, the verbal label of their specific classification was communicated to all women. For 73.8 % of those women a numerical label was provided as a supplement to the verbal labels. The provision of additional numerical information was not related to sociodemographic or medical features of the study population. However, a significant effect was found for the counsellors' evalation of the counsellees' openness to receiving information. If counsellors rated women as being more open to receiving information they more frequently provided numerical information in addition to the verbal label ($t = 2.384$; $P = .0019$). For all other patient evaluations, no differences were observed.

As we used a convenience interview sample, we assessed whether we had included a representative group of participants. We conducted chi-square tests on socio-demographic and medical variables to compare the interview sample with the respondents who were not invited for the interview (*personal history of breast cancer, known mutation running in the family, age, marital status, educational level, having children*). The only discrepancy was that women with children were under-represented in the interview sample ($P = .03$). No further differences were detected.

Accuracy of recall

Because we used the objective risk estimation as a golden standard to estimate the level of accuracy, we did not describe the answers of women who did not receive a personal risk estimation, due to a lack of medical information. Of the 103 women who received personal risk information in the first consultation, 93 responded to the question regarding the description of their personal risk of developing breast cancer (again). Eighty-six of them said something about their personal or familial risk of developing breast cancer. (The other seven women merely mentioned the general probability of harboring a mutation, or the 60 to 80% risk percentage for gene carriers. Twenty-one women mentioned this general information in addition to their personal risk information). Thirty women out of the 86 who appropriately responded to the question (34.9%) used exclusively verbal phrases, whereas 24 women (27.9%) reacted only with a numerical response. Thirty-two women (37.2%) described their personal risk in both words and numbers.

Numerical accuracy of recall

As described above, 56 women out of the 86 women who were provided with personal risk information during counselling mentioned numbers to describe their personal risk. Fifty-two out of these 56 (92.9%) mentioned the exact personal

risk numbers as recorded in the checklist of the counselling session (five of these women recalled the exact personal chance of harbouring a mutation). The remaining four women, all from the highest risk category, did not respond with exact numbers. Three of them seemed to confuse the general risk figures with their personal risk. Two women claimed a 50% breast cancer risk. Their answers matched the risk range mentioned in the counselling (i.e., >30%). However, it is more likely that they recalled the 50% chance of passing on a gene (for gene carriers), which is part of the general information in the first consultation. In addition, one woman had had prophylactic mastectomy in the past, and seemed confused by the several risk figures in the consultation. She correctly mentioned the risk figures for mutation carriers, and she identified her remaining personal risk as 1%. However, she also described her personal breast cancer risk as being 10%, which is mentioned as the general population risk in the Netherlands in the counselling session. The last woman reported numbers that did not correspond with either personal or general counselling information.

Verbal accuracy of recall

Sixty-two women out of the 86 women, who were provided with personal risk information during the counselling, mentioned words to describe their personal risk (See Table 2). Sixteen of these 62 (25.8%) responded in exactly the same words as mentioned in the counselling (i.e., population risk, slightly raised, moderately raised, and highly raised). In addition, 19 women (30.6%; all from the moderately raised and highly raised risk categories) used the unspecified word "raised" without further qualification.

To check whether the remaining verbal answers matched the objective risk, we classified them as low or high. Low-risk wordings were for example "practically nil", "not high", or "it is probably not hereditary". High-risk answers were responses like "high", "high risk", "it runs in the family like nobody's business". The verbalizations matched the objective risk information quite well (Table 2). In particular, the women with a relatively low or a high risk used words congruent with their risk status. Women with a slightly raised risk, or a risk that equaled the population risk, responded with low-risk words, whereas women with a high risk used high-risk words. Mixed responses were found for the women who heard that they had a moderately raised risk, which was neither high nor low. Only one response was identified as inaccurate. This high-risk woman provided a contradictory response. She described her risk as "great, clearly riskier", which would be a high-risk response and "just as much chance as anybody else", which would be a low risk response. As she had already had breast cancer, she may have assumed that the high risk applied to her healthy daughter (i.e., familial breast cancer risk), and that she herself was relatively safe from another breast cancer.

To sum up, how precisely the verbal responses matched the objective risk information depended on the criteria applied. If a correct response was defined as an exact match with the verbal label, accuracy of recall was 25.8%, or 56.5% (including "raised" as an accurate response for all women with a raised risk). However, if less stringent criteria were applied, (i.e., a more global awareness of having a high versus low risk), accuracy of recall was very good (98.4%; 61 "correct" responses out of 62).*

The level of correct responses for the combination of verbal and numerical responses also depends on the criteria applied. For the eighty-six women who were provided with personal risk information during the counselling 67.4% (exact match) or 95.3%* mentioned at least one correct response (either verbal or numerical).

Table 2. Classification of verbal responses versus objective risk

Objective risk	Same words	Low	High	'Raised'	Contra-dictory
Population risk (N = 6)	3	3	-	-	-
Slightly raised (N = 7)	1	6	-	-	-
Moderately raised (N = 23)	10	6	2	4	1
Highly raised (N = 26)	2	-	9	15	-
Total (N = 62)	**16**	**15**	**11**	**19**	**1**

Personal meaning of being at risk for breast cancer

One hundred and fifteen women responded to the question about what their breast cancer risk meant to them (8 women stated that they did not know, or said that they did not know because they did not learn new facts about their personal risk). Most answers were relatively short; we coded 233 text fragments (number of categorised text fragments per woman = 2.03; see Table 3).

Appraisal

Appraisal is an internal process in which one evaluates the nature and amount of danger, and assesses one's resources to deal with the threat (*primary and secondary appraisal*[122]).

Concerning the magnitude of the risk, 25 women reported some evaluation of the probability of their breast cancer risk. In addition, several women sponta-

* Correct response: both high- and low risk words were coded as 'correct' for women with a moderately raised risk.

neously mentioned the threatening consequences of getting cancer, especially the mutilating effects of surgery on the feeling of femininity, and the possible lack of survival. Women who mentioned such consequences also more frequently expressed fear and worries (χ^2 = 4.57; P = .033).

We identified *idiosyncratic risk beliefs* about and *personal experiences* with breast cancer as personal attributes that may affect the way the threat is appraised. Fourteen women, of whom relatively many (N = 5) had not received a personal breast cancer risk estimation (yet), expressed beliefs about their personal risk. Misconceptions and statistical biases were detected. For example one woman who had not received a personal risk estimation (yet) reasoned:

> "Out of four sisters, two have it and two don't. I'm in the healthy 50%. I don't think I'm going to get it, I'm in the right half.". (#249)

Another woman, with a "moderately raised risk", who said she learned from a Chinese doctor that her grief about the death of her nephew had caused her breast cancer stated:

> "I think the chance [of getting breast cancer again] is nil. That's not naive. Now I know how it is. I'm not neglecting my body now. I'm much more aware of my mind. There is now a symbiosis of mind and body."

Some women were certain that they would either definitely yes or definitely not develop breast cancer. Three said that they were certain to escape (another) breast cancer. Two of them felt safe from breast cancer because of a previous diagnosis of breast cancer. On the contrary, four women were sure that they would develop breast cancer or even die from it in the future. For example, one of them who did not receive information about her personal risk in the counselling session stated:

> "If I went to the hospital now and they said, "You've got breast cancer.", I wouldn't find that a bit strange. I'm expecting to get it. I would rather have the certainty." (#267)

Several women spontaneously mentioned a discrepancy between what was known (the objective risk) and what was believed (subjective interpretation), or, how a woman with a relatively low risk put it:

> "That's difficult…the chance of getting it, logically I'm not high-risk. But by having the scan…. I feel as though the risk is very high. My feeling is that if the next scan shows cancer…I wouldn't find that strange." (#348)

In these risk beliefs, but also in general, personal experience with breast cancer seemed to play an important role. Of the forty-seven women who had had breast cancer, fifteen reflected on developing it again and related it to their experience. In addition, twelve unaffected women spontaneously related the meaning of the risk information to experiences of other family members with the disease. Two thirds of the responses of the women with and without a prior diagnosis expressed a pessimistic outlook. The other responses were neutral or quite optimistic. For example, several women drew hope from family members who recovered from cancer. Women with a previous diagnosis of breast or ovarian cancer mentioned personal experiences with cancer significantly more often than women who had experienced cancer only through one or several family members (χ^2 = 5.57; P = .018). However, this effect was only observed for negative experiences (χ^2 = 5.22; P = .022); for positive or neutrally framed experiences no effect of having had breast cancer was detected.

Coping

Coping refers to any effort to manage a threat. Lazarus and Folkman[122] distinguish between two broad categories of coping responses. Problem-focused coping involves dealing with the threat itself, whereas emotion-focused coping involves efforts to modify the distress that accompanies a threat.

Emotion-focused coping

Many women provided a response coded as emotion-focused coping. Eleven of them tried to play down the risk by stating that the probability does not mean that it will happen for sure, or by comparing it to other risks:

> "I could get run over by a bus tomorrow and then all the worry would have been for nothing." (#71)

In addition, some women stated that they actively tried to avoid thinking about the risk or disregarded (further) information. Several responded with what we defined as a "down-to-earth response". They reacted with some kind of resignation. In the words of one of them:

> "I've got it and there's a big chance that I'll get it again, I just have to live with that." (#292)

Only three women explicitly articulated maintaining, or trying to maintain, a positive attitude.

Table 3. Personal meaning of personal breast cancer risk

Stress model	**N = 233 codes**
Appraisal	79
Probability	25
Breast cancer consequences	13
Idiosyncratic risk beliefs	14
Negative cancr experiences	18
Positive or neutral experiences	9
Coping	
Emotion-focused coping	32
Playing the risk down	11
Avoidance	9
Resignation	9
Positive attitude	3
Problem-focused coping	47
Surveillance (being watchful)	26
Risk-reducing surgery	8
Life-style changes	3
Scenario's for the future	3
Information search (DNA test)	5
Maybe no pregnancy	2
Stress	75
Fear, and worries	44
Stress is manageable	19
No feelings of stress	10
Relief	2

Problem-focused coping

Similarly, many women mentioned actions to manage their risk. The most common response was about breast surveillance, or about the need to be alert, usually combined with a phrase about the hope of being in time if breast cancer would be detected. All women who mentioned surveillance were either eligible for intensive screening due to their personal risk, or had been having breast surveillance for many years before genetic counselling was scheduled (see objec-

tive risks in Table 4). Furthermore, women who related screening options to their personal risk, less frequently expressed fears and worries about developing cancer, or dying from it (χ^2 = 5.82; P = .016). Only eight women mentioned prophylactic surgery. Three of the latter group of women had a prior diagnosis of breast cancer. Only two of the women who mentioned prophylactic surgery as a procedure to manage their risk were from the highest risk category (see Table 4) and thus potentially eligible for prophylactic mastectomy. One woman was provided with a relatively low risk; she strongly urged for a contralateral mastectomy to prevent another diagnosis of cancer. In addition, some women reported lifestyle changes, or mentioned the hope of new developments in treatment if they should develop cancer. Five women, who were all offered a DNA test, stated that the risk called for a search for more information about having inherited the mutation. Finally, two women reported that the hereditary nature of the risk might be a reason to refrain from having children. One of them worried about giving birth to a daughter.

Stress

According to Lazarus and Folkman's interactional stress model,[122] stress is the result when one's resources are insufficient to handle the perceived threat. The coping responses modify the nature of the stress. Thus, the stress response results from an interplay between appraisal and coping responses. In our sample, seventy-five women reported some level of, or alternatively a lack of, psychological stress regarding the threat of (developing) breast cancer.

The answers of forty-four women reflected psychological stress, although the nature of the stress varied to some extent. Many women mentioned distress at the thought of getting cancer, or dying from it. For example one woman from a proven BRCA-family stated:

> "Fear! My first reaction when my cousin told me about BRCA was: "now I've got cancer!", I slept badly, I needed medication. Now I've got things a bit more in perspective." (#154).

In addition, several women explicitly reported worries about their children developing breast cancer. Finally, six women reported that the uncertainty regarding the occurrence of cancer induced negative feelings. We found a trent for objective risk: Women who reported high levels of risk-related fear or worry more frequently had a relatively high risk (χ^2 = 3.40; P = .065; Table 4). Thus, their levels of stress seemed rather congruent with their risk status. Only one woman who reported fear or worry related to her personal breast cancer risk was provided with a relatively low risk. She reported being very worried due to a history of cysts for which she was treated several times.

Twenty-nine women spontaneously mentioned that their personal breast cancer risk did not elicit any feelings of stress, or that the threat was at least bearable. Two thirds of them said that although the topic was on their mind frequently, they could manage it quite well. In the words of one woman from the highest risk category:

> "I have an increased chance. That's very tiresome. But it is not ruling my life. It's something you have to consider. It's not something I spontaneously think about." (#327)

Women who mentioned such responses were found to report relatively frequently positive experiences with cancer (χ^2 = 7.34; P = .005).

Ten women spontaneously stated that their breast cancer risk did not bother them. One woman with a "slightly raised risk" responded:

> "I never think about it. What a pain." (#71)

No significant effect for objective risk was observed within the group of women who stated that the risk elicited any or manageable feelings of stress. In general, however, the risk of these women was lower than for the women who expressed relatively high levels of stress or worry. For women who mentioned no or manageable levels of distress a trent was found for negative experiences with cancer: Those women reported somewhat less often negative prior cancer experiences (χ^2 = 3.23; P = .072). Finally, a few women expressed relief now that they knew their personal breast cancer risk; they had expected it to be higher.

Table 4. Personal meaning of personal breast cancer risk and objective risk

	N codes	**low 10-20%**	**moderate 20-30%**	**high > 30%**	**miss.**
Problem-focused coping					
Surveillance (being watchful)	26	4	8	13	1
Risk-reducing surgery	8	1	3	2	2
Information search	5	-	2	2	1
Stress					
Fear, and worries	44	1	13	24	6
Stress is manageable	19	3	4	10	2
No feelings of stress	10	3	2	4	1

DISCUSSION

Effective risk communication is one of the main aims of genetic counselling for breast cancer. As a consequence, concern has been raised about women's inaccuracy in recalling their counseled risk. However, the results of the present study indicate that the accuracy of recall might be a limited outcome measure for the effectiveness of risk communication. The first reason for this is that the level of accuracy of recall depends on how stringently accuracy is defined. Secondly, because the probability of occurrence is just one of the elements comprising perceived risk, accuracy might rather apply to the beliefs, emotions, and behaviours that are elicited by the risk information.

With regard to verbal risk recall, accuracy varied from 26% to 98% (depending on how strict the criteria for concordance were set). Meiser and Halliday[41] already described the variety in accuracy levels in the literature. Studies assessing numerical accuracy do not only differ in the kind of questions asked (e.g., odds or percentages), they also use different criteria to determine accuracy (e.g. correct risk figure, or within 10 or 50% of counseled risk). Consequently, accuracy for women who recall numerical information immediately after counselling ranges from 31%[52] (*correct risk figure expressed as odds ratio*) to 81%[49] (*within twofold of counseled risk*).

The few women who did not correctly recall their personal risk seemed to confuse the risk figures in the general information with their personal risk information. This mixing up of fragments of risk information has been described before[118] and is probably due to the relatively huge amount of risk information provided in genetic counselling.[116] Counsellors should be aware of the possibility of information overload, and always carefully check whether the relevant risk information is understood. A clinical strategy for the latter, as suggested in a recent study on patients' preferences for risk information,[116] might be to ask women explicitly to describe their risk in different risk formats. With regard to the possibility of information overload, it may even be worthwhile to deliver a summary handout of the general (risk) information to enable counsellors to spend less time on formal education, in favor of using the time available for personal and interactional counselling.

Apart from questioning the interpretation of varying levels of recall measured, we want to question the value of measuring accuracy of recall altogether. Although a correct recall might be an indication that the information is remembered, it hardly demonstrates that the information is interpreted correctly. Moreover, we found that the magnitude of the risk information was only one of the many factors that women rated as important in referring to their breast cancer risk. When addressing the effectiveness of genetic counselling, it may be more straightforward; (a) to consider which emotions, cognitions and behavioural

intentions are elicited by the risk information and; (b) to see whether these are congruent with the aims of counselling.

For example, concerning behaviour, women should opt for those interventions, which are medically appropriate or at least available to them after counselling. In this respect, it was reassuring that all of the many women who spontaneously mentioned breast surveillance on the question about the significance of the risk, were indeed either eligible for breast surveillance, or had been having it for many years already. The few women of the latter group only found out during genetic counselling that there was no medical indication for intensive breast surveillance due to their relatively low risk status. Similarly, mentioning a DNA test as a means of acquiring information seemed appropriate as the few women concerned had provided a blood sample, or would be asking an affected family member for blood withdrawal. However, for the behavioural option of prophylactic mastectomy, only two of the few women who explicitly mentioned this were from the highest risk category. The others were ineligible for prophylactic mastectomy and most of them even for genetic testing, due to their risk status. Counsellors should bear in mind that women might not adequately differentiate between management options for proven gene carriers, and the options and information that apply to their personal situation, as a consequence of wrong assumptions about risks.

Another way to address the effectiveness of counselling is to consider whether or not the level of reported distress is appropriate after counselling. We assume that the breast cancer risk information should elicit more responses of high distress among women with a relatively high risk, as long as it does not reach clinical levels. On the contrary, women with a relatively low risk should be reassured after receiving counselling. Indeed, the large number of women who spontaneously mentioned fear or worry about developing or dying from breast cancer seemed to have more frequently a moderately or highly increased breast cancer risk. Although there were relatively somewhat more low risk women who spontaneously stated that the risk did not elicit feelings of distress, some women who mentioned this had a relatively high risk. This might reflect a way of coping, and although the aim of the genetic counselling is probably not to scare women, we have to be careful to ensure that those women feel a need for risk management. Previous research has shown that the absence of distress might result in a lack of adherence to screening[123].

Apart from high or low levels of distress, quite a large number of women described their breast cancer risk as something that did not interfere with their daily lives, although it was frequently on their mind. This medium level of stress was also described by Vickberg,[124] who assessed the fears of women with breast cancer in a qualitative small-sample study. Probably, familial breast cancer is a theme with a fluctuating grade of salience; in the actual period of the occurrence of cancer in the family, or during genetic counselling, the issue is likely to

generate some amount of stress. For most women, if no cues are present, worries about familial breast cancer may not interfere with daily life. However, in the very period of counselling grief and painful cognitions that accompany family illness experiences may inevitably come to the fore, and should be addressed in the counselling process. It is interesting that positive as well as negative personal experiences affected the appraisal of the risk. Some women described witnessing family members surviving breast cancer and others related the risk to painful illness experiences. Furthermore, sometimes broadly similar experiences influenced the amount of perceived threat in a contradictory manner. For example, already having had breast cancer made women either feel safe from breast cancer, or self-confident about their resources to cope with a recurrent cancer, or made them feel more vulnerable of dying from recurring breast cancer. Women who mentioned either neutral or positively framed experiences with cancer also reported significantly more often a relatively low level of stress. Counsellors might be aware that experiences with cancer do not simply seem to add up to the experience of psychological distress. However, negative experiences were mentioned more frequently than positive experiences, especially among women who had had breast cancer.

Finally, in assessing the effectiveness of genetic counselling, we want to mention some women who expressed inaccurate risk beliefs even after counselling. Relatively many of them had not received a personal risk estimate, which might explain why the counselling had no correcting effect. In the current study a few lay beliefs about the heredity of breast cancer were detected, in concordance with earlier studies.[119;125] For example, some of the women reflected on their breast cancer risk in terms of certainty instead of probability. In a small sample study,[126] more than twenty percent of the women had reflected on their breast cancer risk in such a way. Furthermore, in another small sample study[127] thirty-four percent of participants from HNPCC families used a personal theory of inheritance to explain their certainty about inheritance. These strong convictions are probably a way of coping with the uncertainty of risk information.[127] In our sample, only seven women (6%) spontaneously reported that they certainly would develop breast cancer, or, on the contrary, were definitely safe from it. However, if women hold such strong prior beliefs about their risk, the risk communication process can hardly be effective without addressing such convictions and the accompanying assumptions.

A few limitations of this study should be mentioned. First, women with children were under-represented in our interview sample in comparison to the overall study population. As many counsellees mention acquiring knowledge about their childrens' risk as one of their prime motives for applying for genetic counselling,[128] the presence of children may alter women's perception of risk or the meaning of that risk. Secondly, it should be noted that we only recorded responses that were related to the personal risk information. For example, we

did not measure the amount of psychological distress with standardized measures; we only differentiated between women who spontaneously related their personal breast cancer risk to either stress or worry, or a lack of it.

There is an abundance of research that shows that people differ in the way they describe and interpret risk information.[129] The present study provides a vivid illustration of this phenomenon with regard to women receiving genetic counselling for breast cancer. Their responses reveal that the numerical or verbal magnitude of the risk is just one element of what the risk means to women; this is in itself insufficient as a tool for addressing the effectiveness of counselling. Accuracy applies just as well to the wider range of risk beliefs, stress and coping responses that determine what risk means in real life. Prior beliefs and expectations that women hold about their risk status and concomitant levels of stress should play a prominent role in the genetic counselling process in order for such counselling to achieve its aim; a well informed patient, who understands both risks and consequences and acts accordingly.

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4

Genetic counselling and the intention to undergo prophylactic mastectomy: effects of a breast cancer risk assessment

Genetic counselling and the intention to undergo prophylactic mastectomy: effects of a breast cancer risk assessment.
Van Dijk S, Otten W, Zoeteweij MW, Timmermans DRM, Van Asperen CJ, Breuning MH, Tollenaar RAEM, Kievit J.
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ABSTRACT

Introduction

Scientific reports suggest that women at risk for familial breast cancer may benefit from prophylactic mastectomy. However, few data are available about how women decide upon this clinical option, and in particular, what role an objective risk assessment plays in this. The purpose of the present study is to assess whether this objective risk information provided in genetic counselling affects the intention for prophylactic mastectomy. Additionally, the (mediating) effects of breast cancer worry and perceived risk are investigated.

Methods

A total of 241 women completed a questionnaire before and after receiving information about their familial lifetime breast cancer risk in a genetic counselling session.

Results

Path analysis showed that the objective risk information had a corrective effect on perceived risk (ß = .38; P = .0001), whereas the amount of breast cancer worry was not influenced by the counselling session. The objective risk information did not directly affect the intention for prophylactic mastectomy. The intention was influenced by perceived risk after counselling (ß = .23; P = .002), and by the pre-counselling levels of perceived risk (ß = .27; P = .00025) and breast cancer worry (ß = .32; P = .0001), i.e., higher levels of perceived risk and breast cancer worry imply a stronger intention for prophylactic mastectomy. A personal history of breast cancer did not directly influence the intention for prophylactic mastectomy, but affected women who had undergone a mastectomy as surgical treatment were more positively inclined to have a prophylactic mastectomy than women who had had breast-conserving therapy.

Conclusion

The impact of objective risk information on the intention for prophylactic mastectomy is limited and is mediated by perceived risk. Important determinants of the intention for prophylactic mastectomy were pre-counselling levels of breast cancer worry and perceived risk, suggesting that genetic counselling is only one event in the entire process of decision-making. Therefore, interventions aimed at improving decision-making on prophylactic mastectomy should explicitly address pre-counselling factors, such as personal beliefs and the psychological impact of the family medical history.

INTRODUCTION

It is estimated that 5-10% of breast cancer cases are linked to a breast cancer gene mutation.[130] Hereditary breast cancer might be suspected if the family history shows multiple cases of early-onset breast cancer, cases of male breast cancer, or cases of bilateral breast cancer, or if cases of breast and ovarian cancer occur within the same individual or family. For individuals from such families, genetic counselling is available at a family cancer clinic. Based on the family illness history, objective risk information can be provided so that clients can realistically appraise their own risk. Women with a relatively low risk may be reassured, while those with a higher risk can make informed decisions, such as deciding whether or not to undergo a prophylactic mastectomy.

The clinical option of prophylactic mastectomy remains controversial,[131] although evidence for a strong protective effect of prophylactic mastectomy for women with a familial history of breast cancer has been presented,[132] and, more specifically, for women with a BRCA1/2 mutation.[20;133] For instance, Meijers-Heijboer et al.[20] report that of 139 women with a BRCA1/2 mutation, 55% choose to undergo prophylactic mastectomy of whom none developed breast cancer, whereas 45% opted for an intensive-screening program of whom 12% developed breast cancer within 2.9 years of follow-up. In addition, prophylactic mastectomy seems to have positive psychosocial consequences: high levels of psychological morbidity and anxiety before surgery decreased significantly over time after sur-gery, whereas in women who declined prophylactic mastectomy a high anxiety level persisted.[29] This suggests that women may indeed benefit from prophylactic mastectomy, although women who have to deal with surgical complications might warrant psychological help.[134]

Only a few studies have reported on the decision making process on prophylactic mastectomy of high-risk women.[131] In a prospective study, Stefanek et al.[95] described that higher subjective risk estimates, biopsy history, and a higher level of breast cancer related worry might be associated with the decision to have a prophylactic mastectomy. In a cross-sectional study, Meiser et al.[64] investigated a large sample of unaffected women who were awaiting their initial appointment for genetic counselling. The intention to choose for prophylactic mastectomy was predicted by a very high level of breast cancer anxiety and an overestimation of the risk to develop breast cancer, whereas the objective risk of developing breast cancer did not predict intention for prophylactic mastectomy. However, hardly any data are available about the possible role of the objective risk assessment in the decision making process.

The current study presents prospective data on whether the intention to undergo prophylactic mastectomy is influenced by (1) the objective level of risk as provided in genetic counselling; (2) pre- and post-counselling levels of breast cancer worry and perceived risk; and (3) a personal history of breast cancer.

Three features distinguish the present study from other studies of prophylactic surgery decision making, that is, (a) the comparison of a pre- and post-counselling survey; (b) the inclusion of women with a history of breast cancer; and (c) the broad study population inclusive of both low- and high-risk women.

METHODS AND MATERIALS

Participants and procedure

Data were collected within the framework of a larger study on risk perception and decision making by women at risk for hereditary breast cancer. For the integrative study ethical approval was obtained from the hospital's research ethics committee. Participants were at least 18 years of age with a family and/or a personal history of breast cancer who applied for genetic counselling at the Department of Clinical Genetics of the Leiden University Medical Center. Referrals for genetic counselling on breast cancer were based on current national guidelines.[2] In the first (and sometimes only) consultation a clinical geneticist interviewed the women applying a standard counselling protocol, and recorded their family medical history. Information was provided about the hereditary transmission of BRCA1 and BRCA2, and about surveillance, if applicable. Genetic testing was offered if there was a probability of mutation detection of about 10% or more. If sufficient medical information was available, a familial lifetime risk of developing breast cancer was estimated.[5] Four risk categories were distinguished; (1) general population risk, i.e., around 10%; (2) 10-15%; (3) 15-30%; and (4) 30% or more. The standard protocol of the first consultation did not cover any discussion about pros and cons of prophylactic mastectomy. If supplementary medical information had to be collected or if genetic testing was applied, further appointments were scheduled (53% of the women). In general, for women with a relatively low risk, and who were not eligible for genetic testing, no further appointments were made (47% of the women). (Further appointments fell outside the scope of the data reported here, as all measures were conducted before and after the first consultation.)

All new referrals for breast cancer counselling from November 1998 until July 2001 were informed about this study by letter two weeks before their first appointment. Eligible women who returned the written consent form that accompanied the informative letter received the first questionnaire by mail prior to their first appointment. Immediately after this counselling session, a second questionnaire was sent out, irrespective whether follow-up appointments were scheduled. Reminder letters were sent, if appropriate. Women were excluded from the study if they had not received information about their familial lifetime risk during the counselling session, had lost both breasts due to previous surgery, had distant metastases, or if they had an insufficient literacy in the Dutch language.

Measures

Sociodemographic characteristics

Information on personal history of breast cancer (i.e., unaffected or affected women), surgical procedure to treat breast cancer (i.e., mastectomy or breast-conserving therapy), age, educational level, marital status, and number of children was collected.

Breast cancer related worry

In both questionnaires, we assessed breast cancer related worry with two items of the breast cancer worries scale.[63] These items were as follows: "During the last two weeks, how often did you worry about developing breast cancer yourself (again)?", and "During the last two weeks, how often did your worries about breast cancer interfere with your daily activities?" on a 4-point scale ranging from 1 (almost never) to 4 (almost all the time). The mean of both items was calculated (scores ranged from 1 to 4), with higher scores indicating a higher level of breast cancer related worry. The reliability of this scale was satisfactory (pre-counselling: $\alpha = .66$; post-counselling: $\alpha = .73$).

Perceived risk of breast cancer

Perceived risk was assessed in both questionnaires with a comprehensive scale that included various aspects of perceived risk: (1) relative perceived lifetime risk of getting breast cancer was measured with the item "Compared to the average Dutch woman, my risk of developing breast cancer (again) is 1 'very much lower', through 4 'equal to', to 7 'very much higher'", (2) numerical perceived lifetime risk of getting breast cancer was measured with the item "My risk of developing breast cancer (again) is ... out of 100", and (3) verbal risk with the item "Independent of my actual risk, I feel my risk of developing breast cancer (again) is 1 'very low' to 7 'very high'". Perceived risk was measured in both questionnaires. Because the range of items varied, standardised scores of the separate items were used. The pre-counselling measures of perceived risk were each z-transformed. The post-counselling measures were similarly standardised also using the mean and standard deviation of the corresponding pre-counselling items. The mean of the three standardised items constituted the perceived risk scale. The scale had an adequate reliability (pre-counselling: $\alpha = .78$; post-counselling: $\alpha = .73$). Larger values on the scale indicated a higher perceived risk.

Intention for prophylactic mastectomy

In the second questionnaire the intention for prophylactic mastectomy was measured with the item "Do you expect to decide for preventive surgery of your breasts" on a 7-point scale ranging from 1 'certainly not' to 7 'yes, certainly'. This item was considered as potentially confronting to women. Therefore, the

intention for prophylactic mastectomy was measured only after the counselling session.

Statistical methods

The SPSS 10.0 statistical package was used to analyse the data. Path analysis was applied to examine the research questions with several multiple regression analyses.[135] In the first phase we checked whether the objective risk provided in the counselling was related to either having had breast cancer (no or yes), or to the pre-counselling measures of perceived risk and breast cancer worry.

In the second phase, we applied two multiple regression analyses to assess whether there was a change in perceived risk respectively in worry, and, if so, which factors predicted the change. In order to do so, the change scores between the pre- and post-counselling scales of (a) perceived risk and (b) worry were calculated by subtracting the pre-counselling value from the post-counselling value. Thus, a positive value indicated increased worry or perceived risk, and a negative value implied decreased worry or perceived risk after the counselling session. These two change scores served as outcome variables. Four predictor variables were used in each analysis: (a) having had a personal history of breast cancer, (b) the objective risk information, and the pre-counselling measures of (c) perceived risk, and (d) worry. The pre-counselling measures of perceived risk and worry were included, because the possible range of change is determined by the pre-counselling values. However, the interpretation of predictive effects of the pre-counselling measures on the change measures is hampered by the fact that the pre-counselling measure is a constituent part of the change score. Therefore, we will not describe the relations between the pre-counselling measures and the corresponding change scores in the path analysis. (However, Pearson's correlations are presented in Table 3).

In the third phase, the intention for prophylactic mastectomy was predicted from all previous variables. In this phase we also wanted to examine whether the overall model to predict intention for prophylactic mastectomy would differ between women from the highest risk category (i.e., > 30%) and women in the lower risk category (i.e., < 30%). The choice for this dichotomy was based on the fact that only women in the highest risk category will be eligible for genetic testing as the chance to harbour a BRCA mutation must be sufficiently high. Two-way interaction variables with risk status (multiplication of centred scores) were included in the analysis (e.g. interaction between worry, pre-counselling and the change score, and risk status; perceived risk, pre-counselling and the change score, and risk status; and breast cancer history and risk status).

To check whether the observed relations in phase 1 to phase 3 would differ between affected and unaffected women, two-way interaction variables with breast cancer history were included in the analyses in a similar way as described above for risk status interactions (e.g. interaction between worry, pre-counselling

and the change score, and breast cancer history; perceived risk, pre-counselling and the change score, and breast cancer history; and objective risk and breast cancer history). In addition, for affected women we examined whether the surgical procedure to treat their breast cancer served as an additional predictor in the phase 1 to phase 3 regression analyses.

For each multiple linear regression analysis, we report the extent of variance in the criterion explained by the regression (R^2), the significance of the explained variance (F-test), and which predictors significantly contributed to this explained variance (ß-weights). A P-value < .05 was considered to indicate statistical significance.

RESULTS

Study population

Of the 454 women who met the inclusion criteria 350 consented to participate in the study (response rate 77.1 %). Of these 350, 44 women returned their informed consent just at the first counselling session, instead of mailing it beforehand. Therefore, they could not complete the pre-counselling questionnaire. Another 3 were excluded from the analysis because they did not return the pre-counselling questionnaire in time, whereas 13 women did not complete all items of the pre-counselling questionnaire. Finally, 30 women did not return the post-counselling questionnaire, and 19 women did not complete all items of the post-counselling questionnaire. This left 241 women for our analyses.

T-tests and chi-squares showed that the women who did not complete the pre- or the post-counselling questionnaire did not differ from women who did complete all items of both questionnaires on the measures relevant for this study (objective risk, perceived risk, breast cancer worry, intention mastectomy, personal history of breast cancer, known mutation running in the family, age, marital status, educational level). On only one variable these groups differed. Women who did not complete the pre- or post-counselling questionnaire reported having children more frequently (P = .025) than women who did complete all items of both questionnaires.

Sociodemographic characteristics

Table 1 summarises the sociodemographic and medical variables of the study population. The mean age of the group was 41.4 years (range 19-71 years; SD 11.0 years). The majority of the women were married or co-habitating and had one or more children. Almost half of the women were educated to high school or university level. A small minority of the women had at least one close family member in whom a BRCA1 or BRCA2 mutation had been detected.

Table 1. Sociodemographic and medical variables of the study population

	N	%
Variable		
Sociodemographic		
Age		
< 30 years	39	15.9
30-39 years	64	27.1
40-49 years	82	33.5
50+ years	60	24.5
Marital status		
Married or living together	198	80.8
Not married or living together	47	19.2
Children		
Yes	166	67.3
No	79	32.7
Educational level		
High school or university	98	40.0
Less than high school	147	60.0
Medical		
Breast cancer history		
Yes	77	31.4
No	168	68.6
Objective risk		
10% (population risk)	11	4.5
10-15%	23	9.4
15-30%	73	29.8
> 30%	138	56.3
BRCA detected in family		
Yes	25	10.2
No	220	89.8

Description of the outcome and predictor variables

Of the 241 women, 168 were healthy and 73 had been treated for breast cancer (36 mastectomy, 36 breast-conserving therapy, 1 unknown). In the counselling session, more than half of the women (N = 136) were classified into the highest risk category (i.e., a risk of 30% or more to develop breast cancer; see Table 1),

Table 2. Worry and risk perception pre-counselling and post-counselling (means and standard deviations)

Variable	Pre-counselling*	Post-counselling*
Breast cancer related worry (scale)	1.70 (.65)	1.72 (.64)
How often did you worry about developing breast cancer yourself (again)?(1-4)	2.01 (.82)	2.07 (.83)
How often did your worries about breast cancer interfere with your daily activities? (1-4)	1.32 (.62)	1.32 (.61)
Perceived risk (scale)	.00 (.83)	- .24 (.81)
Compared to the average Dutch woman, my risk of developing breast cancer (again) is (1-7)	5.83 (1.21)	5.68 (1.16)
My risk of developing breast cancer (again) is … out of 100	54.93 (21.31)	43.86 (21.03)
Independent of my actual risk, I feel my risk of developing breast cancer (again) is (1-7)	4.72 (1.15)	4.63 (1.23)

Table 3. Pearson correlation between the predictor and the outcome variables (*P < .05, **P < .01, ***P < .001)

Variable		1	2	3	4	5	6
1	Breast cancer (no/yes)						
2	Perceived risk (before)	-.162**					
3	Worry (before)	.104	.389***				
4	Objective risk	-.063	.174**	.098			
5	Perceived risk (change)	.187**	-.429***	-.132*	.286***		
6	Worry (change)	.122	-.151*	-.407***	-.017	.240***	
7	Intention Mastectomy	.071	.284***	.356***	.158*	.103	.000

and were consequently eligible for genetic testing. The objective risk was not related to any of the sociodemographic variables. Not surprisingly, women with a known BRCA1 or BRCA2 mutation in the family had a significantly higher objective risk, than women without a known BRCA1 or BRCA2 mutation running in the family (P = .0001).

Table 2 depicts the mean values of the individual items used to measure breast cancer worry and perceived risk. The majority of the women had no excessive breast cancer related worry either before or after counselling (pre-counselling M = 1.70; post-counselling M = 1.72). Most women stated that they almost never or only sometimes worried about developing breast cancer (pre-counselling 73.8%; post-counselling 72.2%). Similarly, almost all women reported that worries about breast cancer almost never or only sometimes interfered with their daily activities (pre-counselling 94.2%; post-counselling 94.2%).

The perceived risk prior to and after the counselling session was high. The vast majority of the women (pre-counselling 89.2%; post-counselling 86.7%) thought their risk to be higher than the average Dutch woman's risk. In addition, approximately half of the women (pre-counselling 60.2%; post-counselling 55.2%) stated that, independent of their actual risk, they felt they had a high risk of developing breast cancer (again). Finally, most of the women perceived their numerical risk to develop breast cancer (again) to be 30% or more (pre-counselling 86.3%; post-counselling 74.7%).

Figure 1. Intention to undergo prophylactic mastectomy (percentages)

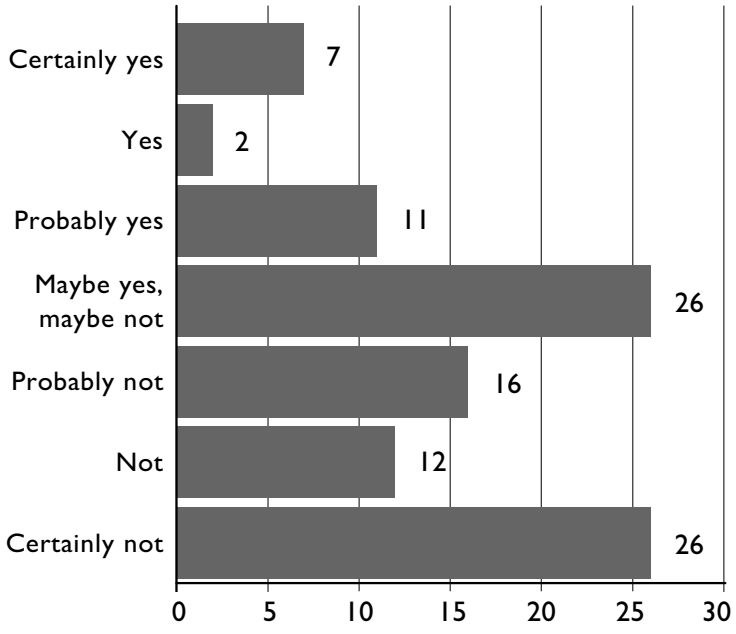
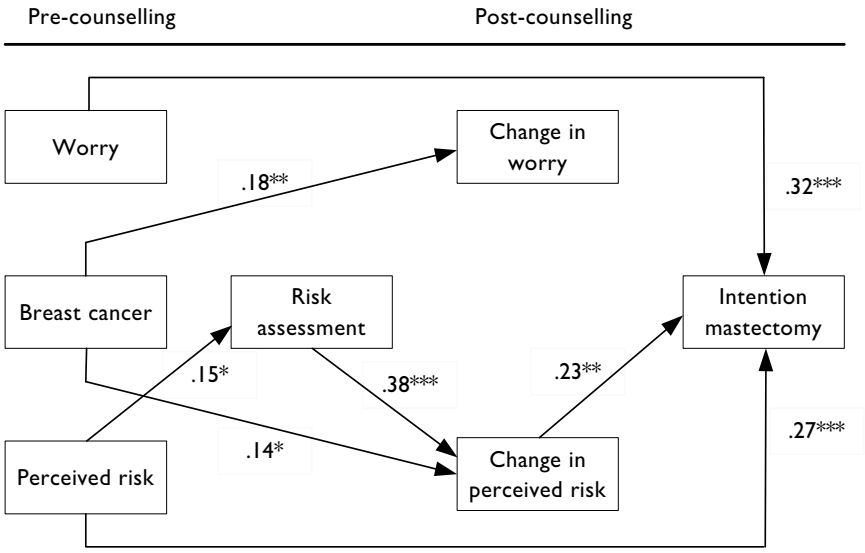


Figure 1 displays the data on the intention to choose for prophylactic mastectomy. Overall, the majority of the women certainly or probably expected to decide against prophylactic mastectomy (54.4%), whereas 19.9% certainly or probably expected to decide for prophylactic mastectomy. A quarter of the women was undecided (25.7%).

Figure 2. Full regression model with Beta's (*P < .05, **P < .01, ***P < .001)



Description of the path analysis

Path analysis was applied to examine our research questions. Below, each multiple regression analysis is described separately. Table 3 shows the zero-order Pearson's correlations between the predictor and outcome variables; Figure 2 depicts the combined results.

Phase 1: Was the objective risk information related to pre-counselling variables?

Neither the pre-counselling measure of breast cancer related worry (P = .53), nor having had a primary breast tumour (P = .51) was associated with the objective risk information. However, the perceived risk women reported before the consult was positively related to their actual risk (ß = .15; P = .037). The model was significant in explaining objective risk (F(3,237) = 2.71, P = .046, R^2 = .033).

Phase 2a: Did perceived risk change after counselling and which factors predicted such a change?
Overall, perceived risk decreased after the counselling session (constant = -1.33; P = .0001). As expected, the objective risk information influenced this change in perceived risk (ß = .38; P = .0001). Women with a relatively low objective risk reported a lower perceived risk after counselling, whereas women with a relatively high objective risk remained at a high level of perceived risk after counselling. This means that after counselling women shifted towards a more accurate perceived risk. To illustrate this point, we looked at the numerical risk estimates that women provided. Before the counselling, 83% of the low-risk women overestimated their risk and after counselling 56% overestimated their risk. In contrast, of the high-risk women 89% correctly identified their high risk status before and after counselling. The change in perceived risk was also predicted by having had breast cancer (ß = .14; P = .015). Unaffected women showed a stronger decrease in perceived risk after counselling than women with a history of breast cancer. The regression model was significant in explaining the change in perceived risk ($F(4,236) = 29.80$, P = .0001, $R^2 = .34$).

Phase 2b: Did the amount of breast cancer worry change after counselling and which factors predicted such a change?
Overall, breast cancer related worry slightly increased after the counselling session (constant = .56; P = .001). The objective risk information as provided in the counselling did not influence the change in breast cancer worry after counselling (P = .61). Having had a primary breast tumour (ß = .18; P = .003) predicted the change in worry. Women who had had a primary breast tumour reported a higher level of breast cancer worry after counselling, whereas unaffected women showed no change in the amount of worry after counselling. The regression model was significant in explaining the change in breast cancer worry ($F(4,236) = 14.35$, P = .0001, $R^2 = .20$).

Phase 3: Which variables predict the intention for prophylactic mastectomy?
Pre-counselling levels of breast cancer worry (ß = .32; P = .0001) and perceived risk (ß = .27; P = .00025) both independently predicted the intention for prophylactic mastectomy. Women who had higher prior levels of breast cancer worry and/or a higher prior perceived risk reported a stronger intention to choose for prophylactic mastectomy. Intention for prophylactic mastectomy was also predicted by the change in perceived risk after the counselling session (ß = .23;
P = .002); women who shifted towards a lower perceived risk, reported a weaker intention for prophylactic mastectomy. As phase 2a showed, this change in perceived risk was influenced by the objective risk information. Although the objective risk did not have a direct effect on the intention (P = .78), the objective

risk information had an indirect effect by adjusting perceived risk, which in turn affected the intention.

The change in worry after the counselling session did not add to the prediction of the intention for prophylactic mastectomy (P = .082). Finally, having had a primary breast tumour had no direct influence on the intention for prophylactic mastectomy (P = .67). However, as shown in phase 2a, having had breast cancer influenced the change in perceived risk and, consequently, had an indirect effect on the intention for prophylactic mastectomy. The full regression model was significant in explaining the intention for prophylactic mastectomy ($F(6,234) = 10.99$, $P = .0001$, $R^2 = .22$).

Interaction effects of risk status on intention for prophylactic mastectomy

The inclusion of the interaction variables with risk status did not affect the overall model as depicted in Figure 2, as all the same main effects remained significant at a similar level. In addition, none of the interaction variables reached significance (P > .102), indicating that the same model applied to low- as well as to high-risk status women.

Interaction effects of breast cancer history and breast cancer surgery

No effect was observed for the interaction variables with breast cancer history in the phase 1 to phase 3 regression analyses, indicating that the relations depicted in Figure 2 similarly apply to healthy and affected women.

For affected women, the kind of surgical procedure to treat their breast cancer did not predict the objective risk estimate, nor the change in perceived risk or breast cancer worry. However, the intention for prophylactic mastectomy was predicted by the kind of surgical procedure (ß = .22; P = .040): women who had had a mastectomy showed a stronger intention to have a prophylactic mastectomy of the contralateral breast than women who had had breast-conserving surgery. Thus, for affected women the kind of surgical procedure served as an additional predictor, next to the pre-counselling levels of perceived risk and worry, and the change in perceived risk after counselling.

DISCUSSION

The impact of the objective risk information provided in genetic counselling on the intention to opt for prophylactic mastectomy is relevant, but limited. First, the objective risk information had an indirect effect on the intention through the perceived risk of developing breast cancer: counselling a lower objective risk decreased the perceived risk after counselling, which related to a weaker intention to opt for prophylactic mastectomy. Second, both stronger breast cancer

worry and a higher perceived risk about developing breast cancer before counselling promoted the intention for mastectomy.

The finding that perceived risk has a stronger impact on preventive intentions than objective risk is consistent with studies assessing those relations before the counselling.[64;95] The present study shows that the impact of the objective risk information on the intention for prophylactic mastectomy is mediated through the change in perceived risk after counselling. These results stress the importance of assessing women's perception of the risk in order to understand their decisions and behaviour regarding prophylactic mastectomy (see also[29]).

The present study clearly shows that the objective risk information had a corrective effect on perceived risk, but it was a moderate impact in terms of explained variance: fourteen percent of the variance in the change of perceived risk was due to the objective risk information. This points at other factors in- or outside the counselling session that possibly affect the change of perceived risk. All in all, our results are in line with previous studies showing that genetic counselling generally improves perceived risk, but often women tend to report an inaccurate risk of developing breast cancer even at one-year follow-up.[41;52;136]

High levels of worry and perceived risk before women approach the geneticist strongly related to the intention for prophylactic mastectomy. This supports the notion that the counselling is not the onset of deliberations regarding prophylactic mastectomy, but an element in an earlier started and ongoing process. The results even suggest that the objective risk information provided in the counselling may be a relatively small event in this process of decision making. This fits recent acknowledgements that pre-counselling factors like past cancer stressors are important determinants for subsequent distress and behaviour.[66;67;125;137] The personal experience of the counsellee, including concomitant fears and emotional beliefs, is an essential element of the counselling interaction. Only if this experience and its emotions are discussed openly and understood, will it be clear to both counsellor and counsellee what the full scale of the problem is, and to what extent objective risk assessment may or may not solve this problem.

About a third of the women who applied for genetic counselling in the present study had had a primary breast tumour. Breast cancer history had no direct impact on the intention for prophylactic mastectomy: affected and unaffected women had the same, somewhat negative, intentions. Moreover, the interaction analyses showed that the same relations applied for both healthy and affected women. This corroborates the findings of Julian-Reynier et al.,[138] that affected women did not differ from healthy women regarding their attitude towards the acceptability of prophylactic mastectomy after multivariate adjustment. However, for affected women the kind of surgical procedure to treat their breast cancer had a direct impact: women who had undergone a mastectomy were more positively inclined towards a prophylactic mastectomy of the contra-

lateral breast than women who had had breast-conserving therapy. Probably, uncertainty reduction and cosmetic reasons do not only apply to the decision how to treat breast cancer, but also to preventive management.

Nonetheless, in the present study breast cancer history did have an indirect effect through risk perception on the intention. Healthy women showed a stronger decrease in perceived risk than affected women, and a decreased risk perception was related to a weaker intention. Affected women were also more worried after counselling, although this did not influence the intention. In contrast, a recent study[54] did not find differences on perceived risk nor worry between affected and unaffected women. An explanation for the present findings is that the recurrence risk of breast cancer constitutes a possible topic in the counselling session. This might induce distress and a sense of vulnerability in affected women who may have felt relatively safe after having had breast cancer.

A few limitations of this study should be noted. First, we want to mention that a relatively large proportion of respondents who provided written informed consent for the study did not complete both questionnaires, mainly due to logistic problems. However, women who did not complete the questionnaires were comparable to women who did. As a consequence, we think the results are generalisable to the population of women that seek genetic counselling.

Secondly, one could view the use of intention instead of actual behaviour as a restriction. The actual use of prophylactic mastectomy will probably fall below levels of intended use.[139] However, the goal of the present study was to prospectively assess the impact of objective risk information on thoughts about prophylactic mastectomy for all women applying for genetic counselling for breast cancer; thus not restricting the sample to either unaffected women or high-risk women who are eligible for genetic testing. The present sample probably covers the variety of women that seek genetic counselling now that hereditary breast cancer and genetic testing have become a topic that receives a lot of media attention. Our data suggest that for both low- and high-risk women their intention is not clearly guided by their objective risk, although only the latter women are eligible for DNA testing, and possibly prophylactic mastectomy. This points at the possibility that women at a lower risk for breast cancer may have similar desires concerning their risk management as women with a very high risk.[140] The effect of DNA testing results on high-risk women's actual decisions regarding prophylactic mastectomy and low-risk women's risk management beliefs and behaviours, will be explored in other papers.

Third, in our study we confined genetic counselling to providing information about the familial lifetime risk to develop breast cancer. This does not acknowledge the interactive features and the many other topics and goals that characterise the counselling process, which may also affect subsequent perceptions and behaviours.[141] The effect of breast cancer history on worry after counselling illustrates this point: apparently, an element other than the objective risk

information provided in the counselling increased the worry in affected women relative to unaffected women.

The main advantages of the present study concern the diversity of the participants, and the prospective design. Most importantly, it shows (a) the relevant, but limited impact of objective risk information on post-counselling deliberations, and (b) the major impact of pre-counselling factors on these deliberations. Healthcare professionals should be aware of the specific limitations of counselling, and of the potential impact of women's personal experiences and beliefs concerning breast cancer. These pre-counselling factors should be explicitly addressed in the genetic counselling protocol, and should be a guiding element in the process of providing information.

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5

Variants of Uncertain Clinical Significance as a result of BRCA1/2 testing: The impact of an ambiguous breast cancer risk message

Variants of Uncertain Clinical Significance as a result of BRCA1/2 testing: The impact of an ambiguous breast cancer risk message.
Van Dijk S, Van Asperen CJ, Jacobi CE, Vink GR, Tibben A, Breuning MH, Otten W. *Genetic Testing* 8: 2004; 235-239

ABSTRACT

Introduction

The identification of an increasing number of Variants of Uncertain Clinical Significance (VUCS) in genetic testing for hereditary breast cancer poses serious problems for genetic counselling, as no data are available about the psychosocial impact of discussing such an unclear risk message. The current study is the first to present data on how test applicants actually understand and cope with such a result if communicated by a geneticist.

Methods

We compared 10 women who received a VUCS result with 34 women who carried the deleterious mutation, 37 women who did not carry the deleterious mutation or 'true negatives', and 160 women who received a so-called uninformative result before and after test disclosure.

Results

Women, with whom a VUCS result was discussed, reported quite a high level of comprehension of the result. In addition, compared with the pre-test measures, they did not report a higher level of perceived risk (P = .58) and even reported a decrease in breast cancer distress (P = .03). They were very comparable to women who received an uninformative result on all post-disclosure measures.

Conclusion

Our results suggest that discussing a VUCS result in genetic counselling does not give rise for concern.

INTRODUCTION

An emerging problem in DNA testing is the increasing number of missense and intronic variants detected as a consequence of the growing technical ability of DNA diagnostic laboratories to sequence disease genes. The risk consequences of those sequence alterations are often unknown, for which reason they are designated as Variants of Uncertain Clinical Significance (VUCS). It is estimated that 13% or 12.5% of the patients who have full sequence analysis of BRCA1 and BRCA2 receive a VUCS result (respectively[15]; personal communication, Myriad/A.M. Deffenbaugh), and that 32% and 53% of all detected BRCA1 and BRCA2 mutations respectively is a VUCS (Breast cancer Information Core, http://research.nhgri.nih.gov/bic/). Hence, a VUCS is detected in a significant proportion of tested individuals. Major differences in whether or not these VUCS results are discussed with counsellees exist between centers.[142;143] Moreover, Petrucelli et al.[142] reported that only 63% of geneticists believed that their counsellees understood the meaning of a VUCS result. Furthermore, they proposed that if patients are found to be carrier of a VUCS, they might experience anxiety and frustration. However, no data are available about whether test applicants actually do understand a VUCS result and about the psychological impact of this result.

In a large prospective study on the psychosocial impact of genetic counselling for familial breast cancer, we could assess the impact of VUCS in the BRCA1 or BRCA2 genes by comparing women who received a VUCS result with three distinct groups of test applicants: (1) counsellees in whom a deleterious BRCA1/2 gene mutation was detected (i.e., a pathogenic BRCA1 or BRCA2 mutation, which is associated with a lifetime risk of 24 to 84% for breast cancer and 11 to 54% for ovarian cancer for unaffected women,[8-11] (2) counsellees who tested negative for a BRCA1/2 mutation, that had been detected previously in one or several family members (i.e., a true negative result), and (3) counsellees who tested negative for a BRCA1/2 mutation, in the absence of a known BRCA1/2 familial mutation (i.e., an uninformative test result, regarding themselves or an affected family member who took the test on their behalf.)

From a clinical point of view, women who receive an uninformative or a VUCS result are comparable in several respects. For both groups clinical management recommendations are based on the pedigree-risk estimation and additional testing of healthy family members is not routinely offered.[143] However, for both deleterious mutation carriers and women who receive a VUCS result, a mutation is actually detected, whereas for women with uninformative results this is not the case. This might be an important difference. For example, in a study on the impact of cystic fibrosis screening, individuals who tested positive for the mutation, reported feeling less healthy after disclosure, despite the fact that the mutation had no health consequences for themselves.[144]

PARTICIPANTS AND METHODS

Data collection and genetic counselling

Ethical approval was obtained for the integrated study from the hospital's research ethics committee. The study comprised of all women who were referred for familial breast cancer counselling in the period 1998-2002, and who met the inclusion criteria of being at least 18 years old, and of not having received genetic counselling elsewhere. Referrals for genetic counselling on breast cancer were based on current national guidelines.[2;121] These guidelines specify how many first or second grade family members should have developed breast cancer either before or after the age of 50, as a prerequisite of referral to a cancer clinic. In the first consultation genetic testing was offered for individuals if a BRCA mutation had been detected within the family previously, and for individuals in which the probability of mutation detection was about 10% or more; usually an affected family member. The possible results of DNA testing, including the detection of a VUCS, were mentioned before blood withdrawal.

When the test results became available, counsellees were invited to an in-person disclosure counselling session of either their own DNA-test result or the result of their affected family member. As testing of relatives of an uninformative or a VUCS proband is ineffective, healthy relatives had normally no access to an additional test for themselves. Hence, an uninformative result or a VUCS result of an affected proband was the definite result for healthy counsellees. Commonly, a final familial lifetime risk of developing breast cancer was estimated.[5] Four risk categories were distinguished: (1) general population risk, i.e., around 10%; (2) 10-15%; (3) 15-30%; and (4) 30% or more. For all women who received either an uninformative test result or a VUCS test result and who had a sufficient strong family history (lifetime risk > 20%) intensive surveillance was recommended, that is, annual mammography screening, breast examination by a physician and monthly breast self-examination. In accordance with current policies for surveillance[145] ovary screening was offered as well, if cases of ovarian cancer were present in the family history. Intensive breast and ovary screening was also available for women who proved to have the deleterious mutation. Counsellees were provided with a letter, which summarized all the constituted information.

Measures

We used the SPSS 11.5 package to conduct ANOVAs to assess: (1) comprehensibility (i.e., mean of two items about how comprehensible and clear the test related information was according to the counsellees after disclosure on a five-point scale; $\alpha = .71$), and MANOVAs with repeated measures to assess differences before and after disclosure on (2) perceived breast cancer risk (i.e., relative risk of developing (another) breast cancer on a seven-point scale ranging

Table 1. Sociodemographic and medical variables of the study population (N = 273)

	VUCS result N = 10	BRCA mutation carrier N = 34	True negative result N = 37	Uninformative result N = 160
	N (%)	N (%)	N (%)	N (%)
Variable				
Sociodemographic				
Age				
< 30 years	3 (30)	4 (12)	5 (14)	13 (8)
30-39 years	1 (10)	14 (41)	10 (27)	43 (27)
40-49 years	3 (30)	7 (21)	10 (27)	67 (42)
50+ years	3 (30)	9 (26)	12 (32)	37 (23)
Marital status				
Married or cohabiting	8 (80)	30 (88)	30 (81)	139 (87)
Not married or cohabiting	2 (20)	4 (12)	7 (19)	21 (13)
Children				
Yes	6 (60)	23 (68)	32 (86)	124 (78)
No	4 (40)	11 (32)	5 (14)	36 (22)
Educational level				
High school or university	3 (30)	8 (24)	9 (25)	51 (33)
Less than high school	7 (70)	25 (76)	27 (75)	104 (67)
Medical				
Breast/Ovarian cancer				
Yes	5 (50)	20 (59)	1 (3)	84 (53)
No	5 (50)	14 (41)	36 (97)	76 (47)
Breast cancer risk*				
< 15%	-	-	37 (100)	17 (12)
15-30%	3 (30)	-	-	60 (40)
> 30%	7 (70)	34 (100)	-	72 (48)
Mutation				
BRCA1	5 (50)	26 (76)	27 (73)	-
BRCA2	5 (50)	8 (24)	10 (27)	-
Prior mutation in family				
Yes	1 (10)	16 (47)	37 (100)	-
No	9 (90)	18 (53)	-	160 (100)

from 1 'very much lower', through 4 'equal to', to 7 'very much higher'), and (3) breast cancer specific distress (Impact of Events Scale; intrusion subscale[74]; α = .88).

RESULTS

Patient characteristics

Of the 850 women who met the inclusion criteria, 658 women consented to take part in the study (response rate 77.4%). They were asked to complete questionnaires before and one month after receiving the summary letter. Not all women who consented to take part in the study were eligible for DNA testing, or chose to have a test. In this report we will only present data of the women who received DNA-test results. In total 315 participants received the result of a DNA test in their summary letter. Nineteen women had lost both breasts due to breast cancer surgery and/or prophylactic surgery, and one woman had a prophylactic ovariectomy in the period in between the measurements. As these surgical proce-dures are assumed to affect not only the objective cancer risks, but also the perceived risk and breast cancer distress, we excluded these women from the analyses. Of the remaining 295 participants, we obtained from 242 women both a pre and post-disclosure questionnaire. One woman was additionally excluded from the analyses, because she tested negative on the VUCS detected earlier in her third-grade family members. In total, 241 women were included.

T-tests and chi-square tests between women who decined participation and women who did consent to the study revealed no differences for either age, having had a personal breast or ovarian cancer history, objective risk in the summary letter, execution of DNA testing, or whether or not a mutation was detected within the family previously.

Of 241 women available for analyses, 10 received a VUCS result (4.1%), 34 were carriers of the deleterious BRCA1/2 mutation (14.1%), 37 were true negatives (15.4%), and 160 women received an uninformative test result (66.4%) (Table 1). Of the VUCS-carriers, six were affected with breast or ovarian cancer. With three unaffected counsellees a VUCS result in a blood sample provided by their affected mother was discussed. In addition, one healthy woman tested positive on the same VUCS detected previously in her deceased father.

Women who received a VUCS result did not differ from all other groups of women regarding: age, having children, marital status, or educational level. In addition, they did not differ from uninformatives and deleterious mutation carriers with regard to whether or not they had a previous history of cancer. Although the mean objective risk after counselling (i.e., 10-15%, 15-30%, >30%) for women who received a VUCS result tended to be somewhat higher than for

Table 2. Perceived risk and breast cancer specific distress before and after test disclosure

				Effect disclosure	
	N	**Pre-disclosure**	**Post-disclosure**	**F**	**P**
Perceived risk (1-7)					
BRCA Mutation (deleterious)	34	5.79 (1.25)[a]	6.79 (.54) [c]	22.47	.0001
True Negative	36	5.67 (1.31) [a]	3.33 (1.22) [a]	129.54	.0001
Uninformative result	148	5.74 (1.04) [a]	5.42 (1.19) [b]	10.50	.001
VUCS result	9	6.11 (.93) [a]	5.89 (1.17) [b]	.29	.588
Distress (0-35)					
BRCA Mutation (deleterious)	34	11.85 (8.56) [b]	13.27 (9.11) [c]	1.60	.207
True Negative	37	7.08 (6.83) [a]	5.84 (7.24) [a]	1.35	.246
Uninformative result	157	12.47 (7.91) [b]	10.13 (7.59) [b]	20.29	.0001
VUCS result	10	11.80 (11.82) [ab]	7.30 (6.87) [ab]	4.79	.03

[abc] If in the column pre-disclosure or post-disclosure groupmeans do not share a similar superscript they differ significantly at $P < .05$ level.

women who received an uninformative result, and lower than for deleterious mutation carriers (Table 1), those differences did not reach a significant level (resp. P = .11; P = .08). However, women who received an uninformative test result had a significantly lower objective risk after counselling than women who carried the deleterious mutation (t = 10.74; P < .0001).

Comprehensibility of the test result

After disclosure the overall level of reported comprehensibility (scores could range from 1 to 5) was very high, but significant differences between the four groups were observed (F = 5.87, P = .001), with true negatives reporting a significantly better comprehensibility of the information (M = 4.91, SD = .37) than all other groups of test applicants. Women with a VUCS result reported the lowest scores (M = 4.13, SD = .98), although they did not differ significantly from either deleterious mutation carriers (M = 4.53, SD = .52) or uninformatives (M = 4.42, SD = .70).

Perceived breast cancer risk before and after disclosure

A significant disclosure by groups interaction effect was observed for perceived breast cancer risk (F = 44.47, P < .0001; Table 2). Before test disclosure, the four groups did not differ on perceived risk (F = .40, P = .75). However, a significant difference between groups was observed after disclosure (F = 58.12, P < .0001). True negatives and deleterious mutation carriers then differed significantly from all other test applicants, with deleterious mutation carriers reporting the highest perceived risk and true negatives having the lowest perceived risk. Uninformatives did report a significant decrease in perceived risk, whereas women with a VUCS result did not. However, the level of perceived risk of both groups was comparable after disclosure.

Breast cancer distress before and after disclosure

Also for level of breast cancer distress we found a significant disclosure by groups interaction effect (F = 3.78, P = .011; Table 2). Before test disclosure, groups differed already (F = 4.51, P = .004), with true negatives reporting a significantly lower level of distress than the other groups and the uninformatives reporting the highest level of distress. After disclosure, a significant difference between groups was again observed (F = 5.93, P = .001), with true negatives remaining at a very low level of distress. However, compared to the pre-disclosure measures, deleterious mutation carriers reported a similar high level of distress after disclosure, whereas women with either a VUCS, or an uninformative result showed a decrease in breast cancer distress. The latter groups did not differ on distress after disclosure.

DISCUSSION

Although concern has been expressed about the possibility that communicating a VUCS result might cause confusion and anxiety, we did not find indications for such adverse effects. We hypothesised that receiving a VUCS result might be similar to having a deleterious mutation, because in both cases a mutation is actually present. However, women who received a VUCS result seemed to be more comparable to women who received an uninformative test result. Women with an uninformative result and women with a VUCS result did not differ with regard to their self-reported comprehensibility of the information, perceived breast cancer risk and level of psychological distress after test disclosure. Both groups of women receive a relatively unclear answer from genetic testing, as genetic testing does not give risk information beyond the pedigree-based risk assessment. In addition, both groups of women were prepared for the possibility of receiving such results before disclosure. A difference between those groups is that overall, for the group of women with uninformative results, a deleterious mutation is less likely after DNA testing, whereas for women in the VUCS group this is less clear. In line with this, uninformative women showed a significant decrease in perceived risk, whereas the VUCS group did not change with regard to perceived risk. Surprisingly, women in the VUCS group did report a significantly lower level of distress after disclosure, similar to the effect observed for uninformative women. We argue that both groups of women remain sufficiently aware of their increased risk after testing, as they did perceive their risk as being higher than that of the average woman.

Some limitations of this report should be taken into account. Obviously, the number of women who received a VUCS result in this report is small and as a consequence the conclusions should be considered with caution. In addition, we did not include a direct measure to check whether women described their risk in an accurate way. Instead of this, we based our conclusions on the self-reported comprehensibility of the information, which is an indirect way of assessing comprehension. Finally, post-disclosure data were already collected one month after disclosure. Studies with larger numbers and longer follow-up are needed to confirm our conclusions. Although this study must be interpreted with caution as stated above, in these conditions, namely that the possibility of receiving a VUCS result was discussed before blood withdrawal, our results give no cause for concern about whether counsellees have problems with understanding or coping with such a test result.

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6

What's the message? Interpretation of an uninformative BRCA1/2-test result for women at risk of familial breast cancer

What's the message? Interpretation of an uninformative BRCA1/2-test result for women at risk of familial breast cancer.
Van Dijk S, Otten W, Timmermans DRM, Van Asperen CJ, Meijers-Heijboer EJ, Tibben A, Breuning MH, Kievit J.
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ABSTRACT

Purpose

To test the 'false-reassurance hypothesis', which suggests that women who receive an uninformative BRCA1/2-test result may incorrectly conclude that they no longer have an elevated risk, with possible harmful consequences for adherence to breast surveillance guidelines.

Methods

A prospective questionnaire design was used to compare183 women with an uninformative BRCA-test result (94 affected and 89 unaffected) with 41 proven BRCA mutation carriers and 49 true negatives before and after BRCA1/2-test disclosure.

Results

After DNA test disclosure, test applicants differed from each other with regard to their perception of the likelihood of carrying a deleterious gene ($P < .0001$). The BRCA mutation carriers reported the highest perceived likelihood and the true negatives reported the lowest. Compared to the pre-disclosure measures, women who received an uninformative DNA-test result reported a lower perceived risk after disclosure ($P < .0001$), suggesting a relatively high level of reassurance because of the test result. However, after DNA test disclosure, only twelve women concluded that the risk of carrying a mutation was non-existent, and perceived likelihood was significantly associated with the pedigree-based risk assessment ($P = .0001$). Moreover, despite the significant decrease in perceived likelihood for uninformative women, intention to obtain mammograms did not change ($P = .71$); it remained at the same almost optimal level as for BRCA mutation carriers.

Conclusion

No support was found for the suggestion that the nature of uninformative test results is misunderstood. Moreover, an uninformative test result did not affect the positive mammography intentions of both affected and unaffected women.

INTRODUCTION

Since the isolation of the BRCA1 and BRCA2 genes, many individuals have requested DNA testing for hereditary breast and ovarian cancer. Although reducing uncertainty is mentioned as the prime motive for applying for genetic counselling and DNA testing,[128] the large majority of test-applicants receive a so-called uninformative test result. This is a negative result in the absence of a mutation detected previously within the family. These individuals remain at risk for developing breast cancer based on the pedigree-based risk assessment. Although only a few studies have presented data on this group of test-applicants, concern has been expressed about whether women understand the nature of an uninformative result. It is suggested that women may incorrectly interpret such a result as a true negative result, with possible negative consequences for their surveillance motivation.[57;59;146;147]

In concordance with this 'false reassurance' hypothesis, Hallowell et al.[57] presented qualitative data describing some affected women who misunderstood the nature of their uninformative result. In addition, Bish et al.[59] reported a significant decrease in the perceived likelihood of carrying a mutation for affected women who received an interim uninformative DNA test report, and they presume that this may be a sign of incorrect understanding. Although perceived likelihood decreased, no effects on self-reported screening behaviours could be detected. However, with regard to the latter finding, women who are affected with cancer are, generally, under medical supervision already. Indeed, in a population-based study, women who had previously had breast cancer were twice as likely to have had a mammogram compared to unaffected women.[148] No data are available for screening intentions with regard to unaffected women who have an uninformative test result.

The aim of the current study is to assess in more detail whether, and to what extent, an uninformative DNA-test result is correctly understood, and how correct or incorrect interpretations influence surveillance intentions. In a prospective design (i.e., both before and after DNA test disclosure) we compared both affected and unaffected women who received an uninformative test result with: (a) counsellees in whom a deleterious BRCA1/2 mutation was detected (i.e., a pathogenic BRCA1 or BRCA2 mutation, which is associated with a lifetime risk of 24 to 84% for breast cancer and 11 to 54% for ovarian cancer for unaffected women[8-11] and, (b) participants who tested negative for a BRCA1/2 mutation that runs in the family, and who can be considered true negatives, i.e., their lifetime risk reverts to that of the general population.

METHOD

Participants and Procedures

Ethical approval was obtained for the integrated study from both hospitals' research ethics committees. The study comprised of all women who were referred for familial breast cancer counselling in the period 1998-2002, who met the inclusion criteria of being at least 18 years old, with sufficient understanding of the Dutch language, and had not received genetic counselling elsewhere. Referrals for genetic counselling regarding breast cancer were based on current national guidelines.[2;121] These guidelines specify how many first-degree or second-degree family members should have developed breast cancer either before or after the age of 50, as a prerequisite of referral to a cancer clinic. Genetic counselling was provided by either a clinical geneticist or a genetic nurse. In the first consultation BRCA1/2 testing was offered to individuals if a BRCA mutation had been detected within the family previously, and to individuals where the probability of mutation detection was about 10% or more; usually an affected family member. The possible results and consequences of BRCA1/2 testing were discussed extensively with women who were eligible for genetic testing. After counselling, those women could freely decide whether they would proceed with DNA testing or whether they would ask a family member to take the test for them.

When the DNA-test results became available for counsellees who actually had decided to have DNA testing, the women concerned were invited to attend a disclosure counselling session of either their own BRCA1/2 test result, or the result of their affected family member. In the latter case, the woman concerned was present, or had provided explicit permission for her result to be discussed with the family member concerned in addition to a personal DNA test disclosure session. As testing of relatives of an uninformative proband is ineffective, unaffected relatives usually had no access to an additional test for themselves. Hence, an uninformative DNA-test result of an affected proband was the definitive result for unaffected counsellees. Normally, a final familial lifetime risk of developing breast cancer was estimated for women from families in which no BRCA1/2 mutation was previously detected.[5] Four risk categories were distinguished: (a) general population risk, i.e., around 10%; (b) 10-15%; (c) 15-30%; and (d) 30% or more. Women with an uninformative result were told that they remained at about the same estimated familial lifetime risk, although generally, the likelihood of a high risk mutation was actually lower after their negative DNA-test result. Intensive breast and ovary screening was available for women who proved to have the deleterious BRCA1/2 mutation. For all women who received an uninformative test result and had a sufficient strong family history (lifetime risk > 20%), intensive breast surveillance was recommended, i.e., annual mammography screening, breast examination by a physician and monthly breast self-examination.

In accordance with current policies for surveillance[14], ovary screening was also offered, if cases of ovarian cancer were present in the family history. Women who tested negative for a BRCA1/2 mutation which had been detected previously within the family, and women with an uninformative result and a relatively weak family history were informed that intensive surveillance was not recommended. However, they were encouraged to take part in the national population-based screening program for those aged 50 and over. All counsellees (including the affected women who provided a blood sample for their family member) were provided with a letter, which summarized all the established information.

All new referrals for breast cancer counselling in Leiden from November 1998, and in Rotterdam from January 2000 until June 2002 were invited to participate in the study by letter. Eligible women who provided written informed consent, received questionnaires at various stages. Here we report data from the questionnaire immediately after the initial counselling session in which BRCA1/2 testing was offered and from the questionnaire that was sent out one month after the provision of the summary letter.

Psychological Measures

Socio-demographic characteristics

All available information about personal history of breast cancer (i.e., unaffected or affected), lifetime risk, BRCA1/2-test result, access to intensive breast surveillance, age, educational level, marital status, and number of children was collected.

Perceived likelihood of having inherited a deleterious mutation

Perception of likelihood as assessed in both questionnaires with the item, "Sometimes you may have asked yourself if you have inherited a characteristic or gene which increases your chances of developing cancer. What do you think the likelihood is that you have inherited such a characteristic/gene? I think that the chance that I have inherited a gene that increases my risk of getting cancer is: 1 'very low' through 4 'neither high nor low' to 7 'very high'. In the second questionnaire, which is after DNA test disclosure, we expanded the scale to a nine-point scale with, on both extremes of the scale, the phrases 'non-existent', and 'it is certain, the characterictic/gene is detected'. This was done to make it possible for women who had now learned that they either carried or did not carry a BRCA1/2 mutation to provide a correct answer. We assumed that the mean perceived likelihood of women with an uninformative result would decrease, which would be a correct response. However, for these women the answers "non-existent" and "certain, the genetic mutation is detected" are incorrect by definition. Hence, we used this item to assess the amount of false reassurance in more detail and we expected women who would incorrectly interpret their result as a true negative result would provide the answer 'non-existent'. In this report, we used perceived likelihood of carrying a deleterious mutation rather

than perceived risk of developing breast cancer. Both measures are related, but perceived likelihood of carriership is a more direct measure of comprehension about the nature of the test result, whereas perceived breast cancer risk might resemble a somewhat more global interpretation of several aspects of risk communication and personal risk beliefs.

Intention regarding mammography screening and prophylactic mastectomy
In both questionnaires the intention to obtain mammograms was measured with the item "Do you think you will have a mammogram (at least) once every year?" and intention for prophylactic mastectomy was measured with the item "Do you expect to decide to have preventive surgery of your breast(s)". Answers on both items could range from 1 'no, certainly not' through 4 'maybe, maybe not', to 7 'yes, certainly'.

Statistical Methods

The SPSS 11.5 statistical package was used to analyse the data. Frequencies were used to describe the study population. We conducted chi-squares and t-tests to compare (1) participants who did complete both questionnaires with participants who did not complete both questionnaires, and (2) women with different BRCA1/2-test results, on medical and socio-demographic variables. MANOVAs with repeated measures were used to assess differences between groups and between the pre-test and post-test measures for perceived likelihood of carrying a mutation and intention to obtain a mammogram in the forthcoming year. If the groups by DNA test disclosure interaction was significant, simple main effect analyses were conducted. First, the differences between groups were examined separately for the pre-test and post-test measures. Secondly, the differences between the pre-test and post-test measures were examined in separate groups. The latter analyses were also conducted for the subgroup of unaffected women, as affected women are generally under medical supervision already.

RESULTS

Study Population

Of the 997 women who met the inclusion criteria, 768 (response rate 77%: Leiden; N = 657, Rotterdam; N = 111) consented to participate in the study. Not all women were eligible for DNA testing or chose to have a test. In total 374 participants received the result of a DNA test as part of their evalutation and counselling. Of those women, 75 did not complete the pre-disclosure or post-disclosure questionnaire. Of the remaining 298 participants who received a BRCA1/2-test result, 12 women were told that a variant of uncertain clinical significance was detected; we will report on these women elsewhere. In addition,

13 women had no remaining breast tissue due to previous surgery (breast cancer surgery and/or prophylactic surgery), and one woman underwent a prophylactic ovariectomy in the period between our measurements. As these surgical procedures are assumed to affect not only the objective cancer risks, but also cancer screening recommendations, we excluded these women from the analyses. This left 273 women for our analyses.

With t-tests and chi-square tests we assessed potential differences between women who completed all measures and women who did not complete either one or both of the questionnaires. No differences were observed for socio-demographic and medical variables (i.e., lifetime risk, BRCA1/2-test result, personal history of breast cancer, marital status, educational level, age, having children).

BRCA1/2-test result

Of the 273 women who received a BRCA1/2-test result, 41 women tested positive for a BRCA1 mutation (N = 32) or a BRCA2 mutation (N = 9). Of those mutation carriers, 25 carried the deleterious BRCA1/2 mutation that had been detected previously within the family, whereas a new BRCA1/2 mutation was found in the other 16 women. In addition, 49 women tested negative for the BRCA1/2 mutation that had been detected previously within the family (BRCA1: N = 34; BRCA2: N = 15). Finally, 183 women received an uninformative test result; either no mutation was detected in their own blood sample (N = 108), or no mutation was found in an affected family member who provided a blood sample on their behalf (N = 75).

Socio-demographic and medical characteristics

Table 1 summarises the socio-demographic and medical variables of the study population. The mean age of the group was 42.3 years (range 21-72 years; SD 10.6 years), and most women were married or co-habiting and had one or more children. With t-tests and chi-squares we did not observe any differences between the group of test applicants with regard to age, marital status, having children and level of education. Not surprisingly, percentages of women with a personal history of breast or ovarian cancer were unequally distributed throughout the groups of DNA-test results; almost all women with a true negative result were unaffected, whereas in the groups of both BRCA mutation carriers and uninformatives, about half of the women had a prior diagnosis of breast or ovarian cancer. Half of the women who received an uninformative test result remained at a high-risk level (>30%). Of the 89 unaffected women who received an uninformative result, 8 women did not have a high enough risk to be eligible for annual mammograms (>20%), and 11 women were still too young for mammography screening. In addition, 4 women participated in the national population-screening program (i.e., once every two years a mammogram):

Table 1. Socio-demographic and medical variables of the study population (N = 273)

	BRCA mutation carrier N = 41	**True negative result N = 49**	**Uninformative result N = 183**
	N (%)	**N (%)**	**N (%)**
Variable			
Socio-demographic			
Age			
< 30 years	4 (10)	8 (16)	19 (10)
30-39 years	17 (42)	13 (27)	50 (27)
40-49 years	8 (20)	11 (22)	76 (42)
50+ years	12 (29)	17 (35)	38 (21)
Marital status			
Married or living together	36 (88)	37 (75)	154 (84)
Not married or living together	5 (12)	12 (25)	29 (16)
Children			
Yes	28 (68)	40 (82)	136 (74)
No	13 (32)	9 (18)	47 (26)
Educational level[a]			
High school or university	8 (20)	12 (25)	56 (31)
Less than high school	32 (80)	36 (75)	122 (69)
Medical			
Breast cancer			
Yes	22 (54)	2 (4)	94 (51)
No	19 (46)	47 (96)	89 (49)
Objective risk[a]			
< 20%	-	49 (100)	22 (13)
20-30%	-	-	65 (40)
> 30%	41 (100)	-	78 (47)
BRCA detected in family			
Yes	16 (39)	49 (100)	-
No	25 (61)	-	183 (100)

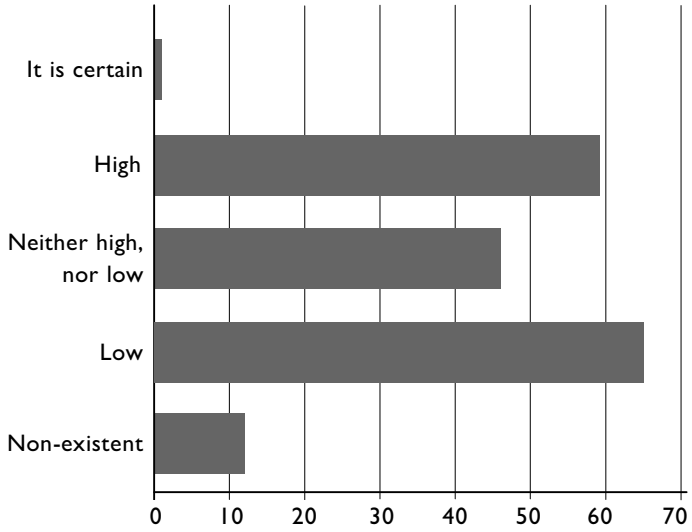
[a] because not all women with an uninformative result were provided with an objective risk, and because not for all women level of education could be concluded from questionnaires, some categories do not add up to 273.

additional screening was not considered necessary. In total, 66 unaffected women who received an uninformative result were currently eligible for annual mammograms.

Perceived likelihood of carrying a deleterious mutation

The impact of DNA test disclosure on the perceived likelihood of carrying a mutation was significantly different between groups of test applicants (interaction effect: $F = 193.95$, $P < .0001$). Before DNA test disclosure, the three groups differed slightly on the perceived likelihood of carrying a mutation ($F = 3.97$, $P = .02$), with the uninformatives reporting the lowest perceived likelihood (See Table 2). However, after DNA test disclosure, all groups differed greatly from each other ($F = 219.88$, $P < .0001$). All women who learned that they carried the BRCA1/2 mutation shifted to the upper extreme, whereas women who received a true negative result generally shifted to the lower extremes of the scale (see Table 2 for the effects of DNA test disclosure within groups). Comparable to the true negatives, the women with an uninformative test result perceived the likelihood of carrying a deleterious mutation as being significantly lower after DNA test disclosure.

Figure 1. Perceived likelihood of carrying a deleterious mutation after receiving an uninformative BRCA1/2 test result



Number of responses on the nine-point scale transformed to a five-point scale.

After disclosure, the group of uninformative women showed a wide variation of responses (Figure 1), which was significantly correlated with the objective risk estimation, based on the pedigree ($r = .35$, $P < .0001$). We expected women who would incorrectly conclude that their result was a true negative result, to rate the likelihood of carrying a deleterious mutation as being "non-existent". Only ten affected and two unaffected women actually did choose this response (6.6%). Six of the women who chose this response had no elevated risk or a relatively low risk, whereas the other six women had either a moderately increased risk or a highly increased risk. Finally, one woman incorrectly stated that the deleterious mutation was detected. She had only a moderately increased risk (i.e., 15-30%). However, she suffered from mastopathy and already reported a strong desire for prophylactic mastectomy in the first consultation, which might be a motivational reason to interpret her uninformative result as a proof of carriership.

Intention regarding mammography screening

The impact of DNA test disclosure on the intention to obtain mammograms within the next year was significantly different between groups of test applicants (interaction effect: $F = 59.29$, $P < .0001$). Before disclosure, the three groups already had a significantly different screening intention ($F = 4.33$, $P = .014$), with women with a true negative result having a significantly lower intention than BRCA1/2 mutation carriers and uninformatives (Table 2). However, compared to the other groups, the group of true negatives contained very few women who were under medical supervision, due to a previous diagnosis of breast cancer. Therefore, we examined whether the observed pre-disclosure difference was due to this variation. Indeed, if we selected only unaffected respondents for the same analysis, the groups did not differ on intention regarding mammography screening before DNA test disclosure ($F = 1.87$, $P = .16$).

After disclosure the three groups differed very significantly with regard to screening intention ($F = 99.22$, $P < .0001$) and this effect remained very strong if we selected only unaffected women ($F = 68.31$, $P < .0001$). BRCA mutation carriers and uninformatives did not change their intention after disclosure, whereas women with a true negative result reported a highly significant decrease in intention, in accordance with their now negative indication for annual mammography (See Table 2).

With regard to the uninformatives, 151 out of 173 women (87%) reported a positive intention. If we selected the unaffected women who were currently eligible for annual mammography ($N = 66$), the results were very compatible with the overall results; the overall level of mammography screening intention remained at a high level, with even 63 out of 66 women (95%) reporting a positive intention after DNA test disclosure (Table 2). For the 12 uninformative women who seemed to interpret their result incorrectly as a true negative result (i.e., "the likelihood is non-existent") we inspected responses regarding the intention

Table 2. Perceived likelihood and screening intention before and after DNA-test disclosure

		Mean (SD)		Effect disclosure within groups	
	N	**Pre-disclosure**	**Post-disclosure**	**F**	**P**
Perceived risk carriership (0-8)					
BRCA mutation-carrier	41	5.37 (1.43) [b]	8.00 (.00) [c]	97.96	< .0001
True negative result	49	5.14 (1.14) [ab]	.67 (1.48) [a]	337.03	< .0001
Uninformative result	181	4.79 (1.34) [a]	3.50 (1.88) [b]	102.84	< .0001
Intention mammography (1-7)					
BRCA mutation-carrier	40	6.18 (1.55) [b]	6.20 (1.80) [b]	.01	.922
True negative result	46	5.54 (1.62) [a]	2.74 (1.90) [a]	139.93	< .0001
Uninformative result	173	6.25 (1.38) [b]	6.30 (1.37) [b]	.14	.706
Uninformative subgroup*	66	6.29 (1.33)	6.55 (.86)	1.52	.220

[abc] If in the column pre-disclosure or post-disclosure groupmeans do not share a similar superscript they differ significantly at P < .05 level.

* Intention for the subgroup of uninformative women who were unaffected and eligible for mammography.

to have at least annual mammograms; eleven women had a positive intention (i.e., score > 5), whereas one woman was undecided (score = 4). Thus, the potential false reassurance did not clearly result in a failure to adhere to regular screening.

The intention to have a yearly mammogram remained very strong amongst BRCA mutation carriers (88% reported a positive intention). Four carriers reported a (somewhat) negative intention (i.e., score < 3), and one woman was undecided after DNA test disclosure (score = 4). To check whether the choice for prophylactic mastectomy as an alternative risk-management option would explain negative intentions, we excluded 19 women who had decided to undergo prophylactic mastectomy (i.e., they said that they would definitely have prophylactic mastectomy). After this selection, all BRCA mutation carriers were found to have an optimal positive intention to obtain annual mammograms (M = 6.90; SD = .30).

In general, women with a true negative result reported a negative intention after BRCA1/2 testing, which seemed appropriate given the subsequent contra-indication for intensive surveillance. However, 8 out of 46 women (17%) mentioned a (somewhat) positive intention. For six of them this seemed to be quite understandable, as they were under medical supervision due to a previous breast cancer (N = 1) or mastopathy (N = 1), or were taking part in the national population-screening program (N = 4). For two women who received a true negative result it remained unclear from a medical point of view why they would opt for intensive breast surveillance.

DISCUSSION

In several studies concern has been expressed about the possible ambiguity of an uninformative DNA-test result for breast cancer. Women might incorrectly interpret this as a true negative result, with possible negative consequences for their adherence to surveillance recommendations. In the current prospective clinic-based sample of BRCA1/2-test applicants, we found a strong indication that either a familial or personal uninformative test result might provide reassurance with regard to their perceived likelihood of carriership. However, we did not find evidence that this reassurance was due to a lack of understanding of the nature of an uninformative DNA-test result. Perceived likelihood of carrying a deleterious mutation decreased significantly after DNA test disclosure for women with an uninformative result, which can be considered appropriate, as the likelihood of a high penetrance mutation is actually smaller after an uninformative result. However, the perceived likelihood of carriership was not only significantly different from that of BRCA mutation carriers, but also from that of true negatives. Moreover, only a very small minority concluded that the likelihood of a deleterious mutation is non-existent after DNA test disclosure.

For the whole group, the pre-test level of intention for obtaining mammograms was rather high. After test DNA test disclosure, true negatives significantly decreased their intention, whereas the intentions of BRCA mutation carriers and the overall group of uninformative women remained stable. The lack of change in the latter two groups is likely attributable to the high baseline mammography screening intention. We also found that unaffected uninformatives did not change their strong intention. This is important, as the single study that reported on (a high rate of) mammography utilization among women who receive uninformative test results was restricted to affected women.[59] Unlike affected women, unaffected women, who learn that they are eligible for screening due to their increased cancer risk, are generally not included in a standard surveillance protocol yet. Thus, it is reassuring that their mammography intentions remain very positive after DNA test disclosure.

Regarding screening behaviours, recently concern has been expressed about a possible sub-optimal utilization of surveillance options for BRCA1/2 mutation carriers.[149;150] Reports of mammography uptake among proven mutation carriers vary from 59%[149] to 88%.[151] In the current study, we observed a very strong intention towards having a mammogram for both the groups of uninformative women and BRCA1/2 mutation carriers. Moreover, if we controlled for a very positive intention for prophylactic mastectomy amongst the BRCA1/2 mutation carriers, all carriers expressed a very positive intention. Thus, in this report about intention, rather than actual behaviour, we do not find reasons for concern.

In a recent study, adherence to mammography proved to be strongly associated with physicians' recommendations.[151] We hypothesize that this might be an explanation for our very positive screening intentions, as in our clinics in both Leiden and Rotterdam multi-disciplinary medical care is available, especially for women with a strong family history of cancer. In both clinics high-risk women are encouraged to opt for intensive screening and in Leiden, a first appointment for a mammogram was even automatically scheduled after the surveillance recommendations of the clinical geneticist. Thus, our results support the suggestion of Tinley et al.,[151] that education and support for screening from primary providers might be (part of) a clinical solution for optimization of adherence to screening. Another explanation for the positive screening intentions might be that mammography screening is relatively easy to obtain within the Dutch health care system. Different intentions might be observed in a system where access to screening services is dependent upon availability, or ability to pay.

A few limitations of the current study must be noted. First of all, although intention to have a mammography is a main predictor for actual utilization,[152] intentions for mammography, even very strong intentions, as in our sample, might not always translate into actual behaviour. Follow-up data are needed to check whether actual utilization remains as strong amongst the group of BRCA1/2

mutation carriers and women who receive an uninformative result. Secondly, the few women who report that the likelihood of carrying a mutation is "non-existent" or "certain", in the face of an uninformative result, do not necessarily misunderstand such a result. These women may simply not believe or accept the message. In this respect it is interesting that the woman with an uninformative result, who stated incorrectly that the deleterious mutation was found, was probably psychologically motivated to interpret her result this way; she desired a prophylactic mastectomy, because of her anxiety about developing breast cancer. Furthermore, uninformative women who do not rate the likelihood as "non-existent" or "certain", do not necessarily understand their result in a proper way.

However, given the perceived likelihood and the mammography intentions reported, we do not think there is a tendency to interpret an uninformative result as a true negative result. Apparently, genetic counselling is effective in assisting women in understanding their DNA-test result. Moreover, an uninformative test result also had no negative impact on screening intention.

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7

Clinical characteristics affect the impact of an uninformative DNA-test result: the course of worry and distress experienced by women who apply for genetic testing for breast cancer

Clinical characteristics affect the impact of an uninformative DNA-test result: the course of worry and distress experienced by women who apply for genetic testing for breast cancer.
Van Dijk S, Timmermans DRM, Meijers-Heijboer EJ, Tibben A, Van Asperen CJ, Otten W.
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ABSTRACT

Purpose

DNA-mutation testing for breast cancer usually yields an uninformative result, which is a negative result in the absence of a known BRCA mutation within the family. However, very few data are available on the psychological impact of this result. Moreover, the clinical heterogeneity within this group has not yet been considered. The current study provides prospective data about the course of cancer-specific worry and distress for different groups of test applicants.

Methods

All DNA test applicants (N = 238) completed three questionnaires: before, and respectively one and seven months after disclosure of a DNA-mutation test. With repeated measures analysis of variance, differences were assessed between BRCA1/2-positive women (N = 42), BRCA1/2 true-negative women (N = 43), and women with an uninformative test result (N = 153).

Results

On group level women with an uninformative result seemed to be reassured after disclosure ($P < .001$), but to a lesser extent than those women who received a true-negative result. However, not all women with an uninformative result reacted similarly: Higher levels of worry and distress could be explained by relatively straightforward clinical variables, namely a personal history of cancer ($P < .001$) and a higher pedigree-based risk ($P < .005$). Furthermore, these clinical variables determined whether these women were either comparable to women who received a true-negative result or to BRCA carriers.

Conclusion

Women with an uninformative result form a heterogeneous group of test applicants. The subpopulation of those with both a personal history of cancer and a relatively high pedigree-based risk expressed the highest levels of worry seven months after DNA testing.

INTRODUCTION

Since the identification of the BRCA1 and BRCA2 genes, many individuals have requested genetic testing for Hereditary Breast and Ovarian Cancer (HBOC). From meta-analytic studies we now know that BRCA-mutation testing generally does not lead to a decline in patient well-being.[42;153]

Those reviews are based on women who opt for informative testing. However, as the known BRCA mutations only account for 20-25% of familial aggregation,[13] the majority of women applying for BRCA testing receive an uninformative result. Data on this group of test applicants who receive a negative result in the absence of a known BRCA1/2 mutation are relatively scarce. Despite concern about the possible harmful effects of continuing uncertainty associated with the result, no increased levels of distress have been observed till now.[59] However, one of the very few studies that actually compared women who received an uninformative result with women who learned that they carry the high risk BRCA1/2 mutation did observe the same levels of distress six months after disclosure.[56]

A possible explanation for these seemingly contrasting findings may be the clinical heterogeneity of the group of women receiving an uninformative result. Although a positive family history is commonly a prerequisite for DNA-mutation testing, some families remain very suspect with regard to a hereditary cancer syndrome after an uninformative result, whereas within other families a hereditary pattern of cancer transmission is less obvious. In other words, women tend to differ with regard to the extent of their pedigree-based breast-cancer risk, which might have an important impact on levels of worry and distress. Another important distinction is whether a woman has a personal history of cancer. The aim of the current study is to assess whether: (1) the pedigree-based familial risk estimation, and (2) the personal cancer history, can explain cancer worry and distress among women who receive an uninformative DNA- result. In addition, we will compare groups of women with an uninformative DNA-test result with women who received either a true negative or a positive DNA-test result.

PARTICIPANTS AND METHODS

Data collection and genetic counselling

The study comprised of all women who made an initial appointment for familial breast cancer counselling at the Department of Clinical Genetics in Leiden or Rotterdam in the period 1998-2002. Ethical approval was obtained from the hospitals' research ethics committees. Eligible women were at least 18 years old, and had not received genetic counselling elsewhere. Referrals for genetic counselling were based on national guidelines.[2;121]

In the first consultation DNA testing was offered for individuals from families in which a pathogenic BRCA mutation was previously detected, and for individuals in whom the probability of mutation detection was about 10% or more, usually an affected family member.[6] All women who opted for DNA testing were invited to an in-person counselling session about the personal implications regarding either their own result or the result of their affected family member when the DNA test became available. In this session, the pedigree-based familial lifetime risk was derived from the Claus tables,[5] and was conveyed to patients. Four risk categories were distinguished: (a) general population risk, i.e., around 10%; (b) slightly raised; 10-15%; (c) moderately raised; 15-30%; and (d) highly raised; 30% or more. Counsellees were provided with a letter, which summarized all the constituted information.

All participants completed questionnaires at several points in time: T_1, a pre-test-disclosure questionnaire, sent up to two weeks after the first counselling session*; T_2, a post-disclosure questionnaire that was sent one month after women had received the summary letter; and T_3, a follow-up questionnaire that was sent six months after completion of the post-disclosure questionnaire.

Measures

Patient characteristics

Information about age, educational level, marital status, and number of children was collected. In addition, all relevant medical information was obtained from counsellees' medical records.

Breast-cancer worry

In all questionnaires, we assessed breast-cancer-related worries with one single item, "During the last two weeks, how often did you worry about developing breast cancer (again)?" on a 4-point scale ranging from 1 'almost never' to 4 'almost all the time'.[63] Throughout the text we will refer to this measure as 'worry'.

Breast-cancer specific distress

In each questionnaire, we included the Impact of Events Scale,[74] which assesses the level of intrusion and avoidance, tailored to breast cancer, on a 4-point scale ranging from 0 'not at all', 1 'seldom', 3 'sometimes', to 5 'often'. The reliability of the scale was good (α ranged from .89 to .92). We will refer to this breast-cancer-specific distress in the text as 'distress' or 'IES'.

* Thus, at the moment of completing this first questionnaire, women had received risk information already, in line with the standard counselling protocol.

Statistical analyses

The SPSS 11.5 statistical package was used to analyse the data. Repeated measures analysis of variance was used to assess differences between and within groups regarding courses of worry and distress.

For comparisons among women who receive an uninformative result we dichotomized the personal risk estimation into relatively low risk (i.e., < 30%) or relatively high risk (> 30%). This cut-off was chosen in line with the cut-off points of the Claus tables,[5] and to obtain an optimal distribution. Please note however that all women with a relatively low risk had a sufficiently high risk to receive DNA testing. In conjunction with having had a personal history of breast or ovarian cancer (yes, no), we first tested with repeated measures analysis of variance whether significant effects of these two variables could be detected. Subsequently, on the basis of these two clinical variables we created four different groups of women with an uninformative result and compared them to women with either a positive or a true-negative result.

RESULTS

Patient characteristics

Of the 997 eligible women, 762 consented to participate in the study (response rate 76.4%: Leiden; N = 652, Rotterdam; N = 110). Not all women were eligible for BRCA1/2-mutation testing or chose to have a test. Furthermore, of the remaining women not all (fully) completed three questionnaires over time (response rate 69.2%). Figure 1 represents a flow chart of those available for the analyses (N = 238).

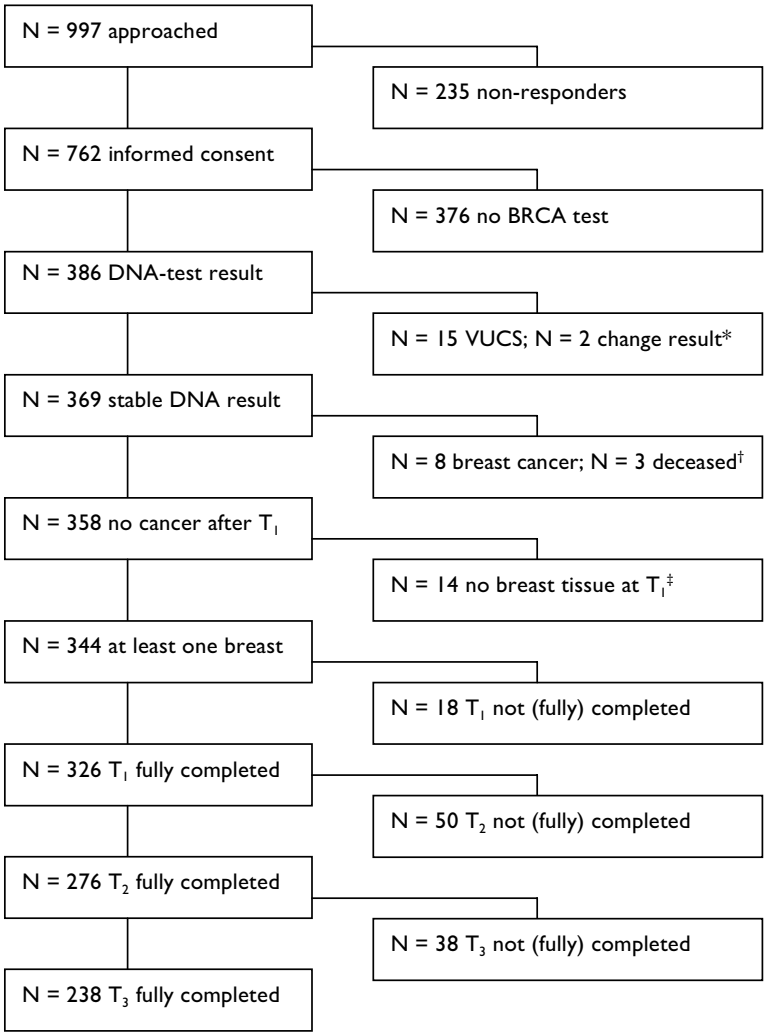
Participants who did not complete the full set of questionnaires did not differ from those who did on any of the socio-demographic or clinical variables, although women who did not complete the full set tended to be somewhat younger ($t = 1.88$, $P = .062$). Finally, neither for worry, nor for distress, were any differences observed at any time (P-values ranged from .27 till .90).

Groups of test applicants

Of the 238 women who received an in-person DNA-mutation test-disclosure session, 42 were carriers of a BRCA1/2 mutation, 43 received a true-negative result, and 153 women received an uninformative test result.[†] Groups did not

[†] In four cases a tested woman as well as her untested relative were included. We assessed whether the inclusion of these relatives could potentially affect our results, by repeating all analyses without these women, or with either the tested or the untested women. It turned out that this did not weaken the results or conclusions. Therefore, we decided to include these women in our final analyses.

Figure 1. Flow of participants



* We have reported on women with a Variant of Unclear Significance in Chapter 5. For two women with an uninformative result, a BRCA mutation was deteced still before T_3.

† These women developed cancer or died in between T_1 and T_3.

‡ As having no breast tissue is assumed to affect breast cancer distress, we excluded these women.

differ regarding socio-demographic characteristics (Table 1). Furthermore, no differences with respect to breast-cancer history were observed between women with an uninformative result and BRCA-mutation carriers. Finally, within the group of women with an uninformative result, the familial pedigree-based risk was not associated with having a previous breast-cancer diagnosis (χ^2 = 1.38, P = .24).

Overall levels of worry and distress

The three groups of test applicants reported different levels of worry and distress over time (Figures 2 and 3: worry F = 14.41, P < .0001; IES F = 6.85, P = .001). In addition, for worry a significant interaction effect between groups and time was observed (F = 4.91, P = .001), whereas for distress this interaction effect was marginal (F = 2.24, P = .064). In the next paragraphs we first focus on each group of test applicants separately. Subsequently, comparisons between groups will be presented with the group of women who received an uninformative result as the referent group.

An uninformative DNA-test result

Women who received an uninformative result reported a much lower level of worry and distress one month after DNA-mutation test disclosure and this remained stable up to seven months after disclosure (Figure 2 and 3: linear effect of time; worry F = 27.90, P < .001; IES F = 25.50, P < .001).

We assessed whether this impact of DNA-mutation testing applied to all women who received an uninformative test result. Both a personal cancer-history as well as a higher pedigree-based risk was independently associated with higher levels of breast-cancer worry and distress (personal cancer history: worry F = 11.64, P = .001; IES F = 27.85; P < .001; risk: worry F = 10.10, P = .002; IES F = 8.10, P = .005). In addition, for personal cancer-history a linear interaction with time was observed, indicating less relief after disclosure among women with a personal history of cancer (worry with time F = 5.51, P = .02; IES with time F = 7.17, P = .008).

Subgroup analyses revealed that this interaction effect of personal breast-cancer-history with time could only be observed among women at a relatively high risk (worry F = 4.64, P = .033, IES F = 5.75, P = .018). Among women with a relatively low risk, unaffected women did not react differently than women with a personal history of breast cancer (worry F = 1.13, P = .29, IES F = 1.78, P = .18). Three out of the four subgroups of women with an uninformative result reported a significant linear decrease in both worry and distress over time (P-scores for worry and distress ranged from < .001 till .033). In contrast, for women with a prior history of cancer and with a relatively high risk, no linear changes in worry or distress over time were observed (worry F = .55, P = .46, IES F = .50, P = .48).

Table 1. Characteristics of the study population

Variable	BRCA mutation carrier N = 42 N (%)	True negative result N = 43 N (%)	Uninformative result N = 153 N (%)
Socio-demographic			
Age			
< 30 years	5 (12)	6 (14)	14 (9)
30-49 years	27 (64)	21 (49)	104 (68)
50+ years	10 (24)	16 (37)	35 (23)
Children			
Yes	28 (67)	35 (81)	115 (75)
No	14 (33)	8 (19)	38 (25)
Marital status			
Married or living together	35 (83)	34 (79)	131 (86)
Not married or living together	7 (17)	9 (21)	22 (14)
Educational level*			
High school or university	10 (25)	13 (31)	50 (34)
Less than high school	30 (75)	29 (69)	95 (66)
Medical			
Breast/Ovarian cancer			
Yes	20 (48)	2 (5)	83 (54)
No	22 (52)	41 (95)	70 (46)
Breast cancer risk†			
< 30%	-	43 (100)	85 (56)
≥ 30%	42 (100)	-	67 (44)
Blood sample BRCA test‡			
Counselee herself	42 (100)	43 (100)	96 (63)
Counselee's family member	-	-	57 (37)

* level of education could not be concluded for all women from questionnaires.

† for one woman who received an uninformative result it was not possible to make a clear-cut estimation.

‡ the factor 'having a personal history of breast cancer' overlaps to a great extent with 'having provided a personal blood sample' among women with an uninformative result. We have no Indications that observed effects can be attributed to the latter variable (data not shown).

A true-negative BRCA-test result

Women who learned that they have not inherited the BRCA1 or BRCA2 mutation that was detected within their family previously, report a linear decrease in worry and distress over time (Figures 2 and 3: worry $F = 29.64$, $P < .001$; IES $F = 10.27$, $P = .003$). They seemed to be relieved one month after the disclosure, and these decreased levels of worry and distress remained rather stable up to seven months after disclosure.

BRCA1/2-mutation carriers

The amount of distress of women who learn that they carry a BRCA1 or BRCA2 mutation did not change over time ($F = .05$, $P = .95$). However, with regard to breast-cancer worry a quadratic interaction effect was observed ($F = 5.08$, $P = .03$). Immediately after disclosure a slight increase was reported. However, in the period after disclosure the overall level of worry significantly decreased (T_2-T_3: $F = 8.26$, $P = .006$).

Some BRCA-mutation carriers (19%) had undergone prophylactic mastectomy within the period under study, which could be a sufficient explanation for the decrease in worry between T_2 and T_3. This factor (i.e., having had prophylactic mastectomy) neither affected the level of worry over time ($F = 1.35$, $P = .27$), nor the amount of distress over time ($F = .75$, $P = .48$). Nevertheless, the observed effect regarding the decreasing levels of worry between T_2 and T_3 was no longer significant if we excluded the 8 women who had had prophylactic mastectomy (T_2-T_3: $F = 3.74$, $P = .062$).

Furthermore, we could not detect different overall levels of worry or distress between affected and unaffected women (worry $F = 2.36$, $P = .13$; IES $F = .81$, $P = .38$). However, an interaction effect over time was observed for distress ($F = 4.17$, $P = .048$). Within the group of BRCA-mutation carriers with a personal cancer-history the amount of distress slightly decreased, whereas for unaffected BRCA-mutation carriers the level of distress slightly increased after disclosure. Still, unaffected BRCA-mutation carriers did not differ from affected BRCA-mutation carriers at any point in time regarding both worry and distress (See Table 2).

Women with an uninformative DNA-test result versus other test applicants

Finally, the four subgroups of women with an uninformative result were compared with subgroups of women with either a true-negative or a positive DNA-mutation test result at each point in time. In line with the classification regarding subgroups of women with an uninformative result, we differentiated within the group of BRCA-mutation carriers between those who were unaffected and those who were affected with breast cancer. Since only two women in the group of true-negatives were affected, we only made comparisons between unaffected

Figure 2. Course of breast-cancer worry for groups of test applicants

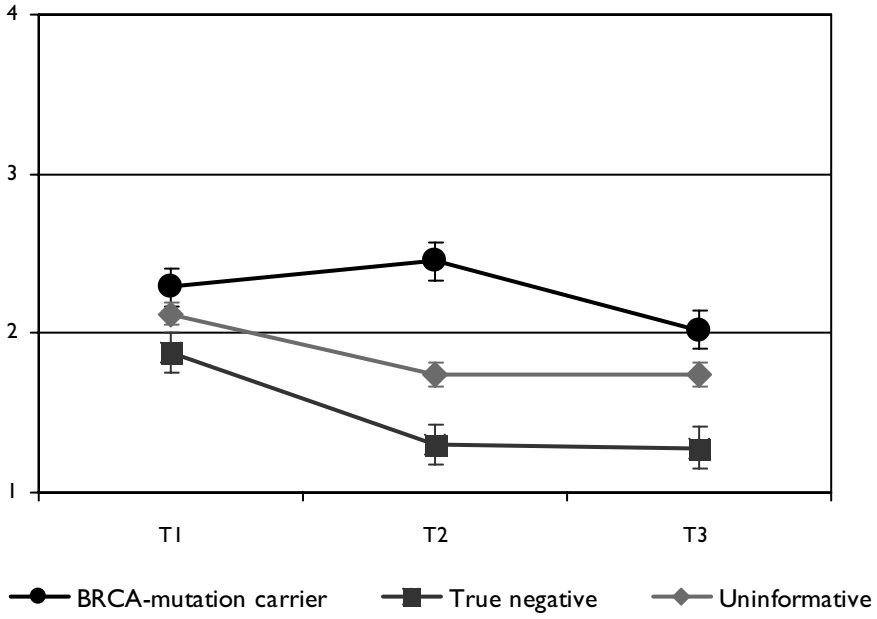


Figure 3. Course of breast cancer distress for groups of test applicants

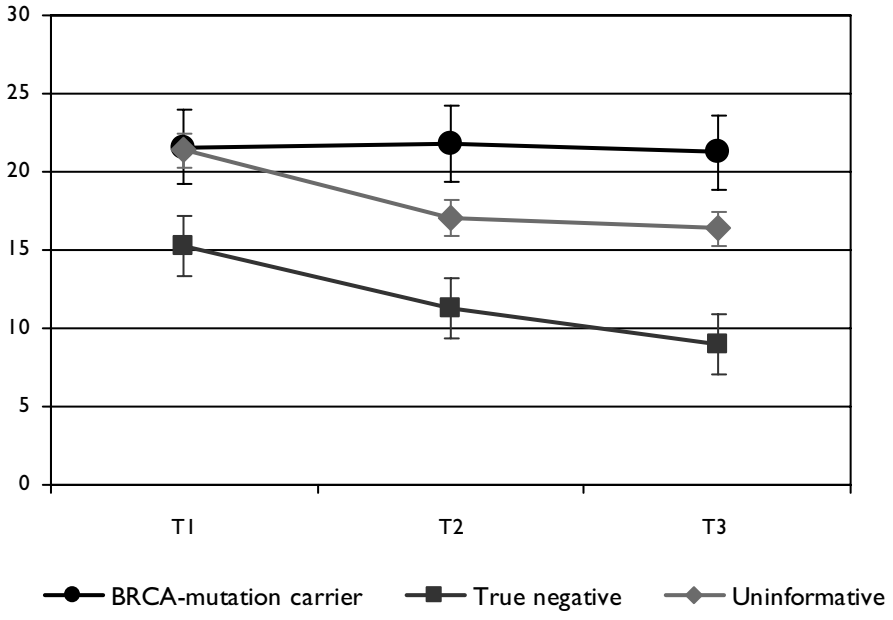


Table 2. Course of worry and distress among subgroups of test applicants

	Uninformative			BRCA mutation		True negative	
	unaffected & low risk (N = 35)	**unaffected & high risk (N = 34)**	**affected & low risk (N = 50)**	**affected & high risk (N = 33)**	**unaffected (N = 22)**	**affected (N = 20)**	**unaffected (N = 41)**
Worry							
T_1	1.94 (.73)^{a}	2.21 (.81)^{ab}	2.08 (.94)^{ab}	2.42 (.94)^{b}	2.41 (.73)^{b}	2.15 (.81)^{ab}	1.88 (.87)^{a}
T_2	1.51 (.66)^{ab}	1.68 (.81)^{abc}	1.72 (.86)^{bc}	2.06 (.90)^{c}	2.64 (1.00)^{d}	2.25 (.85)^{cd}	1.29 (.75)^{a}
T_3	1.37 (.55)^{a}	1.59 (.66)^{ab}	1.74 (.85)^{b}	2.30 (.73)^{c}	2.18 (.96)^{c}	1.85 (.81)^{bc}	1.24 (.70)^{a}
Distress							
T_1	13.54 (11.97)^{a}	22.53 (14.22)^{b}	23.66 (13.33)^{b}	25.15 (13.81)^{b}	21.55 (14.70)^{b}	21.60 (16.54)^{b}	14.85 (11.99)^{ab}
T_2	7.40 (8.57)^{a}	14.38 (12.41)^{ab}	20.86 (13.10)^{c}	23.91 (14.10)^{c}	24.14 (13.21)^{c}	19.20 (12.87)^{bc}	10.85 (13.62)^{a}
T_3	6.31 (8.44)^{a}	14.00 (14.51)^{bc}	20.00 (15.35)^{d}	23.67 (13.86)^{d}	24.09 (15.57)^{d}	18.15 (13.29)^{cd}	8.32 (13.30)^{ab}

^{abc} If those group means in a row do not share a similar superscript they differ significantly at $P < .05$ level.

women with a true-negative result and unaffected women with an uninformative result. Table 2 depicts comparisons between subgroups of test applicants at T_1 till T_3. Below, some of these comparisons between subgroups at T_3 are described in some more detail.

Seven months after disclosure of a DNA-test result unaffected women with an uninformative result at a relatively low risk reported the same very low levels of worry and distress as women with a true-negative result (T_3 worry $F = .55$, $P = .46$; IES $F = .41$, $P = .53$). In contrast, these unaffected women with an uninformative result at a relatively low risk were highly dissimilar from unaffected DNA-mutation carriers seven months after disclosure (T_3 worry $F = 15.76$, $P < .001$; IES $F = 22.86$, $P < .001$).

In addition, affected BRCA-mutation carriers reported about the same levels of worry and distress seven months after disclosure as affected women with an uninformative result at a relatively low risk (T_3 worry $F = .31$, $P = .58$; IES $F = .26$, $P = .61$). In addition, the reported level of distress seven months after disclosure did not differ between affected BRCA-mutation carriers and affected women with an uninformative result at a relatively high risk (T_3 $F = 2.03$, $P = .16$). Remarkably however, the reported level of worry for the latter group of uninformative women was higher than that of affected BRCA-mutation carriers (T_3 $F = 4.54$, $P = .034$).

DISCUSSION

An uninformative result was not associated with psychological harm. Quite the contrary, on a group level these women seemed to be reassured upon learning their result, but to a lesser extent than those women who received a true-negative result. However, the overall results probably provide an incomplete picture of the psychological impact of BRCA1/2-mutation testing for individuals who receive an uninformative result. This is because relatively straightforward clinical variables influenced the level of distress and worry. The women with an uninformative result with a previous cancer diagnosis reported higher levels of worry and distress than those who were unaffected. Besides the influence of a personal cancer history, we also found an overall effect of familial breast cancer risk. Within the group of women who received an uninformative result, those with a relatively strong family history reported higher levels of worry and distress than women with a less elevated risk, also after DNA test disclosure.

This is quite adequate from a clinical point of view: The likelihood that a high-risk mutation is actually present is lower after an uninformative test result, but this is especially true for women with a less suspicious family history of breast or ovarian cancer. Moreover, it corroborates an important, but subtle, difference within the group of women with an uninformative result with regard to the

primary aim of DNA-mutation testing. Whereas women with a relatively low risk may opt for testing to rule out the relatively small possibility of having a BRCA mutation, those women with a relatively strong family history may undergo DNA testing with the motive of making a BRCA mutation manifest.

Hallowell et al.[57] described that affected women with an uninformative result reacted with anger and frustration at being unable to confirm the aetiology of their own and their family cancer history, which would also provide the opportunity for informative DNA testing for their unaffected family members. Furthermore, in a study of Loader et al.[154] about half of the affected women waiting for their DNA-test result wished for a positive result, presumably for the same reasons as indicated by the women in the qualitative study of Hallowell et al.[57] In concordance with these observations, affected women, and especially those at higher familial risk for cancer, did not only express higher levels of distress and worry. They were also less relieved by their test result than unaffected women. Moreover, for these affected women with a relatively high risk, no changes in worry or distress were observed, as compared to their baseline values, seven months after disclosure. At follow-up, a quarter even had distress levels above a cut-off score indicating traumatic distress[155] (score >35; data not shown).

The categorizations of women who received an uninformative result also determined whether these women were either more or less comparable to women who received an informative result. Unaffected women at a relatively low risk who received an uninformative result were very comparable to women who received a true-negative result. Additionally, affected women with an uninformative result, independently of whether they had a relatively low or high pedigree-based risk, were rather comparable to affected BRCA-mutation carriers seven months after disclosure.

With regard to BRCA-mutation carriers, 19% had had prophylactic mastectomy seven months after disclosure. In line with the results in a recent study,[55] we could not find clear-cut evidence that having a prophylactic mastectomy reduced the levels of worry or distress. This finding is alarming and requires further research, as the major psychological benefit from prophylactic surgery is assumed to be relief from anxiety.

Several limitations of the current study should be noted. First, subgroup analyses were conducted on relatively small sample sizes. Additionally, a relatively high number of women did not fully complete the set of three questionnaires. However, women who completed all questionnaires reported the same levels of worry and distress as women who completed less than three questionnaires. Therefore, we think that the results are still representative for the population seeking genetic testing nowadays.

Another limitation may be the selection of only two clinical characteristics to characterize women with an uninformative result. One reason to select these

clinical variables was that they are relatively straightforward in the practice of genetic counselling. However, we do not want to claim that there are no other, and perhaps even more important, predictors of worry and distress among women with an uninformative result. A previous study has, for example, described the presence of negative life events as predictors of distress among counsellees.[156] Moreover, describing different levels of worry and distress, as we have done in the present study, is not the same as explaining the wide variety of psychological responses towards BRCA1/2-mutation testing. Future studies should have a longer follow-up period, and larger numbers of respondents than in the current report. Furthermore, other measures besides distress, but also more well-validated measures of distress, may demonstrate the impact of genetic testing for women with an uninformative result in an even more meaningful way.

Traditionally, standard protocols for psychological counselling have especially focused on healthy women from HBOC families, analogue to the protocol for Huntington disease.[157] In contrast to this, our results with regard to an uninformative result suggest that women with a personal history of breast cancer, and especially among those with a high familial risk, may end up having at least as high levels of worry and distress after DNA-mutation testing as those testing positive. They may be a relatively neglected, but vulnerable subpopulation of DNA-mutation test applicants.

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8

Summary and General discussion

SUMMARY AND GENERAL DISCUSSION

The cumulative lifetime risk of developing breast cancer for a Dutch woman is about 12%.[1] In some families breast cancer seems to occur even more frequently or women fall ill at a relatively young age. Such families may have a genetic susceptibility towards breast cancer. To learn more about the likelihood of this susceptibility actually being present, members of such families may be eligible for genetic counselling and perhaps DNA testing.

The main purpose of this thesis is to provide more insight into the psychological impact of genetic counselling and DNA testing for breast cancer. Hereby we focus on risk perception, psychological well-being, and intentions for risk-management behaviours. The chapters in this thesis reflect different parts in the process of genetic counselling and DNA testing for breast cancer susceptibility. The first part focused upon the first consultation at the department of clinical genetics (Chapters 2 to 4). The second part dealt with the psychological effects of DNA testing, and especially the effect of an uninformative or inconclusive DNA result (Chapters 5 to 7). **Chapter 1** introduces the procedures and implications of genetic counselling and DNA testing for breast cancer. In addition to this, it provides an overview of the psychological research in this field.

The current chapter briefly summarises the main findings regarding the first genetic counselling session (first part) and DNA testing (second part). At the end of each part, some issues will be discussed in more detail. This Chapter concludes with some limitations and suggestions for future research.

GENETIC COUNSELLING FOR BEAST CANCER SUSCEPTIBILITY: FIRST CONSULTATION (CHAPTER 2 TO 4)

During an initial appointment, a counsellor records the family medical history and provides general information about hereditary transmission and the implications of high-risk mutations, such as BRCA1 and BRCA2. Based on the family pedigree, individualised estimates about the probability of detecting a BRCA1/2 mutation and the family's breast cancer risk status are usually made.[5] Four breast cancer risk categories can be distinguished: (1) general population risk, (2) a slightly increased risk, (3) a moderately increased risk, and (4) a highly increased risk. Depending on this personalized risk estimation, further medical options may be available, that is, a DNA test and/or risk-management options.

Chapter 2 addressed the motives of women applying for breast cancer counselling, as indicated in the pre-counselling questionnaire. One of the primary goals of an initial breast-cancer counselling session is to provide education about a wide range of risks and risk management options. To facilitate this comprehensive task,

a standard protocol is usually applied. This standard approach seems to ignore the fact that counsellees vary greatly with regard to their medical and socio-demographic background. Given the heterogeneity of the population of women who request counselling, we hypothesised that not all women would have the same counselling needs.

Our first goal was to identify clusters of informational needs. For example, would women who are primarily interested in obtaining surveillance of their breasts, be less interested in extensive counselling regarding prophylactic surgery, and desire relatively little information about the cancer risk to other family members. Results showed that it was not possible to form such clusters; almost all women had their own unique combination of motives. Hence, we could not discover specific counselling profiles that would better suit the needs of the individual counsellee.

Our second goal was to assess whether the sociodemographic and medical background of women would be associated with particular motives. Several relationships were indeed observed with regard to (a) the age of the counsellee, (b) whether she had children, (c) whether a BRCA mutation had been detected within the family previously, and (d) whether she had a personal history of breast cancer. For example, women with a personal history of breast cancer seemed relatively more interested in information regarding their children's risk than in knowledge about their own risk. Furthermore, worries about another cancer more often formed a motive for counselling.

In summary, although no specific clusters of motives could be identified, several medical and sociodemographic characteristics were associated with specific motives for applying for genetic counselling. Counsellors may benefit from knowing these differences in making the counselling tailored to the needs of the individual counsellee.

Whereas Chapter 2 dealt with pre-counselling issues, **Chapter 3** presented data from face-to-face interviews with women after the first counselling session. We focused upon women's personal ideas about the development or the reoccurrence of breast cancer and addressed the concept of an accurate risk perception. Normally, an accurate risk perception is conceptualised as the ability to mark the appropriate number of, or to label, a limited range of fixed answers. The general conclusion from such studies is that risk recall is poor and that this lack of accuracy gives reason for concern. In contrast to the usual methodology, we measured risk recall in the face-to-face interviews by allowing women to use their own words. Subsequently, we rated whether these verbalisations matched the objective risk.

We observed that women did not exclusively use numbers or qualitative phrases. Almost all women who spontaneously provided a numerical response used the same numbers as the counsellor had used. The few women, who did not provide

the correct numbers, seemed to be confused by the many risk figures that are communicated during the counselling session. In addition to this, the level of accuracy of qualitative phrases was hard to determine; it depended very strongly on the stringency of the criterion. For example, if we restricted the definition of an accurate response to the answers that exactly matched the terminology applied in the counselling (e.g., "highly increased"), only 26% of the counsellees provided a correct response. However, if we expanded the definition to all responses that reflected a correct notion of having a high or a relatively low risk, almost all counsellees met this criterion.

A second goal was to learn about the personal meaning and implications of being at risk for breast cancer. The wide range of responses we recorded seemed to match a well-know psychological theory about how people deal with stress, namely the Stress Coping Model of Lazarus and Folkman.[122] Several women expressed idiosyncratic risk beliefs, and some of them referred to their breast-cancer risk in terms of certainty instead of probability. Apart from beliefs about the risk and the magnitude of the risk, many women also spontaneously expressed stress responses and behaviours that were associated with their personal risk.

We were interested in whether these stress responses and perceived behavioural implications would be congruent with the objective risk and the related medical options. In general, this seemed to be the case. For example, all women who stated that they associated their personal risk with breast surveillance were or had been indeed eligible for mammography screening. We concluded that the conventional definition of an accurate risk perception that focuses exclusively on recall is not a sufficient indicator of the effectiveness of genetic counselling.

At the time of publication of **Chapter 4**, virtually nothing was known about decision-making for prophylactic surgery, and even less data were available on the potential influence of genetic counselling on this decision-making process. We wondered which factors would predict the intention to undergo prophylactic mastectomy. More specifically, we wanted to learn whether, and in particular how, providing personalised risk information contributed to the strength of this intention. We applied a path model that included this risk information, but also pre and post-counselling levels of worry, perceived risk of developing breast cancer, and having already had breast cancer.

We observed that the objective risk information was neither related to pre-counselling levels, nor to the change in the level of worry after counselling. Although the overall levels of anxiety slightly increased after counselling, this could not be attributed to the objective risk estimation. The only predictor of post-counselling worry in our model was whether or not women had had breast cancer. Women who had had breast cancer reported a higher level of worries after counselling, whereas the level of worry of unaffected women remained

stable. A similar effect was found for perceived risk after counselling. Unaffected women showed a somewhat stronger decrease in perceived risk after counselling, compared to affected women.

Furthermore, women only seemed to have a weak notion of their objective risk prior to counselling. This association between women's perceived risk and their objective risk improved with counselling, especially amongst women who learned that their personal risk was relatively low and who had previously overestimated it.

Finally, we examined which factors in our path model predicted the intention to have prophylactic mastectomy. Our findings suggest that the objective risk information during a first counselling session has a significant, but modest influence in determining the intention to undergo prophylactic mastectomy. Its influence seemed to be limited because the association between the objective risk and intention was indirect and relatively weak: conveying a relatively low objective risk diminished the desire for prophylactic mastectomy, and it diminished it by correcting the overestimated risk women reported before counselling. The most powerful and independent predictors of the intention to undergo prophylactic mastectomy were pre-counselling levels of both worry and risk perception. Worry and perceived risk were positively associated ($r = .39$), but they are clearly no substitutes for each other. They may each separately cover unique aspects of the process of decision-making for prophylactic mastectomy. Whereas risk perception may reflect a more cognitive awareness of being at risk, worry may have a more emotional underpinning. Both pre-existing emotions and cognitions predicted a higher desire for prophylactic mastectomy after a first counselling session.

Breast cancer history had no direct impact on the intention for prophylactic mastectomy. However, for affected women the kind of surgical procedure to treat their breast cancer seemed to be important: women who had undergone a mastectomy were more positively inclined towards a prophylactic mastectomy of the contralateral breast than women who had had breast-conserving therapy. Probably, uncertainty reduction and cosmetic reasons do not only apply to the decision how to treat breast cancer, but also to preventive management.

TOPICS REGARDING GENETIC COUNSELLING

In the following I will elaborate on some themes addressed in the first part. I will focus on the concept of an accurate risk perception. Secondly, some considerations regarding genetic counselling are described, and the potential impact of having experienced a personal diagnosis of breast cancer.

An accurate risk perception

One of the core goals of genetic counselling is to communicate complex risk messages. Therefore, comprehension of these risks is considered an important indicator of the effectiveness of counselling. This kind of effectiveness has been assessed by using a very narrow definition of risk perception, namely whether counsellees can rehearse the exact probability of a risk that has been communicated by a genetic counsellor. In Chapter 4, we observed that after genetic counselling the perceived relative-risk category was much more congruent with the relative-risk category communicated by the counsellor. However, many women still did not feel they belonged to the same risk category as that communicated by the counsellor. These findings are in line with other studies, including studies in other domains of health care,[117] that report a relatively poor recall of the correct risk estimate, even if improvements caused by genetic counselling are taken into account.[40;41;158] Commonly, concern is expressed about the low level of recall in those studies and it is usually concluded that in this respect the effectiveness of genetic counselling is quite low.

However, it is debatable whether such pessimistic conclusions are justified. One reason for this is that it may be too rigid to set the objective lifetime risk as the only golden standard, as women's actual breast cancer risk is not the same for all ages, but varies across the lifespan. Another reason concerns the validity of the method to measure risk recall; it is likely that the usual manner of measuring risk perception confounds risk recall with a personal evaluation of the risk. A typical example of such a question is, "What do you feel your lifetime risk of developing breast cancer is?".[159] Such questions can on the one hand elicit mere recall of the risk figures. In that case, responses can very well demonstrate whether the information has been brought across, yet it does not show whether it is interpreted in a correct manner. On the other hand, these questions may probe the interpretation or personal evaluations of the danger of the threat, without showing that the counsellee does not actually remember what is communicated. In other words, drawing conclusions from common means of measuring risk perception is problematic, because it is not clear what exactly has been measured: recall, or a personal interpretation of the risk.

Besides that this method confounds risk recall and a personal interpretation of the risk, it is also unclear which of these two concepts gives the most meaningful outcome. At first sight, a definition of perceived risk as mere recall may seem attractive. It makes sense that measuring recall demonstrates whether the information has been brought across. However, there are two major problems with this possible indicator of the effectiveness of genetic risk communication.

First, although an assessment of recall appears very robust and objective, it is less clear how answers should be interpreted. That is, the level of accuracy depends heavily on the error margins used for scoring accuracy. In Chapter 3, we

observed that accuracy greatly improved if we shifted our criterion from mere recall to a kind of global awareness of being at low or high risk. This relates to the second reason why risk recall is not the most relevant indicator of the effectiveness of genetic counselling. Although a correct retainment of the exact probabilities or categories may be a suitable first step, an appropriate interpretation of what the probabilities mean and which possible behavioural implications they indicate, reflects the effectiveness of genetic counselling in a better way. In other words, it depends on less clear-cut goals of genetic counselling whether inaccuracies are tolerable and which kind of inaccuracies must be corrected, because they may cause emotional or behavioural harm. Moreover, as shown in Chapter 3, the magnitude of the risk is only one facet of risk appraisal and must be integrated with prior risk beliefs, and the emotional and behavioural implications of risk. Risk information will only be effective if it is integrated into these beliefs, and translated into personal evaluations of what the risk means in real life. These reflections, such as, "am I in danger?" and "what is to be done?" may seem vague. Nevertheless, they should be a guiding element in determining whether counselling has been effective or not.

Considerations regarding genetic counselling for breast cancer

Genetic counsellors usually have more time to spend on their consultations than physicians in other medical specialities. Yet, at the moment, a lengthy consultation is inevitable, as the standard protocol requires that counsellees should not only receive a personalised risk estimation, but also should be educated about the hereditary basis of breast cancer, the probability of detecting a mutation and the probabilities and implications associated with having a BRCA1 or BRCA2 mutation. Results discussed in Chapter 3 suggest that several women tend to confuse these BRCA-related risks and medical options with their personal situation. This is probably due to information overload. At the same time, we did not find clear indications about how to reduce the large amount of information to prevent overload (Chapter 2). More specifically, we could not detect clusters of (informational) needs to tailor the information for each counsellee. A simple and practical solution for information overload is to provide a brochure of the general information before women arrive at the clinic. Presumably, a brochure will prevent counsellees from being overwhelmed and will make them more prepared with regard to the content of the counselling. This enables both counsellees and counsellors to spend less time on standardised education, in favour of using the time available for personalised and interactive counselling. For the time being, counsellors could do well to realise that counsellees might be burdened by information overload, and should always check carefully whether the relevant information is understood in a proper way.

Regarding the notion of highly personalised and interactive counselling, our results in chapters 3 and 4 suggest that prior beliefs and emotions may consti-

tute an important topic for the first assessment. In Chapter 4, we observed that pre-existing high levels of worry and perceived risk were the most powerful predictors of the intention to undergo a prophylactic mastectomy. In line with this, other studies show that pre-existing levels of distress are the most profound indicators of distress after counselling and DNA testing.[31] Probably, counselling is only a 'minor' event in the experience of dealing with the risk of breast cancer in the family.

In this respect it is important to keep in mind that familial breast cancer is presumably something that is not always prominent; during genetic counselling painful or hopeful cognitions and grief due to losses caused by cancer may come to the fore. For many women, if no cues are present, worries about familial breast cancer may not interfere with daily life (Chapter 3). Not only may the counselling itself be a cue for cancer-related memories, it is likely that many counsellees have been confronted with cancer shortly before referral. This is because the occurrence, or reoccurrence, of breast cancer in the family is often a reason for referral for genetic counselling. It remains unclear whether the burden of such cancer-related events can be separated from the experience of genetic counselling and DNA testing. Moreover, it is even conceivable that applying for genetic counselling may be a way to cope with the uncertainty and distress that are inherent to life-threatening diseases. The personal experience of the counsellee, including fears and emotional beliefs, is an essential element of the counselling interaction. Addressing prior risk appraisals and experiences, and openly discussing expectations about the consequences of the risk status, are important elements in making genetic counselling effective. It can be very helpful in tailoring the risk-communication process.

The impact of a previous breast cancer diagnosis

Recently, the psychological impact of genetic counselling and DNA testing for women who have had a previous cancer diagnosis has received more attention than previously.[160;161] In our study, women with breast cancer reported different motives for applying for genetic counselling than women who were unaffected. In line with other studies,[105] these women primarily seemed motivated to obtain knowledge for the sake of other family members (Chapter 2). Notably, affected women reported somewhat higher levels of worry after counselling than they reported pre-counselling. Furthermore, only unaffected counsellees perceived their risk as slightly lower after counselling (Chapter 4). A possible explanation for this is that affected women underestimate the implications of genetic counselling for themselves. Affected women may have felt relatively safe after having had breast cancer, and then learn during counselling about the risk of developing a new primary breast cancer.

A related point is, which perceived risk did we measure among affected women? We were interested in the perceived risk of developing a new primary

breast cancer, and worries associated with this event. However, it seems somewhat artificial to disentangle the risk of cancer recurring and the risk of a new primary tumor. Imagine a woman who is in follow-up for a breast cancer that has been treated some years ago. Can we expect her to make a clear-cut distinction between worries about her recurrence risk and worries about her risk of developing a new primary breast cancer? In comparing levels of worry and distress between groups of unaffected and affected women, it is likely that risk objects are not fully similar for everybody. In addition to this, it is very difficult for counsellors to estimate the exact risk of a second primary breast cancer. Therefore, the familial risk is usually conveyed. Although this familial risk also refers to affected individuals, to which extent it does so remains unclear.

We should be aware of these issues if we explicitly compare women who have had breast cancer with those who have not. The themes that are perceived as relevant, along with the psychological implications, may be somewhat different. However, all in all, it can not be concluded that a first genetic counselling session has negative psychological effects on most women who have had breast cancer.

DNA TESTING FOR BREAST CANCER (CHAPTER 5 TO 7)

A DNA test for breast cancer can yield five different results: (1) A mutation is detected on the BRCA1 gene, or (2) a mutation is detected on the BRCA2 gene. Both are associated with a dramatically increased lifetime risk of developing breast or ovarian cancer. Another possibility is a negative result for a family-specific BRCA1 or BRCA2 mutation, usually designated as (3) a 'true negative result'. These three results are usually called informative or conclusive. The remaining two types of results can both be considered inconclusive, as they formally provide no information beyond the pedigree-based risk assessment. They are: (4) a negative result in the absence of a family-specific BRCA1 or BRCA2 mutation, also called an uninformative test result, and (5) a variant is detected, of which it is unknown whether this is a pathogenic mutation or an innocent variant, also called a Variant of Uncertain Clinical Significance (VUCS).

Research about the psychological impact of receiving a DNA-test result has been quite narrowly focused on women without a personal cancer diagnosis who receive a conclusive result. Despite the narrow focus on this group of test applicants, the large majority of women who undergo DNA testing receive an uninformative result. In addition, many women who present for DNA testing do have a personal history of breast cancer. A prime aim of this thesis was to provide more insight into the psychological effect of an uninformative DNA test, for women with or without a personal history of breast cancer.

Chapter 5 described an explorative study on the impact of DNA testing which reveals a Variant of Uncertain Clinical Significance (VUCS). Concern has been expressed about possible anxiety and confusion associated with the communication of a VUCS result. Nevertheless, the psychological consequences of this type of result are even more under-researched than those of an uninformative result. This is indeed the first report that compared women who receive a VUCS result with other groups of test applicants. A serious limitation of the present report is that we could only include a small number of women who received a VUCS result. Therefore, the results should be considered as preliminary.

A priori, we were unsure about how women with a VUCS result would compare to other DNA test applicants. We identified some reasons why women with a VUCS result would react in a similar way to either women who learn that they carry a BRCA mutation, or to women with an uninformative result. In the first view, the psychological impact of a VUCS result is comparable to that of the detection of a deleterious BRCA mutation. This is because, in contrast to an uninformative result, both results mean that a variant in the gene is actually present. However, in case of a VUCS result it remains unclear whether the variant is harmless (polymorphism) or whether it is associated with a high cancer risk (mutation). In the second view, a VUCS result is comparable to that of an uninformative result. Arguments for this view are that in both cases the DNA test provides no clear-cut information beyond the pedigree-based risk assessment. As a consequence, clinical management recommendations are based on the pedigree-based risk estimation. Another similarity is that additional testing for family members is not routinely offered, whereas this is common practice in case of a BRCA mutation.

We found preliminary evidence for the latter view, as women who received a VUCS result reported the same overall levels of distress and perceived breast cancer risk as women with an uninformative result after disclosure. Furthermore, women with a VUCS result reported about the same perceived risk after DNA test disclosure as they did before disclosure. Surprisingly, they reported a significantly lower level of distress after learning their result. In addition, women with a VUCS result reported the lowest mean level of self-reported understanding of their result. However, this was not significantly different from women with either an uninformative result or BRCA-mutation carriers: All groups of test applicants had a significantly lower overall level of self-reported understanding than women who received a true negative result. All in all, women with a VUCS result seemed to be more comparable to women who received an uninformative result than to women who learned that they carry a BRCA1/2 mutation. Moreover, we did not find evidence that the communication of a VUCS result has a negative impact on psychological well-being.

Our goal in **Chapter 6** was to examine the false reassurance hypothesis. According to this hypothesis, women who receive an uninformative result may incorrectly conclude from this that they are no longer at an elevated risk. Put differently, they understand their result as if it was true negative in stead of uninformative. This assumed false understanding may be harmful for women's motivation to adhere to recommendations for breast screening, because they will possibly perceive no good reason to do so.

Our results suggest that an uninformative result may indeed provide reassurance regarding the perceived likelihood of carrying a deleterious mutation. Overall, women who learned that their result was uninformative reported a much lower perceived likelihood than they did before disclosure. On a group level this is appropriate, as the likelihood of a mutation being actually present is smaller. Despite this decrease, women with an uninformative result still reported a much higher likelihood than women who received a true negative result. In addition to this, only 12 out of 181 women who received an uninformative result reported that the likelihood of having a deleterious mutation was non-existent after DNA-test disclosure, which is an incorrect response by definition. Hence, although an uninformative result seemed to be reassuring regarding the perceived likelihood of carrying a deleterious mutation, we did not find indications that this reassurance was due to a widespread lack of understanding with concern to the meaning of the result. In other words, we did not find evidence for the false reassurance hypothesis.

In addition, the intention to have mammography screening did not change after an uninformative result. In the group of 66 unaffected women with an uninformative result who were eligible for screening at that time, 95% reported a positive intention. Even the few women who seemed to be falsely reassured did not report negative screening intentions. Only in women who received a true negative result, did we observe a large drop in the intention to have mammograms.

Finally, all women who learned that they carry a BRCA1 or BRCA2 mutation correctly responded that the mutation was detected. In addition to this, their overall levels of intention to have mammograms remained very high after testing. Moreover, if we excluded the women who reported that they would have a prophylactic mastectomy for certain, all remaining mutation carriers expressed a very positive intention towards mammography screening. Hence, we did not find indications for concern about a possible suboptimal level of mammography screening for both women with an uninformative result or BRCA-mutation carriers.

In the previous chapters we observed that women who receive an uninformative DNA-test result seem to respond with relief rather than expressing raised levels of distress. This finding was replicated in **Chapter 7**, and we found that relatively

low levels of worry and distress were maintained seven months after DNA-test disclosure. Therefore, we could not find evidence for the hypothesis that the uncertainty associated with an uninformative result causes distress. However, we argue that this might provide an incomplete picture, as women who receive an uninformative result constitute a group with a heterogeneous medical background. In the current chapter we indeed observed that two binary clinical features influenced the course of worry and distress of women who received an uninformative result; namely (a) having a personal history of breast cancer or not, and (b) having received a relatively low or a relatively high pedigree-based objective risk estimation.

The effect of the objective risk estimation was straightforward: women with a relatively high risk expressed more worry and distress than women with a relatively low risk. We observed a similar effect for having had a previous breast cancer: affected women reported higher overall levels of worry and distress than unaffected women. Besides this overall effect, affected women reported less relief from DNA-test disclosure than unaffected women. A comparison with the other groups of test applicants provided a frame of reference for interpreting these results. Women without a prior history of breast cancer and with a relatively low risk reported similar very low levels of worry and distress as women who received a true negative result. In contrast, affected women with a relatively high risk reacted rather different. Although their levels of worry and distress did not increase, they reported the same levels of worry and distress as BRCA-mutation carriers.

TOPICS CONCERNING THE EFFECTS OF DNA TESTING

In the following I will focus on some topics addressed in chapters 5 to 7. First, the effects of a conclusive DNA-test result will be outlined, that is the psychological and behavioural effects for women who learned that they carry a BRCA1 or BRCA2 mutation and the women who received a true negative result. Secondly, I will integrate results of part II on women with an inconclusive result, in particular for the women who receive an uninformative result. Finally, some general themes will be discussed: limitations and suggestions for future research.

A conclusive DNA-test result: psychological impact

It may be traumatic for currently healthy women to learn that they have a risk as high as 45 to 85% of developing breast cancer, especially as many of them have seen close family members suffering from the same condition. Despite this conceivable reaction to receiving an unfavourable result, we nowadays know that the majority of BRCA-mutation carriers do not experience alarmingly high levels

of distress. Our findings in the second part of this thesis are very much in line with what has been reported in the literature hitherto:[42;55] we observed rather stable levels of worry and distress among women who learned that they carry a BRCA mutation (Chapter 5 and Chapter 7). Their somewhat higher levels of worry immediately after disclosure returned to baseline levels seven months after test disclosure (Chapter 7). Furthermore, this lack of emotional harm did not seem to be caused by a false understanding of their new high risk status: BRCA-mutation carriers marked a higher relative risk category after disclosure (Chapter 5). In addition, all carriers indicated that they had the deleterious mutation for certain (Chapter 6).

In contrast to the relatively stable levels of worry and distress of BRCA-mutation carriers, women who received a true negative result seemed to experience relief after disclosure. In Chapter 5 no decrease in distress was observed, probably due to the low baseline levels of distress. However, in Chapter 7 we could observe a decrease still. Here we observed that women's already low levels of reported worry and distress decreased even further and were sustained up to seven months after disclosure. Moreover, these women reported a much lower perceived risk after disclosure (Chapter 5). Therefore, our results reinforce the currently optimistic view on the emotional consequences of DNA testing. It may be concluded that opting for genetic testing is psychologically beneficial for those who learn that their risk reverts to about average population risk level. Furthermore, it appears to do no harm to most women who prove to be BRCA-mutation carriers.

A conclusive DNA-test result: impact on risk management

Apart from the psychological effects, conclusive DNA testing for breast cancer may be beneficial from a clinical point of view. This is because, in contrast to several other genetic conditions, for example Huntington's disease, risk management options are available for those individuals who test positive. For women who prove to have a BRCA mutation, frequent surveillance of both breasts and ovaries is available. In addition, they may undergo prophylactic surgery on breasts and/or ovaries. Women who prove to have no special genetic vulnerability towards cancer do not face the potential dilemma of deciding for or against having prophylactic surgery, and may wish to withdraw from unnecessary surveillance. In line with the latter, we observed that women who received a true negative result reported a large decrease in their intentions to present for mammography screening in the forthcoming year compared to their intentions before DNA-test disclosure.

Regarding screening behaviours of BRCA-mutation carriers, concern has been expressed about a possible sub-optimal utilisation of surveillance options for BRCA1/2 mutation-carriers.[150;162] However, in Chapter 6, we found similar high levels of intended uptake among BRCA-mutation carriers to those women with

an uninformative result. Perhaps international differences in screening may reflect differences in healthcare systems, and whether availability depends upon coverage by assurance.[162] Moreover, in Leiden and Rotterdam, high-risk women have been very much encouraged to opt for intensive screening, which has been recognised as an important predictor of adherence to mammography.[151]

Another explanation for our favourable results is the relatively low level of cancer-specific distress among the women in our study. Although many studies support the notion of a motivating effect of breast-cancer worries,[72] some suggest that women who report more serious levels of distress will not adhere to screening guidelines.[163] In our study, we could not address hypotheses about the association between mammography use and distress, due to the very high levels of intended adherence of the large majority of women. Therefore, it remains possible that the positive intentions within our sample can be attributed to an absence of severe psychological cancer distress.

The follow-up time in our study was not sufficient to obtain a clear picture of the percentage of BRCA-mutation carriers actually undergoing prophylactic mastectomy. In Chapter 7 we did observe that 19% (8 out of 42) had a prophylactic mastectomy as soon as seven months after DNA-test disclosure. This percentage is certainly an underestimation of the percentage of women who will eventually undergo prophylactic mastectomy. Because of the small number of women who had had prophylactic mastectomy, it is premature to draw firm conclusions about the impact of this procedure on psychological functioning. Still, it is remarkable that we did not find a clear decrease in cancer worries and distress among these women. Our preliminary findings seem to be in line with Watson et al.[55], but contradict the report of Hatcher et al.[29] In the latter study, the levels of anxiety decreased among accepters of prophylactic mastectomy, with the decrease being greater the longer the time after surgery. This may suggest an explanation for our results: perhaps the relief from anxiety becomes more pronounced after having totally recovered from the procedure. The few women in our study who were operated upon responded to the questionnaire very soon after having had the surgery; we could have found more relief from surgery with a longer follow-up period.

An inconclusive or uninformative DNA-test result: psychological impact and screening intentions

In the literature, two contradicting hypotheses about the impact of an uninformative DNA test for breast cancer susceptibility have been posed: the 'false reassurance' hypothesis, and the 'uncertainty is harmful' hypothesis. The results in the second part of this thesis do not provide clear support for either of these hypotheses. They suggest that, as a group, women seem to be reassured upon learning their uninformative result, but to a lesser extent than women who received a true negative result. Only a small minority of women with an unin-

formative result incorrectly concluded that the chance of a mutation being present was non-existent (6.6%), which we used as a proxy for a false understanding (Chapter 6). Also in other studies a small subgroup of women does not seem to understand the uninformative result properly.[57;82;164] However, our results in Chapter 6 do clearly show that there is no evidence for widespread misunderstanding of an uninformative result. This is in line with recent findings in a large study which also included measures of relief from an uninformative result.[164]

In addition, an uninformative result did not seem to attenuate women's motivation with regard to complying with mammography screening (Chapter 6). It is especially important that unaffected women with an uninformative result also remain very motivated with regard to having mammograms. That is, because unaffected women are generally not yet included in a standard surveillance protocol. In summary, our results do not support the false reassurance hypothesis, nor the notion of potentially related adverse motivations to comply with screening guidelines.

Furthermore, we could not find support for the 'uncertainty is harmful' hypothesis, as we did not find any indication that either an uninformative result or a VUCS result was associated with psychological harm (Chapter 5 and Chapter 7). This was in particular the case for unaffected women with a relatively low objective-risk estimation who received an uninformative result (Chapter 7).

Why exactly affected women with a relatively high familial risk reported similar levels of worry and distress as proven BRCA-mutation carriers remains a topic of speculation until more in-depth data are available. Probably, this is associated with a subtle difference within the group of women with an uninformative result with regard to the primary aim of DNA-mutation testing. Women with a relatively low risk may opt for testing to gain additional reassurance from the finding that no BRCA1 or BRCA2 mutation will be proven. In contrast to this, women who had had breast cancer and who have a relatively strong family history may undergo DNA testing with the motive of making a BRCA mutation manifest. They now cannot confirm the aetiology of their own and their family cancer history, and they are unable to provide a new opportunity for informative DNA testing for their unaffected family members.

LIMITATIONS

Some limitations of the current study should be considered. One of these limitations is that our study predominantly relies on data from a single Dutch department of genetic counselling. Moreover, we could solely approach women who made an appointment for genetic counselling, and who were perhaps psychologically different from women at risk who did not present for counselling. In the

following paragraphs I will elaborate on the heterogeneity of the sample, and on problems associated with assessing distress.

Assumed similarities within subgroups of women

In this thesis we have assessed differences between groups of counsellees with regard to their personal cancer history, sociodemographic background or risk status. By doing so, we have suggested that individuals within these subgroups represent women with quite comparable backgrounds. However, it should be noted that within each subgroup individual differences still exist. For example, women who have had breast cancer differ greatly in the extent to whether, and if so how, they are still coping with their illness, partly due to differences in treatment and in time since their cancer diagnosis. But also unaffected women are dissimilar in their experiences with the illness. Indeed, women sometimes even put a very different meaning to the same kind of personal breast cancer experiences (Chapter 3).

A last example is that we did not distinguish between women who received an uninformative result from their own DNA test, or from their family member's DNA test. We think this is justified, mainly because the counselling procedure was very sensitive to the personal meaning and personal risk management implications of DNA-test results, rather than simply providing women with a family member's result. However, it may be still disputable whether the psychological impact is the same in both cases.

Assessing distress

Our conclusions regarding the lack of psychological harm due to DNA testing should be accompanied by some critical notes. A first important point is that reassuring conclusions in the literature, as well as in our own study, apply to the mean levels of psychological functioning after a DNA test-result. Thus, it can not be concluded that everybody will benefit from DNA testing, and we know that some will actually experience psychological harm.[57;165]

A second point is that the results are based on self-report on standardised questionnaires. Although the 'Impact of event scale' has been satisfactorily validated among a sample of women at risk for breast cancer,[166] concern has been expressed about the clinical interpretations that can be derived from the scale.[79] This criticism stresses the possibility of overestimating the level of psychological distress that reaches clinical levels. However, it is also suggested that standardised questionnaires may underestimate the real levels of distress. There are several indications that conclusions from these measures may conceal a subgroup of women who deny,[167] or trivialise their distress.[168] To summarise, it is not fully clear whether the Impact of event scale overestimates or underestimates the actual levels of distress. However, throughout this thesis we generally use these measures to detect potential changes over time instead of inspecting the absolute

levels of psychological functioning. In other words, the purpose of our study makes our measures somewhat less vulnerable towards most potential psychometric disadvantages or problems in the interpretation of scores.

Finally, although measures of risk perception, worry and distress are useful proxies to determine the psychological impact of DNA testing, they do not tell the whole story. Perhaps other measures besides risk perception and distress may demonstrate the impact of genetic counselling and DNA testing in an even more meaningful way. In addition to this, future studies may determine how they precisely fit into broader psychological models about coping and human health behaviour.

FUTURE RESEARCH

Rapid testing protocols for breast cancer patients

A relatively new development in the application of DNA testing is so-called rapid DNA testing in women who are newly diagnosed with breast or ovarian cancer. Results of this testing can be useful for cancer-treatment decision making. For example, if a BRCA1/2 mutation is detected, women may wish to undergo radical mastectomy on the affected breast, along with immediate prophylactic mastectomy on the contralateral breast. A drawback of this new development is that cancer patients are pushed towards genetic counselling and DNA testing. Moreover, they may be confronted with harsh news from genetics right at the time of their psychological adjustment to the shock of their cancer diagnosis.

With regard to having a prior cancer diagnosis, we have observed in the current study that it seems appropriate to be particularly sensitive to the psychological needs of former cancer patients who have a relatively high familial risk. This potential burden of a prior cancer diagnosis for women who opt for DNA testing may be important to keep in mind when considering new developments of rapid DNA testing. Cancer patients in these rapid testing protocols may be even more prone to worry and distress than the cancer patients in our study, who took the initiative themselves to acquire information about their genetic status. Studies are underway to assess whether this kind of knowledge immediately after a cancer diagnosis causes an overload of emotional stress,[169] or whether it does not.[170] In addition, it is examined whether women in these circumstances are sufficiently capable of informed decision making.

Counselling protocols: the counselling model versus the teaching model

In the literature on genetic counselling, two different styles of genetic counselling have been identified, the 'counselling model' and the 'teaching model'.[171] Content analyses usually show that genetic counselling protocols represent the teaching

or educational model.[38;172-174]. This means that counsellees receive much medical information from a counsellor who verbally dominates the dialogue, and little communication is devoted to psychological issues. Nevertheless, traditional definitions of genetic counselling not only reflect the goals of educational counselling. They also explicitly stress the importance of the counselling model, in which the needs and concerns of counsellees are the primary focus.[32;38] Indeed, counsellors mentioned responding to counsellees' needs as the main purpose of genetic counselling.[33]

In the current study we did not audiotape or objectively analyse the exact interactional content of the counselling process (see Pieterse[175] for a psychological view on the interactional content). Indeed, we even confined the counselling process to providing information about the familial life time risk and the disclosure of a DNA test-result, which does little justice to the more subtle interactional processes involved in genetic counselling. A consequence of disregarding these processes is that we do not precisely know whether important features of the interactional model were present or not. Moreover, these features will vary among individual counsellors, depending on their personal communication style and on the interaction with counsellees. Still, our data strongly suggest that applying (elements of) the counselling model is important in making counselling effective. That is, a dialogue in which women's prior beliefs, their evaluation of the risk information presented and concomitant levels of stress, are central.
However, to date it is unclear whether applying a protocol that is sensitive to pre-counselling needs and emotions will automatically lead to better patient outcomes. For example, Lobb et al.[173] showed in a prospective design that counselling which explicitly addressed emotional concerns resulted in higher levels of self-reported anxiety after counselling than mere educational counselling. They emphasise that distress is not necessarily a negative outcome of counselling. Probably, women need to discuss and experience their anxiety and feelings of grief first, to enable coping with these emotions and making decisions that reflect their personal values as well as a sensible knowledge about the medical information.[47;176] Further data are needed to clarify which combination of the counselling and educational model and accompanying skills lead to women's optimal psychological adaptation and optimal informed decision making.

Tailoring to individual needs

In this thesis we have presented evidence that predominantly reflects counsellees who seem to cope very well with knowledge about their risk status. Hence, our results support the view that genetic counselling and DNA testing do not lead to psychological harm in most counsellees.[40;42] In line with the latter, counselling protocols do not prescribe automatically referral to psychological counselling for women who present for conclusive DNA testing any longer.[3] However, further data are needed to safely assure the detection of the presumably few individuals

who will suffer from clinically significant levels of distress. In this respect, recent efforts to create short psychological checklists to identify individual counsellees who may have psychological difficulties during the process of genetic counselling are encouraging.[177]

With regard to the referral for psychological counselling, it may be important to realise that alarming levels of psychological distress are not a sole indication for psychological counselling. Perhaps the strong focus on supposed high levels of distress has been too one-sided. It may have hampered a clear focus on other, and perhaps more common, psychosocial needs of women at risk for genetic counselling. For example, psychologists and social workers may assist counsellors in guiding women's decision-making. They can help women to better anticipate the consequences of their decision and to identify personal values and adequate coping strategies. Furthermore, they can also support women with their new role as communicator of information about familial cancer risks, which is often experienced as a difficult duty.[178] Future research should continue with identifying womens' more specific needs and strengths, and how counsellors and psychosocial workers can adequately respond to these.

Nederlandse samenvatting

Kansen en veranderingen: De psychologische invloed van genetisch counselen en DNA-onderzoek voor borstkanker, gericht op vrouwen die een niet-informatieve uitslag krijgen.

In Nederland krijgt 1op de 8 vrouwen tijdens haar leven te horen dat zij borstkanker heeft. In sommige families lijkt nog vaker borstkanker voor te komen of ontwikkelen vrouwen borstkanker op een relatief jonge leeftijd. In dergelijke families zou sprake kunnen zijn van een speciale genetische gevoeligheid voor borstkanker. Om hier meer over te weten te komen, kunnen personen uit deze families in aanmerking komen voor genetische counseling en eventueel ook voor een DNA-test voor borstkanker.

Het voornaamste doel van dit proefschrift is om enkele aspecten van de psychologische invloed van genetisch counselen en DNA-onderzoek in kaart te brengen. We hebben in het bijzonder de invloed onderzocht op de waargenomen kans, psychisch welzijn en op de voornemens van vrouwen met betrekking tot borstcontrole en een preventieve borstoperatie.

Het proefschrift valt uiteen in twee verschillende delen. Het eerste deel richt zich op het begin van de genetische counseling (hoofdstuk 2, 3 en 4). Hierbij keken we vooral naar de invloed van een risico-inschatting door de counselor. Het tweede deel (hoofdstuk 5, 6 en 7) concentreert zich op de vrouwen die een DNA-uitslag te horen krijgen. We besteedden hier voornamelijk aandacht aan het effect van een zogenaamde 'inconclusive' of 'niet-informatieve uitslag'.

In **hoofdstuk 1** wordt de lezer vertrouwd gemaakt met de procedures en implicaties van genetisch counselen en DNA-onderzoek. Ook wordt er een overzicht gegeven van het psychologische onderzoek op dit terrein. Ten slotte wordt de opzet van het algehele onderzoek beschreven.

Eerste deel: genetisch counselen voor borstkanker, het eerste gesprek

Gedurende een eerste afspraak brengt de genetisch counselor de medische familiegeschiedenis in kaart met het tekenen van een stamboom. Ook wordt informatie gegeven over de overervingspatronen van mutaties en over de implicaties van mutaties die een hoog risico geven op borst- en eierstokkanker, zoals de zogenaamde BRCA1- en BRCA2-mutatie (BRCA=BReast CAncer). Op basis van de stamboom worden kansschattingen gemaakt. Bij de schatting van het familiaire risico om tijdens het leven borstkanker te krijgen wordt gewerkt met vier verschillende risicocategorieën, namelijk: (1) het populatierisico, (2) een licht verhoogd risico, (3) een matig verhoogd risico, en (4) een sterk verhoogd risico. Ook wordt de kans berekend om met een DNA-test een BRCA1- of BRCA2-mutatie zichtbaar te maken. Afhankelijk van de hoogte van deze risicoschattingen kunnen verdere medische opties besproken worden. Daarbij valt te denken aan

een DNA-test om wellicht meer te weten te komen over de hoogte van het risico of aan intensieve borstcontrole.

Hoofdstuk 2 gaat in op de redenen om een afspraak te maken voor genetisch counselen. Bij de eerste afspraak wordt meestal een standaardprotocol gebruikt om een grote hoeveelheid informatie te bespreken. Door een dergelijke standaardprocedure lijkt er weinig oog te zijn voor de individuele verschillen tussen adviesvragers. Gezien de nogal uiteenlopende sociaal-demografische en medische achtergronden van vrouwen die een afspraak maken, meenden wij dat waarschijnlijk niet alle vrouwen aan dezelfde aanpak en informatie behoefte hebben.

Ons eerste onderzoeksdoel was om specifieke behoeften aan informatie af te bakenen. Zou het bijvoorbeeld zo kunnen zijn dat vrouwen die voornamelijk geïnteresseerd zijn in een verwijzing voor intensieve borstcontrole, weinig behoefte hebben aan een uitgebreide uiteenzetting over profylactische chirurgie? Onze analyses wezen uit dat het niet mogelijk was dergelijke clusters of specifieke sets van behoeften in kaart te brengen: bijna alle vrouwen rapporteerden een exclusieve combinatie van redenen om een afspraak te maken. Doordat er maar weinig redenen leken te zijn die elkaar overlappen, konden we geen specifieke profielen ontwikkelen die beter aansluiten op de individuele behoeften van adviesvragers.

Het tweede onderzoeksdoel was gerelateerd aan het eerste doel, maar dan vanuit een ander perspectief: we wilden weten of de medische of sociaal-demografische kenmerken van de vrouwen samenhangen met specifieke redenen om een afspraak te maken. Inderdaad konden we samenhangen traceren voor een aantal kenmerken: (a) de leeftijd van de adviesvraagster, (b) het al of niet hebben van kinderen, (c) of er al of niet een BRCA-mutatie in naaste familieleden is aangetoond, en (d) of men zelf al of niet in het verleden borstkanker heeft gehad. Vrouwen die zelf borstkanker hadden gehad bleken bijvoorbeeld relatief vaak geïnteresseerd te zijn in risico-informatie met betrekking tot hun kinderen. En hoewel zij juist veel minder informatie over hun eigen risicostatus wensten dan 'gezonde' adviesvraagsters, gaven zij relatief vaak aan dat zorgen over het krijgen van een nieuwe kankerdiagnose redenen waren voor het maken van een afspraak.

Kortom, hoewel geen specifieke clusters van redenen gevonden konden worden, bleken verscheidene medische en sociaal-demografische kenmerken wel degelijk gerelateerd te zijn aan bepaalde motieven om een afspraak te maken. Het zou counselors kunnen helpen om alert te zijn op deze verschillen, zodat de counseling goed aansluit op de individuele behoeften van adviesvraagsters.

In tegenstelling tot hoofdstuk 2, waarin vrouwen vragen beantwoordden voordat zij daadwerkelijk een consult hadden gehad, bespreken we in **hoofdstuk 3** de gegevens van 'face-to-face'-interviews met vrouwen die hun eerste gesprek net achter de rug hadden. We onderzochten hoe vrouwen aankijken tegen de kans op het (opnieuw) krijgen van borstkanker. Daarbij richtten we ons op het hebben

van een 'accurate risicoperceptie'. In de onderzoeksliteratuur wordt vaak gesproken van een accurate risicoperceptie wanneer een respondent het juiste cijfer of label weet aan te kruisen op een lijstje met voorgedrukte antwoordmogelijkheden. Het juiste cijfer of label, ook wel het objectieve risico genoemd, is hierbij de risicoschatting die een genetisch counselor heeft verteld. In het algemeen is de conclusie uit dergelijke onderzoeken dat er reden tot zorg is, aangezien adviesvraagsters zich het objectieve risico slecht lijken te herinneren. Bij de face-to-face-interviews gebruikten we geen voorgedrukte antwoordmogelijkheden, maar noteerden we hoe vrouwen in eigen woorden hun risico omschreven. Vervolgens beoordeelden we in hoeverre deze persoonlijke verwoording overeenkwam met het objectieve risico.

Het bleek dat vrouwen hun risico op borstkanker niet uitsluitend in cijfers of in kwalitatieve termen uitdrukten. Daarbij viel op dat veruit de meeste vrouwen die spontaan een getal gebruikten, hetzelfde getal naar voren brachten dat de counselor had genoemd. De weinige vrouwen uit deze groep die niet het juiste getal noemden, leken hun eigen risico soms te verwarren met de risicogetallen die samenhangen met het hebben van een BRCA1/2-mutatie. De accuratesse van de vrouwen die hun risico spontaan in kwalitatieve termen uitdrukten was lastig te bepalen. Het hing er namelijk heel sterk van af hoe strikt de definitie geformuleerd werd van wat accuratesse inhield. Als we bijvoorbeeld bepaalden dat een verwoording exact overeen moest komen met de term die de counselor had genoemd (bijvoorbeeld 'sterk verhoogd') kon maar 26% van de antwoorden als accuraat bestempeld worden. Als we het criterium versoepelden, bleken er echter veel meer antwoorden juist te zijn. Als we bijvoorbeeld alle overgebleven antwoorden indeelden in een dichotomie van antwoorden die een hoog of juist laag risico reflecteerden, leken bijna alle respondenten een redelijk goede notie van hun risico te hebben.

Niet alleen wilden we weten hoe (goed) vrouwen hun eigen risico op borstkanker verwoorden, ook wilden we graag meer te weten komen over wat het risico op borstkanker voor vrouwen betekent. Op deze vraag kregen we zeer uiteenlopende reacties, die redelijk goed leken aan te sluiten bij een bekende psychologische theorie over hoe men met stress omgaat, namelijk het stress-coping model van Lazarus en Folkman.[122] Zo vertelden verscheidene vrouwen over hun persoonlijke theorieën met betrekking tot hun risico op borstkanker. Een aantal van hen beschreef hun risico niet in termen van een bepaalde kans, maar in termen van hun persoonlijke overtuiging om het al of niet te krijgen. Naast persoonlijke visies over het risico op borstkanker, noemden veel vrouwen gevoelens en gedragingen die voor hen met hun risico samenhingen.

We vroegen ons af of die gevoelens en gedragingen te herleiden zijn tot het objectieve risico en de medische (gedrag)opties die deze vrouwen te horen hadden gekregen. Dit bleek in het algemeen zo te zijn. Vrouwen die bijvoorbeeld spontaan vertelden dat hun risico voor hen betekende dat ze alert moesten zijn

door hun borsten goed te laten controleren, bleken in aanmerking te komen voor intensieve borstcontrole.

Op basis van onze resultaten concludeerden we dat een conventionele definitie van een accurate risicoperceptie, die zich dus exclusief richt op het letterlijk kunnen herhalen van risico-informatie, geen voldoende indicatie kan geven of de counseling effectief is geweest. Relevanter zou een inschatting zijn of de mate van psychische stress in verhouding staat tot het risico dat verteld wordt. Daarnaast is het belangrijk dat de gevolgtrekkingen die vrouwen maken over hoe ze het risico beheersbaar kunnen maken, overeenkomen met de medische opties die daadwerkelijk van toepassing zijn.

Op het moment dat we de gegevens voor **hoofdstuk 4** analyseerden, was er nagenoeg niets bekend over de besluitvorming rondom preventieve borstverwijdering. We vroegen ons af welke factoren zouden kunnen voorspellen of vrouwen al dan niet van plan zouden zijn om hun borst(en) preventief te verwijderen. Meer specifiek gesteld wilden we weten of het geven van een risicoschatting door de counselor van belang is bij het voornemen om een dergelijke operatie te laten uitvoeren. Om dit te onderzoeken maakten we gebruik van een zogenaamd padmodel, waarin de risicoschatting opgenomen was. Daarnaast keken we naar het waargenomen risico op borstkanker (risicoperceptie) en de mate van zorgen over het risico, zowel voor als na het horen van de risicoschatting. Ook hielden we er rekening mee of vrouwen al of niet borstkanker gehad hadden en zo ja, wat voor soort operatie zij hadden ondergaan.

Het bleek dat de hoeveelheid zorgen die men voor het eerste gesprek rapporteerde, niet samenhing met de risicoschatting van de counselor. Ook veranderingen in de hoeveelheid zorgen na het consult konden niet worden herleid tot de objectieve risicoschatting die vrouwen te horen hadden gekregen. Wat wel een verandering in de mate van zorgen leek te kunnen verklaren, was of vrouwen al of niet borstkanker hadden gehad. Vrouwen die in het verleden borstkanker hadden gekregen, rapporteerden gemiddeld meer zorgen na het eerste consult, terwijl de mate van zorgen van 'gezonde' vrouwen stabiel bleef. Een soortgelijk effect werd gevonden voor het waargenomen risico. Gezonde vrouwen leken hun schatting van het risico in sterkere mate naar beneden bij te stellen dan vrouwen die borstkanker hadden gehad.

Daarnaast waren vrouwen zich ogenschijnlijk slechts in beperkte mate bewust van hun objectieve risico, als we ons baseerden op de antwoorden op onze risicoperceptie-vragen. Geheel volgens verwachting verbeterde de samenhang tussen het objectieve risico en de perceptie van dat risico nadat vrouwen het objectieve risico hoorden. Dit was voornamelijk het geval bij vrouwen die vooraf meenden dat hun risico erg hoog was, terwijl ze in feite een relatief laag risico bleken te hebben.

Ten slotte onderzochten we welke factoren in ons padmodel konden voorspellen of vrouwen een preventieve borstverwijdering overwogen. Uit onze gegevens bleek dat een lage objectieve risicoschatting van de counselor ertoe bijdroeg dat men in mindere mate overwoog een preventieve operatie te laten doen. Dit effect was echter klein en bovendien indirect. Eerst had het objectieve risico namelijk een corrigerend effect op het waargenomen risico na de counseling. En vervolgens voorspelde dit waargenomen risico de intentie. Krachtiger voorspellers van een positieve intentie voor preventieve borstverwijdering waren een relatief hoog waargenomen risico en een hogere mate van zorgen die vrouwen al voor het eerste consult rapporteerden. Het waargenomen risico en de mate van zorgen hingen wel met elkaar samen ($r = .39$), maar bleken allebei onafhankelijke voorspellers. Dat betekent dat zij waarschijnlijk allebei afzonderlijk een relevant aspect zijn van het besluitvormingsproces en dus niet onderling inwisselbaar zijn. Waarschijnlijk reflecteert risicoperceptie een meer cognitief bewustzijn van het risico, terwijl de mate van zorgen meer de emotionele beleving weergeeft.

Wat geen directe invloed had op het voornemen om een borstverwijdering te laten doen was of vrouwen in het verleden borstkanker hadden gehad. Wel vonden we een verschil binnen de groep vrouwen die zelf borstkanker gehad hadden; degenen die een borstsparende operatie hadden gehad stonden afwijzender tegenover een preventieve operatie van hun borsten dan vrouwen die een zogenaamde radicale borstverwijdering hadden ondergaan. Wellicht spelen cosmetische overwegingen of overwegingen om zo weinig mogelijk risico te nemen niet alleen bij de behandeling van borstkanker een rol, maar ook bij de beslissing om borst(en) preventief te verwijderen.

Tweede deel: Een DNA-test voor borstkanker

Bij het doen van DNA-onderzoek zijn er vijf verschillende uitslagen mogelijk: (1) er wordt een mutatie aangetroffen op het BRCA1-gen, of (2) een mutatie op het BRCA2-gen, (3) een 'werkelijk negatieve uitslag', dat wil zeggen dat er bij het zoeken naar een BRCA1- of BRCA2-mutatie die binnen de familie bekend is, niets wordt gevonden. Deze resultaten worden vaak informatief genoemd. De andere resultaten worden inconclusive of niet-informatief genoemd, omdat zij, strikt gesproken, geen risico-informatie opleveren in aanvulling op de risicoschatting die op de stamboom is gebaseerd. Het gaat om een niet-informatief resultaat en om een variant met een onzekere klinische betekenis (VUCS).

Onderzoek naar de psychologische invloed van het horen van een DNA-uitslag is vooral gericht geweest op vrouwen uit families waar al een BRCA1/2-mutatie bekend is. Dit waren vrouwen die zelf geen borstkanker hebben gehad en die een duidelijke uitslag van een DNA-test krijgen. In de literatuur is tot nu toe weinig aandacht besteed aan het psychologische effect van een niet-informatieve

uitslag, terwijl de meeste vrouwen juist met deze uitslag worden geconfronteerd. Bovendien hebben veel vrouwen die een DNA-test ondergaan een borstkanker-diagnose gehad. In dit deel richten we ons met name op de psychologische invloed van een niet-informatieve DNA-uitslag. Daarbij betrekken we zowel 'gezonde' vrouwen als vrouwen die zelf borstkanker gehad hebben.

Hoofdstuk 5 is de weerslag van een exploratieve studie naar de psychologische invloed van een VUCS-resultaat. In het verleden is geopperd dat vrouwen een dergelijk resultaat slecht zouden begrijpen en dat ze zich er angstig en verward door zouden voelen. Ondanks die bezorgde verwachting was er over de psychologische invloed van een VUCS-resultaat zelfs nog minder bekend dan over de invloed van een niet-informatieve uitslag. De hier beschreven gegevens waren dan ook een eerste stap om in kaart te brengen hoe vrouwen op een VUCS-resultaat reageren. Aangezien er maar heel weinig vrouwen met een VUCS-resultaat met ons onderzoek meededen, moeten de resultaten met de nodige voorzichtigheid geïnterpreteerd worden.

Vooraf wisten we niet goed of de psychologische invloed van een VUCS-resultaat meer met die van een niet-informatieve uitslag te vergelijken was of meer met de invloed van een informatieve uitslag dat er daadwerkelijk een BRCA1- of BRCA2-mutatie gevonden is. Vrouwen met een VUCS-resultaat zouden bijvoorbeeld vergelijkbaar kunnen reageren als vrouwen die horen dat ze drager zijn van een BRCA1/2-mutatie, omdat men in beide gevallen geconfronteerd wordt met een daadwerkelijk aangetoonde variant of afwijking op het BRCA1- of BRCA2-gen. Een verschil is echter dat het bij een VUCS-resultaat onzeker is of het om een mutatie gaat die een zeer hoog risico veroorzaakt, terwijl dat bij de BRCA1/2-draagsters wél zeker is. Het is ook mogelijk dat een VUCS-resultaat als iets soortgelijks wordt ervaren als een niet-informatieve uitslag. Een reden hiervoor is dat er in beide gevallen, strikt genomen, geen aanvullende risico-informatie door de DNA-test wordt toegevoegd. Dat betekent dat de risicoschatting op basis van de stamboomgegevens van toepassing blijft en dat eventuele screeningsadviezen gebaseerd blijven op deze risicoschatting. Bovendien wordt na beide DNA-testuitslagen in principe geen DNA-test voor naaste familieleden aangeboden, terwijl dat na een nieuw aangetroffen BRCA1/2-mutatie altijd wel wordt gedaan.

In de huidige studie vonden we aanwijzingen dat het psychologische effect van een VUCS-resultaat inderdaad vergelijkbaar kan zijn met dat van een niet-informatieve uitslag. Beide groepen vrouwen rapporteerden namelijk na het krijgen van de DNA-test uitslag een vergelijkbare mate van psychische stress en ze meenden zelf gemiddeld een even hoog risico te hebben. Het waargenomen risico van vrouwen met een VUCS-resultaat veranderde nauwelijks nadat ze van de uitslag op de hoogte waren gesteld. Opmerkelijk was dat ze gemiddeld minder psychische stress rapporteerden na het horen van de uitslag. Verder meenden ze

zelf de uitslag iets minder goed begrepen te hebben in vergelijking met vrouwen die een andere DNA-uitslag kregen. Die inschatting was echter niet duidelijk afwijkend van die van vrouwen met een niet-informatieve uitslag en die van BRCA1/2-mutatiedraagsters. Alleen de vrouwen die een werkelijk negatieve DNA-uitslag kregen meenden dat ze de uitslag beter hadden begrepen dan alle andere vrouwen. De voorlopige conclusie uit dit hoofdstuk is dat de psychologische effecten van een VUCS-uitslag meer vergelijkbaar zijn met de effecten van een niet-informatieve uitslag dan met die van een daadwerkelijk aangetoonde BRCA1/2-mutatie. Bovendien had het meedelen van een VUCS-uitslag geen zichtbaar negatieve invloed op het psychologische welzijn van de betreffende vrouwen.

Ons doel in **hoofdstuk 6** was om de zogenaamde 'valse-geruststellings-hypothese' te onderzoeken. Volgens deze hypothese zouden vrouwen die een niet-informatieve uitslag krijgen dit ten onrechte opvatten als een 'werkelijk negatieve' DNA-uitslag. Of anders gezegd, zij zouden de conclusie trekken niet langer een verhoogd risico te hebben. Dat laatste is belangrijk, omdat vrouwen die een duidelijk verhoogde kans op borstkanker hebben aangeraden wordt voor intensieve borstcontrole te kiezen. Een verkeerd begrepen niet-informatieve DNA-uitslag zou negatief kunnen uitpakken voor de motivatie om gehoor te geven aan dat advies. Als iemands kans op borstkanker niet verhoogd is, waarom zou iemand dan extra alert blijven en voor intensieve controle kiezen?

Onze resultaten wijzen uit dat een niet-informatieve uitslag gemiddeld inderdaad een geruststellend effect heeft wat betreft het waargenomen risico op een mutatie. Na het krijgen van een niet-informatieve uitslag rapporteren vrouwen gemiddeld een lager waargenomen risico dan voordat ze de uitslag kregen. In feite is dit op groepsniveau een juiste conclusie, omdat de kans dat er toch nog sprake is van een mutatie inderdaad afgenomen is. Daarnaast was het belangrijk om te merken dat vrouwen met een niet-informatieve uitslag, ondanks hun lagere waargenomen kans om een borstkankergerelateerde mutatie te hebben, die kans veel hoger schatten dan vrouwen die een werkelijk negatieve uitslag kregen. Bovendien leken slechts 12 van de 181 vrouwen met een niet-informatieve uitslag ten onrechte te concluderen dat de uitslag betekende dat de kans om een mutatie te hebben uitgesloten was. Kortom, hoewel een niet-informatieve uitslag in het algemeen als geruststellend werd ervaren wat betreft het waargenomen risico op het hebben van een mutatie, leek er geen sprake te zijn van een grootschalig onbegrip over wat de uitslag betekent. We vonden geen steun voor de valse-geruststellings-hypothese.

In aanvulling hierop leek het voornemen om een mammogram te laten maken niet beïnvloed te worden door een niet-informatieve uitslag. In de groep van 66 gezonde vrouwen met een niet-informatieve uitslag die in aanmerking kwamen voor intensieve borstcontrole wilde 95% in het komende jaar een mammogram

laten maken. Zelfs de weinige vrouwen die de uitslag verkeerd leken te begrijpen, rapporteerden geen negatieve voornemens. Alleen vrouwen die een werkelijk negatieve uitslag kregen, waren in het algemeen niet langer van plan om een mammogram te laten maken.

Ten slotte leken alle vrouwen die hoorden dat zij draagsters van een BRCA1- of BRCA2-mutatie waren, dit goed begrepen te hebben. Ook bleven ze in het algemeen van plan een mammogram te laten maken. Sterker nog, als we alle vrouwen die aangaven dat ze zeker hun borsten preventief zouden laten verwijderen buiten beschouwing lieten, bleek dat alle draagsters vast van plan waren om een mammogram te laten maken. We vonden daarom geen reden tot zorgen over een suboptimaal gebruik van mammografie, net zomin voor vrouwen met een BRCA1/2-mutatie als voor vrouwen met een niet-informatieve uitslag.

In de hoofdstukken 5 en 6 wezen de resultaten uit dat een niet-informatieve DNA-uitslag in het algemeen eerder als geruststellend werd ervaren dan dat hij psychische stress tot gevolg had. In **hoofdstuk 7** bleek dit zeven maanden na de uitslag niet veranderd te zijn. De psychologische invloed van een niet-informatieve DNA-test hoeft echter niet voor iedereen hetzelfde te zijn. Onze conclusies zijn namelijk op het *gemiddelde* gebaseerd, terwijl de groep vrouwen die met een niet-informatieve uitslag worden geconfronteerd heterogeen is wat betreft hun medische achtergrond. De werkelijke psychologische invloed van een niet-informatieve uitslag zou dus wel eens wat minder eenduidig kunnen zijn.

We vonden inderdaad twee medische kenmerken die veranderingen in zorgen en psychische stress in de loop van de tijd konden verklaren, namelijk (a) of vrouwen al of niet zelf borstkanker hadden gehad, en (b) of vrouwen op basis van hun stamboomgegevens een hoge of minder hoge risicoschatting hadden.

Het effect van een hoge of lage kansschatting bij vrouwen met een niet-informatieve uitslag lag in de lijn der verwachting: vrouwen met een relatief hoog risico uitten in het algemeen meer psychische stress en zorgen over hun kans dan vrouwen met een lager risico. Een soortgelijk effect was zichtbaar voor vrouwen die zelf borstkanker hadden gehad. Zij rapporteerden in het algemeen meer psychische stress en zorgen over hun kans dan vrouwen die geen borstkanker hadden gehad. Bovendien bleken ze iets anders te reageren op de DNA-uitslag: vrouwen die borstkanker hadden gehad leken namelijk minder gerustgesteld te worden door een niet-informatieve uitslag dan gezonde vrouwen. Om onze resultaten in perspectief te zien, vergeleken we ze met de hoeveelheid zorgen en psychische stress van enerzijds BRCA1/2-mutatiedraagsters en anderzijds vrouwen met een werkelijk negatieve uitslag. Het bleek dat gezonde vrouwen met een relatief lage kans na het horen van een niet-informatieve uitslag ongeveer even weinig zorgen en psychische stress rapporteerden als vrouwen met een werkelijk negatieve uitslag. Vrouwen die borstkanker hadden gehad en die bovendien een relatief hoge kans op borstkanker hadden leken een niet-informatieve

uitslag echter duidelijk anders te ervaren. Hoewel hun zorgen en psychische stress niet toenamen na de uitslag, rapporteerden zij ongeveer dezelfde mate van zorgen en psychische stress als BRCA-mutatiedraagsters.

In **hoofdstuk 8** staat een samenvatting van de andere hoofdstukken, die in grote lijnen overeenkomt met deze Nederlandse samenvatting. Bij elk deel worden bovendien een paar onderwerpen nader toegelicht en van kanttekeningen voorzien. Na het deel over het eerste gesprek bij de klinische genetica (hoofdstuk 2, 3 en 4) ga ik verder in op het hebben van een accurate risicoperceptie, zoals dat naar voren komt in hoofdstuk 3. Ook probeer ik enkele conclusies ten aanzien van de counseling te trekken en komen eventuele verschillen tussen vrouwen die in het verleden met borstkanker geconfronteerd zijn en hen die geen borstkanker hebben gehad aan de orde. Na het tweede deel over het doen van een DNA-test (hoofdstuk 5, 6 en 7) geef ik een algemeen overzicht van de psychologische gevolgen van een informatieve en een niet-informatieve DNA-testuitslag. Ten slotte komen enkele beperkingen van het algehele onderzoek aan bod en mogelijke onderwerpen voor toekomstig onderzoek.

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Publications and Curriculum Vitae

PUBLICATIONS

Van Dijk S, Timmermans DRM, Meijers-Heijboer EJ, Tibben A, Van Asperen CJ, Otten W. Clinical characteristics affect the impact of an uninformative DNA-test result: the course of worry and distress experienced by women who apply for genetic testing for breast cancer. Journal of Clinical Oncology, 24: 2006; 3672-3677.

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CURRICULUM VITAE

Sandra van Dijk werd op 19 juli 1972 geboren in Harderwijk. De middelbare school doorliep zij in Amersfoort. Na haar eindexamen aan de Kardinaal de Jong MAVO in 1988, haalde zij in 1990 een HAVO-diploma aan het Eemland Noord College en in 1992 een VWO-diploma aan 't Hooghe Landt College. Vervolgens studeerde ze psychologie aan de Universiteit van Amsterdam. Daar genoot zij onder andere een opleiding tot trainer in sociale vaardigheden bij het Social Skills Lab en gaf in het kader van deze opleiding trainingen aan psychologiestudenten. In 1997 verwierf ze een zogenaamde Erasmus-beurs om haar afstudeeronderzoek binnen de richting sociale psychologie op te zetten en uit te voeren te Erlangen in Duitsland. Het werd een onderzoek naar de invloed van optimisme bij het verwerken van gezondheidsgerelateerde risicoinformatie. Tevens maakte ze een literatuurstudie over de verklaringen van het welbekende verschijnsel glimlachen.

Na het behalen van haar doctoraal examen in 1998 begon zij met promotieonderzoek in dienst van de Universiteit Leiden in het Leids Universitair Medisch Centrum bij de afdeling Medische Besliskunde en de sectie Erfelijkheidsadvisering van de afdeling Klinische Genetica. Het onderzoek werd door het Koningin Wilhelmina Fonds gesubsidieerd en de resultaten zijn in dit proefschrift beschreven. In 2003 werd haar en haar collega's een nieuwe subsidie voor onderzoek van het Koningin Wilhelmina Fonds toegekend. Ze werd post-doc onderzoeker bij dezelfde afdeling Medische Besliskunde, maar nu in dienst van het Leids Universitair Medisch Centrum. Een van de voornaamste doelstellingen van dit onderzoek is het in kaart brengen van de de psychologische gevolgen van een niet-informatieve DNA-uitslag op de lange termijn.