Editorial Commentary

Looking for *BRCA1* and *BRCA2* mutations in Asian women with breast cancer

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Ang *et al.* evaluated various criteria for genetic testing of newly diagnosed breast cancer patients in two Asian countries, Malaysia and Singapore (1). Their goal is to maximize the number of mutations found, given available resources. What criteria yield the greatest number of mutations? What additional criteria will add to the total of carriers found? The majority of new breast cancer cases now occur in Asia, with China being the largest contributor world-wide (2). Zang *et al.* have conducted large genetic surveys of breast cancer patients in Beijing (3) and Kwong *et al.* have been active in cancer genetics in Hong Kong for years (4). Many other surveys have been conducted in Asian countries, including Pakistan (5,6), the Philippines (7) and Japan (8). In my opinion, genetic testing criteria should be few, simple, easy to apply and as general as possible. It is not clear if it is helpful to develop an elaborate testing protocol specifically for Asian women. The mutation frequency and distribution might vary widely from country to country within Asia—according to geography and ancestry (9). Further, it is not clear that these criteria are also applicable to Asian women who live outside of Asia, such as in Canada. In Ontario, we would be reluctant to adapt our testing criteria to include racial ancestry (the current exception being Ashkenazi Jewish women).

In a review of our recent testing outcomes in Ontario we found that two criteria—age of onset less than 50 and triple-negative status—allowed us to pick up the majority of mutation carriers (10). Adding in family history-testing of women with one or more first-degree relatives with ovarian cancer or early-onset breast cancer (less than age 40) picked up a few more. I think that these three criteria should be adopted universally. For some countries Ashkenazi Jewish ancestry is an indication for testing three founder mutations which contribute to the high prevalence of mutations in Jewish women (11,12). The highest prevalence of all countries among unselected patients is in the Bahamas (13). In Poland we have identified 9,000 BRCA1 carriers in Pomerania by applying a very relaxed set of testing criteria and limiting testing to six common founder mutations (14). Full sequencing, which is much more expensive is reserved for those with a strong family history (14). I don't think it is practical to use a risk calculator that has been calibrated for two countries. Ideally, each country should evaluate their own criteria and prevalence of mutations. In particular, if the majority of carriers carry a founder mutation these can be used to generate an inexpensive panel. Are there founder mutations in in other genes such as PALB2 which could be added to the panel?

The important question is "why test breast cancer patients in the first place?" The answer may appear surprising. To me, the number one reason to test is to perform a preventive salpingo-oophorectomy on those who test positive. This prevents the development of secondary malignancies of the ovary and fallopian tube, which are all too common in survivors of breast cancer patients with a BRCA mutation. Preventive oophorectomy has a strong therapeutic impact on mortality from breast cancer in breast cancer patients with *BRCA1*, *BRCA2*

and *CHEK2* mutations (15-17). This is a one-time life-saving operation that can be done by gynecologists and gynecology oncologists in most settings worldwide. An additional reason for testing is to give the patient the option for bilateral mastectomy. Early studies show this does improve lifespan (18,19) but the data so far are not robust. Magnetic resonance imaging (MRI) has been shown to be helpful in downstaging breast cancers and in screening in unaffected women (20,21) but has not yet been shown to improve outcome when used as a screening tool for second primary breast cancers. Data on the best chemotherapy for carriers (neoadjuvant or adjuvant) is emerging but there is no consensus yet. Importantly the drug Olaparib has been shown to be beneficial for high-risk breast cancer patients in the adjuvant setting but the drug is expensive and is not readily available in low- and middle-income countries (22). We must be cautious in asking women with limited resources to pay for Olaparib out of pocket. If olaparib were to be come affordable and accessible, then the motivation to provide genetic testing widely to breast cancer patients at diagnosis will increase.

The range of cancer types associated with mutations in BRCA1 and BRCA2 varies in different ethnic groups. Breast and ovarian cancer appear to be universal attributes of mutations in both genes, but the risk of other cancers is less well established and appears to vary across ethnic groups. Momozawa and colleagues found greater numbers than expected in the number of gastric, biliary and esophageal cancers in BRCA1 and BRCA2 carriers from Japan (8). We have not seen an excess of any of these cancers in our large cohort of BRCA1 and BRCA2 carriers from North America and Europe (although we confirm an excess of pancreatic cancer in BRCA1). It is not clear if there is an advantage to knowledge of mutation status so that one can prevent or screen for cancer other than ovary, such as pancreas, colon, esophagus and the biliary tree. In Japan it seems reasonable to ask whether all individuals with newly diagnosed gastric, esophageal or biliary cancer should be tested for these mutations, but only after they have considered what clinical strategy is suitable for those who test positive. Should we test for mutations in other genes? In our office we advocate for PALB2 testing but we consider CHEK2 and ATM to be still in the research phase. More to come. Studies on these topics will need to be lead from Asia.

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