Commentary

An international initiative to identify genetic modifiers of cancer risk in *BRCA1* and *BRCA2* mutation carriers: the Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* (CIMBA)

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Abstract

BRCA1 and *BRCA2* mutations exhibit variable penetrance that is likely to be accounted for, in part, by other genetic factors among carriers. However, studies aimed at identifying these factors have been limited in size and statistical power, and have yet to identify any convincingly validated modifiers of the *BRCA1* and *BRCA2* phenotype. To generate sufficient statistical power to identify modifier genes, the Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* (CIMBA) has been established. CIMBA contains about 30 affiliated groups who together have collected DNA and clinical data from approximately 10,000 *BRCA1* and 5,000 *BRCA2* mutation carriers. Initial efforts by CIMBA to identify modifiers of breast cancer risk for *BRCA1* and *BRCA2* mutation carriers have focused on validation of common genetic variants previously associated with risk in smaller studies of carriers or unselected breast cancers. Future studies will involve replication of findings from pathway-based and genome-wide association studies in both unselected and familial breast cancer. The identification of genetic modifiers of breast cancer risk for *BRCA1* and *BRCA2* mutation carriers will lead to an improved understanding of breast cancer and may prove useful for the determination of individualized risk of cancer amongst carriers.

The search for genetic modifiers of *BRCA1* and *BRCA2*

Female carriers of deleterious *BRCA1* and *BRCA2* mutations are predisposed to high lifetime risks of breast and ovarian cancer. Initial estimates indicated that around 80% of carriers of mutations in *BRCA1* and *BRCA2* from multiple-case families would develop breast cancer by age 70 [1,2], and genetic counseling is usually carried out on the assumption that penetrance estimates apply to all women. However, a later pooled analysis from population-based studies estimated an average risk by age 70 in this context of 66% in *BRCA1* carriers and 45% in *BRCA2* carriers [3]. It has also been reported that cancer risks vary by the age at diagnosis and the type of cancer in the index case [3,4]. Such observations are consistent with the more plausible hypothesis that cancer risks in mutation carriers are modified by genetic factors or other risk factors that cluster in families. Segregation analysis has also demonstrated that models that allow for other genes to have a modifying effect on the breast cancer risks conferred by *BRCA1* and *BRCA2* mutations fit significantly better than models without a modifying component [5]. Further evidence for genetic modifiers arises from studies of risk factors that are themselves influenced by genetic factors. For example, mammographic density that has a strong genetic component [6] has been recently shown in one study to modify the breast cancer risks in *BRCA1* and *BRCA2* mutation carriers [7].

Although there has been considerable interest in finding genetic modifiers of cancer risk in *BRCA1* and *BRCA2* mutation carriers, the number of published studies is still fairly modest and has focused around genes involved in a limited number of pathways: detoxification of environmental carcinogens, DNA repair and steroidogenesis. Several studies have evaluated the CAG repeat length polymorphism in the androgen receptor (*AR*) gene as a modifier of breast cancer risk among mutation carriers. However, the data from different studies are contradictory and no firm conclusions can be drawn as to the magnitude of such an effect, if any [8-11]. Many studies have also evaluated a repeat length polymorphism in *AIB1* as a modifier of risk among *BRCA1* or

CIMBA = Consortium of Investigators of Modifiers of *BRCA1* and BRCA2; SNP = single nucleotide polymorphism.

BRCA2 mutation carriers. Although an effect of high numbers of repeats on cancer risk in carriers was first reported by Rebbeck and colleagues [12], three large subsequent studies failed to replicate this result [13-15]. *RAD51* currently provides the most convincing evidence for the existence of a modifier gene, at least for *BRCA2* mutation carriers. Levy-Lahad and colleagues [16] first reported that the -135G>C single nucleotide polymorphism (SNP) in the 5′ untranslated region of *RAD51* modified the breast cancer risk in *BRCA2* carriers and this finding has been substantiated by others [17,18]. The function of the -135G>C SNP in *RAD51* is not clear, but it could affect mRNA stability or translational efficiency.

Choosing candidate SNPs or genes to evaluate as modifiers of *BRCA1* and *BRCA2* suffers from the same problem faced by all candidate-based genetic association studies, namely the poor understanding of the relevant pathways and hence the small *a priori* likelihood that any of them are true modifiers [19]. These issues may be overcome in the future through the identification of candidate genomic regions associated with breast cancer risk by linkage analyses [20], or more plausibly by the identification of candidate SNPs by adequately powered genome-wide association studies [21]. In addition, the publication of convincingly validated SNPs associated with breast cancer in the general population [22] will provide some new candidates to test as modifiers of breast cancer risk among *BRCA1* or *BRCA2* mutation carriers. However, since SNPs associated with breast cancer in the general population may not act in the same way among *BRCA1* and *BRCA2* mutation carriers, pathway-based and perhaps genome-wide association studies in *BRCA1* and *BRCA2* carriers are also needed.

Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* (CIMBA)

A number of large studies and consortia have been established that aim to identify genetic modifiers of cancer risk in *BRCA1* and *BRCA2* mutation carriers, including Modifiers and Genetics in Cancer (MAGIC), Epidemiological study of BRCA1 and BRCA2 mutation carriers (EMBRACE), Genetic Modifiers of cancer risk in *BRCA1/2* mutation carriers (GEMO), the Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConFab), the German Consortium for Hereditary Breast and Ovarian Cancer (GCHBOC) and the Breast Cooperative Family Registry (Breast-CFR). However, with current sample sizes of less than 1,500 carriers, none of these groups have adequate power to identify genetic modifiers with confidence. To address this problem, a 'consortium of consortia', the Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* (CIMBA), was established in 2005 (see Additional file 1 for a list of current contributors). The operating principles of CIMBA are: CIMBA is open to any group that can contribute genotypic and basic phenotypic and epidemiological risk factor data from at least 100 female *BRCA1* and *BRCA2* mutation carriers with or without a cancer diagnosis - groups with smaller collections of carriers are encouraged to participate through partnership with a larger group; panels of SNPs for genotyping are selected at face-to-face meetings every six months; only SNPs that show significant associations (arbitrarily set at $p < 0.01$) with breast cancer risk in carriers, either in the published literature or in data from a member group, or are convincingly identified as associated with breast cancer in the general population, are considered; each group is free to participate, or not, in any round of genotyping; genotyping quality control standards must be followed (>2% duplicates, call rates >95%, no-template controls on every plate and randomized arrangement of affected and unaffected carriers for genotyping); all epidemiological risk factor data and genotyping data from carriers are submitted to the CIMBA data coordinating centre at the University of Cambridge; and genotyping data from participating centers are pooled for analysis. There are currently about 30 groups from North America, Europe and Australia who plan to contribute to some or all of the collaborative CIMBA projects, and collectively they have DNA and minimum required clinical and epidemiological data from more than 10,000 *BRCA1* and 5,000 *BRCA2* carriers.

Statistical considerations

Most association studies are case-control studies, in which genotype frequencies in a series of cases are compared with those in series of controls. The analysis of *BRCA1* and *BRCA2* modifiers is potentially more complex, because a high proportion of carriers become affected. Thus, modifiers would be expected to influence not just whether a carrier became affected but also the age at diagnosis. More powerful analyses can, therefore, be conducted by treating breast cancer as a survival (age at onset) rather than a simple binary endpoint. An additional problem, however, is introduced by the fact that mutation carriers are mainly ascertained through cancer genetics clinics. In these settings, the first tested individual in a family is usually someone diagnosed with cancer at a relatively young age. Such study designs tend, therefore, to lead to an over-sampling of affected individuals and standard analytical methods like Cox regression may lead to biased estimates of the risk ratios [5]. CIMBA aims to address this potential bias by using standard analytical methods, such as weighted Cox regression, or by analyzing the data within a retrospective likelihood framework [5]. In addition, analyses restricted to incident cases, defined as carriers diagnosed with cancer no more than five years prior to ascertainment, are applied to account in part for ascertainment and possible survival bias. One of the aims of CIMBA is also to further develop the statistical methodology used to analyze such data. Among *BRCA1* mutation carriers and at a threshold of $p < 0.0001$, CIMBA currently has a power of over 80% to detect polymorphisms with minor allele frequencies greater than 10% that confer risk ratios in excess of 1.2 (Table 1). The power is somewhat lower among the current sample of

Table 1

Simulated power (%) to detect a polymorphism with varying minor allele frequency and risk ratio, under a multiplicative model at a significance level 10^{-4}

Minor allele frequency	Relative hazard	Sample size: 5000	Sample size: 10,000
0.10	1.1	2	7
	1.2	33	80
	1.3	86	100
0.20	1.1	5	26
	1.2	74	100
	1.3	100	100
0.30	1.1	10	44
	1.2	89	100
	1.3	100	100

Simulations performed as in [5].

BRCA2 mutation carriers. However, it is still far greater than the power that be achieved by each study individually - at a minor allele frequency of 20% and risk ratio of 1.2, the corresponding power would be <5% for a sample size of approximately 1,000 carriers. Moreover, most of the participating CIMBA centers are actively recruiting carriers, and larger sample sizes are expected in the future.

Conclusions

The identification of convincingly validated modifiers of breast cancer risk for *BRCA1* and *BRCA2* mutation carriers will help to understand the biology of hereditary breast tumors and, in the case of *BRCA1*-mutation-associated risk modifiers, will also provide candidate low penetrance genes for 'sporadic' basal cell breast cancers because of their similarity to *BRCA1*-related breast tumors [23,24]. In the long term it might be possible to include information on genetic modifiers in risk prediction models, to give individualized advice to mutation carriers on individual breast cancer risks, and to have sufficient power to evaluate the risk of other cancers in *BRCA1* and *BRCA2* mutation carriers.

Additional file

The following Additional file is available online:

Additional file 1
Current contributors to CIMBA.
See http://breast-cancer-research.com/content/supplementary/bcr1670-s1.doc

Competing interests

The authors declare that they have no competing interests.

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