Impact of genetic counseling for hereditary breast and ovarian cancer disposition on psychosocial outcomes and risk perception: A population-based follow-up study

PhD thesis

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Preface

This PhD thesis is based on studies carried out during my employment at the Centre for Innovation in Nursing Education in the County of Aarhus, and at the Department of Clinical Epidemiology, Aarhus University Hospital.

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This PhD thesis is based on the following papers:

I. Mikkelsen EM, Sunde L, Johansen C, Johnsen SP. Psychosocial conditions of women awaiting genetic counseling: A population-based study. Submitted.

II. Mikkelsen EM, Sunde L, Johansen C, Johnsen SP. Risk perception among women receiving genetic counseling: A population-based follow-up study. Submitted.

III. Mikkelsen EM, Sunde L, Johansen C, Johnsen SP. Psychosocial consequences of genetic counseling: A population-based follow-up study. Submitted.

Abbreviations

RCT	Randomized controlled trial
HBOC	Hereditary breast ovarian cancer
HRQOL	Health related quality of life
IES	Impact of event scale
HADS	Hospital anxiety and depression scale
SF-36	The Medical Outcome Study Short Form 36 Health Survey

Introduction

Breast and ovarian cancer

Breast cancer is the most prevalent cancer in Danish women, accounting for 23% of all new cases. The standardized incidence rate of breast cancer has doubled over the past 50 years, and more than 4,000 new cases are currently identified each year. The lifetime risk of developing breast cancer for a Danish woman is approximately 10%. While ovarian cancer is less prevalent, 610 new cases were diagnosed in Denmark in 2001 (1). Important risk factors for breast cancer include sex, age, hormonal factors, family history of breast cancer, alcohol use, and obesity. It is estimated that having one first degree relative with breast cancer inflicts a relative risk of 2-4, while two first degree relatives increases the relative risk to over 4 (2). Knowledge about risk factors for ovarian cancer is sparser, but includes age, a family history of ovarian cancer, and/or early onset of breast cancer (3). Five-year relative survival among patients with breast and ovarian cancer, compared to the background population in Demark, has been estimated at 77% and 32%, respectively. Between 1986 and 1995, survival of breast cancer patients improved from 73% to 77%, while survival of ovarian cancer patients remained unchanged (4). These estimates indicate the diseases' severity and limitations of current treatment options.

Most cases of breast and ovarian cancer are non-hereditary. They develop when somatic mutations accumulate and transform normal cells into malignant cells (5-7).

Hereditary breast or ovarian cancer results from a germline mutation in a cancer susceptibility gene combined with a number of somatic mutations. Two highly penetrant cancer susceptibility genes, BRCA1 (8) and BRCA2 (9), have been identified at the long arms of chromosomes 17 and 13, respectively. Cancer susceptibility due to mutations in the BRCA1 and BRCA2 genes

follows autosomal dominant transmission. It is estimated that mutations in these genes are responsible for approximately 7% of all breast cancers and 10% of all ovarian cancers (10). Carriers of mutations in the BRCA1 or BRCA2 genes have a substantially increased lifetime risk of developing both breast and ovarian cancer (HBOC). Their lifetime breast cancer risk has been estimated at 40%-85%, and their lifetime ovarian cancer risk at 15%-40%. Carriers of mutations in BRCA1 have a higher risk of both breast and ovarian cancer compared to carriers of mutations in BRCA2 (11-15). As a consequence of the autosomal dominant transmission, men and women are at equal risk of inheriting mutations in a cancer susceptibility gene. However, men rarely develop breast cancer.

Hereditary breast cancer is characterized by early onset (< 50 years), increased number of affected family members in two or more generations, increased risk of bilateral breast cancer, and a strong association with ovarian cancer (2;16). Hereditary ovarian cancer usually occurs in the context of hereditary breast cancer and does not differ markedly from non-hereditary ovarian cancer in respect to clinical and pathological features (3).

Genetic counseling

International and national clinical guidelines developed for genetic counseling address referral criteria, risk assessment, genetic testing, surveillance, and treatment (17-20).

The aims of genetic counseling have been described in the international literature as follows (6;20-22):

- to prevent disease and promote health
- to enhance the accuracy and usefulness of risk perceptions
- to promote informed decisions about surveillance, genetic testing, and treatment options

- to facilitate psychological well-being in risk adaptation.

Traditionally, physicians have provided genetic counseling in Denmark and the main focus of the counseling process has been information provision (17;23-25). The Danish Breast Cancer Cooperative Group (DBCG) (17) recently developed national genetic counseling guidelines for hereditary breast and ovarian cancer. The literature describing Danish genetic counseling practices, including current guidelines, stresses that the counseling process should be non-directive, to promote autonomy and a sense of personal control (7;18;23;25).

Genetic counseling includes obtaining a pedigree followed by medical record confirmation of cancer diagnoses. During the counseling process, clients' risk perceptions and experiences with cancer in their families are explored. Furthermore, clients receive information on breast cancer incidence, genetics, inheritance patterns, treatment and prevention options, and a personal risk assessment (17;23;25).

Individual risk is assessed in one of two ways: when appropriate, it is calculated on the basis of a predisposing familial mutation or a pedigree indicating an autosomal dominantly inherited risk; otherwise, risk is assessed according to empirical data, *e.g.*, Claus *et al.* (26).

If indicated and feasible, clients are offered genetic testing. This consists of DNA analysis to detect hereditable disease-related mutations (27). Before testing, it is necessary to identify the mutation associated with the disease in a client's family. A primary mutation screening thus is offered to a cancer-affected individual in the family (22;28). When the mutation associated with

the disease has been identified in the family member, unaffected relatives then have the option of predictive testing.

Prevention guidelines

In Denmark, women found to be mutation carriers or who are estimated to be at considerably increased risk of breast cancer (> twice the risk of the background population) are referred to surveillance programs, which include mammograms, clinical breast examinations, and ultrasound scanning. In cases in which the risk of ovarian cancer is considerably increased, gynaecological examinations, serum CA125 levels, and vaginal ultrasound also are provided. Surveillance programs are designed individually, depending on age, level of risk, and personal preferences. Prophylactic mastectomy and oophorectomy are discussed as options for mutation carriers and other women at high risk (29).

Referral criteria

Genetic counseling is offered to men and women thought to be at risk of hereditary breast/ovarian cancer, independent of their own cancer status.

In Denmark, the tax-financed public health system offers counseling upon referral by a medical doctor. According to DBCG criteria, non-affected individuals can be referred if they are a first-degree relative of the following patients (or second degree relative via a male) (17):

- A patient diagnosed with breast cancer <40 years,
- A patient diagnosed with both breast and ovarian cancer,
- Two patients diagnosed with breast cancer or ovarian cancer <50 years,
- Three patients diagnosed with breast cancer across two generations, or

- A patient with a known mutation.

However, individuals who do not quite fulfill the criteria e.g. a woman who are diagnosed with breast cancer at early age or a person with another family history of cancer may still receive these services.

Genetic counseling for breast and ovarian cancer is offered at five departments of clinical genetics and one clinical oncology department in Denmark. A number of clinical departments provide surveillance programs and prophylactic surgery (17).

Outcomes of genetic counseling

Genetic counseling has been available for more than a decade in Denmark. The scarcity of primary prevention options for breast and ovarian cancers, together with positive expectations for genetic counseling, has increased the demand for this prevention strategy for hereditary cancer (23;30-32). While the number of individuals referred each year for genetic counseling for HBOC in Denmark is unknown, 215 new families with a hereditary disposition to HBOC were reported to the DBCG Registry in 2000, and this number increased to 685 in 2005 (33;34).

As well as other health care interventions genetic counseling has to be evaluated in terms of its outcomes. A simple way to summarize outcomes has been described as the five “Ds” – Death, Disease, Discomfort, Disability and Dissatisfaction (35). The "D´s" encompass a range of outcomes from death to emotional reactions. Genetic counseling is based on a multidimensional health concept incorporating physical, behavioural, social and psychological perspectives. The research related to the outcomes of genetic counseling should therefore reflect all these aspects.

Clinical outcomes

One of the aims of genetic counseling is to reduce cancer mortality and cancer incidence through genetic testing, clinical surveillance, and prophylactic surgery. However, because follow-up time for women who have received genetic counseling for HBOC is still limited, no studies to date have reported on these outcomes (18;19;28).

Instead, a number of studies have addressed intermediate clinical outcomes related to genetic counseling. In a randomized controlled trial (RCT), Schwartz *et al.* examined the rate of self-reported mammography following risk counseling and found no effect. (36). In a follow-up study, Meiser *et al.* detected no change in adherence to mammography surveillance after genetic counseling, but found a significant decrease in adherence to clinical breast examination 12 months later (37). Lerman *et al.* examined prophylactic surgery and surveillance behaviour during the year following BRCA1 or BRCA2 testing. They concluded that the vast majority of BRCA1 and BRCA2 carriers do not opt for prophylactic surgery and many do not adhere to surveillance recommendations (38).

Other studies have addressed the effect of specific surveillance and treatment procedures among women identified as mutation carriers or estimated to be at high risk. Breckelmans *et al*. found a lower sensitivity of mammography screening among BRCA1 and BRAC2 carriers and women under the age of 40 in a study of high-risk women (39). Oei *et al.* studied the effect of gynaecological screening of women at high risk of hereditary ovarian cancer. The procedure was found to be highly inefficient, in light of the high number of surveillance visits and the advanced stage of ovarian cancers detected.

Alcohol consumption and obesity are known risk factors for breast cancer (2). Together with other health behaviours, such as physical exercise and smoking, they may also influence the risk of hereditary breast cancer. To date, however, no studies have addressed the impact of genetic counseling on any of these health behaviours.

Psychological outcomes

The complexity of providing risk information (40;41), ethical dilemmas (42;43), and possible psychological distress (44;45) have spurred a large number of research projects on the cognitive and affective impacts of genetic counseling (18;19;46). Studies on cognitive outcomes mainly have focused on risk perception and knowledge of cancer genetics. The affective outcomes most frequently studied are generalized anxiety, generalized psychological distress, depression, and cancer-specific distress (47-49).

Review of the literature

I aimed to review the literature systematically to assess the effect of genetic counseling on risk perception and psychosocial outcomes.

Search strategy

The MEDLINE literature search used the following MESH terms: “genetic counseling” combined with “risk assessment”, “breast neoplasm (major subheadings)”, “ovarian neoplasm (major subheadings)”, “anxiety”, “depression”, and “stress, psychosocial”. Each search was limited to studies of female human adults aged 19+years, conducted during the period January 1, 1990 to May 21, 2006, and published in English with abstracts available. In addition, I searched MEDLINE for publications by key authors, and reviewed reference lists of the selected publications for other relevant articles.

I focused on studies that evaluated the impact of genetic counseling on risk perceptions in relation to breast cancer, and on the following psychosocial outcomes; anxiety, depression, cancer distress/worry, and health-related quality of life. A number of other outcomes related to genetic counseling were not considered, *e.g.*, knowledge (37;50;51), patient satisfaction (51;52), duration of counseling (53), compliance with breast cancer screening (37), intention to test (50), decisional conflict (50), decision to test (54), and general health (55).

I excluded all studies that were not designed as RCTs or as follow-up studies with at least one pre- and one post-counseling assessment (a minimum of 4 weeks after counseling) (56-58). In addition, I excluded studies that included only women affected with cancer (59) and studies in which data were not analyzed separately for affected and unaffected women (50;60-62).

In total 15 papers were reviewed in depth.

Studies on risk perception

The impact of genetic counseling on risk perception and risk accuracy at least four weeks after counseling has been assessed in 11 studies (13 papers) (Table 1).

Perceived risk

Perceived risk is defined as a client's perception of her personal risk of developing breast cancer during her lifetime. Three RCTs (30;51;63) and one follow-up study (64) examined the impact of genetic counseling on level of perceived risk, using four different assessment methods. A statistically significant reduction in perceived risk were observed for both the intervention and the control groups in the three RCTs, however, only one of the RCT found a statistically significant effect of genetic counseling (63) (estimates presented in Table1).

Risk accuracy

Risk accuracy has been described as the difference between a woman's perceived lifetime risk of developing breast cancer and her objective risk, as assessed by a medical professional. Most studies have classified women as "underestimators", "accurate estimators", or "overestimators". Altogether seven studies have examined the impact of genetic counseling on risk accuracy, using different models of object risk assessment (Gail, Claus, pedigree) and at least five different definitions of risk accuracy. One RCT (32) and four follow-up studies (65-68) found a statistically significant improvement in risk accuracy following counseling (estimates presented in Table1). Another RCT detected no difference between the intervention group and the control group (53). The remaining RCT (32) did not provide absolute estimates from the inter-group

analysis; however the published odds ratio (OR: 3.5, 95% CI, 1.3;9.5) indicates that the women who received genetic counseling were more likely to improve their risk perception, compared with women who received general health counseling . The proportion of women with accurate perceptions of their lifetime risk of developing breast cancer following counseling varied greatly across studies, ranging from 17% to 87%.

Table 1. Studies evaluating the impact of genetic counseling on perceived risk and accuracy of risk perception

Author Country, year	Design	Study-population	Outcome measure	Results
Brain *et al.* UK, 2000, 2002 (51;69)	RCT Multi-disciplinary genetic counseling (I) vs. surgical assessment (C)	Women with significant family history of breast cancer[1a] Referral: GP N=545 Complete follow-up: 55%	Perceived risk (range 2-10): Baseline 9 months	Mean score (sd) I: 7.3(1.2) C: 7.3(1.2) I: 6.7(1.3) C: 6.9(1.3) S reduction. NS differences between groups.
Cull *et al.* UK, 1998 (53)	RCT Video before genetic counseling (I) vs. video after genetic counseling (C)	Women with significant family history of breast cancer[1a] Referral: agent not reported N=95 Complete follow-up: 60%	Accuracy of risk: Accurate (2x obj. risk) Underestimate(>=0.5x obj. risk) Overestimate(>= 2x obj. risk) Obj. risk: not reported	PP: Baseline - 1 months I: 59% 81% C: 59% not reported I: 27% 18% C: 27% 38% I: 14% 2% C: 14% not reported S difference between groups for underestimate
Bish *et al.* UK, 2002 (64)	Follow-up study	Women with significant family history of breast cancer[1a] Referral: agent not reported N=143 Complete follow-up: not deducible	Perceived risk (range -4-+4): Baseline 6 months 12 months	Mean score women at moderate risk (sd) 1.2 (0.7) 1.0 (0.8) 1.1 (0.6) NS reduction
Fry *et al.* UK, 2003 (30)	RCT Community genetic counseling (I) vs. Standard regional genetic counseling (C)	Women with family history of breast cancer[1c] Referral: GP N=247 Complete follow-up: 43%	Perceived risk (low, moderate, high): Baseline 4 weeks 6 months	PP: perceived risk (moderate + high) I: 96% C: 97% I: 92% C: 92% I: 91% C: 92% S reduction in both groups. NS differences between groups

Table 1. (continued)

Author Country, year	Design	Study-population	Outcome measure	Results
Watson *et al.* UK, 1999 (68)	Follow-up study	Women with family history of breast cancer[1c] Referral: agent not reported N= 229-263 Complete follow-up: 76%-87%	Accuracy of risk recall: Accurate (= obj. risk) Underestimate (<obj. risk) Overestimate (>obj. risk) Obj. risk: Claus model	PP: Baseline - One year 9% 17% 18% 26% 52% 42% S increase in accuracy
Bowen *et al.* USA, 2004 (63)	RCT Psychosocial counseling (I) vs. genetic counseling (Ia) compared to a control group of no intervention (C)	Women with family history of cancer[1c] Referral: relative or calling a study line N=345 Complete follow-up: 62%	Perceived risk (lifetime risk 0-100%): Baseline 6 months Obj. risk: Gail and Claus model	Mean score (sd) I: 50.8(21.9) Ia: 48.5 (27.9) C: 53.0 (25) I: 24.2 (21.8) Ia: 23.4 (20.3) C: 49.0 (23) S decrease in perceived risk for I and Ia compared to control group(C)
Hopwood *et al.* UK, 1998, 2003 (66;70)	Follow-up study	Women with family history of cancer[1b] Referral: GP, clinicians N= 111 Complete follow-up: not deducible	Accuracy of risk: Accurate (= obj. risk) Underestimate(<obj. risk) Overestimate (>obj. risk) Obj. risk: Claus model	PP: Baseline - 3 months - 12 months 12% 67% 63% 49% 12% 9% 39% 21% 28% S increase in accuracy from baseline
Hopwood *et al.* Uk, 2001 (67)	Follow-up study	Women with moderate risk of breast cancer[1b] Referral: GP and clinicians N=330 Complete follow-up: not deducible	Accuracy of risk: Accurate (= obj. risk) Underestimate (<obj. risk) Overestimate (>obj. risk) Obj, risk: Claus model	PP: Baseline - 3 months 15% - 42% 37% - 29% 33% - 23% S increase in accuracy

Table 1. (continued)

Author Country, year	Design	Study-population	Outcome measure	Results
Evans *et al.* UK; 1994 (65)	Follow-up study	Women with family history of cancer[1c] Referral: GP and clinicians N=78 Complete follow-up: not deducible	Accuracy of risk: Accurate Inaccurate Accurate: within 50% of obj. risk Obj. risk: Claus model	PP: Baseline - 12 months 8% - 38% 92% - 62% S increase in accuracy
Meiser *et al.* Australia, 2001 (37)	Follow-up study	Women with family history of breast cancer[1c] Referral: not reported N=218 Complete follow-up: 79 %	Accuracy of risk: Accurate Underestimate Overestimate Accurate: within or one response category below or above obj. risk Obj. risk: pedigree	PP: Baseline - 12 months 54% - 55% 12% - 14% 34% - 31% NS increase in accuracy
Lerman *et al.* USA, 1995 (32)	RCT Genetic counseling (I) vs. general health counseling(C)	Women with family history of cancer[1c] Referral: relative N=200 Complete follow-up: 46%	Accuracy of risk: Accurate (= obj. risk +/-10%) Obj. risk: Gail model	PP: Baseline 3 months I: 6.6% C: 11% I: 14.6% C: 9.4 S increase in accuracy in I group. OR= 3.5 (CI: 1.3;9.5) for improvement in I group vs. C group

[1a]Women at high risk of HBOC (classical characteristics), [1b]Women with moderate lifetime risk of breast or ovarian cancer
[1c]Women with any family history of cancer or minimum one first degree relative with breast or ovarian cancer
GP: General practitioner, N: Number of participants who completed both baseline and follow up assessment
Complete follow-up: Participation based on the number invited/eligible
NS: statistical non significant, S: Statistical significant, sd: standard deviation, CI: 95% confidence interval, PP: Prevalence proportion
Obj. risk: Objektive risk assessed by the professionals using pedigree or different risk prediction models

Studies of psychosocial outcomes

10 studies (10 papers) that evaluated psychosocial outcomes at least four weeks after genetic counseling were identified (Table 2).

Depression

One RCT (63) and two follow-up studies (37;64) assessed the impact of genetic counseling on depression, using the Hospital Anxiety and Depression Scale or Beck Depression Inventory. None found an effect.

Anxiety

Three RCTs (51;53;63) and three follow-up studies (37;64;68) evaluated changes in general anxiety following counseling, as measured by the Hospital Anxiety and Depression Scale, the Spielberger State Anxiety Inventory, or the Brief Symptom Inventory. None found a substantial change in anxiety after counseling.

Cancer-specific distress

Four RCTs (30;51;63;71), one controlled trial (52), and four follow-up studies (37;64;67;68) investigated cancer-specific distress following genetic counseling. Three different scales were used to measure such distress: Impact of Event Scale, Cancer Worry Scale, and Cancer Anxiety and Helplessness Scale. Seven studies reported a statistically significant reduction in cancer-specific distress following counseling. However, only one of the four RCTs comparing an intervention group with a control group found that cancer-specific distress was significantly reduced by counseling (63) (estimates presented in Table 2).

Table 2. Studies evaluating the impact of genetic counseling on anxiety, depression and cancer-specific distress

Author Country, year	Design	Study-population	Outcome measure	Results
Brain *et al.* UK, 2000 (51)	RCT Multi-disciplinary genetic counseling (I) vs. surgical assessment (C)	Women with significant family history of breast cancer[1a] Referral: GP N=545 Complete follow-up: 55%	Anxiety (STAI)[2a] Baseline 9 months Cancer distress (Worry scale)[2b] Baseline 9 months	Mean scores (sd) I: 35.9 (11.1) C: 35.5 (10.9) I: 36.4 (12.3) C: 35.2 (11.8) No change. NS differences between groups I: 11.8 (3.4) C: 11.5 (3.0) I: 10.6 (3.2) C: 10.6 (2.9) S Reduction in both groups. NS differences between groups
Bish *et al.* UK, 2002 (64)	Follow-up study	Women with significant family history of breast cancer[1a] Referral: agent not reported N=144 (non-affected) Complete follow-up: not deducible	Anxiety (HADS)[2c] 2 weeks, 6 months, 12 months Depression (HADS)[2c] 2 weeks, 6 months, 12 months Cancer distress (Worry scale)[2b] Baseline 6 months 12 months	No changes - estimates not reported No changes - estimates not reported Mean score for women at moderate risk (sd) 12.4 (3.1) 10.3 (2.9) 10.6 (3.0) S Reduction in cancer stress
Cull *et al.* UK, 1998 (53)	RCT Video before genetic counseling (I) vs. video after genetic counseling (C)	Women with significant family history of breast cancer[1a] Referral: agent not reported N=95 Complete follow-up: 60%	Anxiety (STAI)[2a] Baseline 1 month	Mean scores (sd) I: 35 (11) C: 38 (14) I. 32 (9) C: 35 (13) No differences between groups

Table 2. (continued)

Author Country, year	Design	Study-population	Outcome measure	Results
Lerman *et al.* USA, 1996 (71)	RCT Risk counseling (I) vs. general health counseling (C)	Women with family history of breast cancer[1c] Referral: relative N= 239 Complete follow-up: not deducible	Cancer distress (IES)[2d] Baseline 3 months	Mean scores (sd) I: 13.1 (12.0) C: 15.3 (12.8) I: 10.3 (12.7) C: 14.4 (14.4) Reduction in both groups. Between group analysis not reported.
Hopwood *et al.* UK, 2001 (67)	Follow-up study	Women with moderate risk of breast cancer[1b] Referral: GP and clinicians N=330 Complete follow-up: not deducible	Cancer distress (Worry scale)[2b] Baseline 9.4 months, mean (range 2-21 months)	Mean (sd) 11.93 (3.2) 11.83 (3.2) NS Reduction
Meiser *et al.* Australia, 2001 (37)	Follow-up study	Women with family history of breast cancer[1c] Referral: not reported N=218 Complete follow-up: 79%	Anxiety (STAI)[2a] Baseline 12 months Depression (BDI)[2e] Baseline 12 months Cancer distress (IES)[2d] Baseline 12 months	Mean scores (sd) 35.8 (12.3) 37.3 (12.8) 6.2 (6.4) 7.4 (7.9) 15.1 (15.0) 13.8 (15.3) S Reduction
Watson *et al.* UK, 1998 (52)	Controlled follow-up study Standard counseling + tape (I) vs. standard counseling (C)	Women with family history of breast cancer[1c] Referral: agent not reported N=91 Complete follow-up: 67%	Cancer distress (Worry scale)[2b] Baseline 1 month 6 months	Mean scores (sd) I: 11.1 (3.2) C: 11.4 (3.4) I: 10.5 (3.3) C: not reported I: 10.2 (2.9) C: not reported S Reduction in intervention group Between group analysis not reported.

Table 2. (continued)

Author Country, year	Design	Study-population	Outcome measure	Results
Watson *et al.* UK, 1999 (68)	Follow-up study	Women with family history of breast cancer[1c] Referral: agent not reported N= 229-263 Complete follow-up: 76%-87%	Anxiety (STAI)[2a] 6 months 12 months Cancer anxiety (CAHS)[2f] 6 months 12 months Cancer distress (IES)[2d] 12 months	Mean difference in score from baseline (CI) 0.02 (-0.29;0.33) -0.17 (-0.49;0.14) 0.09 (-0.32;0.50) 0.38 (-0.04;0.79) -0.29 (-1.91;1.33)
Bowen *et al.* USA, 2004 (63)	RCT Psychosocial counseling (I) vs. genetic counseling (Ia) compared to a control group of no intervention (C)	Women with family history of cancer[1c] Referral: relative or calling a study line N=345 Complete follow-up: 62%	Anxiety (BSI)[2g] Baseline 6 months Depression Baseline 6 months Cancer distress (Worry scale)[2b] Baseline 6 months	Mean scores (sd) I: 0.45 (0.41) Ia: 0.44 (0.49) C: 0.49 (0.56) I: 0.32 (0.35) Ia: 0.40 (0.42) C: 0.50 (0.48) NS reduction I: 0.45 (0.47) Ia: 0.50 (0.54) C: 0.57 (0.58) I: 0.44 (0.39) Ia: 0.46 (0.43) C: 0.54 (0.52) NS reduction I: 6.1 (1.7) Ia: 6.0 (1.7) C: 6.2 (1.7) I: 5.2 (1.3) Ia: 5.3 (1.3) C: 6.2 (1.4) S reduction in both groups compared to control group
Fry *et al.* UK, 2003 (30)	RCT Community genetic counseling (I) vs. Standard regional genetic counseling (C)	Women with family history of breast cancer[1c] Referral: GP N=247 Complete follow-up: 43%	Cancer distress (Worry scale)[2b] Baseline 4 weeks 6 months	Mean scores (sd) I: 11.5(3.2) C: 11.3(3.0) I: 10.3(2.4) C: 10.2(2.7) I: 9.9(2.5) C: 9.7(2.7) S reduction in both groups. Between group analysis not reported

[1a]Women at high risk of HBOC (classical characteristics) ,[1b]Women with moderate lifetime risk of breast or ovarian cancer, [1c]Women with any family history of cancer or minimum one first degree relative with breast or ovarian cancer

[2a]Spielberger State Anxiety Inventory, [2b]Cancer worry scale, [2c]Hospital Anxiety and Depression Scale, [2d]Impact of Event Scale,[2e]Beck Depression Inventory, [2f]Cancer Anxiety and Helplessness Scale, [2g]Brief Symptom Inventory,

GP: General practitioner, N: Number of participants who completed both baseline and follow up assessment, Complete follow-up: Participation based on the number invited/eligible, NS: statistical non significant, S: Statistical significant, sd: standard deviation, CI: 95% confidence interval.

Methodological considerations

Study designs

While six RCTs explored the impact of genetic counseling, only one study compared the effect of genetic counseling to no counseling (63). The five other controlled trials compared the effects of different counseling methods, *e.g*., counseling with and without a video (53), counseling with without an audio tape (52) and the effect of different health professionals as counseling providers (30;51). Furthermore, inter-group analyses were presented rarely despite the use of controls in the study design. None of the follow-up studies included control groups.

Study populations

The studies included in this review recruited participants through such means as public announcements (63), family referrals (32), and medical referrals (65). None was population-based, and study populations varied greatly. Inclusion criteria also differed, with participants in some studies required to be at risk of hereditary cancer (64), while in others participants qualified on the basis of any family history of breast cancer (63).

Based on the number of women eligible/invited to enroll, the completion rate for long-term follow-up varied from 43% to 79% across studies. For some studies it was not possible to deduce the completion rates (64-67;70;71). In addition, the size of the study population was rather small in a number of studies (52;53;64-66;70).

Most of the studies included in the review were conducted in United Kingdom. A few studies were done in the USA (32;63;71) and a single study came from Australia (37).

Study outcomes

In the studies reviewed, effect sizes are difficult to compare because of the many different methods used to assess perceived risk, risk accuracy, and cancer-specific distress. Most studies reported mean values for anxiety, depression, cancer-specific distress and perceived risk even though it appeared that the data were not normal distributed. In addition, tests of statistical significance were often stressed in the presentation of differences between baseline and follow-up scores or inter-group scores. Results such as P-values or a reduction in the mean value of a score, such as 1.3 points on the IES (37), are often difficult to interpret and have questionable clinical relevance. None of the studies reporting a statistically significant reduction in perceived risk or in cancer-specific distress commented on the clinical relevance of the effect size.

Conclusion

In this review I focused on the long-term (>= 4 weeks) impact of genetic counseling in terms of risk perception and psychosocial outcomes.

Overall, genetic counseling does not seem to have an adverse effect on general anxiety and depression. It does appear to improve the accuracy of risk perception and to decrease cancer-specific distress to levels that reach statistical significance; however the size and the clinical relevance of these improvements are unknown. A number of methodological concerns hamper interpretation of reported outcomes: use of heterogeneous measures for the same construct (perceived risk, anxiety, depression, cancer-specific distress), lack of suitable control groups (no counseling), lack of inter-group analysis, and highly selected study populations. The relevance of study findings to Denmark is unclear, as none were conducted in countries with a similar culture and health system.

Well-designed studies with comparison groups and unbiased study populations are needed to clarify the impact of genetic counseling for hereditary breast and ovarian cancer. Standardized methods should be utilized to allow comparisons across studies.

Aims of the thesis

1. To compare the psychosocial conditions of women awaiting genetic counseling for hereditary breast and ovarian cancer risk with those of women awaiting mammography and those of a random sample of women from the general population. (Study I)

2. To examine possible clinical and socioeconomic differences between study respondents and non-respondents and between participants with complete follow-up and drop-outs. (Study I)

3. To assess the impact of genetic counseling over time on perceived personal lifetime risk of cancer, accuracy of risk perception, and to identify possible predictors of inaccurate risk perception among women who receive genetic counseling for hereditary breast and ovarian cancer. (Study II)

4. To assess the psychosocial impact of genetic counseling over time on hereditary breast and ovarian cancer risk, in terms of anxiety, depression, cancer-specific distress, and health-related quality of life. (Study III)

Subjects and methods

This thesis is based on a follow-up study of women referred for genetic counseling compared to two reference groups.

Study population

The Genetic Counseling Group

We included all women (N=567) referred for genetic counseling, independent of their own cancer status, to the following clinics: Department of Clinical Genetics, Aarhus University Hospital; Department of Clinical Genetics, Rigshospitalet, Copenhagen University Hospital; Oncology Department, Rigshospitalet, Copenhagen University Hospital; or the J. F. Kennedy Institute. The referral period was September 15, 2003 to September 15, 2004. Participants had to fulfill the following inclusion criteria:

- > 18 years of age
- referral because of a family history of breast or ovarian cancer or their own diagnosis of breast or ovarian cancer at an early age
- initial counseling session scheduled.

Reference Group I

To compare the impact of genetic counseling with the impact of an alternative approach to cancer prevention, we utilized women referred for mammography as a reference group (Reference Group I, N=689). This reference group was recruited at two hospitals. From Aalborg Hospital, we included all women aged 18-75 years who were referred for mammography for non-acute clinical indications during the period from March 15, 2004 to December 31, 2004.

From Rigshospitalet, we included all women aged 50-69 years who were enrolled in a breast cancer screening program during the period from November 25, 2003 to December 1, 2003.

Reference Group II

We chose a random sample of Danish women as an alternative reference group (Reference Group II) to represent women with an unknown risk of developing breast or ovarian cancer. This sample consisted of female Danish residents between 18 and 75 years of age (N = 2,000) randomly sampled from the Danish Central Personal Registry. This Registry is continuously updated with information regarding vital status and address changes for all permanent and temporary Danish residents.

Data collection

We obtained self-reported data from the women participating in the study (Fig. 1), registry data from six public medical registries, and data from the physicians providing genetic counseling.

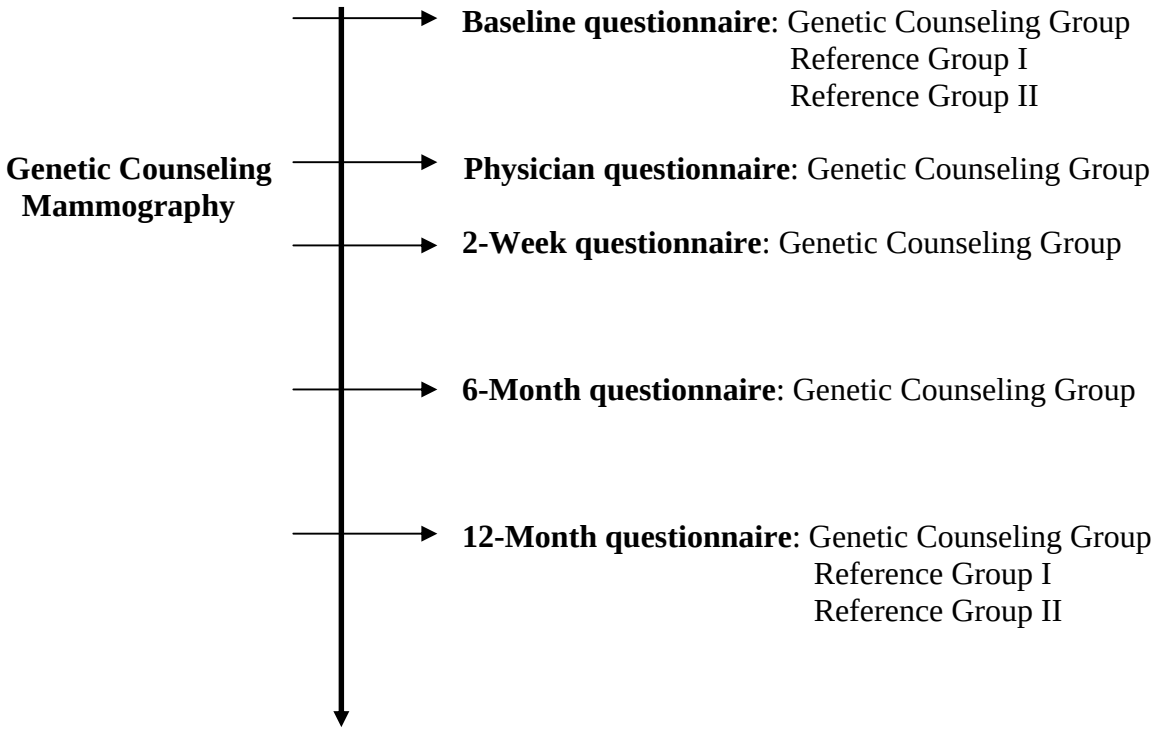
We used self-administered, standardized, mailed questionnaires to obtain self-reported data from the entire study population. Data from the Genetic Counseling Group were collected one to four weeks before the first counseling session and two weeks, six months and 12 months afterwards. Data for Reference Group I were collected one to four weeks before mammography and 12 months afterwards. Data for Reference Group II were collected at the time of enrollment of the first woman in the Genetic Counseling Group and follow-up data were collected 12 months later. At each time point, participating women received a questionnaire and a prepaid return envelope. One reminder was mailed two weeks later if the first questionnaire was not returned.

For women who received genetic counseling, the physicians who provided the counseling completed a questionnaire ("physician questionnaire") immediately after the counseling session. The clinicians received one reminder if a questionnaire was not returned two weeks after the scheduled counseling date.

Questionnaires were designed using the computer program Teleform and entered optically with the Teleform Reader at the maximum confidence level (99%).

In order to link data from the different data sources, we used the civil registration number, a unique ten-digit personal identification number assigned to all permanent and temporary residents in Denmark since 1968.

Figure 1. Overview of study questionnaires



Self-reported and physician-reported data

Cancer-specific distress (Aims 1 and 4)

We used the Impact of Event Scale (IES) (72) to asses self-reported cancer-related distress. IES consists of 15 items; each item is scored 0, 1, 3, or 5, with a higher score reflecting a more stressful impact. A score below nine was used as the cut-off point for no cancer-specific distress (72).

Anxiety and Depression (Aims 1 and 4)

We used the Hospital Anxiety and Depression Scale (HADS) (73) as a measure of self-reported generalized anxiety and depression. HADS consists of 14 items, seven on anxiety and seven on depression, forming two subscales. Each scale has a maximum score of 21, with a higher score reflecting more severe depression and anxiety symptoms. A score below eight was used as the cut off for "no anxiety" and "no depression", respectively.

Health- related quality of life (Aims 1 and 4)

Self-reported health-related quality of life (HRQOL) was assessed by the Medical Outcome Study Short Form 36 Health Survey (SF-36) (74). SF-36 consists of 36 items forming eight subscales, and two summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS). Scoring was executed according to Danish guidelines (75). We defined impaired health-related quality of life as a score below the 25^{th} percentile for each subscale in the SF-36 data, as suggested by Rose *et al*. (76). We used the 25^{th} percentile of unaffected women from the population sample (no personal history of breast or ovarian cancer) as the cut-off point for all three study groups.

Perceived risk (Aim 3)

In the questionnaires, respondents were asked to estimate and report their perceived lifetime risk of developing breast cancer as a percentage (0-100%).

Objective risk (Aim 3)

For each woman in the Genetic Counseling Group, the physicians reported the estimated lifetime risk of breast cancer as a percentage (0-100 %). The lifetime risk for women in the two reference groups was estimated to be 10% (77).

Risk accuracy (Aim 3)

Risk accuracy was calculated as the difference between a woman's perceived risk and her objective risk. Women were classified as perceiving their risk at three levels of accuracy (32;56):

Accurately: -10% < risk accuracy <10%

Underestimated: risk accuracy >= -10%

Overestimated: risk accuracy >= 10%.

Risk expression (Aim 3)

Physicians reported how estimated lifetime risk was communicated to their clients, *i.e.*, using numbers (percentage), using risk categories (low, moderate, high), using other words, or using a combination of these approaches.

Registry data (Aim 2**)**

We obtained registry data for the entire study population (respondents and non-respondents) from the six Danish public registries, all of which are nationwide, population-based, and continuously updated.

The Danish National Hospital Registry

We used the Danish National Hospital Registry (DHR) to identify non-cancer diagnoses related to the breast or uterus, in addition to all diagnoses included in the Charlson comorbidity index (78) for the period 1994 to 2003. The Charlson comorbidity index is a weighted index of the number and the seriousness of comorbid diseases. The DHR contains detailed information on date of hospital admission and discharge, and up to 20 discharge diagnoses and procedures for all patients admitted to a non-psychiatric hospital in Denmark since 1977 (including all outpatient and emergency contacts since 1995) (79).

The Danish Cancer Registry

All cancer diagnoses recorded for the 1988 - 2004 period were obtained from the Danish Cancer Registry. This registry contains records of all cancer cases diagnosed since 1943, including tumour characteristics and treatment procedures (80).

The Danish Psychiatric Central Registry

We identified all psychiatric diagnoses from 1994 to 2003 from the Danish Psychiatric Central Registry. This Registry contains data on admissions and discharges, diagnoses, and treatment codes for all patients admitted to a psychiatric hospital in Denmark since 1969, including all outpatient contacts since 1995 (81).

The National Prescription Database

Data regarding prescribed anxiolytic and anti-depressant drugs were obtained from the Danish Prescription Database for the 1996 - 2003 period. The Danish Prescription Database contains data on drug type and prescription date for all prescriptions filled in Denmark since 1996.

The Fertility Database, Statistics Denmark

Using the Fertility Database, we retrieved the number of biological daughters and sons born to each Danish woman from 1960 to 2003. The Fertility Database is updated every year with demographic and sociological data for both men and women of childbearing age, and with basic information related to their children (sex, birth weight, age, and cause of death, if relevant) (82).

The Integrated Database for Longitudinal Labour Market Research

Total household income in 2002, level of education, and marital status were retrieved from the Integrated Database for Longitudinal Labour Market Research, which includes comprehensive socio-economic data on the education, employment, and income for the entire Danish population.

Ethical considerations

The study was conducted according to the guidelines of the Biomedical National Ethics Committee System. It was approved by the National Board of Health (J.nr. 0-604-04-20/E/EHG) and the Danish Data Protection Agency (CVR-nr.11-88-37-29).

Statistical analyses

Characteristics of the three study groups were described using medians, ranges and proportions. Prevalence-proportion ratios (PPR) and 95% confidence intervals (CI) were used to explore

differences in socio-demographic and clinical variables between study groups, between respondents and non-respondents, and between participants with complete follow-up and drop-outs (Aims 1 and 2). For the first comparison (respondents vs. non-respondents) we used registry-based data and for the other comparison (participants with complete follow-up vs. drop-outs) we used self-reported data.

Changes in perceived risk and HRQOL within groups and between groups were examined using Student's paired t test and Student's t test, respectively, after testing for the assumption of normality (Aim 4). We used the Wald test to compare differences between study groups in the proportion of women who changed from inaccurate to accurate risk perceptions (Aim 3) and from a cancer-specific stress score above a sub-clinical level to a score at a sub-clinical level (Aim 4). We used logistic regression analysis to estimate odds ratios (OR) and 95% confidence intervals (CI), adjusted for age, to compare HRQOL baseline scores among groups (Aim 1). In addition, logistic regression analysis was used to identify possible predictors for inaccurate risk perception after 12 months of follow up (Aim 3). We included a number of possible predictors that had been suggested in the literature (age, education, cohabitation, cancer-specific distress at baseline, inaccurate risk perception at baseline) and others that had not been examined previously (number of daughters, number of affected first-degree relatives, known mutation in the family, smoking habits, risk expression).

We used multivariate linear regression analysis to compare changes (follow up scores minus baseline scores) in outcome variables (cancer-specific distress, anxiety and depression) among the study groups, adjusted for socio-demographic and clinical variables (Aim 4).

We computed Cronbach´s alpha to assess internal consistency of IES and HADS (83;84). To explore the number of factors in HADS we used an explorative factor analysis (83;84).

All analyses were performed using Stata Statistical Software version 9.0 (College Station, TX: Stata Corporation).

Results

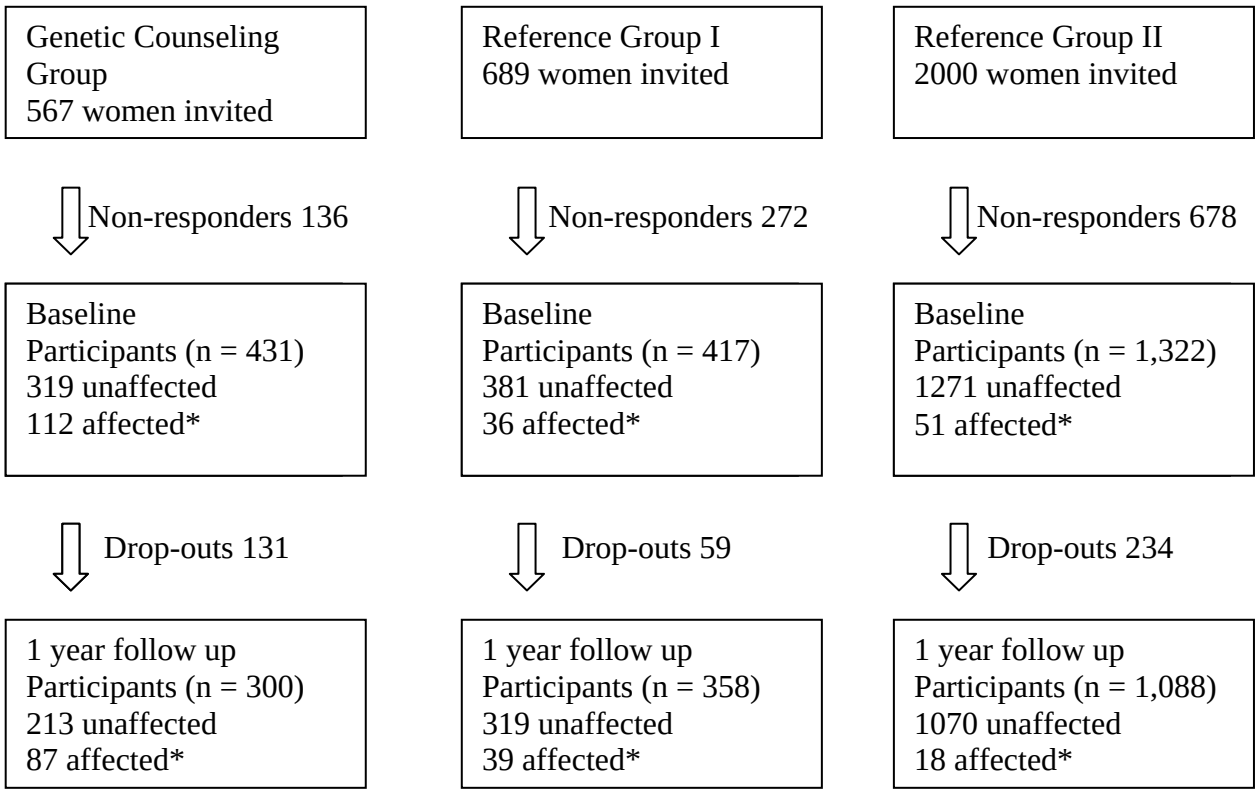
The main study results are summarized below.

Participation

As shown in Figure 2, 431 (76%) of the 567 eligible women in the Genetic Counseling Group entered the study. Of these, 348 women (61%) completed two weeks of follow up, 312 (55%) completed 6 months of follow up, and 300 (53%) remained in the study for the final follow up at 12 months. Of the 689 eligible women in Reference Group I, 417 (61%) entered the study and 358 (52%) completed one year of follow up. Out of the 2000 women invited to participate in Reference Group II, 1,322 (66%) women agreed to take part, and 1,088 (54%) completed one year of follow up.

Baseline characteristics of the entire study population (including respondents and non-respondents) are shown in table 3. All data presented were obtained from nationwide population-based registries.

Figure 2. Flow of the study population



* Affected with breast or ovarian cancer, including women whose cancer status was not reported or inconsistently reported.

Comparison of respondents across the three study groups

Respondents in the Genetic Counseling Group had a lower median age and fewer biological children than respondents in Reference Group I. In addition, fewer women in the Genetic Counseling Group had filled one or more prescriptions for anxiolytics and antidepressants, compared to respondents in Reference Group I. The prevalence of breast cancer was substantially elevated for respondents in the Genetic Counseling Group compared to respondents in both Reference Group I and Reference Group II. We found no other major differences between respondents in the Genetic Counseling Group and those in Reference Group II (Table 3)

Table 3. Characteristics of respondents and non-respondents in the study population.

	Genetic Counseling Gr.[1]			*Reference Gr. I*[1]			*Reference Gr. II*[1]		
	Response (n=431)	*Non-response (n=136)*	*PPR(CI)*[2]	*Response (n=417)*	*Non-response (n=272)*	*PPR (CI)*[2]	*Response (n=1322)*	*Non-response (n=678)*	*PPR (CI)*[2]
Age, median	41	39		56	57		45	49	
Range	18-78	18-76		26-76	25-78		18-75	18-75	
Married / cohabiting, %	73	59	1.23 (1.06;1.44)	69	58	1.20 (1.07;1.36)	71	64	1.10 (1.03;1.18)
Biological offspring, %									
≥ one daughter	53	55	0.98 (0.82;1.17)	63	62	1.03 (0.91;1.16)	53	54	0.99 (0.91;1.08)
≥ one son	53	46	1.17 (0.95;1.43)	62	60	1.03 (0.91;1.17)	55	52	1.05 (0.96;1.15)
Further education, %									
None	34	36	1.03 (0.90;1.19)[7]	33	39	0.95 (0.87; 1.03)[7]	38	53	0.92 (0.88; 0.96)[7]
Short	34	30		40	38		39	31	
Medium	23	22		24	16		18	12	
Long	10	12		4	7		4	4	
Household income, %									
Low	10	20	0.47 (0.30;0.74)[8]	6	10	0.61 (0.36;1.01)[8]	10	18	0.57 (0.46;0.72)[8]
Medium	31	31		42	51		36	42	
High	60	49		52	39		54	40	
Breast cancer diagnoses[4], %	23	13	1.82 (1.13;2.93)	7	3	1.17 (1.05;4.51)	2	2	0.70 (0.36;1.35)
Other breast diagnoses[4], %	3	4	0.82 (0.30;2.26)	2	3	0.58 (0,23;1.48)	1	0	4.17 (0.96:18.07)
Genital cancer diagnoses[4], %	3	4	0.88 (0.32;2.41)	2	1	2.17 (0.60;7.83)	1	0	1.91 (0.54;6.82)
Uterus-related diagnoses[4], %	2	4	0.57 (0.19;1.67)	4	4	1.04 (0.48;2.27)	3	2	1.71 (0.87;3.33)
Co-morbidity[5], %									
Charlson low	92	91	1.01 (0.95;1.07)[7]	88	87	1.01 (0.95;1.07)[7]	94	90	1.04 (1.01;1.07)[7]
Charlson medium	7	9		11	11		6	9	
Charlson high	1	0		1	2		0	1	
Psychiatric diagnoses[4], %	5	7	0.81 (0.38;1.70)	4	11	0.36 (0.20;0.65)	4	8	0.49 (0.34;0.72)
Prescriptions filled[6], %									
Anxiolytics	15	18	0.87 (0.57;1.33)	29	40	0.72 (0.58; 0.88)	17	26	0.66 (0.55;0.79)
Antidepressants	14	15	0.95 (0.59;1.51)	20	27	0.75 (0.57;0.99)	13	18	0.74 (0.60;0.91)

[1]Registry data were not available for 4 women in the Genetic Group, 3 women in Reference Gr. I, and 6 women in Reference Gr. II
[2] Prevalence-proportion ratio, response vs. non-response, 95% confidence interval
[3] Pre-tax household income, year 2002; low ≤ $20,670, medium ≥ $20,671 & ≤ $64,134$, high > $64,134
[4]≥ one diagnosis , [5]Charlson co-morbidity index,[6]≥ one prescription,
[7]none + short vs. medium + long ,[8]low vs. medium + high.

Respondents vs. non-respondents (Aim 2)

Within the three study groups, respondents and non-respondents were similar in terms of age, number of biological children, educational level, and comorbidity. In addition, in the Genetic Counseling Group, history of psychiatric diagnoses, other non-cancer diagnoses, and filled prescriptions for anxiolytics and antidepressants appeared similar for respondents and non-respondents. In all three groups, respondents had a higher likelihood of living with a partner and a higher income compared to non-respondents. Within the two reference groups, a lower proportion of respondents had been diagnosed with psychiatric disease and/or had filled prescriptions, compared to non-respondents. Furthermore, we found a higher prevalence of breast cancer among respondents than among non-respondents in the Genetic Counseling Group and in Reference Group I.

Participants with complete follow-up vs. drop-outs (Aim 2)

We also explored possible differences between unaffected women who completed 12 months of follow up (full participants) and unaffected women who dropped out during the study period (drop-outs) in all three study groups, using self-reported baseline characteristics. We found no substantial differences between full participants and drop-outs in the Genetic Counseling Group and Reference Group I (Appendix, Paper II, Table 1). Full participants in Reference Group II, however, were characterized by a lower proportion of smokers (PPR 0.74, 95%CI: 0.61; 0.89), and a lower proportion with little or no education (PPR 0.87, 95% CI: 0.78; 0.98), compared to drop-outs.

Psychosocial conditions of women awaiting genetic counseling (Aim 1)

We analyzed baseline data on anxiety, depression, and cancer-specific distress separately for affected and unaffected women, based on self-reported cancer status. The number of affected women differs in the self-reported data vs. registry data, due to delay in the availability of registry data.

Anxiety, Depression, and Cancer-specific distress

At baseline, approximately three-fourths of women in all three study groups experienced no anxiety and more than 90% experienced no symptoms of depression.

When we compared the Genetic Counseling Group to the reference groups, we did not find any substantial differences in overall anxiety and depression at baseline. In terms of cancer-specific distress, however, both affected and unaffected women in the Genetic Counseling Group appeared to have somewhat higher scores than the reference groups (Table 3). The largest difference was found between the Genetic Counseling Group and Reference Group II.

Table 4. Cancer-specific distress among women awaiting genetic counseling compared to the women in the Reference Groups

Cancer status[1]	*Cancer-specific distress (IES)*[2]	*Gen. C. Gr.*	*Ref. Gr. 1.*	*Gen. C. Gr. vs. Ref. Gr. I. PPR (CI)*[3]	*Ref. Gr. II*	*Gen. C. Gr. vs. Ref. Gr. II. PPR (CI)*[3]
Un-affected		n = 319	n = 381		n = 1264	
	Sub-clinical	46%	57%		68%	
	Mild	34%	26%	1.25 (1.07;1.40)	22%	1.67 (1.47;1.91)
	Moderate	16%	14%		9%	
	Severe	4%	3%		1%	
Affected		n = 110	n = 31		n = 38	
	Sub-clinical	36%	42%		53%	
	Mild	38%	32%	1.11 (0.80;1.55)	18%	1.36 (0.95;1.96)
	Moderate,	20%	19%		21%	
	Severe	6%	7%		8%	

[1] Self reported data. Women not reporting cancer status were excluded.
[2]Cancer-specific distress score 0-75; sub-clinical = 0-8, mild = 9-25, moderate = 26-43, severe = >44.
[3]Prevalence-proportion ratio, 95% confidence interval, mild + moderate + severe combined.

Internal consistency of the scales

We assessed the internal consistency of IES with Cronbach´s alpha, and found values between 0.90-0.92 in all three study groups. We found similar values for the HADS subscales (Anxiety, Depression), *i.e*. anxiety ranges between 0.84-0.88 and depression ranges between 0.80-0.83. An explorative factor analysis for HADS, with the number of factors defined by eigenvalues ≥1, revealed a two-factor structure in all three study groups, explaining from 50% to 54% of the total variance.

Risk perception among women receiving genetic counseling (Aim 3)

In the analyses of risk perception, we excluded all women who were affected with breast or ovarian cancer at baseline or who developed cancer during the follow-up period. We excluded them because they were at risk both of developing a second primary breast cancer and having a relapse of the first cancer. In addition, the small number of affected women did not allow us to conduct definitive separate analyses for this group.

Level and change in perceived risk

At baseline, women in the Genetic Counseling Group perceived their own risk to be 50% (median value) (Table 5). Two weeks after genetic counseling their perceived risk had decreased to 30% (median value) and remained at this level both after 6 and 12 months of follow up. Perceived risk at baseline was substantially higher among women in the Genetic Counseling Group compared to women in the reference groups (10% median value).

Based on paired analysis, perceived risk decreased 6.6 percentage points (95% CI: 3.0%; 10.2%) on average in the Genetic Counseling Group between baseline and 12 months of follow up. This contrasted with the reference groups, for which perceived risk remained relatively stable. The inter-group analysis of change in perceived risk therefore also showed a statistically significant difference between the Genetic Counseling Group and Reference Group I (-8.2 percentage points, 95% CI:-12.2%; -4.1%) and Reference Group II, (-7.7 percentage points, 95% CI:-11.4%; -4.0%).

Table 5. Perceived absolute lifetime risk (%) of breast cancer

Group	*Baseline*	*12 months Follow up*	*Intra-group changes*[2]	*Inter-group changes*[3]
	Median (25^{th}-75^{th})	Median (25^{th}-75^{th})	Mean (95% CI)	Mean (95% CI) *Gen. C. Gr. vs. Ref. Gr. I.*
Gen. C. Gr. (n=192)[1]	50 (20-50)	30 (18-50)	-6.6 (-3.0;-10.2)	-8.2 (-12.2;-4.1)
Ref. Gr. I. (n=278)[1]	10 (5-25)	10 (5-30)	1.6 (3.6;-0.5)	*Gen. C. Gr. vs. Ref. Gr. II.*
Ref. Gr. II.(n=972)[1]	10 (5-25)	10 (5-30)	1.1 (2.2;0.0)	-7.7 (-11.4;-4.0)

[1]Participants who reported perceived risk both at baseline and at 12-month follow up.
[2]Participants served as their own controls.
[3]Average change in the Genetic Counseling Group vs. average change in the reference groups.

Accuracy of perceived risk

At baseline, 53% of women referred for genetic counseling overestimated their personal risk of developing breast cancer, and 25% perceived their risk accurately (Table 6). Twelve months following counseling, the proportion of women in this group who perceived their risk accurately had increased to 41%. This clearly exceeded the changes observed in Reference Group I (p=0.03) and Reference Group II (p=0.01).

Table 6. Accuracy of perceived lifetime risk of breast cancer

	Time	*Gen. C. Gr. (n=138)*[1]	*Ref. Gr. I. (n=278)*[2]	*Ref. Gr. II. (n=972)*[2]
Underestimated, %	Baseline	22	-	-
	12 months follow-up	18	-	-
Overestimated, %	Baseline	53	29	32
	12 months follow-up	41	34	34
Accurate, %	Baseline	25	71	68
	12 months follow-up	41	66	66

[1]Participants in the Genetic Counseling Group, who reported their perceived risk both at baseline and follow up and for whom objective risks were available.
[2]Participants in Reference Group I and Reference Group II, who reported their perceived risk both at baseline and at 12-month follow up. Underestimates do not apply to the reference groups.

Predictors of inaccurate risk perception 12 months after genetic counseling

Table 7 presents the results of a logistic regression analysis of possible predictors of inaccurate risk perception following genetic counseling.

Factors which appeared associated with inaccurate risk perception included risk communicated only in words, inaccurate risk perception at baseline, presence of a familial mutation, and, to a lesser degree, having one or more daughters or a high level of cancer-specific distress at baseline.

Table 7. Predictors of inaccurate risk perception at 12-month follow up for unaffected women who received genetic counseling.

Predictor variable	*OR (95% CI)*
Age (ref.: >35years)	1.81 (0.72;4.55)
Education: None + short	Ref.
Medium	0.96 (0.38;2.45)
Long	0.93 (0.30;2.90)
≥One first degree relative with cancer (ref.: none)	2.10 (0.70;6.31)
Smoking (ref.: no smoking)	2.22 (0.91;5.39)
Daughters (ref.: no daughters)	2.68 (1.02;7.05)
Married / cohabiting (ref.: single)	1.44 (0.55;3.81)
Cancer-specific distress pre-counseling (ref.: no stress)	1.85 (0.80;4.28)
Inaccurate risk perception pre-counseling (ref.: accurate)	5.07 (2.07;15.79)
Risk expression, words only (ref.: words + numbers)	5.50 (1.88;16.10)
Mutation found in the family: No	Ref.
Yes	4.38 (1.32;14.48)
Don´t know	0.45 (0.14;1.45)

Psychosocial impact of genetic counseling (Aim 4)

Cancer-affected and cancer-unaffected women who are referred for genetic counseling cannot be considered a homogenous group. Affected women presumably opt for genetic counseling for other reasons than do unaffected women, who may seek counseling to avoid development of an initial breast or ovarian cancer. The small number of affected women kept us from examining this group separately. Consequently, we excluded all women who were affected with breast or ovarian cancer at baseline or who developed cancer during the follow-up period

Anxiety and Depression

In the group of women receiving genetic counseling, the prevalence of anxiety (borderline + case level, see Table 8) remained unchanged from baseline to one year of follow up, compared to increases of 4.1% (95% CI:-3.1; 11.3) and 5.9% (95% CI:2.1; 9.6) in Reference Groups I and II, respectively (Table 8).

In all three study groups, the prevalence of depression above non-case level increased equally (5-6 %) between baseline and one year of follow up. Similar results were found when we analyzed changes in anxiety and depression scores separately in a multivariate linear regression analysis, adjusting for age, educational level, number of biological children, number of first-degree relatives with breast or ovarian cancer, and perceived personal risk of breast cancer (data not shown).

Table 8. Anxiety and Depression among unaffected women in the Genetic Counseling Group and in the Reference Groups.

HADS	*Gen. C. Gr. Baseline (n=213)*	*Gen. C. Gr. 12 months (n=213)*	*Ref. Gr. I Baseline (n=319)*	*Ref. Gr. I 12 months (n=319)*	*Ref. Gr. II Baseline (n=1,070)*	*Ref. Gr. II 12 months (n=1,070)*
Anxiety[1]						
Non-case	73%	73%	70%	66%	76%	70%
Borderline	18%	10%	18%	15%	16%	13%
Case	9%	17%	12%	19%	8%	17%
Depression[1]						
Non-case	94%	89%	93%	87%	95%	90%
Borderline	5%	5%	5%	7%	3%	5%
Case	1%	6%	2%	6%	2%	5%

[1]Score 0-21, non-case = 0-7, borderline = 8-10, case = 11-21
Cancer-specific distress

At baseline, 52% of the women referred for genetic counseling experienced some degree of cancer-specific distress. This proportion decreased to 50% after two weeks of follow up, to 41% after 6 months of follow up, and remained at this level after 12 months of follow up. In Reference Groups I and II, 41% and 32%, respectively, experienced some degree of cancer-specific distress at baseline. These proportions were reduced by 6.3% (95% CI:-1.3; 13.8) and 1.6% (95% CI:-2.3; 5.5) at 12 months of follow-up, respectively (Table 9).

The 10.8% (95% CI:1.4; 20.8) decrease in cancer-specific distress observed in the Genetic Counseling Group between baseline and 12 months of follow up exceeded the decrease observed

in both reference groups, although only the comparison with Reference Group II reached statistical significance (p=0.006). A multivariate linear regression analysis of the change in cancer-specific distress score, adjusting for the same possible confounders as described above, confirmed these findings (data not shown).

Table 9. Cancer-specific distress among unaffected women in the Genetic Counseling Group and in the Reference Groups.

IES[1]	*Gen. C. Gr. Baseline (n=213)*	*Gen. C. Gr. 12 months (n=213)*	*Ref. Gr. I Baseline (n=319)*	*Ref. Gr. I 12 months (n=319)*	*Ref. Gr. II Baseline (n=1070)*	*Ref. Gr. II 12 months (n=1070)*
Sub-clinical	48%	59%	59%	65%	68%	70%
Mild	34%	26%	25%	25%	22%	20%
Moderate	14%	12%	13%	8%	9%	8%
Severe	4%	3%	3%	2%	1%	2%

[1]Cancer-specific distress score 0-75, sub-clinical = 0-8, mild = 9-25, moderate = 26-43, severe = 44-75.

Health related quality of life

We found a small increase in the summary score for physical quality of life (PCS) in the Genetic Counseling Group between baseline and 12 months of follow up, in contrast to the reference groups where the PCS decreased (Table 10). In the inter-group analysis of changes in PCS, these opposite patterns resulted in notable differences between the Genetic Counseling Group and Reference Group I (2.4 points, 95% CI: 1.2; 3.6) and between the Genetic Counseling Group and Reference Group II (1.2 points, 95% CI: 0.2; 2.2). Further, we observed an increase in the summary score for mental quality of life (MCS) in both the Genetic Counseling Group and in Reference Group I, whereas a decrease was seen in Reference Group II. The changes observed in MCS were small in all three groups and the inter-group analysis showed no statistically significant differences.

Table 10. Changes in quality of life for unaffected women in the Genetic Counseling Group compared to women in the Reference Groups.

	PCS[1]		*MCS*[2]	
Group	*Inter-group change*[3] *Mean (CI)*	*Intra- group change Mean (CI)*	*Inter-group change*[3] *Mean (CI)*	*Intra- group change Mean (CI)*
		Genetic vs. Ref. Gr. I.		*Genetic vs. Ref. Gr. I.*
Gen. C. Gr. (n=197)	0.9 (-0.1;1.8)	2.4 (1.2;3.6)	0.6 (-0.8;2.0)	-0.6 (-2.3;1.2)
Ref. Gr. I (n=287)	-1.5 (-2.3;-0.7)	*Genetic vs. Ref. Gr. II.*	1.2 (0.2;2.2)	*Genetic vs. Ref. Gr. II.*
Ref. Gr. II (n=996)	-0.3 (-0.7;0.1)	1.2 (0.2;2.2)	-0.6 (-1.1;-0.1)	1.2 (-0.3;2.7)

[1]Physical Component Summary
[2]Mental Component Summary
[3]Difference in scores between baseline and after 12 months of follow up

Methodological considerations

Interpretation of the findings presented in this thesis is dependent on a critical evaluation of the factors with impact on the validity of our risk estimates. The optimal design for examining the psychosocial impact of genetic counseling is doubtlessly a randomized controlled trial (RCT). Because this was not feasible for ethical and practical reasons, we undertook a follow-up study of women referred for genetic counseling and two reference groups of women.

Selection problems

In this study, the existence of possible selection biases related to sampling procedures, non-respondents, and drop outs during follow up must be considered. These issues may affect both the external and internal validity of the study findings.

Sampling

The decision whether to undergo genetic counseling is complex, usually requiring time and serious reflection. When a decision has finally been made, most women experience a waiting period before the first counseling session. By the time of the session, most women are likely to have reached a peak level of anxiety, depression, cancer-specific distress, and perceived risk. These concerns may spontaneously decrease after counseling, erroneously indicating a positive effect of genetic counseling. Thus, to estimate the true impact of genetic counseling, it is necessary to compare findings among women receiving counseling with those from appropriate reference groups.

We included women above the age of 18 years in both the Genetic Counseling Group and the reference groups. We were not able to use family history of breast and ovarian cancer as an inclusion criterion for the reference groups.

Reference Group I, composed of women undergoing mammography, was chosen in order to observe possible changes in psychosocial conditions among women receiving an alternative approach to breast cancer prevention. We expected women referred for mammography to be concerned about developing breast cancer, a situation similar to that experienced by the women in the Genetic Counseling Group. Reference group II was drawn from the general population to provide information about the natural variation in psychosocial conditions of women over a one-year period.

The Genetic Counseling Group was recruited from four clinical departments offering genetic counseling that serve a well-defined geographical region of Denmark (75% of the total Danish population). Denmark's tax-financed health care allows women to be referred free-of-charge for genetic counseling and mammography, independent of age, health, socioeconomic situation, or place of residence. Reference Group I consisted of women referred for mammography at two clinics serving two well-defined geographical regions of Denmark. Some women may receive mammograms outside these clinics, but this group is most likely very small, allowing us to consider Reference Group I to be a population-based sample. Reference Group II was a random sample of the Danish female population drawn from the Danish Central Population Registry. Thus our study may be characterized as a population-based multi-centre study in that sense, all women referred for genetic counseling or mammography in a given geographic area within a given time period were included (85). In this context we have to consider if the study sample was biased by non-respondents or drop-outs.

Non-respondents

Our response rates of 76% (Genetic Counseling Group), 61% (Reference Group I), and 66% (Reference Group II) have the potential to introduce selection bias. Denmark's nationwide public registries provided us with an exceptional opportunity to compare information regarding respondents and non-respondents within each study group. There appeared to be no major differences, except for the higher proportion of respondents living with a partner and higher household incomes among respondents. As well, in the Genetic Counseling Group and in Reference Group I, breast cancer was more prevalent among respondents than non-respondents. Only 13 women had missing registry data out of the 3,256 women invited to participate in the study. Thus our non-response analyses may be assumed to be very accurate, indicating that willingness to participate in our study did not introduce major bias.

Drop-outs

In the Genetic Counseling Group, 70% of women who entered the study remained active participants during the 12 months of follow up. In Reference Group I 86% and in Reference Group II 82% remained in the study for 12 months. Despite these rather high retention rates, drop-outs may still introduce selection bias. To address this issue, we compared self-reported baseline characteristics of full participants and those of drop-outs, and found no important differences. This led us to conclude that selection bias due to drop-outs was not a major problem in our study.

Despite limitations in the sampling procedure, non-response rates, and drop out rates, the study population was likely to be a representative sample.

Information problems

In this study, shortcomings in data collection instruments and data collection procedures may have produced information problems. In order to cause bias, however, information problems must be distributed differentially among the study groups. Because data were collected prospectively and systematically using standardized questionnaires and procedures for data collection were identical in the three study groups, possibilities for information bias were reduced.

Validity and reliability of measurement scales

It is not possible to observe and directly measure the psychosocial health outcomes that we undertook to assess. Instead, we used three different psychometric scales (IES, HADS, SF-36) as surrogate measures. It is important to consider the validity and the reliability of these scales when used in our study population. We did not test any of the scales against a gold standard which would be the optimal way of examining the validity. However, the three scales are well-established and have been found to work well in a number of other populations (86-88). We found no systematic patterns of non-response to single items or scales, and the internal consistency of IES and HADS, as assessed by Cronbach´s alpha, was high (>0,80) in all three study groups. An explorative factor analysis of HADS showed, as expected, a two-factor structure in all three study groups, explaining 50% or more of total variance. Based on these results, we have no reason to believe that our findings were weakened by low validity and reliability in the assessment of psychosocial outcomes. Furthermore, the scales seemed to work similarly in the three study groups. This suggests that any misclassification would have been non-differential, reducing the magnitude of differences found among the study groups.

Ceiling and floor effects

Ceiling and floor effects occur when a high proportion of respondents grade themselves as having the maximum or minimum score (83). When the impact of an intervention is assessed by comparing baseline scores with follow-up scores, ceiling and floor effects may introduce bias. Our baseline data for the eight SF-36 subscales showed some ceiling effects, equal to that of Danish norm data (75). To circumvent this problem, we used the two summary scores PCS (physical quality of life) and MCS (mental quality of life), which are not susceptible to ceiling effects. We were not able to eliminate a possible floor effect in the HADS and IES scales, and our findings should be interpreted with this in mind.

Cut-off points

We calculated total sum-scores for the IES and the two HADS subscales and then transformed these scores into categorical outcomes using cut-off points. While these cut-off points have been suggested in the literature (72;73;83;88-90), they have not been examined in depth. We performed the transformations for several reasons: first, single scores were not normally distributed; second, we wished to enhance the clinical relevance of our findings. Because the cut-off points may be questionable, we cannot entirely exclude the possibility of misclassification.

Pilot testing

Genetic assistants and a physician from one of the genetics departments participated in the development of the patient and the physician questionnaires. Patient questionnaires were pre-tested on women outside the target groups and physician questionnaires were pre-tested in three

clinical departments. Both questionnaires were revised before the start of a one-month period of pilot testing our study instruments and procedures.

All major scales and questions were adopted from previous studies carried out in Denmark and no translations were required. Extensive pilot-testing and use of well-established scales ensured the feasibility of the study and increased the validity of the instruments used.

Confounding

The study design, with two reference groups and no randomization, raises the question whether the observed effects of genetic counseling on perceived risk, risk accuracy and cancer-specific distress are influenced by confounding. In general, little is known about the causal pathway and the factors that might confound the relationship between genetic counseling and psychosocial outcomes.

We analyzed changes in the psychosocial outcome scores and perceived risk with paired analyses. This approach is preferred because each woman serves as her own control and variation between individuals is eliminated. Thus, our intra-group findings on changes over time could not be affected by confounding. However, inter-group comparisons do have this potential.

Primary concerns in regard to confounding were differences between the Genetic Counseling Group and the reference groups in terms of age and personal and family history of breast and ovarian cancer. In order to eliminate possible confounding due to personal cancer history, we performed separate analyses for affected and unaffected women in Aim 1. Similarly, to handle potential confounding, we excluded affected women in the analyses related to Aims 3 and 4.

To present clinically relevant information, we focused on absolute estimates instead of relative estimates derived from multivariate analyses. Nevertheless, we used multivariate linear regression analyses as a method of handling potential confounding in relation to Aim 4. Our findings regarding changes in anxiety, depression, and cancer-specific distress remained materially unchanged when a number of possible confounders were taken into account in our model, suggesting that confounding was not an important issue in our study. However, unaccounted confounding may have occurred, as we were able to adjust only for first-degree family members with breast or ovarian cancer and not for the full family history. In addition, we can not exclude the possibility that other unknown or unmeasured confounders, such as coping strategy or locus of control, influenced our findings.

Statistical precision

When possible, we used 95% confidence intervals to indicate the precision of our estimates. Despite the rather large size of our study compared to existing studies, it should be noted that some subgroups were small and the estimates were imprecise, as shown by the widths of the confidence intervals. Caution is needed particularly in interpreting findings for affected women (Aim 1) and findings on the accuracy of risk perception and predictors of accurate risk perception among unaffected women (Aim 3).

Conclusion

The follow-up design with appropriate reference groups was an efficient and feasible approach for evaluating the impact of genetic counseling on psychosocial outcomes and risk perceptions. Our study's internal validity was enhanced by use of valid, well-established psychometric scales and identical procedures for data collection in the three study groups. However, the use of less

established cut-off points and floor effects of HADS and IES are possible shortcomings. While confounding does not seem to be a major problem, unknown and unmeasured confounding may have affected our results. The study populations appear to be population-based samples, which improves the external validity of our findings - at least for the population of Danish women receiving genetic counseling.

Study findings in relation to the existing literature

The following discussion is organized by the four aims of this thesis.

Psychosocial conditions of women awaiting genetic counseling (Aim 1)

We were not able to identify any studies that specifically focused on the psychosocial conditions of women awaiting genetic counseling. However, a number of studies have touched on this topic, assessing psychological conditions of women in the waiting room or at an unspecified and variable point in time before the first counseling session. With few exceptions these studies report only mean values for psychosocial health scores (37;51-53;63;68;69;71).

Our study showed that 26% of unaffected women experienced some degree of anxiety and 7% experienced some degree of depression one to four weeks before their initial genetic counseling session. On the basis of mailed questionnaires, Bish *et al*. (64) found higher proportions of anxiety (41%) and depression (11%) prior to genetic counseling. However, the exact time frame was not provided, and the proportions were reported for a sample that included both affected and unaffected women.

We found that 54% of unaffected women and 64% of affected women awaiting genetic counseling experienced some degree of cancer-specific distress. Of these, only 4% and 6%, respectively, experienced a severe level of cancer-specific distress. In contrast, Carlsson *et al*. (91), assessing cancer-specific distress two to four weeks before genetic counseling, found that 20% experienced such distress at a severe level. Unlike our study, Carlsson's sample included affected and unaffected and referred and self-referred men and women at risk of breast or colorectal cancer. As well, a lower cut-off point was used to define a severe level of cancer-

specific distress. In another study of 302 women attending their first genetic counseling session, cancer-specific distress was measured in the waiting room (68). The results indicated high levels of distress, but only mean values were reported, making comparisons with our results difficult.

To our knowledge, HRQOL data for individuals awaiting genetic counseling for breast or ovarian cancer have been reported previously only by Carlsson *et al.* (91). Despite the difference in study populations, our findings accord with Carlsson's, indicating that unaffected women awaiting genetic counseling had the same HRQAL as women from the general population and better HRQAL scores than women awaiting mammography.

Respondents at baseline and participants with complete follow-up (Aim 2)

Our response rates of 76% (Genetic Counseling Group), 61% (Reference Group I), and 66% (Reference Group II) at baseline are comparable to those of a number of other studies (51;53;63;69;71). We examined differences between respondents and non-respondents for a large number of characteristics and found only a few differences (higher prevalence of breast cancer, greater likelihood of living with a partner, and higher household income among respondents). We have not been able identify any studies that have compared respondents and non-respondents to a similar degree.

Based on the number of women invited to participate in our study, proportions with complete follow-up were 61% in the Genetic Counseling Group, 55% in Reference Group I, and 53% in Reference Group II. While some studies reported similar completion rates (51-53;63;68;69), a number of others noted lower rates or failed to report them (30;32;64-67;70). Consistent with the

literature, we found no substantial differences between participants with complete follow-up and drop-outs (30;64;69).

Impact of genetic counseling on perceived risk and accuracy of risk perception (Aim 3)

Our findings indicate that genetic counseling can lead to a considerable decrease in perceived risk, maintained even a year after counseling. Our findings accord with those of a RCT (63) and a follow-up study (56), which reported even larger reductions in perceived risk after counseling. However, these two studies did not include paired analyses of the study participants, and the follow-up was restricted to one week. Our findings contrast with the results of a RCT conducted by Brain *et al*., (51) which did not find a decrease in perceived risk associated with genetic counseling compared to surgical counseling. As well, the initial decrease in perceived risk found in both the intervention and the control group diminished within the following 12 months.

A decrease in perceived risk is only of interest if it results in more accurate risk perception among women receiving counseling. Our findings indicate that genetic counseling is associated both with a decrease in perceived risk and with an improvement in accuracy of risk perception. Sixteen percent of women in the Genetic Counseling Group improved their accuracy following counseling. Still, after 12 months of follow up, 41% of women in this group continued to overestimate their perceived risk, compared to 34% of women in the reference groups. Our findings are consistent with those of the RCT conducted by Lerman *et al*., (32) in which the proportion of women who perceived their risk accurately increased by 8% after counseling, while two-thirds continued to overestimate their risk. We used the same method of measuring accuracy and the same definition of the level for overestimating perceived risk as Leman *et al*., strengthening the comparison. Other studies have found that 11-55% of women perceive their

risk accurately post-counseling, but methods of assessing accuracy and defining levels of accurate perception have varied widely (37;65;67;68). Unlike Lobb *et al*., (58) we found that women who received risk information only in words were more likely to perceive their risk inaccurately after counseling than women who received the information in a combination of words and numbers. As the women were not randomly assigned to one of the risk communication strategies, we cannot entirely exclude the possibility of confounding, *i.e*., if numerical information was provided mainly to women who were able to comprehend numbers. Consistent with the findings of Huiart *et al*., (57) we also found that inaccurate risk perception at baseline was strongly associated with inaccurate risk perception 12 months later.

Impact of genetic counseling on psychosocial outcomes (Aim 4)

The prevalence of anxiety in women receiving genetic counseling remained unchanged from baseline to 12 months of follow up. During this period the prevalence of anxiety increased only slightly in the reference groups. These findings indicate that genetic counseling does not reduce generalized anxiety in the long term, in accordance with findings from the RCT conducted by Brain *et al.* (51) and from three uncontrolled studies with 12 months of follow up (37;64;68).

The prevalence of depression increased equally among women in our three study groups. This suggests that the increase observed in the Genetic Counseling Group is unlikely to be caused by genetic counseling itself. Instead, the exercise of completing the questionnaires may have drawn the women's attention to their psychological well being. Our findings support those of a number of uncontrolled prospective studies (37;64;92), which indicated that genetic counseling for hereditary breast or ovarian cancer is not associated with an increase in depressive symptoms.

Women in both the Genetic Counseling Group and in Reference Group I received an intervention with the potential to reduce cancer-specific distress. As expected, the prevalence of cancer-specific distress decreased in both groups, although the decrease reached statistical significance only in the Genetic Counseling Group. The proportion of women in Reference Group II who experienced no cancer distress increased only slightly after 12 months of follow up, consistent with their lack of exposure to an intervention. The increase in the proportion of women who did not experience a clinically relevant level of cancer distress was substantially larger in the Genetic Counseling Group than in Reference Group II.

Previous studies on the long-term impact of genetic counseling on cancer-specific distress have shown conflicting results. A randomized trial of multidisciplinary genetic counseling compared to specialized surgical counseling (51) and two prospective studies (37;64) found a reduction in cancer-specific distress, though the reduction reported in the trial was small. In contrast, a meta-analysis based on three RCTs, including the RCT noted above, found no association between genetic counseling and cancer-specific distress (47). The reduction in cancer-specific distress we observed in the Genetic Counseling Group compared to the reference groups supports the hypothesis that genetic counseling reduces cancer-specific distress over the long term in a population-based sample of women.

To our knowledge, our study is the first to address the impact of genetic counseling on HRQOL as assessed by SF-36. Our findings suggest that counseling is not likely to have a major impact on HRQOL. While we found small changes in the two summary scores for HRQOL and a statistically significant improvement in the PCS for the Genetic Counseling Group compared to the reference groups, none of these changes are close to the five-point level considered clinically meaningful (75).

Main conclusions

The following are the main conclusions of this thesis, organized according to its aims.

1. Women who have decided to undergo genetic counseling, and who are awaiting their first counseling session, experience more cancer-specific distress, but do not suffer from more anxiety or depression, than women scheduled for mammography or women from the general population.

2. The findings showed no major differences among respondents and non-respondents. There also appeared to be no important differences between participants with complete follow-up and drop-outs. Despite limitations introduced by the sampling procedure, non-response rates, and drop-out rates, the study population was likely to be a population-based sample.

3. The findings indicated that genetic counseling leads to a decrease in perceived risk and to a considerable improvement in accuracy of risk perception, maintained even a year after counseling. In addition, women who received risk information only in words were more likely to perceive their risk inaccurately after counseling than women who received the information in a combination of words and numbers.

4. Genetic counseling leads to a substantial decrease in cancer-specific distress among women with a family history of breast and ovarian cancer. Furthermore, genetic counseling does not appear to have an adverse impact on general anxiety, symptoms of depression, or health-related quality of life.

Perspectives

Overall the findings of this thesis are reassuring as regards psychosocial outcomes and risk perceptions following genetic counseling for HBOC. However, the findings also highlight some facets which need improvement in order to optimize the effect of genetic counseling.

We found that anticipation of genetic counseling for HBOC can be burdensome for both affected and unaffected women. Therefore it is important to address cancer-specific distress at referral and at the first counseling session. Although we found a substantial decease in cancer-specific distress 12 months after counseling, 41% of clients were still affected by it. There is a need for future studies to examine whether it is possible to further alleviate cancer-specific distress.

As 41% of the women still overestimated their perceived risk after counseling, counseling practices need to be strengthened, particularly regarding risk communication. Our findings suggest that professionals providing genetic counseling should use a multi-faceted communication strategy that expresses risk both in words and numbers. Extra attention should be given to women who indicate an inaccurate risk perception during their first genetic counseling session and to women from families where genetic testing already has been initiated.

In this thesis I have focused on anxiety, depression, cancer-specific distress, and risk perception as outcomes of genetic counseling. A number of other outcomes may also be relevant, such as compliance with recommended surveillance and the impact of genetic counseling on other health behaviors known to be risk factors for breast cancer. As well, I have addressed only women who received genetic counseling for HBOC. Genetic counseling is also offered in regard to other cancers, and in the future may become available for diseases such as diabetes, Alzheimer's, and

some heart conditions. Psychosocial consequences and risk perceptions may differ in these contexts, due to disease-specific genetic features, prognoses, and prevention options. As our findings cannot be applied directly to such diseases, new studies will be required. When RCTs are not feasible, our prospective study design using reference groups could be used as a model.

This thesis focuses only on the psychosocial impact of genetic counseling. Its clinical impact also needs to be addressed. The population-based registries, which we used only to examine selection issues, also provide an opportunity to follow our study population in the future. One strategy may be to examine the impact of genetic counseling for our study population beyond 12 months of follow-up, looking at clinical outcomes such as incidence of breast and ovarian cancer, mastectomy and compliance to recommended surveillance.

Summary

Much research has focused on the psychosocial impact of genetic counseling for HBOC risk, however results have been inconsistent. Moreover, the studies have been prone to limitations due to highly selected samples of women, a lack of control groups and none were population-based.

The aims of this thesis were: 1) to compare the psychosocial conditions of women awaiting genetic counseling for HBOC with those of women awaiting mammography and those of a random sample of women from the general population; 2) to examine possible clinical and socioeconomic differences between study respondents and non-respondents and between participants with complete follow-up and drop-outs; 3) to assess the impact of genetic counseling over time on perceived personal lifetime risk of breast cancer and accuracy of risk perception and to identify possible predictors of inaccurate risk perception; 4) to assess the impact of genetic counseling over time on anxiety, depression, cancer-specific distress and HRQOL.

We conducted a population-based follow-up study of 431 women who received genetic counseling for hereditary breast and ovarian cancer, 417 women who underwent mammography (Reference Group I), and a random sample of 1315 women from the general population (Reference Group II). We obtained self-reported data using self-administered, standardized, mailed questionnaires and registry data from six nationwide registries.

Women, awaiting their first counseling session, experienced more cancer-specific distress, but did not suffer from more anxiety or depression than women in the reference groups.

The study showed no substantial differences between respondents and non-respondents and between participants with complete follow-up and drop-outs.

Women who received genetic counseling decreased their perceived risk by an average of 6.6 percentage points (95% CI: 3.0%; 10.2%) between baseline and 12 months of follow-up. In contrast, perceived risk remained relatively stable in the reference groups. The proportion of women who accurately perceived their risk increased by 16% in the group receiving genetic counseling, compared to a reduction of 5% (p=0.03) and 2% (p=0.01) in Reference Groups I and II, respectively.

Furthermore, we found the following predictors for inaccurate risk perception: 1) Risk communicated only in words; 2) inaccurate risk perception at baseline and 3) presence of a familial mutation.

52% of the women referred for genetic counseling experienced cancer-specific distress at a clinical level at baseline and this proportion decreased to 41% after 12 months of follow up. This 10.8% (95% CI:1.4; 20.8) decrease observed in the Genetic Counseling Group exceeded the decrease observed in Reference Group I, 6.3% (95% CI:-1.3;13.8) and Reference Group II, 1.6% (95% CI:-2.3;5.5). In addition, genetic counseling did not lead to an increase in general anxiety and depression or a decrease in HRQOL among women in the Genetic Counseling Group compared to the women in the reference groups.

This population-based study indicates that genetic counseling can help Danish women with a family history of breast and ovarian cancer to alleviate their cancer-specific distress and improve their risk perception.

Dansk resumé

Der har i forskningen været megen fokus på de psykosociale konsekvenser af genetisk rådgivning for arvelig bryst- og æggestokkræft (HBOC), men tidligere undersøgelser af dette felt har vist inkonsistente resultater. Der har ikke tidligere været foretaget danske undersøgelser af dette område, og de udenlandske undersøgelser bærer præg af en række metodiske svagheder som f.eks. manglende kontrolgrupper og højt selekterede studiepopulationer.

Formålet med denne PhD afhandling var at undersøge de psykosociale konsekvenser af genetisk rådgivning for HBOC, ved: 1) at sammenligne den psykosociale helbredstilstand for kvinder, der afventer genetisk rådgivning med kvinder, der afventer mammografi og med kvinder fra en tilfældigt udtrukket stikprøve fra baggrundspopulationen 2) at kortlægge eventuelle helbredsmæssige og sociodemografiske forskelle mellem deltagere og ikke deltagere i studiet samt mellem kvinder, der gennemfører hele studiet og kvinder, der udgår i løbet af studiet 3) at vurdere genetisk rådgivnings indflydelse over tid på oplevet risiko for brystkræft samt identificere prædiktorer for ukorrekt risiko opfattelse 4) at vurdere konsekvenserne over tid af genetisk rådgivning i forhold til angst, depression og cancerbekymring samt helbredsrelateret livskvalitet.

Undersøgelsen blev gennemført som et populationsbaseret follow-up studie af 431 kvinder, der var henvist til genetisk rådgivning for HBOC, 417 kvinder, der fik foretaget mammografi (reference gruppe I), samt 1315 kvinder udtrukket fra CPR- registeret (reference gruppe II). Data blev indsamlet ved brug af selvudfyldte standardiserede spørgeskemaer samt data fra 6 nationale registre.

Kvinder, der afventede deres første genetiske rådgivning, oplevede større grad af cancer bekymring, men ikke større grad af angst eller depression sammenlignet med kvinder i referencegrupperne.

Vi fandt ingen afgørende helbredsmæssige eller sociodemografiske forskelle mellem kvinder, der deltog i studiet, og kvinder, der ikke deltog i studiet. Ligeledes fandt vi ingen afgørende forskelle mellem kvinder, der gennemførte hele studiet, og kvinder, der faldt fra undervejs.

Kvinder, der gennemgik genetisk rådgivning, reducerede i gennemsnit deres opfattelse af risiko for brystkræft med 6,6 procent point (95% CI: 3,0%; 10,2%) mellem baseline og 12 måneders opfølgning. Kvinderne i de 2 reference grupper ændrede derimod stort set ikke deres opfattelse af risiko for brystkræft indenfor den samme periode. Blandt de kvinder, der modtog genetisk rådgivning, fik 16% flere en korrekt opfattelse af deres risiko i forhold til den objektivt vurderede risiko. Til sammenligning faldt den tilsvarende andel i henholdsvis i reference gruppe I med 5% (p=0,03) og i reference gruppe II med 2% (p=0,01). Vi fandt desuden følgende prædiktorer for ”ukorrekt” risikoopfattelse: 1) risiko formidlet i udelukkede i ord ved rådgivning, 2)”ukorrekt” risikoopfattelse før rådgivning samt 3)viden om en identificeret cancer-disponerende mutation i familien.

Før den første genetiske rådgivning var 52% af de henviste kvinderne påvirkede af cancerbekymring, hvilket 12 måneder efter rådgivningen var reduceret til 41%. Forekomsten af cancer specifik bekymring faldt også hos kvinder i referencegrupperne, men reduktionen (10,8%, 95% CI:1,4; 20,8) blandt kvinder, der gennemgik genetisk rådgivning, oversteg reduktionen

både i reference gruppe I (6,3%, 95% CI:-1,3;13,8) og i reference gruppe II (1.6%, 95% CI:-2,3;5,5).

Genetisk rådgivning medførte ingen stigning i generel angst og depression eller et fald i helbredsrelateret livskvalitet sammenlignet med reference grupperne.

Denne populationsbaserede undersøgelse viser, at genetisk rådgivning for HBOC kan mindske cancer specifik stress og forbedre kvindernes risikoopfattelse til at blive mere i overensstemmelse med den objektivt vurderede risiko.

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Appendices – Papers (I-III) and Questionnaires (IV)