King syndrome: what’s in a name?

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Hereditary breast and ovarian cancers have been associated with pathogenic genetic variants in the \textit{BRCA1} and \textit{BRCA2} genes for nearly 30 years due to the arduous work of Dr. Mary Claire King. Dr. King and her research team identified the location of the \textit{BRCA1} gene in 1990\cite{1}. Unfortunately, patent protection enlisted by a biotechnology company limited access to \textit{BRCA} genetic testing and research for nearly 20 years. In June 2013, after the U.S. Supreme Court unanimously ruled that isolated human genes cannot be patented, access and research on \textit{BRCA1/2} genes greatly expanded.

Yet, a gender bias likely exists which limits access to \textit{BRCA} testing for males by a syndromic name that only associates \textit{BRCA} pathogenic variants with breast and ovarian cancers. It is estimated that 1 in 400 individuals harbor a germline \textit{BRCA1} or \textit{BRCA2} mutation and that estimate increased to 1 in 40 individuals of Ashkenazi Jewish ancestry\cite{2}. There are disparities which exist for access to \textit{BRCA} genetic testing with regard to education level, insurance status, and race/ethnicity\cite{3}. Gender is an additional disparity as men and women equally harbor these mutations, yet there is a significant difference in testing with women tested significantly more often than men\cite{4}. If the syndrome associated with mutations in \textit{BRCA1/2} was changed to King syndrome, the myopic view would not just be on breast and ovarian cancers, which have a preponderance for the female population.

\textbf{BRCA AND MALE SPECIFIC CANCER}

Prostate cancer is one of the most common cancers in men and those impacted with aggressive or metastatic disease should complete genetic testing with next generation sequencing of the \textit{BRCA} genes. For the past years, the National Comprehensive Cancer Network (NCCN) guidelines\cite{5} for hereditary breast and
ovarian cancer have included the consideration of \textit{BRCA1} and \textit{BRCA2} genetic testing for men who meet certain criteria, including a prostate cancer diagnosis with Gleason score of $\geq 7$ or metastatic prostate cancer (NCCN, Genetic/Familial High-Risk Assessment Breast and Ovarian 2019a). Pritchard et al.\cite{6} identified the importance of germline genetic testing in men with metastatic prostate cancer, \textit{BRCA2} representing the most identified pathogenic variant.

There is clinical utility in establishing the presence of mutations in DNA repair genes, such as \textit{BRCA}, to define cancer subtypes that have distinct vulnerabilities to specific therapeutic such as Poly [adenosine diphosphate (ADP)-ribose] polymerase (PARP) inhibitors\cite{7}. Poly (ADP-ribose) polymerase is a cellular mechanism for repairing single-strand DNA breaks. If \textit{BRCA} is mutated, PARP must repair both types of DNA breaks, and cells depend on the PARP repair mechanism. Therefore, use of the PARP inhibitors class of medications in individuals with \textit{BRCA1} and \textit{BRCA2} mutations should result in cancer cell death through a type of directed synthetic lethality\cite{8}. Poly (ADP-ribose) polymerase inhibitors are a consideration for the treatment of ovarian and breast cancers with germline \textit{BRCA1} and \textit{BRCA2} mutations and have activity in castration-resistant prostate cancer with germline or somatic mutations in certain DNA repair genes, such as \textit{BRCA1}, and \textit{BRCA2}\cite{7}.

**HAVE BEEN HERE BEFORE**

There has been a similar circumstance in cancer genetics with the re-naming of hereditary non-polyposis colorectal cancer to Lynch syndrome\cite{9}. Lynch syndrome is a hereditary cancer syndrome associated with an increased lifetime risk of developing colorectal cancer as well as stomach cancer, ovarian cancer, hepatobiliary tract cancer, urinary tract cancer, and cancers of small bowel, brain, and skin. Lynch syndrome is associated with pathogenic genetic variants in multiple different genes, including \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, and \textit{PMS2}, which are considered to mismatch repair genes and have therapeutic implications specific to immunotherapy\cite{10}. Previous research demonstrated the benefit of testing tumors and patients for Lynch syndrome as the questionable benefit of standard systemic chemotherapy regimens based on cisplatin and 5-fluorouracil in the setting of mutations in mismatch repair genes\cite{11-14}. Lynch Syndrome provides an early adoption of molecular analysis of solid tumor patients to guide individual oncology treatment and by removing the colorectal cancer focus to the syndrome, a wider net became available to capture cancers associated with mutations in the mismatch repair genes.

It is timely and necessary to rename hereditary breast and ovarian cancer syndrome to King syndrome, to assume a wider assessment of cancer that has occurred, or may occur, and due pathogenic variants in \textit{BRCA1} or \textit{BRCA2}. Genetic testing and molecular analysis for oncology patients of all genders (female, male, and trans) and cancer types (breast, ovarian, pancreas, and prostate) is necessary if the true benefit of personalized medicine is to be gained for the entire population. King syndrome would raise awareness and expand health care provider consideration of genetic testing for cancers other than only breast and ovarian. By a simple name change, King syndrome provides a broader scope to impact health outcomes and save lives.

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