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Hereditary breast cancer in Jews

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Abstract

A family history of breast cancer poses higher risks for Jewish *versus* non-Jewish women, particularly for early-onset breast cancer. This appears to be due in large part to the high prevalence (2.5%) of three *BRCA1* and *BRCA2* founder mutations in Ashkenazi Jews. About 4 to 8% of non-Jewish male breast cancer cases *versus* 19% of Jewish male breast cancer cases carry germline *BRCA* mutations. Jewish women are disproportionately impacted by *BRCA* mutations throughout life, with a 10% carrier rate for breast cancer diagnosed at any age and a 21 to 30% carrier rate for breast cancer diagnosed by age 40. Comparable rates in non-Jewish populations are 6.1% for breast cancer diagnosed before age 50. Lifetime penetrance estimates based on genotyping of probands have ranged widely in Jewish and non-Jewish populations. However, a study of 1008 Jewish women with breast cancer which extended genotyping to relatives found high penetrance rates with considerably smaller standard errors. This study and studies of early-onset incident breast cancer in non-Jews have found that at least half of high-risk cases would be missed by family history screening alone. While the carrier rate in non-Jewish populations is too low to consider genetic screening, the carrier rate in Ashkenazi Jews is high and genetic screening poses fewer technical barriers. The high genetic attributable cancer risks of Ashkenazi *BRCA* founder mutations, the sobering lethality of ovarian and early onset breast cancers, and the increasing clarity about effectiveness of medical interventions make imperative further dialogue and research to keep guidelines for genetic screening up to date.

Abbreviations: BIC – Breast Cancer Information Core; *BRCA1* – breast cancer 1 gene; *BRCA2* – breast cancer 2 gene; CI – confidence interval; HBOC – hereditary breast–ovarian cancer; MIM – Mendelian inheritance in man

Introduction

Breast cancer is an enormous public health problem, and although inroads have been made in decreasing breast cancer mortality, the burden for affected women, their families, and their communities is very high. In 2004, there will be an estimated 217,440 new cases of breast cancer in the US including 215,990 in women and 1450 in men [1]. About 40,580 Americans will die from breast cancer this year. Breast cancer is the leading cause of new cancers in women and comprises a third (32%) of all new cases. Breast cancer ranks second only to lung malignancies in cancer mortality, accounting for 15% of the total deaths from cancer in women. Research which enlightens us as to the causes of breast carcinoma will provide avenues for treatment, early detection, and prevention. One strategy to lessen the burden of breast cancer is to identify women at increased risk and to intervene proactively [2].

The recognition of three highly prevalent founder mutations in Ashkenazi Jews in the *BRCA1* and *BRCA2* genes [3–11] followed quickly upon the heels of the discovery that these genes are associated with the hereditary breast–ovarian cancer (HBOC) syndrome [12–14] and account for the majority of HBOC families [15, 16]. Since then, a multitude of studies have been published on the Ashkenazi Jewish *BRCA* founder mutations. Many studies have capitalized on the ease of founder mutation testing and the willingness of Jewish individuals and families to participate in research. These studies have supplied answers to vital questions that can also be applied to non-Jewish populations. Topics of *BRCA*-related breast cancer research involving major participation by Jewish women have included: interest in

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gene testing [17, 18], prognosis [19], response to treatment [20], efficacy of chemoprevention [21], other *BRCA*-associated cancers [22], the influence of hormonal factors [18, 23–26], tumor morphology [27], gene–gene interactions [28, 29] and estimation of penetrance [30, 31].

The accumulated data and experience have highlighted several effective approaches to cancer prevention and early detection which make *BRCA* gene testing in appropriate individuals an integral part of cancer risk management [32, 33]. This article will examine whether breast cancer is more common in Jewish women and men; whether a higher proportion of breast cancer in Jews is attributable to the *BRCA1* and *BRCA2* founder mutations; the contribution of *BRCA* mutations to early and late onset breast cancer; and the lifetime cancer risks associated with the founder mutations. We will also pose the rather charged question of whether population screening for the Ashkenazi founder mutations should be considered, and examine the role of family history in carrier screening.

BRCA1 and *BRCA2*

King et al. [34] published the first study providing quantitative evidence for an autosomal dominant breast cancer susceptibility allele, accounting for an estimated 4% of breast cancer families and conveying an 82% lifetime risk of breast cancer. Following their report of linkage to chromosome 17q21 for early-onset hereditary breast cancer [35], *BRCA1* (MIM 113705) [36] was isolated via a positional cloning strategy in 1994 [12]. Subsequently *BRCA2* (MIM 600185) [36], a second breast–ovarian cancer susceptibility gene, was localized to chromosome 13q12-q13 and cloned [13, 14]. *BRCA1* and *BRCA2* mutations and polymorphisms are catalogued in the Breast Cancer Information Core (BIC), an open access online database hosted by the National Human Genome Research Institute [37].

Numerous ethnic-specific mutations have been described across the globe [37, 38]. About 2.5% of Ashkenazi Jews that are unselected for a family history of cancer carry one of three founder mutations: *BRCA1* 187delAG (also called 185delAG), *BRCA1* 5385insC (also called 5382insC) and *BRCA2* 6174delT [10]. About 78 to 96% of Ashkenazi Jews with detectable mutations using DNA sequence analysis carry one of the founder mutations. Thus, further analysis is merited in high-risk, founder mutation-negative families to identify the non-founder mutations and provide accurate counseling [39, 40]. The cost of complete DNA sequencing is an order of magnitude higher than founder mutation testing (~\$3,000 *versus* ~\$400); this cost differential has made testing more accessible for Ashkenazi Jews. In most families a single mutation is found and relatives who are subsequently tested require analysis only of the familial mutation. However, there have been several reports of Jewish families segregating more than one founder mutation and of individuals harboring both a *BRCA1* and a *BRCA2* mutation, demonstrating that it is prudent to repeat the entire Ashkenazi panel in mutation-positive Jewish families [41, 42].

Is breast cancer more common in Jewish women?

As compared with colorectal cancer in Jews (see Locker and Lynch, this issue), there are fewer data available with which to assess the incidence of breast cancer in Jews. However, this question is important because risk stratification is necessary to target breast cancer surveillance and prevention. If breast cancer rates are higher in Jews then the next logical question is whether this is mainly attributable to the *BRCA1* and *BRCA2* founder mutations. If so, then risk assessment could efficiently proceed by way of genetic risk evaluation.

Initial reports of an excess breast cancer risk in Jews were published well before the discovery of *BRCA1* and *BRCA2*, showing lack of bias in this respect [43, 44]. Egan, Willett and colleagues examined Jewish religion and breast cancer in a well-conducted population-based case–control study consisting of 6611 women with invasive breast cancer identified through state cancer registries and 9026 controls in Maine, New Hampshire, and Wisconsin [45]. During telephone interviews, participants were queried about religion and family history of breast cancer in mothers and sisters. Catholic women who had no family history of breast cancer were used as the main reference group but were comparable to Protestants. As expected, a positive family history was associated with increased relative risks for Catholics, Protestants, and Jews, but the effect of family history was about 2-fold higher for Jewish women ($P = 0.05$, heterogeneity test). Jewish women with a positive family history had a relative risk of 3.7 compared with Jewish women without a family history. Statistical adjustments were made based on a comprehensive list of breast cancer risk factors, but the overall effect of adjustment on relative risks was minimal. Not only was the interaction between breast cancer risk and religion unique to Jews, but the interaction was even stronger for cases with breast cancer aged 50 years or less. The relative risk for Jewish women with early-onset breast cancer was 10.5 compared with young Catholic women without a family history ($P = 0.04$; 95% CI 1.10–99), an effect expected for a dominantly inherited trait such as a germline *BRCA1* or *BRCA2* mutation. The relative risk for Jewish women of all ages combined was raised only among those with early-onset breast cancer (1.55) but did not reach statistical significance ($P = 0.10$).

The New York University Women's Health Study, a prospective mammographic screening study of 14,275 women, corroborated the findings of Egan et al., but found smaller relative risks [46]. Among the screening cohort, 10,273 reported religious upbringing and 44% were Jewish. The relative risk of Jewish women with a first-degree family history was 1.69 (95% CI 1.16–2.45) as compared to Catholic women without a family

history. Young age of breast cancer was associated with an increased relative risk in Jewish women (2.33; 95% CI 1.35–4.02) but the effect was more modest than in the Egan study.

There have been few epidemiologic studies targeted to breast cancer in Jewish women making it difficult to state with certainty whether or not breast cancer is more common in this group. It does seem surprising that Jewish physicians, who have played a prominent role in medicine and science [47], have not remarked upon an excess of breast cancer in Jewish men or women, particularly in young women. This lack of commentary could be due to missed observations, but it also seems plausible that breast cancer incidence rates have changed over the centuries as a result of lifestyle factors, longer life expectancies, and changing causes of mortality. Interestingly several studies have shown a birth cohort effect, whereby *BRCA* carriers born after 1930 or 1940 have higher lifetime cancer risks than women born earlier [31, 48–50].

The above studies suggest that a family history of breast cancer conveys more risk for Jewish women than for non-Jewish women, and that the effect is even greater for women with early-onset breast cancer. These findings were supported by a study which found that 21% of Jewish women with diagnosed breast cancer at age 40 or younger were *BRCA1* 185delAG mutation carriers [8]. Subsequent studies, reviewed below, have established that there is a high attributable genetic risk for early-onset breast cancer in Jewish women. Whether this effect is due solely to the *BRCA* genes has not been established, but the *BRCA* genes are the predominant cause of breast cancer risks in mutation-positive families [51]. However, there is emerging evidence for other genetic factors in the Ashkenazim such as the *HER2 I655V polymorphism,* which conveys a modest effect on lifetime breast cancer risk that is stronger at younger ages and in women with a family history of breast cancer [52].

Is breast cancer more common in Jewish men?

About 0.8% of breast cancers occur in men. Risk factors include age, testicular disease, benign breast conditions, gynecomastia, previous liver diseases, never being married, Jewish ancestry (Mantel–Haenszel exposure odds ratio (EOR) for being Jewish = 2.1; 95% CL = 1.4, 3.2), African ancestry, family history of female breast cancer (EOR for first-degree relative with breast cancer = 2.5; 95% CL = 1.7, 3.7), Klinefelter syndrome (47, XXY), androgen insensitivity syndrome caused by mutations in the androgen receptor gene, and mutations in *BRCA1* and *BRCA2* (53–55). Although *BRCA2* is the gene best known for its association with male breast cancer [13, 56], over a third of mutations in men having testing for the two genes were found in the *BRCA1* gene [39].

A few studies have indicated that Jewish men have relatively higher rates of breast cancer. An early report from the Israel Cancer Registry indicated a higher rate of male breast cancer in Israel as compared with the US [57]. A study ascertaining male breast cancer cases from the Israel Cancer Registry 1980 to 1997 (131 cases) and from 2 medical centers in Israel from 1960 to 2000 (470 cases) found 131 cases in Jewish men, of which 78% were Ashkenazi. The odds ratio for male breast cancer was 1.8 for Ashkenazi *versus* Sephardic Jews (95% confidence interval, 1.4–2.3; $P = 0.001$) [58].

Is a higher proportion of breast cancer in Jewish men attributable to the BRCA1 and BRCA2 mutations?

The contribution of *BRCA2* (and in some reports, of *BRCA1*) to male breast cancer has been assessed in population-based studies as well as in high-risk clinics (which introduces a selection bias). In a population-based series of male breast cancer cases from southern California using pathology specimens, only 4% (2 out of 54) of cases had germline *BRCA2* mutations (no *BRCA1* mutations were found; family history was not assessable) [59]. In another US study, 7 out of 50 (14%) men with breast cancer unselected for family history had a *BRCA2* mutation. This rate may be higher in part due to a higher proportion of Jewish males in the study, and all but one of the male *BRCA2* carriers had a positive family history of female and/or male breast cancer [60]. A population-based study of 94 male breast cancer cases in the UK found germline *BRCA2* mutations in 8% (95% CI = 3–19), and all cases had a positive family history. Studies show generally low *BRCA2* mutation rates for unselected male breast cancer cases or when family history is negative [54, 55]. However, male breast cancer in association with a positive family history of breast and/or ovarian cancer is predictive of a *BRCA2* germline mutation, as suggested by the Breast Cancer Linkage Consortium (77% estimated probability of linkage) [56] and a large referral-based study on direct mutational analysis [39].

The highest genetic attributable risk for male breast cancer, 40%, was found in the Icelandic population, due to the *BRCA2* founder mutation 999del5 [61]. Studies of *BRCA2* in Ashkenazi Jewish men with breast cancer also indicate a higher genetic attributable risk than for men in the general US population. Struewing et al. assessed *BRCA1* and *BRCA2* mutation status in 121 specimens from 165 male breast cancer cases ascertained through 5 Israeli hospitals from 1980–1997 [62]. A total of 19 carriers were identified; 17 among the 89 Ashkenazi Jews, 2 among the 21 non-Ashkenazi Jews, and none among the 14 Arabs. The finding of a 19% founder mutation carrier rate was somewhat higher than the above-cited studies, particularly as this group was unselected for a family history of cancer. The mean age of breast cancer diagnosis in carriers (age 64) was similar to that of the non-carriers (age 68). In a large US referral-based study, male breast cancer patients of Ashkenazi ancestry had a higher carrier rate than non-Jewish patients (39% (11 out of 28) *versus* 21% (10 out of 48)) but this difference was not statistically significant

[39]. The median ages of breast cancer onset were: 59 for men with negative gene testing results, 59 for *BRCA2* carriers, and 52 for *BRCA1* carriers.

The penetrance to age 70 for male breast cancer has been estimated as 6% for *BRCA2* carriers and is presumably less for male *BRCA1* carriers [63, 64]. Closer follow-up is warranted, but the needs of male carriers have not been addressed in-depth [65]. Men who choose to have genetic testing do so primarily in order to clarify risks to their daughters.

Is a higher proportion of breast cancer in Jewish women attributable to the BRCA1 *and* BRCA2 *mutations?*

Jewish ancestry has repeatedly emerged as a significant predictor of a positive *BRCA* gene test result [66–68] and genetic risk analysis without assessment of Jewish ancestry is incomplete [69]. A large population-based study of 5318 Ashkenazi Jews in the Washington, DC area found a 2.3% carrier rate for one of the 3 common founder mutations [30]. A study of the founder mutations in Australian Jews found similar mutation frequencies as in the US, suggesting generalizability of genetic epidemiologic studies to dispersed Ashkenazi Jewish populations [70]. The *BRCA* mutation carrier rate in the general population has been estimated at about 1 in 345 to 1 in 1000, far lower than in Ashkenazi Jews [15, 71–73]. The question of whether the high mutation prevalence in Ashkenazi Jews correlates with a higher proportion of hereditary cancer depends on the penetrance of the founder mutations in Jews. Studies assessing penetrance in Jewish populations are addressed below. If penetrance estimates are similar between Jewish and non-Jewish populations, then Jewish women would be expected to bear a high proportion of genetic risk. If the penetrance is lower (which could be a function of the particular mutations or due to genetic and environmental modifiers of penetrance), then the lower disease burden would mean there is less reason to intervene medically or to do genetic screening.

What is the contribution of BRCA1 *and* BRCA2 *mutations to early-onset and older-onset breast cancer in Jewish women?*

An early indication that the Ashkenazi *BRCA1* 185 delAG founder mutation contributed heavily to early-onset breast cancer in Jewish women (21% of hospital-based cases diagnosed by age 40) was provided in 1996 [8]. The carrier rate of Jewish women diagnosed with breast cancer in their forties was 10% (11 out of 109) in a large population-based study of healthy Jewish individuals [74]. The role of *BRCA2* has appeared in some studies to be less prominent, possibly due to higher median ages of breast cancer onset [75]. Studies of all three founder mutations in Jewish women with prevalent breast cancer, unselected for family history, have found mutation rates of 7% [76] and 12% [77] suggesting a significant contribution of founder mutations across the age spectrum. In an Israeli study, 30% of breast cancers diagnosed in Jewish women under age 40 had one of the three founder mutations and 10% of Jewish women diagnosed over age 40 were carriers [78].

In contrast, a population-based study of incident, early-onset breast cancer in the UK found *BRCA1* or *BRCA2* mutations in 5.9% of women diagnosed before age 36, and in 4.1% of women diagnosed at ages 36 to 45 [73]. They estimated that 6.1% of women diagnosed with breast cancer before age 50 are mutation carriers, and that only 1.2% of women diagnosed age 50 or older are carriers. The weight of evidence shows that Jewish women are disproportionately impacted by the *BRCA* genes throughout adult life.

Are the cancer risks associated with the Jewish founder mutations associated with similar or different penetrance values than non-Jewish populations?

Penetrance, the lifetime risk of cancer, was estimated from the original linkage studies as being especially high, i.e., about 85% for breast cancer, and 40 to 65% for ovarian cancers in *BRCA1* carriers and 20% for *BRCA2* carriers [56, 79]. An accurate measure of penetrance is crucial, as medical decisions such as prophylactic mastectomy depend on this estimate. Because severely affected families were chosen for linkage studies to enhance the chances of success in mapping and cloning the *BRCA* genes, confirmation of penetrance was required using samples with less potential for selection bias. Many but not all studies have found much lower penetrance estimates [30, 31, 50, 76, 77, 80–88]. These study populations have included incident breast cancer cases in hospitals or in the general population (sometimes focusing on younger women) unselected for family history of cancer, unselected ovarian cancer cases in Jewish women, cases from breast cancer risk evaluation clinics, and pooled pedigree data from multiple studies. The methodology of penetrance estimation is a key factor in assessing the accuracy of study designs [24, 89–92].

Data from the *BRCA1* and *BRCA2* penetrance studies are summarized in Table 1. Excluding the New York Breast Cancer Study, which is detailed below, lifetime penetrance of breast cancer (to age 70) for Jewish populations ranged from 36 to 60% for *BRCA1*, and from 21 to 56% for *BRCA2*. Breast cancer penetrance for non-Jewish populations ranged from 40 to 73% (age 70) for *BRCA1* and 37 (age 70) to 74% (age 80) for *BRCA2*. Breast cancer penetrance estimates (to age 70) based on pooled data on 8139 index cases with breast cancer from 22 studies were: *BRCA1*: 65% (95% confidence interval 44–78%); *BRCA2*: 45% (31–56%). While the lower estimates for Jewish populations are outside the 95% confidence interval for the study using pooled data, several studies in Jewish populations fall well within range of the results in non-Jewish populations.

Table 1. Penetrance of breast cancer in Jewish and non-Jewish populations.

A) Jewish-only ethnicity studies						
	Struewing 1997	Fodor 1998	Warner 1999	Satagopan 2001	Satagopan 2002	King 2003
Study population	Healthy men and women; Washington, DC	Incident BC; New York	Incident BC; Toronto	Hospital-based BC; New York	Hospital-based ovarian cancer; New York, North America, Israel	Incident BC referred by physicians; New York
BRCA1 BC penetrance	56% (age 70)	36%	60% (age 70)	46% (age 70) 59% (age 80)	37% (age 70)	81% (age 80)
BRCA2 BC penetrance		36%	28% (age 70)	26% (age 70) 38% (age 80)	21% (age 70)	85% (age 80)
B) Primarily non-Jewish and Jewish/non-Jewish ethnicity studies						
	Anglian BC study group 2000	Thorlacius 1998	Hopper 1999	Risch 2001	Brose 2002	Antoniou 2003
Study population	Population-based BC age < 55; Britain	Population-based BC; Iceland	Incident BC age < 40; Australia	Incident ovarian cancer; Ontario	Cancer risk evaluation programs; Michigan, Pennsylvania	Pooled pedigree data from multiple studies
BRCA1 BC penetrance	48% (age 80)			68% (age 80)	73% (age 70)	65% (age 70)
BRCA2 BC penetrance	74% (age 80)	17% (age 50) 37% (age 70)	40% (age 70)			45% (age 70)

BC = breast cancer.

Notably, the highest *BRCA1* penetrance estimate (73% to age 70) among the studies is from the single study where subjects were selected from a cancer risk evaluation program [85]. While this seems to reconfirm that the selection criteria for penetrance studies is a key determinant of magnitude of the effect, the effect may be methodological. Because clinic-based designs include more identified mutation carriers they may provide more accurate estimations of penetrance than population-based designs [90]. Due to the presence of unmeasured, shared risk factors, penetrance estimates based on cases may overestimate risk. The use of case probands in the population-based and clinic-based studies may inflate penetrance estimates but there is much debate about methodology [89, 90, 93–97].

Penetrance of the *BRCA* genes was further examined in the New York Breast Cancer Study which genotyped 1008 Jewish women with incident invasive breast cancer diagnosed and referred by physicians in 12 major cancer centers in the greater New York City area [31]. The founder mutation carrier rate among probands was 10.3% (104 out of 1008). This rate is similar to the 7 to 12% rate in unselected Jewish breast cancer populations discussed previously [76, 77], suggesting that although physician referral might pose a selection bias leading to an overestimation of prevalence and bias penetrance estimates, this was not a factor. Indeed, half of the families had no history of breast or ovarian cancer in mothers, sisters, aunts, or grandmothers. This has important implications for genetic screening, addressed below.

The New York Breast Cancer Study differed from other studies examining penetrance in that relatives were directly genotyped. Penetrance could thereby be directly evaluated from genotypes rather than from inference by the degree of relatedness, cancer status and age. The penetrance of breast cancer was 81% for *BRCA1* and 85% for *BRCA2*, or 82% for either gene. Standard errors were considerably smaller than in other studies (e.g., 0.05 for *BRCA1* and *BRCA2*). The ability to directly assess genotypes in relatives also revealed that so-called low-penetrance families had similarly high cancer risks as the other families. The appearance of low penetrance occurred in instances of paternal transmission, chance inheritance of the wild-type *BRCA* allele in female relatives, small family size, few female relatives, and cancer involvement in more distant branches of the family.

Should population-based screening be considered for Ashkenazi Jews?

Although it is not clear whether breast cancer rates are higher in Jewish women, a family history of breast cancer is associated with higher risk in Jewish women *versus* non-Jewish women, particularly for women with early-onset breast cancer. Neither is it clear whether there is a higher incidence of breast cancer in Jewish *versus* non-Jewish men. However, the contribution of *BRCA1* and *BRCA2* mutations to breast cancer is higher for Jewish men and women than for non-Jews. Roughly 10% of female breast cancer and 19% of male breast cancer in Ashkenazi Jews occurs in carriers of the *BRCA* Ashkenazi founder mutations, a far higher rate than is seen in most non-Jewish populations. The *BRCA* mutation carrier rate is much higher when young age of cancer onset or family history of breast and ovarian cancer is considered, both in absolute terms and in

comparison to non-Jews. Estimates of the lifetime risk of cancer in Jewish and non-Jewish *BRCA* carriers have varied widely, but very high penetrance values were found in the New York Breast Cancer Study.

Screening for hereditary cancer is generally accomplished by asking about a family history of cancer or by focusing on cancer types that herald cancer syndromes. Family history evaluation and gene testing are the only methods available to identify people who have not yet had cancer but who are at high genetic risk. This is a particularly vital issue for women who are at high genetic risk of ovarian cancer, due to the high lethality of this cancer, lack of reliable symptoms and signs for early detection, and high efficacy of surgical prevention. While there are limitations to screening using family history [98], the carrier rate is too low in most populations to consider other strategies such as genetic screening. However because the carrier rate of *BRCA* founder mutations is high in Jews, the cancer risks appear also to be high, and the technical barriers to gene testing are low, the question of whether to screen the general Jewish population for *BRCA* mutations is open to further dialogue [74]. Invited commentary on the New York Breast Cancer Study noted that "…the time has come for research studies to examine testing for *BRCA1* and 2 mutations in the general population to determine if cancer risks are sufficient to justify general screening"[99].

One important factor in considering population-based genetic screening is the fraction of high-risk cases that would be missed by family history evaluation alone. In the New York Breast Cancer Study, 50% of mutations were found in families with negative family histories. Yet, there was evidence that mutations in these families posed risks as high as in other mutation-positive families. Carriers with non-obvious family histories appear to represent a high proportion of carriers in non-Jewish populations as well [73, 88, 100]. In a British study of 30 female *BRCA* carriers with breast cancer diagnosed by age 45, 57% had no family history of breast or ovarian cancer within three generations [73]. In an Australian study, 72% (13 out of 18) of carriers diagnosed with breast cancer under age 40 had no family history within two generations [88]. While a positive family history is a significant predictor of a germline mutation, a negative family history may have limited predictive value. Therefore, family history-based screening may miss a significant proportion of the at-risk population. Since genetic screening could identify many high-risk women that would otherwise be missed, waiting for cancer to occur in these families and then concentrating prevention efforts in sisters and other female relatives is an exceedingly unappealing approach.

A screening program is more than a laboratory test [101]. While a strong case can be made that genetic screening of Ashkenazi Jews may be the only way for many at-risk individuals to learn of their high-risk status and take advantage of early breast cancer detection and ovarian cancer prevention, the issue goes well beyond medical decision making. Critical factors in determining whether to initiate a genetic screening program include: testing-related anxiety [102], stigmatization, privacy, genetic discrimination (perceived *versus* actual, in the domains of health, life and disability insurance as well as employment) and effectiveness and breadth of legislation [103–106], cost–benefit analysis [107, 108], psychological effects within families [109, 110], community attitudes and fears, and access to genetic counseling, genetic testing and medical interventions, to name a few. The high genetic attributable cancer risks of *BRCA* founder mutations in Ashkenazi Jews, the sobering potential lethality of early onset breast cancer and ovarian cancer, and the increasing clarity about effectiveness of medical interventions make imperative further dialogue and research to keep guidelines for genetic screening up to date.

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