How useful are hereditary cancer susceptibility syndromes for modeling sporadic cancers? If the biology of cancers developing within hereditary syndromes follows the same pathways to malignancy as does a substantial proportion of sporadic cancers, then prevention trials focused on hereditary high-risk individuals can lead to important gains in the sporadic setting. McKusick struggled with this fundamental issue of genetics in his classic 1969 article “On lumpers and splitters, or the nosology of genetic disease” (1).

One of the first large studies to compare BRCA1/2-associated with sporadic breast cancers was reported by Lakhani et al. on behalf of the Breast Cancer Linkage Consortium. In univariate analyses, they found relatively less ductal carcinoma in situ (DCIS), a common precursor of sporadic invasive ductal cancers, and less lobular carcinoma in situ (LCIS), a histologic marker of increased breast cancer risk, in association with invasive breast cancer in BRCA1 or BRCA2 mutation carriers than in association with sporadic cancers (2). In the multivariate analysis, the differences for both DCIS and LCIS remained significant only for BRCA1-associated tumors. Tumors in women with BRCA1 mutations were more likely than were sporadic breast cancers to lack expression of estrogen receptors (ER) and progesterone receptors, to be high grade, and to have “pushing margins.” The BRCA1 tumors were also more often node negative than would be expected for tumors of their size, but without the relatively improved prognosis that node-negative status generally confers (2). In contrast, BRCA2-associated tumors could not be distinguished from the majority of sporadic breast cancers.

Perou and colleagues made the fundamental observation that breast cancer can be reliably divided by molecular profiling into at least five subtypes (3). This observation has had a significant effect on the field. Up to 80% of BRCA1-associated breast cancers cluster in a basal-like gene expression pattern, or subtype, and share this subtype’s characteristic absence of expression of ER and progesterone receptor (4, 5). In contrast, ~80% of BRCA2-associated breast cancers cluster in a luminal gene expression pattern and share this subtype’s characteristic expression of ER and progesterone receptor (6). Neither BRCA1 nor BRCA2-associated breast cancers have amplified human epidermal growth factor receptor-2 as a rule, although all breast cancer subtypes can occur in the setting of either mutation (2). Given that BRCA1 and BRCA2 proteins are thought to cooperate as essential molecules in DNA repair, it is puzzling that the absence of one versus the other leads to fundamental differences in tumor biology. Considered early by Foulkes (5), one current hypothesis to explain the differences is that basal-like (BRCA1) and luminal (BRCA2) breast cancers develop from different cells of origin. Investigators from the Wicha laboratory have used in vitro systems and a mouse model to show that BRCA1 expression is required for the differentiation of ER-negative progenitor cells to an ER-positive cell type (7, 8). They also identified lobules exhibiting the progenitor cell marker aldehyde dehydrogenase-1 and loss of heterozygosity for BRCA1 in histologically normal breast tissue from women carrying germ-line BRCA1 mutations, but not from normal (noncarrier) controls. In comparison, the adjacent aldehyde dehydrogenase-1-negative lobules had normal BRCA1. The investigators concluded that BRCA1 likely plays a critical role in the normal differentiation of ER-negative precursor cells to ER-positive luminal cells. If confirmed, their observations also suggest potential opportunities for tissue biomarker measurements, potentially at a relatively early point in BRCA1-associated cancer development, which could allow more precise risk predictions and timely interventions to prevent progression to invasive breast cancer in this group.

A large body of elegant basic research has elucidated important roles of normal BRCA1 and BRCA2 proteins in the maintenance of genetic integrity. The absence of either protein causes defects in homologous recombination repair of double-strand DNA breaks and defective cell cycle checkpoint and mitotic regulatory activities that result in genomic instability (reviewed in ref. 9, 10). These findings led to the recent development of therapeutic strategies that exploit the vulnerabilities induced by BRCA1/2-associated DNA repair defects in the tumors of patients with germ-line BRCA1/2 mutations. Whereas one copy of the BRCA1 or BRCA2 gene functions sufficiently to maintain normal DNA repair in normal cells of mutation carriers, tumor cells of mutation carriers generally have lost their only functioning copy of the BRCA1 or BRCA2 gene. A series of studies in model systems and mice have shown the remarkable sensitivity of breast cancer cell lines lacking intact BRCA1 or BRCA2 to DNA cross-linking agents (11–13). A small, preliminary clinical trial of the DNA cross-linking agent cisplatin (alone) before definitive surgery for newly diagnosed breast cancer in germ-line BRCA1 mutation carriers achieved a remarkable 90% rate of pathologic complete response—disappearance of all tumor—consistent with the laboratory prediction (14).

Ashworth and colleagues are leading therapeutic efforts to exploit inhibition of poly(ADP-ribose) polymerase (PARP), an enzyme involved in another DNA repair pathway, break excision repair, which is a key pathway in the repair of single-strand DNA breaks. In the presence of BRCA1 or BRCA2 dysfunction, cells are sensitized to the inhibition of PARP enzymatic activity, and chromosomal instability is increased;
these processes lead to cell cycle arrest and apoptosis (15). Early clinical trials of PARP inhibitors in women with advanced ovarian cancers have shown promising results (16). Because some of the available PARP inhibitors are oral, there has been interest in the potential of these relatively nontoxic agents for chemoprevention (17). The observations that other proteins involved in DNA repair also to confer sensitivity to PARP inhibition suggest that the drugs may have therapeutic or preventive utility outside of BRCA1/2-associated tumors (18). Exploiting specific molecular defects conferring a very high risk of breast and ovarian cancer has exciting potential for intelligent therapeutic and, ultimately, preventive targeting.

The increasing evidence that BRCA1-associated breast tumors are largely hormone independent has raised concerns that early analyses that did not distinguish between BRCA1 and BRCA2 mutation carriers in assessing the risk-reducing effects of salpingo-oophorectomy may have reached misleading conclusions. One of the first efforts to separate BRCA1 from BRCA2 mutation carriers was a large case-control study by Eisen and colleagues (19). The reduction in breast cancer risk following premenopausal oophorectomy was significant for BRCA1 mutation carriers and nonsignificant for BRCA2 mutation carriers. It is anticipated that these data will be updated with larger patient numbers. In contrast, the reduction in breast cancer risk following premenopausal salpingo-oophorectomy was statistically significant and large (72%) in BRCA2 mutation carriers and not statistically significant in BRCA1 mutation carriers in a recent analysis by Kauff, Domchek, and colleagues of the multicenter prospective cohort data from the Prevention and Observation of Surgical Endpoints (PROSE) investigators and Memorial Sloan Kettering (20). The associations of BRCA1 mutation with ER-negative and of BRCA2 mutation with ER-positive cancers, the findings of Kauff et al. are consistent with the data from other high-risk populations that hormonal interventions reduce the incidence of ER-positive, but not ER-negative, breast cancers (21–23). However, additional studies will be essential to clarify this issue. If hormonal interventions are found to reduce the risk of BRCA-associated ER-negative breast cancers, then these tumors may have a unique biology and thus may not be an appropriate model for sporadic ER-negative breast cancer prevention. On the other hand, if hormonal interventions do not prevent ER-negative tumors in BRCA1 mutation carriers (as is the case in the sporadic setting), future trials in these high-risk women may provide a model for preventing sporadic ER-negative disease. To the extent that BRCA-associated breast cancers seem to respond to hormonal influences as do sporadic luminal breast cancers, they seem to be an appropriate model for hormone-mediated risk reduction strategies in ER-positive breast cancer.

Whether the pathways of BRCA1/2-associated breast cancer and sporadic breast cancer are distinct or similar has also been assessed in studies of the development of BRCA1/2-associated breast cancer over time. The higher rate of interval cancers for women with BRCA mutations (versus BRCA2 mutation carriers and noncarriers) undergoing yearly screening mammograms and breast magnetic resonance imaging (reviewed in ref. 24) prompted a recent attempt to quantify whether BRCA1/2 tumors grow faster than sporadic breast cancers. This analysis was based on preliminary findings from three ongoing prospective breast cancer screening trials among high-risk women [the Rotterdam, Canadian, and United Kingdom Magnetic Resonance Imaging in Breast Screening (MARIBS) studies; ref. 24]. The estimated growth rate, or tumor volume doubling time, from the previous imaging study to the diagnostic image, was fastest at youngest ages and declined with increasing age across three groups of high-risk women: BRCA1 mutation carriers, BRCA2 mutation carriers, and women with no identified mutation. Within each age group, the estimated growth rate was relatively faster among mutation carriers than among high-risk mutation-negative women. Although awaiting confirmation, these findings suggest that mutation status and age influence tumor biology and may lead to more targeted recommendations for breast cancer surveillance in various high-risk populations.

Several groups have addressed whether the pathway to breast cancer in BRCA1/2 mutation carriers includes all of the usual histologic hallmarks in the pathway from normal to malignant mammary epithelium in sporadic cases (25–27). The relationship between DCIS, invasive breast cancer, and BRCA1 and BRCA2 mutation status has been studied in most permutations, producing inconsistent data that cross a wide range of risk estimates (28–30).

In an important contribution from Memorial Sloan Kettering, Smith et al. (31) compared the frequency of BRCA1/2 mutations in women with DCIS alone in each of three different clinical cohorts with this frequency in control women with invasive breast cancer matched on age. The frequencies of mutations were 0% in the incident and 4.8% in the prevalent groups of Ashkenazi Jewish women with DCIS alone, versus 5.2% and 11.5%, respectively, in the incident and prevalent controls with invasive breast cancer. The mutation frequency was 12.7%, however, among high-risk women with DCIS alone who were evaluated in the Memorial Cancer Genetics clinic, nearly equal to the 14% frequency among high-risk clinical controls with invasive breast cancer. These collective findings show that the source of women with DCIS will affect the overall mutation frequency estimate. For example, women identified from high-risk clinics may be more likely to have family history as well as DCIS and, therefore, a higher likelihood of an underlying mutation (versus women with usual risk and DCIS detected on routine screening). Regardless of differences in mutation frequency among various source populations, however, mutation carriers from different cohorts should be similar in the biology of their DCIS and invasive breast cancer.

In this issue of the journal, Arun and colleagues (32) report a study in the M. D. Anderson Cancer Center high-risk-clinic cohort of women who received genetic counseling and testing that addresses the controversial question of whether DCIS precedes invasive BRCA1/2-associated breast cancers, thus paralleling sporadic cancer development. The absence of DCIS before BRCA1/2-associated breast cancer development would imply substantially different pathways of development between germ-line mutation–associated and sporadic cancers. The prevalence of preinvasive lesions associated with invasive cancer was similar in 73 BRCA1/2 carriers and 146 controls with a confirmed absence of mutations; a higher prevalence of DCIS occurred among BRCA2 mutation carriers than among BRCA1 mutation carriers. All specimens were reviewed by a breast pathologist. Somewhat modest patient numbers made it uninformative to compare BRCA1 mutation
carriers with BRCA2 mutation carriers for all patient and tumor characteristics. The authors concluded that premalignant lesions, especially DCIS, are associated with invasive cancers in BRCA1/2 mutation carriers, providing evidence for similar tumorigenesis among mutation carriers and women developing sporadic breast cancer. The results of this study are consistent with Smith et al.'s findings in the Memorial high-risk clinic cohort and controls, and remind us of the challenges that persist in trying to answer certain unresolved fundamental questions of cancer prevention. In light of all of the foregoing data, can BRCA1- and BRCA2-associated breast cancers serve as potential models of sporadic breast cancer, or not? In other words, should we focus on the ways in which BRCA1- and BRCA2-associated tumors are like sporadic breast cancers, like each other, or different? It is now established that sporadic breast cancers do not constitute a uniform group by molecular subtyping, and they are almost always divided by at least ER, progesterone receptor, and human epidermal growth factor receptor-2 status for treatment or prevention interventions. The most consistent data reviewed above unexpectedly show that there are significant differences between BRCA1- and BRCA2-associated cancers. However, there are important similarities between them as well, which may make it possible to target novel treatment approaches, such as PARP inhibition, toward common aspects of their potentially unique biologies. If approaches such as PARP inhibition are successfully advanced from treatment to prevention in mutation carriers, it may be possible eventually to address their utility in a larger, sporadic-risk population as well. This translation would be a significant advance in cancer prevention. Furthermore, clinical testing of PARP inhibitors (or other potential preventive drugs) first in mutation carriers would have design advantages (stemming from the high mutation-associated cancer risk) that include a potentially greater willingness to tolerate agent toxicity and a smaller sample size (versus trials in populations at a lower, sporadic cancer risk). Further understanding of the possible parallels in underlying biology between BRCA1/2-associated cancers and sporadic breast cancers of various subtypes is likely to have important effects on other aspects of risk management: refined risk assessment, early detection, and hormonal and other risk reduction strategies. For example, data cited above suggest that BRCA2 mutation carriers, but not BRCA1 carriers, could benefit from hormonal prevention strategies, although both are excluded from current phase III prevention trials of hormonal interventions. On the other hand, if future studies suggest that the development of BRCA1-associated ER-negative breast cancer relates to the development of sporadic ER-negative breast cancer, then BRCA1 mutation could become a useful model for testing agents to prevent sporadic ER-negative breast cancer. Many studies, including some discussed here, have had to consider BRCA1 and BRCA2 mutation carriers together to have large enough sample sizes to conduct the analysis. Future studies should strive to include sufficient numbers of both BRCA1 and BRCA2 mutation carriers to have adequate power to compare and contrast them for their clinical and biological implications and outcomes. As we learn more about the biology of BRCA1 and BRCA2 functions in general and in breast cancer, the specific study settings where their similarities or differences are important—when to lump and when to split—will become clearer, which may have important implications for cancer prevention in mutation carriers and other at-risk populations.

Disclosure of Potential Conflicts of Interest

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BRCA1/2-Associated and Sporadic Breast Cancers: Fellow Travelers or Not?

Judy E. Garber


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