Review Article
Infection and Cervical Neoplasia: Facts and Fiction

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Abstract: Whilst there is strong evidence that human papillomavirus (HPV) is the principal aetiological agent in cervical neoplasia, some other sexually transmitted agents may either contribute or protect against cervical carcinogenesis, such as the herpes virus family (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV) or Chlamydia trachomatis (CT). Epidemiological studies suggest that HSV may have a role in cervical neoplasia, but there is no clear supportive experimental evidence. Serological studies have also failed to reveal a difference in the prevalence of antibodies to CMV and EBV between patients with cervical cancer and controls. However, longitudinal seroepidemiological studies have provided evidence that CT is an independent risk factor for the development of cervical squamous carcinoma and this association is serotype specific. The increased risk of cervical neoplasia in patients infected with HIV has been recognised for over a decade and HIV may interact with HPV either by alternating HPV gene transcription or by immunosuppression. Finally extensive experimental and limited epidemiological evidence suggests that adeno-associated viruses (AAV) may have antioncogenic activity in man and may protect against the development of cervical cancer. At present the mechanism of this action is unclear but may relate to AAV-induced regulation of HPV gene expression and the HPV life cycle. In this review we summarize the current literature relating to the associations and mechanisms of cervical carcinogenesis by each of these infectious microorganisms.

Key Words: Human papillomavirus (HPV), cervical neoplasia, sexually transmitted infections (STI), microbiology

Introduction

Sexual activity has both life-giving and life-endangering effects. The association of cervical carcinoma and sexual activity has been known over 150 years. As any sexually transmitted infection, cervical carcinoma is more common in woman who have had multiple sexual partners or whose partner is promiscuous, and is absent in virgins. Rigoni-Stern in 1842 noticed that cervical carcinoma occurred only in married woman [1].

In the UK, about 2300 woman per year are diagnosed as having cervical cancer, 95% of cases occurring in woman over the age of 35 years [2]. However, the number of deaths from cervical cancer has decreased by more than 40% during the last 20 years, and the incidence of cervical cancer is now more than that, for example, breast cancer (41,000 new cases per year) [3-6]. This decrease is directly related to implementation of cervical screening programs. It is estimated that 471,000 new cases of cervical cancer are diagnosed every year worldwide, 80% of which occur in less developed countries [2-4, 6-12].

About 15% of human cancer can be attributed to virus infection, and viruses are second only to tobacco as a risk factor for cancer. In the future, a major proportion of these infections may be preventable by immunization, significantly reducing the worldwide cancer burden. The importance of the experimental study of tumour viruses in animals and human illustrated by the fact that oncogenes and tumour suppressor genes were first identified through their interaction with tumour virus proteins [13-26]. There are two major mechanisms by which oncogenic viruses induce tumours [16, 27-30]. In direct oncogenesis, the virus infects a progenitor of the clonal tumour cell population, and usually persists in the tumour cells. Indirect oncogenesis occurs when the virus does not necessarily infect the tumour progenitor cell, but exerts an indirect effect on cell and tissue turnover or in the immune system, predisposing to tumour development.
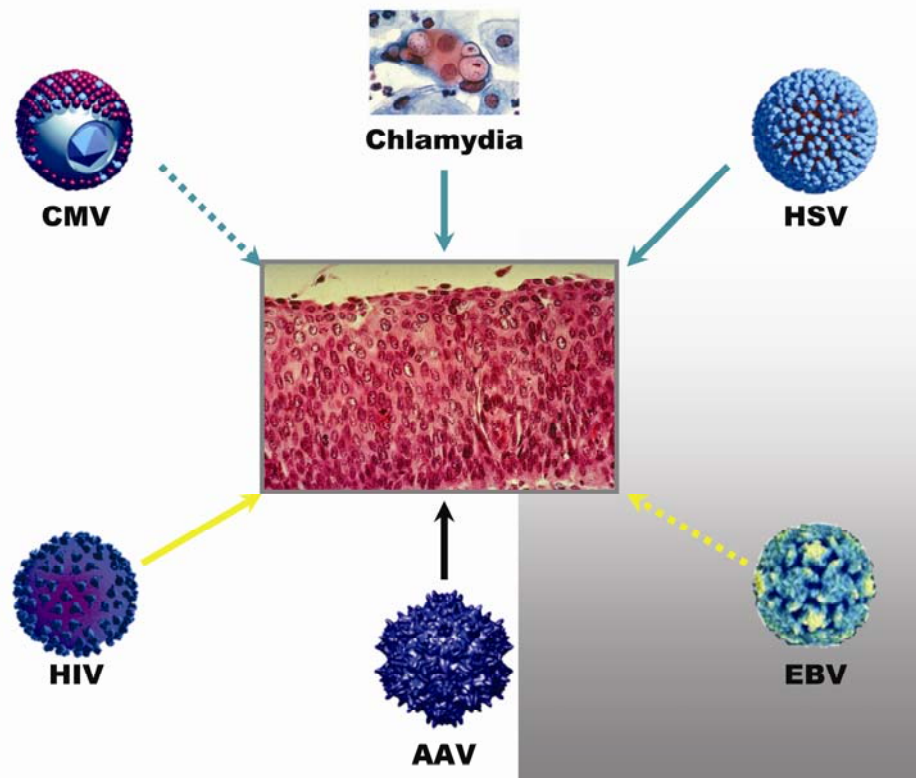
Figure 1 An illustration of the relationship between cervical neoplasia and infectious micro-organisms.

However, assessing an infectious aetiology can be difficult [16]. Firstly, subclinical infections are common and this may lead to misclassification bias. Secondly, complex interactions can result because many sexually transmitted infections do occur simultaneously. Thirdly, the presence of a latency period between exposure and outcome, which vary considerably, is another problem. Finally, clinical follow-up studies always remain inconclusive [16, 27, 28, 30-41].

Whilst there is strong evidence that human papillomavirus (HPV) is the principle aetiological agent in cervical neoplasia [13, 27, 42-64], some other sexually transmitted organisms may either contribute to or protect against cervical carcinogenesis [65-82] (**Figure 1**).

Papillomaviruses

HPV group currently comprises more than 130 distinct types [83, 84], causing lesions of the genital, upper respiratory and digestive tracts, and cutaneous lesions at various sites [85,

86]. For each virus type, the site of infection is very restricted. The lesions caused are usually benign [86-102].

Cervical neoplasia is known to be induced in different ways, such as via multiple pregnancies [103-106], radiation [107-112], smoking [113-119] and viral infection. HPV is regarded as the most significant risk factor for cervical carcinoma. Cancer of the cervix was identified as a sexually transmitted disease in 1834, and the hypothesis that HPV is involved was suggested in the mid-1970's [50, 105, 120-130]. The risk varies according to the infecting HPV subtype, for example, high risk (types 16 and 18), moderate risk (types 33 and 35) and low risk (types 6 and 11). Subsequent studies have shown that almost all cervical cancers are HPV-positive and that only certain HPV types are associated with invasive carcinoma (most commonly HPV-16, HPV-18, HPV-31, and HPV-45) [131-138]. These and other HPVs are also found in other anogenital cancers [139-142] and may cause cancers at other sites such as the head and neck [142-152], oesophagus [102, 149, 151,

153-156] and skin [87, 88, 157-166].

α-Herpesviruses

HSV-2 is the main cause of primary and genital herpes. Because of changing sexual practices, many causes of primary genital herpes are caused by HSV-1, though this virus is less likely to reactivate from the sacral ganglia than is HSV-2. Current research on genital herpes focuses on asymptomatic patients as a common course of infection.

The role of HSV in the development of cervical neoplasia has been a subject of extensive research. Patients with cervical carcinoma have consistently been shown to demonstrate the presence of higher levels of HSV-2 antibody than controls. An interaction between HSV and HPV-16/18 in the causation of cervical carcinogenesis has been suggested by several groups [167-170]. Two hypotheses have been devised to explain this: the 'hit and run' hypothesis and synergism between HSV and HPV [171]. Of these there is more epidemiological and experimental support of the latter. HSV is known to contain regions on its genome capable of transforming cells *in vitro* which could make it a candidate for oncogenic transformation *in vivo*. On the other hand, in a study by Vecchione *et al* (1994) investigating the interaction between HPV types 16 and 18, HSV-2 and p53 inactivation, none of the 41 cervical biopsies (ranging from low to high grade cervical intraepithelial neoplasm) tested positive for HSV-2. In addition, this study showed that the infection with HPV-16 and the alteration of p53 expression were the most important associations [172].

However, the potential interaction between HPV and HSV is supported with several lines of evidence [167-170, 173, 174]. First, ulcerative herpetic lesions facilitate HPV access to the basal layer. Second, the inflammatory response induced by herpes may suppress the T helper cell mediated immune response. Third, herpes infection does induce the production of nitric oxide resulting in cellular DNA damage together with direct actions by herpes viruses on host cellular DNA. Fourth, Herpes virus infection accelerates replication of HPV and increases the integration of HPV DNA sequences.

In a pooled analysis of 7 case-control studies to examine the effects of HSV-2 as an HPV cofactor, blood and exfoliated cervical cells obtained from 1263 cases of cervical cancer and 1117 age-matched controls were investigated using Western blot analysis, PCR and ELISA [170]. The odds ratio (ORs) and confidence intervals (CIs) computed from unconditional logistic regression models are summarised in **Tables 1-3**. ORs and CI of HSV seropositivity and cervical cancer from previous case-control studies are summarised in **Table 4** [175-179].

Lehtinen *et al* in a longitudinal nested case control study in Nordic countries using 1974-1993 data showed that smoking- and HPV positive-adjusted relative risks for HSV-2 were 1.0 (95% CI 0.6) and 0.7 (95% CI o.3, 1.6) respectively for HPV seropositives. Comparing results with those of meta-analysis revealed that the relative risk for HSV-2 was 0.9 (95% CI 0.6, 1.3). In addition, HSV was shown not to play a role in cervical carcinogenesis [180]. It is important to note that conflicting seroepidemiological evidence of an interaction between HSV and HPV in cervical carcinogenesis has been shown by different authors. In addition, *in vitro* observations are not yet confirmed *in vivo*.

β-Herpesviruses

Cytomegalovirus (CMV), human herpes virus-6 and -7 (HHV-6 and HHV-7) are members of the β-herpesvirus group and are found universally throughout all geographic locations and socioeconomic groups. HHV-6 was identified in 1986 and causes roseola infantum (exanthema sabitum) in infants. HHV-6 is clearly neurotropic and has recently been suggested, but not confirmed, as an aetiological factor in multiple sclerosis [181-184]. HHV-7 was first described in 1991 and causes roseola infantum in a few patients, but seems to be less pathogenic than HHV-6.

CMV, HHV-6 and HHV-7 have all been detected in the cervix [185]. CMV spreads mainly by sexual and transfusion routes. Infection of the genital tract with CMV evidenced by inclusion bodies on the cervical smear is uncommon. CMV infection of the genital tract in immunocompetent females is generally regarded as incidental and self-limiting. In immunocompromised patients, CMV is an opportunistic infection that has been reported in the genital tract. This was reported in two

Table 1 Seroprevalence of HSV antibodies and HPV DNA in invasive cervical cancers and controls

	N	% HSV-2 seropositive (95% CI)	% HSV-1 seropositive (95% CI)	% HPV DNA positive (95% CI)	Median age, years (range)
Squamous Cell Carcinoma	1158	44.4 (41.5-47.3)	80.3 (77.9-88.3)	94.8 (93.5-96.1)	49 (18-84)
Adeno- or adenosquamous carcinoma	105	43.8 (34.2-53.5)	85.7 (76.3-95.2)	90.5 (84.4-96.2)	48 (28-69)
Controls	1117	25.6 (23.0-28.2)	89.6 (87.0-92.1)	14.7 (12.6-16.8)	47 (21-77)

Table 2 Odds ratios of invasive cervical cancers and 95% confidence intervals among HPV positive women according to HSV-2 seropositivity

	Case patients HSV2$^+$/HSV2$^-$	Control subjects HSV2$^+$/HSV2$^-$	OR	95% CI
Squamous cell carcinoma	497/601	49/115	2.19	1.41-3.40
Adeno- or adenosquamous carcinoma	43/52	39/100	3.37	1.47-7.74

Table 3 Odds ratios of invasive cervical cancers and 95% confidence intervals among all cases and controls according to HSV-2 seropositivity

	Case patients HSV2$^+$/HSV2$^-$	Control subjects HSV2$^+$/HSV2$^-$	OR	95% CI
Squamous cell carcinoma	514/644	286/831	1.72	1.21-2.44
Adeno- or adenosquamous carcinoma	46/59	241/726	2.43	1.22-4.81

Table 4 HSV seropositivity and cervical cancer from previous case-control studies

Study (Year)	OR	95% CI
Jha *et al* (1993) [175]	2.2	1.1-4.5
Dillner *et al* (1994) [176]	1.4	0.81-1.8
Daling *et al* (1996) [177]	1.2	0.8-1.8
Hildesheim *et al* (1991) [178]	1.5	1.2-1.9
Lehtinen *et al* (1996) [179]	0.6	0.2-1.4

patients with HIV undergoing colposcopy, in which one patient developed asymptomatic pelvic inflammatory disease and disseminated infection in the other. In paraffin embedded sections from 34 Ugandans patients with cervical carcinoma, CMV was detected in five of the 34 cases using immunohistochemistry. In all cases CMV antibody reactivity was confined to the cervical epithelial tissue. These results were interpreted as evidence for association between CMV and cervical carcinoma. However, the immune status of these patients and their HPV status were not correlated to the immunostaining findings [186]. Several studies using PCR analyses have also revealed CMV in women with

cervical cancer. For example CMV was found in 67% of Taiwanese woman with cervical cancer [187], but only 4% in Australian woman.

In a PCR-based study involving 388 women attending colposcopy clinics by Chan *et al* [188], the association between these viruses and cervical neoplasia was analysed with respect to the HPV status. Positive rates for CMV, HHV-6 and HHV-7 were 9.5%, 3.6% and 3.4%, respectively. HPV positive patients carried a high risk of high grade cervical lesions, whereas those positive for CMV, HHV-6 and HHV-7 did not. Chan *et al* concluded that these viruses are bystanders rather than cofactors in oncogenesis of cervical cancer. More recently, Yang *et al* studied the correlation of viral factors (including CMV) with cervical cancer and concluded that CMV might not be involved in the oncogenic processes directly but might enhance the possibility of oncogenesis or infect cancer tissues opportunistically [189].

HHV-6 was found in 38% and 20% of women with cervical carcinoma using in situ hybridisation [190] and PCR [191, 192], respectively. Two groups have studied the prevalence of HHV-6 and HHV-7 in the female genital tract [185, 193-195]. Leach *et al* found HHV-6 in 10% of vaginal swabs of women attending Genito-Urinary Medicine (GUM) clinics [193-195], whereas Okuno *et al* found HHV-6 (the B variant only) in 19.4% of cervical swabs from 72 pregnant women compared to 34 non-pregnant controls, and HHV-7 in 2.7% of pregnant women and none in the non-pregnant controls. In addition, 1% of woman with abnormal smears were positive for HHV-6 [196-200]. In another study performed in Wessex, UK, HHV-6 was detected in 18% of samples examined [201]. Overall, the high incidence of HHV-6 and HHV-7 in cervical smears may indicate that these viruses are sexually transmitted. Alternatively, the presence of HHV-6 and HHV-7 in cervical samples could be due to macrophages or lymphocytes from the tissue or blood that are simultaneously collected with cervical cells or latently infected epithelial cells. In this case, detection of these viruses in the cervix may therefore represent dissemination of a systemic infection rather than sexually acquired infection. Therefore, it appears that HHV-6, HHV-7 and CMV are unlikely to have a direct role in the carcinogenesis of cervical neoplasia.

γ-Herpesviruses

Kaposi's sarcoma-associated herpesvirus (KSHV) or human herpes virus-8 (HHV-8) was first described in 1994 and has been linked to several malignancies in the human population such as Kaposi's sarcoma (KS), primary effusions lymphomas (PEL) and multicenteric Castleman's disease (MCD). It is believed that HHV-8 transforms cells through a paracrine mechanism since there is a plethora of evidence of high levels of cytokines and growth factors in lesions of KS and MCD. HHV-8 has been shown to infect but not immortalise CD19-positive B cells *in vitro*, perhaps due to technical difficulties in culture system. In contrast, HHV-8 can immortalise primary bone marrow derived endothelial cell; the virus induces cell proliferation, anchorage independence and survival of these cells. Interestingly, only a subset of the transformed endothelial cells contained viral DNA, suggesting that uninfected cells survived through a mechanism involving cytokines secreted by the infected cells. These observations suggest that HHV-8 transformation is highly dependent on paracrine factors as well as the cellular microenvironment, a concept gaining favour in other tumour models as well.

The relation between HHV8 and cervical carcinoma has also been investigated [188, 202-210]. Recently, Taylor *et al* found that the prevalence of HHV-8 DNA was 32% in saliva samples, 28% mouth swabs, 4% in cervical swabs, 2.3% in vaginal swabs, 9% in plasma samples and 18% in peripheral-blood mononuclear cell sample from HIV seropositive and seronegative Kenyan women [211]. Similar results were found in oral and genital secretions of Zimbabwean women. On the other hand, a real-time PCR study showed that no cervical secretion or leukocyte samples contained detectable HHV-8 DNA. However, the latter study detected antibodies to HHV-8 of serum samples. Lanham *et al* showed that there was no link with cervical intraepithelial neoplasia status and the detection of HHV-8 [212].

Epstein-Barr Virus (EBV)

EBV was the first human tumour virus discovered from biopsy tissue samples of the childhood malignancy African Burkitt lymphoma. It is one of the most efficient

cellular growth-transforming viruses known, but in most infected individuals (more than 90% of the world population) it coexists with the host asymptomatically. Infected individuals become lifelong carriers. Under certain conditions, however, its potential as a tumour-causing agent is realised, and EBV is associated with a wide spectrum of clinical conditions, many of which are malignant. Three lymphoproliferative disorders have known associations with EBV: Hodgkin lymphoma, Burkitt lymphoma and lymphoma in immunocompromised individuals. Although the lymphotropism of EBV is well recognised, it is becoming increasingly clear that EBV may have epitheliotropic qualities. For example, an association with EBV was established with nasopharyngeal and gastric carcinoma. In addition, several studies suggested a possible connection between EBV and cervical neoplasia although no serological evidence of such an association has been reported.

Landers *et al* randomly studied selected cases of invasive cervical carcinoma as well as cases with varying degrees of cervical intraepithelial neoplasm (CIN) and normal cervices. Their results showed that neither normal cervices nor CIN 1 specimens contained EBV, but that 8% of cases of both CIN 2 and CIN 3 and 43% cases of cervical carcinoma contained EBV detected by PCR and/or in situ hybridisation [213]. However, Hilton *et al* tested the presence of EBV in epithelial cells and showed, using in situ hybridization, that none of 10 CIN cases or 24 cervical carcinoma cases were EBV positive [214]. Thus, the positive results of the Landers study may simply reflect EBV in stromal cervical lymphocytes. To clarify the relationship between EBV and CIN, given the conflicting results of Hilton *et al* and Landers *et al*, 30 CIN cases were evaluated of which 20 were EBV positive using PCR. The authors stated that PCR results should always be confirmed by a morphological technique [213, 215, 216]. PCR and in-situ hybridisation have also shown that the expression rates of genes such as EBNA-2, LMP-1 and EBER-1 were also significantly higher in cervical carcinoma and CIN than in the normal cervix [217-219].

Overall, these studies support a possible sexual route of transmission for EBV. However, there is no convincing evidence that EBV infection has a direct role in the pathogenesis of cervical neoplasia or even HPV-mediated carcinogenesis. However, EBV-infected tumour infiltrating lymphocytes might contribute indirectly to cervical carcinogenesis via producing viral IL-10 expressed from BCRF-1 gene, which causes a reduction in local immunity leading to suppression of the response to HPV-transformed cells.

Human Immunodeficiency Virus (HIV)

It remains debatable whether HIV infection itself increases the incidence of invasive cervical carcinoma. Cervical cancer was added to the Centre for Disease Control (CDC) classification for AIDS defining illness in 1993 despite sparse evidence for a causal relationship. Smith *et al* found no association between the detection of HPV and immunosuppression or CIN, but rather immunosuppressed HIV-positive females had a higher incidence regardless of the presence or absence of HPV, EBV or HSV for which subjects were tested. An odds ratio of 4.9 for an association between HIV and cervical dysplasia was found in a meta-analysis of five studies [220, 221].

The interaction between HPV and HIV in the affected cervical tissue leads to the persistence of HPV infection and cervical neoplasia by depleting Langerhans cells or their MHC class presenting ability of the host immune response. An alternative explanation is at the cellular level; HIV specific Tat protein upregulates expression of HPV E6 and E7 oncogenes and enhances their oncogenetic transformation efficacy. These two mechanisms are, however, not exclusive and a joint effect(s) most likely takes place at early stages of CIN [222-231].

Both HPV infection and CIN are common in woman with HIV infection. HIV disease may be asymptomatic, however, and therefore woman with rapidly progressive CIN should be tested for HIV. Recurrence rates are disappointingly high with standard local ablative therapy for CIN. Frequent and regular cervical smears are recommended. Woman with any degree of abnormal cytology must be referred for colposcopy. Invasive cervical carcinoma in HIV-positive woman is usually advanced, and more likely to relapse following treatment. The incidence is unchanged with highly active anti-retroviral therapy (HAART). Management is as in seronegative woman and involves chemoradiotherapy, but the prognosis is worse [222-231].

Adeno-Associated Viruses (AAV)

AAV is a ubiquitous human helper-dependent common genital parvovirus that may protect, at least, in part against HPV-associated cervical cancer. AAV may also be sexually acquired. This virus has many features of parvovirus but relies on co-infection with other viruses to replicate. AAV has not been associated with any disease in humans despite its ability to integrate in the cell genome. In fact, limited epidemiological studies indicate a negative correlation between AAV infection and the incidence of cervical cancer, although some groups reported no association with either CIN or invasive squamous cell carcinoma. AAV antibodies are detectable in 45% of the population and 60% of the adult population specifically, but antibody titres in patients with cervical carcinoma are well below those of age-matched controls. In addition, using a whole virus AAV sandwich enzyme linked immunosorbent assay, no relationship was found between AAV antibodies and the presence or grade of neoplasia in 291 cervical specimens from 291 Jamaican woman and 79 United States university students enrolled in one study. Extensive experimental evidence suggests that AAV have an anti-oncogenic activity and may protect against the development of cervical carcinoma [232]. At present the mechanism of this action is unclear but may be related to AAV induced regulation of HPV gene expression and HPV life cycle. Using a raft culture system, Mayers et al demonstrated a complex interaction between AAV, HPV and skin during dual infection [233]. As AAV has a relatively fast life cycle generating infectious progeny, Agrawal et al suggested that AAV has a significant effect upon the temporal kinetics of the HPV life cycle in natural host tissue [234]. Furthermore, AAV was shown to inhibit bovine papilloma virus 1 and HPV 16 and HPV 18 oncogenic properties in tissue culture via the rep 78 protein. It is known that the primary AAV infection usually occurs in childhood, but unstable AAV antibody response may allow lifelong reinfection or reactivation of persisting virus. Lanhham et al found AAV in similar proportions of high and low grade CIN samples in all age groups studied, indicating that reactivation of latent infection rather than reinfection would be the most likely source of AAV [212]. This suggests that many women will have latent AAV infection from an early age

and hence the possible susceptibility to HPV transformation if cells in the endocervix are infected. Interestingly, Coker et al demonstrated that AAV positivity was associated with significantly reduced risk of high-grade intraepithelial lesions (HSIL) [235], but not LSIL and not associated with race, HPV status, age or sexual risk factors. In contrast, Walz et al detected AAV in 63% of samples from high grade CIN biopsies [236], and in a larger study by Strickler et al, no evidence was found of AAV infection in either CIN samples or CIN normal cervical samples [237].

It seems that the inverse association between AAV and cervical neoplasia may be due to an ability of AAV to change the role of HPV in cervical carcinogenesis in particular in late stages of carcinogenesis. This conclusion needs to be verified in additional epidemiological studies and undoubtedly merits further experimental work.

Chlamydia trachomatis (CT)

Chlamydia is an obligate intracellular bacterium, and is the most sexually transmitted micro-organism in the developed world, causing genital and ocular disease. Serovars A-C cause trachoma; serovars D-K affect primarily the genital tract. It is estimated that 3-5% of sexually active young women are infected, and up to 10% in selected groups. Chlamydial infection is associated with age under 25 years, a new sexual partner or more than one sexual partner in the recent past, lack of barrier contraception, use of oral contraceptive pill, and termination of pregnancy.

In earlier prospective studies an association between past infection with CT and cervical cancer was found, but strength of evidence was limited either due to inability to control for effects of HPV 16 or due to limited number of cases [238]. Exposure as assessed by serology has been shown that CT to be significant and independent risk factor for cervical neoplasia. For example, Bjorge et al suggested that effects of CT are specific for cervical cancer and not other anogenital cancers [239, 240]. In addition, higher rates of progression to CIN3 have been noted in females whose cervical smears had changes suggestive of CT infection, although this is a relatively insensitive method for detection.

Koskela *et al* found in a longitudinal study that antibodies to CT were associated with increased risk of squamous cell carcinoma (SCC) (HPV and smoking adjusted OR, 2.2; 95% CI, 1.3-3.5) and this risk increased with increasing time from serum sampling to cancer diagnosis, and the OR for metastatic disease were larger than for localised disease [241]. These results are surprising since the increased risk was specific for SCC and not adenocarcinoma, and since endocervical glandular cell are the targets for CT. This might be related to metaplastic cells being permissive to CT. Whether or not infection with CT could alter the proportion of cells permissive to the oncogenic HPV types also remains to be determined, but interaction between the two micro-organisms in cervical carcinogenesis remains possible.

In another longitudinal nested case-control study within a cohort of 530,000 women who provided samples to serum banks in Finland, Norway and Sweden, the association between exposure to different CT serotypes and subsequent development of cervical SCC was investigated. Interestingly, of specific CT serotypes, serotype G was most strongly associated with SCC (adjusted OR, 6.6; 95% CI, 1.6-27.0). Other serotypes associated with SCC are the I serotype (OR, 3.8; 95% CI, 1.3-11.0) and the D serotype (OR, 2.7; 95% CI, 1.3-5.6). Furthermore, the serum IgGs to more than one serotype increased the ORs for SCC (p<0.001 for trend) [242].

The molecular mechanisms underlying cervical carcinogenesis induced by CT are not fully understood. Genetic damage and neoplastic changes induced *in vitro*, release of nitric oxide and the inhibition of host cell apoptosis by blockade of mitochondrial cytochrome c release and caspase activation might account, at least, in part for such mechanisms [243].

In summary, this contribution focuses on HPV and non-HPV causes of cervical neoplasia. The role of these infectious non-HPV organisms in the prevention, diagnosis, vaccination and treatment of cervical neoplasia merits further clinico-pathological-molecular studies.

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