

HERITABLE CANCER RISK:

Q&A with Bradley Arrick, MD, PhD

There are many things that families share other than their genetic makeup. For instance, families generally share common dietary habits and have the same environmental exposures. The question therefore remains, what does it mean when cancer “runs in the family?” Bradley Arrick, MD, PhD, section chief of hematology/oncology at Dartmouth-Hitchcock’s Norris Cotton Cancer Center and associate professor of medicine and medical education at Geisel, answers questions related to heritable cancer risk.

Brad Arrick, MD, PhD
Photo courtesy Dartmouth-Hitchcock.

Q: GENERALLY SPEAKING, HOW MUCH OF CANCER INCIDENCE CAN BE ATTRIBUTED TO HERITABILITY AND HOW MUCH TO ALL OTHER CAUSES, INCLUDING THE ENVIRONMENT AND RANDOM GENETIC CHANGES INCURRED DURING LIFE?

Arrick: Recently, this exact question has been addressed by a consortium in Scandinavia, where health outcomes of families have been monitored for generations. For this analysis, they compared the incidence of cancers, by type, among individuals who have a sibling twin. As expected, identical twins had the greatest concordance. That is to say, the relative risk for a specific cancer for an individual whose identical twin already had been diagnosed with that cancer was elevated significantly. When they looked at non-identical twins (i.e., dizygotic twins), who share on average only 50 percent of their genes, the rate of concordance was lower. This difference was attributed to the fact that identical twins shared 100 percent identity at the DNA level. From these data, the heritable component of various cancer risks was then estimated.

The investigators estimated heritability being responsible for 25-58 percent of many tumor types including prostate, breast, colon, uterine, testicular, ovarian, and lung cancer, as well as melanoma (Mucci, et al., 2016).

Q: HOW DO GENES SPECIFICALLY PLAY A ROLE IN INHERITED CANCER RISK?

Arrick: Identification of genes which, when mutated in a family, predispose the carriers to significantly increased risk of cancer has been the objective of investigators for decades. Two of the best known genes of this sort are BRCA1 and BRCA2. These two genes provide examples of many features we have come to recognize in families and patients in the genetic testing process.

Q: WHAT ARE SOME OF THESE IDENTIFIED FEATURES?

Arrick: One, is that inherited mutations in these genes predispose individuals to more than just one type of cancer. Even though they were identified by examining families with excessive amounts of

breast cancer, affecting women in multiple generations, it was evident early on that these women were also at risk for ovarian cancer. Other tumor types, such as pancreatic cancer, also can occur at increased frequency in carriers. There are thousands of possible mutations in these two genes (BRCA1 and BRCA2) which predispose the carrier to cancer. With current technology, until it is determined which gene mutation is in a specific family, a negative genetic test result in the members of that family cannot be interpreted as ruling out the possibility of a heritable predisposition. In other words, if you don't know what you're looking for, not finding it isn't a conclusive answer.

Q: WHAT DOES A POSITIVE TEST FOR THE BRCA1 AND BRCA2 MUTATION MEAN FOR FUTURE PLANNING?

Arrick: The age of diagnosis is typically younger than is seen in the general public. That said, just knowing the lifetime risk for a certain cancer may not be as helpful to people as knowing the risk over the short-term. Many find that thinking of a 10-year period is a more helpful framework for comparing options of prevention and screening. For instance, a 30-year-old BRCA2 carrier's risk of being diagnosed with ovarian cancer over the next 10 years is only 1 in 200; over 85 percent of her lifetime risk comes after age 40 (Chen, S. and Parmigiani, G., 2007). Understanding this time frame is valuable to family and future planning.

Q: IS A CANCER CAUSED BY INHERITED GENE MUTATIONS TREATED ANY DIFFERENTLY THAN A CANCER CAUSED BY ENVIRONMENT?

Arrick: Knowing the underlying inherited genetic change that caused the cancer can help guide treatment decisions. As we learn more about how it is that cancers arise in carriers, insights as to how best to treat the cancer are beginning to play a role in management of these patients. For instance, ovarian and breast cancers arising in BRCA1/2 carriers may be sensitive to DNA damaging agents when combined with inhibitors of a specific pathway for DNA repair known as the PARP pathway (Lord, C.J. and Ashworth, A., 2016). PARP inhibitors now are entering into the armamentarium of oncologists.

Q: WHAT ADVANCEMENTS HAVE BEEN MADE IN GENETIC TESTING?

Arrick: Testing for inherited mutations in BRCA1 and BRCA2 has become more comprehensive over time. The initial test methodology, when these genetic tests first became commercially available, was unable to detect a class of mutations (called deletions) that we now know account for approximately 10 percent of all mutations. Therefore, it is important to keep in mind that a negative test result from over 10 years ago may have been a falsely negative result, and more testing now might be appropriate. More genes that increase the risk for cancers are being identified. Many of these genes have a less dramatic effect on risk, and, therefore, we have less data with which to craft recommendations for screening and prevention. Advances in the technology of gene analysis, termed next-generation sequencing techniques, have led to the development of

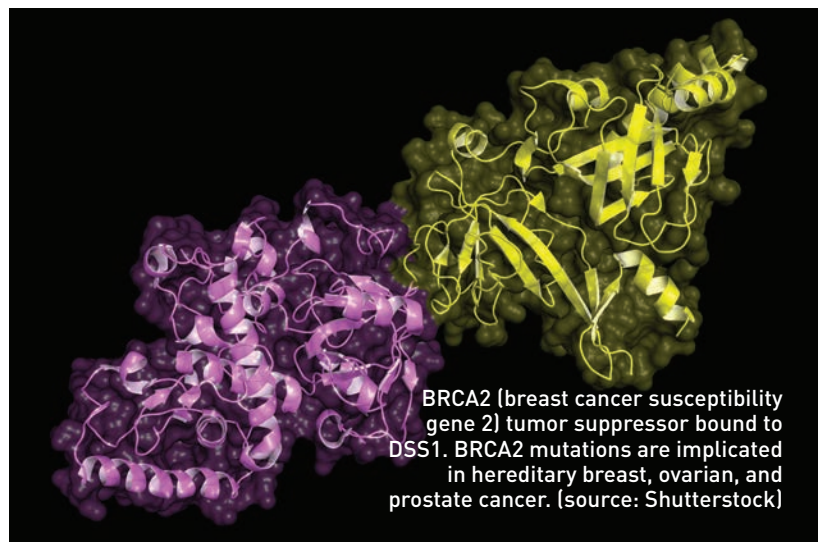
large panels of genes tested at one time (NH CCC Emerging Issue Brief, Aug 2014). These panels include the genes discussed above, with smaller effects on an individual's risk. While these panels can provide more comprehensive testing, they often lead to results that are more difficult to understand and incorporate into clinical practice.

Q: HOW DOES HEALTH INSURANCE PLAY A ROLE IN TESTING?

Arrick: The criteria used by insurers and Medicare differ when approving testing. Some insurance companies, such as Cigna and United Healthcare, now are requiring that people be seen by a certified genetic counselor before testing can occur. Thankfully, New Hampshire recently established a formal process of certification for genetic counselors in the state.

Q: IS GENETIC TESTING ONLY FOR COMMON CANCER TYPES?

Arrick: Many other rare tumor types have been linked to genes that can lead to an inherited risk of cancer. Some of these cancers warrant genetic counseling and testing even when there is no known family history of cancer. Examples include adrenocortical carcinoma, medullary thyroid cancer, and pheochromocytoma. An excellent summary and related statement by the American Society of Clinical Oncology was published recently (Lu, K.J., et al., 2014).



References:

- Chen, S. and Parmigiani, G. (2007). Meta-Analysis of BRCA1 and BRCA2 Penetrance. *J. Clin. Oncol.* 25:1329-1333. doi:10.1200/jco.2006.09.1066.
- Desmond, A., et al. (2015). Clinical Actionability of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer Risk Assessment. *JAMA Oncol.* 1(7):943-951. doi:10.1001/jamaoncol.2015.2690.
- Lord, C.J. and Ashworth, A. (2016). BRCAness revisited. *Nature Reviews Cancer.* 16(2): 110-120. doi:10.1038/nrc.2015.21
- Lu, K.H., et al. (2014). American Society of Clinical Oncology Expert Statement: Collection and Use of a Cancer Family History for Oncology Providers. *J.Clin.Oncl.* 32(8): 833-840. doi:10.1200/jco.2013.50.9257.
- Mucci, L.A., et al. (2016). Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. *JAMA* 315(1): 68-76. doi:10.1001/jama.2015.17703.