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Risk-reducing mastectomy in *BRCA1/2* mutation carriers: Factors influencing uptake and timing

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ABSTRACT

Introduction: Strategies in case of high risk of breast cancer in *BRCA1/2* mutation carriers are either intensive breast cancer screening or risk-reducing mastectomy (RRM). Both options have a high physical and psychosexual impact. The aim of this study is to investigate who chooses when to undergo RRM.
Methods: BRCA1/2 mutation carriers have been prospectively registered at the family cancer clinic between 1994 and 2011. Analyses were performed to assess the relation between characteristics of the *BRCA1/2* mutation carriers and an earlier decision for RRM.
Results: A cumulative percentage of 35.6% of all women chose to undergo RRM within the first five years after disclosure of DNA test results. Women needed less time to choose for RRM measured from the first visit, if they were younger than 50 years of age (hazard ratio (HR) = 2.67, 95% confidence interval (CI) = 1.30–5.48) or had a mother who had had breast cancer (HR = 1.51 95% CI = 1.04–2.18). Also, women needed less time to choose for RRM in case of a previous breast cancer (HR = 2.25, 95% CI = 1.55–3.27). After a previous unilateral therapeutic mastectomy as a treatment for breast cancer, women needed less time to choose for RRM of the contralateral breast (HR = 2.69, 95% CI = 1.29–5.62) compared to women who had had breast-conserving therapy.
Conclusion: BRCA1/2 mutation carriers aged under 50, having a mother with breast cancer, who had previous unilateral breast cancer and previous unilateral therapeutic mastectomy chose more often and earlier for RRM.

1. Introduction

Women with a *BRCA1* or *BRCA2* mutation have a significantly higher lifetime risk of developing breast cancer and are diagnosed at a younger age compared to the general population [1–4]. The lifetime risk at the age of 70 years for breast cancer was found to be 57–65% for *BRCA1* and 45–49% for *BRCA2* mutation carriers [1,2].

BRCA1/2 mutation carriers have to make major decisions regarding the medical management of their increased breast cancer risk. To reduce the risk of death due to breast cancer, women can choose for risk-reducing mastectomy (RRM) or they can opt for intensive breast cancer screening aiming at early detection [5,6]. When performed at a young age, before the cancer risk is rising, RRM is associated with an actual breast cancer risk reduction of 90–95% [7]. However, RRM has been associated with a negative impact on body image [8].

A review including 43 published articles identified three main types of factors that influence high-risk women's decisions about risk-reducing strategies: (a) medical and physical factors, (b) psychological factors and (c) social context factors. How these factors operate in women's lives over time remained unknown [9].

The purpose of this study was to identify baseline characteristics of *BRCA1/2* carriers that opt for RRM early on following the disclosure of DNA test results. Identifying which characteristics influence the (early) decision for RRM can indicate important topics to be discussed during counseling.

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2. Methods

2.1. Patients

Women with an increased risk of carrying a *BRCA1/2* mutation are referred to the clinical genetic department of the University Medical Center Groningen for genetic risk assessment. Those that have a high cancer risk are followed-up at the Family Cancer Clinic (FCC) with a multidisciplinary team including clinical geneticists, surgical oncologists, gynecological oncologists, plastic surgeons, social workers, nurse practitioners and a psychologist [10]. When visiting the FCC women were asked to give informed consent for entering their data into a prospectively maintained password protected FCC database. Protection of the patients' identity was guaranteed by assigning study-specific, unique patient numbers. According to Dutch law no further Institutional Review Board approval was needed for this study.

2.2. Data collection

Women were included in this study if they were proven *BRCA1/2* mutation carriers and had visited the FCC between April 1994 and November 2011 at least once. As according to Dutch guidelines RRM should preferably be offered to women from the age of 25 years, only women ≥25 years of age were included in this study. We considered the disclosure date of the *BRCA1/2* mutation to the patient as the first moment of contact and the last visit was considered to be the most recent visit to the FCC or the most recent visit to the FCC before RRM. The date of first contact and the date of the last visit were extracted from the (digital) patient files and used to calculate follow-up times. For this study, characteristics concerning the patient as well as her family were collected. Patient characteristics concerned: age, mutation status and medical history. The medical history concerned previous breast and/or ovarian cancer, related treatment and risk reducing strategies. Patient characteristics were retrieved from the prospectively maintained FCC database. Family characteristics concerned: number and age of children and breast and/or ovarian cancer within the family, both at the time of the first visit to the FCC. Family characteristics were derived from non-electronic clinical genetics records.

2.3. Statistical analysis

Survival analysis was chosen to demonstrate the course of decision making over time, since this method adjusts for variable follow-up time. Univariate and multivariate survival analyses were performed over the total group of women (women opting for RMM as well as opting for intensive breast cancer screening), in order to calculate the cumulative percentage of women undergoing RRM over time, hazard ratios (HR) and the 95% confidence intervals (CI) of the baseline characteristics where the timing of the decision to undergo RRM was considered dependent.

The disclosure date of the *BRCA1/2* mutation to the patient was considered as the first moment of contact. The last moment of contact was considered to be the most recent visit or the most recent visit to the FCC before RRM. All tests were performed in SPSS Statistics 20 package and all *p*-values were two-tailed and considered significant if $p \leq 0.05$.

3. Results

3.1. Description of the population

From April 1994 until November 2011, 508 *BRCA1/2* carriers ≥25 years of age had visited the FCC (Fig. 1). Women were excluded if a RRM was performed before the first visit to the FCC ($n = 10$), if they had had bilateral breast cancer or disseminated disease ($n = 38$) and if their clinical files were not available ($n = 21$) or were incomplete ($n = 30$). Two women were excluded due to mild mental retardation and inability to make their own decisions ($n = 2$). The number of women included in the analysis was 407. Patient characteristics are given in Table 1.

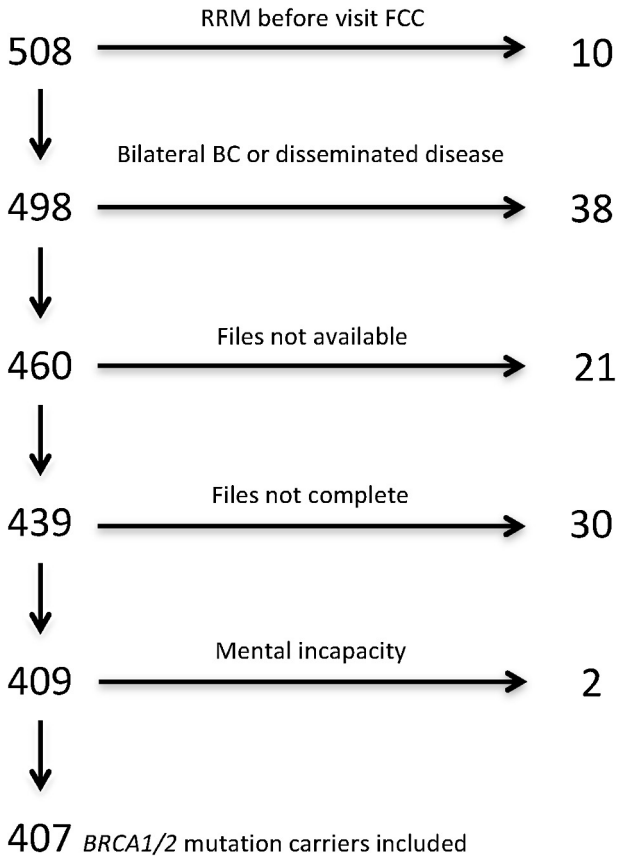

Fig. 1. Population flowchart.
All *BRCA1/2* mutation carriers ≥25 years old entered in the FCC database at November 2011 ($n = 508$) from April 1994 to November 2011).

3.2. Determinants of the timing of the decision to undergo RRM

Within the first five years after disclosure of DNA test results a cumulative percentage 35.6% women chose to undergo RRM (Table 1). In Table 2, it is shown that in the multivariate survival analysis, women younger than 50 years needed less time after counseling to decide for RRM than women >50 years of age (HR = 2.87 95% CI = 1.40–5.92, $p = 0.0042$). Furthermore women who had a mother with breast cancer needed less time to decide for RRM (HR = 1.51 95% CI = 1.04–2.18, $p = 0.031$). Women previously diagnosed with unilateral breast cancer decided earlier for RRM of the contralateral breast than women without a breast cancer history (HR = 2.54, 95% CI = 1.74–3.70, $p < 0.001$). Of the women with previous breast cancer, those who underwent therapeutic mastectomy as a therapy for a unilateral breast cancer needed less time to choose for RRM of the contralateral breast (HR = 2.69, 95% CI = 1.29–5.62, $p = 0.008$) compared to women who had breast conserving therapy (Table 3).

4. Discussion

Women needed less time to choose for RRM if they were younger than 50 years of age (HR = 2.87 95% CI = 1.40–5.92), had a mother