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Very high uptake of risk-reducing salpingo-oophorectomy in *BRCA1/2* mutation carriers: A single-center experience

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HIGHLIGHTS

- Deciding not to undergo RRSO is highly exceptional in *BRCA1/2* mutation carriers counseled at our Family Cancer Clinic
- Almost all *BRCA1/2* mutation carriers undergo RRSO at the currently recommended age, if applicable
- Minimizing the short and long term health consequences of premature surgical menopause is the next challenge to science

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ABSTRACT

Objective. Risk-reducing salpingo-oophorectomy (RRSO) is the only effective surgical strategy to reduce the increased risk of epithelial ovarian cancer in *BRCA1/2* mutation carriers. Given the long-term health consequences of premature surgical menopause, we need insight in uptake and timing of RRSO to guide us in improving healthcare.

Methods. A single-center retrospective cohort study of *BRCA1/2* mutation carriers diagnosed and counseled at the multidisciplinary Family Cancer Clinic of the Radboud university medical center in Nijmegen, The Netherlands, between 1999 and 2014. Descriptive statistics were used to analyze uptake and timing of RRSO.

Results. Data of 580 *BRCA1/2* were analyzed. The uptake of RRSO among mutation carriers who are currently above the upper limit of the recommended age for RRSO, is 98.5% and 97.5% for *BRCA1* and *BRCA2* mutation carriers, respectively. The vast majority undergoes RRSO ≤40 (*BRCA1*) or ≤45 (*BRCA2*) years of age, provided that mutation status is known by that age: 90.8% and 97.3% of *BRCA1* and *BRCA2* mutation carriers, respectively.

Conclusions. The uptake of RRSO among *BRCA1/2* mutation carriers who were counseled at our Family Cancer Clinic is extremely high. High uptake might be largely attributed to the directive and uniform way of counseling by professionals at our Family Cancer Clinic. Given the fact that RRSO is often undergone at premenopausal age in our population, future research should focus on minimizing long-term health consequences of premature surgical menopause either by optimization of hormone replacement therapy or by investigating alternative strategies to RRSO.

1. Introduction

The cumulative risk of developing epithelial ovarian cancer (EOC) at age 70 in women harboring a germline *BRCA1* or *BRCA2* mutation is about 39% (95% confidence interval 34–44%) and 16% (95% confidence interval 12–20%), respectively [1]. Most women with EOC present with advanced-stage disease leading to a poor five-year survival. Screening for ovarian cancer using ultrasound and serum levels of tumor marker Ca125 has been proven ineffective in *BRCA1/2* mutation carriers [2]. Risk-reducing salpingo-oophorectomy (RRSO) is the only effective surgical intervention in the prevention of EOC, reducing the risk by at least 80% [3,4].

EOC risk increases at the end of the fourth decade in *BRCA1* mutation carriers, and from the beginning of the sixth decade in *BRCA2* mutation carriers [5]. Most international guidelines recommend RRSO to both *BRCA1* and *BRCA2* mutation carriers between age 35 and 40 if childbearing is completed [6,7]. The Dutch guideline, however, slightly differs from these international guidelines. Initially, it was recommended to

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undergo RRSO before the age of 40 or five years prior to the youngest age at which a relative was diagnosed with EOC to all *BRCA* mutation carriers. Since 2010, distinction is made in recommended age for RRSO between *BRCA1* and *BRCA2* in Dutch daily practice: between 35 and 40 years for *BRCA1* and between 40 and 45 years for *BRCA2* [8]. This distinction is based on the risk of EOC increasing at older age in *BRCA2* mutation carriers.

Uptake of RRSO varies from 17% to 89% worldwide [9]. Research on uptake of risk-reducing surgery in *BRCA1/2* mutation carriers has mainly been concentrated on demographic and psychosocial predictors [10,11]. Main predictors for uptake of RRSO are family history of EOC, personal history of breast cancer, and age older than 40 years [12]. However, a turning point with respect to age has been observed as well, i.e. women older than 60 years were less inclined to undergo RRSO [13,14].

The objective of this study was to investigate the uptake of RRSO among *BRCA1/2* mutation carriers in our tertiary hospital with a Family Cancer Clinic, and whether RRSO is usually performed within the recommended age range.

2. Methods

2.1. Study population

A retrospective single-center study was performed among all women diagnosed with a germline *BRCA1/2* mutation at the laboratory of Human Genetics of the Radboud university medical center in Nijmegen, The Netherlands, between January 1999 and December 2012. Only *BRCA1/2* mutation carriers who were subsequently counseled at the Family Cancer Clinic of the Radboud university medical center were included. The integrated care for *BRCA1/2* mutation carriers at the Family Cancer Clinic is organized within the context of a multidisciplinary team including all professionals involved in prevention and management of either breast or ovarian cancer: clinical geneticists, gynecologic oncologists, medical oncologists, (plastic) surgeons, pathologists, radiologists, and social workers. Mutation carriers and their families are discussed within this multidisciplinary team during a weekly session in order to coordinate care and to avoid mixed messages to these patients.

According to the Dutch law, no Institutional Board Review approval was needed for this retrospective study of medical records in which participants' anonymity was guaranteed by assigning study-specific, unique patient numbers.

2.2. Setting

For the 17 million inhabitants of The Netherlands, genetic counseling and germline *BRCA1/2* mutation testing is concentrated in eight university medical centers and one specialized cancer institute. The laboratory that identifies the first *BRCA1/2* mutation within a family will test all following family members, independent of the center in which counseling takes place. After diagnosis of a germline *BRCA1/2* mutation, women are generally referred for counseling on breast and ovarian cancer risk management by a specialist in breast surveillance and a gynecologic oncologist at the Family Cancer Clinic of one of the nine above-mentioned centers.

During counseling at the Radboud university medical center, *BRCA1* and *BRCA2* mutation carriers are told that estimated lifetime risks of EOC are 30–60% and 5–20%, respectively. Furthermore, it was emphasized that RRSO is the only evidence-based approach to reduce this elevated risk of EOC, and recommended ages for RRSO are mentioned. Until 2010, recommended ages for RRSO were equal for both *BRCA1* and *BRCA2* mutation carriers: between 35 and 40 years old, or five years before the age of onset of EOC in a relative if that relative was diagnosed with EOC before the recommended age of RRSO. In 2010, however, the recommended age for RRSO for *BRCA2* mutation carriers was increased to 40–45 years. Use of hormone replacement therapy is recommended from RRSO until the age of 48–50, if not contra-indicated because of a breast cancer history. Additionally, breast cancer risk reduction by half when RRSO was performed before onset of natural menopause was communicated to all women in this cohort, based on the available evidence at that time. Lastly, *BRCA1/2* mutation carriers in our hospital were offered annual ovarian cancer screening consisting of transvaginal ultrasounds and Ca125 testing until September 2011. Since then, patients have been counseled about the ineffectiveness of ovarian cancer screening in terms of prognosis and false positive findings, and ovarian screening have not routinely been offered anymore. An overview of key elements addressed in each counseling session by a gynecologic oncologist at our Family Cancer Clinic can be found in Box 1.

2.3. Data collection

Information on demographics, clinical characteristics and risk-reducing surgeries was obtained from medical records, including age at *BRCA1/2* mutation diagnosis, mutation status, parity, family history of breast and ovarian cancer, personal history of breast and ovarian cancer, date of RRSO, and time from *BRCA* diagnosis to RRSO (time to surgery). Consultation of medical records took place in April 2014. Whenever medical records did not mention RRSO, the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) was consulted to find out whether and when RRSO was possibly undergone in another Dutch hospital.

2.4. Analyses

All statistical analyses were performed using IBM SPSS Statistics version 22. Descriptive statistics were used to summarize patient characteristics and to present uptake and age at RRSO. RRSO within the recommended age is up to and including age 40 for *BRCA1*, and up to and including age 45 for *BRCA2* mutation carriers. We determined the median time from diagnosis of the *BRCA1/2* mutation to RRSO in three groups classified by age at mutation diagnosis: before, at or after the recommended age for RRSO. Differences in time to surgery between women with and without a personal history of breast cancer at the time of mutation diagnosis were tested for statistical significance using the Mann-Whitney test for non-parametrically distributed data.

3. Results

3.1. Population

A germline *BRCA1/2* mutation was diagnosed in 1038 women between January 1999 and December 2012. Of these, 609 visited the Family Cancer Clinic at least once with first visits between April 1999 and February 2014. Twelve women were excluded because they had already

Box 1
Key points emphasized by gynecologic oncologist during counseling sessions.

- Cumulative risk of EOC 30–60% (*BRCA1*) and 5–20% (*BRCA2*)
- Poor survival of EOC
- Ovarian screening is ineffective (since September 2011)
- RRSO is the only evidence-based approach to reduce EOC risk
- Recommended age for RRSO: age 35–40 (and age 40–45 for *BRCA2* since 2010)
- Breast cancer risk reduced by half if performed before natural menopause (until 2015)
- No need for prophylactic hysterectomy
- Use of hormone replacement therapy is recommended until the age of 48–50 if not contra-indicated (e.g. breast cancer history)