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BRCA1 and BRCA2 Mutation Carriers as Potential Candidates for Chemoprevention Trials

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Abstract The identification of cancer susceptibility genes offers new avenues for selecting high-risk individuals as subjects for chemoprevention trials. Because carriers of predisposing mutations are at high risk, they are more likely to enroll and comply with chemoprevention trials, and meaningful results can be achieved with smaller numbers of participants and shorter periods of follow-up. Such studies have immediate benefits for carriers themselves, but they are also likely to result in effective chemopreventive strategies for the general population. In this review, we discuss BRCA1 and BRCA2 carriers as potential candidates for breast and ovarian cancer chemoprevention trials. The existence of a large population with a high frequency of easily identifiable BRCA1/2 mutations can provide ample opportunity for such studies. However, the possibility that tumor characteristics and hormonal profile of BRCA1/BRCA2 related cancers are not completely equivalent to cancers in the general population should be borne in mind. J. Cell. Biochem. Suppl. 34:13–18, 2000.

Key words: breast cancer; ovarian cancer; cancer genetics; Ashkenazi Jews; Israel

The recent identification of a growing number of genes associated with inherited cancer syndromes offers a unique opportunity to define asymptomatic individuals at increased risk of cancer, who are most likely to benefit from preventive measures. Chemoprevention clinical trials in the general population usually require long-term, large-scale studies, which are costly and often difficult to perform. In order to improve the feasibility and yield of such trials, alternate strategies have been proposed. These include the use of surrogate or intermediate endpoints, rather than the diagnosis of cancer, and studying high-risk groups, instead of the general population. In high-risk groups, the burden of carcinogenesis is increased, so any chosen end-point will occur at a higher rate. The statistical power to detect an effect is therefore achieved with much smaller sample sizes, and within a shorter time frame. In addition, problems with recruitment, motivation and compliance, which are common in general population studies, are of lesser magnitude in high-risk cohorts. This approach has been applied successfully in secondary prevention trials, where the endpoint is the occurrence of a second primary tumor in patients with a previous malignancy. Agents shown to be effective in secondary prevention trials are much more likely to prove effective in primary prevention [Hong and Sporn, 1997]. Genetic analysis has the advantage of identifying healthy high-risk subjects for primary prevention studies. Results of such studies are of immediate benefit to carriers, but like secondary prevention trials, can also provide experimental evidence for chemoprevention in the general population. However, the carcinogenic process in carriers of specific mutations may not be representative of that in sporadic tumors and, in such cases, chemopreventive agents may have differential effects in carriers and noncarriers.

In this review, we summarize our experience with BRCA1 and BRCA2 testing in Ashkenazi

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(European) Jews and discuss the feasibility and potential yield of clinical chemoprevention trials in this genetically defined group which is predisposed to both breast and ovarian cancer.

HIGH FREQUENCY OF BRCA1 AND BRCA2 MUTATIONS IN ASHKENAZI JEWS

Epidemiological analysis suggested that in the U.S. population, the frequency of any dominant, highly penetrant breast cancer gene is approximately 1:300 [Claus et al., 1991], with a 1:800 frequency of BRCA1 mutations [Peto et al., 1996]. However in Ashkenazi Jews, both in Israel and the United States, the population frequency of BRCA1 and BRCA2 mutations combined is significantly higher, approaching 2.5% (1:40). This is the result of three ancestral mutations: 185delAG (ca. 1%) and 5382insC (0.1%) in the BRCA1 gene, and 6174delT in the BRCA2 gene (ca. 1.4%) [Struewing et al., 1995; Oddoux et al., 1996, Roa et al., 1996]. Although ancestral BRCA1/BRCA2 mutations have been observed in other countries and ethnic groups, they were found to be common in families with breast/ovarian cancer but rare in the general population [Szabo and King, 1997]. Thus, the high prevalence of BRCA1/2 mutations in the general Ashkenazi population is unique. It should be noted that similarly high carrier rates for other diseases (e.g., Tay-Sachs) have been observed in Ashkenazi Jews, probably reflecting the unique evolution and structure of this population [Motulsky, 1995]. In Israel, with more than 1 million Ashkenazi women, approximately 30,000 women are expected to be BRCA1/2 carriers.

BRCA1/2 MUTATIONS AND BREAST CANCER

Worldwide, BRCA1 and BRCA2 mutations account for up to 8% of all breast cancer, unselected for family history [Brody and Biesecker, 1998]. In Ashkenazi Jews, one of the three ancestral mutations was found in 6.7% of breast cancer patients [Fodor et al., 1998]. In a series of more than 100 consecutive Ashkenazi women with breast cancer, we have found the frequency of ancestral BRCA1/BRCA2 mutations to be approximately 11% (unpublished data). However, in certain subgroups of breast cancer patients, the frequency of these mutations is significantly higher. They account for approximately 75% of Ashkenazi families with a history of both breast and ovarian cancer, 50% of Ashkenazi families with multiple cases of breast cancer and no history of ovarian cancer [Tonin et al., 1996; Levy-Lahad et al., 1997], and 30–40% of breast cancer in women diagnosed before age 40–42 (Table I).

It should be noted that the histology of breast cancer in BRCA1/2 carriers differs from that found in sporadic cases. Tumors in BRCA1/2 carriers are more highly proliferative (more likely to be of histological grade III) and are more likely to be estrogen receptor (ER) negative and Her2/neu negative [Breast Cancer Linkage Consortium, 1997; Karp et al., 1997; Robson et al., 1998]. Differences have also been observed between BRCA2- and BRCA1-associated tumors, with comparatively lower histologic grade and less tubule formation in BRCA2-related tumors [Breast Cancer Linkage Consortium, 1997]. Although these adverse prognostic features do not appear to affect sur-

TABLE I. Frequency of Ancestral BRCA1/2 Mutations in Ashkenazi Jewish Women With Breast Cancer

Selection criteria	BRCA1 185delAG (%)	BRCA1 5382insC (%)	BRCA2 6174delT (%)	Total (%)	No. tested	Reference
Age at diagnosis <42 yr	20	3.7	7.5	31	80	Offit et al. [1996] Neuhausen et al. [1996]
Age at diagnosis ≤40 yr	21	Not done	Not done		39	Fitzgerald et al. [1996]
Age at diagnosis ≤40 yr	16	7	7	30	43	Abeliovich et al. [1997]
Diagnosis at 42–50 yr Positive family history[a]	30	3.7	7.4	41	27	Offit et al. [1996] Neuhausen et al. [1996]
Diagnosis at 42–80 yr Positive family history	14	Not done	3		29	Oddoux et al. [1996]
Ashkenazi, unselected	3	0.75	3	6.7	268	Fodor et al. [1998]

[a]Positive family history defined as one first-degree or two second-degree relatives affected with breast or ovarian cancer, one before age 50.

vival in BRCA1 carriers [Watson et al., 1998, Verhoog et al., 1998], they suggest that the underlying pathogenesis of BRCA-related tumors may not be representative of non-BRCA-related tumors. This clearly has implications for using BRCA carriers as a test group for chemopreventive agents, as the same agent may have different effects in BRCA1/2-related vs non-BRCA1/2-related cancer. Tamoxifen is perhaps a case in point. Interim analysis of the UK tamoxifen prevention trial [Powles et al., 1998] did not show tamoxifen to be protective against breast cancer, whereas the NSABP-P1 trial in the United States found that tamoxifen reduced breast cancer risk by 49% overall [Fisher et al., 1998]. This discrepancy may in part be the result of different inclusion criteria. The UK trial is likely to have included a relatively larger proportion of BRCA1/2 carriers that have a higher frequency of estrogen receptor (ER)-negative tumors [Powles et al., 1998]. ER-negative tumors were not prevented by Tamoxifen in the NSABP-P1 study, so in a high-risk group with a tendency to develop ER-negative tumors (e.g., BRCA1/2 carriers) a tamoxifen effect may not be apparent.

Additional issues in assessing chemopreventive strategies in BRCA1/2 carriers include risk stratification. Originally, BRCA1/2 mutations were thought to be associated with an approximately 85% lifetime risk of breast cancer [Ford et al., 1994; Easton et al., 1995]. However, these figures were based on extremely high-risk families used for linkage analyses. Studies that are more population based found lower lifetime risks, ranging from 56% to as low as 36% [Struewing et al., 1997; Levy-Lahad et al., 1997a; Fodor et al., 1998]. Although such differences could be explained solely by ascertainment bias, they also raise the possibility that family history influences risk in mutation carriers, perhaps as a result of other genetic factors segregating within families. In addition, most studies have found that the common BRCA2 mutation is associated with lower breast cancer risk than the BRCA1 mutations [Roa et al., 1996; Levy-Lahad 1997b; Struewing et al., 1996]. Thus, chemoprevention studies in BRCA1/2 carriers may have to take into account both family history and specific mutation status. Although such studies are clearly worthwhile for the large carrier population in Israel and elsewhere, extrapolation of results from carriers to noncarriers and vice versa will require additional investigation. A detailed analysis of the tumors prevented is one of the tools to verify the appropriateness of using data from clinical chemoprevention trials in specific high-risk groups to the general population and vice versa.

BRCA1/2 MUTATIONS AND OVARIAN CANCER

In most malignancies, approximately 5–10% of cases are expected to be caused by dominant genes with high penetrance. The attributable risk of BRCA1/2 mutations in Ashkenazi breast cancer patients is close to this 5–10% range. However for ovarian cancer in Ashkenazi Jews, the attributable risk of BRCA1/2 mutations is considerably higher. In different series of unselected cases of ovarian cancer, approximately 40% of patients were found to be carriers of one of the ancestral BRCA1/2 mutations (Table II). Thus, in contrast to the situation in breast cancer, chemoprevention of ovarian cancer in BRCA1/2 carriers could have a major impact on the incidence of ovarian cancer in Israel, where approximately two-thirds of affected women are of Ashkenazi descent.

Comparisons of ovarian tumor histology in BRCA1/2 carriers vs noncarriers have been less

TABLE II. Frequency of Ancestral BRCA1/2 Mutations in Ashkenazi Jewish Women With Ovarian Cancer

Selection criteria	BRCA1 185delAG (%)	BRCA1 5382insC (%)	BRCA2 6174delT (%)	Total (%)	No. tested	Reference
Sequential[a]	25	4.1	19	48	48	Levy-Lahad et al. [1997a]; unpublished data
Ashkenazi/Israeli born	34	Not done	Not done		65	Modan et al. [1996]
Sequential[a]	19	Not done	Not done		31	Muto et al. [1996]
Sequential[a]	30	0	28	58	43	Abeliovich et al. [1997]

[a]Consecutively tested patients, not necessarily diagnosed consecutively.

extensive than those performed for breast tumors, but in general, no differences have been observed in tumor type, grade or stage at diagnosis. In both groups, most epithelial ovarian cancer are serous, and most are diagnosed with stage III disease [Muto et al., 1996; Rubin et al., 1996]. A potential difference, which is highly controversial, is in the natural history of ovarian cancer in BRCA1 carriers compared to noncarriers. The original study that found improved survival in BRCA1 carriers compared with noncarriers [Rubin et al., 1996] was problematic because the control group was historical, and may not reflect current improvement in ovarian cancer therapy. A similar but smaller study in Japan (25 cases) [Aida et al., 1998] confirmed these results, again using historical controls. However, population based studies [Johansson et al. 1998; Ben David et al., 1998] found that ovarian cancer survival in BRCA1 carriers was similar to that of matched controls. We are currently following 48 sequentially ascertained women with ovarian cancer, of whom 14 are BRCA1 carriers and 9 are BRCA2 carriers (Table II). and preliminary results indicate that time to disease progression and survival are similar in BRCA1 carriers and noncarriers but are significantly longer in BRCA2 carriers. Whether this effect is common to all BRCA2 mutations or is specific to the ancestral 6174delT mutation remains to be seen, but points to the fact that genetically defined high-risk groups are likely to be complex and cannot be assumed to be homogeneous, even before comparisons to sporadic cases are made.

The risk of ovarian cancer is different for BRCA1 and BRCA2 carriers. Original estimates, based on high-risk families, suggested a lifetime risk of up to 63% for BRCA1 and 10–20% for BRCA2 carriers [Easton et al., 1995; Wooster et al., 1994]. A study based on self-reported family history suggested lifetime risk ofovarian cancer in Ashkenazi carriers may be much lower (16% by age 70) [Struewing et al., 1996], but data based on direct mutation analysis and medical records in Israel suggest that ovarian cancer risk is at least 27% by age 65 [Levy-Lahad et al., 1997b].

With BRCA1/2 mutations in Ashkenazi Jews accounting for a substantial proportion of ovarian cancer in this group, and with tumor characteristics that appear to be similar to those of sporadic ovarian cancer, chemoprevention studies in BRCA1/2 carriers are likely both to have an impact on ovarian cancer incidence in Israel and in Ashkenazi Jews worldwide and to be relevant to sporadic ovarian cancer. An example is oral contraceptive agents, which are known to reduce sporadic ovarian cancer risk, possibly by inhibiting ovulation [Whittemore et al., 1992]. A recent study suggests that the same effect may be apparent in BRCA1 carriers [Narod et al., 1998]. Although these results were based on a control group that included noncarriers and did not take into account the protective effect of prophylactic oophorectomy, they suggest that hormonal modulation of ovarian cancer is similar in carriers and noncarriers [Rubin, 1998]. Because prophylactic oophorectomy is highly effective in prevention of ovarian cancer in BRCA1/2 carriers [Rubin, 1998] and is generally offered to carriers at completion of childbearing, it should be incorporated either to the design and analysis of future chemoprevention trials.

CHEMOPREVENTION STUDIES IN BRCA1/2 CARRIERS

Chemoprevention studies in BRCA1/2 carriers offer the advantages of using a high-risk population. Factors which need to be taken into account are baseline risks, differential effects of mutations in different genes, tumor characteristics, and existing preventive measures (e.g. prophylactic oophorectomy). Another issue is that BRCA1/2 carriers have substantially increased risk for more than one type of tumor (i.e., both breast cancer and ovarian cancer). Chemoprevention studies aimed at one of these malignancies should also include the other as a measured endpoint, to ensure that benefits in respect to one tumor are not counterbalanced by an increased risk of the other.

In Israel, we estimate the BRCA1/2 carrier population to number at least 30,000 women. Because of the high frequency of recurrent, ancestral mutations, molecular identification of large numbers of BRCA1/2 carriers is technically feasible, whereas in other countries it would require large-scale sequencing efforts. Because large numbers of women can be reached at the population level, biases inherent in studies based on high-risk women can be minimized. In addition, concerns about ethnic stigmatization, which have occurred in the United States, are not relevant to Ashkenazi Jews in Israel. In our experience, mutation carriers are

highly motivated and would be willing to participate in chemoprevention clinical trials. Such trials would be of immediate benefit to BRCA1/2 carriers themselves, and may also result in effective chemopreventive strategies for women in general.

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