Rapid genetic counseling and testing in newly diagnosed breast cancer

Surgical and psychosocial implications

Wevers, M.R.
Introduction

Breast cancer affects approximately one in eight women in Western countries. More than 14,000 women in the Netherlands receive a breast cancer diagnosis every year [1]. Approximately 5% of these women have a recognizable hereditary cancer syndrome with a proven genetic cause of the disease [2,3].

Hereditary breast cancer: BRCA1 and BRCA2

Germline mutations in several genes lead to a breast cancer predisposition. Of these, germline mutations in the BRCA1 and BRCA2 genes cause the hereditary breast and ovarian cancer (HBOC) syndrome and are responsible for the majority of cases of hereditary breast cancer. Women who are a carrier of a mutation in one of these genes have a risk of 27-88% to develop breast cancer at some point during their lives, and a risk of 6-59% to develop cancer of the ovaries or Fallopian tubes (for practical reasons often taken together as ovarian cancer) [4-7]. The risk of ovarian cancer is higher for BRCA1 mutation carriers than for BRCA2 mutation carriers, i.e. on average 35-45% versus 10-20% [8].

Hereditary breast cancer can also be part of other rarer cancer syndromes, such as Li Fraumeni syndrome, caused by mutations in the TP53 gene or PTEN Hamartoma Tumor Syndrome, caused by mutations in the PTEN gene. Furthermore, the 1100delC germline mutation in the CHEK2 gene is considered a risk factor that increases the risk of developing breast cancer [9].

Relevance of knowing a breast cancer patient's genetic status

Discriminating between women whose breast cancer is hereditary and those whose breast cancer cannot be proven to be hereditary is important for both the affected woman and her relatives.

For the affected woman, it is important to know that, if her breast cancer is hereditary in nature, she has an increased risk of developing another primary tumor. In addition to the treatment proposed for her breast cancer, such a woman may also be eligible for more intensive screening and/or risk-reducing surgery. For the relatives of a woman with hereditary breast cancer, it is important to know that they may also be predisposed to this cancer syndrome, and that genetic counseling and (predictive) DNA testing are available to them, if so desired.

Risk of second primary tumors in women with BRCA1/2 associated breast cancer

Besides being at risk of developing ovarian cancer, women with hereditary breast cancer are at risk of developing a second primary breast tumor that will typically affect the contra-
lateral breast. Depending on the gene involved and the age at first breast cancer diagnosis, this risk can be as high as 20-55% [4,5,10,11]. Women who are young (i.e., younger than 30 years of age) when first diagnosed with breast cancer and who have a BRCA1 gene mutation are confronted with the highest risks.

Preventive options for women with hereditary breast cancer

The prognosis of women with breast cancer is determined primarily by the characteristics and treatment of their first breast tumor [12]. In case of a favorable prognosis, women with hereditary breast cancer have two options for dealing with their increased risk of developing another breast cancer: regular surveillance by mammography and MRI according to (inter) national guidelines, or proceeding to risk-reducing surgery of the remaining breast tissue. The goal of surveillance is to detect a second tumor at an early, treatable stage. However, it does not prevent a second primary tumor. Risk-reducing surgery does prevent almost all second primary breast tumors. For women who were primarily treated with breast conserving surgery, secondary risk-reducing breast surgery implies that both the remaining part of the affected breast and the unaffected breast are removed, i.e. a bilateral mastectomy. For women who were primarily treated with a mastectomy, the contralateral breast is removed, which is called a contralateral risk-reducing mastectomy (RRCM). An RRCM leads to a reduction in the risk of developing another primary breast tumor of up to about 95% [12,13]. Furthermore, there is increasing evidence that an RRCM also reduces breast cancer-specific and overall mortality [12-15]. Therefore, the possibility of an RRCM should always be discussed with women with hereditary breast cancer who have a favorable prognosis. Additionally, a bilateral risk-reducing salpingo-oophorectomy is recommended for these women because of their increased risk of developing ovarian cancer.

Psychological status of breast cancer patients

It is well known that newly diagnosed breast cancer patients often experience increased levels of psychological distress, especially feelings of anxiety and/or depression [16-19]. Although in most patients distress levels diminish in the first year after surgery, about two years after diagnosis upwards of 20% of (early stage) breast cancer patients still experience levels of distress [20]. Little is known about the additional psychological burden, if any, of being diagnosed with a hereditary form of breast cancer.

Genetic counseling and testing in breast cancer

Genetic counseling and testing (GCT) are offered to breast cancer patients when a hereditary cause is suspected. Generally, during the first genetic counseling session with a clinical geneticist or genetic counselor it will, amongst other things, be determined whether the patient is eligible for DNA testing of the BRCA1 and BRCA2 genes and if so, DNA testing is offered.

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In general, women are eligible for GCT when they are diagnosed with breast cancer and: 1) are relatively young, i.e. below 35-40 years; 2) have multiple relatives affected with breast cancer, at least one of whom was below the age of 50 at diagnosis; 3) have a family member who was diagnosed with ovarian cancer or prostate cancer below the age of 60; 4) have a male relative diagnosed with breast cancer, and/or 5) have bilateral breast cancer with at least the first diagnosis below the age of 50 years. The criteria used in the study described in this thesis are in accordance with the Dutch guidelines that were valid in 2008; they are described in detail in Chapter 4. Since then, the criteria have been modified when new knowledge has become available [21-24].

Timing of genetic counseling and testing in breast cancer patients

Traditionally, GCT was offered after primary breast cancer treatment, since DNA test results were available only after 3-6 months [25]. Also, GCT shortly after diagnosis has been considered by many to be too burdensome for some if not most patients [26]. Decisions on (secondary) risk-reducing surgery in women affected with breast cancer have therefore typically been made after their primary treatment. However in the last few years, in the Netherlands as in other countries, the time required to report DNA test results has been significantly reduced to about 4 weeks. This has provided the possibility of performing genetic counseling and DNA testing in the time period between breast cancer diagnosis and primary surgery. In the remainder of this thesis, this rapid procedure will be called rapid genetic counseling and testing (RGCT).

Rapid genetic counseling and testing – treatment decisions

The main advantage of RGCT in breast cancer patients is that, when DNA-test results are available before primary surgery, these results can be incorporated into treatment decisions. A woman with breast cancer who learns that she carries a *BRCA1/2* gene mutation, and therefore has an increased risk of developing another primary breast tumor, may opt for a direct bilateral mastectomy (BLM). In BLM, breast cancer surgery and risk-reducing surgery are performed during the same session, thereby potentially avoiding an extra surgery.

Several studies have been published on the impact of GCT relatively shortly after diagnosis on surgical treatment decisions. These studies suggest that women with breast cancer who undergo GCT before definitive surgery and who learn that they carry a *BRCA1/2* gene mutation opt for a BLM or RRCM more often than those without a mutation [27-33]. However, the conclusions drawn from these studies must be interpreted with caution because women often were self-referred, and the timing of GCT was not always comparable.

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Another advantage of RGCT is that breast cancer patients may avoid radiotherapy by not choosing a breast conserving surgery. This is favorable when considering breast reconstruction, since radiotherapy causes damage to the skin and underlying tissue. Radiotherapy to a reconstructed breast after skin-saving mastectomy leads to more late complications and a worse cosmetic outcome [34,35].

The main potential disadvantage of RGCT in breast cancer patients is that waiting for DNA test results may, in some cases, require some, usually short delay in undergoing surgery. At least some breast cancer patients may not wish to delay their breast surgery, even in the interest of obtaining information relevant to treatment choice. However, the rate of uptake (and decline) of RGCT in this population has not been established empirically.

Rapid genetic counseling and testing – psychological well-being
Theoretically, RGCT could have two opposing psychological effects. On the one hand, women may experience less distress because they do not have to postpone receiving an answer to their questions on the possible hereditary nature of their breast cancer until after completing primary therapy. On the other hand, undergoing RGCT may increase distress levels if it is experienced as being too much of a burden in an already very stressful time shortly after diagnosis of breast cancer [26]. In general, there is no evidence that genetic counseling and testing for cancer causes adverse psychological reactions [36,37]. However, the studies performed to date have been in the context of traditional GCT, not RGCT.

Attitudes of patients and caregivers towards RGCT
Finally, there is a paucity of information on the attitudes of breast surgeons and patients towards RGCT. In a study by Schlich-Bakker et al. in women who were offered genetic counseling and testing between primary surgery and radiotherapy, the majority agreed with this timing, and some even preferred to have been offered genetic counseling and testing at diagnosis or before primary surgery [38]. Most women previously diagnosed with breast cancer who participated in an Australian pilot study had a positive attitude towards RGCT [39], and reported that they would want to be informed about the (possibility of) RGCT at or around their diagnosis [40]. About half of these women actually had RGCT before participating in the study. In a study by Douma et al., Australian professionals reported concerns about some practical issues, for example who should refer women for RGCT [41]. To the best of our knowledge, the possibility of RGCT is being discussed more frequently on online patient forums, and (hereditary) breast cancer patient associations in the Netherlands agree RGCT could be considered.
Aim and outline of this thesis

The main body of this thesis describes the design and results of a prospective, randomized clinical trial named the “TIME-trial” (Timing in Mammacarcinoom Erfelijkheidsonderzoek-trial). In addition, retrospective data on uptake of risk-reducing surgery in women with hereditary breast cancer, and retrospective data on the impact of RGCT are presented.

Aims of the Timing in Mammacarcinoom Erfelijkheidsonderzoek-trial

The overall aim of the TIME-trial was to assess the behavioral and psychosocial impact of offering RGCT to women newly diagnosed with breast cancer.

More specifically, our aims were to assess the impact of offering RGCT as compared to usual care on:
1. The choice of primary surgery, and specifically on the uptake of direct bilateral mastectomy;
2. Levels of cancer-related distress, cancer worries and perceived cancer risk;
3. Body image, sexuality and health-related quality of life;
4. Satisfaction with treatment decisions.

TIME-trial design

We performed a multicenter, randomized clinical trial in women with newly diagnosed breast cancer who had at least a 10% chance of carrying a BRCA1/2 gene mutation. They were recruited as soon as possible after diagnosis from one of 12 participating hospitals in the Netherlands: the Netherlands Cancer Institute in Amsterdam, University Medical Center Utrecht, St. Antonius Hospital in Nieuwegein, Diakonessen Hospital in Utrecht, Meander Medical Center in Amersfoort, Gelre Hospitals in Apeldoorn, Kennemer Gasthuis in Haarlem, St. Lucas Andreas Hospital in Amsterdam, Onze Lieve Vrouwe Gasthuis in Amsterdam, Rivierenland Hospital in Tiel, Tergooi Hospitals in Blaricum/Hilversum, and Zuwe Hofpoort Hospital in Woerden.

After providing informed consent and completing the baseline questionnaire, participants were allocated to an intervention group who was offered RGCT, or a control group who was offered usual care. Both study groups completed two follow-up questionnaires, at 6 and 12 month after diagnosis. Data on sociodemographics, treatment choice, psychological distress, cancer worries, health-related quality of life, perceived cancer risk, and (if applicable) experiences with RGCT were extracted from the medical records and/or self-reported questionnaires. Additionally, surgeons and specialized breast cancer nurses from the 12 participating hospitals were asked to complete a questionnaire on their experiences with

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and attitudes towards RGCT before and after the recruitment period. Furthermore, a subgroup of patients was interviewed after completing the last questionnaire about their experiences with RGCT.

Outline of this thesis

Chapter 2 presents retrospective data on the uptake and timing of risk-reducing breast surgery in Dutch breast cancer patients who carry a BRCA1/2 gene mutation between 1995 and 2009. In Chapter 3, results are reported from a retrospective pilot study on the impact of RGCT. Chapter 4 describes in detail the design of the TIME-trial. Chapter 5 reports on the impact of RGCT on primary surgical treatment, and Chapter 6 reports on its psychosocial impact. In Chapter 7 the attitudes and experiences of both patients and breast cancer surgeons/nurses towards RGCT are described. Chapter 8 reports on the psychological well-being of newly diagnosed breast cancer patients with and without knowing to be at high-risk of having hereditary breast cancer. Finally, in Chapter 9 the main findings are summarized and discussed, and implications for clinical practice are suggested.

Relevance

The studies reported in this thesis provide more evidence-based knowledge on the potential benefits and disadvantages of offering RGCT to newly diagnosed breast cancer patients who are at risk of having hereditary breast cancer.

Thoroughly investigating the impact of offering RGCT may be especially important because we all know that procedures and treatments that are technically possible, will often be offered anyway. In the case of RGCT, it is very likely that this will increasingly be the case for two reasons. First, results of genetic testing of breast cancer predisposition genes will probably be available even sooner in the near future due to further improving techniques and logistics. Second, genetic status will be increasingly used not only to inform the choice of primary surgery, but also the choice of adjuvant chemotherapy.

It is our hope that the results from this study will contribute meaningfully to our understanding of the impact of RGCT on treatment choice and on the psychological well-being of women at heightened risk of having an hereditary form of cancer. Such understanding will increase the likelihood that the introduction of RGCT in routine breast cancer care will be done in a thoughtful manner, and that women will have both optimal clinical and psychosocial services at their disposal.

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CHAPTER 1

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