

Cervical cancer

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P J van Diest, H Holzel

A sexually transmitted disease?

Cervical cancer continues to be a major health care problem worldwide. Over the past few decades, it has become more and more apparent that the human papillomavirus (HPV) is strongly associated with cervical cancer. Several other associations between infections with microorganisms and cancer have been described, such as Epstein-Barr virus (EBV) and gastric cancer,¹ lymphoepithelioma-like cancer,² and lymphomas³⁻¹⁰; *Helicobacter pylori* and gastric cancer¹¹⁻¹⁸ and mucosa associated lymphoid tissue lymphoma^{19,20}; and human herpesvirus 8 and Kaposi sarcoma.²¹⁻²³ However, these associations are of a different strength. For example, *H pylori* is probably indirectly related to gastric cancer—it causes a chronic infection that may eventually lead to atrophy, intestinal metaplasia, dysplasia, and cancer. The relation between EBV and lymphoma is biologically stronger because EBV produces proteins with oncogenic properties. Real causal relations between microorganisms and cancer are difficult to prove. This requires many well designed studies providing evidence on this relation regarding: (1) strength, (2) consistency, (3) specificity, (4) temporality, (5) biological gradient, (6) plausibility, (7) coherence, (8) experimental evidence, and (9) analogy, as proposed by Hill.²⁴

In their review paper in this issue of *JCP*, Bosch *et al* provide a very good case for the causal relation between HPV and cervical cancer.²⁵ Of course, the idea of a causal relation between HPV infection and cervical cancer is in itself not new, and many of us have believed in such a causal relation for some time. However, in their very careful review of the epidemiological and molecular data in the literature, Bosch *et al* are able to conclude the following: (1) there is a very strong relation between the presence of HPV DNA and the subsequent development of cervical cancer; (2) this relation is consistent in a large number of studies in different countries and populations; (3) the association between HPV DNA and cervical cancer is fairly specific; (4) HPV infections precede cervical precancerous lesions by a substantial number of years; (5) the risk of cervical cancer seems to be related to viral load; (6) in vitro experiments, animal experiments, and observations in humans make the association

between HPV and cervical cancer plausible; (7) the association is coherent with previous knowledge; (8) there is increasing molecular evidence for the direct interaction between HPV and essential regulatory mechanisms of cellular growth; and (9) the HPV and cervical cancer model is analogous to many other examples of papilloma virus induced papillomas and carcinomas, and cancers caused by other viruses.

“Real causal relations between microorganisms and cancer are difficult to prove”

The conclusion drawn that HPV is a necessary cause of cervical cancer thereby fulfills all the criteria of Hill²⁴ and makes the conclusion evidence based. This means that one will not get cervical cancer without an HPV infection, but on the other hand it does not mean that all HPV infections will lead to cancer. First of all, probably only infections with the oncogenic HPV types will cause cancer, and second, many HPV infections are cleared, and only lasting infections seem to lead to cancer.

JCP is very happy to host this ground breaking paper. It fits well within the cross specialty scope of the journal,²⁶⁻²⁸ and over the years many papers published in *JCP* have contributed to the mounting evidence for the hypothesis provided.²⁹⁻³⁶ The review by Bosch *et al* provides for the first time the case for a causal relation between infection with a microorganism and cancer, and sets the stage for the implementation of HPV testing in screening programmes. This may range from adding HPV detection to Pap smear based screening programmes that are up and running in some countries, to primary screening with HPV testing in those countries that do not have such schemes. Implementation of self lavage to obtain cervical samples may lower the psychological threshold to undergo HPV testing.³⁷ Furthermore, it justifies developing vaccination programmes to prevent HPV infections and thereby cervical cancer.

Now, does all this mean that cervical cancer is a sexually transmitted disease? No, not really, because it is not the cancer

that is sexually transmitted, but only the virus causing the cancer. Thereby, the predisposition is transmitted with the virus. Bosch *et al* clearly point to sexual factors in the transmission of the virus and the risk of developing cancer. The number of sexual partners and the age at which sexual intercourse is initiated are established risk factors for HPV infection. Furthermore, it is clearly stated that the risk of cervical cancer for a given woman is predictable by the sexual behaviour of her husband as much as for her own sexual behaviour, and it has been confirmed that male circumcision protects the wives of husbands who have been circumcised from cervical cancer.^{25,38} This clearly shows that male sexual behaviour is a central determinant of the incidence of cervical cancer.^{39,40}

The future may establish similar causal relations between HPV and other types of cancer such as skin cancer,^{41,42} tonsillar cancer,⁴³ oesophageal cancer, and lung cancer.⁴⁴

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Authors' affiliations

P J van Diest, Department of Pathology, VU University Medical Centre, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands
H Holzel, Formerly at Great Ormond Street Hospital for Children NHS Trust, London WC1N 3 JH, UK.

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Abbreviations: EBV, Epstein-Barr virus; HPV, human papillomavirus

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