Inherited Cancer Risks: New Insights from MSK Presented at 2023 ASCO Meeting

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By Julie Grisham, **Monday, June 5, 2023**

(Clockwise from upper left) Dr. Alicia Latham, Dr. Michael Walsh, genetic counselor Megha Ranganathan, and Dr. Zsofia Stadler presented research related to hereditary cancer genetics at the 2023 ASCO meeting.

Researchers from Memorial Sloan Kettering Cancer Center (MSK) revealed new findings about hereditary cancers and genetics at the recent 2023 American Society of Clinical Oncology (ASCO) annual meeting.

Genetic mutations that are passed down through families cause a significant percentage of cancers — between 5 and 10%, and as high as 15 to 20% in people with advanced cancers. Patients with certain hereditary cancers may especially benefit from many of the latest cancer treatments, including targeted drugs and immunotherapies. Their families also may benefit from being monitored for early signs of cancer.

Among the recent advances in MSK's research into understanding how inherited DNA mutations affect cancer development and treatment, four presentations at the ASCO meeting highlighted new analysis of early-onset disease, hereditary cancers in transgender people, a new gene linked to lung cancer, and the importance of genetic testing for younger people with gastrointestinal cancers.

What Defines Early-Onset Cancers and How Should They Be Treated?

Amid growing concern about an increase in cancers occurring in younger people, clinical geneticist and gastrointestinal oncologist Zsofia Stadler, MD, presented research that found the age for so-called "early-onset" cancer can vary widely depending on the type of cancer. Dr. Stadler stressed the need to have clear criteria to define early-onset cancers, because her research also found these cancers are more likely to be linked to an inherited genetic mutation. Knowing whether a cancer is caused by a hereditary mutation is important because it can make a difference in choosing the right treatment. It's also a signal that members of a patient's family should consider genetic testing.

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"We know the incidence of early-onset cancer is increasing for some tumor types, but when we think about what early onset means, we realize it's actually poorly defined," says Dr. Stadler, Clinical Director of MSK's Clinical Genetics Service. "These cancers are usually defined as those arising before the age of 50 for any type of solid tumor. But the fact is, there is a dramatic variation in the average age of onset across different tumor types."

The research had two aims: The first was to determine what age should be considered early onset for a variety of solid tumors. The second was to determine how often different types of early-onset cancers were likely caused by inherited genetic mutations.

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> 
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First, the investigators used a National Cancer Institute database to determine the average age at which patients typically developed 32 types of solid tumors. Based on those ages, researchers then used a formula to calculate what age would be considered early onset for each of these cancers. That age ranged from the late 30s for cervical and thyroid cancers to about 60 for mesothelioma and bladder cancer. "If we considered 50 the cutoff age for every type of solid tumor, there are a lot of early-onset cancers that we would miss," Dr. Stadler explains.

To answer the study's second major question, the researchers then used these new classifications to analyze how often early-onset cancers were linked to an inherited genetic mutation. (This is an alteration in DNA that is passed on by a parent and present in every cell in the body.)

Overall, researchers found that early-onset cancers were much more likely to be linked to hereditary mutations — 19% versus 15.5% in people whose cancers developed at an average age. For hereditary mutations defined as "high penetrance" (meaning they were extremely likely to cause cancer), the difference was even more dramatic: 13% of early-onset cancers were linked to inherited mutations versus 5% of cancers occurring at an average age.

Researchers arrived at this conclusion using data from about 29,000 patients whose DNA was analyzed with MSK-IMPACT®, a test that identifies genetic mutations linked to cancer. It can find mutations that are only in tumors as well as inherited mutations that may increase the risk of developing cancer.

"The diagnosis of an early-onset cancer is an impetus for doing genetic testing to look for inherited risk factors," Dr. Stadler says. "The findings from this study illustrate how important it is that early-onset cancers be correctly classified."

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Caring for Transgender Patients With Hereditary Cancer Syndromes

Genetic counselor Megha Ranganathan, MS, CGC, participated in a panel discussion focused on caring for transgender patients with inherited mutations in the BRCA1 and BRCA2 genes. Mutations in these genes can increase the risk for several cancers, including breast, ovarian, and prostate cancer.

"There are more than 1.6 million people in the United States who identify as transgender, and that number is likely an underestimate," Ranganathan says. "The data is so limited that many providers are often unsure how to best manage cancer risk in these people, especially those at higher risk due to an inherited genetic predisposition."

Ranganathan and her co-presenters discussed two cases demonstrating the challenges for these patients. The first case involved a transgender woman (a person who is assigned male at birth but identifies as a woman). After her mother was diagnosed with ovarian cancer, genetic testing revealed the transgender woman had a *BRCA2* mutation. "At that point, the patient had already been receiving gender-affirming estrogen therapy for about 10 years," Ranganathan said. "We know that prolonged estrogen exposure is a risk factor for breast cancer, but it is unknown how much it increases her risk, especially because she has a *BRCA2* mutation.

"Despite the lack of reliable data, increased breast cancer surveillance or risk-reducing surgery may be reasonable options," she added. "We encourage these patients to talk to their doctors to determine the best option for them depending on their gender-affirming goals." Another issue for this patient: Because she was assigned male at birth, she has a prostate, and this gene mutation puts her at increased risk for prostate cancer as well.

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> Megha Ranganathan
> genetic counselor

The second case involved a young transgender man (a person who is assigned female at birth but identifies as a man). He had a *BRCA1* mutation and was considering top surgery (surgery to remove breast tissue and make the chest look more masculine). Would having top surgery reduce his risk for breast cancer? The panel suggested more extensive surgery such as a full mastectomy could be considered to prevent breast cancer in this situation.

Ranganathan and her co-presenters also discussed several ways healthcare providers can create a more inclusive environment for gender-diverse people. The panelists explained key concepts and terms, how to represent someone's gender and sex assigned at birth on family trees, and how to request a patient's chosen name and pronouns.

"Many transgender people avoid the healthcare system altogether because they fear discrimination and stigmatization. Research is lacking on how best to care for them," says Ranganathan. "As an institution that is dedicated to reducing healthcare disparities, we at MSK want patients to be aware that this is something we're thinking about and that we aspire to provide excellent care for all patients, regardless of gender identity."

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A New Gene Potentially Linked to Inherited Risk of Lung Cancer

Pediatric oncologist and clinical geneticist Michael Walsh, MD, presented new research that found for the first time that mutations in the cancer predisposition gene *POT1* are associated with increased rates of lung cancer. Previously, mutations in *POT1* have been associated with sarcoma, certain types of leukemia, and clonal hematopoiesis, a blood condition linked to aging.

"Compared with other cancers like breast, ovarian, and prostate cancers, we know less about the inherited risks of lung cancer," Dr. Walsh says. "We know that lung cancer is strongly linked to environmental causes like smoking. These findings shine a light on potential inherited factors that may also play a role in causing lung cancer."

Dr. Walsh and his team were able to make this discovery thanks to the cancer genetic test MSK-IMPACT. In addition to sequencing patients' tumors, MSK-IMPACT can also analyze the genetics of normal tissue, so experts can determine whether a cancer is linked to an inherited genetic mutation or developed at random. In this case, a study of data from patients' normal DNA allowed investigators to undercover new findings about inherited mutations in *POT1*.

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"*POT1* has been added to the list of genes detected by MSK-IMPACT relatively recently, so it hasn't been studied as well as some other cancer genes," Dr. Walsh explains. "But when we looked at data for about 7,000 patients, we found that the incidence of lung adenocarcinoma in people with this inherited mutation was much higher than expected."

After the MSK-IMPACT analysis, Dr. Walsh and his colleagues found that other large databases of cancer genes supported their findings. They will continue studying the link.

Dr. Walsh says one day this discovery might provide insights leading to new treatments for cancer.

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Increasing Genetic Testing for Younger People with Gastrointestinal Cancers

In response to the alarming increase in colorectal cancer cases in younger people, MSK clinical geneticist and family medicine physician Alicia Latham, MD, MS, urged more testing to determine possible inherited risks of cancer.

"As MSK offers genetic testing to more of our patients, we're finding that some of these gene mutations are more common than we previously believed," says Dr. Latham, who spoke at an ASCO session focused on gastrointestinal (GI) cancers. "But there are questions about whether these mutations are truly related to the cancer or are instead incidental findings."

Dr. Latham specializes in treating people with Lynch syndrome. This hereditary condition carries an increased risk of certain types of cancer, including colon cancer and rectal cancers. Lynch syndrome cancers are characterized by a feature called microsatellite instability, which makes them especially responsive to immunotherapy drugs called checkpoint inhibitors.

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Because these mutations have important implications for treatment, there is a move toward testing more patients with GI cancers for these genes, especially younger patients, Dr. Latham explains.

"This is a real change from what we've done in the past," she says. "But because findings from these tests can have such important implications for treatment, we want everyone to be aware of these connections and the importance of testing."

She adds that several collaborative advisory groups in North America and Europe are also backing the recommendations to test more patients for inherited conditions.

Dr. Latham leads MSK's Comprehensive Assessment, Treatment, and Prevention of Cancers with Hereditary Predispositions (CATCH) program, which provides surveillance and monitoring for people who have genes that are linked to inherited cancer predisposition syndromes.