Study finds new risk factor for melanoma in younger women

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Researchers may have found a more potent risk factor for melanoma than blistering sunburns, freckling, or family history of the deadly skin disease. In a new study, scientists at NYU Langone Medical Center report that a genetic variation leads to a nearly four-fold increase of melanoma in women under the age of 50. The new study was released online March 24, 2009, in the journal *Clinical Cancer Research* and will be published in the April 1, 2009, issue of the journal.

"If this number turns out to be reproducible, it is higher than a lot of the other clinical risk factors that we know, such as blistering sunburns, freckling, and family history," said David Polsky, M.D., Ph.D., associate professor of dermatology and director of the Pigmented Lesion Section of the Ronald O. Perelman Department of Dermatology at NYU School of Medicine, and the study's lead author.

"Potentially, we have a genetic test that might identify pre-menopausal women who are at higher risk for melanoma," said Dr. Polsky. "And if that's the case, then we might want to have increased surveillance of those patients including more frequent visits to the doctor, more rigorous teaching of skin self-examination, and other preventive steps."

Melanoma, the most deadly form of skin cancer, was expected last year to strike 62,480 Americans, and kill an estimated 8,420 diagnosed patients, according to the American Cancer Society.

For largely unknown reasons, melanoma is more common among women than men under the age of 40. Between 40 and 50 the incidence is about equal in both sexes, and over the age of 50, melanoma incidence skews markedly toward men. Polsky and his co-authors suspect the difference may be linked to the activity of estrogen, mediated in part by a genetic variant in a gene called MDM2.

When estrogen binds to this gene, it turns on production of MDM2, a potential oncogene (cancer promoting gene) in cells. In the presence of the genetic variation in MDM2, originally identified by the laboratory of Dr. Arnold Levine at the Institute for Advanced Study, Princeton, the estrogen binds more strongly, resulting in far greater production of the MDM2 protein.

Women with higher estrogen levels and who also have the genetic variation would be expected to have higher estrogen-related MDM2 protein that could increase their melanoma risk, explains Dr. Polsky.

The MDM2 genetic variant appears in the gene's promoter, a power switch that determines when the gene is turned on and how many copies are produced within a cell. This promoter region is normally regulated by p53, a tumor suppressor gene implicated in as many of 50 percent of all cancers. Part of MDM2's normal function is to inhibit p53 when its levels get too high in a cell. If MDM2 is turned on independently of p53, it can keep p53 levels low, reducing the cell's protection against turning into a cancer cell.

Scientists have shown that the substitution of a single letter of DNA at a specific point in the MDM2 promoter can significantly ramp up gene production. The new study evaluated the effects of this natural genetic variation in 227 melanoma patients enrolled in NYU's Interdisciplinary Melanoma Cooperative Group between August 2002 and November 2006. Dr. Polsky and colleagues from NYU School of Medicine recorded each patient's MDM2 and p53 genetic variations, as well as age, sex, personal and family history of melanoma, and tumor thickness.

The results showed that more than 40 percent of women diagnosed with melanoma under the age of 50 had the genetic variation in the MDM2 gene promoter. In contrast, only about 16 percent of

women diagnosed after the age of 50 had the variation.

The difference in the frequency of the variation corresponded to a 3.89-fold increase in melanoma risk for women under the age of 50—an elevated risk over background levels that increased more among even younger women, according to the study. When the researchers compared the MDM2 genotypes to patients' ages at diagnosis, they found that about 38 percent of women with the variation had been diagnosed between the relatively young ages of 30 to 39—a much higher melanoma incidence than among older women patients with the variation.

Beyond validating the risk in a larger group of patients, Dr. Polsky hopes to begin formulating a stronger model of cancer risk that incorporates genetic information and other factors. "Can we look at people's sun exposure history, hormonal status and a panel of genetic markers in addition to MDM2 and ask, 'Does this help identify more high-risk people?'" he said.

Source: New York University School of Medicine (news : web)