From the Editor

Cancer Susceptibility Genes Do Not Act in Isolation

Debu Tripathy, MD
Editor-in-Chief

It is estimated that about 30% of cancer risk is attributed to inherited susceptibility. This figure is based on models and estimates – it is not possible to derive this number experimentally or through observations of even very large cohorts. We know mostly about high penetrance genes whose loss of function creates cancer patterns easily to recognize in family pedigrees. Two of these prototypical genes are BRCA 1 and 2 that encode DNA repair genes – in which inactivating mutations result in a 50-80% lifetime risk of breast cancer and 30-40% risk of ovarian cancer. Since genomic variations can also be used to map populations geographically along with the migration patterns, and "founder" mutations can identify distinct populations, we are able to partially discern the ethnic/regional origins of some specific mutations. An important and only partially answered question is whether mutation status or specific mutations impact on histology and outcome.

In this issue of AJHO, Dr. Safra and colleagues address the question as to whether patient diagnosed with epithelial ovarian cancers and who carried a BRCA 1 or 2 mutation (23% of all cases tested) had a distinct outcomes and whether the specific mutations mapped to their ethnicity and had an impact on survival. In their multi-ethnic cohort, they found as has been reported previously that patients of Ashkenazi Jewish (AJ) background preferentially had 185delAG and 5382insC mutations in *BRCA1* and 6174delT in *BRCA2*, genotypes known to cluster in this group, whereas others ethnicities had a greater diversity of other mutations, including the AJ cluster. Papillary serous histology was the most common in BRCA mutation carriers as opposed to undifferentiated in non-carriers. Survival was also better in BRCA mutation carriers as has been reported before. Interestingly, there were differences among specific mutations in overall and progression-free survival, but the numbers were not sufficient for robust statistical testing for significance. While the data was not shown, patients with BRCA unclassified variants of unknown significance (generally handled as non-mutations until later clarified), had clinical features similar to mutation carriers.

The availability of lower cost and more extensive analysis of germline mutations and variations will continue to improve our ability to discern risk as well as disease characteristics, outcomes and even optimal therapies as long as efforts to obtain share longitudinal data are expanded (a key objective of the national Moonshot Program).

***The American Journal of Hematology/Oncology* is accepting manuscripts for consideration.**

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MD Anderson Cancer Center
Houston, TX

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Assistant Professor of Medicine
University of Chicago
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Managing Editor
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aberberabe@mjhassoc.com

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Editorial Offices
Physicians' Education Resource®, LLC
666 Plainsboro Road, Ste 356
Plainsboro, NJ 08536
(609) 378-3701

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