Men who carry BRCA2 mutations are known to have an increased risk of being diagnosed with prostate cancer (1,2). In this issue of the Journal, Tryggvadóttir et al. (3) report that 29 prostate cancer patients who carried the Icelandic founder mutation 999del5 in BRCA2 had unusually advanced disease at diagnosis and poor survival. Using registry data from the entire Icelandic population, the investigators compared stage and grade at diagnosis and length of survival between carriers and noncarriers. This work may clarify when and how BRCA2 mutations alter carcinogenesis.

More generally, it offers an avenue (4) for improving the accuracy of information available to patients when they are diagnosed with cancer. Nonetheless, the immediate clinical utility of these findings is limited, despite unusually rigorous design and analysis.

Tryggvadóttir et al. (3) face important challenges in assessing the effects of genes on the clinical course of prostate cancer. The key strength of this work is Iceland’s comprehensive historic data on cancer diagnosis and death, which dates back to 1955 (3). Changes in screening practices over time, the inherent ambiguity in the date of diagnosis, and the small number of BRCA2 mutation carriers in the population all present considerable obstacles to this and other investigations of this kind.

Changes in screening practice present a methodologic pitfall for this type of research. As expected, overall survival improved after 1985 as screening and effective treatments became more widespread, but it was unexpected that prognosis among carriers did not improve over time. It is not clear whether the lack of improvement in survival reflects chance, is due to the small numbers, or signals a real difference.

Clinical recognition of disease only loosely approximates the true timing of the occurrence of cancer. This inherent uncertainty presents problems for delineating the stages in the natural history of the disease. For example, a genetic variant might simply mask early signs or symptoms, leading to diagnosis at a more aggressive stage of disease. Advancing this arbitrary point of reference has three effects: an increase in the age at diagnosis, a corresponding decrease in survival time, and no change in age at death. Consequently, for carriers as a group, estimates of age-specific risk and survival will both be reduced by artifact. If a genetic variant only delays recognition of disease onset but does not affect age at death, it may yet serve as a useful prognostic marker at the time of diagnosis for the individual patient. This theoretic possibility seems unlikely in this study, inasmuch as both incidence and survival were worse in BRCA2 mutation carriers.

Another methodologic nuance pertains to adjustment for stage and grade at diagnosis, which can “absorb” some or all of the mutation’s statistical effect on prognosis. Measurement without adjustment addresses the more global and biologic questions. Measurement with adjustment addresses the marginal clinical value of gene testing. Adjustment shows the impact of the mutation on survival above and beyond its influence on the grade, age, stage, or any other clinical indicators available at diagnosis. By contrast, the simple overall effect of the gene on prognosis is shown when one does not adjust for stage and grade.

BRCA1 and BRCA2 mutations are rare, and carriers are hard to find. Tryggvadóttir et al. (3) were able to use 29 of only 30 identified carriers of BRCA2 founder mutations from 60 years of registry data. In another study, Giusti et al. (5) found only 14 carriers of the BRCA2 6174delT mutation among 940 tested prostate cancer patients who were Ashkenazi Jewish men diagnosed in Israel. When they examined tumors from those BRCA2 carrier patients, along with 15 carriers of BRCA1 founder mutations, they discovered no distinctive histopathology as compared with tumors in noncarriers. The failure to identify a difference between BRCA2 and other tumors may be diluted by the inclusion of the 15 BRCA1 mutation carriers. Small numbers combined with the multitude of different founder mutations seen in distinct ethnic groups force researchers and clinicians and patients to draw scientific conclusions and develop treatment plans with only pieces of the puzzle.

In the short run, few men newly diagnosed with prostate cancer will gain much assurance from learning that they do not carry BRCA2 mutations. Estimated prognosis is only slightly better in noncarriers compared with all patients. The overall survival rates are not very different between noncarriers and all men because carriers are rare, even among Icelandic men with prostate cancer. A possible exception is a man whose close relatives are known carriers or who has extensive family history of breast and ovarian cancers—noncarrier status may convey some assurance. A man with prostate cancer who discovers he is a BRCA2 mutation carrier may change his evaluation of watchful waiting, with consideration of other clinical factors.

In the longer run, genomic research will expand to consider clinical outcomes and efficacy of treatment. Studies of the joint effects of treatment and genetic factors on prognosis and survival may allow for more tailored treatment decisions. Studies that are primarily etiologic could also collect information about treatment, pathology and molecular characteristics of cancer tissue, and survival (6). Randomized prevention, screening, and treatment trials also provide rich resources to detect interactions between interventions and genetic factors. On the heels of the successful genome-wide studies of prostate cancer etiology (7–10), there is tremendous potential value from efficient (11,12) genome-wide
association studies of prognosis in a consortium of prostate cancer trials assembled for this purpose.

References


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