

[“HPV in the Etiology of Human Cancer” \(2006\) by Nubia Muñoz, Xavier Castellsagué, Amy Berrington de González, and Lutz Gissmann](#) ^[1]

By: Arslan, Maeen Keywords: [Gardasil](#) ^[2] [IARC](#) ^[3] [Harald zur Hausen](#) ^[4] [Cancer prevention](#) ^[5] [Sexually transmitted infections](#) ^[6]

In 2006, the article "HPV in the Etiology of Human Cancer," hereafter "HPV and Etiology," by Nubia Muñoz, Xavier Castellsagué, Amy Berrington de González, and Lutz Gissmann, appeared as the first chapter in the twenty-fourth volume of the journal *Vaccine*. Muñoz and colleagues discuss the role of the Human Papillomavirus, or HPV, in uterine cervical cancers. The authors introduce the mechanisms of HPV infection that lead to genital and non-genital cancers, establishing a link between HPV and multiple human cancers. The authors end by mentioning how other factors, such as [pregnancy](#) ^[7], smoking, and age, can influence HPV progressing into cervical cancer, which can be fatal. In the article, Muñoz and colleagues use meta-analyses of case studies and clinical trials to show which specific types of HPV are linked to cervical and other human cancers and the impacts of cofactors on the development of those cancers.

The authors of "HPV and Etiology" collaborated across several institutions in different countries. The article contains data adapted from eleven studies provided by the International Agency for Research on Cancer, or IARC. At the time of publication, Muñoz worked in Lyon, France, as an epidemiologist, or someone who studies diseases and their patterns. Castellsagué worked in Barcelona, Spain, as a cancer researcher and physician. Berrington worked in Baltimore, Maryland, as a cancer epidemiologist. Gissmann worked in Heidelberg, Germany, as a virologist, or someone who studies viruses, which are infective agents that can invade a host and cause diseases. The funding came from three public health organizations in Spain, and the authors report that the source of funding did not influence the results of the project.

"HPV and Etiology" is about HPV, which is a common sexually transmitted infection that can cause genital warts, regular skin warts, and cervical cancer. Prior to the 1980s, there was not experimental evidence linking HPV and cervical cancer. However, by the end of 1980s, new types of molecular and genetic analysis enabled substantial sampling of genital warts, which are linked to HPV. In 1983 and 1984, the German researcher Harald zur Hausen had discovered that the strains HPV-16 and HPV-18 are linked to genital warts, which may then become cervical cancer. He found that the strains HPV-6 and HPV-11 are linked to genital warts as well, but do not progress into cervical cancer. Research into the links between HPV and cervical cancer then continued into the 1990s. Cervical cancer is uncontrolled cell division in the [cervix](#) ^[8], the lowest part of the [uterus](#) ^[9]. When HPV progresses, it can disrupt [regulation](#) ^[10] of the cell cycle for cells in the [cervix](#) ^[8]. The cell cycle is the series of events that occur as a cell grows and divides, and various checkpoints monitor the cycle. When the cell cycle is not regulated properly, cells can begin to divide uncontrollably, leading to cancer. There are over a hundred strains of HPV, but only some strains affect the cell cycle. Within those, only certain strains are linked to cervical cancer. The numbers of the strains correspond to when they were discovered. Cervical cancer can progress to other vital organs such as the kidneys causing multiple organs to fail, which can lead to death.

Using the established knowledge from the 1980s and 1990s, the authors of the different articles in the twenty-fourth volume of *Vaccine* provided information current as of 2006 about HPV and vaccine development. During HPV research leading up to that point, there was little known about why HPV causes cancer. Those causes are addressed in "HPV and Etiology" as well as the diseases that can accompany HPV or diseases HPV can cause.

The authors of "HPV and Etiology" discuss the different forms of cervical cancer, which can take the form of various types of carcinomas. The main types are either squamous cell carcinomas which is cancer in thin, flat cells in the outermost layer of the skin, and adenocarcinomas which are invasive tumors in the [epithelium](#) ^[11], or outer lining, of secretion organs like the pancreas, liver, kidney and reproductive organs.

"HPV and Etiology" is a review of the linkages between HPV and human cancer that includes meta-analyses of clinical trials and case studies to find which specific strains of HPV are cancerous. A meta-analysis is a large-scale statistical study that combines results of many studies. A meta-analysis provides a more concrete level of evidence than a single analysis from a few cases on the relationship between two variables.

"HPV and Etiology" has five sections. Within those five sections, the authors lay out their two-part hypothesis that HPV has a major link to cervical cancer and yet that HPV alone may not be enough for cervical cancer to occur. They argue that other stimuli must also be present. In section one, the authors discuss the mechanisms directly involved in the progression of HPV infection to cancer to show how an HPV infection disrupts the cell cycle to lead to uncontrolled growth. Section two contains the analysis of case studies from the IARC to provide evidence that adenocarcinoma and squamous-cell carcinoma can primarily be

attributed to HPV-16 and HPV-18. Sections three and four convey that HPV can be involved in both genital and non-genital related human cancers aside from cervical cancer. In section five, the authors communicate the importance of cofactors that operate together in the presentation of cervical cancer highlighting the claim that an HPV infection is not enough to cause the cancer on its own.

In section one, the authors begin by discussing the features of HPV and how it causes various cancers. The virus has DNA that codes for eight proteins. Six of those proteins are necessary for the replication of viral DNA and assembling new viral particles. The remaining two proteins provide structure to the virus. The cycle of viral replication begins when infectious particles reach the basal, or bottom, layer of the host's [epithelium](#)^[11]. The particles do so by travelling through small breaks in the tissue and binding to healthy [stem cells](#)^[12], or unspecialized cells. The authors then discuss the replication of HPV, which occurs in two steps. First, the virus infects the basal cells through small breaks in the tissue and integrates viral DNA into the host cell. That means that the HPV has infected those host cells. The infected basal cells move to the next layer and can no longer develop more specific functions or replicate. So, as new cells replace those inactivated cells, they become infected and start to divide. The second step includes the viral proteins. Those proteins disrupt the normal cell cycle and cause uncontrolled cell growth by blocking receptors needed for controlled cell growth.

The second section is broken into analyses of a variety of individual studies to provide statistical evidence for the link between HPV and cervical cancer. In their meta-analysis, the authors pooled over ten thousand cases of patients with cervical cancer and found that a set of strains of HPV have a correlation with about ninety percent of all cervical cancers. The data that the authors used came from over twenty countries. They found that infection with HPV-16 or HPV-18 was associated with about seventy percent of squamous cell carcinoma cases and eighty-six percent of adenocarcinoma cases.

In the third section, Muñoz and colleagues discuss the role of HPV in other cancers of the genitals and anus. They report that sixty-four to ninety-one percent of vaginal cancers contain DNA from HPV. They also report that eighty-eight to ninety-four percent of anal cancers contain DNA from HPV. The authors state that a majority of cancers of the penis and vulva are related to HPV as well. That means that an overwhelming majority of genital cancers, aside from just cervical cancer, are linked to HPV infections, as HPV inserts its DNA into host cells. The authors reference evidence that HPV-16 is the most common type detected in the aforementioned cancers, with HPV-18, HPV-31, and HPV-33 commonly present but to a lesser extent than HPV-16.

In the fourth section, the authors discuss the role of HPV in non-genital cancers. They cite a review from 2005 for evidence of the role of HPV in head and neck cancer. The prevalence of DNA from HPV was higher in oropharyngeal cancer, which is cancer of the upper part of the throat in the back of the mouth, than in oral or laryngeal cancer. Oral cancer occurs in the mouth, and laryngeal cancer occurs in the part of the throat with vocal cords that also aids in breathing, swallowing, and talking. HPV-16 accounted for 86.7 percent of oropharyngeal cancers with HPV DNA in them. Researchers found that HPV-18 was the next most frequent strain with the largest presence in oral, then laryngeal, and lastly oropharyngeal cancers.

The authors also discuss the effect of HPV on skin cancers in the fourth section. They focus on the way other conditions in the immune system impact HPV's progression to skin cancer. DNA from HPV is present in thirty to fifty percent of nonmelanoma skin cancers in people who have functioning immune systems and up to ninety percent in immunosuppressed people, or those who have a weakened immune system. The particular group of immunosuppressed people the authors discuss are recipients of organ transplants. The authors state that that HPV infections can combine with other factors, such as UV [radiation](#)^[13] or immunosuppression, to increase the risk of skin cancer developing.

The fifth section introduces the idea of cofactors, or contributory causes of a disease, that aid the progression from HPV infection to cervical cancer. The authors describe three categories of cofactors, which are environmental, viral, and host cofactors. Environmental cofactors include what the person is exposed to. Viral cofactors relate to specific viruses and viral infections, and host cofactors include individual predispositions such as their genetics. The authors found links between the presence of some of those cofactors with the onset of cervical cancer highlighting the need for early screening for cervical cancer if one is exposed to those cofactors. Despite outlining three categories of cofactors at the beginning of the fifth section, the authors primarily discuss environmental factors in the rest of the section.

The first two environmental factors the authors discuss are having given birth and smoking. Muñoz and colleagues reference a study published in 2006 by The International Collaboration of Epidemiological Studies of Cervical Cancer, or ICESCC. The ICESCC study revealed a higher chance of invasive cervical cancer with every full-term [pregnancy](#)^[7]. Such an increased possibility of cervical cancer can provide reason for women to be tested for cervical cancer after having one full-term [pregnancy](#)^[7]. Current smokers have a higher chance of cervical cancer in the [cervix](#)^[8] as compared to past smokers. The authors state that smokers may have a weaker immune system, and their body is prone to infection. An infection of a cancer-causing HPV strain can use that weakened immune system as an easier way to initiate cancer. Smoking can also cause genetic damage, which makes the body more vulnerable and prone to errors in the cell cycle, enabling uncontrolled cell growth. That means that [pregnancy](#)^[7] and smoking can increase the risk of cervical cancer in an individual upon HPV infection. Smoking can also affect metabolism of female [hormones](#)^[14] and cause damage to the mechanisms that balance those [hormones](#)^[14]. Those [hormones](#)^[14] can promote or suppress tumor development. If a specific [hormone](#)^[15] promotes tumor development, it becomes easier for cervical cancer to spread.

The next environmental factors the authors discuss are hormonal contraceptives and co-infection with other sexually transmitted infections. Hormonal contraceptives may enhance HPV gene expression in the cervix^[8]. The authors found that the risk of cervical cancer is higher with a longer period of using oral contraceptive. Using oral contraceptives for ten years doubles the risk of cervical cancer compared to someone who never took those contraceptives. For other sexually transmitted infections, the authors analyzed a study at the IARC. In that study, women who tested positive for herpes simplex virus 2, or HSV-2, had greater odds of having cervical cancer. That points to a potential correlation between HSV-2 and cervical cancer. The authors mention how those results could warrant the need for early screening for individuals who have had other sexually transmitted infections.

The last set of environmental cofactors Muñoz and colleagues touch on in the article "HPV and Etiology" were nutritional factors. None of those analyzed provided statistically convincing evidence for being correlated to cervical cancer. That means that the authors were not able to verify that the combination of nutrition and sexually transmitted infections such as HPV is linked to the onset of cervical cancer.

"HPV and Etiology" has been cited over a thousand times by many articles pertaining to the HPV vaccine, specific cancerous strains of HPV, and external factors being the trigger to the presentation of cervical or other human cancers. As of 2022, researchers are looking deeper into cofactors for future drug development and understanding of the triggers that HPV needs to initiate cancer. The lead researcher, Muñoz, won the Richard Doll Prize in Epidemiology in 2008 and subsequent awards for her research with the IARC. She also played a role in understanding the connections between hepatitis viruses and liver cancer. Research on HPV like that of Muñoz and colleagues contributed to the development of an HPV vaccine of Gardasil in 2006, which receives mention in the same volume of *Vaccine*, and of Cervarix, whose trials are mentioned in a later edition of the journal in 2009.

Building on work from zur Hausen and others in the preceding decades, Muñoz and colleagues provide a large-scale view of how HPV leads to cervical cancer in "HPV and Etiology." The authors provide strong statistical correlations and a variety of cofactors, reinforcing scientific knowledge of the risks and consequences of HPV while a vaccine for the virus was first receiving approval.

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Publisher

Arizona State University. School of Life Sciences. Center for Biology and Society. Embryo Project Encyclopedia.

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Last Modified

Tuesday, June 21, 2022 - 22:42

DC Date Accessioned

Tuesday, June 21, 2022 - 22:25

DC Date Available

Tuesday, June 21, 2022 - 22:25

DC Date Created

2022-06-21

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