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Poster Abstracts

Poster 1

Visual inspection with acetic acid (VIA) and lugols iodine (VILI) is a feasible screening tool for cervical cancer in rural India

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Background

Available screening methods are cumbersome technically, both from the patient's perspective and the infrastructure required. This stimulated the Government of Tamil Nadu to look for an appropriate screening tool for cervical cancer in a low resource setting.

Method

Women within the age group 30–60 years were screened using a combination of Visual Inspection with Acetic acid (VIA) and Lugols Iodine (VILI) in two districts of Tamil Nadu, between February 2007 and January 2010. Women who tested positive were evaluated using colposcopy, followed by microscopic confirmation. Two strategies: a primary intervention aimed at creating awareness and achieving behavioural change; and a secondary intervention aimed at screening with referral and management, were carried out in all the Primary Health Centers, Government Hospitals, and Medical College and Hospital in the intervention districts.

Results

A total of 196,559 women in Theni and 291,525 women in Thanjavur were screened using VIA/VILI. Of the 2.59% VIA/VILI positive women in Theni, 62.8% underwent colposcopy (98.6% – satisfactory; 1.4% – unsatisfactory), and 46.6% had a biopsy. Of the 5.4% VIA/VILI positive women in Thanjavur, 54.5% underwent colposcopy (80.6% – satisfactory, 19.4% – unsatisfactory), 55.8% had a biopsy and 28.7% had ECC. In total, 16.2% in Theni and 21.7% in Thanjavur of the biopsy subjected women were confirmed with cervical cancer, of which 31.5% in Theni and 54.9% in Thanjavur were treated.

Conclusions

The pilot proves VIA/VILI as a promising screening tool in low resource settings and demonstrates the potential for scale up of the programme in all other districts of the State, provided that the appropriate service delivery strategies are practised for efficient follow up.

Keywords

Cervical cancer, VIA/VILI, Theni, Thanjavur

Poster 2

Visual inspection with acetic acid (VIA) compared with cytology and HPV DNA testing for cervical cancer screening, experiences at the University of Pavia, Italy, to increase screening and treatment at Lacor Hospital, Northern Uganda

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Introduction

Uganda, like other developing countries, has a high incidence of cervical cancer. Lacor hospital is collaborating with the University of Pavia to increase screening services in northern Uganda using VIA.

Objectives

To compare the sensitivity and specificity of VIA to that of cytology and HPV-DNA testing so that it could be used as the cheaper and more feasible screening method at Lacor Hospital, northern Uganda.

Methods

A doctor from Lacor Hospital travelled to the University of Pavia and trained in colposcopy at department of Obstetrics and Gynecology San Matteo Hospital, carrying out VIA, pap smear cytology and HPV DNA tests for the patients attending the colposcopy clinic. The sensitivity and specificity of the three screening tests were calculated.

Results

A total of 138 women were examined with VIA, of which 26.8% were positive. 130 (94.2%) had cytology results available and 93 (67.4%) had HPA-DNA test results available. VIA showed an 80% sensitivity in detecting a high grade lesion compared with 88.9% for cytology and 100% for HPV- DNA tests, but it was the most specific (59%) compared to cytology (26.3%) and HPV-DNA tests (6.9%).

Conclusion

VIA has a comparable sensitivity in detecting high grade lesions to that of cytology and is even more specific than the cytology and HPV-DNA testing, and is therefore, recommended as the sole screening method for Lacor Hospital.

Keywords

VIA, HPV, cytology, sensitivity

Poster 3

Feasibility and potential application of brush cytology for detection of oropharyngeal HPV-infection and HPV-related squamous cell carcinoma

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Background

The prevalence of human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC) is dramatically increasing. However, little is known about the risk factors and the natural course of oropharyngeal HPV infection, as well as its clinical and prognostic significance in OPSCC. This is in part due to the lack of adequate sampling methods. The aim of the study was to validate the diagnostic potential of oropharyngeal brush cytology for the detection of OPSCC, precancerous lesions and HPV infection.

Methods

Brush samples and corresponding biopsies were taken from the tumor, normal appearing mucosa around the tumor and distant mucosa in 11 patients with OPSCC undergoing panendoscopy. Cytological and histological analyses and P16 immunostaining were performed using routine methods. Cytological assessment was done according to the Bethesda guidelines. For HPV testing, the L1C1/2 method with sequencing was used. Serum samples were tested for antibodies to the L1, E6 and E7 proteins of HPV types 16 and 18.

Results

Eleven consecutive patients, 4 females and 7 males with a mean age of 60 years (range 30–81) have been prospectively enrolled in the study. All brush samples contained sufficient cell material. The samples from the distant mucosa revealed neither cytologically nor histologically dysplastic or cancerous changes. In the normal appearing mucosa 3/11 histological samples showed high grade dysplasia compared to 6/11 cytological specimen. 9/11 brush samples and 11/11 biopsies from the tumor site were positive for invasive carcinoma. The sensitivity, specificity, PPV and NPV of brush samples compared to biopsy was 86%, 84%, 80% and 89%, respectively. In 9/11 (82%) patients the tumor was positive for HPV-high risk types (8 HPV 16 and 1 HPV 16 and 33). Results of ongoing analyses of HPV-detection and immunocytochemistry as well as HPV serology will be reported.

Conclusion

Based on our preliminary results, brush cytology seems to be a feasible and reliable method to detect pathological cellular changes in the oropharyngeal mucosa.

Keywords

Brush cytology, HPV, squamous cell carcinoma, oropharynx

Poster 4

Human papillomavirus prevalence and genomic integration in situ and infiltrating cervical carcinoma by HIV status

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Background

Human papillomavirus type prevalence, and particularly type HPV-16 in cervical cancers of women with and without human immunodeficiency virus (HIV-1) infection is a current topic.

Objective

To provide data on the HPV type prevalence and the viral integration of HPV-16 and HPV-18 in cervical cancer by HIV status.

Study design

Retrospective multicentre descriptive study of a cohort of HIV-positive women and a matched cohort of HIV-negative women.

Patients and Methods

Between 1987 and 2008, 31 HIV-infected women diagnosed as in situ or infiltrating cervical squamous cell carcinoma were identified, and 109 HIV-negative subjects were matched by cervical histological diagnosis and age. HPV detection and typing was performed by multiplex fluorescent PCR and HPV integration by multiplex real-time PCR.

Results

The most common HPV type in HIV-positive versus HIV-negative women was: HPV-16 (60% versus 75%, OR:0.5, 95%CI:0.2–1.2), HPV-33 (17% versus 8%, OR:2.4, 95%CI:0.7–7.9), HPV-52 (7% versus 2% OR:3.6, 95%CI:0.5–26.8), HPV-58 (7% versus 5%, OR:1.4, 95%CI:0.2–7.6) and HPV-18 (7% versus 4%; OR=0.6, 95%CI:0.3–10.2). Prevalence of multiple HPV infections was 13% in HIV-positive and 17% in HIV-negative women. The integration of HPV-16 was 39% in HIV-positive and 45% in HIV-negative women, and the HPV-18 integration was 50% in both groups.

Conclusion

Our data suggest that although HPV-16 seems to be the most prevalent type in cervical carcinomas in HIV-positive and HIV-negative women, a trend toward a lower prevalence of this type was detected in the HIV-positive women. No differences have been observed for HPV-16 and HPV-18 integration in cervical carcinomas in both groups. These data provide information about HPV-infection in cervical carcinoma in general and HIV population in Catalonia (Spain), one of the areas in the world with the lowest incidence of cervical carcinoma.

Keywords

Cervical carcinoma, Human Papillomavirus type distribution, HIV-positive women, HPV infection

Poster 5

The effect of social deprivation on exposure to material promoting HPV vaccination: evidence from England

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Background

In 2008 the health departments of the United Kingdom implemented a Human Papilloma Virus (HPV) vaccine campaign in schools to reduce the incidence of cervical cancer. This campaign, targeting adolescent girls, was supported by the Royal Society for Public Health (RSPH) with educational materials for use in school curriculum.

Study design

A cross-sectional study was conducted to examine the relationship between area deprivation and the take-up of educational materials, related to HPV and cervical cancer and the HPV vaccination, by schools in England.

Methods

The RSPH contacted 4,624 schools (enrolling girls aged 12–13 years) in England, offering access to free-of-charge HPV educational materials, including professionally developed teaching materials. The relationship between the take-up of the educational materials and the level of social deprivation of the area within which the school was located was analysed using logistic regression, including as covariates geographic location, school type, and school size.

Results

Of the schools invited to receive the educational materials, 1,395 schools (30.17%) responded. After controlling for other covariates, schools in the most deprived areas (the fourth and the fifth quintiles of deprivation) were the least likely (OR=.64, p<.000 and OR=.77, p<.017) to request materials, compared with the schools in the least deprived areas (the first quintile).

Discussion and Conclusion

Requests for educational materials supporting the HPV vaccination campaign were unevenly distributed across England, and the level of social deprivation was significantly associated with the take-up of materials by schools. At least a part of the reason that educational activities are often less effective in socially deprived areas is because the level of exposure is less, rather than that the people are less responsive to these activities. This has specific implications for the delivery of education campaigns targeting HPV and cervical cancer and the HPV vaccination through schools.

The project *Evaluation of HPV education programme of the Royal Society of Public Health* was funded by the Royal Society of Public Health.

Keywords

HPV educational materials, area deprivation, school, England

Poster 6

Human Papillomavirus (HPV) L1 capsid protein and HPV Type 16 as prognostic markers in cervical intraepithelial neoplasia 1

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Introduction

The aim of the study was to determine whether human papillomavirus (HPV) L1 capsid protein and the HPV genotype can predict the disease course as prognostic markers for cervical intraepithelial neoplasia 1 (CIN1).

Methods

Immunohistochemical staining was performed for HPV L1 capsid protein in 101 women who had been confirmed to have CIN1 by histology and HPV high-risk infection by HPV genotyping. The disease course was analyzed by follow-up histology according to the HPV L1 capsid protein and HPV genotype over a minimum of 12 months.

Results

CIN1 regressed spontaneously in 60.4% of the women; most cases of regression occurred within 1 year (90.9% of regression cases). HPV L1 capsid protein-positive patients had a spontaneous regression rate of 72.7% (48/66) and a rate of persistent disease or progression to higher grade disease of 27.3% (18/66). HPV L1 capsid protein-negative women had a regression rate of 37.1% (13/35), and a rate of persistent disease or progression of 62.9% (22/35; p<0.001). HPV16-infected patients had a regression rate of 38.6% (17/44) and a rate of persistent disease or progression of 61.4% (27/44), whereas non-HPV16-infected patients had a regression rate of 77.2% (44/57) and a rate of persistent disease or progression of 22.8% (13/57; p<0.001).

Conclusion

HPV L1 protein expression is closely related to spontaneous disease regression, but HPV16 infection is related to persistent disease or progression to high grade lesions in patients with CIN1.

Keywords

HPV, L1 capsid protein, CIN, prognostic marker

Poster 7

Acceptance and barriers of human papillomavirus vaccination in Chinese female university students

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Purpose

This study aims to investigate the factors associated with the acceptance of human papillomavirus (HPV) vaccination in Chinese female university students

Methods

This is a case control study using a self-administered questionnaire. Female university students who had received HPV vaccination in a local vaccination campaign were invited to fill in the questionnaires. Controls matched with their major studies were recruited from students who did not receive the HPV vaccination at the university. The questionnaires consisted of 5 parts: 1) demographics; 2) awareness and perception of HPV and related disease; 3) acceptance and barriers of vaccine in general and HPV vaccine; 4) attitude toward vaccination campaign; and 5) sexual and cervical screening practice. Data were analyzed by chi square and followed by logistic regression.

Results

282 subjects who had been vaccinated against HPV in the campaign completed the questionnaire with a response rate of 69.1%. 280 matched controls completed the same questionnaire. Comparing the two groups, we have found that safety concerns, particularly because this was a new product was the main barrier to acceptance of this vaccine. Peer group was the most influential factor in the student's decision. We found that there was no association in the cervical screening practice and sexual behaviour with vaccination acceptance. Neither their family income nor whether they came from overseas or mainland China were independent associating factors.

Conclusion

Vaccine acceptance is the crucial element in the success of a population vaccination programme. Health promotion and education can be targeted to increase the vaccination uptake. Moreover, our study clarified the misconception that HPV vaccination is associated with sexual behaviour and cervical screening practice.

Trial registration

N/A

Funding

No external funding

Keywords

HPV vaccination, Chinese, acceptance

Poster 8

Performance of the APTIMA high-risk HPV mRNA assay in a referral population in comparison with Hybrid Capture 2 and cytology

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Objective

To evaluate the ability to detect high-risk HPV mRNA and DNA in disease-positive LBC specimens (CIN2+).

Materials and Methods

424 clinical specimens (collected from patients with abnormal cytology and controls after treatment) were stored in LBC vials at room temperature for up to 3 years. All LBC specimens were tested for E6/E7 mRNA of 14 high-risk HPV types in the APTIMA HPV (AHPV, Gen-Probe) and for high-risk HPV DNA in the Hybrid Capture 2 (HC2, Qiagen) test. Results were compared to cytology and histology.

Results

AHPV was positive in 148 out of 150 CIN 3 and 11 out of 12 cervical carcinoma specimens (sensitivity 98.1% for CIN 3+). The one cervical carcinoma specimen missed by AHPV contained exclusively HPV 53, a type considered low-risk and not included in AHPV assay. HC2 was positive in 146 out of 150 CIN 3 and 10 out of 12 cervical carcinoma specimens (sensitivity 96.3% for CIN 3+). One of the two cervical carcinoma specimens missed by HC2 contained HPV18, the other was HPV DNA negative in the Linear Array HPV Genotyping test. Both specimens were positive in the AHPV assay, indicating high risk HPV mRNA expression. AHPV had a significantly (p<0.0001) higher specificity (75.0%) compared to the HC2 assay (61.0%) for the detection of CIN 2+.

Conclusions

AHPV and HC2 test were both more sensitive and the AHPV assay also more specific than cytology. The only four patients with positive AHPV and negative HC2 and cytology results after treatment showed recurrence of CIN2+ (with the identical HPV type) at follow-up testing after more than one year. The AHPV assay appears to be a very sensitive and specific test of cure.

Keywords

High-risk HPV, HPV mRNA, comparison, HPV DNA

Poster 9

CEACAM-1 expression in cervical tissues from patients with recurrence lesion of cervical intraepithelial neoplasia 2 and 3 grade

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Carcinoembryonic antigen-related cell adhesion molecule-1 (CEACAM-1) is involved in several cellular functions such as angiogenesis, proliferation, morphogenesis, apoptosis, intercellular adhesion, tumor suppressor and invasion promoter. Recently, CEACAM-1 has become the focus of intense immunological research due to its differential expression in several tumor tissues and immune cells. In cases of malignant transformation, a down-regulation or loss of CEACAM-1 has been shown in patients with cervical cancer. Currently, cervical cancer detection is mainly directed to identify and treat CIN2-3. The rate of recurrence for CIN2-3 after treatment ranges between 5% and 20%. We consider it important to measure the expression of this molecule in patients with recurrence lesions and believe it could be a prognostic marker of recurrence and progression to cancer.

This study was intended to assess the CEACAM-1 expression in cervical tissue and peripheral blood from patients with or without CIN2-3 recurrence after treatment. Inclusion of women at cohort was made at the moment of CIN2-3 diagnosis. Our study cohort enrolled 69 patients diagnosed by histopathological criteria as CIN2-3. The patients were treated by Loop Electrosurgical Excision Procedure and were monitored at 6 and 12 months. CEACAM-1 in cervical lesions was determined by immunohistochemistry and in peripheral blood by flow cytometry.

At this time we did not find significant differences in CEACAM-1 expression from patients with and without post-treatment recurrence; however, our results show a high expression of CEACAM-1 in tissues of patients without recurrent lesion and a decrease in the expression of CEACAM-1 in patients with recurrent lesion. These data suggests that this decrease in the CEACAM-1 expression could be associated with a phenotype compatible with a greater degree of malignant transformation; however, to evaluate with more confidence the role of this molecule it will be necessary to increase the patient cohort and examine more women with recurrence lesions.

Keywords

Cervical cancer, cervical intraepithelial neoplasia, CEACAM-1, recurrence lesion

Poster 10

Antiviral approaches to treat HPV-related tumors : The Institute Gustave Roussy experience from preclinical data to clinical trials

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The knowledge of high risk HPV implication in a significant proportion of squamous cell carcinoma of the cervix, anus, head and neck raises the question of biologically-driven therapeutic approaches for these tumors^(1,2). Large-scale anti-HPV vaccination will require at least one or two decades before affecting the incidence of HPV-related cancers. We have developed an original approach aiming at sensitizing HPV-related tumors to ionizing radiation and chemotherapy using an antiviral agent Cidofovir. Cidofovir is a nucleoside analog. Combination of Cidofovir increases radiation sensitivity in vitro and in vivo. Of interest, preclinical findings suggest that this radiosensitizing effect is HPV-dependant, suggesting a tumor relative specificity in the clinic. Exposure to Cidofovir indeed correlates with a decrease in HPV-related oncoproteins and a restoration of the tumor suppressor protein levels p53 and pRB⁽³⁾.

In addition, exposure to cidofovir is associated with a sharp decline in metastatic potential, reflecting the inhibitory effects on the cxc4/SDF1 chemotacticism as well as a restoration of the p53 inhibition on VEGF.

We also found that Cidofovir can also exert synergistic cell killing in combination with antiEGFR targeted agents. Preliminary data of the first clinical trial combining Cidofovir to chemoradiation in the setting of HPV positive cervical cancer will be presented as well the strategy implemented to treat metastatic HPV related tumors using antiEGFR combined to cidofovir .

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Keywords

HPV, radiosensitization, Cidofovir, clinical trial

Poster 11

Neutralization of closely-related non-vaccine HPV genotypes by HPV vaccine sera

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Background

As the majority of cervical cancers are associated with HPV genotypes from two distinct Alpha-Papillomavirus clades (A7: HPV18, 39, 45, 59, 68 and A9: HPV16, 31, 33, 35, 52, 58), the extent to which the current HPV16/18 vaccines will protect against related genotypes is an important unresolved issue. Few published data are available on the frequency or titer of neutralizing antibodies against closely-related non-vaccine types, for example HPV31 and HPV45.

Objectives

To determine the frequency and titer of cross-neutralizing (HPV31 and HPV45) antibodies in sera from individuals immunized with CervarixTM within the UK National HPV Immunization Programme.

Methods

Blood samples were collected from 13–14 year old girls (n=70), after a median of 5.9 months (IQR 5.7–6.0) from receiving their third dose of CervarixTM vaccine. Neutralization assays were performed using L1L2 pseudoviruses representing HPV16, 18, 31, 45 and the control BPV1.

Findings

Cross-neutralizing antibodies against HPV31 (76% of sera, 95% CI 64–85%) and HPV45 (20%, 95% CI 11–31%) were evident among this group of vaccinees. The low prevalence of these HPV types in the population and the ages within the study cohort, suggest these responses are due to vaccination. Cross-neutralization titers against HPV31 and HPV45 were substantially lower than for vaccine types (GeoMean for HPV31 of 0.96% [95%CI, 0.48–1.92%] the HPV16 titer; for HPV45 of 0.39% [95%CI, 0.19–0.80%] the HPV18 titer).

Interpretation

Here we show that neutralizing antibody responses against closely-related, non-vaccine types are relatively common, but the antibody titers are very low ($\leq 1\%$ of type-specific titer). Studies have shown that HPV16/18 neutralizing titers in genital secretions are much lower than those found in the periphery. It is unclear, therefore, whether these low levels of HPV31/45 antibodies would be sufficient to protect against infection in the absence of other immune mechanisms. Their utility as surrogate markers of protection remains to be determined.

Keywords

Antibodies, cross-neutralisation, vaccine

Poster 12

Markers of HPV infection in HPV vaccinated Czech women

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Purpose

Currently two prophylactic HPV vaccines are commercially available to prevent HPV16/18 infection and associated lesions. It has been shown that vaccination of females incidentally or persistently infected with vaccinal HPV types is less effective or ineffective. The aim of the study was to assess the proportion of sexually active women who were at risk of reduced vaccine efficacy and compare the strength of antibody response elicited by particular vaccines one year after the third dose.

Methods

Altogether 222 women (16–49 years, mean 23.4 years) were enrolled. Before the first vaccine dose and one year after the third dose, a sample for HPV DNA detection and typing and blood for anti-HPV antibodies assessment were taken. HPV DNA detection and typing was done by PCR and RLB/sequencing, sera were tested for presence of antibodies to VLPs derived from HPV6, 11, 16, 18.

Results

HPV DNA prevalence in the whole cohort (38.7%) was age dependent. Vaccinal types were found in 13.1% of females, not present in women over 30 years. Overall 23.4% of women were anti-HR VLP seropositive, in women above 30 years the positivity was as high as 59%. Incident infection (HPV DNA+/Ab-) with vaccinal HPV types was observed in 5.0% and persistent infection (HPV DNA+/Ab+) in 7.2%. About 19% women cleared the HPV16/18 infection. Geometric mean titer of HPV16/18 antibodies was available for 71/35 women vaccinated by Silgard/Cervarix. For both antigens antibody levels were higher after Cervarix application.

Conclusions

Our study has shown that at least about 60% of women enrolled have already encountered the HPV infection. HPV vaccination might have reduced efficacy in more than 10% of vaccinated women who were positive for HPV16/18 DNA at the first dose of vaccine application.

Funding

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Keywords

HPV vaccine, HPV DNA, HPV antibody

Poster 13

Role of transcription factor AP-1 in esophageal squamous cell carcinoma: Alterations in activity and expression during Human Papillomavirus infection

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Background

Esophageal squamous cell carcinoma (ESCC) is a leading cause of cancer-related deaths in the Jammu and Kashmir (J&K) region of India. A substantial proportion of esophageal carcinoma is associated with infection of high-risk HPV type 16 and HPV18, the oncogenic expression of which is controlled by host cell transcription factor Activator Protein-1 (AP-1). We have therefore investigated the role of DNA binding and expression pattern of AP-1 in esophageal cancer with or without HPV infection.

Methods

Seventy five histopathologically-confirmed esophageal cancer and an equal number of corresponding adjacent normal tissue biopsies from Kashmir were analyzed for HPV infection, DNA binding activity and expression of AP-1 family of proteins by PCR, gel shift assay and immunoblotting respectively.

Results

A high DNA binding activity and elevated expression of AP-1 proteins were observed in esophageal cancer, which differed between HPV positive (19%) and HPV negative (81%) carcinomas. While JunB, c-Fos and Fra-1 were the major contributors to AP-1 binding activity in HPV negative cases, Fra-1 was completely absent in HPV16 positive cancers. Comparison of AP-1 family proteins demonstrated high expression of JunD and c-Fos in HPV positive tumors, but interestingly, Fra-1 expression was extremely low or nil in these tumor tissues.

Conclusion

Differential AP-1 binding activity and expression of its specific proteins between HPV-positive and HPV-negative cases indicate that AP-1 may play an important role during HPV induced esophageal carcinogenesis.

Keywords

Activator Protein-1 (AP-1), Human Papilloma Virus (HPV), esophageal cancer, Kashmir

Poster 14

Low integrated status of Human Papillomavirus in combination with low viral load is associated with poor radiotherapy outcome in uterine cervical cancer

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Purpose

To examine the physical status of human papillomavirus in locally advanced cervical cancer and its effect on radiotherapy outcome.

Patients and Methods

Patients were treated by radiotherapy±cisplatin concurrent chemotherapy between 2003 and 2006. The physical status of the human papillomavirus (HPV) gene was examined in cervical tumours from 111 radiotherapy patients and was compared with the viral load measured by Hybrid Capture II (HCII). To quantitatively estimate integrated viral genes in individual tumours, real-time polymerase chain reaction was performed for HPV type-specific E6 and E2. The amount of integrated viral gene was calculated by equation of E6-E2/E6 and was grouped into two using cut-off value of 0.5. Four combinational groups were made using the E6-E2/E6 and HPV viral load value using the median value (E6-E2/E6 \leq 0.5/low viral load (Group 1), E6-E2/E6 \leq 0.5/high viral load (Group 2), E6-E2/E6 $>$ 0.5/low viral load (Group 3), and E6-E2/E6 $>$ 0.5/high viral load (Group 4)). Disease-free survival was compared between the designated groups.

Results

There was a considerable variation in the physical status of HPV in cervical cancer. The presence of a high proportion of integrated physical status tends to be associated with superior treatment outcome. There were 18 Group 1, 33 Group 2, 36 Group 3, and Group 4 patients. Univariate Cox analysis showed physical status, histologic grade, metastatic lymph node, tumor size, and clinical stage as significant factors for poor prognosis. On multivariate analysis, Group 1 (low viral load and low integrated status) showed significantly inferior disease-free survival (DFS) compared with the Groups 2,3,4 (HR of group 2,3,4=0.13, 0.16, 0.17, p=0.003, 0.006, and 0.009, respectively). Other prognostic factors included poorly differentiated grade (p=0.02) and advanced stage (p=0.009).

Conclusion

Cervical cancer with a lower amount of integrated HPV virus and low HPV viral load is associated with inferior disease-free survival. Our result suggests strong host factors in the prognosis of uterine cervical cancer treated primarily by radiotherapy.

Keywords

Cervical cancer, viral load, physical status, radiotherapy

Poster 15

Detection of Human Papillomavirus DNA in breast cancers

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Background

Several studies reported the detection of the HPV within breast cancer tissues in the past, with an ample range of positivities.

31 breast cancers and 12 controls were investigated for the presence of HPV DNA; secondary aims were a) to detect the HPV DNA in metastatic nodes; b) to investigate positive patients for a possible cervical HPV co-infection; and c) to evaluate the E6 and E7 mRNA expression in HPV positive breast cancer tissues. Exclusion criteria: past breast/cervical cancers, neo-adjuvant treatments.

Methods

Cancers: 29 ductal and 2 lobular cancers, mean age 57 years, range 35–78. Controls: 10 fibroadenomas and 2 papillomas, mean age 27 years, range 25–35.

HPV genotyping was performed after DNA extraction from paraffin-embedded surgical specimens (cancers, controls and nodes) or from cytological cervical samples.

After RNA extraction, stored frozen HPV positive cancer tissues were further investigated for E6 and E7 mRNA expression.

Results

HPV DNA was detected in 9 cancers (29%), HPV 16 the most frequent. All controls resulted negative for HPV (p 0.04).

Among 9 HPV positive breast cancer patients, 6 patients resulted co-infected at the cervix, sharing at least one the HPV types.

Just 1 out of 8 patients with metastatic nodes was tested positive for HPV infection, the others resulted negative.

A search for the E6 and E7 mRNAs expression was conducted in 5 patients. The analysis failed in detecting the expressions in all the patients.

Discussion

The rate of HPV infection within breast cancer patients was significant if compared with controls, however since positive cancers did not express the viral mRNAs, its role in oncogenesis remains unclear.

2/3 of the patients who tested positive for HPV at the breast site shared at least one of the HPV types at the cervical site, however the mechanism of transmission (mechanical/systemic spreading) remains unclear.

Keywords

HPV, breast cancer

Poster 16

Improving cervical cancer screening by HPV testing of vaginal specimens self-collected at home: the MARCH randomized controlled trial

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The Mexican Appraisal of Routine Cytology versus vaginal HPV screening (MARCH) for detecting cervical intraepithelial neoplasia grades 2, 3 or cancer (CIN 2+) in underserved women.

Methods

A population-based randomized controlled trial (RCT) of 22,866 mostly rural women aged 25 to 65 years in central Mexico. Randomization was to: 1) self-collection of vaginal specimens at home to determine high risk (HR) HPV status by the Hybrid Capture 2 test (the HPV arm; n=9,202), and 2) routine cervical cytology smears collected at primary healthcare centres (the cytology arm; n=13,664). Positive tests were referred to colposcopy and biopsy as required. An intention to screen analysis was conducted in Stata 10.1 adjusting for non-compliance and contamination, weighting rates according to the age structure and level of social deprivation using proportional fixation criteria.

Results

The prevalence of HPV was 9.6% (95% CI 8.5–12.1), and the cytology abnormal rate was 0.43% (95% CI: 0.23–0.71). HPV testing identified 114.6/10,000 (95% CI 93.2–136.0) CIN 2+ versus 38.95/10,000 (95% CI 26.42–51.47) by cytology, a 2.94-fold (95% CI 2.86–3.03) greater relative sensitivity. Similarly HPV detected 3.98-fold more invasive cancers than cytology. The positive predictive value (PPV) of HPV testing for CIN 2+ was 12.3% (95% CI 10.2–14.5) and for cytology was 62.7% (95% CI 50.4–75.0).

Conclusions

Self-collection of vaginal specimens at home for HR-HPV DNA detection was highly sensitive for identifying CIN 2+ with an acceptable PPV and was readily established and maintained. Despite a lower PPV we favour frontline HPV testing for low resource settings because such women will be screened at most a few times in their lives and the high sensitivity of a single HPV screen is of paramount importance.

Funding

The Health Ministry and Public Health Institute of Mexico, and QIAGEN Corp. provided funding; sponsor entities had no role in study design, data collection, analyses, or interpretations.

Keywords

HPV, cervical cancer, RCT, cervical cytology

Poster 17

Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of HPV-associated oropharyngeal cancer

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Background

Patients with head and neck squamous cell carcinoma (HNSCC) are at significantly elevated risk of second primary malignancies (SPM), most commonly within the head and neck, lung and esophagus (HNLE). Our objectives were to identify subsite-specific differences in SPM risk and distribution, and to describe trends in risk over the past three decades, both before and during the era of HPV-associated oropharyngeal SCC.

Methods

Population-based cohort study of 75,087 patients with HNSCC in the SEER program. Excess SPM risk was quantified using standardized incidence ratios (SIR), excess absolute risk (EAR) per 10,000 person-years at risk (PYR), and number needed to follow. Trends in SPM risk were analyzed using joinpoint log-linear regression.

Results

In HNSCC patients, the SIR of second primary solid tumor was 2.2 (95%CI 2.1–2.2), representing an EAR of 167.7 cancers per 10,000 PYR. Lung cancers were the most common, followed by head and neck and esophagus. The risk of SPMs was highest for hypopharyngeal SCC (SIR=3.5, EAR=307.1 per 10,000 PYR), and lowest for laryngeal SCC (SIR=1.9, EAR=147.8 per 10,000 PYR). Prior to the 1990s, oropharyngeal cancers carried the second highest risk of SPM, after hypopharyngeal cancers. Since 1991, SPM risk has fallen significantly among patients with oropharyngeal SCC (annual percentage change in EAR = -4.6%, p=0.03). Oropharyngeal cancers now carry the lowest risk of SPM of any head and neck subsite.

Conclusions

Since the early 1990s, the risk of second cancer after oropharyngeal SCC has fallen dramatically. This trend has occurred contemporaneously with the rise of oncogenic HPV-associated oropharyngeal cancer. It is likely that the risk of second primary cancer is substantially lower in HPV+ versus HPV- head and neck cancer. These findings may have implications for current interest in de-escalation of systemic therapy in HPV-associated HNSCC.

Figures

Excess absolute risk (EAR) of second primary malignancy (SPM) in solid tumor sites and the head and neck, lung and esophagus (HNLE) over time, by subsite of index head and neck cancer (OC: oral cavity, OP: oropharynx, L:larynx, HP:hypopharynx)

Keywords

Second primary cancer, second primary malignancy, oropharynx, HPV

Poster 18

Treatment of anal neoplasia – A long-term outcome study

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Background

Currently there are no guidelines for the treatment of high-grade anal intraepithelial neoplasia (AIN 2/3).

Aim

To identify the benefits, if any, of treatment of AIN 2/3.

Methods

Analysis of treatment and follow-up data of AIN 2/3 in a specialist unit in the UK.

Results

Eighty four patients with intra-anal (77) or external (7) disease underwent treatment and had regular follow-up for more than 36 months. 87% were men and 82% were men who have sex with men (MSM). 61% were HIV positive. 3 patients had other immune defects. 33.3% had AIN3 while 66.7% had AIN2. 87% received laser ablative treatment, while the rest had excision or topical imiquimod treatment. The median follow-up was 60 months (mean 65; range 36–169). All recurrent disease was treated, after biopsy for histology verification. Histology of repeat biopsies in 64 patients after initial treatment revealed 11 cases of AIN3, 14 cases of AIN2 and 26 cases of AIN1 (total 88 biopsies; 39% AIN 2/3). In total there were 72 further treatment attempts in these 64 patients during follow-up (laser 65, imiquimod 5 and excision 2). None of the treated patients developed invasive anal squamous carcinoma (anal cancer) or treatment related complications.

Discussion

Currently available follow-up studies of high-grade AIN (AIN 2/3) show a progression rate of 9–14% to anal cancer, over a 60 month period, despite some intervention. In our cohort no one developed anal cancer (p<0.05). Recurrent disease was limited in volume and repeated treatment was acceptable. Moreover, there was no sequel to treatment. We now need prospective large scale studies to verify this outcome and modelling studies are needed to establish cost-benefit analysis of treatment.

Keywords

Anal cancer, high-grade anal neoplasia, treatment of AIN 2/3, cancer prevention

Poster 19

Concordance between paired cervical and urine samples in HPV-DNA detection and HPV genotyping

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Background

Low adherence rates to cervical cancer screening programs based on cervical samples collection limits the efficacy of this strategy; less invasive and effective sampling could be helpful for the screening of high risk or low adherent women such as adolescent/young women, immigrants, women in developing countries.

Agreement between HPV infection/genotyping on cervical and urine paired samples to define the efficacy of a preventive strategy based on an easier-to-collect sample is evaluated in this study.

Methods

Paired cervical and urine samples were collected in the same day from 107 women attending STD Unit, L Sacco Hospital (Italy). Multiplex-PCR on the HPV-L1 gene for viral genome and RFLP (Restriction Fragment Length Polymorphism) technique using 3 restriction enzymes (RsaI, HaeIII, DdeI), Recombinant Enzyme, BioLabs inc, New England) for HPV genotyping were used.

Agreement between tests was assessed using Kappa statistic (k). Fisher's exact test was performed to test difference between paired proportions.

Results

The prevalence of HPV infection was 65.4% and 62.6%, respectively in cytobrush and urine samples (concordance rate and 95%CI: 97.2%; 91.4–99.3). High concordance rates were observed also for single or multiple infections (k 93.7; 81.8–98.4), for infection from HR or LR types (k 89.1; 75.6–95.9), and for single genotypes: HPV-16 – k 95.7 (87.2–98.9); HPV-18 – k 100 (93.5–100); HPV-6 – k 94.3 (85.3–98.1); HPV-11 – k 97.1 (89.1–99.5); HPV-53 – k 95.7 (87.2–98.9); HPV-56 – k 97.1 (89.1–99.5).

The sensitivity of this method for HPV-DNA, any HR-HPVs, HPV-16 and HPV-18 were 96%, 91%, 80% and 100% respectively. Negative predicting values over 95% were observed for HPV-16, -18, -6, -11, -53, -56.

Conclusion

Urine-based assay for detection of HPV-DNA and HPV genotyping could be suitable for a wider and effective screening approach based on the molecular diagnosis of high-risk HPV infections for the high concordance rate observed with results obtained on cervical samples.

Keywords

Molecular screening, cervical samples, urine samples, tests agreement

Poster 20

Differential gene expression and HPV in penile carcinoma

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Penile cancer (PC) is an invasive epithelium tumor, representing more than 10% of the malignancies in men in some developing countries, mainly in Brazil. Studies on the aetiopathogenesis of this cancer have focused on its association with HPV. Patients with PC without treatment usually die within 2 years following diagnosis, because of uncontrollable loco regional disease or from distant metastasis.

The aim of this study is to evaluate the possible role of HPV in the development of PC and the use of the RaSH technique to analyze gene expression in normal tissues and penile tumors. HPV detection was carried out by PCR with generic primers GP5+/GP6+, and HPV typing was done by direct sequencing. RaSH methodology identified differentially expressed genes, generating subtractive cDNA libraries.

The presence of HPV was analyzed in 58 samples of patients with PC and a high prevalence (85.12%) of HPV was observed. Of the 16 samples sequenced, HPV-16 was found in 14 (87.5%) samples, HPV-11 in 1 (6.3%) and HPV-35 in 1 (6.3%). The RaSH subtractive libraries identified the presence of 57 genes differentially expressed between both samples; 30 in tumor samples and 27 in the normal tissue. The genes PBEF1, ANX1, RPL6 and KIAA1033 were over-expressed in the tumors. On the other hand, the gene p16 was over-expressed in normal tissue. Finally, the expression of the selected genes was confirmed by qRT-PCR. Only ANX1 was validated with over-expression in 80% of all samples.

The results obtained are capable of revealing differences in the patterns of gene expression between normal and tumor tissues. Moreover, a high prevalence of HPV was observed, suggesting an important role of this virus in penile carcinogenesis. Such information will contribute to develop a possible marker for penis tumor diagnostic and prognostic, improving the development of directed therapies against this new putative marker.

Keywords

Penile cancer, gene expression, HPV, RaSH

Poster 21

The impact of HPV-status on survival in patients treated with radiochemotherapy for advanced inoperable oropharyngeal cancer

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Background

HPV-status is an independent prognostic indicator of survival in oropharyngeal squamous cell carcinoma (OSCC). It is reported that HPV-positive OSCC show better response to radiochemotherapy (RCT) than HPV-negative OSCC. Our patients are primarily treated with surgery. Definitive RCT is therefore solely used for advanced inoperable tumor stages. The influence of HPV status on survival in this subgroup of patients was studied.

Patients and Methods

We included patients with inoperable OSCC treated with RCT at our institution. The patients received either 69.2Gy with concomitant boost (ccb) technique or 70Gy conventionally fractionated (cf). Concurrent chemotherapy was administered weekly (paclitaxel 40mg/m², carboplatin AUC1) for 6 weeks. We analyzed tumor specimens for presence of HPV-DNA. Furthermore, p16 expression was evaluated as a surrogate marker for HPV associated tumors. Overall survival and the disease-free survival rates were calculated using the Kaplan-Meier method.

Results

We included data of 60 patients with stage IV disease. 36.7 % were HPV positive and 63.3% HPV negative. 51 patients (85%) received ccb and 9 patients (15%) cf radiotherapy. Mean follow up was 22.4 months. The 3-year disease free survival was 42.9% for p16-positive patients and 13.5% for p16-negative patients (p=0.007). The 3-year overall survival was 37.3% for all patients and did not significantly differ between HPV positive and negative patients.

Conclusion

The HPV-status influences the disease free survival in patients with advanced, inoperable tumor stages. However, the overall survival in this subgroup of OSCC patients seems not to be correlated with the HPV-status. Comorbidity in this subgroup of patients with inoperable tumor stages seems to have stronger influence on overall survival than the potential prognostic impact of HPV-status.

Keywords

Radiochemotherapy, advanced head and neck cancer, inoperable, prognosis

Poster 22

Molecular variants of Human Papillomavirus Type 16 (HPV-16) and 18 (HPV-18) in Italy

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Background

The prophylactic HPV vaccine protects against HPV-16 and HPV-18, two high-risk HPV genotypes that are the cause of about 70% of cervical cancer worldwide. This vaccine has been prepared using the L1 protein since its immunodominant epitopes elicit high-titre neutralizing antibodies. Intratypic variants of L1 gene of HPV-16 and HPV-18 have been described. The present study aims to evaluate the genetic diversity of HPV-16 and HPV-18 L1 gene.

Methods

26 HPV-16 and 5 HPV-18 positive cervical samples obtained from Italian women were analyzed in their L1 coding gene sequences (HPV-16: 1,498 bp, nt. 5,603–7,101; HPV-18: 1,489 bp, nt. 5,613–7,101). Phylogenetic analysis of the amino acid sequences was conducted by Neighbor-Joining method and Amino Poisson correction model, using MEGA package (version 4.1.). A bootstrap analysis (n=1,000) was performed.

Results

Most (25/26, 96.1%) sequences belonged to the HPV-16 European prototype lineage (similarity range: 99.4–99.7%), and one to the non-European lineage (similarity: 99.6%). Eighteen amino acid variations were observed in the study sequences. Six (33%) of these mutations fell into the immunodominant loop: three in FG loop, two in DE loop, and one in BC loop. One HPV-18 sequence belonged to the HPV-18 African lineage (similarity: 99.8%) and presented the variation from valine to histidine in position 384. The other HPV-18 sequences fell into the European lineage (similarity range: 99.5–100%) and presented four mutations, one of them into FG immunodominant loop.

Conclusions

These data indicate the presence of amino acid changes in HPV-16 and HPV-18 L1 partial sequences. The biological role of these mutations is still unknown. Particular attention may be addressed to assessing whether HPV intratypic variants correlate with the clinical outcome of the disease and with clinical implications for the long-term use of an L1-virus-like particle-based prophylactic vaccine.

Keywords

HPV-16 variants, HPV-18 variants, L1 gene

Poster 23

Anal cancer incidence trends in US and UK: age-period-cohort analysis

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Background

HPV is implicated in the development of anal carcinoma. Incidence rates of anal cancer are increasing in many populations. To better understand the basis to these trends, we analysed incidence trends in US and UK populations using age-period-cohort (APC) models.

Methods

Using the Surveillance Epidemiology and End Results (SEER: whites, 1973 to 2006) and the Office of National Statistics (ONS; 1971 to 2007) registries, we estimated world standardized incidence rates (SIRs) using direct methods; constructed separately period and birth cohort descriptive curves; and examined combined effects of age, period and cohort using iterative reweighted least squares regression modelling with unconstrained internal estimation methods (IEM).

Results

In total 26,494 (SEER: 8,970; ONS: 17,524) cases were recorded. Incidence rates increased three-fold in both the US and UK registries. By 2006, rates were higher in the US for men compared with women [standardized incidence rate (SIR) = 1.65 (95% CI: 1.45, 1.85) v 1.45 (1.27, 1.63)], but higher among women in the UK [SIR = 0.74 (0.65, 0.83) v 0.94 (0.85, 1.04)]. The APC analysis revealed a significant period effect ($P < 0.0001$) for US and UK population in both genders, but differences in cohort effects. Specifically, for the US population, there was a bimodal birth cohort effect with increases in effect after the birth year 1945, particularly for men.

Conclusions

APC modelling of anal cancer rates for the US and UK revealed common period effects since the early 1970s consistent with a common environment influence, such as increasing HPV or HIV prevalence. There were contrasting patterns in birth cohort effects generating hypotheses that modes of HPV transmission and/or processes of anal cancer development differ between populations, implying that screening and early detection programmes need to be population-specific.

Keywords

Incidence of anal cancer, Time trends, Birth cohort, Age effect

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