

Update in BRCA by: Dr. Dawna M. Gilchrist, MD, FRCPC, FCCMG, DHMSA

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I have now attended all 3 International Symposia on Hereditary Breast and Ovarian Cancer. These are held every second year in Montreal and attract world leaders in research, diagnosis and management from around the world. The main advances discussed at this meeting can be described in four categories.

Diagnosis

Item #1 We now do not ever expect to find BRCA3. Rather, most of breast cancer will turn out to be due to cumulative interactions of many genes, which are still being defined. We need ALL of these genes to be well defined, and combined with a sophisticated computer program, before there can be testing for any and all genetic predispositions to breast and/or ovarian cancer.

Item #2 There was considerable discussion on Unclassified Variants. Approximately 8% of our results are described as unclassified variants and I know how frustrating it is for patients to be told that they have a variant in their BRCA1/2 gene but we do not know what it means.

It was pointed out that these variants are really not unclassified; however, they are of uncertain significance. Therefore, we are now describing them as Variants of Unknown Significance (VUS). Recently, a large consortium has been created to define all VUS into benign vs. pathogenic. About 80% will eventually turn out to be benign and 20% pathogenic.

I have decided to pull together all the VUS we have had in the program over the years and periodically compare them to publications coming out from the consortium. It will probably take several years to define all VUS. (I promise that I will communicate with you if your VUS becomes defined.)

Modifiers

Why do some people with BRCA mutations get breast cancer, some get ovarian cancer, some get both and some get neither? Why do some get cancer early, others later. The answer to these questions is that there are other factors beyond BRCA1/2 - genetic, environmental and personal - that contribute to cancer.

Dr. Doug Easton, a major researcher in the UK, is working on modifiers in BRCA2. His research focuses on a way to predict the likelihood of breast cancer in BRCA2 mutation carriers based on 3 factors:

1. the position of the gene mutation (individuals with mutations in BRCA2:exon 11 are more likely to get ovarian cancer and less likely to get breast cancer than other BRCA2 mutation carriers)
2. presence or absence of 11 other genetic factors
3. breast density

This is currently ONLY at the research level, and only refers to breast cancer in BRCA2 mutation carriers, but I guarantee that it will be the wave of the future – and require more genetic testing and even fancier computer programs.

For those of you with BRCA1 mutations, there is modification as well, but less than in BRCA2 mutation carriers.

Treatment

The average cell has several mechanisms to repair DNA. The major mechanism is called homologous repair and BRCA is involved in this type of repair. When a cell loses BRCA function, it has to switch to a secondary method of DNA repair. One of those secondary mechanisms involves PARP. If PARP is inhibited in a woman who has a BRCA mutation and breast cancer, the normal cells are not affected. However, the cancer cells cannot tolerate having two DNA repair mechanisms fail and they selectively die. So far, PARP-inhibition studies are looking promising but we have to await conclusion of clinical trials.

What's coming down the pipe

1. more specific genetic testing
2. computer programs that combine factors to generate more specific risk estimates
3. genome wide association studies (GWAS) to find all the genetic factors involved in common diseases of adulthood (not just cancer)