Genetic Counseling for Colorectal and Breast Cancer: Who Should Be Screened and Tested?

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ABSTRACT

Breast cancer and colorectal cancer are the two most common malignancies for which a substantial proportion (5% or more) of cases may be found to carry a simple genetic predisposition. When key clinical features are present, as many as 80% of subjects in some series can be provided a specific genetic diagnosis. Over the past 10 years the molecular basis for the usual form of familial breast and breast/ovarian cancer and the two major types of inherited colorectal cancer predisposition have been clarified. In Familial Adenomatous Polyposis (FAP), there is the *APC* gene. Subjects who present with little or no family history and/ or an adenoma burden that is very modest or "attenuated" (so-called attenuated FAP or AFAP) may often not bring FAP to mind. In such cases, genetic testing may be important in confirming the underlying genetic basis for disease, significantly change management, and carry with it opportunities for guiding surveillance in the next generation. Attenuated cases lacking substantial family history may be tested for and found to carry biallelic mutations in the *MYH* gene. Behaving as a recessive the predictive testing implications for children and sibling differ from the autosomal dominant form of FAP and AFAP.

In many respects familial breast/ovary cancer (BRCA 1 & 2 genes) has much in common with Hereditary Nonpolyposis Colorectal Cancer HNPCC (mismatch repair "MMR" genes). In these conditions the clinical presentation can strongly suggest but cannot by itself confirm the presence of a BRCA or HNPCC condition, unlike the pathognomonic adenomatosis of FAP. In BRCA and HNPCC clinical strategies for case selection and mutational testing are similar. A key difference is the increasing role for microsatellite instability (MSI) or immunohistochemical (IHC) testing in HNPCC. No counterpart for these intermediary evaluations has yet been identified in BRCA, so mutational testing is often recommended when one or more models yield a 10% or greater *a priori* likelihood of a mutation.

Genes for the nonadenomatous polyposis disorders, Peutz-Jegher syndrome and Juvenile Polyposis have been identified, but are rare and generally dealt with in tertiary centers. Other breast cancer susceptibility genes, including those for the Li- Fraumeni (p53) and Cowden syndrome (PTEN) have been identified and must be considered, depending on characteristics of family history. If not considered previously, attention may be directed to these conditions when BRCA mutational testing is nondiagnostic. The tasks for the clinician are to: 1) recognize the sometimes subtle clinical presentations of all these conditions; 2) assess if there is potential for benefit to the patient and/or family through the acquisition of a genetic diagnosis; 3) provide for genetic counseling and appropriate genetic testing; and 4) arrange optimal clinical diagnostic and management services.

There are tremendous opportunities as well as challenges afforded by the ready access to lay and scientific materials on these conditions through the world-wide web. Among these are various statements of practice guidelines available to clinicians and patients alike. Sources and content of practice guidelines for genetic counseling and testing for BRCA, FAP, HNPCC, and their variants will be emphasized.