More than a decade after the discovery of the BRCA1 and BRCA2 genes, a consensus has yet to emerge regarding the frequency and precise magnitude and spectrum of cancer risks for individuals carrying mutations of these genes. Although these questions constitute a topic of heated debate among cancer epidemiologists (1–9), they are also of clinical concern to women and men considering BRCA testing and the various options, including preventive surgeries, if such testing produces a positive finding (10,11). The study by Risch et al. (12) not only helps to settle some of these issues but also adds interesting new data to an already extensive literature.

Expanding their previous analysis (13) of 649 case patients to 1171 case patients with epithelial ovarian cancer and 8680 first-degree relatives ascertained in Ontario for a 5-year period, Risch et al. analyzed DNA samples for BRCA mutations and documented self-reported family history information. When a subset of 977 case patients with invasive ovarian cancer was analyzed, BRCA mutations were found in 129 (13.2%). Among BRCA1 and BRCA2 mutation carriers, corresponding risks for breast cancer to age 80 years were 90% and 41% and corresponding risks for ovarian cancer 24% and 8.4%. For BRCA1 mutation carriers, increased risks were noted for gastric, hepatobiliary, renal, and testis cancers, as well as leukemia. For BRCA2 mutation carriers, increased risks of prostate and pancreas cancers were described. The estimated carrier frequency for combined BRCA1 and BRCA2 mutations was estimated as 1 in 100 in the Ontario population.

For the most part, the findings of this study that were derived from direct measurement confirm previous studies, whereas other estimates derived from indirect measurements vary somewhat from the literature. For example, the estimate of the proportion of ovarian cancers attributable to BRCA mutations is fully consistent with previous estimates of approximately 10% (in contrast to the Ashkenazi subset of case patients with BRCA-linked ovarian cancer, in which the proportion is four times higher), and the associations of cancer risks according to position of the mutation within the BRCA2 gene are consistent with previous reports (14).

In contrast, the estimates of the associated cancers and frequency of BRCA mutations from Risch et al. reflect the strengths and the limitations of their study design. Because there was no confirmation of the pathology of cancers reported by family history, the spectrum of cancer risks reported share the potential biases of previous self-report studies (15–17). The penetrance estimates of this report are also limited by sample design. The case proband or genotyped affected proband approach (1,18) used by Risch et al. was also population based, with the index case patients selected without regard to family history of other factors (19). Even such population-based designs remain vulnerable to bias because of partial participation, as reflected by the fact that half of eligible case patients could not be included in the study. In contrast to hospital-based and volunteer case proband series, population-based ascertaintions have generally resulted in lower age-specific penetrance estimates for BRCA-associated breast cancer (Fig. 1). However, one of the notable aspects of the study by Risch et al. is the 90% breast cancer risk by age 80 years estimated for BRCA1 mutation carriers, the highest yet reported for a population-based study (Fig. 1). However, the estimate for ovarian cancer risks for BRCA2 mutation carriers in the study by Risch et al. is among the lowest reported. A recent study that used a retrospective likelihood approach to

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correct for bias that was induced by oversampling of participants with a positive family history resulted in risk estimates similar to those obtained in the population-based approaches (31). Explanations for the differences in risk estimates among these studies include the biases in case patient (and control subject) selection because of selective participation or other methodologic factors (1–9), differing environmental or other modifying genetic factors, and genotype–phenotype associations that impact on kindreds segregating BRCA mutations.

Perhaps the most robust method to measure cancer risks in BRCA mutation carriers has come from follow-up of ongoing prospective cohort studies. Two such prospective series (37,38) have provided an estimate of the risk of breast cancer for BRCA1 mutation–positive individuals: each study has found an annual risk of 2.5%. This value is within the range derived from linkage studies and the estimates obtained by Risch et al.

Among the most provocative findings of the study by Risch et al. is the very high frequency of BRCA mutations estimated in this population: 1 in 100 compared with previous estimates of approximately 1 in 800. The estimates by Risch et al. were imputed on the basis of mutation frequency in case patients and volunteers, all of affected proband type (20), except for the Washington, DC, area control proband volunteer study (32). References for each study are to the right.

Finally, it should be emphasized, as Risch et al. themselves remind us, that the clinical implications of these findings are generally consistent with current practice in clinical cancer genetics. Although somewhat lower than previous estimates, the ovarian cancer penetrance rate associated with BRCA2 mutations in this report still warrants consideration of risk-reducing surgery, albeit at a somewhat older age than that recommended for BRCA1 mutation carriers. Although penetrance estimates continue to vary between studies, BRCA mutation status remains one of the strongest markers for risk of this disease, warranting increased surveillance with such modalities as magnetic resonance imaging.
hormonal and other chemoprevention, and, in selected circumstances, preventive surgery (10,11,39).

REFERENCES


NOTE

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