Commentary

Variation in breast cancer risk in BRCA1 and BRCA2 mutation carriers
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Abstract
Genetic testing for BRCA1 and BRCA2 (BRCA1/2) mutations can provide important information for women who are concerned about their breast and ovarian cancer risks and need to make relevant prevention and medical management decisions. However, lifetime risks of breast cancer in individual BRCA1/2 mutation carriers have been confusing to apply in clinical decision-making. Published risk estimates vary significantly and are very dependent on the characteristics of the population under study. Recently, Begg and colleagues estimated cancer risks in a population-based study of BRCA1/2 mutation carriers. Here, we discuss the clinical decision-making implications of this research in the context of risk factors that may influence risk estimates in BRCA1/2 mutation carriers.

Variation in breast cancer risk in BRCA1 and BRCA2 mutation carriers
In 1995, Easton and colleagues [1] provided an estimate of greater than 80% for the lifetime risk of breast cancer in BRCA1 carriers. This estimate, the highest reported, was based on families with at least four individuals with breast and/or ovarian cancer collected for linkage analysis to identify genes associated with familial breast cancer. In contrast, studies of unselected breast cancer patients have estimated risks in the 40% to 60% range, while studies examining risk estimates in families attending high-risk clinics have intermediate risk estimates of 60% to 80% [2-5]. These wide-ranging risk estimates, as well as studies that suggest wide interindividual variability in risk even within families with the same BRCA1/2 mutation, suggest that there is no ‘correct’ risk estimate that can be applied to all women, and there are risk modifiers in BRCA1/2 mutation carriers. These modifiers are likely to include reproductive and environmental exposures, genes at other loci, and the nature of an individual’s family history.

Family history matters
In families with BRCA1/2 mutations, relatives of probands with ovarian cancer have a higher risk of ovarian cancer, and relatives of probands with breast cancer have a higher risk of breast cancer. For example, Lee and colleagues [6] examined the lifetime risk of cancer in first-degree relatives (FDRs) of BRCA1/2 mutation carriers with breast or ovarian cancers. The standardized incidence ratio for breast cancer was 10.6 (95% confidence interval 5.2 to 21.6) in FDRs of breast cancer probands and 3.3 (1.4 to 7.5) in FDRs of ovarian cancer probands (p = 0.02). Similarly, the standardized incidence ratio for ovarian cancer was 7.9 (1.2 to 5.3) for FDRs of breast cancer probands, and 11.3 (3.6 to 31.9) for FDRs of ovarian cancer probands, although this difference was not statistically significant (p = 0.37). Why should this be? Phenotype-genotype correlations of specific gene mutations exist that suggest that some mutations are more likely to confer risk of ovarian cancer versus breast cancer [7,8]. However, it is not likely that such genotype-phenotype association is sufficient to explain the wide ranges of risks that have been observed. Thus, exposures or genes at other loci may also modify risk.

Exposures
Factors including parity, age at menarche and first birth, duration of breast feeding, mammographic density, exogenous hormone exposures, and dietary factors, including alcohol intake, are known to impact breast cancer risk in the general population (reviewed in [9-13]). These factors may also cluster in families. The impact of reproductive factors on breast cancer risk in BRCA1/2 mutation carriers is largely unresolved, although recent large-scale studies have reported that exogenous hormone exposures (for example, oral contraceptives) and reproductive history may alter breast cancer risk [14-17]. Other environmental exposures have been investigated among BRCA1/2 mutation carriers, including cigarette smoking and caffeine intake, but results have been inconsistent [18-21].

Medical interventions, such as risk-reducing salpingo-oophorectomy (RRSO), have also been demonstrated to
decrease breast and ovarian cancer risk, but are often not considered in studies estimating penetrance [22,23]. Since it has been observed that use of RRSO varies by population [24], difference in risk estimates may also be affected by variable use of these preventive options.

Finally, variability in cancer risks have been reported by year of birth [5], suggesting that changes in reproductive history, exposures or other risk factors that vary by birth cohort may influence cancer risks [5]. While it is not clear whether these effects are due to true cancer risk modification rather than selection biases, birth cohort effects could have influenced cancer risks and risks in different reports.

**Modifier genes**

There is increasing evidence that genetic modifiers of BRCA1/2 risk exist. The most clear-cut is modification of BRCA2-associated breast cancer risk by RAD51 [25], but other genes, including FGFR2, TNRC9, AURKA, and MAP3K1 [26-28], have been suggested as risk modifiers. Although their effects are quite modest, interactions of genotypes with exposures, birth cohort effects, reproductive factors, and interventions such as RRSO may provide significant information about risk.

**The Begg study**

Begg and colleagues [29] examined cancer risks using 2,098 women diagnosed with breast cancer between 1985 and 2000 (1,394 with unilateral breast cancer, 704 with bilateral breast cancer) who participated in the Women’s Environmental Cancer and Radiation Epidemiology (WECARE) study. A total of 109 BRCA1 and 72 BRCA2 mutation carriers were identified. Cancer risks were estimated for FDRs of these women. The study found risk estimates significantly lower than in studies of high-risk families [1], with a cumulative risk of breast cancer to age 70 of 36% to 48% for BRCA1 carriers, and 47% to 59% for BRCA2 carriers. Increased risk was associated with a younger age of the proband, and a trend toward increased risk was seen for relatives of probands with bilateral versus unilateral breast cancer.

Despite the useful information provided by this research, there are several considerations to be made in interpreting this study. Despite the large population based sample, only 181 mutation carriers were identified (with 598 FDRs, of whom 50% were estimated to be mutation carriers), thus limiting the power to estimate cumulative risks. A very large number of BRCA1/2 mutation carriers, 58%, had no FDR affected with breast cancer; however, several reasons based on the design of the study may account for this. First, only FDRs were examined and thus breast cancer in the paternal lineage was not considered. Information is not given on the percentage of probands with no sisters or daughters, a fact particularly relevant in those with a mutation inherited from the paternal lineage. It is not known if probands or their FDRs were aware of their mutation status and, if so, what prophylactic measures might have been taken, such as mastectomy or oophorectomy. Both of these interventions would significantly alter cancer risk. Ovarian cancer was not considered as an endpoint. The study population was uniquely selected as patients were eligible only if they had node negative breast cancer diagnosed under the age of 55 between 1985 and 2000, and then were recruited between 2000 and 2004. Therefore, survival and other biases may exist. Finally, the authors did not consider potential birth cohort effects, which have been identified in multiple studies and may have influenced some results.

The major limitation in making clinical inferences from this study, however, is that the sample studied by Begg and colleagues may not represent the women who currently undergo genetic testing. Individuals without a significant family history are not recommended to have genetic testing [30] and this population will not have routine insurance coverage for genetic testing. Thus, the clinical implications of Begg and colleagues (and other studies of this type) are limited by sampling/design issues.

**What do we need to know before changing clinical recommendations?**

Individualized risk assessment is the holy grail of the human genome - not only for BRCA1/2 mutation carriers but for the general population. Such assessment may be possible: proband cancer type matters, evidence for genotype-phenotype correlations exist; there is evidence for modifier genes. However, the most important question is whether decision-making will change when this information is available. Will we ever feel comfortable telling a mutation carrier that she does not need RRSO, particularly if we continue to have no effective ovarian cancer screening strategy? Will physicians ever insist on prophylactic mastectomy? Will women make different decisions based on a 40% lifetime risk of breast cancer versus a 60% lifetime risk? These and many other unanswered questions remain even as we strive for improved risk estimation and stratification.

**Competing interests**

The authors declare that they have no competing interests.

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