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 lymphoma¹⁹⁻²⁰; 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 women 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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REFERENCES

- zur Hausen A, van Grieken NC, Meijer GA, *et al*. Distinct chromosomal aberrations in Epstein-Barr virus-carrying gastric carcinomas tested by comparative genomic hybridization. *Gastroenterology* 2001;**121**:612-18.
- Leung SY, Yuen ST, Ho CM, *et al*. Presence of Epstein-Barr virus in lymphoepithelioma-like carcinoma of the middle ear. *J Clin Pathol* 1998;**51**:602-5.
- Sadahira Y, Kumori K, Mikami Y, *et al*. Post-transplant malignant lymphoma with monoclonal immunoglobulin gene rearrangement and polyclonal Epstein-Barr virus episomes. *J Clin Pathol* 2001;**54**:887-9.
- Caussinus E, Meggetto F, Delsol G, *et al*. Simultaneous occurrence of Epstein-Barr virus associated Hodgkin's disease and HHV-8 related multicentric Castleman's disease: a fortuitous event? *J Clin Pathol* 2001;**54**:790-1.
- Gomez-Bouchet A, Delisle MB, Vital A, *et al*. Immunohistochemical assessment of human herpesvirus 8 infection in primary central nervous system large B cell lymphomas. *J Clin Pathol* 2001;**54**:617-18.
- Bethune CA, Gompels MM, Taylor C, *et al*. Treatment of EBV driven lymphoproliferation with erythrophagocytosis: 12 year follow up. *J Clin Pathol* 2001;**54**:328-31.
- Engel M, Essop MF, Close P, *et al*. Improved prognosis of Epstein-Barr virus associated childhood Hodgkin's lymphoma: study of 47 South African cases. *J Clin Pathol* 2000;**53**:182-6.
- Hopwood P, Crawford DH. The role of EBV in post-transplant malignancies: a review. *J Clin Pathol* 2000;**53**:248-54.

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

- 9 **Brink AA**, Dukers DF, van den Brule AJ, *et al.* Presence of Epstein-Barr virus latency type III at the single cell level in post-transplantation lymphoproliferative disorders and AIDS related lymphomas. *J Clin Pathol* 1997;**50**:911–18.
- 10 **Oudejans JJ**, Dukers DF, Jiwa NM, *et al.* Expression of Epstein-Barr virus encoded nuclear antigen 1 in benign and malignant tissues harbouring EBV. *J Clin Pathol* 1996;**49**:897–902.
- 11 **Twisk M**, Kusters JG, Balk AG, *et al.* Colonisation density and topographic localisation of *Helicobacter pylori* do not depend on the *cagA* status. *J Clin Pathol* 2001;**54**:771–3.
- 12 **Yea SS**, Yang YI, Jang WH, *et al.* Association between TNF- α promoter polymorphism and *Helicobacter pylori* *cagA* subtype infection. *J Clin Pathol* 2001;**54**:703–6.
- 13 **El-Zimaity HM**, Ramchatesingh J, Saeed MA, *et al.* Gastric intestinal metaplasia: subtypes and natural history. *J Clin Pathol* 2001;**54**:679–83.
- 14 **Chen XY**, van Der Hulst RW, Shi Y, *et al.* Comparison of precancerous conditions: atrophy and intestinal metaplasia in *Helicobacter pylori* gastritis among Chinese and Dutch patients. *J Clin Pathol* 2001;**54**:367–70.
- 15 **Shimoyama T**, Everett SM, Fukuda S, *et al.* Influence of smoking and alcohol on gastric chemokine mRNA expression in patients with *Helicobacter pylori* infection. *J Clin Pathol* 2001;**54**:332–4.
- 16 **Peters TM**, Owen RJ, Slater E, *et al.* Genetic diversity in the *Helicobacter pylori* *cag* pathogenicity island and effect on expression of anti-CagA serum antibody in UK patients with dyspepsia. *J Clin Pathol* 2001;**54**:219–23.
- 17 **Yoshimura T**, Shimoyama T, Tanaka M, *et al.* Gastric mucosal inflammation and epithelial cell turnover are associated with gastric cancer in patients with *Helicobacter pylori* infection. *J Clin Pathol* 2000;**53**:532–6.
- 18 **Danielsson D**, Farmery SM, Blomberg B, *et al.* Co-expression in *Helicobacter pylori* of *cagA* and non-opsonic neutrophil activation enhances the association with peptic ulcer disease. *J Clin Pathol* 2000;**53**:318–21.
- 19 **Yoshino T**, Omonishi K, Kobayashi K, *et al.* Clinicopathological features of gastric mucosa associated lymphoid tissue (MALT) lymphomas: high grade transformation and comparison with diffuse large B cell lymphomas without MALT lymphoma features. *J Clin Pathol* 2000;**53**:187–90.
- 20 **Kobayashi K**, Yokota K, Yoshino T, *et al.* Detection of *Helicobacter pylori* associated antigen and heat shock protein 60 on follicular dendritic cells in the germinal centres of low grade B cell lymphoma of gastric mucosa associated lymphoid tissue (MALT). *J Clin Pathol* 1998;**51**:396–8.
- 21 **Kennedy MM**, Biddolph S, Lucas SB, *et al.* Cyclin D1 expression and HHV8 in Kaposi sarcoma. *J Clin Pathol* 1999;**52**:569–73.
- 22 **Delabesse E**, Oksenhendler E, Lebbe C, *et al.* Molecular analysis of clonality in Kaposi's sarcoma. *J Clin Pathol* 1997;**50**:664–8.
- 23 **Cathomas G**, McGandy CE, Terracciano LM, *et al.* Detection of herpesvirus-like DNA by nested PCR on archival skin biopsy specimens of various forms of Kaposi sarcoma. *J Clin Pathol* 1996;**49**:631–3.
- 24 **Hill AB**. The environment and disease: association or causation? *Proc R Soc Med* 1965;**58**:295–300.
- 25 **Bosch FX**, Lorincz A, Muñoz N, *et al.* The causal relation between human papilloma virus and cervical cancer. *J Clin Pathol* 2002;**55**:244–65.
- 26 **Holzel H**, Van Diest PJ. The new millennium: time for a change! *J Clin Pathol* 2000;**53**:1–2.
- 27 **Van Diest PJ**, Holzel H. The Journal of Clinical Pathology goes online (<http://www.jclinpath.com>)! *J Clin Pathol* 2000;**53**:887–88.
- 28 **Van Diest PJ**, Holzel H, Burnett D, *et al.* Impactitis: new cures for an old disease. *J Clin Pathol* 2001;**54**:817–19.
- 29 **Zerbini M**, Venturoli S, Cricca M, *et al.* Distribution and viral load of type specific HPVs in different cervical lesions as detected by PCR-ELISA. *J Clin Pathol* 2001;**54**:377–80.
- 30 **Lanham S**, Herbert A, Watt P. HPV detection and measurement of HPV-16, telomerase, and survivin transcripts in colposcopy clinic patients. *J Clin Pathol* 2001;**54**:304–8.
- 31 **Bosch FX**, Rohan T, Schneider A, *et al.* Papillomavirus research update: highlights of the Barcelona HPV 2000 international papillomavirus conference. *J Clin Pathol* 2001;**54**:163–75.
- 32 **Rozendaal L**, Westerga J, van der Linden JC, *et al.* PCR based high risk HPV testing is superior to neural network based screening for predicting incident CIN III in women with normal cytology and borderline changes. *J Clin Pathol* 2000;**53**:606–11.
- 33 **Meijer CJ**, Walboomers JM. Cervical cytology after 2000: where to go? *J Clin Pathol* 2000;**53**:41–3.
- 34 **Jacobs MV**, Snijders PJ, Voorhorst FJ, *et al.* Reliable high risk HPV DNA testing by polymerase chain reaction: an intermethod and intramethod comparison. *J Clin Pathol* 1999;**52**:498–503.
- 35 **Nindl I**, Lotz B, Kuhne-Heid R, *et al.* Distribution of 14 high risk HPV types in cervical intraepithelial neoplasia detected by a non-radioactive general primer PCR mediated enzyme immunoassay. *J Clin Pathol* 1999;**52**:17–22.
- 36 **Clavel C**, Masure M, Putaud I, *et al.* Hybrid capture II, a new sensitive test for human papillomavirus detection. Comparison with hybrid capture I and PCR results in cervical lesions. *J Clin Pathol* 1998;**51**:737–40.
- 37 **Nobbenhuis MAE**, Helmerhorst TJM, van den Brule AJC, *et al.* Primary screening for high-risk HPV by home-obtained cervicovaginal lavage is an alternative screening tool for unscreened women. *J Clin Pathol* [In press.]
- 38 **Castellsague X**, Bosch FX, Muñoz N, *et al.* Male circumcision, penile human papillomavirus (HPV) infection and cervical cancer. *N Engl J Med* [In press.]
- 39 **Beral V**. Cancer of the cervix: a sexually transmitted infection? *Lancet* 1974;*i*:1037–40.
- 40 **Skegg DC**, Corwin PA, Paul C, *et al.* Importance of the male factor in cancer of the cervix. *Lancet* 1982;**2**:581–3.
- 41 **O'Connor DP**, Kay EW, Leader M, *et al.* p53 codon 72 polymorphism and human papillomavirus associated skin cancer. *J Clin Pathol* 2001;**54**:539–42.
- 42 **Harwood CA**, McGregor JM, Proby CM, *et al.* Human papillomavirus and the development of non-melanoma skin cancer. *J Clin Pathol* 1999;**52**:249–53.
- 43 **Niedobitek G**, Pitteroff S, Herbst H, *et al.* Detection of human papillomavirus type 16 DNA in carcinomas of the palatine tonsil. *J Clin Pathol* 1990;**43**:918–21.
- 44 **Miyagi J**, Tsuchiko K, Kinjo T, *et al.* Recent striking changes in histological differentiation and rate of human papillomavirus infection in squamous cell carcinoma of the lung in Okinawa, a subtropical island in southern Japan. *J Clin Pathol* 2000;**53**:676–84.