Current Breast Cancer Reports (2024) 16:98–105
https://doi.org/10.1007/s12609-024-00528-3

REVIEW

Breast Cancer in the Ashkenazi Jewish Population

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Accepted: 15 January 2024 / Published online: 16 February 2024

Abstract

Purpose of Review Ashkenazi Jewish people have an elevated risk for breast cancer, driven largely by genetic pathogenic variants in the BRCA1/2 genes. In this review, we explore breast cancer within this population, focusing on both medical and cultural perspectives.

Recent Findings BRCA1/2 carriers have a lifetime breast cancer risk approaching 70%. Furthermore, carriers experience early age of cancer onset, greater likelihood for contralateral breast cancer, increased risk of triple-negative histology, more advanced stage of disease, and overall worse prognosis. It is critical to consider the complex interplay of religion, culture, and cancer for all patients. This is especially true for Ashkenazi Jewish individuals, where community values and customs can directly impact treatment decisions.

Summary Ashkenazi Jewish individuals have an elevated risk for aggressive breast cancers that develop at an early age. Provider awareness of the distinctive clinical and cultural implications of breast cancer for this population is critical to provide optimal patient care.

Keywords Breast cancer · Ashkenazi Jewish · BRCA1/2 mutations

Introduction

The American Cancer Society estimates that in the USA in 2023, there will be 300,590 new cases of invasive breast cancer and 43,700 breast cancer deaths [1]. Approximately, one in eight women (12%) will develop breast cancer; however, for women with pathogenic variants (also referred to as mutations) in the BRCA1/2 genes, this risk can exceed 70% [2]. In the general population, approximately 1 in 400 people carry a BRCA1/2 pathogenic variant; however, among Ashkenazi Jewish individuals, this risk is approximately 1 in 40 [3, 4]. Women with BRCA1/2 pathogenic variants have a significantly elevated lifetime risk for additional malignancies including ovarian cancer, fallopian tube cancer, primary peritoneal cancer, and pancreatic cancer [5]. The purpose of this review is to describe breast cancer within the Ashkenazi Jewish population and to review both cultural and religious factors that might influence cancer management and the uptake of genetic testing and cancer screening in this cohort.

Ashkenazi Jewish Founder Mutations

In Ashkenazi Jewish people, there are three predominant founder mutations in the BRCA1/2 genes (185delAG and 5382insC in BRCA1 and 6174delT in BRCA2) which account for 20% of breast cancers and 40% of ovarian cancers in this population [6, 7]. However, there are also other founder mutations among Ashkenazi Jewish people that confer an elevated risk for cancer, and multigene

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panel testing has resulted in increased identification of these pathogenic variants. CHEK2, another gene linked to breast cancer, has two Ashkenazi Jewish founder mutations: CHEK2 c.1283C > T (p.Ser428Phe) pathogenic variants are found in 2.4–5% of Ashkenazi Jewish people, and CHEK2 c.470 T > C (p.Ile157Thr) in 0.46–1.2%. Together, these two CHEK2 founder mutations occur in approximately 3–4% of Ashkenazi Jewish people. The APC founder mutation c.3920 T > A (p.Ile1307Lys) has a frequency of 6.1–12% in Ashkenazi Jewish people and, while not linked to breast cancer, does result in a doubling of lifetime colorectal cancer risk. Finally, Ashkenazi Jewish founder mutations have also been identified in the MSH2 gene (1906G > C, frequency 0.4–0.7%), MSH6 gene (3984_3987dupGTCA, frequency 0.30%, and 3959_3962delCAA, frequency 0.11%), and GREM1 gene (40 kb dup, frequency 0.70%) [8].

BRCA1/2 Pathogenic Variants and Breast Cancer

People with BRCA1/2 pathogenic variants have an elevated lifetime risk for developing breast cancer and develop breast cancers with distinct disease patterns and tumor characteristics. BRCA1/2-driven breast cancers are more likely to be diagnosed at a young age and with a more advanced stage associated with overall poorer prognosis, and individuals with BRCA1/2-driven breast cancers are more likely to develop contralateral breast cancers and/or tumors with triple-negative histology [9, 10].

Breast cancer management can also be affected by BRCA1/2 status. As women with BRCA1/2 pathogenic variants are at increased risk for developing a second breast cancer, many opt for bilateral mastectomy instead of breast-conserving therapy. For those women who do not undergo bilateral mastectomy, annual mammography and breast magnetic resonance imaging (MRI) are recommended for screening of the remaining breast tissue [11]. Additionally, for people with BRAC1/2 pathogenic variants and high risk, early stage, human epidermal growth factor receptor 2 (HER2)-negative breast cancer, adjuvant treatment with olaparib, an inhibitor of poly(ADP-ribose) polymerase (PARP), has been shown to improve disease-free survival [12•, 13]. Olaparib has regulatory approval by the US Food and Drug Administration for this population following neoadjuvant or adjuvant chemotherapy [14].

Personalized Breast Cancer Prevention

Traditionally, breast screening has relied on the "one-size-fits-all" model of annual mammography according to age-based guidelines. However, there is a growing appreciation that the risk of breast cancer is influenced by many variables, including but not limited to genetic susceptibility, lifestyle factors, and reproductive history [15]. Many experts now suggest a paradigm shift, moving away from the traditional approach to screening and towards a precision medicine-based approach with screening and risk-reducing strategies tailored to individual risk factor profiles [15, 16, 17•]. Furthermore, research demonstrates that tailoring treatment to risk can lead to significant improvements in oncologic outcomes and quality of life [17•]. One of the most powerful options currently available to personalize breast cancer risk assessment is germline genetic testing. Individuals found to carry a breast cancer–associated pathogenic variant, including BRCA1/2, can undergo genetically tailored cancer prevention and risk reduction [18–20].

Genetically Tailored Cancer Risk Reduction

Individuals found to have a hereditary cancer syndrome including BRCA1/2 can pursue cancer screening and risk reduction interventions that have been shown to impact cancer incidence, morbidity, and mortality. Established guidelines for individuals at significantly elevated lifetime risk for breast cancer recommend either enhanced breast surveillance or risk-reducing mastectomy [21]. For those selecting enhanced breast screening, guidelines recommend annual magnetic resonance imaging (MRI) beginning at age 25 years and mammography beginning at age 30 years [21]. The addition of MRI to traditional mammography for breast cancer surveillance results in an increased identification of breast cancer, diagnosis at an earlier stage, and is cost-effective [21–25]. Patients with BRCA2 pathogenic variants, who are at elevated risk for hormone receptor positive breast cancers, can also consider chemoprevention with selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) to reduce the risk of breast cancer [26–29]. Retrospective and prospective observational studies demonstrate that risk-reducing bilateral mastectomy decreases the incidence of breast cancer by at least 90% [19, 30–32]. Risk-reducing removal of ovaries and fallopian tubes reduces the risk of ovarian cancer and decreases overall mortality [32–34]. A 2014 meta-analysis by Marchetti et al. [35] found that risk-reducing salpingo-oophorectomy in BRCA1/2 carriers was associated with an 80% reduction in ovarian cancer and a 68% reduction in all-cause mortality.

Population-based BRCA1/2 Genetic Testing in Ashkenazi Jewish Populations

Traditionally, germline genetic testing has been offered to individuals with a personal or family history of cancer, even among the Ashkenazi Jewish population. However, studies

demonstrate that more than half of Ashkenazi Jewish individuals found to carry a BRCA1/2 pathogenic variant have little or no personal or family history of BRCA-related cancers [36–38]. Additionally, family history in Jewish people is sometimes unknown due to the Holocaust and vast migration of families [39, 40••]. Based on the prevalence of pathogenic variants and well-established cancer risks and benefits of medical interventions, several experts now advocate for population-level BRCA1/2 screening for individuals of Ashkenazi Jewish ancestry. Population-level BRCA1/2 Ashkenazi Jewish founder mutation testing has been advocated for in Canada, the UK, and Israel [37, 38, 41].

Manchanda and colleagues [37] evaluated population-based genetic testing for Ashkenazi Jewish individuals in a randomized controlled trial and found, compared to family history-based testing, that population-based testing detected 56% more carriers without adversely affecting psychological/quality-of-life outcomes. Additionally, this group performed a cost-effectiveness analysis demonstrating that population testing for BRCA mutations with varying levels of Ashkenazi Jewish ancestry is cost-effective in the UK and the USA [42]. Acceptance of population-based genetic testing among Ashkenazi Jewish individuals has also been evaluated, and high levels of interest have been demonstrated across religious/cultural identities and denominational affiliations [43••, 44].

Ashkenazi Jewish Cultural Considerations

The approach to breast cancer management is typically multidisciplinary, involving medical, surgical, and radiation oncologists in addition to myriad support services focusing on mitigating treatment toxicity, rehab medicine, psychosocial health, and palliation. Furthermore, a patient's racial, ethnic, religious, and/or cultural values may be of critical importance to the uptake of cancer treatment and prevention. As outlined above, Ashkenazi Jewish individuals have a significantly increased risk for developing breast cancer due to the high prevalence of breast cancer–related germline founder mutations. Here, we explore some of the nuances at the intersection of Ashkenazi Jewish culture/religion and breast cancer care. Like other cultures, Ashkenazi Jewish communities exhibit a wide spectrum of cultural practices and level of observance. Therefore, many of the below concerns may be applicable to some, but not all, Ashkenazi Jewish people. We have included patient perspectives and changed all names to protect privacy.

Hair Covering and Wigs

In some communities, Jewish women do not show their hair in public following their wedding. Hair is covered with a headscarf or wig as a signal to others that they are married. This custom can complicate the experience of cancer treatment. Clinicians may incorrectly assume that chemotherapy-induced alopecia is less stressful for women who already cover their hair. However, for women living in communities where hair covering is observed, the process which was previously associated with the positive experience of marriage and adulthood represents now, instead, a stigma of cancer therapy toxicity. Furthermore, although individuals may cover their hair in public, these women can still enjoy their hair in private with their partner.

Sarah, 28 years old with breast cancer undergoing chemotherapy:

> *When I was alone, and removed my wig, looking in the mirror made the cancer a reality.*

Concept of Destiny

Many Jewish communities cherish the concept that "it is all meant to be" or that everything that happens is preordained by God. While for some this value is comforting, it can raise challenging spiritual questions when one is facing a cancer diagnosis. For some, the belief that cancer was their destiny and chosen by God can create tension with religious beliefs. For others, hope and prayer for good health and putting one's destiny in God's hands can provide tremendous value and comfort. Combining these different ideas surrounding destiny is of utmost importance for Ashkenazi Jewish cancer survivors as they approach a cancer diagnosis from a place of tremendous spirituality and belief in God.

Fran, breast cancer patient:

> *Throughout my diagnosis and treatment, I found myself asking: What is there to learn from these challenges? How might I garner the strength to face what lies ahead? When will I believe that this experience is just one more fold in the fabric of my life? In grappling with these questions, I discovered that my spiritual life helped carry me through* [45].

Stigma of Cancer

Overall, there is growing knowledge and acceptance of increased rates of breast cancer and BRCA1/2 pathogenic variants among Ashkenazi Jewish people. However, there are communities (in many cultures, not limited to Judaism) where a cancer diagnosis or hereditary cancer predisposition syndrome holds significant stigma. This stigma can result in individuals not sharing information with friends and relatives, resulting in further isolation at a time when social support can be most important. The stigma surrounding BRCA1/2 pathogenic variants also creates a barrier

to genetic testing, with some individuals preferring not to know whether they carry a familial mutation even if resulting health implications exist.

Modesty

Some Jewish communities consider modesty both a critical value and religious duty. As part of modesty, individuals in the community may be dissuaded from discussing female organs including breasts, ovaries, and fallopian tubes as they are deemed "private." Additionally, the publication and circulation of the image of a woman's body may be discouraged. Practices that limit discussion of breast and ovarian cancer and options for cancer prevention (e.g., breast screening) may prevent individuals from taking advantage of potentially life-saving medical interventions. Additionally, several communities avoid technology including smart phones, internet, and television, and therefore, access to health information may be very limited.

Mikvah (Ritual Bath)

The mikvah is a ritual bath that is commonplace in some Jewish communities. Women use the mikvah as a symbol of purification after menstruation, childbirth, and medical treatments as well as to celebrate life changes and transitions. As the mikvah is commonly associated with fertility, the mikvah can be a regular reminder of this loss for women with cancer, transforming a sacred custom into an emotional challenge. Furthermore, women recovering from surgical procedures often cannot use the mikvah until they have recovered completely. However, with the proper culturally sensitive support services, the mikvah can be a source of comfort and healing for many Jewish women undergoing cancer treatment.

Hannah, a member of a cancer support organization recounts her experience with Stella, a woman with metastatic breast cancer, at the mikvah:

> *Stella felt a strong desire to tap into the strength of Jewish women throughout history who have immersed in these waters. Her body bore the brunt of her illness with scars from the multiple surgeries. When Stella emerged from the water she began to sing Yedid Nefesh (Beloved of the Soul). Stella was an opera singer; a soprano. Hearing Stella's voice reverberating off the mikvah walls was one of the most magnificent sounds I have ever heard. Stella shared that "For the first time in months, I feel hopeful* [45, 46]."

Bikkur Cholim or Visiting the Sick

Bikkur Cholim is a core value among many in the Jewish community whereby members of the community and religious leaders commit to visiting the sick. This act of support can offer a tremendous amount of encouragement and light for the sick and those recovering from surgery or chemotherapy. However, individuals with breast cancer often feel the need to balance the experience of receiving Bikkur Cholim with concerns regarding modesty and the stigma of cancer for them and their family.

Jewish Holidays and Community

Preparing for the Jewish holidays and focusing on one's relationship with God can be spiritually uplifting. However, for those facing a cancer diagnosis or undergoing treatment, focusing on one's relationship with God can be both physically and emotionally draining, raising questions including "why me?". The High Holidays in particular, including Rosh Hashanah and Yom Kippur, present a unique challenge for people with life-threatening illnesses. Many Jewish individuals spend the holidays in synagogue hearing the prayer "who shall live and who shall die," which can prompt mindsets of difficult self-reflection and fear. Alternatively, some may be too weak to attend synagogue even on the most auspicious days of the year and, as a result, struggle with feelings of isolation and hopelessness as they are not able to celebrate and mark the occasion with their community.

Leah, 32-year-old with breast cancer and two young children:

> *I had to undergo chemotherapy on Yom Kippur, the holiest day in the Jewish calendar. I was emotional, as under any other circumstances I would have been in synagogue. But, when I heard my community praying for me to be written into the Book of Good Life, I knew I'd survive my cancer.*

Jessica, breast cancer patient undergoing chemotherapy:

> *I began chemotherapy treatment right around the time of Rosh Hashanah. It was challenging to prepare for guests when I felt numb and disconnected from the routine of Jewish life. But that year, my prayers took on greater meaning as I prayed for healing, for health, and for a long life of celebrations. Though the holidays brought with them a roller coaster of emotions — fear, anxiety, and deep sadness — they also created some moments of true calm and connection to the friends and family whose support proved invaluable* [45].

The Sabbath

Some Ashkenazi Jewish individuals observe the Sabbath or a day of religious reflection and abstinence from work, travel, and other activities from Friday evening to Saturday evening as well as on religious holidays. The Sabbath can

complicate scheduling surgeries and treatments (patients are often unable to travel home after sundown on Friday evenings). Some will postpone surgeries and treatments to work around the Sabbath and holidays. However, there is a significant Jewish value placed on preserving and maintaining one's health, and community members will seek ways to uphold this value while also respecting the Sabbath and major holidays.

Ashkenazi Jewish Culturally Sensitive Cancer Support and Advocacy

Studies suggest that breast cancer information is most effective when it is personally relevant and targeted to both a patients' age and culture. There are several organizations dedicated to supporting those living with breast cancer as well as those living with an elevated lifetime risk for developing breast cancer. Additionally, there are a handful of culturally sensitive organizations with services geared specifically towards Jewish individuals including Sharsheret, the Rofeh Cholim Cancer Society, and the Sephardic Cancer Center. Here, we highlight Sharsheret (https://sharsheret.org/) to demonstrate the potential power and downstream benefits of culturally tailored patient support organizations (Fig. 1).

Patient testimonials regarding their experience with a culturally sensitive, cancer-focused patient organization:

> *The kits were so thoughtful. I cried when I received the cosmetic kit and makeup. I'm not ready to lose all my hair and look like a mannequin. The makeup and helpful hints made me feel better. Today, I received the One Bite at a Time cookbook, extra informational binder, and fitness band. Since starting chemotherapy, I have been working out at home and avoiding the open gym. My daughter was THRILLED with her busy box!! The (left) mastectomy and DIEP flap surgery and recovery are going really, really well. You've played a critical role in my cancer journey. Frankly, were it not for your early support and understanding, I likely would have given up hope on fulfilling my desired treatment path. Your continued outreach has helped buoy my spirits and helped me maintain a proactive outlook along the way. Your work is important and life changing.*

> *It was such a pleasure to talk with you on the phone. Afterwards, I felt more hopeful and calmer about my breast cancer diagnosis. It will be mentally and physically challenging to battle cancer over the next 6 months of chemotherapy. Then surgery…then radiation…then the uphill climb to recover and regrow. All the information from Sharsheret has been very helpful for me and family. Even though I had researched a lot about breast cancer, there were many questions that I had not even considered. I just wanted to thank-you again for the long telephone conversation, helpful information, and gifts.*

> *This BRCA1/2 webinar was very informative; I am so grateful to the providers for taking the time to explain their stories and their opinions on some of the options available. As someone recently diagnosed with a BRCA1 gene mutation, this webinar helped me understand some of the options available as well as provided me with topics to discuss with my provider. Thank you!*

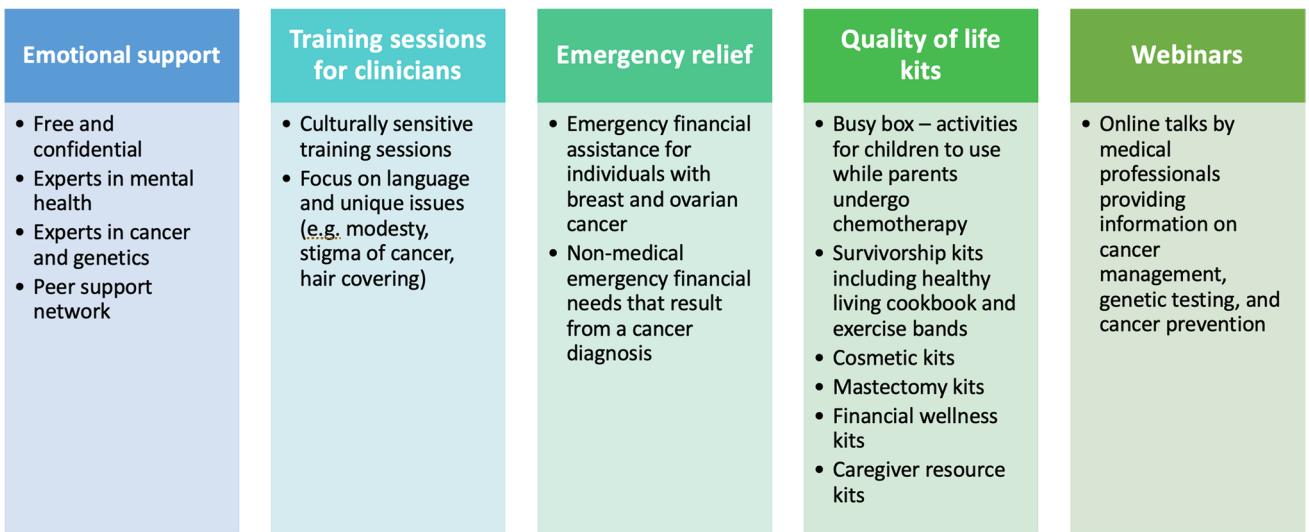

Fig. 1 Resources provided by Ashkenazi Jewish culturally sensitive support and advocacy organizations

Conclusions

In this review, we focus on breast cancer among the Ashkenazi Jewish population with the understanding that decisions regarding cancer treatment, genetic testing, and cancer risk reduction involve a complex decision-making process that may be impacted by both religious and cultural variables. Providers treating Ashkenazi Jewish breast cancer patients and programs designed for genetic testing and cancer prevention must cautiously consider the way an individual's religious and cultural identity affects the utilization of health interventions to maximize each patient's individual experience and offer care that is aligned with the values of patients and their families.

Author Contribution M. K. F., L. R. P., A. K. F., and E. S. wrote the main manuscript text, and M. K. F. prepared Fig. 1. J. T. B. helped to draft sections of the manuscript, assist with editing, and format citations. A. K. F. and E. S. helped to draft and edit sections of the manuscript, as well as select which patient testimonies to include.

Data Availability No datasets were generated or analyzed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

Conflict of Interest There are no disclosures to report.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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