The Psychosocial Impact of Prophylactic Mastectomy and Salpingo-Oophorectomy

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The Psychosocial Impact of Prophylactic Mastectomy and Salpingo-Oophorectomy

De psychosociale impact van preventieve mastectomie en salpingo-ovariëctomie

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Voor mijn kinderen

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Introduction:
Background of Hereditary Breast and Ovarian Cancer

'My mother died from ovarian cancer when she was 52 years of age. Two of her sisters died from breast cancer before they reached the age of 60. Only one of my aunts survived breast cancer. My cousin developed breast cancer when she was 41 years of age. She and I are the same age. She sent me a so-called family letter after she was told to be a mutation carrier. That's how I found out that the breast cancers and ovarian cancers in our family were of an hereditary origin.'

Breast cancer accounts for about a quarter of all female cancers. The majority of all breast cancers worldwide occur in the USA and Europe. Of 12,000 to 13,000 new breast cancer cases that are annually diagnosed in the Netherlands, mostly in women above the age of 50 years, approximately 3,500 women (28%) die of the disease. The lifetime risk for breast cancer for a woman in the Netherlands is 12-13%. It is estimated that 5-10% of all breast cancer cases are caused by a definable genetic predisposition, which then is characterized by a young age at onset and a familial aggregation following a dominant inheritance pattern (www.cbo.nl).

Of 1500 cases of ovarian cancer that are yearly discovered in the Netherlands, 1100 women (73%) die of the disease (www.oncoline.nl). The lifetime risk of ovarian cancer is 1,5%. Ten percent of all discovered ovarian cancers are assumed to be of hereditary origin.

Since the cloning of the breast cancer susceptibility genes *BRCA1* and *BRCA2*, in 1994 and 1995 respectively, it became possible to identify families and individual women having a mutation in one of these genes. Mutations in those genes also explained the frequent association with ovarian cancer. Actually, it is estimated that *BRCA1/2* mutations are involved in 2-3% of all breast cancers. Other identifiable breast cancer susceptibility genes associated with a significantly increased risk of breast cancer, such as TP53 and PTEN*, occur less frequently[1,2].

1.1 Hereditary breast and ovarian cancer: the breast cancer risk

Women with an identified *BRCA1/2* mutation have a cumulative lifetime risk for breast cancer of 43-87% up to the age of 70 years, becoming relevant from age 25-30 years onwards[1-3]. Furthermore, after a history of unilateral breast cancer, mutation carriers face a significantly increased risk of 20-60% or 3% per year of developing contralateral breast cancer[4-6].

Although genetic testing for *BRCA1/2* and other susceptibility genes opened new perspectives for many families with breast cancer, in 75% of such families no causative breast cancer gene mutation is found. In such families, the individual risk of developing breast and ovarian cancer is estimated using pedigree data and genetic-epidemiological tables. For first degree relatives of breast cancer patients, the lifetime breast cancer risk will be significantly higher than the population risk, but not exceeding 50%[7,8].

1.2 Hereditary breast and ovarian cancer: the ovarian cancer risk

Next to a significantly increased breast cancer risk, women with a *BRCA1* or *BRCA2* gene mutation have lifetime risks of respectively 40-62% and 15-20% of ovarian/fallopian tube cancer[3,9], which is much higher than the population risk of 1,5%. The mean age at onset of ovarian/fallopian tube cancer is 50-54 years in *BRCA1* and *BRCA2* mutation carriers, respectively, some 10 years after the mean age of breast cancer at 41 years. The actuarial risk of developing ovarian cancer within a decade of breast cancer in BRCA1/2 carriers is 13% and 7% respectively[10]. In hereditary breast/ovarian cancer (HBOC) families (having no identified causative breast cancer gene mutation) the risk for ovarian cancer depends on the family history of ovarian/fallopian tube cancer.

For reasons of readability, *BRCA1* and *BRCA2* mutation carriers will be referred to as 'mutation carriers' and women from HBOC families will be referred to as '50% risk carriers' throughout this thesis. In combination, they will be referred to as 'high-risk women', with the exception of text where specifications about mutation status are necessary.

1.3 Management options

When a familial or genetic predisposition for breast and ovarian cancer is established in a woman, there are several management options, consisting of regular surveillance, chemoprevention or prophylactic surgery.

* Associated with resp. Li-Fraumeni syndrome and Cowden syndrome (cf. Oldenburg 2007).

1.3.1 Regular surveillance

Regular surveillance of the breasts enables the early detection of breast cancer for high-risk women, but that does not guarantee the detection and treatment of a tumor before metastasis has occurred. In the nineties, optimal breast cancer surveillance included a monthly breast self-examination, biannual clinical breast examination, and yearly imaging by mammography, starting at 25 years of age for a mutation carrier or 5 years earlier than the youngest case of breast cancer in the respective HBOC family. Recently, magnetic resonance imaging (MRI) was validated as superior compared to mammography for the early detection of invasive breast cancer in (inter)national studies, including the Dutch MRISC study[11,12]. The MRI scan for breast imaging is now part of the regular surveillance program for high-risk women in the Netherlands (www.ikcnet.nl/IKR).

Regular surveillance of the ovaries includes annual gynecological examination, serial transvaginal ultrasound examination and serum CA-125 assay. It starts at 35 years of age or 5 years younger than the earliest ovarian cancer case in the family, equally for mutation carriers and women from HBOC families[13]. Ovarian cancer may start in the ovaries, fallopian tubes, omentum or peritoneum and metastasizes very early, while the sensitivity and specificity of the screening techniques are relatively low. Therefore, the majority of screen-detected cases are diagnosed at a late and difficult or incurable stage[14]. A recent study in 3532 high-risk women has shown that screening did not differentiate between carriers and non-carriers. The authors concluded that periodic surveillance in high-risk women is ineffective in improving survival in *BRCA1/2* mutation carriers[15]. In the Netherlands, gynecologists and other involved specialists will therefore generally advise prophylactic (bilateral) salpingo-oophorectomy (P(B)SO) as of 40 years onwards.

1.3.2 Chemoprevention

Chemoprevention by tamoxifen may reduce the breast cancer risk in high-risk women by approximately 50%. Tamoxifen also reduces the risk of (contralateral) recurrence of breast cancer in both *BRCA1* and *BRCA2* mutation carriers[16,17] By its anti-estrogenic action, it is associated with side effects such as hot flashes, emotional mood disturbances and an increased risk of endometrial cancer[18] in postmenopausal women. Studies on the effect of tamoxifen in high-risk women were of small sample sizes, while complete data on the hormonal receptor status of the breast tumors were generally unavailable[16,17]. Moreover, sufficient data on the value of the agent are lacking for very young women. Therefore, it is not yet recommended as a preventive measure for unaffected high-risk women or outside of a clinical trial in the Netherlands.

For premenopausal women not yet considering P(B)SO, the use of oral contraceptives remains a matter of debate as this has been shown to decrease the risk of ovarian cancer by 60% in mutation carriers[19]. However, it is unclear whether the benefits on the ovarian cancer risks outweigh the increased breast cancer risk associated with oral contraceptives[20].

1.3.3 Prophylactic mastectomy

Prophylactic mastectomy (PM), i.e. the preventive removal of all fibroglandular breast tissue, is a radical risk-reducing strategy. It involves a *bilateral* PM in unaffected high-risk

women and breast cancer patients after breast conserving therapy, or a *contralateral* PM in breast cancer patients after unilateral mastectomy. In unaffected women, bilateral PM yields an approximate 95% risk reduction of breast cancer[12,20-22]. After unilateral cancer, it reduces the risk of cancer in the contralateral breast with >90%, however, without improving overall survival, as this mainly is dictated by the prognosis of the primary breast cancer[23].

Initially, most women (94%) at our institution opted for immediate breast reconstruction (IBR) after PM[22]. Previously, the surgical technique of PM and IBR in our centre consisted of implantation of a silicone prosthesis into a pocket created below the pectoral muscles[24]. Actually, delayed breast reconstruction (BR) using several techniques including tissue expanders/prosthesis implantation and breast reconstruction by means of autologous tissue are generally used[25], allowing a more individual approach for the respective women. Throughout this thesis, prophylactic mastectomy with or without (immediate) breast reconstruction will be referred to as PM/(I)BR unless further details on the actual procedure are relevant and specified.

Complications are experienced by nearly one-third of all women after PM/(I)BR, such as bleeding, capsular formation and poor cosmetic appearance[25-27]. These may lead to additional surgical interventions, or aesthetically unsatisfactory results. Furthermore, breast cancer treatment prior to (contralateral) PM might compromise the result of breast reconstruction. Radiotherapy was reported as a cause of early and late complications and unfavorable cosmetic outcome of PM/(I)BR[27]. Recent experience showed identical complication rates in unaffected women and women with a history of breast cancer (hereafter called 'affected') undergoing PM/(I)BR[23].

1.3.4 Prophylactic (bilateral) salpingo-oophorectomy

Prophylactic (bilateral) salpingo-oophorectomy (P(B)SO) is preferably done by laparoscopic removal of the ovaries and the fallopian tubes. If during surgery problems arise, e.g. because of previous abdominal surgery or bleeding, the gynecologist has to convert to a laparotomy to perform the oophorectomy. P(B)SO reduces the risk of ovarian/fallopian tube cancer with approximately 80%[9]. Moreover, P(B)SO in premenopausal women gives a substantial risk reduction of breast cancer of approximately 50% [28,29].

The cancer risk cannot be eliminated completely by P(B)SO. The residual risk for an abdominal (peritoneal, omental) cancer is 2-4%[9], as the peritoneal mesothelium shares its embryological origin with the ovarian germinal epithelium. Therefore, women may still feel vulnerable after P(B)SO.

P(B)SO may be associated with surgical complications such as bleeding and infection, especially after an abdominal procedure, being the case in approximately 5-11,5% of all patients[29,30]. Other physical consequences of P(B)SO are related to the surgically induced menopause. Menopausal symptoms are more severe and of rapid onset when induced surgically[31]. Hormone replacement therapy (HRT) might alleviate menopausal complaints such as impaired quality of life and might postpone possibly unwarranted effects with respect to bone and cardiovascular health. However, HRT might in turn negate the risk reducing effect of P(B)SO on the development of breast cancer.

1.4 Uptake of prophylactic surgery

There is a very wide variation in uptake of prophylactic surgery worldwide. In a recent survey, the largest uptake of PM/(I)BR is found in the USA (36,3%) and of P(B)SO in Norway (73,5%)[17].

At our centre, the average uptake for PM/(I)BR and P(B)SO is 32,7% and 64,2% respectively, consisting of both affected and unaffected high-risk women[17]. One third of the total group of 358 women undergoing PM/(I)BR at our centre between 1994-2004 were 50% risk carriers[25]. The uptake of prophylactic surgery for mutation carriers specifically was 35% of affected and 51% of unaffected mutation carriers for PM/(I)BR, and 49% of affected and 64% of unaffected mutation carriers for P(B)SO[32,33].
The majority (approximately 60%) of all women having PM/(I)BR also opted for P(B)SO[25,34].

1.4.1 Predictors of uptake of PM/(I)BR and P(B)SO

Age and a family history of breast and/or ovarian cancer were found to be predictive for the uptake of both PM/(I)BR and P(B)SO[32-37]. Younger age (<50 years) was related to the uptake of PM/(I)BR in both unaffected and affected mutation carriers[32,33]. (Older) age also proved to be predictive regarding the uptake of P(B)SO in both (namely unaffected) mutation carriers[32] and in 50% risk carriers[37]. An explanation for age being predictive for the uptake of P(B)SO might be that physicians following ovarian cancer risk management guidelines would recommend P(B)SO to high-risk women aged 35 or older, and be less directive towards oophorectomy when younger women are concerned[38,39].

1.4.2 Predictors of uptake of PM/(I)BR

Parenthood seemed to be a predictive factor for the uptake of PM/(I)BR (opted for by 61% of mothers vs. by 14% of childless women). Interestingly, this effect was even larger when combining age <50 years and parenthood, resulting in 70% of mothers aged <50 years opting for PM/(I)BR[32]. Though the authors made no attempt in explaining this finding, it might reflect a motivation for PM/(I)BR, namely the responsibility felt by women towards family members[40].

Two studies reported on the effect of increased risk-perception in women opting for PM/(I)BR. Metcalfe et al.[41] found that women with a limited or strong family history of breast cancer displayed 'exaggerated' perceptions of their breast cancer risk before surgery. Only mutation carriers were found to have an adequate estimate of their breast cancer risk. However, the retrospective nature of their study and the lack of a reference group weaken their results. Moreover, they do not explain what they considered as 'exaggerated', so results and/or conclusions cannot be extrapolated. Bebbington Hatcher et al.[42] found that women opting for PM/(I)BR had higher risk-perception than women who did not opt for PM/(I)BR (43% vs. 18% respectively). However, they did not report on possible differences between both groups on actual risks (that were probably known to the participants in their study, since they mentioned that genetic status was determined by the referring clinician in all before referral for surgery) and therefore this result is not founded for a solid conclusion. Further research is necessary in order to establish the effect of risk perception on the actual uptake of PM/(I)BR.

1.4.3 Predictors of uptake of P(B)SO

A personal history of cancer was found to be predictive of the uptake of P(B)SO[36]. Expected relief from cancer worry predicted P(B)SO uptake for both affected and unaffected high-risk women[44]. Moreover, mutation carriers who were more likely to opt for P(B)SO had poorer perceived general health, believed in the incurability of ovarian cancer and had higher levels of perceived benefits of P(B)SO compared to mutation carriers who did not opt for this procedure[43]. The effect of these variables in 50% risk carriers remain yet to be investigated.

In a study on 160 mutation carriers opting for either P(B)SO (n=118) or regular surveillance (n=42), lower educational level was reported as strongly related to the uptake of P(B)SO[43]. Mutation carriers in the low, middle and high educational level opted for P(B)SO in 85%, 75% and 60%, respectively. The authors found that the low educational group had a good reported knowledge on the risks associated with the disease and the differences of between P(B)SO and surveillance. However, they started speculating on 'too promptly' following physician's advice to decide for P(B)SO, and on missing the larger sets of considerations of deciding for or against P(B)SO, that might be open to mutation carriers with higher education. These speculations are distracting from the fact that the women in the low educational group potentially made perfectly reasonable and motivated choices in view of a realistic perception of their severe health risks. A more realistic conclusion would have been that the choice for the highest protection seemed to be the most difficult for the high educational group.

PM/(I)BR and P(B)SO have been increasingly performed since the discovery of the *BRCA1/2* gene mutations. Results of studies on the psychosocial impact of these prophylactic surgeries are discussed in Chapter 2.

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2

Introduction:
Literature Review of Psychosocial Aspects of Prophylactic Mastectomy and (Bilateral) Salpingo-Oophorectomy

'Surgery itself turned out better than I expected, but the cosmetic results are very disappointing. The worst thing of all is that my husband does not want to touch me anymore. Nothing is left of our sex life. When I turn emotional, he pretends to not see my crying. I really long for him to wrap his arms around me. I haven't talked to him about it because he is not a talkative person. Moreover, I am afraid he will confirm my ugliness.'

As PM/(I)BR and/or P(B)SO are momentarily the most effective risk reducing strategies for high-risk women, better knowledge of the psychosocial consequences becomes increasingly important in order to adequately inform and support these women when considering and deciding for prophylactic surgery. Moreover, diligently exploring expectations and experiences of high-risk women and their partners might assist them in anticipating and jointly adapting to the outcomes of PM/(I)BR or P(B)SO.

In the past decade, data were presented on decision making regarding prophylactic surgery, satisfaction and regrets with the procedure and its consequences, distress in the period prior to and after prophylactic surgery, and the effect of prophylactic surgery on body image and sexuality. In the following paragraphs the data from the literature are reviewed.

2.1 The psychosocial impact of PM/(I)BR

2.1.1 Population characteristics

In the reported literature, the average age at time of PM/(I)BR in high-risk women was 35-46 years (range 20-73)[1-12]. Most cohorts consisted of mutation carriers (13-100%) and/or 50% risk carriers (55-100%), and the majority of women did not have a personal history of breast cancer (92-100%)[1,2,4,5,7,10,13,14]. Affected mutation carriers who opted for PM/(I)BR were more likely to have their breast cancer manifested after the identification of a *BRCA1/2* mutation in the family[13], or were more often treated with mastectomy instead of breast conserving therapy[15]. The majority (63-100%) of high-risk women had opted for (I)BR after PM[1-6,8,10,11,14,16] and 14-63% of women who underwent PM/(I)BR also underwent P(B)SO[7,9,17,18].

2.1.2 Decision making

High-risk women reported concurrent considerations for opting for PM/(I)BR. Nodular breasts and worrisome biopsies[3] were strong motivators. Also, risk reduction[3], expected relief of fear of developing breast/ovarian cancer[3,6], the obligation felt by women towards family members[8,19] and physician's recommendation[3,6] were found to be driving motivations for women to decide for PM/(I)BR.

2.1.3 Satisfaction and regrets

Most women (70-100%) reported being satisfied after PM/(I)BR[1-5,10,11,14,19]. Women who were satisfied with their decision to undergo PM/(I)BR were aged 50 years or older and had a limited family history of breast cancer[10]. Moreover, women who opted for PM/(I)BR because of their family history or women who opted against breast reconstruction, were more likely to be satisfied with the procedure[3]. When PM/(I)BR had had little or no impact on the sexual relationship[3], such women were more likely to be satisfied with their decision.

Dissatisfaction or regrets about PM/(I)BR are reported in 5%[2]. These women more often indicated that they followed their physician's advice[2,3]. They also reported lack of (emotional) support[3,6] and insufficient information about the procedure and its possible consequences[3]. Post-surgery, they experienced pain[6], surgical complications[3,6,20] or prosthesis related complaints[6,20,21]. When the breasts were reconstructed, dissatisfied women were more likely to be worried that the implants would impede the detection of breast cancer[6]. Finally, women with regrets were also dissatisfied with the cosmetic results of PM/(I)BR or had a diminished self-image and experienced less sexual satisfaction[6].

One study, that was conducted in Ontario during 1991-2000, addressed satisfaction with the cosmetic result of immediate breast reconstruction after PM[11]. Most women (97%) in their cohort of 60 women felt satisfied (17%) or extremely satisfied (80%) with their decision. Women with an increased risk perception before and after surgery, who experienced increased worry of developing breast cancer and a worsened body image after the procedure, and who reported a lasting experience of physical discomfort as a result were more likely to be dissatisfied with the cosmetic outcome of IBR. Type of PM (total 88% or subcutaneous 12%) and type of IBR (51% saline implants versus 49%

transverse rectus abdominis musculocutaneous (TRAM) flap) were unrelated to satisfaction with the cosmetic result of IBR[11].

2.1.4 Distress

Generally, distress was increased in high-risk women prior to PM/(I)BR[8,16]. Increased distress before surgery seemed related to knowing of being at risk, approaching the age at which relatives had been diagnosed with cancer, the development of breast cancer in relatives, and/or parenthood[8]. These causes of distress were reported by several women, without attempts at quantification.

After PM/(I)BR, most women experienced a decrease in distress until it reached normal levels[3,6-10,14,16,22]. Interestingly, post-surgical distress remained at a stable level up to 3,5 years[4]. However, not all women experienced a decrease in distress. Metcalfe et al.[10] found that 8% of all women post-surgically experienced cancer-related distress at a clinical level. Women who experienced increased distress up to 5 years post-PM/(I)BR were more likely to be younger and at higher actual breast cancer risk[10], to have children under the age of 15 years, to experience a less open communication of cancer issues within their family and changes in relationships with relatives, or to doubt about the genetic test outcome[9]. They were often worried about their children's risk or their personal risk of developing ovarian cancer[8]. Furthermore, they were more likely to have an inaccurate[4] or continued increased risk-perception[3,10]. Finally, the level of cancer-related distress at baseline proved to be predictive of post-surgical distress, up to 5 years post-surgery[9].

2.1.5 Body image

Inherent to the nature of PM/(I)BR one may expect changes of the body image after such radical surgery. Also after P(B)SO, especially in premenopausal women, the surgically induced menopause may cause symptoms associated with bodily changes. Accordingly, many studies[3,4,6,7-11,14,16,22] analyzed effects on body image as an outcome variable.

Generally, a *negative* impact on body image after PM/(I)BR was reported. Five years after test disclosure, most mutation carriers opting for PM/(I)BR reported less satisfaction with general and breast-related body image than non-carriers[9]. More specifically, a quarter to nearly half or 12-53% of all women reported adverse effects on the appearance of their body (i.e. were self-conscious about their appearance, felt less physically attractive, were dissatisfied with their body, naked and dressed, all as a result of PM/(I)BR with and without breast reconstruction)[3,4,6,10,11,22] and an equal proportion of women reported a change in feelings of femininity[3,4]. Dissatisfaction with the surgical scars was reported by a third to almost half of all women (33-44%)[4,22]. Moreover, women without breast reconstruction were less satisfied with their bodies than women with breast reconstruction[4,10].

In a retrospective study on 370 high-risk women who underwent PM/(I)BR, 16% judged their cosmetic results as unacceptable[2]. However, this study collected cases from all over the United States between 1945 and 1996 and therefore reflected the experiences of several small and large centers of that period. Moreover, in analyzing retrospective data, one is also missing the expectations of the patient on the outcomes of PM/(I)BR on body image. Results of a prospective study performed in our centre[7] have shown that mutation

carriers opting for PM/(I)BR reported having more problems with body image already *prior to* PM/(I)BR compared to mutation carriers who opted for regular surveillance. Though these first results ask for validation, it stresses the importance of pre-surgical assessments in order to be able to adequately interpret post-surgical results.

The effect of PM/(I)BR on body image was earlier analyzed in 79 high-risk UK women[16] reporting no 'detrimental' effect on body image. However, they did not present pre-PM/(I)BR levels to judge the meaning of the post-PM/(I)BR values. Their conclusion about unchanged body image seemed therefore not supported by their data.

In two studies of whom all participants had (I)BR after PM, an *improved* body image was reported by 64-87% [5,1]. A positive effect on body image was also noted in the US retrospective series (1979-1999) by observing that 79% of women were somewhat to not at all self-conscious about their appearance after PM/(I)BR, while 58% of them were very much to quite a bit satisfied with their appearance when dressed[14]. The majority of women (84%) in that study had (I)BR following PM. However, a major limitation of that study is that the researchers administered a self-developed survey, based on a very limited amount of questions from existing questionnaires on satisfaction, distress, body image and sexuality[14]. The study might have been more valuable if their psychometric values had been validated. Still, these positive reports on body image support the hypothesis by Metcalfe et al.[10] that breast reconstruction may improve body contours, but that scars and disfigurements may cause problems in intimate situations.

Finally, type of prophylactic mastectomy (total or subcutaneous) did not seem to have an impact on body image[10], though this result was based on unequal percentages of both types of PM (88% total vs. 12% subcutaneous) in a relatively small sample (n=60).

2.1.6 Sexuality

Most women in studies on the effect of PM/(I)BR on sexuality were sexually active before (57%) and after (68-84%) PM/(I)BR[9,10,16]. Two prospective studies found no effect of PM/(I)BR on habit, discomfort or sexual activity[16,22]. Still, adverse effects of PM/(I)BR on sexuality were reported by several studies [4,6,7,9,10,14,22]. One prospective study[16] initially found no differences in quality of sexual life after PM/(I)BR, but together with their interview data[8], the same problems were reported by some women as in other studies: problems with touching of the breasts because dislike of the sensation, and detrimental or positive effects for a few. The different outcomes reported from questionnaire or interview data of the same group of women is not unusual: traditionally, many respondents express themselves not easily on intimate matters in questionnaires, which explains their 'average or unchanged scores' for all these items. However, when asked confidentially in an in-depth interview, they are very willing to explain their sorrows.

Generally, half (48%-55%) of all women felt less sexually attractive after PM/(I)BR[4,22] and 32-69% of them experienced untoward changes in their sexual relationship[6,7,9,10,22], such as difficulty in reaching an orgasm and less pleasure during intercourse. An estimated 43% of high-risk women were satisfied with their post-PM/(I)BR sex lives[14], which equals the 38% of women being under gynecologic surveillance, who expressed satisfaction with sexuality. Changes in the sexual relationship seemed independent of type of PM or presence or absence of breast reconstruction[10]. Some of the problems with sexuality

might have been present before prophylactic surgery or genetic testing, as was observed by Lodder et al.[7]. Unfortunately, further data of larger cohorts on possible pre-surgical intimacy problems are lacking.

2.2 The psychosocial impact of P(B)SO

2.2.1 Population characteristics

Average ages of women opting for P(B)SO were 39-51 (range 31-70)[18,23-28]. Studied cohorts consisted of mutation carriers (40-100%)[17,18,26,28,29] and/or 50% risk carriers (52-93%)[23,24,26,27]. A third to all (29-100%) studied women were premenopausal prior to P(B)SO[17,18,23,25,26,28-30], and 20-83% had a personal history of breast cancer [17,18,23,25,26,28].

Many studies compared women opting for P(B)SO with women choosing regular surveillance[17,18,23-25,28,31,32]. Women opting for P(B)SO were older (>35 yrs), were more likely to have children, and were more likely to have undergone PM/(I)BR than women opting for regular surveillance[17,18]. Moreover, women who opted for P(B)SO were more likely to have a personal history of breast cancer[17,23], a strong family history of breast cancer[25] or have a *BRCA1/2* mutation[17]. Finally, women opting for P(B)SO were more likely to have a first degree relative who died from ovarian cancer than women who opted for surveillance (87% vs. 41%)[24]. Recent prospective data showed that mutation carriers opting for P(B)SO were more likely married and postmenopausal compared to mutation carriers opting for surveillance[18]. Furthermore, mutation carriers had poorer general health perceptions, higher levels of risk-perception levels, increased (ovarian) cancer worry for themselves and relatives at risk, experienced more intrusive thoughts, viewed ovarian cancer more often as an incurable disease and perceived P(B)SO as having more pros and regular surveillance as having less pros than mutation carriers opting for regular surveillance[18].

2.2.2 Decision making

For P(B)SO similar motivations were reported as for PM/(I)BR, such as risk reduction[25,31], expected relief of fear of developing breast/ovarian cancer[24,31], the obligation felt by women towards family members[24,25,27] and physician's recommendation[25,27].

Age was another important motivation for high-risk women opting for P(B)SO[25,31], combined with childbearing issues[25]. Other motivations concerned the family history of ovarian cancer or one's personal mutation status[31], regular surveillance concerns (i.e. worries about effectiveness[25,31] and aversion/inconvenience of attending the clinic on a regular basis[27]), cessation of menstruation[27,31], and longing for relief of (benign) gynecological problems[25,27]. Also, the patient's belief she will become affected by ovarian cancer was a powerful motivator, as was found in 35% of British women who had decided for P(B)SO[24]. 'Many' other women in that study were motivated by the death of a mother, a sister or a relative in a similar generation (i.e. cousin). Finally, fear of dying from ovarian cancer is a clear motivator for deciding for P(B)SO[25].

Medical indications for P(B)SO may occasionally arise during the decision process, like abnormal results of a screening test or abdominal pain. In the Hallowell study[24], in one of five of such cases, ovarian carcinoma caused by a *BRCA1/2* mutation was found.

2.2.3 Satisfaction and regrets

Most women (79-97%) reported being satisfied after P(B)SO[17,25-27,30,32,33]. Seven to thirteen percent of women reported regrets. The occurrence of sexual problems (i.e. painful penetration, lack of desire and arousal, difficulty in reaching an orgasm and vaginal dryness in 42%-58%) predicted lesser satisfaction with P(B)SO[26].

2.2.4 Distress

Most high-risk women (96%) who opted for P(B)SO reported increased anxiety pre-surgery[24], which was influenced by their experiences with cancer in the family. After P(B)SO, most high-risk women experienced decreased cancer-related distress[17,26,30,33], with distress levels equal or lower than in women who opted for regular surveillance[17,23]. Not surprisingly, given the effect of PM/(I)BR on levels of distress, levels of cancer worry in P(B)SO women who also had undergone PM/(I)BR were lower than those of women in the regular surveillance group who had undergone PM/(I)BR[17]. This relief of cancer worries also led to a decrease in cancer worries about the risks of relatives, and improved mood and functioning[17].

P(B)SO did not eliminate distress in all women; a variable percentage of women (9-21%) had continuing significant ovarian cancer-specific worries[17,26], with some (9-26%) at clinical levels[17,18]. The factors that contributed to this ongoing distress were not clarified by the authors, and remain yet to be investigated.

2.2.5 Body image

The effect of P(B)SO on body image is unclear, with two studies reporting no effect[28,33] and two reporting adverse effects[23,27]. Recently, a one year follow up of 38 high-risk women opting for P(B)SO and 37 being on regular surveillance showed no differences in body image between both groups[28]. However, Fry et al.[23] found a difference in body image at item level ('I find it hard to look at myself naked') in women after P(B)SO compared with women in the gynecologic surveillance group. This difference was suggested to be partly accounted for by previous diagnoses of breast cancer in the surgical group. However, when excluding this group of affected women, the difference remained significant. Unfortunately, the authors made no attempt at explaining this finding.

In an in-depth study of 14 women, most women (93%) reported no adverse effects of P(B)SO on feelings of femininity[33]. However, Hallowell et al.[27] registered reduced feelings of femininity in 13% (n=3) of 23 women during a short period after P(B)SO. Scars, possibly related to concomitant – but non-standard – hysterectomy, were brought forward by the authors as a possible explanation for this observation, but they did not elaborate further on this subject. In the same study, some women reported a negatively altered body image due to premature aging, resulting in less firm breasts and more rounded bellies[27]. Unfortunately, exact numbers and percentages of women who reported about these adverse changes in body image were not given by the authors.

2.2.6 Sexuality after P(B)SO

The effect of P(B)SO on women's sexuality will be experienced differently, depending on individual and social circumstances. For instance, a 40 year old woman who has been on

anti-estrogenic treatment for years because of breast cancer probably will experience P(B)SO differently compared to an unaffected woman of 40 years of age undergoing P(B)SO. Moreover, effects of an intervention on sexuality are difficult to document long after that intervention, especially if the information is collected by questionnaires only.

P(B)SO did not seem to have a lasting adverse impact on sexual activity, that seemed only to 'dip' for a short period after P(B)SO[28], followed by a recovery to normal levels for most women[23,31]. A recent study performed in women undergoing a P(B)SO (n=38) versus women following a surveillance program (n=37) found that 67% of the women reported decreased sexual activity at one month following P(B)SO, while 24% of them did so pre-surgery and 39% at 12 months post-surgery. Women under surveillance had similar figures at all assessments, and did not show the post-surgical dip as did the P(B)SO group[28]. The authors concluded that the adverse effects of P(B)SO were apparently temporarily. The Edinburgh group [23,31] questioned approximately 30 high-risk women after P(B)SO or gynecologic surveillance. They found worse results on the General Health Questionnaire in the P(B)SO group and apparent identical results on a 'sexual activity scale' with the surveillance group, but the P(B)SO group had significant evidence for body image problems. The conclusion of 'identical level of sexual activity' distracted from the real problems in the P(B)SO group, which might have been clarified by additional interview studies.

As for sexual functioning, women who had undergone P(B)SO reported more discomfort and less sexual pleasure during intercourse than women in the regular surveillance group, corroborating previous results[17,29]. These adverse affects of P(B)SO-induced menopause were ascribed to estrogen deprivation (i.e. hot flashes and vaginal dryness)[17,28] and occurred irrespective of HRT use[17,29]. A recent observation of increased frequency of estrogen-deprivation associated complaints in middle age women prior to P(B)SO[28] suggested that a subgroup of them might be premenopausal; no information on anti-estrogenic cancer therapy was given, which is important because 30% of the women in that study had a personal history of breast cancer.

Also positive effects of P(B)SO on sexuality were observed, sometimes despite interfering menopausal symptoms[26,33]. An Australian interview study (n=14) established that some premenopausal women reported an increased libido, possibly due to reduced cancer anxiety and no birth-control worries[33]. These women all started HRT after P(B)SO, which was suggested to mitigate the impact of the procedure on sexuality[33]. However, another study reported on an unspecified number of women reporting loss of libido following P(B)SO, despite HRT-use[27]. A post-P(B)SO questionnaire study in 59 US high-risk women showed that 65% experienced equal or better quality of their sexual lives, though 42-58% of the total group had disturbing symptoms of estrogen deprivation (e.g. vaginal dryness, problems with orgasms, lack of desire and arousal, and painful penetration). Clearly reduced quality of sexuality was experienced by 13%[26].

In conclusion, both positive and negative effects of P(B)SO on sexuality can be expected. Also, the impact of any previous breast cancer surgery or PM/(I)BR may also play a role in the studied groups.

2.3 The role of hormonal replacement therapy (HRT)

Though hormonal replacement therapy (HRT) may increase the risk of developing breast cancer, 37%-100% high-risk women reportedly received HRT after P(B)SO[17,23,27,30]. High-risk women who used HRT after P(B)SO were generally unaffected (73%), were more likely to have undergone PM/(I)BR (62%) and opted for P(B)SO at younger ages than non-HRT users (41 vs. 44 yrs).The majority (72%) started using HRT directly after P(B)SO[29]. Generally, HRT was reported to relieve the menopausal symptoms, that occurred more acute and intensively in women after P(B)SO than in women under gynecologic surveillance[29]. However, HRT was found being ineffective in controlling menopausal symptoms by 48% of premenopausal women undergoing P(B)SO[27]. Moreover, side effects of HRT, such as water retention, spots, itchy and blotchy skin and weight gain may induce a negative body image[27].

2.4 The role of previous breast cancer

PM/(I)BR is expected to have its maximal advantage when done before the occurrence of breast cancer. After unilateral breast cancer, the prognosis and outcome are mainly determined by the tumor characteristics, the administered treatment and the individual patient. Quality of life and functioning on different levels may be affected by breast cancer therapy. This implies that a large number of risk profiles may be hidden under the diagnostic category 'breast cancer'.

In one study on the effects of P(B)SO[28], the authors acknowledged the possible inequality between the surgery group and the regular surveillance group regarding the percentages of affected women (29% and 11% respectively), but concluded that both groups were equal because a difference between both had not been reflected in most QOL scores. However, they did not acknowledge the possibility that a prior history of breast cancer, including possible physical and emotional effects of breast cancer treatment, might have resulted in an altered level of sexual activity and functioning before baseline measurement. It might have been noticed, that the two groups were different on their risk-management strategies and associated personal characteristics, which eventually might have affected the results of this study. Another example of inequality of groups can be seen in a study by Robson[26] on 54 women who underwent a P(B)SO. The majority of the women (83%) had a history of breast cancer, and 50% were identified mutation carriers. They compared the overall health related quality of life (HRQL) of the patients (all belonging to the highest social-developmental level) to scales representing the general population or long-term breast cancer survivors. Finding equal scores for their patients as in the comparison groups, the authors concluded that there was no effect of breast cancer on their cohort's HRQL. However, patients may have adapted their internal standards to any physical changes ('response shift'), thereby stabilizing quality of life[28,34]. This might explain in part the similarity of HRQL values in apparently life-stricken groups like cancer patients in general and the cancer patients in this study. In our opinion, this concept should be taken into account in future research. Interestingly, Fry et al.[31] found that a history of breast cancer was never reported on the questionnaire by the women who opted for P(B)SO. Additional analyses showed that a history of breast cancer did not alter the results, leaving the authors to conclude that prior breast cancer was not

significant for high-risk women when considering either P(B)SO or regular surveillance[31]. However, this should be further investigated in prospective studies with larger cohorts.

2.5 Limitations of the reviewed studies

Though these results has led to an increase in knowledge on the psychosocial aspects regarding prophylactic surgery in the past decade, many limitations of the conducted studies are interfering with comparisons and interpretations of results. Most studies were retrospective[2-6,9-12,14,19,20,23-26,31,33], while one combined retrospective and prospective study designs[30]. Moreover, most studies had sample sizes of ≤30 patients[1,5-7,9,19,23-25,27,30-33], a number had cohorts sized between 37 and 81 women[4,8,10-12,16,20,22,26,28] and relatively few studies were done on large samples (with sample sizes ranging from 106 to 572 high-risk women)[2,3,14,17,18,29]. Three of these large retrospective studies[2,3,14] investigated satisfaction with and distress around prophylactic mastectomies that were performed between 1960 and 1999, when surgical techniques might not have been as refined as they have been in the past decade. In contrast, high-risk women in the retrospective part of the cross-sectional study by Madalinska et al.[17,29] underwent P(B)SO between 1996 and 2001 with median time between study and surgery being 2 years. To our knowledge, only two studies combined a median to large sample size with a prospective design (n= 81-118)[18,22].

In conclusion, several studies have contributed to a growing knowledge of the psychosocial impact of PM/(I)BR and P(B)SO in high-risk women. However, differences in study design and lack of variables such as previous breast cancer make these results unrepresentative and only partially fit for extrapolation to the clinical setting. Therefore, a study called the 'PREVOM-B study' was conducted in our centre, including unaffected and affected high-risk women opting for PM/(I)BR and/or P(B)SO. The research questions and study design of this study are addressed in Chapter 3.

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3

Introduction:
Scope and Outline of this Thesis

'The decision for preventive surgery was made by me alone. I want to have it done so I can live the rest of my life like a normal, healthy person. My husband still has to get used to the idea. He thinks it's a very radical surgery. I am sorry that he is not backing me up, but it's my decision and I will go through with it anyway. I expect him to come to terms with the decision eventually.'

In 1999, an observational study started on the psychosocial outcomes of prophylactic surgery in women at risk for breast and ovarian cancer, called the PREVOM-B study. Data on the psychosocial effects of prophylactic surgery in Dutch women were limited, while a growing number of high-risk women was opting for this risk-reducing procedure (for details see Chapter 1). The observational study had a retrospective and a prospective part. It was funded by the Netherlands' Organization for Health Research and Development (grant no. 210-00-013) and approved by the Medical Ethics Committee of the Erasmus Medical Centre (MC) Rotterdam (protocol no. DDHK 98-15). The study was performed at the Department of Medical Psychology and Psychotherapy of the Erasmus MC, in close collaboration with the Departments of Medical Oncology, Surgery and Psychiatry of the Daniel den Hoed Family Cancer Clinic (Erasmus MC), the Department of Obstetrics and Gynecology, division of Gynecologic Oncology (Erasmus MC) and the Department of Clinical Genetics (Erasmus MC). All patients received their oncological, genetic,

psychological and surgical care at the Daniel den Hoed Family Cancer Clinic, except for some women who underwent P(B)SO.

3.1 Aims of the study

The PREVOM-B study aimed at uncovering the psychosocial impact of prophylactic surgery on high-risk women, being either *BRCA1/2* mutation carriers or women from a hereditary breast/ovarian cancer (HBOC) family.

The main research questions in this thesis were:

1. What is the satisfaction with the cosmetic outcomes of PM/(I)BR (Chapter 4)?
2. What are the motivations of high-risk women for undergoing prophylactic surgery and what is their effect on emotional distress (Chapter 5)?
3. What are the levels and courses of emotional distress in high-risk women opting for prophylactic surgery (Chapter 6) and their partners (Chapter 7)?
4. What are the predictors of emotional distress in high risk women who underwent prophylactic surgery (Chapter 8)?
5. What is the effect of coping on emotional distress after undergoing prophylactic surgery (Chapter 9)?

3.2 Retrospective study

Retrospectively, we explored satisfaction with the cosmetic outcomes of PM/(I)BR in 136 women who underwent this procedure at our centre between 1994 and 2002[1]. All women were either a *BRCA1* or *BRCA2* mutation carrier, or a 50% risk women from a hereditary breast/ovarian cancer (HBOC) family whereby genetic testing had not yet identified a mutation. In 92% of all women, (I)BR was done by means of a subpectorally implanted silicone prostheses, as this was the preferred breast reconstruction technique during that period of time. A minority of women (8%) underwent (I)BR by another technique because of a previous unilateral mastectomy. Sixty-five women (57%) also underwent P(B)SO, while 31 women (27%) used HRT at any time. Consenting women filled out a questionnaire containing 16 questions covering four domains: 1) general and PM/(I)BR-specific satisfaction; 2) feeling informed about the procedure and its possible consequences; 3) peri- and postoperative complications, physical complaints and limitations due to PM/(I)BR; and 4) effects of PM/(I)BR on body image and sexuality. Eighty four percent of the women (n=114) completed and returned the questionnaire by mail. Since our main objective was to investigate the level of satisfaction in these women irrespective of interpersonal medical differences, we adjusted for i) age at the time of PM/(I)BR; ii) years elapsed since PM/(I)BR; iii) history of breast cancer; iv) PBSO; and v) HRT. Each predictor variable was tested on the outcome variable separately, including the variables that were adjusted for. Results of this study are described in Chapter 4.

3.3 Prospective study

Between August 1999 and February 2003, 129 high-risk women who decided to undergo PM/(I)BR and/or P(B)SO at the Family Cancer Clinic of the Erasmus MC-Daniel den Hoed Cancer Centre were approached for participation in the prospective part of the PREVOM-B

study. Eligible women were either BRCA1/2 mutation carrier or women from a HBOC family without an identified BRCA1/2 mutation, without signs or suspicion of breast cancer or ovarian cancer at pre-surgical examination (performed within 3 months prior to prophylactic surgery).

Consenting women were assessed within a month prior to prophylactic surgery (baseline; T0), at six months (T1) and twelve months after prophylactic surgery (T2). At all three assessments, participants were asked for completion and return of the completed questionnaire, that were sent to them by mail. Also the partners of all participating women were approached for study participation. After consent, the same questionnaires were sent to the partners at the same assessment moments as their wives.

At T0, data on demographic (e.g. age, marital status, parenthood) and medical data (e.g. carrier status, history of breast cancer) were collected. Also at T0, neuroticism was assessed by use of the neuroticism (N-)scale of the Amsterdam Biographical Questionnaire (ABQ)[2], thus assessing vulnerability to psychological distress[3].

At T0, T1 and T2, coping strategies were assessed by the Utrecht Coping List (UCL)[4,5], a general coping questionnaire that addresses active coping, palliative and passive reaction patterns, seeking social support, expression of emotions and the habit to reassure oneself by comforting thoughts. Cancer-related distress was assessed by means of the Impact of Events Scale (IES)[6-9], an established instrument for measuring feeling overwhelmed by intrusive and avoidant thoughts and feelings related to a traumatic event, and the tendency to adapt one's behaviour to these thoughts and feelings. In our study, these thoughts, feelings and behaviour were anchored to breast cancer and/or ovarian cancer. General distress was measured with the Hospital Anxiety and Depression Scale (HADS)[10]. The Hospital Anxiety and Depression Scale has two scales for anxiety and depression, respectively.

Further, all participants (high-risk women and partners) were interviewed separately at their homes at T0, T1 and T2. The interviews were of a semi-structured nature with topics concerning risk-perception, motivations for deciding for prophylactic surgery, expectations about prophylactic surgery, support from family members and relatives, experience of and need for social support, body image, sexual relationship and global assessment of functioning. Except for results on motivations (Chapter 5), the interview data will be presented elsewhere.

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4

Satisfaction with Prophylactic Mastectomy and Breast Reconstruction in Genetically Predisposed Women

Background *Prophylactic mastectomy (PM) with breast reconstruction (BR) is a risk-reducing strategy for women at increased risk of breast cancer. It remains a very radical intervention while long-term data on satisfaction are insufficiently available. In the present follow-up study, we assess satisfaction with PM and BR and its impact on the sexual relationship.*

Methods *Retrospective study using a short self-report questionnaire in 114 genetically predisposed women who underwent PM and BR mainly by subpectorally implanted silicone prostheses, performed at one institution.*

Results *The median follow-up time between PM/BR and completion of the questionnaire was 3 years. Sixty percent of all participants were satisfied with the result of PM/BR. Satisfaction was significantly and negatively correlated with: perceived lack of information, experienced complications, ongoing complaints, whether or not the reconstructed breasts feel 'like your own', and not choosing this type of BR again. Adverse effects in the sexual relationship were strongly correlated with perceived lack of information, discrepant expectations, ongoing complaints and limitations, whether or not the reconstructed breasts feel 'like your own', altered feelings of femininity, partner's negative perception on femininity and sexuality, and not choosing this type of BR again.*

Conclusions *In spite of adverse effects of PM/BR, the majority of women would opt for PM/BR again. However, having experienced adverse effects and untoward changes in the perception of the sexual relationship due to PM/BR need to be addressed and explored in the counselling of women at high risk to optimise an informed choice, and enable adequate adjustment after PM/BR.*

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4.1 Introduction

Women identified with a *BRCA1/2* mutation have a cumulative lifetime risk for breast cancer of 39-85% and for ovarian cancer of 11-63% at age 70 years[1-4]. Furthermore, the lifetime risk of contralateral breast cancer for genetically predisposed women after a history of breast cancer is 48-64%[5]. At this moment, bilateral or contralateral prophylactic mastectomy (PM) is the most effective, although radical, strategy to reduce the risk of breast cancer in high-risk women[6, 7].

At the Family Cancer Clinic of the Erasmus Medical Centre - Daniel den Hoed Cancer Centre in Rotterdam, between 35 and 51% of the identified mutation carriers opt for prophylactic mastectomy with breast reconstruction (PM/BR)[6, 8]. Satisfaction with PM has been reported to vary between 70%[9, 10] and (nearly) 100%[11-15]. However, major limitations of the published studies were that satisfaction with (immediate) breast reconstruction after prophylactic mastectomy was either not a primary focus of the study[12, 13, 16] or it was investigated in a small (sub)sample[10, 16].

In the present study, we assessed satisfaction with breast reconstruction after prophylactic mastectomy in the longer term in 114 women at increased risk of (contralateral) breast cancer due to a *BRCA1/2* mutation or a supposed genetic predisposition.

4.2 Patients and Methods

4.2.1 Study population

From the database of a follow-up study on the medical effects of PM in genetically predisposed and high-risk women, we approached all women (n=136) who underwent bilateral or contralateral PM/BR at our institution between 1994 and 2002. PM/BR was performed because of an increased risk of (a new) breast cancer due to either a *BRCA1* or *BRCA2* mutation, or a 50% risk carrier status in women from hereditary breast/ovarian cancer families. All women were from families with cancer following an autosomal dominant pattern of inheritance and were offered genetic testing before undergoing PM. Some of these women remain at increased risk of breast and/or ovarian cancer without the possibility that this risk can be specified further. They may however opt for PM.

Reconstruction was done by means of subpectorally implanted silicone prostheses, as has been described in detail elsewhere[17]. A history of breast cancer was not an exclusion criterion. Women who previously underwent unilateral mastectomy for a primary breast cancer (n=9) were at that side reconstructed with another technique. Follow-up was performed at the Family Cancer Clinic of the Erasmus MC-Daniel den Hoed Cancer Centre in Rotterdam. The institutional review board approved the study. Written informed consent from participants was obtained.

Sixty-five women also underwent a prophylactic bilateral salpingo-oophorectomy (PBSO), which was performed either before, simultaneously with, or after PM/BR. P(B)SO was not necessarily performed at our institute. Thirty-one women used hormone replacement therapy (HRT) at any time during the follow-up period.

4.2.2 Questionnaire

We developed a brief self-report questionnaire based on clinical experience with high-risk women and on questionnaires that are currently used in follow-up studies, in order to measure the satisfaction of women with the outcome of PM and BR.

Sixteen questions covered four domains: 1) general and PM/BR-specific satisfaction (three questions); 2) feeling informed about the procedure and its possible consequences (two questions); 3) peri- and postoperative complications, physical complaints and limitations because of PM/BR (three questions); and 4) effects on body image and sexuality (eight questions). All questions addressed BR specifically. Three questions concerning body image and sexuality addressed the perception of the women about their partners' satisfaction.

Answers were rated on a five-point scale ranging from Yes!, Yes, ? (neutral), No, to No!. Questions that implicated the presence of a partner could also be scored as 'not applicable'.

4.2.3 Procedure

The questionnaire was mailed to all patients who met the inclusion criteria. Two patients apparently moved without giving notice of their new address. Eighty four percent of the women (n=114) completed and returned the questionnaire by mail.

4.2.4 Statistical analysis

We present the frequencies and percentages for the responses on the questionnaire. Given that women with a history of breast cancer may have had different priorities when considering PM with BR, we performed analyses not only on the complete sample, but also on women with and without previous breast cancer separately. Furthermore, logistic regression analyses were performed with 1) satisfaction and 2) adverse effects in the sexual relationship as outcome variables. Hereto, we dichotomised the original 5-point scale by combining the 'Yes!' and 'Yes' answers on the one hand and the '?', 'No' and 'No!' answers on the other hand for the outcome variables alone. This kind of dichotomization was performed to study more specifically the satisfied versus the remaining ('non-satisfied') patients. The influence of each of the other questions of the questionnaire on the outcome variable was investigated. Since our main objective was to investigate the level of satisfaction in these women irrespective of interpersonal medical differences, we adjusted for i) age at the time of PM/BR; ii) years elapsed since PM/BR; iii) history of breast cancer; iv) PBSO; and v) HRT. Each predictor variable was tested on the outcome variable separately, including the variables that were adjusted for. A p-value ≤ 0.05 (two-tailed) was considered as statistically significant.

4.3 Results

4.3.1 Sample Characteristics

Of 136 women who received the questionnaire, 114 participated in this study (84%). Two-third of these women (n=77) were unaffected *BRCA1/2* mutation-carriers (n=63) or 50% risk carriers (n=14); 22 women had previously been treated for breast cancer by either breast conserving therapy (n=13) or unilateral mastectomy (n=9). Fifteen women decided

for bilateral mastectomy with reconstruction when breast cancer was diagnosed. None of these women experienced a recurrence of breast cancer in the years after surgery until time of assessment. Thirteen out of 37 women with a history of breast cancer were proven *BRCA1/2* mutation-carriers.

Table 1
General characteristics of 114 participants who underwent prophylactic mastectomy (PM) and breast reconstruction (BR) from 1994 – 2002

	Unaffected women [1] (N=77)		**Affected women**[2] (N=37)		**Total group** (N=114)	
	Median	*Range*	*Median*	*Range*	*Median*	*Range*
Age	41	25-59	46	30-65	44	25-65
Age at time of PM/BR	38	23-55	43	26-59	40	23-59
Follow-up in years	3	0-8	4	0-8	3	0-8
	n	*%*	*n*	*%*	*n*	*%*
Living with a partner	68	90	32	86	100	88
Risk status						
BRCA1/2 mutation carriers	63	82	13	35	76	67
Women at >50% risk[3]	14	18	24	65	38	33
Additional						
PBSO*	48	62	17	46	65	57
HRT*	30	39	1	2	31	27

*PBSO: prophylactic bilateral salpingo-oophorectomy; HRT: hormone replacement therapy
[1]Women *without* a history of breast cancer.
[2] Women *with* a history of breast cancer.
[3] Based on a family history suggestive for a breast/ovarian cancer syndrome.

Some women did not answer all questions, resulting in different totals. Median follow-up after surgery for the complete sample was three years (range two months-eight years). Respondents and non-respondents (n=22) did not differ demographically. Characteristics of the participants are presented in Table 1.

4.3.2 Overall evaluation

Women with and without a history of breast cancer differed not significantly in responses on the questionnaire. Therefore, we performed the analyses on the total sample.

As is shown in Table 2, 68 (60%) women were satisfied with the result of PM and BR. One hundred and six (95%) women would opt for PM again, would they have to choose again, 89 (80%) women would choose for the same type of BR again, and 95 (85%) women felt sufficiently informed.

Forty-eight women (43%) reported peri- and/or postoperative complications, and 35 women (32%) mentioned that they experienced ongoing physical complaints in one or both reconstructed breasts. Twenty-eight women (25%) reported to experience limitations in daily life due to (the aftermath of) PM/BR.

The sensation of the breasts altered in nearly all women (97%), fifty-eight (51%) women rated their breasts as *not* feeling 'like their own', and 32 (29%) women reported altered feelings of femininity after PM/BR, while only 8 women (8%) thought their partners found them less feminine. Ten women (13%) experienced positive changes in their sexual relationship due to PM/BR. Forty women (44%) reported an adverse change in

their sexual relationship due to PM/BR. Finally, 10 of the partners (13%) were thought to have experienced a positive change in the sexual relationship, whereas 27 partners (35%) were thought to have experienced an adverse change in the sexual relationship.

Table 2
Women's experience with prophylactic mastectomy and breast reconstruction[1]

		YES! and YES		? (neutral)		NO and NO!	
Answers on	**N**[2]	*n*	*%*	*n*	*%*	*n*	*%*
Being satisfied with result PM/BR	113	68	60	13	12	32	28
Would opt for PM again	112	106	95	5	5	1	1
Would opt for BR again	112	89	80	12	11	11	10
Feeling sufficiently informed	112	95	85	1	1	16	14
Surgery did not meet expectations	112	35	31	8	7	69	62
Complications[3]	113	48	43	2	2	63	56
Ongoing complaints	111	35	32	5	5	71	64
Limitations in daily life	112	28	25	6	5	78	70
Change in feeling of the breasts	114	111	97	0	0	3	3
Breasts do not feel 'like your own'	113	58	51	7	6	48	43
Changes in femininity[4]	111	32	29	4	4	75	68
Positive effects in sexuality[4]	77	10	13	11	14	56	73
Adverse effects in sexuality[4]	90	40	44	9	10	41	46
Partner's perceptions							
Lessened femininity[4]	100	8	8	3	3	89	89
Positive effects in sexuality[4]	79	10	13	11	14	58	73
Adverse effects in sexuality[4]	77	27	35	10	13	40	52

[1] Row totals deviating from n=114 indicate missing data.
[2] N = sample size; number of women who had a response on this item.
[3] I.e. self-reported complications, including secondary reconstructive surgery.
[4] *due to PM/BR*

4.3.3 Satisfaction

We dichotomised the total group into satisfied patients (n=68) and the non-satisfied patients (n=45), based on the question: 'Are you satisfied with the result of breast reconstruction?' The answers were analysed taking into account various confounders as described in the methods section. Significant differences were found between satisfied patients and non-satisfied patients, as is shown in Table 3.

Non-satisfied patients felt significantly less informed than satisfied patients (*p=.02*). They also reported significantly more complications (*p=.01)* and more physical complaints *(p=.001)* than satisfied patients. Moreover, non-satisfied patients reported significantly more than satisfied patients that their breasts do not feel like belonging to their body (*p=.02*). Finally, non-satisfied patients reported significantly more often that they would not opt for BR again *(p=.01)*.

4.3.4 Impact on perception of sexual relationship

Nearly half of the women who filled out the questions about the sexual relationship (n=90) reported that (the result of) PM/BR had negatively affected their sexual relationship (44%). Therefore, we performed a logistic regression analysis with as outcome

variable the impact on the sexual relationship. We adjusted for the same confounders as described in the methods section. Results are shown in Table 4.

Table 3

The relationship between satisfaction and women's experience with prophylactic mastectomy and breast reconstruction[1]

	Non-satisfied patients (n=45)			**Satisfied patients** (n=68)			
	N[2]	*n*	*%*	*N*[2]	*n*	*%*	*p*[3]
Feeling insufficiently informed	43	10	23	68	6	9	.02
Surgery did not meet expectations	45	17	38	67	18	27	.08
Complications	44	23	52	68	24	35	.01
Complaints	42	26	62	68	9	13	.001
Limitations in daily life	43	13	30	68	15	22	.33
Change in feeling of the breasts	45	45	100	68	65	96	.75
Breasts do not feel 'like your own'	44	28	64	68	30	44	.02
Change in feelings of femininity	44	14	32	66	17	26	.53
Positive effects sexual relationship	26	5	19	50	5	10	.70
Adverse effects sexual relationship	32	18	56	57	22	39	.31
Would not opt for PM again	44	1	2	67	0	0	.28
Would not opt for BR again	43	10	23	68	1	2	.01
Partner's perception							
Decrease wife's femininity	37	4	11	62	4	7	.94
Positive effect on sexual relationship	28	6	21	50	4	8	.07
Adverse effect on sexual relationship	26	13	50	50	14	28	.06

[1]Logistic regression analysis, adjusted for: i) age at the time of PM/BR; ii) years since PM/BR; iii) history of breast cancer; iv) PBSO; and v) HRT.
[2] N = sample size; number of women who had a response on this item.
[3] A p-value ≤ 0.05 (two-tailed) was considered as statistically significant.

Table 4

The relationship between adverse effects on the sexual relationship and women's experience with prophylactic mastectomy and breast reconstruction[1]

	No effect (n=50)			**Adverse effect** (n=40)			
	N[2]	*n*	*%*	*N*	*n*	*%*	*p*
Does not feel sufficiently informed	50	2	4	40	12	30	.01
Surgery did not meet expectations	48	9	19	40	18	45	.001
Complications	49	18	37	40	20	50	.34
Complaints	48	8	17	40	18	45	.01
Limitations in daily life	50	7	14	39	18	46	.01
Non-satisfied result reconstruction	50	14	28	40	18	45	.07
Changed feeling in one or both breasts	50	49	98	40	38	95	.48
Breasts do not feel 'like your own'	50	18	36	40	27	68	.01
Change in feelings of femininity	49	9	18	39	20	51	.01
Would not opt for PM again	49	0	0	39	1	3	.25
Would not opt for BR again	50	0	0	39	7	18	.01
Partner's perceptions							
Decrease in his wife's femininity	50	1	2	36	7	19	.04
Adverse effect on sexual relationship	48	6	13	27	20	74	.001

[1] Adjusted for: i) age at the time of PM/BR; ii) years since PM/BR; iii) history of breast cancer; iv) PBSO; and v) HRT.
[2] N = sample size; number of women who had a response on this item.

Women who reported adverse changes in their sexual relationship stated more likely that they felt insufficiently informed about the procedure and its possible consequences (*p=.01*), that surgery had not met their expectations (*p=.001)*, that they were experiencing more complaints (*p=.01)* and more limitations in daily life (*p=.01).* They were also more likely to report that the reconstructed breasts do not feel 'like their own' (*p=.01*), that they experienced altered feelings of femininity (*p=.01)*, and a decrease in their partner's perception of his wife's femininity (*p=.04)*. They were more likely to perceive an adverse change in the way the partner experienced their sexual relationship (*p=.001)*. Finally, they were more likely to report that they would not opt for BR again (*p=.01)*.

4.4 Discussion

This is the first study that addresses impact of both prophylactic surgery and breast reconstruction in a large sample of genetically predisposed women.

PM/BR was not regretted by the vast majority of women, which is in accordance with other studies[9, 11-15]. Yet, only 60% of the women were satisfied with the results of the breast reconstruction. This is less than observed in other studies [12, 13, 16]. Higher distress or cancer worry has been found in women opting for PM compared with those who favoured surveillance, while the distress had significantly decreased 6 months after surgery [9, 14, 18]. Therefore, we speculate that relief from anxiety of developing (a new) breast cancer characterizes the short-term outcome after PM. Thereafter the growing awareness of the profound consequences of the surgery might have affected the satisfaction with the eventual results. Indeed, significantly more non-satisfied women would not opt for BR again compared to satisfied women.

Frost et al.[9] found in their study (mean follow-up 14.5 years) that 80% of the surveyed women were satisfied with PM. However, they did not explicitly study the satisfaction with BR after PM. Moreover, the mean age of their group at the time of the study was much higher (57 years of age) than in our study. While their findings suggest a positive adjustment on the long term, our data suggest that a favourable outcome of PM/BR and therefore persistent sexual attractiveness may be more valued by younger women.

The level of satisfaction about PM/BR in our study was associated with various factors such as peri- and postoperative complications of PM/BR, and ongoing physical complaints and limitations in daily life. This has been found in previous research[10, 13, 19, 20]. Fewer women reported ongoing complaints in our study, compared with the study by Bebbington Hatcher et al.[15]. In their cohort, half of all women reported ongoing problems due to surgery, even at 18 months after the intervention. Since their study group has been recruited from 20 different centres, the type of surgery or the experience of the surgeons may not have been similar for all women, which might explain the different outcome. Moreover, our follow-up period is longer, which may be an explanation for our lower number of ongoing complaints.

Also the feeling of the reconstructed breasts as belonging to one's body and the type of reconstruction clearly influence the women's satisfaction with the procedure. As was pointed out by Contant et al.[19], the expectation of an unaltered body image is often reported to be a motivation for undergoing BR. When expectations considering body image are not met, this might well be the explanation of dissatisfaction with the outcomes

of surgery. Unfortunately, the design of this study is not such that it explores the women's presurgical attitudes. An ongoing study at our institution, relating the outcome of PM/BR as perceived by both women and a number of experts, will hopefully provide more data on this issue.

Most studies on the psychological effects of prophylactic mastectomy reported few or no detrimental effects on body image and sexuality in the majority of women[12, 15, 16, 18, 19, 21, 22]. Lodder et al.[14] did find some effects, but concluded that the differences in body image and sexuality pre- and postoperatively were not due to PM/BR. Two follow-up studies found comparable effects of PM and BR on the sexual relationship. Recently, Van Oostrom et al.[23] reported that a high percentage of women had experienced untoward changes in their relationship due to PM. Frost et al.[9] found that prophylactic mastectomy could result in adverse effects on the sexual relationship (23%) and feelings of femininity (25%), which is consistent with our findings. However, those studies did not focus on breast reconstruction specifically. In our study, though not related to satisfaction with PM/BR, nearly half of all women experienced untoward changes in their sexual relationship due to PM/BR. This finding was significantly associated with perceived lack of information, expectations that were not met, ongoing physical complaints and limitations in daily life, altered feelings of femininity and body image, and perception of the partner's negative view on his wife's sexual attractiveness. Indeed, women may have experienced pain or hindrance, and therefore the sexual relationship will not be as uncomplicated as it was before surgery.

The absence of a relationship between satisfaction with prophylactic mastectomy and breast reconstruction on the one hand, and changes in the sexual relationship on the other hand is noticeable. We speculate that satisfaction with the result of prophylactic surgery in this group of high-risk women is complex, and may be related with changes in the sexual relationship through as yet unknown variables.

This study has several limitations. First, our sample was heterogeneous with respect to medical history and treatment. We adjusted for the effect of demographic variables by using the method of logistic regression analysis. Due to small subsamples we were not able to perform additional analyses. However, most demographic variables do have an effect on the responses of this sample, and it is advisable to investigate the importance of these variables in a larger population. Second, the questions of the questionnaire aimed at PM/BR and did not take into account the fact that it may be impossible to distinguish between breast reconstruction and the prophylactic mastectomy. Third, the number of women in our sample who had their breasts reconstructed with another type of reconstruction (e.g. TRAM flap or expander based implants) was very low, so no comparison could be made on the level of satisfaction with these other types of reconstruction. In a recent study done by Fogarty et al.[24], no differences were found between the outcome after autologous and nonautologous breast reconstructions, which is reassuring. However, we realise that this issue should be further investigated. Fourth, the instrument we developed has not been tested for reliability or validity. Its sole purpose was to provide insight into possible determinants of (un)satisfaction with the results of PM/IBR, using one item per factor. Currently, a prospective study is conducted

at our institution that investigates the motivations and implications of prophylactic surgery and breast reconstruction.

4.5 Clinical Implications

Although other studies have shown that PM/BR obviously serves to decrease cancer-related anxiety in the short term, the long-term impact on quality of life and especially on the quality of the sexual relationship should not be underestimated. Because the women in our group show few regrets and most of them feel sufficiently informed, we anticipate that the absence of regrets despite the awareness of adverse consequences reflect that the urge to reduce anxiety, remain healthy and to survive predominates any ambivalence regarding the possible (negative) outcomes of PM/BR on the long term. Though physicians must extensively inform their patients about the long-term ramifications of PM/BR, they should be aware that this information is given at the moment that the urge to survive predominates. Therefore, it is important to pay attention to the way the information is processed and assimilated.

Careful exploration of the possible impact upon body image and the sexual relationship enables the women at risk and their partners to recognize the potential risk factors for inadequate coping. If there are any such factors, additional professional attention from a psychologist or social worker may be of help to anticipate untoward experiences after treatment. If needed, follow-up support can be offered after PM/BR.

Finally, it should be further studied which women and/or couples are at high risk for maladjustment and inadequate coping. The subjective well being of these persons may benefit in the long term if the pre-surgical counselling and information has been comprehensively offered and correctly assimilated.

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5

Motivations and Distress in Genetically Predisposed Women Opting for Prophylactic Mastectomy or (Bilateral) Salpingo-Oophorectomy

Background *This study addresses the self reported of motivations for prophylactic surgery (PS) of the breasts and/ or ovaries and uterine tubes, and their association with emotional distress in 36 women at increased risk of hereditary breast and ovarian cancer either because of a BRCA1/2 mutation or family history.*

Methods *Thirty-six high risk women were interviewed at 2-4 weeks pre-PS and again at six months and twelve months post-PS. The motivations for PS were isolated from the transcripts and categorized. At these assessments, women filled out a demographic questionnaire, the Impact of Events Scale (IES) and the Hospital Anxiety and Depression Scale (HADS).*

Results *Motivations were characterised as cognitive (C) or emotional-cognitive (EC). The EC group (n=20) had 'fear for breast or ovarian cancer' and 'supporting daughters' as their principal motivations, together with the cognitive items as risk reduction, uncertainty despite regular surveillance, etc. The C group (n=16) had only the latter set of motivations. Both groups had similar courses of cancer-related and general distress from pre-PS to 1 year post-PS, with no clinically relevant levels for cancer related (intrusion/avoidance) or general (anxiety/depression) distress as measured by IES and HADS, respectively. A separate analysis of 17 women expressing fear of cancer as their principal motivation as compared with 19 otherwise motivated risk carriers showed more depression pre-PS in the cancer-fearing group. After PS, both groups had similar levels of depression. The courses of intrusion differed in both groups with a greater relief of intrusion within 6 months post-PS in the cancer-fearing group, whereas the group of women whose motivations were others than fear showed relief of intrusion after 6 months post-PS.*

Conclusions *Pre- and post-operative counselling might particularly focus on women with a predominantly fear-driven choice for PS to assist them in handling potentially enhanced distress in that period.*

Submitted

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5.1 Introduction

The *BRCA1* and *BRCA2* breast cancer susceptibility genes associated with hereditary breast and ovarian cancer were identified in 1994 and 1995 respectively[1,2]. Female mutation-carriers have a cumulative lifetime risk for breast cancer of 39-85%, and for ovarian cancer of 11-63% at age 70 years[3-6]. Additionally, mutation-carriers with a history of unilateral breast cancer have an increased lifetime risk of contralateral breast cancer, estimated between 20-60% or 3% annually[7,8].

Regular surveillance by mammography, MRI and clinical breast examination[9] aim at early detection of breast cancer, which is much less feasible for ovarian cancer[10]. Prophylactic surgery (PS) of the breasts as well as the ovaries/fallopian tubes (defined as surgical removal in the absence of clinical signs of cancer) is highly effective with respect to cancer risk reduction. Data on the efficacy of prophylactic mastectomy with or without (immediate) breast reconstruction (PM/(I)BR) showed that the remaining risk of developing a primary breast cancer after PM/(I)BR is very low[11]. After prophylactic (bilateral) salpingo-ovariectomy (P(B)SO), it was estimated that only a small residual risk of developing extra-ovarian, peritoneal cancer remains[12]. Furthermore, a P(B)SO reduces the risk of developing breast cancer[13,14].

Psychosocial studies on PS have clarified the motivations of high-risk women for such a far-reaching decision[15-21]. Also, levels and courses of distress have been investigated, with results that indicated that the levels of distress in women opting for PS usually decreased after PS[16,18,19,22-30]. Still, a subgroup of women reported continuing general and cancer-related distress[16,24,31,32].

The present study addresses the possible associations between motivations for PS and the level and course of (ongoing) emotional distress. We used Leventhal's model of self-regulation[33] as a theoretical framework for the relationship between motivations and emotional distress. According to this model, objective-cognitive processes (e.g. medical information on breast and/or ovarian cancer, specific risks provided by the geneticist, etc) are processed in interaction with subjective-emotional processes (e.g. personal experiences with the disease in relatives) resulting in causal beliefs on the disease (e.g. the role of heredity in developing breast and ovarian cancer). These causal beliefs will be the basis for a mental cognitive representation of the health threat in question. Contributing factors for this representation are self-esteem, experienced susceptibility and experienced control. Parallel to this cognitive process, an emotional response (i.e. emotional distress) is invoked, based upon the experienced threat to one's health, cognitive beliefs and behavioural intentions. The cognitive representation leads to problem-focused coping, whereas the emotional response leads to emotion-focused coping. Both problem-focused coping and emotion-focused coping are subject to regular appraisal. Emotion-focused coping may facilitate problem-focused coping in the short term; it can lead to a decrease of extreme emotional distress, so energy is available for problem-focused coping strategies (e.g. decision-making). However, in the long term, emotion-focused coping may interfere with problem-focused coping, for example when it undermines activities like gathering information, weighing the options and adherence to surveillance.

Decruyenaere et al.[34] observed that risk-reducing actions like PS are predominantly cognitively controlled. Based on this principal, emotional responses, i.e. anxiety and emotional distress, will facilitate the (cognitive) decision for PS, because PS reduces the risks of developing breast and ovarian cancer and allows regaining control over the health-threat. Subsequently, this process may lead to reduction of distress.

As motivations reflect both the cognitive representation of the health threat and the invoked emotional response, we expect that women with combined cognitive and emotional motivations will benefit more from PS (experience greater relief) than women with pure cognitive motivations: the latter will experience the emotional relief to a lesser degree.

This study is a prospective exploration of motivations for PS and emotional distress addressing two research questions: 1) What is the nature of motivations of women to undergo PS? and 2) Do women with a combined emotional and cognitive motivation experience a larger reduction in emotional distress after PS than women with a predominantly cognitive motivation?

5.2 Patients and Methods

5.2.1 Study population

Between August 1999 and February 2003, 129 women being at increased risk of hereditary breast and ovarian cancer who decided to undergo PM/(I)BR and/or P(B)SO as risk reducing procedure at the Family Cancer Clinic of the Erasmus MC-Daniel den Hoed Cancer Centre were invited to participate in a psychological follow-up study (PREVOM-B study) on the psychological impact of PS. All women (hereafter called 'high-risk women') belonged to families with an apparent autosomal dominant transmission pattern, and therefore had an associated elevated risk of developing breast and ovarian cancer. The majority of these women were *BRCA1/2* mutation carriers (hereafter called 'mutation carriers'). For women from a hereditary breast and ovarian cancer family without an identified *BRCA1/2* mutation (hereafter called 'risk carriers'), the request for PM/(I)BR or P(B)SO was reviewed at the multidisciplinary working party on hereditary cancer of our institution. The decision to proceed to PM/(I)BR and/or P(B)SO was made after extensive and repeated information and counselling, including a consultation with the institutional psychologist. Factors taken into account into the decision-making process with respect to PS were age, history of breast cancer, risk estimation for (contralateral) breast cancer and ovarian cancer, and consistency of the patient's request and its underlying arguments.

Eligibility criteria for the study were: no signs or suspicion of breast and ovarian cancer at pre-surgical examination (physical and imaging examination, plus Ca125 analysis) performed within 3 months prior to PS. For women with a history of breast cancer, recurrent disease or a new primary tumour had to be ruled out by physical and imaging/dissemination examination (mammography, gynaecological examination and ultrasound, chest X-ray, ultrasound liver, bone scan, liver-function tests, and Ca125/Ca153 analysis), also performed within 3 months prior to PS.

Three women (7,5%) who were originally classified as 50% risk carriers eventually were identified as *non*-carriers of the family *BRCA1/2* mutation. These women were included into analyses for they already had undergone PS at test disclosure. Therefore, we assumed

that their worries and motivations regarding their alleged increased risk of developing cancer were similar to the other women who were included into the study.
Physicians introduced the PREVOM-B study to eligible patients by means of verbal and written information. After written informed consent, participants received questionnaires by mail 2-4 weeks before (T0), and 6 and 12 months after PS (T1 and T2 respectively). The researcher of the project (PB) interviewed women at all three measurement moments at home. For the current analysis the pre-surgery interviews were used. Due to logistics (e.g. the eligible woman and/or researcher were informed too late, making it impossible to meet for an interview prior to surgery) or electronic problems (e.g. the interview being not clearly audible on tape due to circumstantial noise), not all interviews were suitable for transcription or analysis. Finally, 36 pre-surgery interviews were included into the analysis.

5.2.2 Biographical and medical data

Age, marital status, offspring, religious affiliation, educational level, profession, carrier status, history of breast cancer, and type of surgery were recorded at T0 by means of a questionnaire.

5.2.3 Cancer-related distress

The Impact of Events Scale (IES) is an established instrument[35-38] for measuring feeling overwhelmed by intrusive and avoidant thoughts, and feelings related to a traumatic event, and the tendency to adapt one's behaviour to these thoughts and feelings. In our study, these thoughts, feelings and behaviour were anchored to breast- and/or ovarian cancer. The response categories are: not at all (0); seldom (1); sometimes (3); and often (5). The score range for the intrusion scale is 0-35 and for the avoidance scale 0-40. Reliability and validity are satisfactory[35-38]. No norms or cut-off scores are available for the general population. However, from two studies conducted in a clinical setting[39,40], cut-off scores equal or higher than 13 on the intrusion subscale and equal or higher than 11 on the avoidance subscale were reported to be clinically relevant. In the present study, these cut-off values were considered as clinically relevant.

5.2.4 General distress

General distress was measured with the Hospital Anxiety and Depression Scale (HADS)[41]. The HADS has two scales for anxiety and depression, respectively. Every item has four response categories, anchored to that specific item. The scores range from 0 – 21 for both scales. Validity and reliability have proven to be sufficient[42,43]. A score between 8 and 10 on each subscale represents a doubtful case of either anxiety or depression. A score of 11 or higher per subscale is indicative of a clinically relevant level of distress.

5.2.5 Motivations

During the pre-surgery interview, the women were asked about their motivations for undergoing PM, P(B)SO or both. Due to the semi-structured nature of the interview, the motivations could be named in any order, and expressed at any time in the interview. The complete transcriptions of the interviews were examined for the expression of motivations for undergoing PS. No ranking was applied.

The reported motivations were conceptually categorized by three authors (AVG, PB, AT) into two groups: 1) the cognitive motivations group (C group) and 2) the emotional-cognitive motivations group (EC group). Women in the C group reported one or more of the following motivations: for risk reduction, uncertainty of screening, knowledge of one's mutation status, physician's advice, nearing or already in menopause, keeping control over one's health situation, taking precautions, suffering from benign gynaecological problems, having a choice, not wanting cancer (again), not wanting any more children, for peace of mind, for cosmetic advantage (i.e. breast reduction), feeling that regular surveillance is troubling. Women in the EC group reported one or more of the following motivations: fear for breast cancer and/or ovarian cancer, wanting to support daughter in the future, and getting rid of insecurity whether one gets cancer or not. These women also reported one or more of the above cognitive motivations. Three women who reported *only* emotional motivations were categorized into the EC group.

5.2.6 Statistical Analysis

The motivations that were reported in the pre-surgery interviews, were categorized and put into a database using SPSS 11.0 statistical package (SPSS Inc., Chicago).

Chi-square analysis was used to reveal possible interrelations between the motivations. Frequency analysis was used on the biographic and medical variables, as well as on the motivations that were reported by the interviewees. We performed a SQUARE ROOT on the distress variables to correct for their skewness. ANOVA was used to determine differences between the E/C-group and the C-group. General Linear Modelling (GLM) was used to determine the effect of emotion-based versus cognitive based motivations on the course of distress. In order to get an insight into the influence of the separate motivations on the level and course of distress, we performed General Linear Modelling on sufficiently large subsamples.

5.3 Results

Of 97 women who consented to participate in the PREVOM-B study between September 1999 and January 2003, transcriptions of 36 pre-surgery interviews were available for this analysis (40%). The latter group had identical biographic and medical characteristics as the other women in the pre-surgery group (data not shown). Also, the biographic and medical variables of the EC group and the C group (Table 1) were identical for age, mutation carrier status, history of breast cancer, type of prophylactic surgery, marital status, offspring, religious affiliation, educational level, and/or employment.

Ages ranged from 25 to 60, with means of 43,5 and 45 years of age (E/C-group and C-group respectively). Most interviewees were BRCA1/2 mutation carriers (64%). Sixty-one percent of all interviewees (61%) were unaffected women (e.g. had no history of breast cancer or ovarian cancer). Most of the women (69%) had opted for PM/(I)BR, either PM/(I)BR only (31%), or performed simultaneously with (19%) or after (19%) P(B)SO. Most women were married or cohabiting (92%) and had children (89%). The largest part of the interviewees had an average level of education (53%) and over half of them (69%) were employed. Nearly half of all participants (47%) mentioned to be religious.

Table 1
Emotional-Cognitive (EC) versus Cognitive (C) motivated women opting for PS: medical and demographical variables

		EC group (N=20)		**C group** (N=16)		
		M (Sd)	*Range*	*M (Sd)*	*Range*	*p*
Age at surgery		43,5 (9)	25-60	45 (6)	35-56	ns
		N	*%*	*N*	*%*	*p*
Carrier status	*BRCA 1/2*	11	55	12	75	ns
	50% risk carrier	9	45	4	25	
History of	*Yes*	7	35	7	44	ns
breast cancer	*No*	13	65	9	56	
Type of surgery[1]	*PM/(I)BR*	5	*25*	6	*37,5*	ns
	P(B)SO	5	*25*	6	*37,5*	
	PM/(I)BR+P(B)SO	5	*25*	2	*12,5*	
	PM/(IBR) before P(B)SO	0	*0*	0	*0*	
	PM/(I)BR after P(B)SO	5	*25*	2	*12,5*	
Marital status	*Married or cohabiting*	18	90	15	94	ns
	Single or divorced	2	10	1	6	
Children	*Yes*	18	90	14	87,5	ns
	No	2	10	2	12,5	
Education	*Low*	7	35	2	12,5	ns
	Average	10	50	9	56	
	High	3	15	5	31	
Employment	*Yes*	13	65	12	75	ns
	No	7	35	4	25	
Being religious	*Yes*	10	50	7	44	ns
	No	10	50	9	56	

[1]PS: prophylactic surgery; PM/(I)BR: prophylactic mastectomy; P(B)SO: prophylactic (bilateral) salpingo-oophorectomy; PM/(I)BR +P(B)SO: prophylactic mastectomy and salpingo-oophorectomy simultaneously performed; PM/(I)BR before/after P(B)SO: prophylactic mastectomy performed before/after oophorectomy (time elapsed undefined)

Table 2
Self-reported motivations for PS in EC and C motivated women

	EC group (N=20)		**C group** (N=16)	
Emotional motivations	*N*	*%*	*N*	*%*
Fear for BC/OC	17	85	0	0
Wants to support daughter in the future	8	40	0	0
Feeling insecure about BC/OC	3	15	0	0
Cognitive motivations				
For risk reduction	7	35	11	69
Uncertainty screening	7	35	6	37,5
Knowledge of one's mutation status	4	20	5	31
Physician's advice	5	25	2	12,5
Nearing or already in menopause	4	20	1	6
Relief of benign gynecological issues	0	0	1	6
Having a choice	0	0	1	6
Don't want cancer (again)	1	5	1	6
For cosmetic reasons	0	0	1	6
Dislike of screening	0	0	1	6
Taking precautions	1	5	0	0
Wanting peace of mind	1	5	0	0

Sixteen women (44%) reported two different motivations for undergoing PS (range 0-5). Six women (17%) reported one motivation; fourteen women (39%) reported 3, 4 or 5 motivations (22%, 6% and 11% resp.).

Table 2 presents an overview of the number and percentages of emotional motivations and cognitive motivations in the EC group and the C group. Sixteen participants (44%) reported *only* cognitive-based motivations. Seventeen participants (47%) expressed both cognitive-based and emotion-based motivations. Three participants (8%) expressed *only* emotion-based motivations and were included in the EC group. Most women in the EC group (n=17, 85%) reported that fear of developing breast and/or ovarian cancer was a motivation to undergo PS. Two-thirds of the women in the C group (N=11; 69%) stated that they decided for PS because it was considered the most effective risk-reductive strategy opposed to one-third of the women in the EC group (N=7; 35%). Women who named fear for developing breast or ovarian cancer as a driving motivation also reported more frequently that they opted for PS because they wanted to support their daughter in the future (p=.01). No other relationships between the motivations were found.

Table 3 presents the means, standard deviations and significances between the EC-group and the C-group on the course of cancer-related distress (IES) and general distress (HADS). The groups did not differ on level or course of intrusion, avoidance, anxiety or depression at either assessment.

Table 3
Levels and courses of intrusion/avoidance (IES) and anxiety/depression (HADS) prior to, 6 months and 12 months after PS in EC and C motivated women

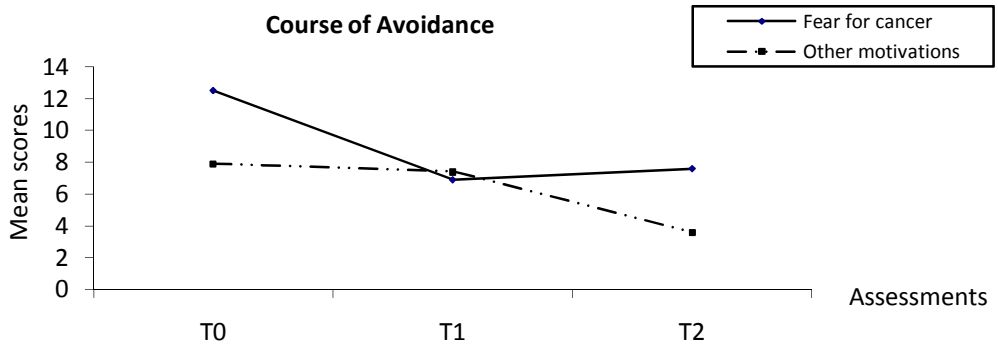
			EC group (N=20)		**C group** (N=16)			
			Mean	*Sd*	*Mean*	*Sd*	P_{level}	P_{course}
Cancer-related distress	*Intrusion*	T0	12,8	10,6	9,9	6,7	ns	ns
		T1	6,6	8,2	5,8	5,4	ns	
		T2	7,6	8,4	8,5	7,3	ns	
	Avoidance	T0	10,8	10,9	9,1	5,2	ns	ns
		T1	6,1	8,6	8,4	8,8	ns	
		T2	6,5	9,0	4,3	4,3	ns	
General distress	*Anxiety*	T0	8,6	5,1	5,9	3,6	ns	ns
		T1	5,2	4,0	4,3	4,0	ns	
		T2	5,8	4.0	4,8	3,4	ns	
	Depression	T0	5,2	4,2	3,1	2,5	ns	ns
		T1	3,3	3,3	2,6	2,7	ns	
		T2	4,1	3,0	3,3	2,8	ns	

Because of small subsamples, separate motivations could not be analysed for their effects on levels and courses of distress. Only the group of women who reported 'fear for developing breast cancer and ovarian cancer' was sufficiently large for such an analysis. Results are shown in Table 4 and in Figure 1. The 17 women who reported fear as a motivation to decide for PS were at baseline averagely more depressed than the other women (p=.02), and had a different course of avoidance (p=.02).

Table 4
Fear for breast cancer and ovarian cancer (n=17) versus otherwise motivated (n=19) PS utilizing women: course of distress prior to and 6 and 12 months after PS

			Fear for cancer		Other motivations				
			Mean	*Sd*	*Mean*	*Sd*	P_{level}	P_{course}	
								L	***Q***
Cancer-related distress	*Intrusion*	T0	14.6	10.5	8.7	6.8	ns	ns	ns
		T1	7.6	8.5	5.1	5.3	ns		
		T2	8.1	8.8	7.9	7.2	ns		
	Avoidance	T0	12.5	11.0	7.9	5.6	ns	ns	.02
		T1	6.9	9.1	7.4	8.4	ns		
		T2	7.6	9.4	3.6	4.2	ns		
General distress	*Anxiety*	T0	9.1	5.2	6.0	3.7	ns	ns	ns
		T1	5.4	3.9	4.4	4.1	ns		
		T2	6.1	3.6	4.7	3.8	ns		
	Depression	T0	5.8	4.3	2.9	2.4	.02	ns	ns
		T1	3.5	3.5	2.6	2.6	ns		
		T2	4.5	3.0	3.2	2.7	ns		

Figure 1
Course of avoidance (IES) for women who report fear for breast cancer and/or ovarian cancer (N=17) and women who report other motivations (N=19)



5.4 Discussion

This paper presents our findings regarding the nature of motivations to undergo PS in women at an increased risk of hereditary breast/ovarian cancer due to either a *BRCA1/2* mutation or family history, and the effect of these motivations on the course of emotional distress. According to the theory of self-regulation, emotional responses will facilitate cognitive processes, that predominantly control risk-reducing actions like PS, which eventually will lead to distress reduction.

The motivations that were reported by the women in this study corroborate earlier findings; six of the seven motivations that were identified in this study were reported in previous studies, namely fear of developing breast and ovarian cancer, risk reduction, the

obligation felt by women towards family members, physician's advice, worries about effectiveness of regular surveillance, and genetic testing[15-21,44]. Though the motivation 'nearing or already in menopause' was not reported previously, higher age has been found to be a factor for opting for P(B)SO[17,45].

We could not confirm our hypothesis that women whose motivations were both cognitive and emotional benefit more from PS in terms of emotional distress reduction than women whose motivations do not have an emotional component. This leads us to two considerations.

First, the report of motivations by the C group may have been influenced by the appraisal of the problem-focused coping, i.e. the decision for PS. This appraisal may have then reduced the previous anxiety and distress as a conscious motivation to decide in favour of PS. Consequently, women may not have experienced anxiety at a conscious level when asked for their motivations to undergo PS, shortly before PS.

A second explanation is that women in the C group were unable or unwilling to report their emotions. They might have repressed them in favour of their cognitions. If that was the case, 'hidden' emotions might surface in intensive pre-operative counselling when focussed hereon. However, they seemed to benefit from PS with regard to emotional distress as much as women who did report emotional motivations. Therefore, suppression of emotional responses in the preoperative period might serve a beneficial function in the waiting period prior to PS.

Interestingly, when categorizing the total cohort into women who reported fear for cancer versus women who reported no such fear, we found that the cancer-fearing group were more likely to experience a reduction in avoidant thoughts and behaviour within six months after PS.

This result raised the question whether or not the categorization as used for analysis in this study was correct. Still, lack or suppression of emotional responses did not seem to have a negative effect on these women, as far as emotional distress was concerned. Research in a larger sample with a longer follow-up should shed additional light on this speculation.

The present study dealt with a number of limitations. Because the observations were made in a small sample, results provided us with an insight into the processes regarding decision-making and the effects on emotional distress, but might not always uncover all the processes that were going on in these women. Moreover, follow-up was thirteen months at its most. In order to determine the emotional effects of the decision for PS in the longer run, future research should focus on larger samples over longer periods of time.

A final remark should be made on the women who did not report any other motivations but fear. Fry et al.[19] suggested that when fear is predominant in women who opt for PS, psychotherapy might be more beneficial than such a radical operation. Based on our results, we cannot answer the question whether or not PS is an adequate option for these women. Only three women in our cohort did not report other motivations except fear, a number far too small for analyses. Psychological counselling may be offered to women who experience extreme fear prior to PS and/or ongoing fear after PS in order to support them in making an informed decision regarding regular surveillance or PS.

Considering the fact that fear for developing cancer proved to be a source of enhanced distress, as our results indicate, we are in favour of extensive research on this topic.
In conclusion, women who reported fear for developing cancer as a motive for undergoing PS experienced enhanced distress prior to PS. Pre- and post-operative counselling might particularly focus on women with a predominantly fear-driven choice for PS to assist them in handling potentially enhanced distress in that period. Women who did not report emotional motivations had mean levels of distress within normal range prior to PS and had experienced a decrease in distress a year after PS. If emotions are suppressed in these women, this might lead to emotional problems in the longer run. In pre-operative counselling of these women, their motivations and levels of distress should be addressed in order to possibly uncover suppressed emotions in order to avoid future emotional problems. Finally, future research should focus on unravelling the longer-term processes that lead to emotional or cognitive motivations.

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6

The Course of Distress in Women at Increased Risk of Breast and Ovarian Cancer Due to an (Identified) Genetic Susceptibility Who Opt for Prophylactic Mastectomy and/or Salpingo-Oophorectomy

Background *The levels and course of psychological distress before and after prophylactic mastectomy (PM) and/or prophylactic salpingo-oophorectomy (PSO) were studied in a group of 78 women.*
Methods *General distress was measured through the Hospital Anxiety and Depression Scale (HADS), cancer-related distress using the Impact of Events Scale (IES). Measurement moments were: baseline (2 to 4 weeks prior to prophylactic surgery), and 6 and 12 months post-surgery.*
Results *After PM, anxiety and cancer-related distress were significantly reduced, whereas no significant changes in distress scores were observed after PSO. At one year after prophylactic surgery, a substantial amount of women remained at clinically relevant, increased levels of cancer-related distress and anxiety.*
Conclusions *We conclude that most women can undergo PM and/or PSO without developing major emotional distress. More research is needed to further define the characteristics of the women who continue to have clinically relevant increased scores after surgery, in order to offer them additional counselling.*

6.1 Introduction

Women with an identified *BRCA1/2* mutation have a cumulative lifetime risk (i.e. up to the age of 70 years) for breast cancer of 39-85%, and for ovarian cancer of 10-63%.

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Furthermore, after a history of breast cancer, the life-time risk of contralateral breast cancer is 35-64%[1]. Female 50% risk carriers from families with an autosomal dominant transmission pattern of breast and/or ovarian cancer without an identifiable *BRCA1/2* mutation also have an increased risk. In these women, the risk of developing breast cancer is estimated by means of genetic-epidemiological tables[2].

Unaffected mutation carriers and 50% risk carriers can either opt for regular surveillance of the breasts and ovaries, or for prophylactic mastectomy (PM) and/or prophylactic salpingo-oophorectomy (PSO). Mutation carriers who have been treated for breast cancer may opt for (bi- or contralateral) PM and/or PSO in selected cases. Both types of prophylactic surgery are associated with substantial risk reduction with respect to the development of a primary breast or ovarian cancer[3-8], while prospective data on the benefit regarding overall survival are not yet available. However, prophylactic mastectomy is associated with the loss of healthy breasts and normal sensation, and is an irreversible procedure[9]. Further, breast reconstruction, either immediate or at a later stage, may require re-operation(s), usually for implant-related issues[9,10]. Research[11,12] pointed out that balanced information is of importance for careful decision making regarding PSO.

Favorable effects of prophylactic surgery on a woman's distress level[13-22] and quality of life[3] in the year following these interventions have been reported[23]. Apparently, the disease-induced fear was relieved after surgery. Most of these observations were obtained from retrospective studies in small samples of women[15,22,24]. To our knowledge, a prospective exploration of the levels and the courses of distress in women undergoing a PM versus a PSO has not been performed yet. Within the framework of a prospective study on the medical and psychosocial effects of prophylactic surgery that started in 1999 at the Family Cancer Clinic of the Erasmus MC in Rotterdam, the levels and courses of general and cancer-related distress were analyzed in women undergoing either a PM and/or PSO.

Our research questions were the following: 1) do women opting for prophylactic surgery experience higher distress levels prior to surgery then women adhering a regular breast cancer surveillance program, 2) is there a relief of distress after PM and/or PSO, and 3) are the scores and the levels of distress different between women opting for PM, and respectively for PSO? Moreover, we explored the frequency of scores considered to indicate clinically relevant distress.

6.2 Patients and Methods

6.2.1 Study population

Between August 1999 and February 2003, 129 high-risk women who decided to undergo PM and/or PSO as risk reducing procedure at the Family Cancer Clinic of the Erasmus MC-Daniel den Hoed Cancer Centre were invited to participate in a psychological follow-up study (PREVOM-B study) on the psychological impact of prophylactic surgery. All women came from families with an apparent autosomal dominant transmission pattern, and therefore had an associated elevated risk of breast/ovarian cancer. The majority of these women were *BRCA1/2* mutation carriers (hereafter called 'mutation carriers').

For women from hereditary breast-(/ovarian) cancer families without a detectable *BRCA1/2*-mutation (hereafter called 'risk carriers'), the request for PM/PSO was reviewed

at the multidisciplinary patient meeting of the working party on hereditary cancer of our institution. The decision to proceed to prophylactic surgery was made after extensive and repeated information and counselling. Factors taken into account were age, previous history of cancer, risk calculation to develop breast cancer and/or ovarian cancer, and consistency of the patient's request and its underlying arguments.

Only women having prophylactic surgery at the Erasmus MC-Daniel den Hoed Clinic in Rotterdam were eligible for this study. Also, no signs or suspicion of breast/ovarian cancer should be present in unaffected women at pre-surgical examination (physical and imaging examination, plus Ca125 analysis) performed within 3 months prior to surgery. Women with a history of breast/ovarian cancer were to have no signs of recurrent disease or a new primary after physical and imaging/dissemination examination consisting of: mammography, gynecological ultrasound, chest X-ray, ultrasound liver, bone scan, liver-function tests, and Ca125/Ca153 analysis; also performed within 3 months prior to surgery.

The participation rate was 75% (n=97). Data of 15 women were excluded from the analyses because less than 75% of the items on the questionnaires were filled out. Based on clinical experience, we expected different levels and courses of distress for women who opted for PM or for PSO. Therefore, the sample was subdivided into a PM and a PSO group. Four women, having PSO first, opted for PM within 3-9 months during the follow-up period of the study. In view of the difficulty to attribute their responses to either one of the types of prophylactic surgery, their data were not used in the analyses. So, the final sample included 78 participants.

Physicians introduced the study to eligible patients with verbal and written information. After written informed consent, participants received questionnaires by mail 2-4 weeks before (T0), and 6 and 12 months after prophylactic surgery (T1 and T2 respectively). The questionnaire included demographic data, and self-rating scales on general[25] and cancer-related[26] distress. The self-rating scales were administered at every measurement moment. Results of in-depth interviews, conducted at T0, T1 and T2, are not included in this analysis.

6.2.2 Reference group

To interpret the levels of distress before surgery, women with comparable increased risks, but opting for regular screening, were selected as a reference group. They participated in a national, prospective study (MRISC study) investigating the value of the magnetic resonance imaging scan (MRI)[27].

The surveillance program consisted of a physical examination twice a year, a mammography and MRI once a year within a 6-weeks period, while women were advised to perform breast self examination (BSE) once a month. For comparison with the PM/PSO group we used the day of the control visit at the clinic as we assumed this moment as the most stressful during the surveillance period. All complete datasets of women who participated in that particular measurement moment were selected for reference, resulting in a 2:1 ratio of either mutation carriers (n_{prevom}=54: n_{mrisc}=27) and a 1:7 ratio of risk carriers (n_{prevom}=24: n_{mrisc}=170) from HBOC-families. Identical self-rating scales were used to assess psychological distress.

6.2.3 Procedure of dividing the study sample into a PM and a PSO group

Of all women in our sample, 34 opted for merely PM and 18 for merely PSO. The remaining 26 women could be divided into five separate categories:

1. PM and PSO were performed simultaneously (n=9);
2. Participant was included before PM, and had undergone PSO prior to PM (n=7);
3. Participant was included before PM, and underwent PSO during or after the follow-up period of the study (n=1);
4. Participant was included before PSO, and had undergone PM prior to PSO (n=5);
5. Participant was included before PSO, and underwent PM during or after the follow-up period of the study (n=4).

For statistical reasons, we did not want to exclude this heterogeneous group, nor view it as a separate group. Therefore, we assigned participants to one of the groups based on the time elapsed between both types of surgery. Guided by clinical experience, we assumed that PM would have greater physical and psychological impact. Therefore, participants who were included in the study because of PM and who underwent PSO prior to (n=7), simultaneously (n=9) or in the year after PM (n=1), were classified in the PM group. For women who were assigned to category 2 and 3, the time that had elapsed between both types of prophylactic surgery varied between 6,5 and 65 months, with an average of 26 months. One participant, who underwent PM within two months after PSO, was included in the PM group. The remaining participants of category 4 and 5 (n=8) were assigned to the PSO group. For these women, the time that had elapsed between both types of prophylactic surgery varied between 12 and 41 months, with an average of 24 months.

6.2.4 Biographical and medical data

Age, marital status, offspring, religious affiliation, educational level, profession, carrier status, history of breast cancer, and type of surgery were recorded at T0.

6.2.5 Cancer-related distress

The Impact of Events Scale (IES) is an established instrument[26,28-30] for measuring feeling overwhelmed by intrusive and avoidant thoughts, and feelings related to a traumatic event, and the tendency to adapt one's behavior to these thoughts and feelings. In our study, these thoughts, feelings and behavior were anchored to breast- and/or ovarian cancer. The response categories are: not at all (0); seldom (1); sometimes (3); and often (5). The score range for the intrusion scale is 0-35 and for the avoidance scale 0-40. Reliability and validity are satisfactory[28-31]. No norms or cut-off scores are available for the general population. However, from two studies conducted in a clinical setting[32-33] cut-off scores equal or higher than 13 on the intrusion subscale and equal or higher than 11 on the avoidance subscale were reported to be clinically relevant. In the present study, these cut-off values were considered as clinically significant.

6.2.6 General distress

General distress was measured with the Hospital Anxiety and Depression Scale (HADS)[25]. The HADS has two scales for anxiety and depression, respectively. Every item has four

response categories, anchored to that specific item. The scores range from 0-21 for both scales. Validity and reliability have proven to be sufficient[34,35]. A score between 8 and 10 on each subscale represents a doubtful case of either anxiety or depression. A score of 11 or higher per subscale is indicative of a clinically relevant level of distress.

6.2.7 Statistical Analysis

The data were analyzed using the SPSS 11.0 statistical package (SPSS Inc., Chicago). Missing values were estimated through multiple imputation. Frequency analysis was used to determine the characteristics of the participants and to calculate means for each subscale per group. Univariate analysis of variance determined differences on biographical variables and medical variables. T-test for independent samples was used to test for differences between the study sample and the reference group. Finally, MANOVA was used to determine whether the courses between the PM group and the PSO group were different. When the courses turned out to be different, it was tested whether the courses differed linearly and/or quadratically. A quadratic course means that the in-between assessment differed from the straight line between the first and the final assessment. All statistical testing took place at 0.05 level of significance (two-sided).

Table 1
Characteristics of the study population (SP; n=78), the prophylactic mastectomy group (PM; n=52) and the prophylactic oophorectomy group (PSO; n=26)

		SP (n=78)		**PM** (n=52)		**PSO** (n=26)		
		M	*Sd*	*M*	*Sd*	*M*	*Sd*	*P*[1]
Age	*(in years)*	43	8.6	40	8.0	47	7.6	.001
		n	*%*	*n*	*%*	*n*	*%*	
Marital status	*Married or co-habiting*	69	89	45	87	24	92	ns
	Single or divorced	9	11	7	13	2	8	
Children	*Yes*	64	82	41	79	23	88	ns
	No	14	18	11	21	3	12	
Religious	*Yes*	31	40	19	37	12	46	ns
	No	47	60	33	63	14	54	
Education	*Low/average*	59	76	42	81	17	65	ns
	High	18	23	10	19	8	31	
	Missing	1	1	-	-	1	4	
Current job	*Yes*	53	68	37	71	16	62	ns
	No	25	32	15	29	10	39	
Carrier status	*BRCA1/2 mutation*	54	69	36	69	18	69	ns
	50% risk carrier	24	31	16	31	8	31	
History of cancer	*No*	50	64	35	67	15	58	ns
	Breast cancer	27	35	16	31	11	42	
	Ovarian cancer	1	1	1	2	-	-	
Type of surgery	*PM*	34	44	34	66	-	-	.04
	PSO	18	23	-	-	18	69	
	PM+PSO	9	11	9	17	-	-	
	PM prior to PSO	6	8	1	2	5	19	
	PM after PSO	11	14	8	15	3	12	

[1] *comparison of means of the PM group with the PSO group*

6.3 Results

6.3.1 Patients characteristics

Characteristics of all respondents, and the PM and PSO group separately are shown in Table 1. Both groups were identical on most biographical and medical data, except that women in the PM group were significantly younger than women in the PSO group (p<.001).

6.3.2 Baseline levels of distress between the study sample and the reference group

Table 2 presents the baseline levels on the outcome variables of the IES and the HADS in women who opted for prophylactic surgery (PREVOM-B study, this study) and women who adhered to regular breast cancer surveillance (MRISC-study).

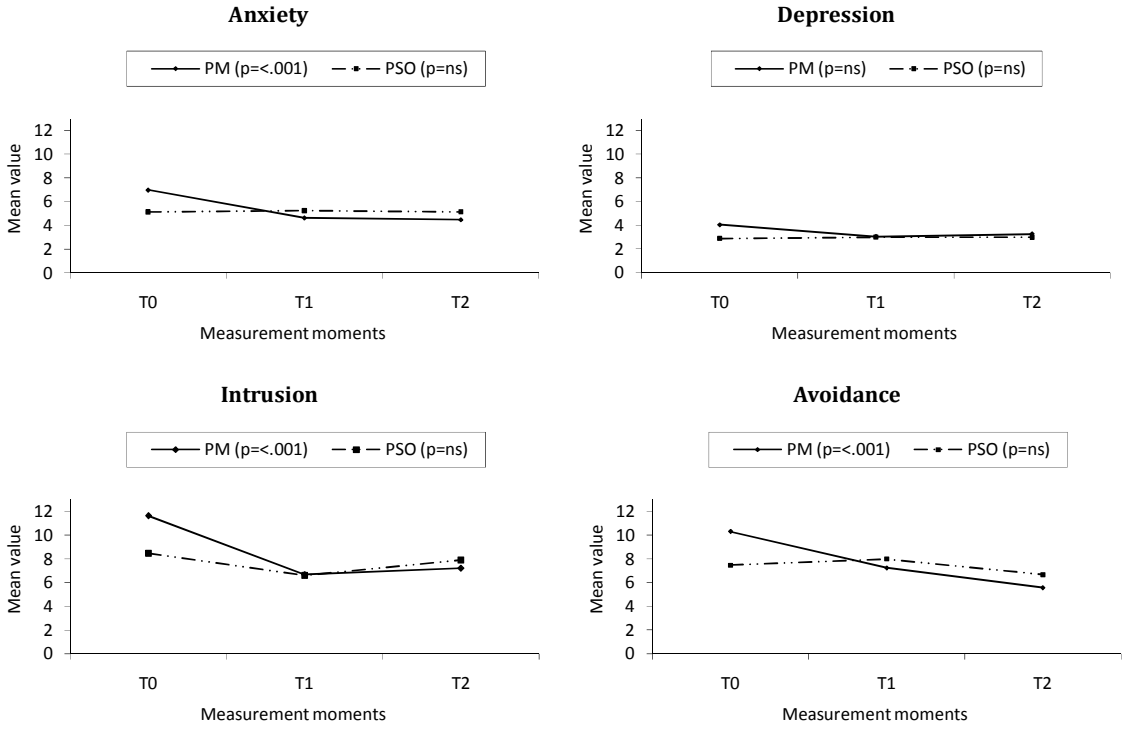
Table 2

Baseline levels on the Impact of Events Scale (IES) and the Hospital Anxiety and Depression Scale (HADS) of women who opted for prophylactic surgery (PREVOM-study) and women who opted for regular surveillance (MRISC-study)

		PREVOM-study *(n=78)*		**MRISC-study** *(n=197)*		
		M	*Sd*	*M*	*Sd*	*p*
General distress	*Anxiety*	6.36	4.4	5.13	3.9	.02
	Depression	3.66	3.5	2.56	3.0	.01
Cancer-related distress	*Intrusion*	10.58	8.9	5.05	6.4	<.001
	Avoidance	9.35	8.4	4.45	6.3	<.001

Figure 1

Mean scores on the HADS and IES at baseline, 6 months follow-up and 12 months follow-up for women who opt for PM (n=52) and PSO (n=26)



The samples only differed on carrier status. The PREVOM-group comprised of twice as much mutation carriers than the MRISC-group, whereas the MRISC-group consisted of seven times as much risk carriers. The samples differed significantly on all measures of distress, whereby the women in the PREVOM-B study consistently had a higher score on the distress variables.

Table 3
Course of general and cancer-related distress for the PM group (n=52) and the PSO group (n=26)

			Mean	*Median*	*Range*	*Sd*	*p (time)*	
PM group *(n=52)*							*L*[1]	*Q*[1]
General distress	*Anxiety*	T0	6.98	6	0-19	4.5	<.001	ns
		T1	4.63	4	0-15	3.8		
		T2	4.47	4	0-14	3.1		
	Depression	T0	4.04	3	0-14	3.8	ns	ns
		T1	3.03	2	0-14	3.1		
		T2	3.27	2	0-11	2.9		
Cancer-related distress	*Intrusion*	T0	11.63	9	0-35	9.3	<.001	ns
		T1	6.66	4	0-31	7.1		
		T2	7.20	6	0-34	7.2		
	Avoidance	T0	10.29	9	0-40	8.8	<.001	ns
		T1	7.22	5	0-34	8.4		
		T2	5.56	4	0-38	7.0		
PSO group *(n=26)*								
General distress	*Anxiety*	T0	5.12	5	0-12	3.9	ns	ns
		T1	5.25	5	0-12	3.7		
		T2	5.14	5	0-12	3.5		
	Depression	T0	2.88	3	0-9	2.5	ns	ns
		T1	2.98	3	0-9	2.6		
		T2	2.97	3	0-9	2.3		
Cancer-related distress	*Intrusion*	T0	8.48	7	0-24	7.6	ns	ns
		T1	6.60	6	0-23	6.4		
		T2	7.91	8	0-26	7.2		
	Avoidance	T0	7.46	6	0-23	7.1	ns	ns
		T1	7.97	8	0-36	8.8		
		T2	6.67	5	0-23	7.2		
PM *versus* ***PSO***				*p*[2] *(means)*			*p(time*type of surgery)*	
							L	*Q*
General distress	*Anxiety*	T0		ns			.003	ns
		T1		ns				
		T2		ns				
	Depression	T0		ns			ns	ns
		T1		ns				
		T2		ns				
Cancer-related distress	*Intrusion*	T0		ns			ns	ns
		T1		ns				
		T2		ns				
	Avoidance	T0		ns			.02	ns
		T1		ns				
		T2		ns				

[1] L=Linear, Q=Quadratic
[2] p-value of means per assessment between groups/type of surgery

6.3.3 Comparison of levels and course of distress

Table 3 presents the means, medians, ranges, and standard deviations of cancer-related and general distress in the PM and PSO group, at baseline, T1 and T2 respectively. Also, the courses per subscale and the relations between the groups on the means per subscale and over time are shown in Table 3, and are graphically shown in figure 1.

In the PM group, intrusion, avoidance and anxiety showed a significant linear decrease over time. However, in the PSO group, no significant changes in the distress levels were observed before and after surgery.

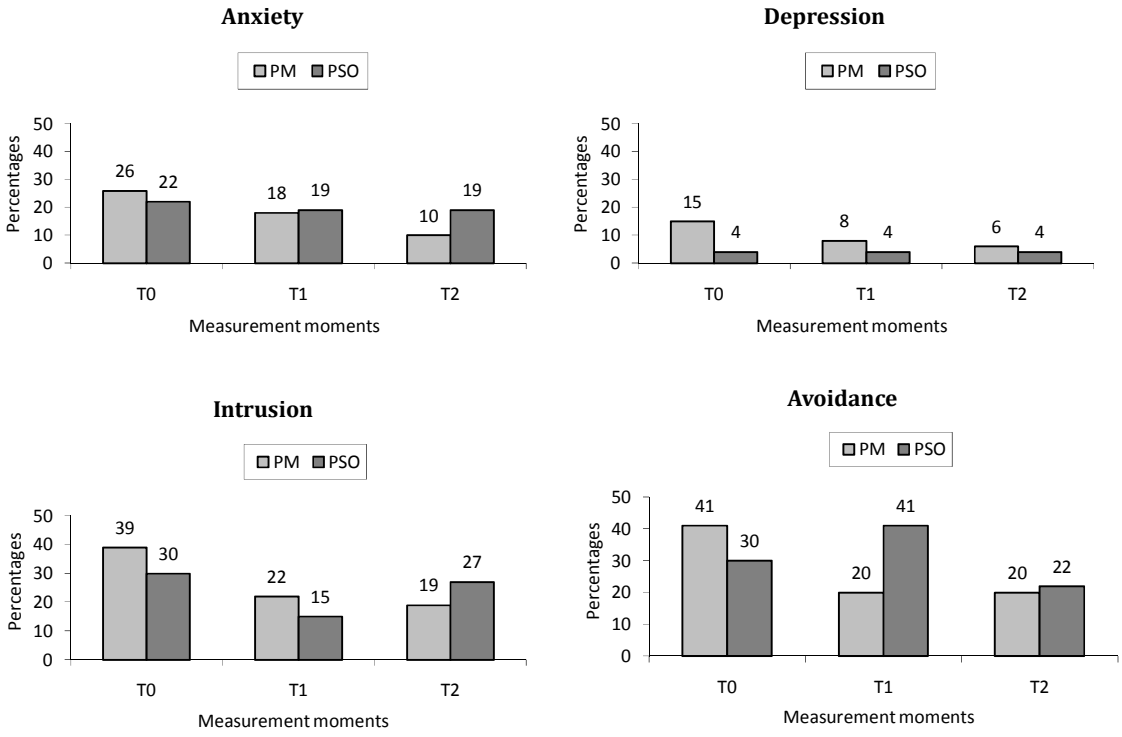
Table 4

Number, means and standard deviations of scores on intrusion, avoidance, anxiety and depression of women in the PM group and women in the PSO group, who scored above cut-off scores.

			PM group (n=52)				**PSO group** (n=26)			
	Cut-off		*N*	*%*	*Mean*	*Sd*	*N*	*%*	*Mean*	*Sd*
General distress	*Anxiety*	T0	13	26	13.62	2.76	6	22	10.33	1.21
	>8	T1	9	18	10.91	2.07	5	19	10.60	1.14
		T2	5	10	11.03	2.33	5	19	10.29	1.49
	Depression	T0	8	15	10.90	2.00	1	4	9.00	-
	>8	T1	4	8	11.00	2.00	1	4	9.00	-
		T2	3	6	10.06	0.91	1	4	9.00	-
Cancer-related distress	*Intrusion*	T0	20	39	21.85	5.88	8	30	18.25	3.33
	>12	T1	11	22	17.95	5.17	4	15	17.00	4.08
		T2	10	19	18.78	6.12	7	27	17.29	4.61
	Avoidance	T0	21	41	18.57	7.80	8	30	16.25	4.33
	>10	T1	10	20	21.44	8.76	11	41	15.65	7.82
		T2	10	20	16.46	8.11	6	22	18.00	3.29

Figure 2

Percentages of women in the PM group and the PSO group who scored above the cut-off score of the HADS and the IES at baseline, 6 months follow-up and 12 months follow-up



6.3.4 Clinical 'cases' of distress

Table 4 shows the clinically relevant cut-off scores per subscale, the percentages per group of women who scored above these cut-off scores, as well as the mean scores for this subgroup on each measurement moment. The percentages of women scoring above the threshold value at either baseline or follow-up are also graphically illustrated in Figure 2. At all time points, substantial percentages of women scored above the cut-off point of both subscales of the IES and above the cut-off point of the anxiety subscale of the HADS. At one year follow-up, 10% of all women who opted for PM, scored above the cut-off score on anxiety, and 6% scored clinically high on depression, compared to resp. 19% and 4% in the group of women who opted for PSO. As for cancer-related distress, 19% of all women who opted for PM, scored above the cut-off score on intrusion, and 20% scored clinically high on avoidance, compared to 27% and 22% resp. of the women who opted for PSO.

6.4 Discussion

The current paper describes the levels of general and cancer related distress and the courses of these measures in genetically predisposed women who opted for either PM or PSO up to 12 months after prophylactic surgery.

Firstly, we observed that levels of distress were increased prior to surgery in our sample as compared to a reference group of women who opted for breast cancer surveillance. This might indicate that the women who opt for prophylactic surgery experienced overall more distress, which might have played a role in their decision for prophylactic surgery instead of surveillance. Of course, other factors, e.g. anxiety related to upcoming surgery, may have played a role in the observed difference. For instance, most of the women who opted for either PM or PSO were mutation carriers, whereas in the reference group the majority were risk carriers from HBOC families. Mutation carriers received information on a higher cancer risk assessment, and consequently on the option of PM/PSO. In addition, one can speculate that the women in the group who chose to undergo surgery might have had more experience with witnessing cancer and death of family members. An impressive family history may also influence the physician's advice to encourage the patient to undergo prophylactic surgery.

Our second research question concerned the levels and course of distress in the PM and the PSO group after prophylactic surgery. As for the course of distress, we found significant decreases with respect to anxiety, avoidance and intrusion in women who underwent PM. This is in accordance with the findings in other studies[13,15,18]. Our results support our clinical impression that women can undergo this type of surgery without further developing emotional distress. The decline of distress in the PM group might indicate that PM has diminished the fear of getting cancer. Moreover, after PM no further breast self examination is needed, and consequently results in less direct physical confrontations with being at high risk of developing breast cancer. In addition, the frequency of surveillance at the clinic is diminished, and there is no further need for regular mammography and/or MRI examinations.

Contrary to earlier findings[22], no measurable changes were found in the distress levels of women who underwent PSO. Again, this indicates that women can undergo this type of

surgery without further developing emotional distress. The levels of distress in the PSO group were not exceptionally high prior to surgery, which might explain why distress did not decrease after PSO, as was observed in the PM group. Because the majority of women who underwent PSO were either nearing menopause or already postmenopausal, the physical consequences of this type of surgery might not have been of importance with respect to the decision for PSO. Moreover, the women who underwent PSO were older and in a different phase of their lives as compared to the women who opted for PM. Starting a family and/or raising young children was no longer an issue in the PSO group.

Our third research question addressed the comparison of the PM group and the PSO group on both the levels and the courses of all measures of distress. Clinically, PM and PSO are different types of surgery regarding the impact on body image, cosmesis, and morbidity. Both types of surgery are performed in different age groups, as is illustrated in Table 1. The decision to separate PM and PSO women as a basis for the main analysis was taken on these clinical grounds. Though the course of distress appeared to be different for the two groups, we could not demonstrate any significant differences between the mean scores of the PM and the PSO group. We speculate that this lack of significance is due to the small sample size, but doubt if investigating a larger group would yield relevant differences between these groups.

Finally, we explored the frequency of scores considered to indicate clinically relevant distress. Substantial percentages of women at baseline and during follow-up scored in the clinical range of both subscales of the IES and the anxiety scale of the HADS. One explanation concerns the anchoring of the variables of the IES to breast and ovarian cancer. Intrusive thoughts on breast cancer might reflect one's concerns with the breast cancer process in relatives, instead of the personal risks. This explanation is supported by the findings of Van Dooren and colleagues[36], who found that high scores on the IES around surveillance appointments were related to the involvement in the care for relatives with cancer. Another explanation is that having children or lacking a stable partnership can cause increased distress after prophylactic surgery, as was found in an earlier follow-up study done in our institute[37]. Further analyses of factors that are predicting enhanced scores on distress are in progress.

To our knowledge, our study is to the first to present prospective data from a group of high-risk women opting for prophylactic surgery. It provides insight into the level and course of general and cancer-related distress of women who opt for PM compared to women who opt for PSO. Moreover, the distress levels of women who opted for prophylactic surgery are compared to the distress levels of women who opted for regular surveillance.

Prophylactic surgery is an irreversible procedure, that is performed in healthy high-risk women on parts of the body that conceivably are related to self-image, sexual attractiveness and perception, etc. Our results show that women can undergo this type of surgery without developing emotional distress to a relevant degree. Further, prophylactic mastectomy even decreased distress. More research is needed to further define the characteristics of the women who continue to have clinically relevant increased scores after surgery, in order to identify them and offer them additional counselling. So far, we

suggest inclusion of a referral to a psychologist or psychosocial worker as part of the preoperative work up for women considering a PM.

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7

Distress in Partners of High-Risk Women Opting for Prophylactic Mastectomy and/or (Bilateral) Salpingo-Oophorectomy

Background *The levels and courses of psychological distress before and after prophylactic mastectomy with or without (immediate) breast reconstruction (PM/(I)BR) and/or prophylactic (bilateral) salpingo-oophorectomy (P(B)SO) were studied in 61 partners of women at increased risk for breast and ovarian cancer, most of the latter being carriers of a BRCA1 or BRCA2 mutation.*

Methods *General distress was measured through the Hospital Anxiety and Depression Scale (HADS), and cancer-related distress using the Impact of Events Scale (IES). Measurement moments were: baseline (2 to 4 weeks prior to prophylactic surgery), and 6 and 12 months post-surgery. Intrusive thoughts decreased after prophylactic surgery (PS).*

Results *A small proportion of partners continued to have increased scores on general and cancer-related distress up to one year after prophylactic surgery. Higher distress scores were associated with BRCA1/2 mutation status, previous cancer of the wife, fatherhood and having a high-level of education.*

Conclusions *The care for families opting for genetic testing and prophylactic surgery might include adequate monitoring of the need for psychological support for both high-risk women and their partners, when either or both show increased general or cancer-related distress levels.*

7.1 Introduction

The *BRCA1* and *BRCA2* breast cancer susceptibility genes associated with hereditary breast and ovarian cancer were identified in 1994 and 1995 respectively[1,2]. Female mutation carriers have a cumulative lifetime risk of 39-85% for breast cancer.

Submitted

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Moreover, their lifetime risk for ovarian/fallopian cancer is 11-63% at 70 years of age[3,6]. Additionally, mutation carriers with a history of unilateral breast cancer have an increased lifetime risk of contralateral breast cancer, estimated between 20-60%, being approximately 3% annually[7,8].

Regular surveillance by mammography, magnetic resonance imaging (MRI) scan, and clinical breast examination[9] aims at early detection of breast cancer, while regular surveillance by means of the current modalities fails to detect ovarian cancer at an early stage[10]. So, ablation of the breasts (i.e. prophylactic mastectomy with or without (immediate) breast reconstruction: PM/(I)BR) as well as resection of the ovaries/fallopian tubes (i.e. prophylactic (bilateral) salpingo-oophorectomy: P(B)SO) in the absence of signs of cancer is a preventive measure, which is highly effective with respect to cancer risk reduction. Studies on the efficacy of PM/(I)BR showed that the remaining risk of developing a primary breast cancer after surgery is very low[11]. Also, after P(B)SO, only a small residual risk of developing extraovarian, peritoneal cancer is remaining[12]. Furthermore, a P(B)SO is estimated to half the risk of developing breast cancer[13,14].

The psychological impact of risk management options was earlier especially addressing *BRCA1/2* mutation carriers and women with similar risks resulting from their family history (hereafter called 'high-risk women')[15-28]. However, the threat of developing breast and ovarian cancer and the consequences of prophylactic surgery may also be distressing for their partners. Only few studies have focused on partners of high-risk women. Generally, partners seemed to adjust well to the increased risk for breast and ovarian cancer of their wives[30-32]. Still, high post-test anxiety scores were reported by 20% of the mutation carriers and 35% of their partners[29]. Moreover, partners of high-risk women reported that decision-making on prophylactic surgery was the most challenging aspect of dealing with their wife's high risk of developing cancer[21,30].

The present study addresses the psychosocial impact of prophylactic surgery in partners of high-risk women. The objectives were to 1) estimate the levels and courses of distress, and 2) identify the factors that contributed to increased distress, before as well as after prophylactic surgery.

7.2 Patients and Methods

7.2.1 Study population

Between August 1999 and February 2003, 129 high-risk women who decided to undergo PM/(I)BR and/or P(B)SO at the Family Cancer Clinic of the Erasmus MC-Daniel den Hoed Cancer Centre were invited to participate in a psychological follow-up study (PREVOM-B study) on the psychological impact of prophylactic surgery. Also their partners were invited to participate. All women were at increased risk of hereditary breast/ovarian cancer, and were either *BRCA1/2* mutation carriers or belonged to a hereditary breast and ovarian cancer (HBOC) family wherein genetic testing did not identify a *BRCA1/2* mutation. For women from a HBOC family, the request for PM/(I)BR and P(B)SO was evaluated by the multidisciplinary working party on hereditary cancer of our institution. Only women undergoing prophylactic surgery at the Erasmus MC-Daniel den Hoed Clinic in Rotterdam were eligible for the present study. Other eligibility criteria included: for unaffected women no signs or suspicion of breast/ovarian cancer at pre-surgical

examination (physical and imaging examination, plus Ca125 analysis) performed within 3 months prior to surgery; for women with a history of breast/ovarian cancer no signs of recurrent disease or a new primary cancer by means of physical and imaging/dissemination examination (including mammography, gynaecological ultrasound, chest X-ray, ultrasound of the liver, bone scan, liver-function tests, and Ca125/Ca153 analysis), also performed within 3 months prior to prophylactic surgery.

7.2.2 Procedure

After signed informed consent of the high-risk women and their partners, all participants received questionnaires by mail 2-4 weeks before (T0), and 6 and 12 months after prophylactic surgery (T1 and T2 respectively). The questionnaires included a survey on demographic data, and self-rating scales on general and cancer-related distress. The demographic questionnaire was filled out at T0, while the self-rating scales were administered at every assessment.

Of the 97 participating high-risk women, 86 (89%) had a partner. Sixty-one of these partners (72%) agreed to participate in our study. All partners of the high-risk women in the present study were male. We were able to obtain demographical data on all participating partners. However, 28 (46%) partners failed to fill out one or more distress measures at T0. We compared the distress scores at T1 and T2 of the partners who failed to fill out the questionnaires at T0 with the distress scores on T1 and T2 of the partners who had completed the baseline survey. No differences between both groups were found (data not shown). Therefore, we considered both groups as equal and present results on distress of the remaining 33 partners who completed the distress questionnaires at all assessments.

7.2.3 Biographical and medical data

AT T0, the following data of the partner were collected: age, offspring, educational level, and employment. Characteristics of the high-risk women undergoing prophylactic surgery including carrier status, history of breast cancer, and type of prophylactic surgery were also used for analyses.

7.2.4 Cancer-related distress

The Impact of Events Scale (IES) is an established instrument[33-36] for measuring feeling overwhelmed by intrusive and avoidant thoughts, and feelings related to a traumatic event, and the tendency to adapt one's behaviour to these thoughts and feelings. In our study, these thoughts, feelings and behaviour were anchored to breast- and/or ovarian cancer. The response categories are: not at all (0 points); seldom (1 point); sometimes (3 points); and often (5 points). The score range for the intrusion scale is 0-35 and for the avoidance scale 0-40. Reliability and validity are satisfactory[34-37]. No norms or cut-off scores are available for the general population. However, from two studies conducted in a clinical setting[38,39] cut-off scores equal or higher than 13 on the intrusion subscale and equal or higher than 11 on the avoidance subscale were reported to be clinically relevant. In the present study, these cut-off values were considered as clinically relevant.

7.2.5 General distress

General distress was measured with the Hospital Anxiety and Depression Scale (HADS)[40]. The HADS comprises two scales, one assessing anxiety and the other assessing depression. Every item has four response categories, anchored to that specific item. The scores range from 0-21 for both scales. Validity and reliability have proven to be sufficient on each subscale[41,42]. A score between 8 and 10 is considered doubtful; a score of 11 or higher per subscale is indicative of a clinically relevant level of distress.

7.2.6 Statistical Analysis

Frequency analysis was used to determine the characteristics of the participants and to calculate means for each subscale per group. To investigate the course of distress, Multivariate analysis of variance (MANOVA) was applied. Analysis of variance (ANOVA) tested differences between biographical and medical variables on the one hand and distress on the other hand. All statistical testing took place at 0.05 level of significance (two-sided). The data were analysed using the SPSS 11.0 statistical package (SPSS Inc., Chicago).

Table 1
Characteristics of partners (N=61) of high-risk women opting for prophylactic surgery[1].

		M (Sd)	*Range*
Age		46 (10)	28-68
Demographic variables of partners		*N*	*%*
Children[2]	*Yes*	47	77
	No	9	15
Education	*Low*	7	11,5
	Average	12	20
	High	27	44
Employment	*Yes*	47	77
	No	2	3
Medical variables of the spouses undergoing prophylactic surgery		*N*	*%*
Carrier status	*BRCA1/2 mutation carrier*	42	69
	50% risk carrier	19	31
History of breast cancer	*Yes*	21	34
	No	40	66
Type of surgery[3]	*PM/(I)BR*	22	36
	P(B)SO	15	24.5
	PM/(I)BR+P(B)SO	7	11.5
	PM/(I)BR before P(B)SO	6	10
	PM/(I)BR after P(B)SO	11	18

[1] Percentages in some categories do not add up to 100% because of missing values (not reported in table)
[2] 19% of all men did not fill out this question. We were able to retrieve 11% of these missing values by using the responses of their spouses.
[3] PM/(I)BR + P(B)SO, prophylactic mastectomy and salpingo-oophorectomy simultaneously performed; PM/(I)BR before/after P(B)SO, prophylactic mastectomy performed before/after oophorectomy (time elapsed undefined).

7.3 Results

7.3.1 Patient characteristics

Table 1 shows the characteristics of the 61 partners of high-risk women who were included in the present analyses.

Partners varied in age between 28 and 68 years, with an average age of 46. Over two-thirds (69%) of the partners had a wife being an identified mutation carrier, and 33% of the women opting for prophylactic surgery had a history of breast cancer. Most women (65%) underwent a PM/(I)BR during the course of the present study. Most couples (77%) had children. Nearly half of the men (44%) were highly educated, and most (77%) of them were employed.

7.3.2 Levels and courses of general and cancer-related distress

Table 2 shows general and cancer-related distress in the 33 partners who completed the questionnaires. Scores on intrusion gradually decreased (p=.002) over the one year period after prophylactic surgery. The courses of avoidance, anxiety and depression showed no changes between subsequent phases.

Table 2
Cancer-related and general distress in partners[1] prior to and after prophylactic surgery of the spouse

		N	*Mean*	*Median*	*Sd*	*Range*[2]	p_{course}[3]		*N*	*%*
Cancer-related distress							***L***	***Q***	***≥ cut-off***	
Intrusion (cut-off ≥13)	T0	50	5.7	4.0	6.5	0-25			7	14
	T1	55	3.4	1.0	5.2	0-22	.002	ns	4	7
	T2	50	1.9	0.0	3.2	0-16			1	2
Avoidance (cut-off ≥11)	T0	49	4.1	2.0	5.1	0-22			4	8
	T1	54	3.7	0.0	6.0	0-26	ns	ns	7	13
	T2	48	3.1	0.0	5.0	0-18			4	8
General distress										
Anxiety (cut-off ≥11)	T0	50	4.9	4.0	4.0	0-14			6	12
	T1	56	4.1	3.0	3.5	0-13	ns	ns	5	9
	T2	48	4.3	4.0	3.6	0-12			5	10
Depression (cut-off ≥11)	T0	51	4.7	4.0	3.8	0-14			5	10
	T1	53	3.9	3.0	3.7	0-16	ns	ns	5	9
	T2	48	3.7	2.5	4.0	0-17			4	8

[1] Means, medians, standard deviations and ranges are based on varied numbers of partners (range 48 – 56); significances of the courses of intrusion, avoidance, anxiety and depression, respectively, were based on 33 cases completely filling out the questionnaires.
[2] Observed range
[3] L = linear course; Q=quadratic course

At all assessments, a relatively small number of partners scored above the threshold value. At baseline, seven partners (14%) scored above cut-off on intrusion and four partners (8%) scored above cut-off on avoidance. A year after surgery, 2% and 8% of the men (n=1 and 4 resp.) still scored above cut-off on intrusion and avoidance respectively.

As for general distress, six men (12%) scored above cut-off on anxiety at T0. At T2, still five men (10%) scored above cut-off on anxiety. Depressive scores were present in 5 men (10%) at T0; while at T2, the scores of four men remained (8%) above cut-off.

7.3.3 Factors associated with increased distress

Table 3 and table 4 show the relationships between the distress measures and the biographical and medical variables. The age of the spouse at time of prophylactic surgery was positively related to increased anxiety in partners prior to prophylactic surgery (p=.04) and increased avoidant thoughts and behaviour in partners at 6 and 12 months post-

surgery (p =.03 and .01 resp.). Partners whose spouses had a history of breast cancer experienced more cancer-related distress, consisting of more intrusion at all assessments (p=.04, .03 and .04 resp.), and more avoidant thoughts and behaviour at both 6 months (p=.000) and 12 months after prophylactic surgery (p=.01). Having children appeared to be related to higher cancer-related distress scores as well. Higher scores on intrusion at T0 (.01) and on avoidance at T0 (p=.003) and T1 (p=.001) were related to fatherhood. Additionally, we found that partners with a higher level of education and partners whose wife was a mutation carrier tended to score higher on depression at T2 (p=.04).

Table 3
Factors associated with distress in partners (♂) of high-risk women (♀) opting for prophylactic surgery (PS): demographic variables

			Age ♂	**Children**	**Education ♂**	**Employment ♂**
Cancer-related distress	*Intrusion*	T0	*ns*	.01	*ns*	*ns*
		T1	*ns*	*ns*	*ns*	*ns*
		T2	*ns*	*ns*	*ns*	*ns*
	Avoidance	T0	*ns*	.003	*ns*	*ns*
		T1	*ns*	.001	*ns*	*ns*
		T2	*ns*	*ns*	*ns*	*ns*
General distress	*Anxiety*	T0	*ns*	*ns*	*ns*	*ns*
		T1	*ns*	*ns*	*ns*	*ns*
		T2	*ns*	*ns*	*ns*	*ns*
	Depression	T0	*ns*	*ns*	*ns*	*ns*
		T1	*ns*	*ns*	*ns*	*ns*
		T2	*ns*	*ns*	.04*	*ns*

Table 4
Factors associated with distress in partners (♂) of high-risk women (♀) opting for prophylactic surgery (PS): characteristics of the high-risk spouses

			Age ♀	**BRCA ♀**	**BC ♀**	**Type of PS ♀**
Cancer-related distress	*Intrusion*	T0	*ns*	*ns*	.04	*ns*
		T1	*ns*	*ns*	.03	*ns*
		T2	*ns*	*ns*	.04	*ns*
	Avoidance	T0	*ns*	*ns*	*ns*	*ns*
		T1	.03	*ns*	.000	*ns*
		T2	.01	*ns*	.01	*ns*
General distress	*Anxiety*	T0	.04	*ns*	*ns*	*ns*
		T1	*ns*	*ns*	*ns*	*ns*
		T2	*ns*	*ns*	*ns*	*ns*
	Depression	T0	*ns*	*ns*	*ns*	*ns*
		T1	*ns*	*ns*	*ns*	*ns*
		T2	*ns*	.04*	*ns*	*ns*

7.4 Discussion

The present study is the first to present data on the emotional wellbeing of partners of women at risk of hereditary breast and ovarian cancer who opt for either PM/(I)BR and/or P(B)SO, covering the time period from 2-4 weeks before until 1 year after prophylactic surgery. Most partners experienced normal levels of distress prior and after surgery of

their wife. Clinically relevant levels of distress were experienced by relatively few partners. Having a wife with a history of cancer and fatherhood were related to elevated levels of cancer-related distress in partners, while a high level of education and having a wife with a *BRCA1/2* mutation were associated with higher general distress at 1 year after the wife's prophylactic surgery.

Most of the partners had normal levels of distress prior to and after prophylactic surgery, although it is known that before the decision on prophylactic surgery is made, the couple has gone through a stressful period of recognition of the genetic nature of cancer in the family, the impact for the women and her family, decisions for genetic testing in view of the different risk management decisions, and the consequences of the test result [29,31] . We speculate that once the decision for prophylactic surgery was made, distress levels may have well regained normal levels. In other words, shortly before prophylactic surgery (at T0), most men appeared to have adjusted well to their spouse's increased risk of breast and ovarian cancer and the decision for prophylactic surgery. Clinically relevant levels of distress were experienced by relatively few partners, which is also observed after genetic testing for a *BRCA1/2* mutation[30,32].

The factors that contributed to elevated levels of distress in the partners were age at prophylactic surgery of the spouse when prophylactic surgery was performed, having a spouse with a *BRCA1/2* mutation or with a history of cancer, fatherhood, and education level.

Prior to prophylactic surgery, higher age of the spouse at time of prophylactic surgery was positively related to increased anxiety in partners. Apparently, these partners were well informed about the risks of developing breast and ovarian cancer that increases with age. The association between (higher) age of the spouse and increased avoidant thoughts and behaviour in partners up to a year post-surgery is more difficult to explain. This relationship might reflect the awareness about the vulnerability when developing breast or ovarian cancer at an increased age, combined with the knowledge that PM/(I)BR and P(B)SO do not protect 100% against the development of a primary cancer or recurrent disease[44-47]. Though anxiety related to increased age in wives disappears after prophylactic surgery, knowing that to date prophylactic surgery is the most effective risk-reducing strategy, avoiding confrontations with anything that had to do with the remaining risks of developing this threatening disease might have been the only way to cope for these partners. The knowledge that prophylactic surgery does not provide definite security might also explain the increased distress in partners whose wife had a *BRCA1/2* mutation or a history of breast cancer. Especially having a spouse who had been treated for breast cancer in the past was strongly distressing. Given the strong associations between cancer-related distress and having a spouse with a history of breast cancer at all assessments safe avoidance at baseline, we speculate that the absence of a relationship between these two variables is an artifact, possibly due to small sample size or other related factors that have yet to be investigated.

Fatherhood was an additional factor associated with increased cancer-related distress, which is in accordance with the findings in other studies on partners[30,31]. The genetic transmission of a *BRCA1/2* mutation, or other highly penetrant unidentified mutations is rather straightforward, and therefore worries about future development of cancer in

one's children are realistic and understandable. Moreover, this result may also have reflected the fear of losing the mother of one's children to breast or ovarian cancer.

Further, higher educational level in partners was associated with more depressive thoughts and feelings, but only at one year after prophylactic surgery. This seemingly contradicts the observation that a higher educational level enhances adjustment to the spouse's increased risk of developing cancer[31]. The full perception of the risks for the beloved wife and the family may lead to a realistic feeling of hopelessness in the partner. Though overall levels of distress were generally within normal values in the present cohort, a small group of well informed partners may benefit from additional support. Future research should shed light on this observation.

A major limitation of the present study concerns the sample size. The small number of partners who completed the periodic questionnaires may partly reflect problems in handling emotional distress. Three-quarters of the partners consented to participate in the present study, but only half of them completed the questionnaires at all assessments. Though we did not find differences at T1 and T2 between partners who did and did not fill out the questionnaires at T0, there might have been a selection bias. Emotional distress in the partners may have interfered with reflecting on emotions prior to the prophylactic surgery of their wife, and therefore they might have avoided filling out the questionnaires[43]. Unfortunately, we were unable to study the motivations of non-responders.

In conclusion, the contact between women at risk, their partners and health care professionals mainly focuses on the physical and psychosocial aspects of prophylactic surgery in the woman. The partner is usually pictured only as a source of social and practical support for the patient. The results of our study show that distress levels of partners of high-risk women were generally within normal limits. The modest proportion of about 10% of partners having clinically relevant distress levels one year after prophylactic surgery of their spouses might indicate that the provided general information, counselling and support is effective and sufficient. Still, the present findings suggest that some partners of high-risk women opting for prophylactic surgery are at risk for increased emotional distress and therefore might be in need of additional support themselves. Therefore, we underscore that the value of distress screening in both high-risk women and their partners is equally relevant for the patient's psychosocial guidance as well as for possible couple interventions[31,48]. Special attention might be warranted for higher educated partners of an identified mutation carriers; feelings of depression in these partners might surface in the longer run.

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8

Who is Prone to High Levels of Distress after Prophylactic Mastectomy and/or Salpingo-Ovariectomy?

Background *The present study aimed to assess predictors of distress after prophylactic mastectomy (PM) and salpingo-oophorectomy (PSO), in order to enable the early identification of patients who could benefit from psychological support.*

Methods *General distress and cancer related distress were assessed in 82 women at increased risk of hereditary breast and/or ovarian cancer undergoing PM and/or PSO, before and six and twelve months after prophylactic surgery. Neurotic lability and coping were assessed before surgery.*

Results *Cancer-related distress and general distress at both follow-up moments were best explained by the level of cancer-related and general distress at baseline. Being a mutation carrier was predictive of increased cancer-related distress at 6-months follow-up (but not anymore at 12 months), and of lower general distress at 12-months after prophylactic surgery. Also, coping by comforting thoughts was predictive of less cancer-related distress at 6-months follow-up.*

Conclusions *Genetically predisposed women who are at risk of post-surgical distress can be identified through any or more of the predictors that were found in this study. Exploration of and/or attention for cancer related distress and coping style before prophylactic surgery may help physicians and psychosocial workers to identify women who might benefit from additional post-surgical support.*

8.1 Introduction

Germline mutations in *BRCA1* and *BRCA2* account for approximately 3-5% of all breast and ovarian cancers. Women with a *BRCA1/2* mutation have a significantly increased cumulative lifetime risk for breast cancer of 39-85%, and for ovarian cancer of 10-63%[1-3].

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Furthermore, for mutation carriers with a history of breast cancer, the life-time risk of developing a contralateral breast cancer is 35-64%[4]. The majority of families with a significant aggregation of breast/ovarian cancer remain genetically unidentified. Women from these families remain at increased risk of developing breast and/or ovarian cancer. Their lifetime risk is less clear but lower than for mutation carriers. For both groups, management options are regular surveillance of the breasts and ovaries and (bilateral) prophylactic mastectomy ((B)PM) and/or prophylactic (bilateral) salpingo-oophorectomy (P(B)SO). Both prophylactic procedures result in a substantial risk reduction with respect to the occurrence of breast and ovarian cance[3,5-9]. Favourable effects of PM and/or P(B)SO on a woman's distress level in the year following these interventions have been reported[10-17]. In mostly all retrospective studies, post-surgical distress was related to surgical complications[18], psychiatric history, perceived risk of breast cancer[14], level of cancer-related distress at baseline, having children under the age of 15 years, less open communication of cancer issues within the family, having doubts about the genetic test outcome, and changes in relationships with relatives[19]. No data are available on factors that are possibly predisposing for persisting increased distress in this group of women. Previously, we published results of a prospective study comprising this sample of women on the levels and course of distress after prophylactic surgery[20]. We found that anxiety and cancer-related distress were clearly diminished up to one year after prophylactic surgery. However, a subgroup remained at clinically significant levels of anxiety and cancer-related distress. In the present analysis, we investigated factors that might be predictive for increased distress at 6 months and 12 months post prophylactic surgery.

8.2 Patients and Methods

8.2.1 Study population

At our Family Cancer Clinic, prophylactic surgery consisting of either PM, P(B)SO or both, is discussed with mutation carriers and sometimes with women from hereditary breast (and/or ovarian) cancer families (HB(O)C) without an identified mutation. Women opting for either PM and/or P(B)SO were invited to participate in a psychological follow-up study. Previously unaffected women with a clinical diagnosis or suspicion of cancer before prophylactic surgery were not eligible for participation. In women with a history of breast cancer, absence of recurrent disease before surgery was established by dissemination examination (chest X-ray, ultrasound liver, bone scan, liver functions and determination of Ca15.3/Ca125). The institutional review board approved of the study.

8.2.2 Procedure

After written consent, patients completed the first questionnaire a week before surgery. This questionnaire contained questions on demographic data, general and cancer related distress, coping, and neuroticism. The second and third questionnaire, containing the outcome measures, was completed six and twelve months after surgery.

8.2.3 Biographical and medical data

Data were obtained on age, marital status, offspring, educational level, profession, and carrier status, history of breast /ovarian cancer, and type of prophylactic surgery.

8.2.4 Neuroticism

The neuroticism (N-scale) of the Amsterdam Biographical Questionnaire ABQ[21] assessed the vulnerability to experience psychological distress[22]. The subscale contains 30 items. Reliability for the neuroticism subscale in men and women between the age of 20-59 has been proven good (respectively .95 and .84)[21].

8.2.5 Coping

Coping was assessed by the Utrecht Coping List (UCL)[23]. This instrument contains 47 items divided into seven scales: Active Dealing (i.e. taking action to solve a problem), Palliative Reaction (i.e. seeking distraction), Avoidance, Social Support Seeking, Passive Reaction (i.e. not taking or not feeling able to take action), Expression of Emotions, and reassuring oneself by having Comforting Thoughts. The scales are sufficiently consistent and independent, and cover most areas of coping. The validity and reliability have been found to be good[24].

8.2.6 Cancer-related distress

Cancer-related distress was assessed with the Impact of Event Scale (IES)[25,26]. The scale has been used extensively in studies on adjustment to genetic susceptibility testing and has satisfactory psychometric properties. The IES measures intrusive and avoidant thoughts, feelings, and behaviour, related to breast- and/or ovarian cancer. The score range for the total scale is 0-75.

8.2.7 General distress

General distress was measured with the Hospital Anxiety and Depression Scale (HADS)[27]. The HADS consists of two scales for anxiety and depression, respectively. The scores range from 0–21 for both scales. The total scale of the HADS has been widely used as a screening instrument in samples with minor psychiatric disorders. Validity and reliability have proven to be sufficient[28].

8.2.8 Statistical Analysis

The data were analysed using the SPSS 11.0 statistical package (SPSS Inc., Chicago). Missing values were estimated using the 'multiple imputation' method. Significant differences on biographical variables (i.e. age, level of education, marital status, employment, children and being religious) and medical variables (i.e. carrier status, type of surgery, history of breast cancer) between participants and drop-outs were determined through Pearson's χ^2 tests. Data were analysed through an elimination process when performing multiple linear regression in MPlus 3.1 program. All possible predictive variables (i.e. demographic variables, neuroticism, coping and mean baseline scores on general and cancer-related distress) were tested for their predictive quality per measure of distress and time of follow-up. The predictive variables 'carrier status' and 'history of breast cancer' were dichotomised (mutation carriers or women with a history of breast cancer were assigned a score of '1'; risk carriers or women without a history of breast cancer were assigned a score of '0'). The variables were categorized into candidate predictor variables on the four outcome variables (cancer-related and general distress at 6

and 12 months after prophylactic surgery). Candidate predictor variables were only eligible if the regression coefficient was significant at the 0.20 level of significance. The candidate predictor variables meeting the eligibility criteria were entered simultaneously into the regression model. Finally, the candidate predictor variables that were significant contributors (p=.05) in estimating the outcome were maintained in the final model. Variables were eliminated from the analysis if the relevant unstandardized regression coefficients were insignificant at the 0.05 level of significance. To gain insight into the robustness of the instrument, the quality of the prognostic instrument (i.e. the 'performance' of the instrument) was measured by tenfold cross-validation. Parameters for the individual variables were the unstandardized regression coefficient (B), the standardized regression coefficient (β), and the standard error of the unstandardized regression coefficient ($\frac{B}{Std.Error}$). As measures of overall performance, R^2 was used in case of continuous outcome variables. R^2-adjusted indicates the adjustment for shrinkage.

Table 1
Characteristics of the women opting for prophylactic surgery (study sample, and 16 'drop-outs')[1]

		Participants (n=82)		**Drop-outs** (n=16)				
		M	*Sd*	*M*	*Sd*	*df*	*F*	*p*
Age	*(in years)*	43	±8.6	43	±8.9	96	.22	ns
		n	%	n	%	df	χ^2	p
Marital state	*Married or co-habiting*	73	89	13	81	3	6.44	ns
	Single or divorced	9	11	3	19			
Children	*Yes*	68	83	11	73	1	.77	ns
	No	14	17	4	27			
Religious		33	40	-	-	-	-	-
Education	*Low/Average*	61	75	-	-	-	-	-
	High	20	25	-	-			
Current job	*Yes*	55	69	9	82	1	.79	ns
	No	25	31	2	18			
Carrier status	*BRCA1/2 mutation*	58	71	12	80	4	1.51	ns
	50% risk carrier	24	29	3	20			
Previous cancer	*No*	52	63	10	63	2	5.23	ns
	Breast cancer	30	37	5	31			
	Ovarian cancer	0	0	1	6			
Type of PS[2]	*PM*	34	42	4	27	4	1.64	ns
	P(B)SO	19	23	4	27			
	PM+P(B)SO	9	11	3	20			
	PM before P(B)SO	5	6	1	7			
	PM after P(B)SO	15	18	3	20			

[1] Numbers deviating from *n*=82 or *n*=16 resp. indicate missing data.
[2] PS: prophylactic surgery; PM: prophylactic mastectomy; P(B)SO: prophylactic (bilateral) salpingo-oophorectomy; PM+P(B)SO: prophylactic mastectomy and salpingo-oophorectomy simultaneously performed; PM before/after P(B)SO: prophylactic mastectomy performed before/after oophorectomy (time elapsed undefined)

8.3 Results

8.3.1 Sample characteristics

Between August 1999 and January 2003, 100 out of 129 eligible women enrolled in the study (78%). Two women were excluded because breast cancer was diagnosed between

enrolment and PM. Further, the data of sixteen women (drop-outs) filling out less than 75% of all items in the three questionnaires were excluded from the analysis. Accordingly, the final study group included 82 women. The study group and the drop-out group were not significantly different with respect to most biographical and medical data (Table 1). The mean age at the time of PM and/or P(B)SO was 43 years. Most women in our study had a partner-relationship (89%), and children (83%). The majority of both participants and drop-outs reported having a job (69% and 82%, respectively). A quarter of the participants in the final study sample finished higher education (vocational training or university) and 40% reported to have an active religious involvement. Most women were mutation carriers (71% and 80%, respectively), a history of breast cancer had occurred in 37% and 31%, respectively, and the majority (77% and 74% respectively) had opted for PM. Coping strategies and neuroticism scores at baseline (Table 2) were compared with those of control women from the same age group. Mean scores of the participants in our study were in the average range[21,24]. Table 3 shows the levels of general and cancer-related distress pre-surgery (T0), and at 6 months (T1) and 12 months (T2) post-surgery. The decrease in general and cancer-related distress after prophylactic surgery was quadratically significant (*p=.000* for both)[20].

Table 2
Means and standard deviations of coping strategies and neuroticism at baseline in the study sample (n=82)

Time	*Questionnaire*	*Mean*	*Sd*	*Range of the average scores for women (age 18-65)*
T0	*Active Coping (UCL)*	18.7	3.4	16-20
	Palliative Reaction (UCL)	18.7	3.7	14-19
	Avoidance (UCL)	15.2	3.0	12-16
	Social Support (UCL)	14.0	3.8	12-16
	Passive Reaction (UCL)	11.1	2.4	9-11
	Expression Emotions (UCL)	5.9	1.5	5-6
	Comforting Thoughts (UCL)	12.9	2.3	10-13
	Neuroticism (ABQ)	44.5	21.5	39-66

Table 3
Means and standard deviations of the outcome variables (general and cancer-related distress) at baseline, 6-months and 12-months follow-up

	General distress (HADS)			**Cancer-related distress (IES)**		
	Mean	*Sd*	*Sign. over time**	*Mean*	*Sd*	*Sign. over time**
T0	10.0	7.3	.000	20.3	15.2	.000
T1	7.7	6.1		13.9	13.2	
T2	7.8	5.4		13.1	11.8	

*Quadratic relation

8.3.2 Predictive model

Analysis of the data provided a final prognostic model for every separate outcome variable. Table 4 presents the factors that explained increased or decreased general and cancer-related distress at 6 and 12 months follow-up. General distress at baseline was

predictive of general distress at both follow-up assessment moments. Being a mutation carrier was predictive of decreased general distress at 12-months follow-up. Three factors were found predictive for cancer-related distress at 6-months follow-up: the level of cancer-related distress at baseline and being a mutation carrier were positively associated, while coping by use of comforting thoughts was negatively associated. Only cancer-related distress at baseline was predictive of cancer-related distress one year after prophylactic surgery. Though adopted in the predictive model, neuroticism and history of breast cancer did not predict for general or cancer-related distress at any measurement. General distress at baseline was predictive of general distress at both follow-up assessment moments (B=.25 and .43 respectively). Being a mutation carrier was predictive of less general distress (B=-3.53) at 12-months follow-up.

Table 4
Predictive factors of general distress and cancer-related distress at 6-months and 12-months follow-up

Predictors				
	General distress (6 months follow-up)			
	B	*β*	*B/std. error*	*Sig.*
General distress (T0)	.25	.30	1.98	.05
Cancer-related distress (T0)	-.09	.22	1.84	.07
Neuroticism	-.05	.18	1.47	.13
	General distress (12 months follow-up)			
General distress (T0)	.43	.58	6.78	.000
BRCA 1/2 carrier status*	-3.53	-.30	-3.51	.001
	Cancer-related distress (6 months follow-up)			
Cancer-related distress (T0)	.46	.54	5.87	.000
BRCA 1/2 carrier status*	5.89	.20	2.23	.03
History of breast cancer*	4.53	.17	1.72	.08
Coping by comforting thoughts	-1.16	-.20	-2.20	.03
	Cancer-related distress (12 months follow-up)			
Cancer-related distress (T0)	.41	.53	5.66	.000

*identified *BRCA1/2* mutation carrier *or* history of breast cancer: score=1; otherwise: score=0.

8.3.3 Performance of the prognostic instrument

The explained variances of the predictive models before and after cross-validation showed predictive qualities with R^2 ranging between .27 and .42. The corresponding values of R^2 after cross-validation are similar, indicating that the findings are robust. General distress at 12-months follow-up had the highest R^2 (.42).

8.4 Discussion

To our knowledge, this is the first study to prospectively investigate predictors of distress after PM and/or P(B)SO in women opting for this type of surgery because of an increased risk of hereditary breast and/or ovarian cancer. The follow-up period extended up to one year after prophylactic surgery. In general, cancer specific and general distress significantly decreased after prophylactic surgery[20]. However, increased levels of general and cancer-related distress at both 6- and 12-months after prophylactic surgery were found to be predicted by their respective baseline levels. Consistent with previous findings[17,20] we observed a decline of general and cancer related distress after surgery. However, it

appears that women who experienced high distress levels prior to prophylactic surgery tended to continue to experience high distress scores after prophylactic surgery. Possibly, their distress is not only related to the event of undergoing prophylactic surgery or the increased risk of developing cancer, but also to other factors, such as specific personality traits, coping strategies or life circumstances. Moreover, they need to learn to live with the possible (physical) consequences of surgery. Alleviation of distress could be related to post-operative counselling. However, we do not have any quantative data on additional counselling in other echelons of health care. Reassurance by having comforting thoughts proved in this study a favourable coping strategy at six months after prophylactic mastectomy/salpingo-oophorectomy, which was also observed in our study in women at increased risk for breast cancer adhering to surveillance[29]. No information is available on the contents of the comforting thoughts, and more research is needed before such coping strategy could be facilitated or offered to specific women in clinical practice. For example, clinical experience has shown that women with young children are highly motivated to opt for far-reaching strategies in order to see their children grow up, which motivation might serve as a comforting or reassuring thought. The role of mutation carrier status as predictive factor was more difficult to interpret. Mutation carriers seem to benefit more after 12 months with regard to lower general distress than risk carriers. However, at 6-months follow-up mutation carriers remained to experience more cancer related distress, which fortunately was not found anymore at 12 months. From previous studies it is known that mutation carriers opting for PM experience higher distress levels than those opting for surveillance, which is likely influenced by several factors (more/longer awareness of the genetic cancer susceptibility in the family, younger age, more often young children)[16,30]. It may be possible that our observation reflects the vulnerability of the group of mutation carriers opting for PM, possibly influenced by personality traits, which is not altered by surgery over a short follow-up period. Certainly, it remains warranted to further address and explore this issue in future studies.

This study underscores that a subgroup of women continues to show signs of mild psychological distress, even after prophylactic surgery. However, it also supports our clinical impression that women take their decision well-informed and not based on forms of maladaptive coping. Our results are relevant in helping to decide which patients might benefit from additional psychological counselling. Further research is warranted to elucidate the factors underlying continuous high levels of distress, and to evaluate possibilities for therapeutic intervention. While the uptake of prophylactic surgery in the Netherlands is quite high amongst at-risk women or mutation carriers, in other Western countries, it is not always a favorable option[8]. However, prophylactic surgery is becoming a relevant risk-reducing management option that can be performed in many different ways (e.g. skin-sparing mastectomy, TRAM flap procedure, DIEP flap procedure), depending on a woman's preference. Therefore, there is a strong need for further studies in this field.

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9

The Impact of Coping on Psychological Distress Before and One Year After Prophylactic Mastectomy and/or Salpingo-Oophorectomy

Background *The effect of coping on distress was studied in 82 women at increased risk of hereditary breast and/or ovarian cancer before and after prophylactic mastectomy (PM/(I)BR) and/or bilateral (salpingo) oophorectomy (PBSO).*
Methods *The Utrecht Coping List (UCL), the Hospital Anxiety and Depression Scale (HADS), and the Impact of Events Scale (IES) were completed 2-4 weeks before (baseline), and 6 and 12 months after prophylactic surgery.*
Results *Passive coping, palliative coping, and lack of seeking social support were associated with higher levels of distress before prophylactic surgery. Furthermore, passive coping was associated with less decrease of distress at one year after prophylactic surgery.*
Conclusions *Coping strategies should be assessed in the working-up before prophylactic surgery. Especially women who have adopted a passive coping strategy may benefit from additional psychosocial support.*

9.1 Introduction

In spite of ongoing research and development of better treatment methods, breast cancer and ovarian cancer are still life threatening diseases. The lifetime risk to develop breast cancer is 12-13% for the Dutch female population (www.cbo.nl). In 15%, these breast cancers are of hereditary origin, whereas in 5% of all cases, a *BRCA1/2* mutation will be found present.

Submitted

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Moreover, of 1500 ovarian cancers that are yearly discovered in the Netherlands, 10% are assumed to be of hereditary origin. Women identified with a *BRCA1/2* mutation have a cumulative lifetime risk (up to the age of 70 years) of invasive breast cancer of 39-85% and of ovarian cancer of 11-63%[1-4]. After a history of breast cancer, the life-time risk of contralateral breast cancer ranges between 35 and 64%[5,6].

Because of these risks, mutation carriers may consider prophylactic surgery. This may consist of either (bilateral or contralateral) prophylactic mastectomy with or without (immediate) breast reconstruction (PM/(I)BR) and/or prophylactic (bilateral) salpingo-oophorectomy (P(B)SO). Retrospective studies have shown a reduction of the risk of developing breast cancer of 95% . After P(B)SO, women have a residual risk up to 4% of developing peritoneal cancer[9,10].

The uptake of PM/(I)BR in our institution is 35% for previously affected mutation carriers[8] and 51% for unaffected mutation carriers[11]. The uptake of P(B)SO in our institution is 49% for previously affected mutation carriers[8] and 64% for unaffected mutation carriers[11]. Parenthood, age and development of breast cancer were related to the decision to undergo prophylactic surgery[8,11].

Since DNA research is evolving and the techniques of PM/(I)BR and P(B)SO are improving, we expect that the uptake of prophylactic surgery will be increasing in the coming years. Therefore, it is crucial to thoroughly investigate the psychosocial impact of these radical procedures. Until now, a limited amount of studies are conducted in this field.

High-risk women who face the decision to undergo prophylactic surgery experienced high levels of psychological distress related to the threat of developing cancer[12-16]. Studies have shown a favourable effect of prophylactic surgery on distress[13,17,18]. The elevated levels of distress prior to surgery decreased or disappeared in the year after prophylactic surgery[13,17,18]. However, a subgroup of women continued to experience increased distress after PS[18-20]. This distress was positively related to the occurrence of surgical complications and levels of distress prior to surgery[19,20]. Briefly stated, distress played an important role both before and after prophylactic surgery. Although coping and distress are different psychological constructs, they often occur simultaneously and are mutually dependent[21]. In order to understand the dynamics of coping and distress and to support our expectations regarding coping and distress in women who opted for prophylactic surgery, the Common Sense Model (CSM) of self-regulation[22] provided us with a conceptual framework. The CSM implies that coping responses, health behaviour and well-being are determined by their personally appraised health representations. The perceived health threat is cognitively coped with by using problem-focused coping strategies (i.e. acting out to alleviate, modify, avoid or minimise the threatening situation), whereas the emotions that accompany the health threat is coped with by using emotion-focused coping strategies (i.e. regulation of the emotions that accompany the threatening situation, by use of comforting thoughts, relaxation, denial or wishful thinking). Though both strategies are employed simultaneously by people, the predominance of one strategy over the other is individually and circumstantially determined[23].

To our knowledge, only two prospective studies have focused on coping strategies in relation to prophylactic surgery in high-risk women[13,20]. Bebbington Hatcher et al.[13] found

that women who opted for PM/(I)BR used more problem-focused coping prior to surgery than women who did not opt for PM/(I)BR. In our cohort of women who underwent prophylactic surgery, we previously found that emotion-focused coping (specifically: coping by comforting thoughts) was predictive of less cancer-related distress at 6-months after prophylactic surgery[20]. Though we found only use of comforting thoughts as being predictive of the decrease of distress in women who underwent prophylactic surgery, we assume that other coping strategies are related to the level of distress at baseline and follow-up.

High-risk women cannot cognitively control the threat of breast cancer and/or ovarian cancer. They can only act on the contemporary options of regular surveillance and/or prophylactic surgery. Being at increased risk while awaiting surgery, and facing a residual risk after surgery, women can try to moderate their emotions and subsequently manage the threat. Based on Leventhal's CSM we therefore hypothesized that emotion-focused coping strategies would predominate at both baseline and follow-up, in order to alleviate the general and cancer-related distress that accompanies the (residual) threat of developing breast cancer and ovarian cancer. In this study we aimed to get solid insight into the impact of different coping strategies on distress.

9.2 Patients and Methods

9.2.1 Study Population

At the Family Cancer Clinic of the Erasmus MC - Daniel den Hoed Cancer Centre (Rotterdam, the Netherlands), women at increased risk of hereditary breast and ovarian cancer are offered a surveillance program[24]. High-risk women are identified *BRCA1/2* mutation carriers and 50% risk carriers from familial/hereditary breast and ovarian cancer families (HBOC) in which a mutation is not found. Both PM/(I)BR and P(B)SO are discussed as an option with mutations carriers, while P(B)SO is discussed with 50% risk carriers from HBOC families. In earlier days, some 50% risk carriers from HBOC families also opted for PM/(I)BR without having received a conclusive DNA test result. Follow-up data are prospectively collected in a central database.

High-risk women who decided for PM/(I)BR and/or P(B)SO were invited to participate in an ongoing follow-up study on the psychosocial impact of prophylactic surgery. The purpose of the follow-up study was to explore the psychosocial effects of prophylactic surgery, being either PM/(I)BR, P(B)SO or both. Prophylactic surgery had to be performed at the Erasmus University MC - Daniel den Hoed Cancer Centre. Clinical and laboratory evaluation established absence of recurrent disease after a history of breast cancer by (chest X-ray, ultrasound liver, bone scan, liver functions and determination of Ca15.3/Ca125). Previously unaffected women with a clinical diagnosis or suspicion of cancer before prophylactic surgery were not eligible for participation in this psychological study. The study was supported by the Netherlands' Organization for Health Research and Development (ZonMw, grant no. 210-00-013) and the institutional review board of the Erasmus MC gave approval of the study (protocol no. DDHK 98-15).

9.2.2 Procedure

Physicians provided eligible patients with both verbal and written information on the purposes of the study. All participants who consented were each given a unique identification code that could only be encrypted by the main researcher of the project.

Participants received questionnaires by mail on the following moments: 2-4 weeks before prophylactic surgery (T0), and 6 and 12 months after prophylactic surgery (T1 and T2 respectively). The questionnaire consisted of questions on demographic data, the Utrecht Coping Scale[25], the Impact of Event Scale[26] and the Hospital Anxiety and Depression Scale[27]. All questionnaires, except the questionnaire assessing demographic data, were administered at every measurement moment. Consistent with prior results[29], the scores on the Utrecht Coping List were constant over time. Therefore, we used only the scores of the baseline measurement for analysis.

9.2.3 Biographical and medical data

Age, marital status, offspring, educational level, profession, carrier status, history of breast cancer and type of prophylactic surgery were recorded during the first assessment moment (T0).

9.2.4 Coping

The Utrecht Coping List (UCL)[25] was used to assess coping strategies. It is a general coping questionnaire that addresses 7 coping strategies: Active Coping (i.e. taking action to solve a problem; 7 items); Palliative Reaction Pattern (i.e. seeking distraction; 8 items); Avoidance and Awaiting (8 items); Seeking Social Support (6 items); Passive Reaction Pattern (i.e. not taking or not feeling able to take action; 7 items); Expressing Emotions (3 items); and reassuring oneself by having Comforting Thoughts (5 items). Participants were presented with the following answer possibilities: 1 (seldom or never); 2 (sometimes); 3 (often); and 4 (very often). The UCL has a number of sufficiently consistent and independent scales covering most areas of coping[28]. The validity and reliability of the UCL have been found to be good[29].

9.2.5 Cancer-related distress

The revised Impact of Events Scale (IES) is a well-recognised measure[26,30-32] for intrusive and avoidant thoughts, feelings, and behaviour about breast- and/or ovarian cancer. The score range for the scale 'Intrusion' (7 items) is 0 to 35 and for the scale 'Avoidance' (8 items) 0 to 40. All items are scored as follows: 0 (not at all); 1 (seldom); 3 (sometimes); and 5 (often).

9.2.6 General distress

General distress was measured with the Hospital Anxiety and Depression Scale (HADS)[27]. The HADS consists of a scale that assesses anxiety (7 items) and a scale that assesses depression (7 items), respectively. Every item has four item-specific answer possibilities, specifically formulated to relate to the item. The scores range from 0 to 21, for both scales. Validities and reliabilities have proven to be sufficient[33,34].

9.2.7 Statistical analyses

Significant differences on biographical variables (i.e. age, level of education, marital status, employment, children and being religious) and medical variables (i.e. carrier status, type of surgery, history of breast cancer) between participants and dropouts were determined through Pearson's χ^2 tests. Missing values were estimated using the 'maximum likelihood' method. The basic data were analysed using the SPSS 11.0 statistical package (SPSS Inc., Chicago).

To simultaneously determine the effect of the seven coping strategies on distress, the conventional MANOVA- and regression approaches are insufficient. Hence, the data were analysed using the method of Structural Equation Modelling (SEM), i.c. growth modelling approach. This approach enables estimating the level and trend of distress, as well as to estimate the impact of the coping strategies on distress. An underlying principle of SEM concerning assessments across time is that individuals may differ not only on level but also on trend of distress. We used the M-Plus 3.1 program[35]. This programme enables to simultaneously analyse several outcome variables assessed across time.

The course of distress was specified in terms of intrusion and avoidance (i.e. breast cancer specific distress; IES), and anxiety and depression (i.e. general distress; HADS). These four specifications of distress resulted in four different courses to be analysed. Baseline measurement (T0) was used as the reference moment. The analyses were executed in two steps.

First we fixed the correlation between the intercept and the trend at 0.00 for the four different courses, meaning that the intercept was independent of the corresponding trend. Additionally, we restricted the autocorrelations between the observed outcome variables to be of first order, which implied that for all four observed outcomes variables the autocorrelation of the T0 with T1 was fixed to be equal to the autocorrelation between T1 and T2. Second, based on the model identified in the first step, the predictive potentialities of the seven UCL-scales was estimated for the four outcome variables, to be distinguished in baseline and trend for all of them. As measures of model performance, χ^2 test was used for determining the adequacy of the model-fit. A non-significant *p*-value ($p>0.05$) and the ratio of $\frac{\chi^2}{df}<1.5$ would represent an adequate model fit. To provide for reliable evaluations of the model, we used the Comparative Fit Index (CFI>0.95), the Tucker-Lewis Index (TLI>0.95), the Root Mean Square Error of Approximation (RMSEA ≈ 0.05) and the Standardised Root Mean Square Residual (SRMR < 0.05).

A t-value equal or greater than +/-2 was considered significant. The related standardised regression coefficients (γ) represent the significant relationships in the most plausible model.

9.3 Results

9.3.1 Study population

Between August 1999 and January 2003, 100 out of 147 eligible women enrolled in the study (68%). After inclusion, two women appeared to have a clinical diagnosis of cancer before prophylactic surgery, and their data were not included in the analysis. Furthermore, only data from women who filled out at least 75% of all items in each

questionnaire were used in this analysis, resulting in the final study group of 82 women. Characteristics of the study group are shown in Table 1. For comparison, the characteristics of the dropout women (n=16) have been included into Table 1. There were no differences between the dropout group and the study group with respect to age, marital status, having children, employment, mutation carrier status, a history of cancer, and type of prophylactic surgery.

Table 1
Characteristics of the study group (n=82) and the dropout group (n=16)

		Participants (n=82)		**Dropouts** (n=16)				
		M	*Sd*	*M*	*Sd*	*df*	*F*	*p*
Age	*(in years)*	43	±8.6	43	±8.9	96	.22	ns
		n	*%*	*n*	*%*	*df*	χ^2	*p*
Marital state	*Married or co-habiting*	73	89	13	81	3	6.44	ns
	Single or divorced	9	11	3	19			
Children	*Yes*	68	83	11	73	1	.77	ns
	No	14	17	4	27			
Religious		33	40	-	-	-	-	-
Education	*Low/Average*	61	75	-	-	-	-	-
	High	20	25					
Current job	*Yes*	55	69	9	82	1	.79	ns
	No	25	31	2	18			
Carrier status	*BRCA1/2 mutation*	58	71	12	80	4	1.51	ns
	50% risk carrier	24	29	3	20			
History of cancer	*No*	52	63	10	63	2	5.23	ns
	Breast cancer	30	37	5	31			
	Ovarian cancer	0	0	1	6			
Type of PS[1]	*PM/(I)BR*	34	42	4	27	4	1.64	ns
	P(B)SO	19	23	4	27			
	PM/(I)BR+P(B)SO	9	11	3	20			
	PM/(I)BR before P(B)SO	5	6	1	7			
	PM/(I)BR after P(B)SO	15	18	3	20			

[1] PS: prophylactic surgery; PM/(I)BR: prophylactic mastectomy; P(B)SO: prophylactic (bilateral) salpingo-oophorectomy; PM/(I)BR+P(B)SO: prophylactic mastectomy and salpingo-oophorectomy simultaneously performed; PM/(I)BR before/after P(B)SO: prophylactic mastectomy performed before/after oophorectomy (time elapsed undefined)

The mean age at the time of prophylactic surgery was 43 years for both participants and dropouts. The majority of all women were married or living together with a partner (89%/81%) and had children (83%/73%). The latter figures are high, compared to the Dutch population (resp. 62% and 36%). Having a job was reported by participants/dropouts in 67%/82% respectively, while vocational training or university education was reported in 25% and active religious involvement in 40% of the women.
Most of the women were identified BRCA1/2 mutation carriers (71%/80%), and the majority had opted for PM/(I)BR, with or without P(B)SO.

Because the dropout women answered several questionnaires incompletely, possible significant differences between both groups regarding education, religion, the UCL, the IES and the HADS were not analysable.

Table 2
Correlation matrix of determinant and outcome variables (2-4 weeks before prophylactic surgery (T0), 6 months after (T1) and 12 months after prophylactic surgery (T2))

	Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	*Active Coping*																			
2	*Palliative Reaction*	.27																		
3	*Avoidance*	-.22	***.37***																	
4	*Social Support*	.21	.17	-.15																
5	*Passive Reaction*	-.19	.23	***.31***	.07															
6	*Expression Emotions*	.18	.07	-.09	***.35***	.08														
7	*Comforting Thoughts*	***.31***	***.54***	.25	-.08	-.13	-.05													
8	*Intrusion (T0)*	.05	***.39***	.13	.15	***.49***	-.03	.07												
9	*Intrusion (T1)*	-.08	09	-.02	.18	25	-.14	-.23	***.48***											
10	*Intrusion (T1)*	-.07	.10	.19	.05	.19	-.08	-.00	***.43***	***.61***										
11	*Avoidance (T0)*	.06	.40	***.34***	-.21	***.43***	-.10	.15	***.57***	***.33***	***.34***									
12	*Avoidance (T1)*	-.10	.14	.16	-.28	***.36***	-.28	-.03	.27	***.51***	***.36***	***.56***								
13	*Avoidance (T2)*	-.04	.25	.21	***-.37***	***.29***	***-.31***	.18	.24	***.37***	***.43***	***.60***	.72							
14	*Anxiety (T0)*	-.04	.19	.16	-.09	***.64***	-.06	-.02	***.62***	***.29***	.16	***.55***	***.36***	***.31***						
15	*Anxiety (T1)*	-.10	.19	.15	-.08	***.51***	-.14	-.04	***.42***	***.51***	***.30***	***.40***	***.52***	***.39***	***.52***					
16	*Anxiety (T2)*	-.02	.06	.09	-.17	***.40***	.03	.11	***.42***	***.31***	***.45***	***.37***	***.30***	***.41***	***.55***	***.63***				
17	*Depression (T0)*	-.12	.20	.26	-.10	***.70***	.02	-.03	***.55***	.18	.19	***.50***	***.36***	***.35***	***.82***	***.53***	***.51***			
18	*Depression (T1)*	.02	.04	.17	-.15	***.48***	-.17	-.17	***.35***	***.45***	***.41***	***.42***	***.54***	***.46***	***.42***	***.74***	***.54***	***.54***		
19	*Depression (T2)*	-.05	.13	.22	-.19	***.43***	-.02	.15	***.35***	.19	***.35***	***.36***	***.31***	***.38***	***.45***	***.55***	***.70***	***.56***	***.65***	
	Mean	19	19	15	14	11	6	13	11	7	7	9	7	6	6	5	5	4	3	3
	Sd	3	4	3	4	2	1	2	9	7	7	8	8	7	4	4	3	3	3	3

9.3.2 Modelling

The mean scores, the standard variations and the estimated intercorrelations of both the outcome and predictor variables are presented in Table 2. The intercorrelations were significant at the 0.01 significance level (two-tailed). The performance of the model, in which the prognostic potentialities of the UCL-scales were explored, was satisfying (χ^2=80.05, df=55, P=0.02; $\frac{\chi^2}{df}$=1.46; CFI=0.97; TLI=0.91;RMSEA=0.08; and SRMR=0.05).

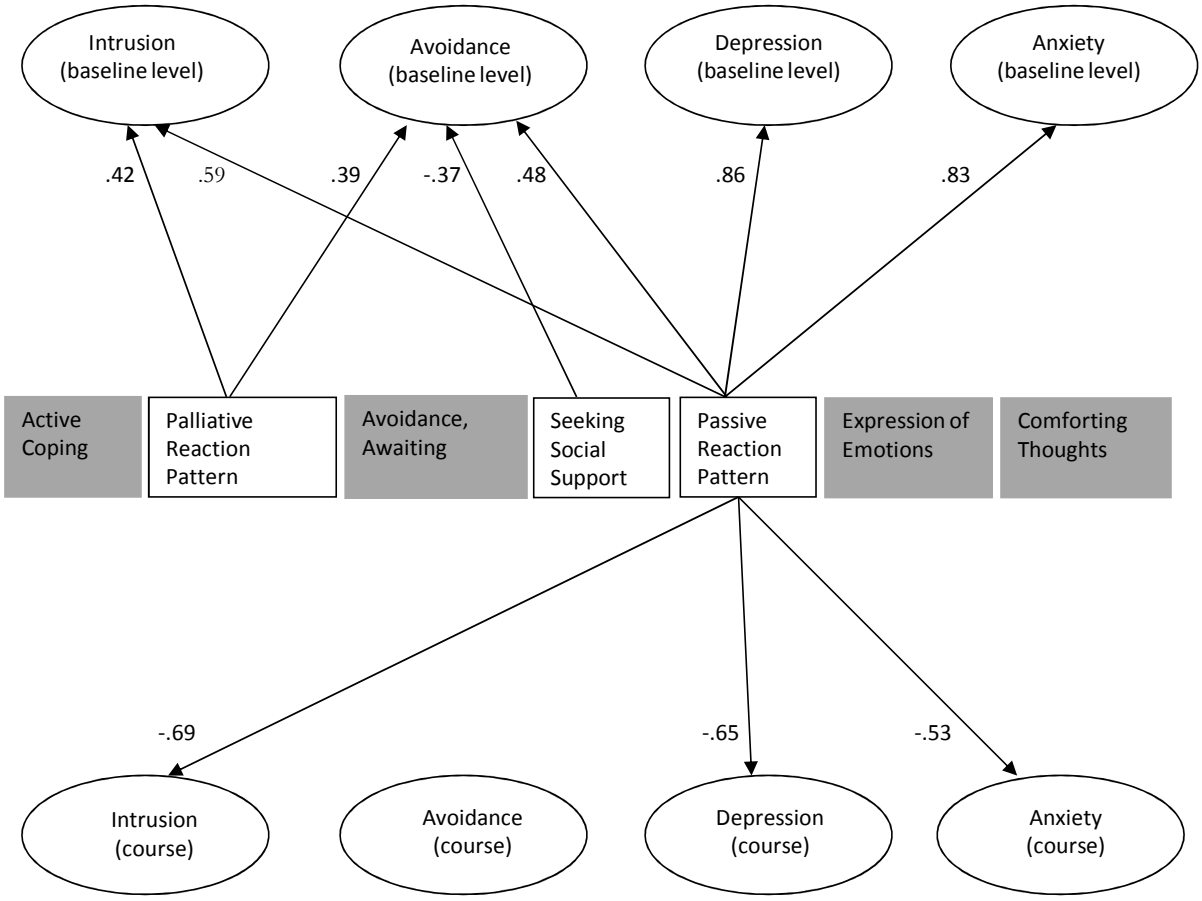
Figure 1 shows the impact of coping strategies on the levels and the trends of distress. The values that are shown are the standardised regression coefficients (γ) . With respect to the *level* of psychological distress, a positive and substantial relationship between the UCL-subscale 'Passive reaction pattern' (not taking action) and all distress measures was found at baseline. Thus, women utilising a passive coping strategy reported more intrusive thoughts (γ=0.59) and avoidant behaviour (γ=0.48), and felt more depressed (γ=0.86) and fearful (γ=0.83) before prophylactic surgery.

To a lesser degree, a palliative reaction pattern and seeking social support were related to psychological distress at the baseline measurement moment. This means that women who had high scores on the UCL subscale 'palliative reaction pattern' (seeking distraction) reported more intrusion (γ=0.42) and avoidance (γ=0.39) before prophylactic surgery. In addition, women who had high scores on the subscale 'seeking social support' reported less avoidant behaviour at baseline (γ=-0.37).

A 'passive reaction pattern' was associated with persistent high levels of psychological distress after prophylactic surgery. We observed that passive coping was inversely related with intrusion (γ=-0.69), depression (γ=-0.65), and anxiety (γ=-0.53). This indicates that passive coping was associated with less decrease of the level of distress over time.

Figure 1

Coping model – the impact of coping (UCL) on baseline levels and course of 'Intrusion' and 'Avoidance' (IES) and 'Depression' and 'Anxiety' (HADS) in genetically predisposed women (n=82)



9.4 Discussion

In this paper, we present a model of coping and distress of women who opt for PM/(I)BR and/or P(B)SO. We hypothesized that emotion-focused coping strategies would predominate both at baseline and at follow-up in order to regulate the general and cancer-related distress that accompanies the (residual) threat of developing breast cancer or ovarian cancer. In line with our expectations, we found strong relationships with emotion-focused coping (passive coping and seeking social support) at baseline. However, also a strong relationship with problem-focused coping (palliative coping) was found.

First, the strong, positive relationship between passive coping and distress at baseline contradicted our hypothesis. Clearly, this emotion-focused coping strategy was not alleviating distress prior to surgery. The distinct presence of passive coping strategies in this cohort might imply that the women in our cohort needed emotion-focused coping in order to regulate the distress accompanying this threatening situation. This is concordant with Pieterse et al.[36], who elaborated on the correspondence of 'learned helplessness' (i.e. responding passively to an uncontrollable stressor) with passive coping. However, since passive coping led to more distress at baseline, tailor-fit psychological support should be offered, that focuses on adapting other, active-oriented coping strategies prior to surgery.

Second, the positive relationships between palliative coping and intrusion and avoidance at baseline indicated that women adapting this coping strategy experienced more cancer-related intrusive thoughts and were more inclined to engage in a pattern of avoidant behaviour regarding breast cancer or ovarian cancer at the baseline assessment than women using other coping strategies. Obviously, this problem-focused coping strategy was by no means effective in adequately reducing cancer-related distress. Pieterse et al.[36] also reported a connection between palliative coping and intrusion and avoidance in their cohort of women who are at increased risk of developing breast cancer and/or ovarian cancer. Their cohort opted for regular breast surveillance, and therefore faced other issues surrounding the threat of cancer in the long run. At our baseline assessment however, (i.e. before prophylactic surgery), both cohorts are similar in the overwhelming threat of developing cancer. We agree with their explanation that by continuously trying to divert oneself from one's problem at hand, the problem remains constantly present, thereby enlarging distress.

Third, the model established a negative relationship between seeking social support and avoidance at baseline. Clearly, the more an emotion-focused way of coping like seeking social support was employed, the less confrontations with breast cancer and ovarian cancer were avoided. In this respect, seeking social support was successful in alleviating distress, thereby confirming our hypothesis.

Finally, only passive coping was discernibly and negatively related to distress after surgery, indicating that this way of coping was associated with less decrease of the level of distress over time. Apparently, this type of emotion-focussed coping strategy was ineffective in reducing both cancer-related and general distress.

Though the CSM proved right in its theory that emotions that accompany the health threat are dealt with by using emotion-focused coping strategies, these results underline that not all emotion-focused coping strategies were adequate in itself. Clearly, passive coping was not alleviating distress, though it seemed to be the most distinguishable coping strategy amongst other emotion-focused coping strategies. Since generally few experiences in life are equally life-threatening, we hypothesize that these results indicate that most women had no experience in coping with the overwhelming emotions that came with the threat of developing breast cancer and/or ovarian cancer. The women who let themselves (passively) overwhelm, experienced more distress while awaiting surgery, and achieved less decrease in distress over time. Would these women have been coached in bending their passive reaction pattern into more active-oriented emotion-focused coping strategies, these relationships would probably not have been standing out so clearly. The absence of relationships between distress and most other emotion-focused strategies does not per se prove them inadequate. It might indicate that women who did not strongly employ passive coping might have used multiple emotion-focused coping strategies simultaneously, thereby not having one of them standing out so strongly as passive coping did. Future research in larger cohorts should corroborate this.

A limitation of this study is that the sample is too small to account for the possible role of demographic variables in the analysis. Other than age and education[37-39], other biographical variables such as marital status, children, religion, and profession, as well as medical variables such as *BRCA1/2* mutation carrier status, history of cancer, type of

prophylactic surgery, hormone replacement therapy, and menopausal status might play a role in coping with distress. In light of these previous findings, women who are dealing with the complex situation of being at increased risk of breast and/or ovarian cancer due to a genetic susceptibility might benefit from good education about the subject of being at risk, the process of prophylactic surgery and the possible consequences of that option. Being aware of this, we hold it in our opinion that further investigation is warranted to examine whether one of these variables is of discriminating value.

In conclusion, both palliative and passive coping strategies can be considered as less favourable ways of stress management in high-risk women who have opted for PM/(I)BR and/or P(B)SO. Furthermore, seeking social support alleviates the level of psychological distress in this group of women. In our opinion, these findings are important for clinical practice, and need to be addressed in the pre-operative counselling of every woman considering prophylactic surgery because of an increased risk of breast and ovarian cancer. We would like to propose that for the purpose of assessment of these and other items, an appointment with a psychologist or social worker should be incorporated in the working-up process towards prophylactic surgery. In case vulnerability is identified, it is worthwhile to offer and incorporate extra counselling sessions in order to try to mirror the negative attitudes for specific women and to focus on more positive, active-orientated habits and coping strategies.

While we emphasize that determination of the way of coping is important to incorporate as part of the working up process before prophylactic surgery in this women, it certainly must be further debated who should identify passive coping styles and subsequent distress. Is it the physician's task or should preference be given to a psychosocial worker? The outcome of the debate may depend on time (is it realistic to expect that the physician comprehensively explores the coping styles?), tools (does the physician have the adequate tools to efficiently identify coping strategies?), and the capacity (are there enough physicians or psychosocial workers available?).

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10

Discussion

Before the mid-nineties, prophylactic surgery, consisting of PM/(I)BR and/or P(B)SO, was only occasionally done in women belonging to families with a strong history of breast and ovarian cancer, also because many clinicians doubted that genes were important in the breast and ovarian cancer risks of the respective women. The identification of the breast cancer susceptibility genes *BRCA1* and *BRCA2* as the explanation for an autosomal dominant inheritance of breast and ovarian cancer and an increased risk of breast and ovarian cancer already occurring at a young age for women from respective families transformed prophylactic surgery into an important and recognized option for high-risk women. Consequently, from 1995 onwards an increasing number of, mainly retrospective, studies investigated factors related to satisfaction with prophylactic surgery and the effects of prophylactic surgery on psychological well-being, body image and sexual functioning. The conducted studies very soon showed a fast decision for and a high uptake of PM/(I)BR and P(B)SO by both mutation carriers and 50% risk carriers. Patients asked for concrete information about the procedures and its possible consequences in order to make an informed choice about whether or not undergoing prophylactic surgery. Also physicians needed information on the psychosocial aspects of PM/(I)BR and P(B)SO in order to be able to provide adequate care and identify those women who might benefit from additional psychological support before and after prophylactic surgery.

The current study on the psychosocial impact of prophylactic surgery in high-risk women is the first prospective study that addressed the aspects of both PM/(I)BR and P(B)SO. This is important because many high-risk women utilize one or both options, with on the one hand different and on the other hand overlapping issues and consequences. Until now, only few other studies have been prospectively conducted, and concentrated

either on PM/(I)BR[1] or on P(B)SO[2,3]. Moreover, the partners of the women opting for and undergoing prophylactic surgery were also included in our study. Data on this group regarding PM/(I)BR and P(B)SO provides unique information enabling health-care professionals to better understand the impact of the decision for and the sequelae of prophylactic surgery also on the spouse, thereby facilitating adequate and appropriate counselling for both partners.

Motivations leading to the decision to undergo prophylactic surgery, distress in high-risk women who have undergone prophylactic surgery and satisfaction with the procedure and its impact on life have been previously investigated in various patient groups and with various study designs. Our study corroborates earlier findings and adds new insights into the psychosocial processes in women being at increased risk for breast and ovarian cancer in the period before and after PM/(I)BR and P(B)SO.

10.1 New insights

10.1.1 Satisfaction with PM/(I)BR

From previous retrospective studies, satisfaction rates with PM/(I)BR varied between 70% and 100%[4-12], although the exact percentages and the types of breast reconstruction in the different studies was mostly not specified. In our retrospective study on 114 high-risk women of whom all underwent PM/(I)BR at our institute between 1994 and 2002, only very few women expressed regrets about PM/(I)BR (5%), whereas the satisfaction rate with the final cosmetic result was only 60%. Despite the latter observation, most women indicated that they still would decide for PM and (I)BR if they had to face the same choice again. Apparently, other factors like the risk-reduction obtained by the removal of all breast tissue and relief of fear for the development of cancer prevailed above the sometimes disappointing cosmetic and physical outcomes of the surgical procedure.

Another major finding of our study was that nearly half of all women experienced adverse effects regarding the sexual relationship, which was unrelated to satisfaction with the procedure. This finding was significantly associated with perceived lack of information, expectations that were not met, ongoing physical complaints and limitations in daily life, altered feelings of femininity and body image, and perception of the partner's negative view of the sexual attractiveness of his wife. Effects of PM/(I)BR on the sexual relationship were only incidentally addressed before[6,14,16], but did not focus on PM with (I)BR specifically. Our data clearly show that after PM/(I)BR women may experience (lasting) pain or discomfort due to the procedure or its complications, or may feel less feminine and suffer from an altered body image. How all this might interfere with the (different aspects of the) sexual relationship deserves further study. Our findings underscore that potential alteration of the sexual relationship is worthwhile to address as part of the information given during the decision-making period and pre-surgical counselling. With respect to the findings of our study, it has to be said that P(B)SO was sometimes done in the same procedure or often in the same time period, making it difficult to distinguish between the effects of major and acute hormonal changes and the surgical effects on body shape, complaints, and perceptions.

Also, the data of our study indicate that proper and sufficient information about the procedure and its possible aftermaths is one of the common and important factors related

to satisfaction with the (cosmetic) outcome as well as the alterations on the sexual relationship. This also has been reported by Frost[6]. Further, clear information also helped to obtain a more accurate view of the different outcomes, as shown in a retrospective study done on effects of P(B)SO[17]. In our opinion and in view of our data, appropriate information about the potential problems of and after PM/(I)BR and/or P(B)SO will lead to enhanced acceptation and hence higher satisfaction with the actual outcomes. This requires the collective and unanimous efforts of the different specialists and healthcare workers at the multidisciplinary family cancer clinic, involved in the care of high-risk women. This might include an appointment with the psychologist aiming at further exploration of the way all information is processed and assimilated. Hereto, an institutional protocol should be elaborated.

10.1.2 Motivations for prophylactic surgery

In Chapter 5, we described the results of the first prospective analysis of the motivations for prophylactic surgery in relation to emotional distress before and after the surgical interventions. We hypothesized that women with combined cognitive and emotional motivations would have less emotional distress than women with purely cognitive motivations. However, both groups had similar levels and courses of emotional distress during the phase of prophylactic surgery until six months after surgery, with the exception of the course of avoidant behaviour. Women expressing fear for cancer as a motivation for prophylactic surgery experienced more depressive thoughts and feelings prior to surgery than women who did not express fear for cancer. Moreover, women expressing fear experienced a greater decline in avoidant behavior in the first six months after surgery whereas the non-fear group showed a decline between six and twelve months after surgery. Although fear is a strong predictor for opting for prophylactic surgery, we speculate that the group of women who did not express fear as motivation may have been already adjusted to the prospect of the risk-reducing effect of prophylactic surgery, or they may have suppressed their emotions regarding breast cancer and ovarian cancer. Clearly, this speculation needs to be further studied.

10.1.3 Emotional distress before and after prophylactic surgery

Our results described in Chapter 6 corroborate previous results[1,6] that women opting for prophylactic surgery have higher levels of anxiety and cancer-related distress before prophylactic surgery than women opting for regular surveillance. After PM/(I)BR, anxiety and cancer-related distress were significantly reduced, mainly within the first six months after prophylactic surgery, which is also in line with previous observations[1,2,6,9,14,18-20]. No significant changes in distress scores were observed before and after P(B)SO. The latter has not previously been reported, and suggests that the impact of PM/(I)BR is greater than the impact of P(B)SO. Therefore, at our institution it has been agreed on that women opting for PM/(I)BR are seen by the psychologist before surgery, which is not the case anymore for women opting for P(B)SO.

As we found that a minority of women after prophylactic surgery is experiencing continuing elevated distress at a clinically significant level, we looked in Chapter 8 for predictors of ongoing distress after prophylactic surgery. As others observed[16], cancer-

related distress prior to surgery was predictive for post-surgical distress both at 6 and at 12 months. Moreover, being a mutation carrier or having a personal history of breast cancer was predictive of high cancer-related distress, six months after surgery. The distress in these women might be explained by other factors such as personality, coping, life circumstances, or a lack of trust that prophylactic surgery has reduced the risk of developing (recurrent) cancer. Future research is needed regarding other risk factors impeding the devolution of general and cancer-related distress after prophylactic surgery.

Finally, coping strategies were shown to be related to emotional distress both before and after surgery. First, having comforting thoughts was predictive of less cancer-related distress at six months following prophylactic surgery (Chapter 8). Second, when studying the role of coping strategies in relation to distress, we found a strong association between passive coping and both cancer-related and general distress (Chapter 9). Passive coping strategies did neither reduce distress prior to surgery, and led to less decrease of distress after surgery. Strikingly, no other association was found between post-surgical distress and any other coping strategies. This might indicate that women not strongly using passive coping applied multiple other coping strategies, resulting in none of them standing out as strongly as passive coping did.

10.1.4 Distress in partners of high-risk women who opt for prophylactic surgery

To our knowledge, distress in partners of high-risk women in relation to the period before and after prophylactic surgery of their wife (Chapter 7) has not been previously studied. Scores on intrusion gradually decreased over the one year period after prophylactic surgery, while the courses of avoidance, anxiety and depression showed no changes between subsequent assessments. Reassuringly, most partners showed overall normal levels of distress both prior to and after prophylactic surgery of their wives. The latter observation is interesting, because earlier studies showed that these couples go through a stressful period once the health threat for the wife becomes clear[14,21]. Apparently, most men were able to adjust rapidly to the knowledge of their spouses' increased cancer risk. Still, 10% of the partners have clinically relevant levels of emotional distress up to one year after prophylactic surgery, and may be candidates for extra support.

Factors associated with increased emotional distress in partners were fatherhood, high educational level and having a spouse with a *BRCA1/2* mutation or a history of breast cancer. Also, the distress level of the spouse proved to be predictive of the distress level of the partner (unpublished results). These findings stress the importance of assessing the distress level of partners of women opting for prophylactic surgery in order to identify those partners who may benefit from psychosocial support.

10.2 Limitations of the current study and suggestions for further research

Partly as a consequence of clinical reality, both the retrospective and the prospective study had a number of limitations. First, both study cohorts were heterogeneous with respect to medical history and treatment. Second, the questions in the retrospective questionnaire did not differentiate between immediate and delayed breast reconstruction. Third, the women in our studies underwent breast reconstruction by means of implants performed in one institution, making any comparisons with

(immediate) breast reconstruction using autologous tissue, and comparisons with other institutions impossible. Currently, a collaborative, multicenter prospective study is performed to study breast reconstruction using either implants or autologous tissue by means of DIEP flap. The prospective study covered a follow-up period after surgery of twelve months which is too short to draw definite conclusions. A study on the long term aspects of PM/(I)BR in the same study cohort is now ongoing at our institute.

10.3 Clinical relevance

The most important conclusion from our study is that the majority of high-risk women go through prophylactic surgery without major adverse physical or psychological consequences. In this respect, PM/(I)BR has a greater impact than P(B)SO. Though increased prior to prophylactic surgery, emotional distress regained normal levels in most women. Also, most women did not regret their decision, even when they were not satisfied with the cosmetic result of breast reconstruction. Finally, partners of high-risk women were well able to keep emotional distress within normal limits regarding their wife's risk and her decision to undergo prophylactic surgery.

Still, special attention is justified to the subgroups of high-risk women and their partners who are vulnerable to increased distress, both before and after surgery. Counselling should preferably be done with both partners present, and the high-risk woman and her partner should be offered psychosocial support separate or together, especially when one or both are displaying increased levels of emotional distress prior to surgery or when the wife has adapted a passive coping strategy. Special attention might also be given to couples of whom the high-risk female partner is an identified mutation carrier, mainly in the follow-up period shortly after prophylactic surgery. Also, couples with children might be offered additional counselling. Finally, issues such as body image and the sexual relationship should be addressed prior to prophylactic surgery, as well as the way both partners deal with problems with those issues, not only individually but also as a couple.

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Summary

Introduction

Breast and ovarian cancer are frequent female cancers, mostly manifesting after 50 years of age. About 5-10% of affected women have a primarily genetically determined form, mainly by mutations in the *BRCA1/2* genes, transmitted as autosomal dominant traits with a risk of 50% for each child. These mutations became identifiable from the mid nineties of the previous century. The age of onset of breast cancer is from 25 years of age with a high risk for bilateral disease, and often associated with ovarian cancer from 35 years of age. A woman with a *BRCA1/2* mutation has a lifetime risk of 39-85% for breast cancer. Moreover, the ovarian cancer risk is 40-63% for *BRCA1* and 11-20% for *BRCA2* mutation carriers. In about 25% of families showing multigenerational transmission of the disease, identifiable mutations are present. The other families are usually classified as Hereditary Breast and Ovarian Cancer (HBOC) families and their risk estimates are based upon family data and empirical risk tables.

Prophylactic surgery, being prophylactic mastectomy with or without (immediate) breast reconstruction (PM/(I)BR) and prophylactic (bilateral) salpingo-oophorectomy (P(B)SO), are the most effective risk-reducing measures used by *BRCA1/2* mutation carriers and women from HBOC families ('high-risk women'). These measures are highly effective in reducing the risk and mortality of breast and ovarian cancer at a relatively young age. However associated sequelae as peri- and post-surgical complications and the emotional and physical impact must not be neglected.

The study

This thesis reports results of a retro- and prospective observational study (PREVOM-B study) on the psychological impact of PM and P(B)SO in high-risk women. The study started in 1999 at the Erasmus Medical Center-Daniel den Hoed Cancer Centre, Rotterdam (the Netherlands). It is the first single center follow-up study on PM/(I)BR and P(B)SO, including partners of the women. The study was funded by the Netherlands' Organization for Health Research and Development (ZonMw, grant no. 210-00-013). The retrospective study included 114 women, the prospective part 97 women.

Chapter 1 addresses the background of hereditary breast and ovarian cancer and the management options for high-risk women. Regular physical surveillance of the breasts and ovaries have important limitations and chemoprevention also cannot prevent metastatic disease. Prophylactic surgery and its uptake show the importance of this option.

Chapter 2 reviews the literature on the psychosocial impact of PM/(I)BR or P(B)SO. Part of previous experience was obtained in retrospective series of PM/(I)BR and P(B)SO before *BRCA* analysis for precise risk identification was possible. The role of hormone replacement therapy (HRT) and a personal history of breast cancer as variables in previous research are also discussed in this chapter.

The research questions of the PREVOM-B study (*Chapter 3*) included satisfaction and effects on the sexual relationship of prophylactic mastectomy and breast reconstruction (PM/(I)BR), and the motivations, levels and courses of distress and coping in women opting for PM/(I)BR and P(B)SO.

Retrospective analysis

The retrospective part of the study addressed satisfaction with PM/(I)BR in 114 women who underwent the procedure between 1994 and 2002 (*Chapter 4*). Satisfaction was reported by 60% of the women, lower than reported by others. We found that dissatisfaction was more often reported by women who felt insufficiently informed prior to PM/(I)BR, and who would not opt for breast reconstruction again. Also women who experienced adverse physical consequences such as peri- and post-surgical complications, women who experienced limitations in daily life and women who reported that their breasts did not feel 'like their own' after PM/(I)BR were less satisfied.

Adverse effects of PM/(I)BR on sexuality were reported by a relevant number of women (n=40; 44%). This is a higher frequency than usually reported. Perceived lack of information, discrepant expectations, ongoing complaints and limitations, the perception that the reconstructed breasts did not feel like one's own and altered feelings of femininity were associated with sexual dissatisfaction. The partner's reactions, that were perceived as negative about the woman's femininity and sexuality, and not opting for breast reconstruction again were also contributing factors. Though apparently PM/(I)BR had negative consequences for some, most women would opt for this procedure again (95% for PM, 80% for (I)BR). The results of the retrospective study indicate that preoperative counseling might benefit from addressing changes in body image and sexuality after PM/(I)BR and from recognizing potential risk factors in women at risk for breast and ovarian cancer.

Prospective analysis

The prospective part of our study on motivations, distress and coping obtained assessments a month prior to (baseline; T0), at six months after (T1) and at twelve months after prophylactic surgery (T2) (*Chapters 5-9*). Assessments included questionnaires and interviews with high-risk women and their partners separately. The prospective study showed that most women and their partners had no major untoward emotional effects after prophylactic surgery. The course of their adaptation and experiences is summarized below.

Motivations of 36 high-risk women were compared with their scores on cancer-related (Impact of Events Scale (IES)) and general distress (Hospital Anxiety and Depression Scale (HADS)). The motivations were categorized in emotional-cognitive motivations (EC group) and cognitive motivations (C group). Both groups were compared on subscales of the distress questionnaires: intrusion and avoidance for the IES and anxiety and depression for the HADS. We found no relationship between motivations and levels and courses of distress.

Women who reported 'fear for developing cancer' were analyzed separately and compared with the others. Their 'fear' resulted in significantly more preoperative depression but less avoidance afterwards.

We hypothesized that women without preoperative fear of cancer either worked through their anxieties before entering the study, or that they suppressed their feelings of distress. Pre-operative counseling might focus on recognizing both a strong fear of cancer and on possible suppressed feelings, in order to avoid future emotional problems.

The analysis on the levels and courses of general and cancer-related distress in 78 high-risk women (*Chapter 6*) revealed that anxiety and cancer-related distress were significantly reduced after PM/(I)BR, but not after P(B)SO. Clinically elevated levels of anxiety and cancer-related distress at one year after surgery were reported by 10-20% women after PM/(I)BR and 19-27% after P(B)SO. Being a mutation carrier and coping by comforting thoughts were predictive for increased distress at the half year assessment. Cancer-related and general distress levels at baseline were predictive for elevated emotional distress up to one year post-surgery (*Chapter 8*). Women who tended to use passive and palliative coping strategies and who lacked seeking social support showed more increased pre-operative distress. Passive coping also led to less decrease of distress at one year after prophylactic surgery (*Chapter 9*).

Pre- and post-surgery, the majority of 61 partners of high-risk women showed average distress scores, all within normal levels (*Chapter 7*). Possibly they received sufficient information and psychological support before and after the procedure. However, a small group of partners (2-10%) showed clinical cancer-related and general distress up to one year after prophylactic surgery of their wife. Increased post-operative distress was amongst others associated with fatherhood, and mutation status and previous cancer of the wife.

Conclusions

In conclusion, genetic testing for mutations in the *BRCA1/ 2* breast cancer genes, choices on options for risk reduction and prophylactic surgery may have a great physical and psychological impact in some women (*Chapter 10*). Long-term studies in the Rotterdam and other groups show how most women and their partners receive sufficient information and support to realize their most wanted gain of health.

The results of the PREVOM-B study provide a number of checkpoints, as improvement for the pre- and postsurgical counselling on PM/(I)BR and P(B)SO in high-risk women. These involve the information on the physical and psychological impact of PM/(I)BR and P(B)SO. High-risk women may benefit from pre- and postsurgical counselling and distress screening to help them effectively cope with feelings of distress and other possible adverse consequences of prophylactic surgery. Both before and after prophylactic surgery, special attention is warranted for high-risk women and their partners who are at an individually determined risk of feelings of anxiety and depression and/or cancer-related distress. For partners, the distress about the future of children at risk of being a mutation carrier is a factor for long term awareness. All these subjects warrant future research, and have relevance to all other genetic diseases.

Based on the results as presented in this thesis, two large prospective studies are currently underway: 1) the long-term effects of prophylactic surgery in the same cohort of women and partners; and 2) the various surgical options for breast reconstruction such as implants or autologous tissue and their effects on patient satisfaction, body image and distress.

Samenvatting

Introductie

Borst- en eierstokkanker zijn frequent optredende ziektes bij vrouwen, die zich meestal na het 50e levensjaar manifesteren. Bij 5-10% van de betrokken vrouwen is er een duidelijke erfelijke aanleg aanwezig. Deze vrouwen met een verhoogde kans op borst- en eierstokkanker hebben meestal een aantoonbare mutatie in één van de borstkankergenen *BRCA1* of *BRCA2*. Hun kinderen hebben 50% kans de afwijkende erfelijke eigenschap te erven. Een draagster van een verandering in het *BRCA1* of *BRCA2* gen heeft gedurende haar leven 39-85% kans op borstkanker. Bovendien is het risico op het ontwikkelen van eierstokkanker 40-63% bij *BRCA1* mutatie draagsters en 11-20% bij *BRCA2* mutatie draagsters. Een genmutatie wordt in ongeveer 25% van geteste families gevonden. Voor vrouwen uit families met borst- en eierstokkanker, waarin nog geen genverandering aantoonbaar is, is de risicobepaling afhankelijk van de familiegegevens. Soms zijn de risico's zodanig verhoogd, dat ook zij kiezen voor een preventieve operatie.

Omdat regelmatige controle een uitgezaaide vorm van kanker niet kan voorkomen, kiest een deel van de betrokken vrouwen voor een operatie uit voorzorg: preventieve mastectomie (verwijdering van borstklierweefsel) met of zonder (directe) borstreconstructie (PM/(I)BR) en preventieve (bilaterale) salpingo-ovariëctomie (P(B)SO; (dubbelzijdige) verwijdering van eierstokken en eileiders). Hoewel deze ingrepen zeer effectief zijn in het reduceren van het risico op kanker en sterfte op een relatief jonge leeftijd, kunnen er complicaties optreden tijdens en na de operatie. Bovendien mag men de emotionele gevolgen van een dergelijke radicale ingreep niet verwaarlozen.

De studie

In 1999 is in de Daniel den Hoed Kliniek van het Erasmus MC in Rotterdam een onderzoek gestart (de PREVOM-B studie) dat tot doel had de psychosociale gevolgen van PM/(I)BR en P(B)SO bij deze groep vrouwen in kaart te brengen. Het is het eerste 'single-centre' follow-up onderzoek naar de psychosociale gevolgen van PM/(I)BR en P(B)SO bij vrouwen met een verhoogd risico op borst- en eierstokkanker en hun partners. Het onderzoek werd gesubsidieerd door Zorgonderzoek Nederland (ZonMw, grant no. 210-00-013). Dit proefschrift doet verslag van de resultaten van dat onderzoek.

Hoofdstuk 1 beschrijft de achtergrond van erfelijke borst- en eierstokkanker en de keuzes die draagsters kunnen maken met betrekking tot regelmatige controle, chemopreventie en preventieve chirurgie. Ook wordt beschreven hoe vaak vrouwen kiezen voor preventieve chirurgie en welke factoren een rol spelen bij die keuze.

Hoofdstuk 2 toont een overzicht van de literatuur over de psychosociale gevolgen van PM/(I)BR en P(B)SO. Die ervaringen zijn nog beperkt, omdat een systematisch aanbod van die optie ontstond na de ontdekking van de *BRCA1* en *BRCA2* mutaties in de negentiger jaren van de vorige eeuw. Tevens zijn de beperkingen van hormoonvervangende therapie (HRT) na eierstokverwijdering aan de orde, als ook de rol van het eerder behandeld zijn voor borstkanker.

De onderzoeksvragen van de PREVOM-B studie (*Hoofdstuk 3*) betreffen de motivaties, tevredenheid en psychologische gevolgen zoals distress[1] en angst voor kanker bij vrouwen met een hoog risico op erfelijk borst- eierstokkanker voor en na de preventieve operatie. Ook de aanwezigheid en mate van distress bij partners van deze vrouwen werd onderzocht.

Retrospectieve analyse

In het retrospectieve deel werd aan 114 vrouwen die PM/(I)BR ondergingen tussen 1994 en 2002 (*Hoofdstuk 4*) terugblikkend gevraagd naar hun tevredenheid met de procedure. Slechts 60% van hen zei tevreden te zijn met de resultaten van PM/(I)BR, lager dan elders. Een relevant aantal vrouwen (n=40; 44%) rapporteerde een negatief effect van de operaties op hun seksuele relatie, terwijl die in andere studies weinig tot niet gevonden werden. De ontevredenheid met zowel de operatie als de seksuele relatie ten gevolge van PM/(I)BR bleek met een aantal factoren samen te hangen. Ontevreden vrouwen, in vergelijking met de overigen 1) zouden minder vaak opnieuw voor borstreconstructie kiezen ; 2) hadden vaker het gevoel onvoldoende geïnformeerd te zijn voorafgaand aan de operatie; 3) rapporteerden vaker complicaties en lichamelijke klachten; 4) voelden zich meer beperkt in hun dagelijks leven als gevolg van de operatie; en 5) vonden hun borsten vaker als 'niet eigen' aanvoelen. Vrouwen met negatieve gevolgen voor hun seksuele relatie hadden daarbij ook vaker 1) verwachtingen die niet uitkwamen; 2) veranderde

[1] De vertaling van 'distress' is 'pijn, leed, verdriet'. In dit proefschrift wordt met distress 'zorgen, spanningen' bedoeld. Kanker-gerelateerde distress verwijst naar indringende, verstorende (intrusieve) gedachten en gevoelens en vermijdend gedrag met betrekking tot borst- en eierstokkanker, en algemene distress verwijst naar gevoelens van angst en depressie. Vanwege het gebrek aan een adequate vertaling van 'distress' in het Nederlands zal het Engelse woord 'distress' in deze samenvatting gehandhaafd worden.

gevoelens van vrouwelijkheid; en 3) het idee dat de partner haar niet meer vrouwelijk en seksueel aantrekkelijk vond na de operatie. In de totale onderzoeksgroep bleek er geen relatie tussen ontevredenheid met de operatie en ontevredenheid met de seksuele relatie te zijn en zouden de meeste vrouwen opnieuw kiezen voor PM/(I)BR (95% voor PM, 80% voor (I)BR). De resultaten van deze retrospectieve studie pleiten ervoor, om tijdens de pre-operatieve counselling de mogelijke negatieve veranderingen in lichaamsbeleving en seksualiteit te bespreken, zodat mogelijke risicofactoren tijdig gesignaleerd kunnen worden.

Prospectieve analyse

In het prospectieve deel van de PREVOM-B studie (*Hoofdstuk 5-9*) werden vrouwen gevolgd van voorafgaand aan de preventieve operatie (T0) tot zes (T1) en twaalf maanden (T2) na de operatie. Steeds werden vragenlijsten afgenomen en werden alle deelneemsters en hun partners apart van elkaar geïnterviewd. De resultaten illustreren dat de meeste vrouwen en hun partners deze ingrepen goed doorstaan zonder verregaande emotionele gevolgen. Het verloop van hun aanpassing en ondervonden problemen worden hieronder samengevat.

In *Hoofdstuk* 5 werden de motivaties van 36 vrouwen vergeleken met hun kanker-gerelateerde (Impact of Events Scale; IES) en algemene 'distress' (Hospital Anxiety and Depression Scale; HADS). De motivaties werden in twee groepen gecategoriseerd: 1) de EC groep: mensen die zowel emotionele als rationele ('cognitieve') motivaties rapporteerden; en 2) de C groep, mensen die alleen cognitieve motivaties rapporteerden. Vervolgens werd voor beide groepen het verband onderzocht met de subschalen van de IES (intrusie en vermijding) en de HADS (angst en depressie). Er bleek geen relatie te zijn tussen de soort motivaties en het niveau of verloop van distress.

Een aparte analyse werd gedaan van vrouwen die 'angst voor kanker' noemden als motivatie, in vergelijking met de overige vrouwen. Die angst leidde tot beduidend meer depressieve gevoelens vóór de operatie maar minder neiging tot vermijding ná de operatie. De overige vrouwen scoorden in de verschillende tests binnen normale grenzen.

Deze resultaten leidden tot de hypothese dat vrouwen die vóór de operatie geen angst voor kanker aangaven ofwel al eerder (voorafgaand aan de studie) hun angsten zodanig verwerkt hadden dat die geen distress meer veroorzaakten, ofwel distress onderdrukten. Bij pre-operatieve counselling zal vooral gelet kunnen worden op sterke angst voor kanker enerzijds of ontbreken van enige vorm van distress anderzijds om toekomstige emotionele problemen op tijd te kunnen onderkennen.

Resultaten met betrekking tot het vóórkomen en verloop van kanker-gerelateerde en algemene distress bij 78 vrouwen (*Hoofdstuk 6*) lieten zien dat er een significante vermindering van angst en kanker-gerelateerde distress was na PM/(I)BR; na P(B)SO was die er niet. Klinisch relevante angst en kanker-gerelateerde distress was tot een jaar na de preventieve operatie aanwezig bij 10-20% van de PM/(I)BR vrouwen en bij 19-27% van de P(B)SO vrouwen. Kanker-gerelateerde en algemene distress vóór de operatie bleken voorspellend voor verhoogde distress een jaar na de preventieve operatie (*Hoofdstuk 8*). Mutatiedraagsters merkten daarbij vaak alsnog een daling van verhoogde distress tussen

6-12 maanden na de operatie. Vrouwen die geruststellende gedachten hanteerden bij het omgaan met dreiging van kanker ('coping') hadden een half jaar na de operatie meer distress dan vrouwen met een andere benaderingswijze. De relatie tussen coping en distress werd ook onderzocht in *Hoofdstuk 9*. Vrouwen die een passieve en palliatieve coping toepasten en geen sociale steun zochten bleken meer last van distress vóór de operatie te hebben. Bovendien bleek passieve coping onvoldoende om duidelijke distress na de preventieve operatie te verminderen.

De 61 partners van vrouwen met verhoogde erfelijke risico's hadden voorafgaand aan en na de preventieve operatie (*Hoofdstuk 7*) gemiddeld normale waarden voor hun mate van distress. Mogelijk hadden zij voldoende aan de informatievoorziening en de eventuele psychosociale steun voor en na de ingreep. Een kleine groep partners (2-10%) had tot een jaar na de preventieve operatie van hun vrouw klinisch zorgelijke kanker-gerelateerde of algemene distress. Oorzakelijke factoren waren onder andere vaderschap, en mutatiedragerschap of een voorafgaande borstkanker van de vrouw.

Conclusies

Erfelijkheidsonderzoek naar dragerschap van een afwijkend borstkankergen, keuzen t.a.v. risicovermindering en het ondergaan van operaties uit voorzorg kunnen ingrijpende en psychisch belastende ingrepen blijken voor sommige vrouwen (*Hoofdstuk 10*). Langdurig onderzoek in de Rotterdamse kliniek en elders toont dat de meeste vrouwen en hun partners voldoende informatie en begeleiding krijgen om deze gebeurtenissen goed te doorstaan en een gezondheidswinst te realiseren die past bij de gemaakte keuze.

De resultaten van het PREVOM-B onderzoek geeft goede aanknopingspunten om in de gesprekken voorafgaand aan preventieve operaties voor te bereiden op de lichamelijke en psychologische effecten van borstverwijdering en reconstructie, en de verwijdering van eierstokken en eileiders. Pre- en post-operatieve counselling en distress screening is relevant voor vrouwen met een verhoogde kans op borst- en eierstokkanker om hen te begeleiden bij het effectief omgaan met distress en andere mogelijke negatieve gevolgen van een preventieve operatie. Tijdens het traject rondom de preventieve operatie is aandacht nodig voor de groep vrouwen en hun partners die een individueel bepaalde, verhoogde kans hebben om extra angst, depressiviteit of kanker-gerelateerde distress te ervaren. Er is met name aandacht nodig voor partners van deze vrouwen, als de consequenties voor opgroeiende kinderen duidelijk worden. Deze onderwerpen zijn ook belangrijk voor andere genetische ziekten, en zullen nader onderzocht moeten worden in toekomstig onderzoek.

Vervolgonderzoek vindt thans plaats naar 1) de langere termijn effecten van preventieve chirurgie in de in dit proefschrift beschreven groep; en 2) de psychosociale effecten van verschillende vormen van borstreconstructie zoals implantaten versus borstreconstructie met lichaamseigen weefsel.

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[*] Uit: Van Dale (www.vandale.nl) en Wikipedia (nl.wikipedia.org)

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Curriculum Vitae

Paula Johanna Catharina Bresser was born on July 10th, 1972 in Rhoon, the Netherlands. She passed her Gymnasium α exam at the St.-Montfort College in Rotterdam in 1991 and obtained her degree in Clinical Neuropsychology at the Catholic University of Tilburg in 1998. In light of her studies, she performed her internship at the Helen Dowling Institute for Psycho-Oncology, assisting in a research project on the effects of group intervention on HIV-infected homosexual men. For her Master's thesis, she conducted a study on the psychometric qualities of the COPE-questionnaire at the same institute.

In June 1999, she started a PhD study on the psychological effects of prophylactic mastectomy (PM/(I)BR) and/or (bilateral) salpingo-oophorectomy (P(B)SO) in women who are genetically predisposed to breast and ovarian cancer (the PREVOM-study) at the Department of Medical Psychology and Psychotherapy at the Erasmus Medical Centre in Rotterdam, in collaboration with the Daniel den Hoed Family Cancer Clinic. Throughout this project, and more extensively from September 1999 until September 2001 and from September 2005 until September 2006, she also worked as a junior lecturer in medical psychology and communication. From September 2005 up to now, she works as a educational counselor at the medical school of the Erasmus University (Dept.: 'Opleidingsinstituut Geneeskunde' (OiG)). Momentarily, she is connected as an advisor to several research projects.

Paula shares her personal life with Martijn Leenders (1974) and their twins Quinten en Yanna (2006). Paula and Martijn are expecting their third child in June 2009.