# Understanding the proportion of cervical cancers attributable to HPV

*Most cervical cancers can be prevented with HPV vaccination and screening*

Since Walboomers and colleagues[1] published their findings in 1999, citing that 99.7% of cervical cancers are related to the human papillomavirus (HPV), this has become the standard understanding of the proportion of cervical cancers attributable to HPV.

Two decades later, and with both HPV vaccination and HPV-based screening programs in place to prevent cervical cancer in Australia, it is prudent to review the available evidence to understand the potential for cervical cancer prevention through HPV-based public health interventions.

## Proportion of HPV-positive cervical cancers in Australia

The rate of HPV positivity in any given set of cervical cancers is dependent on the sensitivity of the methods used to detect HPV, the proportion of different histological types of cervical cancer, the age of the women diagnosed with cancer, and the adequacy and quality of the specimens. A 2017 study reported findings specific to Australia suggesting that HPV could be detected in 92.9% of cervical cancers tested.[2]

Notably, the Australian figure is consistent with the initial findings in the group of specimens sampled in the 1999 study.[1] Walboomers and colleagues subsequently used additional study-specific methods in an attempt to detect HPV missed by standard assays to a very high degree of precision, above and beyond any usual laboratory methods, and then excluded any negative specimens in which there was any concern about specimen quality. The Australian study used methods that were more precise than routine HPV tests, but were less intensive than those used in the Walboomers' study.

Furthermore, the Australian study did not restrict cervical cancers to epithelial types (squamous, the most common type of cervical cancer,[3] and adenocarcinomas), but reflected the cross section of cancer types found in the population, including rarer non-epithelial types. In contrast, the Walboomers' study included predominantly squamous cancers, with a small number of adenocarcinomas and adenosquamous cancers.[1] The Australian figure of 92.9% reported in 2017[2] aligns with recent studies in other countries which cite figures for the percentage of cervical cancers testing positive for HPV of 92.3% (pooled data worldwide for 2006–2010),[4] 90.6% (United States),[5] and 86.2% (Sweden).[6]

## Reasons why some cervical cancers are HPV-negative

Proposed explanations for why some cervical cancer specimens are HPV-negative include misdiagnosed uterine or other cancer types, failure to detect integrated HPV DNA, failed detection due to assay or specimen issues, loss of HPV DNA over time, or HPV never being present.[7]

Cervical cancers for which HPV was never present include a subset of adenocarcinomas (called gastric type adenocarcinomas) that are known to develop without HPV, may be caused by p53 mutations, and may be associated with Peutz–Jeghers syndrome.[8,9] Other rare types of adenocarcinoma that may also fall into this category include clear cell and mesonephric carcinomas. In 2017, a new international pathogenetic classification for cervical adenocarcinomas was proposed, classifying adenocarcinomas into either HPV-associated adenocarcinoma or non-HPV-associated adenocarcinoma.[10] Other rarer cervical cancer types, such as neuroendocrine cancers, are predominantly HPV-positive. A recent meta-analysis identified that over 85% of neuroendocrine cervical cancers are HPV-positive.[11] It has been hypothesised from case reports that it may be possible to develop squamous cell carcinoma of the cervix without HPV, but this is extremely rare.[12]

Having a mature cervical screening program, as in Australia, affects the outcomes of studies assessing HPV detection in cervical cancers. This is because a cytology-based cervical screening program results in proportionately more adenocarcinomas due to the prevention of a large number of squamous cell carcinomas. In Australia, for example, current data indicate that 67% of cervical cancers are squamous cell carcinomas and 24% are adenocarcinomas, with adenosquamous carcinomas, other and unspecified carcinomas, and other and unspecified cervical cancers of non-epithelial origin making up the remainder.[3] In comparison, in 1982, adenocarcinomas made up just 11% of cervical cancers.[3]

Therefore, the proportion of cervical cancers testing positive for HPV will depend on the frequency of cervical cancer types not caused by HPV in that

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population, the sensitivity and aggressiveness with which laboratories attempt to detect HPV in the specimens, and possibly the number of more advanced cancers that present at older ages, when HPV is no longer easily detectable.

## Impact of age on HPV detection

Not finding HPV in a cervical cancer sample does not necessarily mean that the cervical cancer was not caused by HPV, which may have been detectable in the decades before the cancer developed. Data from the 2017 Australian study[2] indicated that HPV is detected in a greater proportion of cancers in younger women across every histological type; that is, the older the woman is at cancer diagnosis, the less likely the cancer is to be HPV-positive. This suggests that more advanced cancers, or those that have taken longer to develop, are cancers in which it is harder to detect HPV DNA. This finding may relate to the integration of HPV into the host DNA over time and to mutations in the HPV sequences. It may also relate to the presence of blood and necrosis in the tumour, which can interfere with HPV assays and can make diagnosis based on examination of cells (as in cytology or histology) problematic.

This correlation between age and the likelihood of detecting HPV in cervical cancer is consistent with other international studies.[5,13–15] In a 2018 analysis of 693 cervical cancers in the United States, HPV-negative cancers were more likely to be poorly differentiated and to be metastatic at presentation, and were associated with poorer survival.[15] Similarly, a nationwide population-based study in Sweden found poorer survival rates in HPV-negative cancers in 2845 cervical cancers diagnosed at older ages, of a later stage at diagnosis and associated with poorer educational status, and were less likely to be detected through cervical cytology screening.[14]

In practice, it is not possible to know the absolute percentage of cervical cancers in a population attributable to HPV, which would be influenced both by cervical screening and the underlying frequency of HPV-negative cervical cancers in that population. Overall, the biological and epidemiological evidence supports that is likely that close to 100% of squamous cervical cancers and up to 90% of adenocarcinomas have oncogenic HPV infection as an underlying cause.

It is paradoxical that, as our current vaccination and screening programs work together to continue to drive substantial, overall reductions in cervical cancer incidence and mortality, preventing cancers caused by HPV, we can expect the relative proportion of HPV-negative cancers to increase. However, in absolute terms, the incidence and mortality due to HPV-negative cervical cancer are not expected to change, which is one of the reasons why the World Health Organization has called for the global elimination of cervical cancer "as a public health problem", with an expected target of four per 100 000 women per year.[16]

## Conclusion

Most cervical cancers are attributable to infection with HPV.

Australian data have shown that HPV can be detected in 92.9% of cervical cancers tested for HPV. However, some cancers in which HPV could not be found at diagnosis may have been HPV-positive in the preceding years and may be HPV-negative now due to the cancer progression, degeneration of the tissue sample, the screening threshold sensitivity (ie, high viral load is required), and the size and genome target of routinely available HPV tests.

The underlying rate of cancers that are truly HPV-negative, and in which HPV was not involved in the cancer development, is very small.

HPV vaccination and HPV-based screening offer effective methods of preventing most cervical cancers. In contrast, any woman who is symptomatic should have cotesting (both cytology and HPV testing) and further investigation as clinically indicated.

Ongoing monitoring of the proportion of cervical cancers associated with HPV should continue, with the expectation that the absolute rate of HPV-associated cancer will fall over time and the absolute rate of HPV-negative cancers will remain stable, resulting in an increase in the relative proportion of HPV-negative cancers. This will be an indicator of the success of our cervical cancer prevention programs.

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