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REVIEW

Evaluating Cancer Risks in BRCA Mutation Carriers

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ABSTRACT

- Inherited mutations that affect a single allele of either *BRCA1* or *BRCA2* are mainly linked with cancers of the breast, ovary, and fallopian tube, whereas the risks of other cancers as colorectal, pancreas and stomach are rather small. Male carriers have also an increased risk of cancer in the breast, prostate and other sites. BRCA1 is the most important gene for cancer susceptibility in women and BRCA2 for men.
- Biallelic germline mutations in BRCA2 are also associated with the very rare D1 complementation group of Fanconi anaemia (FA).
- Women who are born with mutations in BRCA1, BRCA2 genes have a high lifetime risk of breast and ovarian cancer but the magnitude of this risk is controversial.
- Table 1 summarizes the risks in the literature that vary widely among BRCA mutation carriers depending mainly on family history.
- But a latest study on 1,008 New York-area Ashkenazi women (NYBCS; *Science 2003, Oct. 24)* reverses this status. All the relatives of a case, not only those from high-incidence (multiple-cases) families but even those from low-incidence (single case or distant relatives) families have a high lifetime breast-, ovarian cancer risk if they carry a BRCA1 or BRCA2 mutation (breast cancer [82%, for both BRCA1 and BRCA2] and ovarian cancer [BRCA1: 54%; BRCA2: 23%]).

If these findings are validated, clinically important implications will emerge on genetic testing, involving even distant relatives of a case and on risk-reducing prevention strategy, recommending prophylactic surgery rather than surveillance.

There is a well-established link between germline mutations in specific genes and inherited susceptibility to common types of human cancers. Individuals who are born with germline mutations in specific genes have an increased risk – significantly higher than those in the general population- of developing cancer later in their life. There is a close association of gene-specific mutations and increased cancer risk at specific organ(s). This high lifetime cancer risk in germline mutation carriers gives rise to several rare hereditary cancer syndromes including hereditary breast and ovarian cancer syndrome (HBOCS), hereditary diffuse gastric cancer syndrome (HDGCS), hereditary nonpolyposis colon cancer syndrome and others. The evident high lifetime cancer risk for mutation carriers urgently suggests the need for preventive measures but the clinical management of these syndromes remains controversial. Surgery and surveillance are currently offered to individuals with inherited cancer susceptibility but the optimal prevention strategy is unknown. Prophylactic surgery reduces this risk but because of its invasive and irreversible nature is not chosen by many carriers.[1] Surveillance, as a carriers-friendly procedure is a preferable approach, but it is associated with increased risks of cancer and mortality. Cancer risk estimates is one of the most important factors in clinical judgment for the selection of prevention strategy in germline mutation carriers.

Breast cancer, with 215,990 new cases expected in the USA in 2004, is the most common malignancy among women accounting for 32% of all female cancers.[2]

Inherited breast cancer accounts for only 5% to 10%

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of women who are annually diagnosed with breast cancer.

Despite this small proportion, a substantial absolute number of patients is affected by HBOCS. Germ-line mutation in BRCA1 or BRCA2 genes is the cause of breast cancer in approximately 10,800 women (5%) with newly diagnosed breast cancer.

The importance of this incidence becomes clear when we compare it for example with all new -inherited and sporadic- gastric cancer cases (9.300) expected to occur in 2004 among females in the USA.[2] Reliably therefore, research efforts have been focused on the identification of these women before the disease becomes clinically detectable. The goal of prevention is to reduce the incidence of cancer in the breast and ovary, as well as mortality from these diseases.

A decade ago the two breast cancer genes BRCA1 and BRCA2 were discovered. Subsequent studies showed that the inheritance of germline mutations, which affect one allele of either BRCA1 or BRCA2 confers susceptibility to breast and ovarian cancer. With this discovery most scientists were overoptimistic predicting that BRCA genes would illuminate not only this rare form of inherited cancer, but also the most common sporadic breast cancer as well. They supposed that these genes were also involved in sporadic breast cancer carcinogenesis and with advances in understanding the molecular BRCA pathway they would be able to create effective chemoprevention strategies. Now, 10 years later, it is clear that these expectations, regarding sporadic –noninherited- cancer, were elusive.

Despite this disappointment regarding sporadic cancer, dramatic advances have been made in the prediction of a woman's risk to develop inherited breast and ovarian cancer. It has long been known that relatives of a woman with breast cancer have an overall higher, about two-fold, risk of breast cancer than women in the general population. With the availability of genetic test we are able to classify more accurately the relatives of a breast cancer case into high risk and low risk groups. This distinction is of major clinical value. On one hand, women with BRCA-negative test have an approximately similar risk to that of women in the general population. The lifetime risk is generally approximately 10 to 13% for breast cancer and 1% to 2% ovarian cancer. These women should follow the general recommendations for prevention and screening. On the other hand however, significantly higher lifetime risks for BRCA mutation carriers have been reported. It is clear therefore, that preventive measures for these high-risk women are urgently needed.

In addition to this ability in classifying cancer risks individuals, genetic test may also be useful for decision-making in young women with newly diagnosed breast cancer. Since approximately 10% of young women with a new diagnosis of breast cancer are carriers of BRCA mutations and surgical management differs between women with sporadic and inherited breast cancer, genetic testing before initial treatment is critical in surgical intervention.[3] Indeed, the current medical practice for women with sporadic early-stage breast cancer involves breast-conserving surgery whereas for those women with inherited breast cancer bilateral mastectomy, are recommended, salpingoophorectomy or both. [3,4]

Despite advances in understanding the tumorigenesis of inherited breast and ovarian cancer and the increasing amount of clinical data available, clinical management has not been established. Since a lot of personal, phycological and emotional data as well as confidentiality and insurance issues are not included in the direct medical consultation, decision whether a woman should be tested or not is strongly personal. Furthermore, decision-making among a variety of prevention options currently available is very complicated. The prevention choices vary with respect to their ability to protect from cancer and their adverse effects on morbidity and quality of life of women with inherited mutations. Risk estimates appears to be one of the most decisive factors for the ultimate choosing of the appropriate prevention strategy.

Inherited cancer risk estimates in BRCA carriers

Women who are born with a deleterious mutation in BRCA1 or BRCA2 gene have an evident significantly higher lifetime risk of breast cancer and ovarian cancer than women in the general population but the magnitude of this risk is controversial.[5] The reported lifetime risks vary considerably from about 40% to 85% for breast cancer and 15% to 65% for ovarian cancer. This risk is caused by the inherited mutations that affect a single allele of either BRCA1 or BRCA2. This inheritance of germline BRCA mutations gives rise to a hereditary breast, ovarian cancer syndrome (HBOCS).[6] These individuals may also have an increased risk of other epithelial cancers, including those of the pancreas, colon or stomach,[7,8] but the message is that the major cancer risks conferred by BRCA1 are related to cancers of the breast, ovary, and fallopian tube, whereas the risks of other cancers as prostate, colorectal, pancreatic, and stomach are likely to be small.[9]

Biallelic germline mutations in BRCA2 are also associated with the very rare D1 complementation group of Fanconi anaemia (FA). The clinical features of FA-D1 patients, who develop Wilms' tumors, breast cancer and medulloblastoma- differ from typical FA cases. BRCA and FA proteins work in a network of linked biological processes.[10]

Early risk estimate studies of BRCA1 and BRCA2 mutations carriers used high-risk families with multiple cases of breast cancer and ovarian cancer. The estimated risks by the age of 70 years were very high, with an estimated risk > 80% for breast cancer in BRCA1 and BRCA2 carriers and 40% to 66% for ovarian cancer in BRCA1 carriers and 20% in BRCA2 carriers.[11-15] However, such studies were subject to potential ascertainment biases. To offset such biases, recent studies have used data from family members of probands ascertained from population-based incident cases of cancer.

Table 1 summarizes these results. Risk estimates based on studies unselected for family history are significantly

higher to those in the general population but lower to those reported from multiple-cases families.[6,7,16-27] However, even penetrance estimates from case proband studies can be inflated if other factors influence breast cancer risk in addition to the specific genetic abnormality.[28] Thus, women with such genetic abnormalities and a strong family history of breast cancer are likely to possess a much higher risk for breast cancer than women with such abnormalities but without a strong family history.[28]

However, new evidence for a very high risk of breast and ovarian cancer even in the absence of a strong family history is provided by a recent large study. The New York Breast Cancer Study (NYBCS) published recently in Science,[29] merits our special consideration because their findings may substantially influence clinical choice from various preventive options available.

New York Breast Cancer Study (NYBCS)

The NYBCS reverses the up to now widely accepted view that breast and ovarian cancer risks among BRCA carriers have been overestimated. It is likely that this paper may change prevention strategy convincing more BRCA carriers and their physicians to move from a conservative approach to a cancer risk-reducing surgery. In the NYBCS 1,008 New York-area Ashkenazi Jewish women diagnosed with incident, breast cancer between 1996 and 2000 were enrolled. The cohort was composed of Ashkenazi Jewish patients, because this population harbors three ancient BRCA1 and BRCA2 mutant alleles with a combined population frequency of 2.5% [16,18,20,30] and includes very few rare family-specific BRCA1 or BRCA2 mutations.[31] Screening therefore, only a limited number of mutation sites for large numbers of breast cancer patients in Jewish population, the NYBCS can ensure accurate BRCA1 and BRCA2 genetic diagnosis.

Table 1. Breast and ovarian cancer risks estimates for BRCA1 and BRCA2 mutations carriers from studies unselected from family history.

			%* Penetrance (95% CI), of both genes in breast and ovarian cancer			
			Breast Cancer		Ovarian Cancer	
Study	Gene(s)	Mutation carriers	BRCA 1	BRCA2	BRCA1	BRCA2
Struewing et al. [20]	BRCA1/ BRCA2 †	27 case probands‡ 62 control subjects	56 (40 to 73)		16 (6 to 28)	16 (6 to 28)
Thorlacius et al. [25]	BRCA2§	69 case patients (male or female)	-	37 (22 to 54)		
Warner et al. [18]	BRCA1/ BRCA2†	48 case patients	60 (—)	28 (—)		
Hopper et al. [19]	BRCA1/ BRCA2	18 case patients‖	40 (15 to 65)			
Anglian group [24]	BRCA1/ BRCA2	24 case patients¶	48 (7 to 82)	74 (7 to 94)	22 (6 to 65)	22 (6 to 65)
Antoniou et al. [6]	BRCA1/ BRCA2	500 case patients#	65 (44 to 78)	45 (31 to 56)	39 (18 to 54)	11 (2.4 to19)
Risch et al. [23]	BRCA1/ BRCA2	60 case patients#	68 (—)	"No excess risk"	36	
Satagopan et al. [22]	BRCA1/ BRCA2†	79 case patients†† 62 controls	46 (31 to 80)	26 (14 to 50)	NE	NE
Satagopan et al. [27]	BRCA1/ BRCA2†	147 case patients† 62 controls	NE	NE	37 (25 to71)	21 (13 to 41)
Brose et al.[7]	BRCA1/ BRCA2	483 mutation carriers (147 families)	72.8 (67.9 to 77.7) and risk for a second primary breast cancer 40.5 (34.1 to 47)	NE	40.7 (35.7 to 5.6)	NE
Fodor et al [17]	BRCA1/ BRCA2	268 case patients	36 (---)	NE	NE	NE

*CI = confidence interval; — = CIs were not reported in these studies.

‡Case probands include survivors of breast or ovarian cancer.

‖Case patients with breast cancer diagnosed at younger than 40 years of age.

¶Patients with breast cancer diagnosed at younger than 55 years of age.

#Probands are patients with incident cases of ovarian cancer.

**Model-dependent "best estimate" that does not use kin–cohort methodology.

†Hospital-based patients with incident cases of cancer. The same control subjects were used here and by Struewing et al. *(3)*.

§ Family data were not used to estimate penetrance.

Of the 1008 female probands with newly diagnosed breast cancer, 104 (10.3%) carried an ancient mutation in BRCA1 or BRCA2. The frequencies of the individual mutations were: 42 (4.2%) BRCA1.185delAG, 25(2.5%) BRCA1.5382insC, and 37 (3.7%) BRCA2.6174delT. These rates are similar to these previously reported in this population[16-18,20,22]. Of the 104 patients with breast cancer and inherited mutations exactly half (52) were from low-incidence families with no breast or ovarian cancer among mothers, sisters, grandmothers, or aunts. In nearly all these low-incidence families, BRCA1 and BRCA2 mutations proved to be inherited from fathers. In these low-incidence families, breast cancer was also evaluated for second-, third, and fourth-degree (grandmothers, aunts, and cousins) with BRCA1 or BRCA2 mutations. In these distant relatives with the inherited mutations the risk of breast cancer at age 80 was 78%. There was no difference in risk between relatives with mutations in low-incidence or high-incidence families.

By comparing age, family history, cancer status, and other factors, the team determined that the overall lifetime risks for breast cancer were 82% for BRCA1 or BRCA2 carriers and for ovarian cancer were 54% for BRCA1 carriers and 23% for BRCA2 mutation carriers. The most important finding, from the clinical point of view however, as opposed to the until now available data, was the very high risk of breast and ovarian cancer among mutations carriers regardless of family history. In other words, the evidence for the presence of BRCA1 or BRCA2 mutations in a woman represents a very high cancer risk whereas family history has a rather little, nonsignificant, impact on a carrier's cancer risk.

Environmental and genetic modifiers

Why are there differences in cancer risk among BRCA mutations carriers? It is rational to think that both environmental and genetic factors modify the penetrance. King et al.[29] found that non-genetic (environmental) factors may significantly influence the penetrance even of highly penetrant mutations. The increase in breast cancer risk over time among mutation carriers parallels, at much higher levels, the increase in breast cancer incidence among women in general.[32] Changes in the prevalence of many environmental factors, including social changes with late pregnancy of women in the recent decades, may explain the increased breast cancer risk. Early first pregnancy,[33] physical exercise and healthy weight in early life[34] are protective against breast cancer in women generally. In the NYBCS study, breast cancer risk in women born before 1940 is high, but this risk is even higher ($p<0.0001$) for women born after 1940. For example, breast cancer risk by age 50 among mutations carriers born before 1940 was 24%, but among those born after 1940 it was 67%.[29] Evaluation of variables such pregnancy, physical exercise and weight in the NYBCS cohort showed similar associations among probands with or without BRCA1 or BRCA2 mutations. However, the findings cannot explain the rising risk in younger women. Either unknown environmental factors or known risk factors such as age at menarche and age at pregnancy might explain the increased risk observed in women born after 1940. But the NYBCS lacked sufficient statistical power to evaluate these variables in combination was noted in an accompanying perspective article Levy-Lahad and Plon.[35] King et al. underline that identification of environmental exposures, which modify the penetrance of BRCA mutations, suggests new direction for studies of BRCA1- and BRCA2-associated carcinogenesis.

Similarly, data on possible genetic modifiers of the penetrance of BRCA1 and BRCA2 mutations are emerging.[36-39] It is likely that there exist many genetic contributors to breast cancer risk other than BRCA1 and BRCA2 and that variants of these genes represent a further pool of potential modifiers to investigate.[40]

The problem of how best to conceptualize and study interactions between genetic and environmental risk factors, as well as gene–gene interactions (epistasis), is just beginning to attract the attention of biostatisticans, epidemiologists, and statistical geneticists. As in all epidemiologic studies, interaction can be characterized as additive or multiplicative, and several different patterns of gene–environment interaction can be postulated,[41] posing complex analytic challenges. These challenges are magnified when several genetic and environmental risks need to be taken into account. Yet Begg's analysis[28] underscores the pitfalls of failing to address this complexity and its implications for disease prevention.

Cancer risk at other sites

There is convincing evidence that the major cancer risks conferred by BRCA1 and BRCA2 in women are for cancers of the breast, ovary, fallopian tube, and peritoneum. But, is there for these carriers an additional increased risk of developing cancer at other sites? This is a key question in designing surgical or conservative prevention strategy.

Several epidemiological observations have suggested an additional increased risk cancer at other sites such as pancreas, colorectum and stomach. In two recent studies there were increased risks of pancreatic, colorectal and stomach cancer among BRCA1 carriers [7,8], but these risks are likely to be small conclude Gruber and Petersen in an accompanying editorial.[9] Similarly, inherited mutations of the BRCA2 gene give rise to a multi-site cancer phenotype which includes breast cancer, ovarian, pancreatic cancer, ocular and other melanomas, laryngeal, colon and stomach cancer.[43] The position of mutation[43] and the ethnic background of the family[42,43] appear to contribute to the phenotypic variation observed in families with BRCA2 mutations.

Male carriers of mutations in BRCA1 or BRCA2 are also susceptible to cancer. This risk has been studied in a recent review.[45] Male BRCA1 mutation carriers are at increased risk of cancers of the prostate and breast. Evidence supporting increased susceptibility to colon cancer is limited. In contrast to women, who have a greater lifetime risk of cancer with mutations of the BRCA1 gene, BRCA2 is the more important gene for

men. The spectrum of cancers is wide for BRCA2 and some studies report that the overall cancer risk for male BRCA2 carriers exceeds the risk for female carriers. In particular, the relative risk to male BRCA2 mutation carriers is high before age 65 years, largely attributable to breast, prostate, and pancreatic cancers. BRCA2 mutation carriers are also at risk of stomach cancer and melanoma (of the skin and eye). Liede et al. conclude that additional research into risks to male BRCA1 or BRCA2 mutation carriers is necessary, specifically to determine the magnitude of excess cancer risk among BRCA2 carriers and to increase our understanding of the basis for the observed site -specificity in cancer development.

Future

Clinical management of family members with a history of breast or ovarian cancer has been controversial. Currently, genetic testing is recommended in family members with a strong family history. The result of this test determines the preventive measures. The analysis of data reported urgently indicates the need for medical intervention for women with evident BRCA1 or BRCA2 mutation. Prophylactic surgery[45] and surveillance are used to reducing cancer risk and improving survival of these women, but information is insufficient for an ideal medical advice.[1] As preventive choices abound it increases the uncertainty about which of three surgical procedures available - bilateral mastectomy, salpingo-oophorectomy, or both) provides the best prevention at the lower side-effects profile[46-51]. Similarly, controversy exists also for those BRCA carriers who choose a conservative approach. It is unclear whether surveillance should include not only a mammographic and ultrasonographic screening but also modern imaging technology such magnetic resonance imaging as well as whether these women should receive or not chemoprevention.

The findings of the NYBCS may reverse this status. If these findings are validated, they will change both indications for genetic testing and prevention strategy. First, recommendations for genetic testing will be extended including distant relatives of a case with breast or ovarian cancer as well as women with a breast cancer family history on father's side. Second, more physicians and BRCA carriers will be convinced for the high lifetime cancer risk of BRCA carriers irrespective of family history and thereby more women with the mutant genes will choose risk-reducing prophylactic surgery rather than surveillance.

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