Editorial

CHEK2, breast cancer, and the understanding of clinical utility


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CHEK2 (cell cycle checkpoint kinase 2) is one of a number of genes whose products are involved in DNA damage repair (1). The gene product, CHK2, is a serine threonine kinase that is activated in response to DNA damage and plays an important role in transducing the DNA damage signal to downstream repair proteins. CHK2 also participates in the regulation of cell cycle progression after DNA damage, and thus aids in coordinating the complex dance of DNA repair proteins responding to threats to genomic integrity (2). Given the place of CHEK2 at the center of DNA damage repair, it is not surprising that a functionally significant mutation in this gene was first described in a family with Li-Fraumeni syndrome (3). Subsequent research, masterfully reviewed in this issue by Dr Steven Narod, showed that certain mutations in CHEK2 are reproducibly associated with increased risks of female breast cancer (4). Other associations have been more variable, but CHEK2 mutations have been associated with increased risks of colon, prostate, and male breast cancer. Lung and laryngeal cancer are inversely associated in some studies, an intriguing and counterintuitive finding that awaits explanation.

Germline testing for mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 has become an accepted part of clinical care in specific clinical circumstances. However, testing for CHEK2 mutations has not. The difference is not merely one of relative prevalence, as CHEK2 mutations are present in approximately 1–2% of unselected women with breast cancer in certain populations and somewhat greater proportions of early onset and familial cases (4). This does not represent a large fraction of breast cancer cases, but it is not a trivial number, either. Furthermore, only specific CHEK2 alleles have been associated with risk, so testing is relatively straightforward (much simpler than seeking unknown mutations in BRCA1 or BRCA2) and inexpensive.

What has limited the acceptance of CHEK2 testing is widespread uncertainty about the clinical utility of the result (5). One group defines the clinical utility of a test as ‘...its usefulness and added value to patient decision-making compared with current management without genetic testing’ (6). Simply put, healthcare professionals who are considering offering CHEK2 testing find themselves asking, ‘What am I going to do differently if I find a mutation? Or if I do not?’ If their answer is, ‘Nothing’, then the test has no clinical utility and providers will not offer it. Direct comparison to BRCA mutation testing helps one to understand why many believe that CHEK2 testing is of limited clinical utility.

When deciding about genetic testing of women with breast cancer, the first question asked by clinicians is whether the test being considered will change the management of the established disease. Clear-cut prognostic implications may influence decisions about whether to offer systemic adjuvant therapy. Specific markers may predict response to particular treatments (e.g. trastuzumab in HER2 overexpressing cancers and anti-estrogen therapy in hormone receptor positive disease). Neither BRCA nor CHEK2 testing has clearly independent prognostic or predictive impact, although new evidence suggests that BRCA1/2-deficient
The same cannot be said confidently with respect to estimates nearly always exceed action thresholds. Risk has been noted for $BRCA$ unaffected women. Similar situational variation in how to provide robust, clinically valid risk estimates to unaffected women is also of uncertain clinical utility. In any event, the variation makes it difficult to concert with other hereditable factors to increase risk. In any event, the variation makes it difficult to concert with other hereditable factors to increase risk. Another hypothesis is that these variations may be due to ascertainment bias. or early onset breast cancer cases (4). Some of the evidence to support a recommendation for routine contralateral preventive mastectomy in women with $CHEK2$ mutations. In addition, the unclear association with nonbreast second primaries limits the usefulness of testing in directing other preventive surgeries.

$BRCA$ testing of women with breast cancer may be performed to inform risk management of family members, even when the testing has no impact on the immediate management of the cancer itself. However, identifying a $CHEK2$ mutation in an unaffected woman is also of uncertain clinical utility. As carefully described by Dr Narod, the risk estimates provided to unaffected $CHEK2$ mutation carriers vary with the clinical circumstances. Risks appear to be higher when the mutation is identified in the setting of family history than in unselected or early onset breast cancer cases (4). Some of these variations may be due to ascertainment bias. Another hypothesis is that $CHEK2$ is working in concert with other hereditable factors to increase risk. In any event, the variation makes it difficult to provide robust, clinically valid risk estimates to unaffected women. Similar situational variation in risk has been noted for $BRCA$ mutations, but risk estimates nearly always exceed action thresholds. The same cannot be said confidently with respect to $CHEK2$ mutations. The lack of age-specific risk estimates also hampers the use of $CHEK2$ mutation information in clinical settings. Even if one accepts lifetime risk estimates (from birth) of 20–25%, as suggested by Dr Narod for a $CHEK2$ mutation carrier with an affected first-degree relative, one must recognize that most carriers are not identified at birth. The ‘lifetime’ risk for an unaffected woman identified as a $CHEK2$ mutation carrier at age 30 will most probably not be the same as the risk for a woman found to have a mutation at age 55. Mutation carriers identified later in life may not have a risk that exceeds an action threshold because they have ‘used up’ some of their risk. Carriers identified early may not be appropriate candidates for intervention because they may not be at sufficient short-term risk to justify such intervention. Thus, knowledge of age-specific risks is critical to decision making about the necessity for and timing of modalities such as breast magnetic resonance imaging screening and tamoxifen chemoprevention. In the absence of that information, it is difficult to advise women as to when such interventions are likely to be most useful.

Finally, women may undergo genetic testing to identify a $BRCA$ mutation so that unaffected women in the family who test negative for the mutation may be relieved of the need for surveillance or preventive interventions (12). It is not clear that ‘true negative’ women in families with $CHEK2$ mutations can experience similar relief. As noted by Dr Narod, the breast cancer phenotype does not always segregate with the mutation in these families, perhaps due to the segregation of other, unidentified risk alleles. For this reason, even women who test negative may remain at increased risk and need to continue increased surveillance, which negates one of the main benefits of pre-symptomatic testing.

The considerations outlined above highlight the concerns limiting widespread acceptance of $CHEK2$ mutation testing in clinical settings. These considerations also outline a research agenda, overlapping with the one suggested by Dr Narod, which may ultimately facilitate such acceptance. The questions regarding the clinical utility of $CHEK2$ testing are harbingers of those raised by newer genetic tests, such as the low penetrance risk variants identified through genome-wide association studies. Those addressing these challenges are the pathfinders for the new era of genomic medicine.

**Acknowledgement**

Research funding from Kudos pharmaceuticals/Astra-Zeneca, Advisory Board for Pfizer Pharmaceuticals is acknowledged.
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References

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