ABOUT US

The Angeles Clinic and Research Institute was established by a group of physicians who came from academic backgrounds and sought to establish an environment where world-class patient care was the top priority. The Clinic’s physicians include widely recognized oncologists and leaders in cancer medicine who, together with expert radiology services, radiation oncology, specialized oncologic nurses, and a dedicated support staff, have created a state-of-the-art center for oncology in the Los Angeles area. In addition to superb clinical care, our physicians are known for their world-class clinical research. The Institute has earned an international reputation for developing new cancer therapies, providing the best in traditional and experimental treatments, and expertly guiding and training the next generation of clinicians and researchers.

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CONNECTING THERAPEUTIC DISCOVERIES TO HEREDITARY BREAST CANCER GENES

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In the US, the lifetime probability of developing breast cancer is 1 in 8 (12.5%) and that for ovarian cancer is 1 in 72 (1.4%). These risks, however, are influenced by age, environmental, behavioral and genetic risk factors. Hereditary breast cancer refers to cancer attributable to a single hereditary gene mutation and constitutes about 5-10% of all breast cancers. That alterations in inherited genes can confer familial risk of both breast and ovarian cancer was identified less than 20 years ago through the discovery of two breast cancer susceptibility genes, BRCA1 and BRCA2. Since then, an awareness of the implication of these cancer susceptibility genes to health has moved into the public domain. This transition is justified because in women with an inherited BRCA1 mutation, the lifetime risk of development of breast cancer is increased to 65-80% and that of ovarian cancer is increased to 37-62%. For women with inherited mutations of BRCA2, the lifetime risk of development of breast cancer is 45-85% and that of ovarian cancer is 11-23%.

The prevalence of BRCA1 and BRCA2 mutations varies between ethnic groups and geographic location. Populations in which specific BRCA mutations have been identified are emerging and span the globe, including Israel, Iceland, Scandinavia, Europe, Asia and Mexico. Within the general population, the prevalence of BRCA mutation carriers is estimated to be between 1/800 to 1/1000. Among the Ashkenazi Jewish population, however, this prevalence is higher and estimated to be 1/40. The prevalence of BRCA mutations in patients with breast and ovarian cancer unselected for family history or age of onset of cancer is generally low (1-7%). Higher incidences of BRCA mutations, however, can be found amongst patients with breast or ovarian cancer who develop cancer at a young age (less than 50), have bilateral breast cancer or have a family history of BRCA-associated cancers including breast, ovarian, pancreatic and prostate cancers. As breast cancer amongst males is usually very rare in the general population, a personal or family history of male breast cancer is also associated with an increased risk of carrying a
HEREDITARY GENES CONT’D …

BRCA mutation. Guidelines exist for the appropriate selection of candidates for BRCA testing and generally, patients are referred for genetic counseling/testing if the estimated risk of harboring a BRCA mutation is at least 10%. These mutations may originate from either the maternal or paternal line and are inherited in an autosomal dominant pattern. As each offspring of a BRCA carrier has a 50% chance of inheriting the mutation, genetic counseling is not only beneficial for the affected individual, but can also be relevant to additional family members.

Germline mutations in either BRCA1 or BRCA2 lead to increased risks of cancer formation due to disruption of their normal functions in double-strand DNA break repair during a process known as homologous recombination (HR). This form of DNA repair is highly conserved in nature because it is less prone to cause errors. Hence, cells that are deficient in normal BRCA function are more likely to form cancers because of genomic instability resulting from potentially mutagenic DNA repair processes. For reasons that are less clear, inactivation of BRCA1 generally leads to higher grade breast cancers, termed “triple negative”, because they lack expression of both the estrogen and progesterone receptors and they also lack HER2 gene amplification. In contrast, inactivation of BRCA2 does not lead to a distinct breast cancer signature, but these breast cancers are more likely to be hormone receptor positive.

In terms of application to healthcare, the discovery of the association between BRCA mutations and breast cancer risk has led to strategies for breast cancer screening, prevention and treatment. Screening measures have included the incorporation of additional imaging modalities (such as breast MRI) to conventional mammography. For women with known BRCA mutation, there may also be the option of starting breast cancer screening at an earlier age, compared to the general population. In terms of cancer prevention for known BRCA mutation carriers, both prophylactic bilateral mastectomies and ovariectomies have been found to significantly reduce the risk of both breast and ovarian cancer and improve mortality.5

Perhaps what is most exciting about the discovery of BRCA and its association with breast cancer, however, has been the ability to apply the science underlying BRCA function, towards the development of therapeutic strategies. It was shown, for example, that BRCA-deficient breast cancers are particularly sensitive to DNA-damaging chemotherapies such as platinum agents, because these cancers lack the ability to effectively repair damaged DNA.

A more striking example of the translation of lab bench to bedside for BRCA-associated breast cancers has been the development of a class of drugs known as PARP inhibitors.6 PARP1 is an enzyme which is involved in single strand DNA break repair during a process known as base excision repair (BER). In the absence of PARP1, single strand DNA breaks degenerate into double strand DNA breaks which are then repaired by HR, a process dependent on normal BRCA1 and BRCA2 functions. Thus, theoretically, if PARP1 is inhibited in breast cancers among BRCA mutation carriers, neither BER nor HR are possible in response to DNA damage from chemotherapy, presumably resulting in breast cancer cell death. We, at the Angeles Clinic, are very excited in that we are now able to offer patients the ability to participate in a proof of concept clinical trial. Specifically, we are conducting a clinical trial which is aimed at determining the efficacy of the PARP inhibitor, veliparib, when combined with chemotherapy, in patients with metastatic breast cancer and known BRCA1 or BRCA2 mutation. Patients will be randomized to either chemotherapy alone (using a platinum based regimen) or chemotherapy with veliparib. If successful, the outcome of this clinical trial will surely provide a new standard of care for patients with BRCA-associated breast cancer and show the power of connecting science with therapeutic discovery.

References

UPCOMING EVENTS

For further information, please contact Nick Belardo
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REBOUND’S PERFECT 10
A fundraising party to benefit The Angeles Clinic Foundation
October 10, 2013, From 10 AM-10 PM
21723 Vanowen Street, Canoga Park, CA

THE ANGELES CLINIC FOUNDATION PRESENTS
THE BREAST CANCER PHOTO BOOTH
October 25, 2013, From 11 AM-4 PM
at The Original Farmer’s Market
6333 West 3rd Street, Los Angeles, CA
DECREASE IN RATE OF SCREENING MAMMOGRAPHY

By Silvana Martino DO
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Each year, the American Cancer Society estimates the number of new cancer cases and cancer deaths expected in the U.S. during the current year. The Society also updates the incidence, survival and mortality data from the previous years. These results are published and widely disseminated. Review of these data reminds us that cancer remains a major health problem both in our country and worldwide. Presently, one in four deaths in the U.S. is due to cancer.

Breast cancer remains the most common malignancy in women. In the year 2013, it is estimated that 232,340 women in the U.S. will be diagnosed with breast cancer. Early detection using screening mammography remains an important tool that has demonstrated the ability to identify disease at an earlier stage and decrease mortality. However, during the past few years a decrease has been noted in the number of women who have chosen to participate in screening mammograms. Several potential reasons have been offered as an explanation for this decline.

In 2009, a report from the U.S. Preventive Services Task Force concluded that the benefits of screening mammography had been exaggerated and recommended that the age of onset for screening mammography should be raised from age 40 to age 50 with mammograms being done every two years rather than yearly. These recommendations were met with considerable opposition, resulting in the U.S. Preventive Services Task Force softening its position. Never the less, it is likely that their recommendations resulted in many women choosing to avoid yearly mammography. The other component believed to have contributed to the decrease in mammography rate is the argument that mammography leads to a diagnosis of non-invasive breast cancer in a large proportion of screened women. It is further presumed that many of these lesions would not proceed to an invasive breast cancer and therefore, may not need diagnosis at all. In fact, a re-naming of non-invasive carcinoma is being considered, specifically to remove the word carcinoma from the nomenclature. No doubt, these events have created some degree of confusion in the minds of many women. These ideas, coupled with a decline in the U.S. economy, have resulted in a noticeable decrease in the rate of screening mammography.

We at The Angeles Clinic and Research Institute are concerned with this trend. We are in agreement with the opinion expressed by most authorities on this issue; namely that the indications for screening mammography should not be altered.

The American Cancer Society continues to recommend the following guidelines for most adult women:

- Yearly mammograms starting at age 40 and continuing for as long as a woman is in good health.
- Clinical breast exam about every 3 years for women in their 20s and 30s and every year from age 40 and above.
- Women should know how their breasts normally look and feel, and report any breast change promptly to their health care provider. Breast self-exam is an option for women starting in their 20s.
- Some women because of a family history of breast or ovarian cancer, a genetic tendency or other risk factors are at higher than average risk and should be screened with an MRI in addition to mammograms. Additional testing should be considered for women who fall in this category.