No One Should be Tested or Treated for Mutations in BRCA1 or BRCA2.

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Since the mid 1970s, most cancer researchers have worked under the assumption that mutations in normal human genes cause cancer. This assumption implied that cancer could be inherited because mutations can be inherited. Originally, it had been proposed that mutation in a single so-called dominant oncogene was sufficient to cause cancer, implying cancer was a Mendelian (or single gene) disease. The five studies most often cited as providing the evidence that mutations in BRCA1/2 increased susceptibility to breast cancer (Lynch and Krush 1971, Miki et al. 1994, Narod et al. 1991, Newman et al. 1988, Wooster et al. 1994) were based on this simple notion of cancer causation. Consequently, these oft cited researchers used linkage studies that had been employed by epidemiologists to trace the genes causing the truly heritable rare Mendelian diseases. The successes of linkage analysis in identifying the mutations in specific genes causing rare conditions such as hemophilia, Duchenne muscular dystrophy, sickle cell anemia, Tay-Sachs disease, etc., led to the expectation that a similar strategy would be useful in tackling genetic susceptibility to breast cancer. But such optimism has been shattered (Terwilliger and Weiss 2003).

Few researchers nowadays believe a handful of heritable mutations in some individuals can make them susceptible to common cancers. Since all cancers, including breast cancer, are very complex and certainly not single-gene diseases, many are now convinced that linkage analysis should be abandoned and replaced by other approaches (Risch 2000). One alternative to linkage analysis popular these days is Genome Wide Association (GWA). GWA scours the genome to extract from the myriad of genetic mutations the hoped-for few responsible for cancer (Hardy and Singleton 2009). In spite of the apparent promising initial results, this approach has not lived up to expectations leaving researchers frantic about what to try next (Dunkler et al. 2007, Dupuy and Simon 2007, Eden et al. 2004, Koscielny 2008, Massague 2007, Michiels et al. 2005, Michiels et al. 2007, Ntzani and Ioannidis 2003, Pan et al. 2005, Reid et al. 2005, Shi et al. 2008,

Simon et al. 2003). As of March 2011, over 1300 GWAs for 221 traits have been published (http://www.genome.gov/multimedia/illustrations/GWAS_2011_1.pdf). The primary reason for the dismay permeating GWA is simply the results are not reproducible (Shi et al. 2008), to the point "researchers can no longer trust their hunches that a result does—or does not—make sense (Kolata 2011). A recent survey of 18 quantitative papers published in Nature Genetics found reproducibility was not achievable even in principle for 10 (Ioannidis et al. 2009). Baggerly and Coombes recently commented, "A broader question is whether this approach could work if applied correctly. We don't think so. We have tried making predictions from the NCI60 cell lines when we step through the process without the errors noted above, and we get results no better than chance" (Ioannidis et al. 2009). The explanation is easy to see once one realizes that searching tens of thousands of mutations among tens of millions of people will always produce false correlations. "Succinctly put, the law of truly large numbers states: With a large enough sample, any outrageous thing is likely to happen" (Diaconis and Mosteller 1989).

However, even more pressing than the methodological difficulties is the fundamental problem of "cancer-causing" gene mutations in general, and BRCA mutations in particular. Originally, it had been proposed (as noted above) that mutation in a single gene was sufficient to cause cancer. Nevertheless, no one has yet been able to demonstrate that a single mutant gene can cause cancer. This led most researchers to turn to the idea thta it took mutations in 3-6 genes to cause cancer. But, here too, all combinations of mutant genes tested failed to convert normal cells into cancer cells.

The obvious fact that cancer was not inherited but primarily a disease of old age, coupled with the chronic inability to demonstrate cancer-causing mutant genes led to the watered-down notion of cancer susceptibility genes—where mutations don't actually cause cancer but in some mysterious and unspecified way make cells susceptible to cancer. Thus, the once vaunted handful of cancer genes has been superseded by current opinion that mutations in hundreds to perhaps thousands of genes are responsible for the broad spectrum of human cancers.

By 2004, at least 291 gene mutations (more than 1% of the human genome) had been proposed to cause cancer (Futreal et al. 2004). According to the Catalogue of Somatic Mutations in Cancer database and website, the tally of cancer genes was raised to 412in 2009, of which 300 were said to be dominate (http://www.sanger.ac.uk/, (Bamford et al. 2004)). Three-quarters of these cancer genes were associated with leukemias, lymphomas and mesenchymal (connective tissue) tumors even though these account for less than 10% of human cancers. Since the most common cancers are epithelial in origin (including breast cancer), there is considerable scope for the cataloging of many additional gene mutations associated with these cancers. Thus, the total number of human cancer genes (even more so the notion of cancer gene itself) remains a matter for speculation.

All of these cancer genes (comprising an ever growing list) were identified and initially reported on the basis of the presence of mutations and without biological information supporting the cancer-causing effects of the mutations (Forbes et al. 2011, Futreal et al. 2004, Katsios and Roukos 2011, Park et al. 2010, Terwilliger and Hiekkalinna 2006, Wacholder et al. 2010). This is the reason J. Michael Bishop, who shared the 1989 Nobel Prize for the discovery of the cellular origin of retroviral oncogenes, said at a seminar I attended at the Lawrence Berkeley National Laboratory on September 16, 2005, that there was still no proven combination of mutant genes from cancer cells that is sufficient to cause cancer. The title of his seminar was “Mouse models of human cancer”.

From the latest tally, as of July 2010, there were over 136,000 mutations detected in almost 542,000 tumor samples (Forbes et al. 2011). Of the 18,490 genes documented, 4,803 (26%) had one or more mutations. It is remarkable that “cancer-causing” mutations in virtually every gene in the genome have been cataloged, yet there is still no evidence that one or a combination of any of these genes (normal or mutated) can turn normal animal or human cells into cancer cells (Akagi et al. 2003, Augenlicht et al. 1987, Duesberg and Schwartz 1992, Duesberg 1995, Duesberg et al. 2004, Harris 1995, Harris 2005, Hua et al. 1997, Li et al. 2000, Li et al. 2002, Lijinsky 1989, Radford 2004, Schneider and Kulesz-Martin 2004, Stanbridge 1990, Thraves et al. 1991, Weitzman and Yaniv 1999).

Even if it were true mutations in BRCA somehow caused increased susceptibility to breast cancer, its claimed significance is so weak as to be irrelevant. To see this, it is important to know that breast cancer is the most frequent malignant tumor among women, with approximately one million new cases per year around the world (Parkin et al. 2005). About 5% of all breast cancer cases are considered to be caused by an inherited mutation within a family (Nathanson et al. 2001). The breast cancer susceptibility genes BRCA1 and BRCA2 are said to cause approximately 16-17% of inherited breast cancer (Anglian Breast Cancer Study Group 2000, Peto et al. 1999). That means up to 84% of presumed heritable breast cancer cannot be blamed on BRCA mutations—or any other single gene mutation, for that matter (Smith et al. 2006). Furthermore, 16-17% of the 5% of supposedly inherited breast cancer means that only 0.8% of all breast cancer would be accounted for by BRCA1/2 if mutations in those genes actually caused cancer, which is highly problematic as described above.

Aside from the lack of scientific evidence proving mutant genes cause cancer in general, and breast cancer in particular, a 2005 report sponsored by The Agency for Healthcare Research and Quality concluded that, “The evidence base for genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility as a screening strategy is limited by [1] lack of studies demonstrating effectiveness, [2] biases inherent in studies conducted in highly selected populations, and [3] incomplete information on adverse effects” (Nelson et al. 2005a). Furthermore, “It is not known whether testing for BRCA mutations reduces cause-specific or all-cause mortality and improves quality of life” (Nelson et al. 2005b), and diagnoses based on gene mutation have so far not demonstrated any real benefits to patients (Maher 2008). Indeed, others have concluded that the presence of BRCA mutations are at best uninformative (Pradhan et al. 2010, Rennert et al. 2007).

To conclude, the much ballyhooed BRCA1 and BRCA2 mutations have not been proved to cause breast cancer, or possess clinical validity and utility, and no test for either mutation has been approved by the FDA (Secretary's Advisory Committee on Genetics

2008). Nevertheless, widespread testing of women for mutations in BRCA has led to medical interventions of carriers, including early mammography, ovarian cancer screening, and prophylactic mastectomy (Guillem et al. 2006, Secretary's Advisory Committee on Genetics 2008).

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