

A Dedicated Follow-Up Clinic for *BRCA* Mutation Carriers

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ABSTRACT: Women who carry the *BRCA* gene mutation have an up to 80% chance of developing cancer, primarily of breast and ovarian origin. Confirmation of carrier status is described by many women as an overwhelming, life-changing event. Healthy individuals harboring a *BRCA* mutation constitute a high risk population with unique needs, often overlooked by health authorities. As such, we felt the need to create a specialized service dedicated specifically to this high risk population. The clinic staff comprises an experienced multidisciplinary team of health professionals who can support the medical and emotional needs of this population. Since its inception in 2001 the clinic has served 318 women. Their mean age is 46 years. With a median follow-up of 46 months, 21 women have developed malignancies, including 17 breast cancers, 1 ovarian cancer and 3 additional cancers. All but one of the patients above the age of 40 underwent bilateral salpingo-oophorectomy (BSO). The median and mean ages at BSO were 46.5 and 48 years, respectively (range 33–68). However, only 28.3% underwent bilateral preventive mastectomy. A multidisciplinary clinic for *BRCA* mutation carriers provides a “home” for this unique population with unmet needs. The high rate of BSO in women before natural menopause indicates that both the medical community and this population are aware of international guidelines supporting this procedure. We believe that a dedicated clinic with a multidisciplinary team is likely to contribute to the health, quality of life and survival of *BRCA* carriers.

IMAJ 2016; 18: 549–552

KEY WORDS: bilateral salpingo-oophorectomy (BSO), *BRCA* carriers, prophylactic mastectomy

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New technologies that enable efficient genomic sequencing at relatively low cost have been implemented in the last decade. This has enriched our knowledge with respect to gene mutations and their role in disease development. Among the mutations involved in malignant tumor development, those within the *BRCA* genes have become the focus of intensive

research. This special interest is driven by the high incidence of breast and ovarian cancer in female mutation carriers. Women who carry the gene mutation have an up to 80% lifetime chance of developing cancer, primarily of breast and ovarian origin [1,2]. As a result of this statistic, several expert panels have established strict surveillance guidelines for these women. There is a growing body of evidence that adherence to guidelines and recommendations saves lives [3-10].

Approximately 2% of the Ashkenazi Jewish Israeli population carry the *BRCA* gene mutation [2]. Since the 1990s, when the linkage between mutations in the tumor suppressor genes *BRCA1* and *BRCA2* and early-onset breast cancer was identified, great efforts have been made to increase public awareness in an attempt to encourage identification of women at high risk. As a consequence, general practice physicians (GPs), breast cancer surgeons, medical oncologists, gynecologic oncologists and other physicians routinely refer women considered to be at high risk to genetic counseling.

Women with a family history of multiple malignancies, especially breast and ovarian carcinoma, are offered genetic counseling. In some cases, the trigger for such testing is the identification of a mutation carrier within the family, which results in subsequent testing of additional family members. Once the genetic institute identifies a woman as a carrier, she is invited to meet with a genetic counselor who elaborates the significance of the result; namely, the risk of developing various malignancies, the potential preventive treatment options available, and recommended follow-up algorithms. The genetic counselor informs the individual if the test result is positive. While the acknowledgment of mutation carrier status has significant implications for the individual involved, contact with the genetic counselor is not maintained once this information has been imparted. The woman is instructed to inform her GP of the results and encouraged to start rigorous follow-up according to international guidelines.

Confirmation of carrier status is described by many women as overwhelming and, indeed, constitutes a life-changing event. Very soon, the woman realizes that she needs to develop coping strategies as well as a personalized prevention and follow-up plan that suit her personal situation and health care philosophy

[11-20]. Although individualized, the plan should incorporate several important issues:

- Consideration of preventive, risk-reducing surgery of the breasts and ovaries
- Optimal timing of preventive surgery with respect to disease prevention, as well as physiological, psychological and fertility-related considerations
- Appropriate contraception and hormone replacement therapy (HRT) alternatives
- Active chemoprevention options
- Clinical trial participation.

In our experience, healthy individuals harboring a *BRCA* mutation constitute a high risk population with unique needs often overlooked by health authorities. As such, we created a specialized service aimed specifically at this high risk population. It comprises a highly experienced multidisciplinary team of health professionals who can support the medical and emotional needs of these women. Our intention was to offer women the information and guidance necessary to allow them to develop the most appropriate individualized treatment plan. The Institutional Review Board of Rabin Medical Center approved this report.

A dedicated multidisciplinary clinic for *BRCA* mutation carriers provides a “home” for a unique population with unmet needs

THE CLINIC CONCEPT

The clinic is held at the Cancer Center in the afternoon to accommodate otherwise healthy active women. All the women had been identified as mutation carriers prior to admission to the clinic. With the exception of two patients, none had a personal history of malignancy. A multidisciplinary team of professionals work at the clinic, including medical oncologists, breast surgeons, gynecologists, plastic surgeons and psycho-oncologists. The woman first meets with a gynecologist and then with the medical oncologist or breast surgeon, or whoever the patient prefers; for example, a woman interested in prophylactic mastectomy will want to discuss it with the surgeon. Special or challenging cases are discussed at meetings of the multidisciplinary Breast Tumor Board.

Biannual clinic visits are recommended. These include follow-up breast examination, gynecological examination including vaginal ultrasound, and CA-125 blood test. In addition to the physical examination, the women are updated with relevant new information and offered psychosocial support. Psychological support is often required and is encouraged in order to optimize general coping strategies, or at specific junctions to assist in decision making. Additional psychosocial support is provided beyond routine clinic visits when needed.

IMAGING

Each woman undergoes an annual mammogram, ultrasound, and breast magnetic resonance imaging (MRI). Routine imag-

ing is scheduled by the patient at a convenient location of her choice. The three tests are scheduled several months apart. The clinic coordinator arranges urgent tests, including image-guided biopsies.

After each clinic visit, the coordinator updates the patient status in an Excel data file, noting changes regarding prevention strategies or the occurrence of malignancy. If malignancy is diagnosed, the patient is offered continued treatment and follow-up at the Cancer Institute.

CLINICAL OUTCOMES

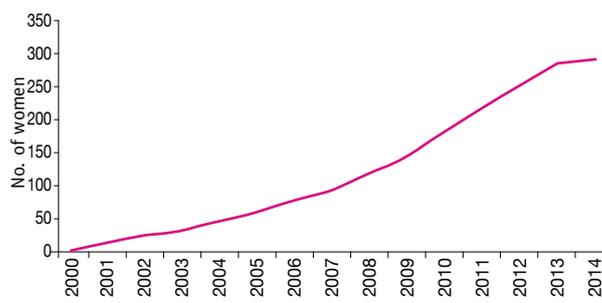
Since its inception in 2001, the clinic has served 318 women [Figure 1]. Twenty-six opted not to be tested for the mutation. All are relatives of a *BRCA* mutation carrier who is being followed in the clinic. These 26 patients were not included in the current report.

The patients' mean age was 46 years (median 43.6) when these data were reported. The median follow-up was 46 months. A total of 168 women were followed for more than 5 years. During this follow-up period, 21 women (21/292, 7.2%) developed

malignancies, including 17 breast cancers, 1 ovarian cancer and 3 additional cancers (Hodgkin's lymphoma, oropharynx carcinoma, cervical carcinoma). The mean age of the women who were diagnosed with breast cancer was 44.7 years. Among these 17 patients, 16 were diagnosed with stage 1 disease. Twelve patients (70.6%) were diagnosed with the aid of MRI, 3 (17.6%) with mammography, and in 1 (5.9%) ultrasound was the first diagnostic test. One woman reported a palpable mass between visits. Two patients were diagnosed at their first clinic visit. All the tumors were invasive. Three women who developed malignancy died, one from ovarian cancer. The cause of death for the other two is not known.

All but one of the patients above the age of 40 underwent BSO. The median and mean age for the BSO procedure was 46.5 and 48 years, respectively (range 33–68). One woman who underwent prophylactic BSO was diagnosed with stage I ovarian cancer. Twenty-eight patients started HRT after BSO; the median use was 2 months only (range 1–39 months).

Figure 1. Number of women joining the clinic since its opening



Only 20.2% (59 patients) underwent bilateral preventive mastectomy. The mean and median age was 40 and 41.2 years, respectively (range 25–67) [Table 1].

DISCUSSION

A dedicated multidisciplinary clinic for *BRCA* mutation carriers provides a “home” for a unique population with unmet needs. Assessing the needs of these women and evaluating the clinic’s performance are essential as we attempt to optimize their care. Caring for a healthy, yet high risk population presents new and different challenges for oncologists, and innovative approaches are required. The number of women joining the clinic indicates the need for a holistic support service for these women.

Since most of these women have not developed malignancy, it is more challenging to evaluate the benefit of the clinic to the participating women. Based on the results presented here, we believe that the following two parameters are indicators of the clinic’s benefit to date:

- The high rate of BSO in women before reaching natural menopause reflects the awareness of international guidelines in this population and in the clinic. This rate is higher than in most other reported registries. The reported uptake of BSO in the literature varies from 8 to 75% [21-26]. It should be noted that the mean age of BSO was 48 years (median 46.5), while the mean age of joining the clinic was 39.9 years. We need to investigate further how to shorten the time interval between joining the clinic and BSO.
- In our cohort the rates of breast and ovarian cancer development are low. The low incidence of malignancy reported to date is probably attributable to the relatively short median follow-up period (4 years). Alternatively, the high rate of BSO may contribute to the low rate of breast and ovarian cancers.

The dedicated *BRCA* clinic provides appropriate, accessible and convenient services. Active surveillance of this population exposes women to up-to-date information on health care and research. It also enables much needed research opportunities via accurate recording of the highly heterogenous clinical phenotypes among carriers, as well as implementation of both investigational and proven prevention strategies.

Various health care disciplines are struggling regarding how to provide the best surveillance and intervention programs for *BRCA* carriers [27-29]. Yet, objective measures are needed to compare the different models of follow-up (e.g., the model described versus a family physician-based model with appropriate referrals to existing services). We did not find similar reports in the PubMed search engine regarding this type of comprehensive service.

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Table 1. Risk reduction surgeries categorized by age

Age	No. of women in the <i>BRCA</i> clinic	BSO*	Bilateral** preventive mastectomy	BSO+ prophylactic preventive mastectomy
≤ 40	119	1 (0.84%)**	10 (8.4%)**	0 (0%)**
40 +	173	151 (87.3%)**	28 (16.2%)**	21 (12.1%)**
Total	292	152 (52%)	38 (13%)	21 (7.2%)

26 patients who had not been checked for *BRCA* mutation were excluded from the report
 *The only preventive surgery
 **Percentages relate to the total number in the age subgroup

To the best of our knowledge, three additional clinics in Israel aim to provide comparable services. Two were recently opened – Hadassah University Medical Center in Jerusalem, and Sheba Medical Center in Tel Hashomer. The clinic at Shaare Zedek Medical Center was established earlier. In contrast to our clinic, some of the centers schedule the breast imaging tests and the visit to the clinic on the same day. The clinic at the Davidoff Cancer Center has the longest follow-up.

The growing needs of this high risk population will require that health authorities evaluate the cost-effectiveness of this service compared to other options. We believe that a dedicated clinic with a multidisciplinary team is likely to contribute to the health, quality of life and survival of *BRCA* carriers.

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