Why some HPV infections go away and others become cancer

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Gardasil vaccine and box. Image: Wikipedia

For people infected with the human papilloma virus (HPV), the likelihood of clearing the infection and avoiding HPV-related cancer may depend less on the body's disease-fighting arsenal than has been generally assumed.

A new study finds that the body's ability to defeat the virus may be largely due to unpredictable division patterns in HPV-infected stem cells, rather than the strength of the person's immune response.

If the mathematical model behind the findings holds up, it could point to ways of tweaking the way infected cells divide in order to make HPV infections go away faster and hence lower the risk of developing cancer, said co-author Marc Ryser of Duke University.

The results appear online in the journal *PLOS Computational Biology*.

More than six million people in the U.S. become infected with HPV every year. Most people clear the virus on their own in one to two years with little or no symptoms. But in some people the infection persists. The longer HPV persists the more likely it is to lead to cancer, including cancers of the cervix, penis, anus, mouth and throat.

To better understand why some HPV infections go away and others progress, Duke mathematicians Marc Ryser and Rick Durrett developed a model of HPV infection at the level of the infected tissue.

HPV spreads through intimate skin-to-skin contact during sex with an infected person, and takes advantage of the tissue's natural internal repair system to reproduce and spread.

The invading virus breaks through the layers of cells that line the cervix and other tissues and infects the stem cells in the innermost layer, called the basal layer.

Usually, when an infected stem cell divides into two, one of the new cells stays in the basal layer and the other cell is pushed outward into the upper layers where it dies and is sloughed off, releasing virus particles that can then infect another person.

But sometimes, in a process called symmetric division, an infected cell produces two cells with the same fate—either they both stay in the basal layer or they both make their way to the surface.

The Duke researchers wanted to find out if the balance between these two modes of division affects the number of infected stem cells in the basal layer over time.

By combining their model with data from a population of 313 teenage girls who were tested for HPV every six months for four years, the researchers were able to measure the influence of symmetric and asymmetric cell divisions on the time it takes to get rid of the virus, and compare it to the body's ability to kill virus-infected cells via immune cells called killer T-cells.

Surprisingly, random division patterns in infected cells were found to play a critical role in eradicating the virus.

In particular, the researchers calculated that as much as 83 percent of the body's ability to clear the infection can be explained by the pattern of divisions in HPV-infected cells.

"There is no doubt that the immune system plays a role in HPV clearance," Ryser said. "However, the contribution from the stem cell division patterns may play a non-negligible role in the process, something that has not been acknowledged in previous studies."

The team's next step is to use their model to try to understand why some people who take oral contraceptives for a long time have an increased risk of developing cervical cancer.

More information: "HPV Clearance and the Neglected Role of Stochasticity," Ryser, M., E. Myers and R. Durrett. *PLOS Computational Biology*. DOI: 10.1371/journal.pcbi.1004113

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