



THE LANCET Conferences
HPV and Cancer



November 12-13, 2010 | Amsterdam

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Welcome Message

Dear Colleague,

On behalf of *The Lancet Oncology*, I would like to welcome you to *The Lancet Conference on HPV and Cancer*. Together with an internationally renowned Scientific Committee, I have worked to put together an exciting and focused conference programme, which will bring together regional and international experts in the field of HPV and Cancer.

HPV accounts for 5% of the total global cancer burden. HPV-associated cancers include those of the cervix, vagina, vulva, anus, and oropharynx. Although the link between HPV and both cervical and non-cervical cancers has been sufficiently proven, there are many unanswered questions and challenges surrounding HPV testing, HPV vaccination, and the management of HPV-associated cancers.

The aim of this conference is to provide an opportunity for regional and international leaders from the oncology community to address the growing public-health issues associated with HPV and cancer and for delegates to debate the critical issues with thought leaders at the highest level.

I would like to express my gratitude to the entire international faculty who have travelled far to participate and bring their expertise to this meeting.

I look forward to welcoming you to what I hope will be an interactive, provocative, and productive meeting in Amsterdam.

A handwritten signature in black ink that reads "E. Grainger".

Dr Emma Grainger

Deputy Editor, *The Lancet Oncology*

Cover Photo Credit: Dr Linda Stannard, UCT/Science Photo Library.



Friday, November 12, 2010

07:30–08:30	Workshop on clinical trial design	John A 'Drew' Ridge
08:50–09:00	Welcome	Jim Bonner
9:00–09:50	Opening keynote lecture	Moderator: Jim Bonner
	HPV-associated cancers on the rise, a growing problem?	Margaret Stanley
09:50–10:20	Coffee break	
10:20–12:00	Joint session	Moderator: Margaret Stanley
	HPV vaccines: current issues in HPV-associated cancers	
10:20	Cervical cancer screening following prophylactic HPV vaccination	Jack Cuzick
10:45	Vaccination for boys: the paediatrician's perspective	Hal Jenson
11:10	Community-randomised phase 4 HPV vaccination effectiveness trial: baseline characteristics and trial deliverables	Matti Lehtinen
11:35	Vaccine development in the developing world	John Sellors
12:00	Session ends	
12:00–13:30	Lunch break	
12:00–12:45	SPONSORED SYMPOSIUM	
	Understanding HPV diseases as preventable: the synergy between basic and human sciences	
13:30–15:10	Parallel session	Moderator: Chris Meijer
	Risk assessment and treatment in cervical cancer	
13:30	Management of women with screen-detected HPV	Guglielmo Ronco
13:55	Risk of high-grade CIN in women with HPV infection: role of persistence and genotyping	Nicolas Wentzensen
14:20	Organisation of HPV-based screening	Ahti Anttila
14:45	Age issues in HPV screening	Guglielmo Ronco
15:10	Session ends	
13:30–15:10	Parallel session	Moderator: Maura Gillison
	New agents in head and neck cancer	
13:30	HPV and incidence trends for head and neck cancer	Anil Chaturvedi
13:55	The new era of targeted agents in head and neck cancer	Jim Bonner
14:20	Side effects of the new targeted agents in head and neck cancer	Jean Pierre Armand
14:45	Critical assessment of the role of chemotherapy, surgery, and radiation therapy in HPV-related oropharyngeal cancer and future clinical trials	Marshall Posner
15:10	Session ends	
15:10–15:40	Tea break	
15:40–17:20	Joint session	Moderator: Marshall Posner
	Clinical trial design in relation to HPV-associated disease	
15:40	HPV and clinical trial design for head and neck cancer	Maura Gillison
16:05	The importance of window of opportunity studies	Amanda Psyrri
16:30	Long-term efficacy of HPV vaccination against hard end-points: Cancer registry based follow-up of phase III efficacy trials	Jorma Paavonen
16:55	Ecological competition of vaccine-type and non-vaccine-type HPVs before and after mass vaccination	Matti Lehtinen
17:20	Session ends	
17:20	End of day	

Saturday, November 13, 2010

9:00–10:40	Parallel session	Moderator: Jorma Paavonen
	HPV testing, translational research, and the clinic	
09:00	HPV testing in the developing world	John Sellors
09:25	Use of biomarkers in HPV screening programmes	Nicolas Wentzensen
09:50	Is HPV prognostic, predictive, or both?	Lisa Licitra
10:15	Therapeutic HPV vaccines	Cornelia Trimble
10:40	Session ends	
9:00–10:40	Parallel session	Moderator: Jens Overgaard
	Management of mouth and oral-pharyngeal cancers in relation to HPV	
09:00	Prevalence, natural history, and transmission of oral HPV in relation to oropharyngeal cancer	Gypsyamber Dsouza
09:25	HPV-specific genetic markers in HPV-associated head and neck and cervical cancers	Peter Snijders
09:50	Neck dissection in the surgical management of oropharyngeal cancer: controversies and outstanding questions	Ian Martin
10:15	Evolving treatment paradigms in the management of oropharyngeal cancer	Maura Gillison
10:40	Session ends	
10:40–11:10	Coffee break	
11:10–12:25	Joint session	Moderator: Joel Palefsky
	Genetics, environment, and lifestyle factors	
11:10	HPV infection in pregnancy: issues in relation to prophylactic and therapeutic strategies	Jorma Paavonen
11:35	Co-morbidity and smoking behaviour in HPV positive and negative HNSCC patients in relation to outcome	Jens Overgaard
12:00	Race and ethnicity in HPV-related oropharyngeal cancer	Kevin Cullen
12:25	Session ends	
12:25–14:00	Lunch break	
14:00–15:15	Parallel session	Moderator: Guglielmo Ronco
	Penile and anal cancers: biology and current management	
14:00	Prevention and treatment approaches to AIN and anal cancer	Joel Palefsky
14:25	Prophylactic vaccines for anogenital cancer	Margaret Stanley
14:50	Circumcision for prevention of anogenital and oral cancers?	Tim Oliver
15:15	Session ends	
14:00–15:15	Parallel session	Moderator: Jean Pierre Armand
	Radiation in HPV-infected head and neck and oral-pharyngeal cancers	
14:00	Radiation in HPV-infected head and neck and oral pharyngeal cancers	Pernille Lassen
14:25	Rationale for radiation dose reduction in HPV-related oropharyngeal cancer	Marshall Posner
14:50	Hypoxia, HPV, and radiotherapy: interactions and implications for outcome	Jens Overgaard
15:15	Session ends	
15:20–16:10	Closing keynote lecture	Moderator: Jim Bonner
	HPV infection in the HIV-positive host: molecular interactions and clinical implications	Joel Palefsky
16:10–16:20	Closing remarks	Jim Bonner

Programme is correct at time of publication

Faculty



Ahti Anttila

Finnish Cancer Registry, Helsinki, Finland

Ahti Anttila serves as a cancer epidemiologist and is the Director of Research of the Mass Screening Registry of the Finnish Cancer Registry, Helsinki. He is also an adjunct professor in epidemiology at the School of Public Health, University of Tampere, Tampere, Finland. His research activities involve environmental and occupational risk factors and prevention of cancer, and evaluation of cancer screening programmes. Dr Anttila is an editor of the current second edition of the EU Guidelines for Quality Assurance in Cervical Cancer Screening and an editor of the supplements to the guidelines on HPV testing and HPV vaccination, currently being developed in a project coordinated by the International Agency for Research on Cancer.

Conflicts of interest

Dr Anttila has disclosed no significant conflicts of interest.



Jean-Pierre Armand

Institut Claudius Regaud, Toulouse, France

Jean-Pierre Armand, certified in medical oncology, is General Director of the Institut Claudius Regaud, Toulouse. Dr Armand is presently in charge of the construction of a new cancer centre in a European research hub created on the Toulouse cancer campus. He is an active member of the medical oncology community. Previously Head of Early Clinical New Drugs Programs and Medical Director of Research and Development at the Institut Gustave-Roussy, Villejuif, Dr Armand has been involved in phase I-II and phase III studies for the treatment of solid tumours. Dr Armand is active in the European Organization of Research and Treatment of Cancer (EORTC) and was past chairman of the EORTC protocol review committee. At the EMEA French Agency (AFSSAPS) he is the representative of oncology at the AMM Commission, in charge of the approval of anticancer agents. Dr Armand has also held the following positions: President of the European Society for Medical Oncology (ESMO); Medical Director of the Federation of European Cancer Societies (FECS); and President of the French Cancer Society (SFC). He is also a member of the international boards of the American Association for Cancer Research (AACR), the scientific committee of the American Society of Clinical Oncology (ASCO) and AACR, the board for clinical trials at Institut National du Cancer (INCa), and is chairman of the president nominating committee of ESMO. He has coauthored more than 300 medical and scientific publications and is a member of the editorial boards of *Annals of Oncology*, the *European Journal of Cancer*, *Journal of Clinical Oncology*, *Investigational New Drugs*, *Anticancer Research*, and *Clinical Cancer Research*. In 2008, he received the Esmo Award for 'European oncologist of the year'.

Conflicts of interest

Dr Armand has disclosed no significant conflicts of interest.



James A Bonner

University of Alabama at Birmingham, Birmingham, Alabama

James A Bonner is the Merle M Salter Professor and Chairman for the Department of Radiation Oncology at the University of Alabama, Birmingham School of Medicine, Birmingham, Alabama. Dr Bonner is affiliated with University of Alabama Hospitals, and the Veterans Administration Hospital. He graduated summa cum laude in chemistry from Duke University, Durham, North Carolina, and received his medical degree from Wayne State University, Detroit, Michigan. He completed his radiation oncology training at the University of Michigan Hospital, Ann Arbor, Michigan. Subsequently, he completed a research fellowship in the Division of Radiation Oncology, Mayo Clinic, Rochester, Minnesota. Dr Bonner was a faculty member at the Mayo Clinic for 8 years prior to moving to the University of Alabama at Birmingham (UAB). While at the Mayo Clinic, the Mayo Fellows Association named him Teacher of the Year in Radiation Oncology in 1994 and 1996, and he was Co-Chair of the Lung Cancer Program of the Mayo-North Central Cancer Treatment Group (NCCTG) from 1994 to 1998. At UAB, he has co-chaired the Experimental Therapeutics section in the cancer center since 1998. Dr. Bonner has had a long research interest in methods of enhancing radiosensitisation, such as combinations of chemotherapy or targeted therapy with radiotherapy. His current laboratory interests are directed at the development of single chain antibodies that target the epidermal growth factor receptor and can be delivered in a gene therapy approach. He has been the principal investigator of several clinical protocols and has published more than 250 manuscripts or abstracts. He is a diplomate of the American Board of Radiology and the National Board of Medical Examiners.

Conflicts of interest

Dr Bonner has made the following disclosure:
Occasional consulting and honorarium: Bristol-Myers Squibb;
ImClone Systems; Oncolytics



Anil Chaturvedi

National Cancer Institute, USA

Dr Chaturvedi is an investigator in the infections and immunoepidemiology branch of the division of cancer epidemiology and genetics, at the National Cancer Institute. He received his MPH and PhD in epidemiology from Tulane University. Dr Chaturvedi's research focuses on the role of infections and inflammation as a cause of head and neck cancer and lung cancer. His current research on head and neck cancer includes the aetiology and population-level epidemiology of HPV-associated head and neck cancers.

Conflicts of interest

Dr Chaturvedi has declared no significant conflicts of interest.



Kevin J Cullen

University of Maryland Marlene and Stewart Greenebaum Cancer Center, USA

Kevin J Cullen is Director of the University of Maryland Marlene and Stewart Greenebaum Cancer Center. Dr Cullen, who specialises in head and neck cancer, is a professor of medicine at the University of Maryland School of Medicine and is head of its programme in oncology. He came to the University of Maryland in January, 2004. A graduate of Dartmouth College and Harvard Medical School, Dr Cullen completed his internship and residency at Beth Israel Hospital in Boston and received additional training at the National Cancer Institute. He served as interim director of the Lombardi Cancer Center at Georgetown University from October, 2000, to September, 2002, and was professor of medicine, oncology, and otolaryngology at Georgetown University School of Medicine. In 2008, the University of Maryland Greenebaum Cancer Center received NCI Cancer Centre designation. In the same year it was named one of the top 50 cancer centres in America by *US News and World Report*.

Conflicts of interest

Dr Cullen has made the following disclosure:
Research supported in part by a grant from Sanofi Aventis.



Jack Cuzick

Cancer Research UK, London, UK

Jack Cuzick is head of the Centre for Epidemiology, Mathematics and Statistics at Cancer Research UK in London. He is also John Snow professor of epidemiology at Wolfson Institute of Preventive Medicine at Queen Mary, University of London. He holds a PhD in mathematics and has previously worked at Oxford University and Columbia University, New York. His current interests are in cancer epidemiology and clinical trials, with special interest in prevention and screening. He is currently chairman of the International Breast Cancer Intervention Study (IBIS) steering group, the independent statistician for the ATAC trial and is also involved in studies on the use of HPV assays for cervical screening, the use of flexible sigmoidoscopy for colorectal cancer screening, and markers for the behaviour of early prostate cancer. He is the statistician for several major breast cancer trials and maintains an active interest in developing new statistical methodology, especially in the area of adjustments for non-compliance and cross-over, and multi-arm clinical trials. He is currently the president of the International Society of Cancer Prevention and is a fellow of the Academy of Medical Sciences, the Royal Statistical Society, and the Institute of Mathematical Statistics. In 2007, he was chosen by Thompson Scientific as one of the twelve hottest researchers in all of science. He is the author of more than 400 peer-reviewed papers and has published in all the major medical journals.

Conflicts of interest

Dr Cuzick has made the following disclosure:
Advisory boards: HPV vaccine – Merck, GSK; HPV screening – Qiagen, GenProbe, Roche, Abbott.



Gypsyamber D'Souza

Johns Hopkins Bloomberg School of Public Health, USA

Dr D'Souza is an epidemiologist whose research focuses on infectious causes of cancer, primarily human papillomavirus (HPV) infection. She received her PhD in epidemiology from Johns Hopkins in 2006. Additionally, Dr D'Souza has a Master of Science in molecular and cellular biology from the University of Wisconsin-Madison (1999) and a Masters of Public Health in disease control from the University of Texas-Houston (2002). Dr D'Souza is currently an Assistant Professor at the Johns Hopkins Bloomberg School of Public Health. Dr D'Souza's research includes evaluation of etiological heterogeneity among patients with head and neck cancer and the causal role of HPV in these cancers. Current research evaluates the natural history of oral HPV, transmission between partners, risk factors for persistent infection, and the effects of HIV-related immunosuppression on infection. Dr D'Souza also studies anogenital HPV natural history and cofactors, the benefits of anal Pap testing in high-risk men, and cervical Pap testing among HIV-infected women.

Conflicts of Interest

Dr D'Souza has made the following disclosure:
Received research support from and is a member of a scientific advisory board for Merck Inc.



Maura Gillison

Johns Hopkins Medical Institutions, USA

Maura Gillison is a head and neck medical oncologist and molecular epidemiologist recruited at Johns Hopkins. Dr Gillison has made significant research contributions to the fields of tumour virology, cancer biology, and epidemiology, and was the first to make the association between HPV and oral cancer. In 2009, Dr Gillison presented data at ASCO 2009 showing that HPV is the most important predictor of clinical response to tumour therapy status and prognosis for patients with head and neck cancers. As a result of these data, the National Cancer Institute has recommended that all clinical trials involving head and neck cancer be stratified by tumour HPV status. Dr Gillison has published extensively in journals such as *The New England Journal of Medicine*, *Journal of The National Cancer Institute*, and the *Journal of Clinical Oncology*. Dr Gillison is NCI R01 and R21 funded and holds the newly created Jeg Coughlin Chair for Cancer Research in the OSUCCC.

Conflicts of interest

Dr Gillison has disclosed no conflicts of interest.



Hal B Jenson

Tufts University School of Medicine, USA

Dr Jenson specialises in clinical infectious diseases and virology. He has an MD from George Washington University School of Medicine and completed a paediatric residency at Rainbow Babies and Children's Hospital at Case Western Reserve University in Cleveland, Ohio, and a fellowship in paediatric infectious diseases at Yale University School of Medicine. He was a visiting fellow in molecular biology in 1984 at the Ludwig Institute for Cancer Research in Cambridge, UK. In 2003, he graduated with an MBA from the University of Texas at Austin. Dr Jenson has been Professor of Pediatrics and Microbiology and Chief of Pediatric Infectious Diseases at the University of Texas Health Science Center at San Antonio, Texas; Professor and Chair of the Department of Pediatrics and Director of the Center for Pediatric Research at Eastern Virginia Medical School and Children's Hospital of The King's Daughters in Norfolk, Virginia; and is currently Chief Academic Officer at Baystate Medical Center, and Professor of Pediatrics and Dean of the Western Campus of Tufts University School of Medicine. Dr Jenson is active in education and clinical activities in paediatric infectious diseases. His research focused on the molecular biology and clinical aspects of infections, especially Epstein-Barr virus and human herpesvirus type 8 and their associated cancers. He has authored more than 250 papers, commentaries, and book chapters, and is an associate editor of *Infectious Disease Alert* and an editor of *Nelson Textbook of Pediatrics*.

Conflicts of Interest

Dr Jenson has declared no significant conflicts of interest.



Pernille Lassen

Aarhus University Hospital, Denmark

Dr Lassen has an MD from University of Copenhagen Denmark, and is currently doing her specialist training in radiation oncology and medical oncology in the department of oncology at Aarhus University Hospital Denmark. Dr Lassen's research focus is how HPV might affect the outcome for patients with head and neck cancer treated with primary radiotherapy and, moreover, to what extent response to the specific radiobiological modifications of radiotherapy might depend on the HPV-status of the tumours. She is expected to receive her PhD in that research field by June, 2010.

Conflicts of interest

Dr Lassen has declared no conflicts of interest.



Matti Lehtinen

University of Tampere School of Public Health and National Institute for Health & Welfare, Finland

Matti Lehtinen is a professor of public health at the University of Tampere School of Public Health, and a research professor at the National Institute for Health and Welfare, Finland. He received his MD in 1983 and PhD in 1985 from the University of Tampere, where he also received professorship qualifications in virology (1991) and epidemiology (2004). He also received awards for best group teacher, best PhD thesis, and assistant professor of the year. In 1994, Dr Lehtinen founded the Nordic Biological Specimen Banks on Cancer Causes and Control (NBSBCCC). He is currently the primary investigator for phase III-IV trials in 60 000 adolescents on safety, efficacy, and effectiveness of human papillomavirus (HPV) vaccination, and a *C. trachomatis*/HPV screening trial in 120 000 adolescents. Dr Lehtinen has been a member of the editorial boards of the *Open Vaccine Journal*, *Sexually Transmitted Infections* and *Journal of Clinical Virology*. He has published more than 200 original articles and reviews in international peer-reviewed scientific journals and has written or contributed to over 30 text books.

Conflicts of interest

Dr Lehtinen has received grants for his HPV vaccination studies from Merck & Co. Inc., and GSK Biologicals through his employers.



Lisa Licitra

Istituto Nazionale Tumori, Milan, Italy

Lisa Licitra is a medical oncologist, with special expertise in the treatment of head and neck cancers. She is currently assistant physician in charge of the head and neck cancer medical oncology unit at the Istituto Nazionale Tumori in Milan, Italy. Dr Licitra is a free-contract professor at the State University of Milan; a member of the clinical editorial board of the *Journal of Clinical Oncology*; Editor of *State of the Art Oncology Europe (START)*, a project of the Alleanza Contro il Cancro, Ministry of Health, Italy; a reviewer of the PDQ Summaries on head and neck cancers; a board member of the European Organization for the Research and Treatment of Cancer (EORTC); and elected chair of the Head and Neck Cancer Cooperative Group of EORTC. She is also co-founder and member of the Italian Group for the Evaluation of Outcomes in Oncology (IGEO), a member of the educational committee of the European Society for Medical Oncology (ESMO), chair of the Head and Neck Faculty of ESMO, co-founder and member of the European Head and Neck Cancer Society, a member of the American Society for Clinical Oncology (ASCO), a member of the Italian Association for Medical Oncology (AIOM), and honorary member of the European Society for Therapeutic Radiology and Oncology (ESTRO). Her main fields of interest are head and neck neoplasms, evidence-based medicine, clinical methodology in oncology, and quality of life. Dr Licitra has written five book chapters and approximately 70 scientific articles.

Conflicts of interest

Dr Licitra has made the following disclosure:
Consultant/advisor: BMS, Glaxo, Lilly, Merck-Serono, Amgen
Research funding: Eisai, Exelixis, Lilly, Merck-Serono, Amgen
Travel expenses to attend medical meetings: Merck Serono.



Ian C Martin

National Confidential Enquiry into Patient Outcome and Death, London, UK

Ian C Martin is a consultant maxillofacial surgeon and the clinical director of head and neck surgery in Sunderland. His main clinical interest is the surgical management of head and neck cancer, including microvascular reconstruction. He is chairman of the British Association of Oral and Maxillofacial Surgeons, president elect of the British Association of Head and Neck Oncologists and clinical coordinator for surgery at the National Confidential Enquiry into Patient Outcome and Death. He is vice president of the Federation of Specialist Surgical Associations and an invited member of Council of the Royal College of Surgeons of England. He also has a medico-legal interest and a degree in law, and is president elect of the North of England Medico-Legal Society. In his spare time Ian is an enthusiastic aviator, and a flying instructor in Newcastle.

Conflicts of interest

Mr Ian Martin has declared no conflicts of interest.



Tim Oliver

Barts and The London Medical School, Queen Mary University of London, UK

Professor Tim (RTD) Oliver gained his medical degree in 1966 from Cambridge University, did his research degree with Professor Hilliard Festenstein and Jean Dausset on the biology of histocompatibility antigens in transplantation and disease, and was Professor in Medical Oncology at St Barts and The London Medical School QMUL. He published over 500 papers on immunotherapy and chemotherapy of Urological and Genital cancer. Since 1995, Professor Oliver has focused on treatment of early cancer of the prostate and testis as well as trials minimising toxic effects of treatment. He retired from the NHS in 2006, but continues to follow up patients recruited to his research trials and pursue his interests in prevention of cancer though his current position as Professor Emeritus within the medical school working with the departments of general practice and sports medicine involved in dissecting the differential health benefits of exercise and sunshine in cancer prevention.

Conflicts of interest

Professor Oliver has declared no significant conflicts of interest.



Jorma Paavonen

University Hospital, Helsinki, Finland

Jorma Paavonen is a professor of obstetrics and gynaecology at the University of Helsinki, and is the physician-in-chief for the department of obstetrics and gynaecology at University Hospital, Helsinki, Finland. Professor Paavonen's research programmes focus on sexually transmitted diseases (particularly chlamydial and HPV infections), prevention of preterm birth, HPV vaccination, levonorgestrel-releasing hormone system (LNG-IUS) in the treatment of menorrhagia, vulvar pain syndrome, abnormal placentation, and others. Major activities include undergraduate and postgraduate teaching and clinical work, both as an obstetrician and a consultant gynaecologist. He is currently the principal investigator for the Women's Health research programme and the principal investigator of the global phase 3 and phase 4 HPV vaccination efficacy trials. He is also a member of the Board of the Biomedicum Helsinki Research Institute. Since 1978, Prof Paavonen has authored more than 400 scientific articles published in peer-reviewed journals (H-Index 48). His most recent major publications are on HPV vaccination, Chlamydia-associated infertility, preterm delivery, and placental abruption. He is or has been the associate editor or editorial board member of *Sexually Transmitted Diseases*, *Sexually Transmitted Infections*, *Infectious Diseases in Obstetrics and Gynecology*, and *International Journal of STD & AIDS*.

Conflicts of interest

Professor Paavonen has made the following disclosure:
Receipt of funding from Merck Co. and GlaxoSmithKline Co. through the Helsinki University Hospital Research Institute to conduct trials on HPV vaccines.



Joel Palefsky

UCSF School of Medicine, USA

Dr Palefsky is a professor of medicine at the UCSF School of Medicine. He completed his undergraduate medical training and training in internal medicine at McGill University and completed his fellowship in infectious diseases at Stanford University. Dr Palefsky is an internationally recognised expert on the molecular biology, treatment, pathogenesis, and natural history of anogenital HPV infections, particularly in the setting of HIV infection. He is the director of the world's first clinic devoted to prevention of anal cancer—the Anal Neoplasia Clinic at the UCSF Cancer Center. He has pioneered diagnostic and treatment methods for anal intraepithelial neoplasia (AIN) and has been an advocate for screening and treatment of AIN in high-risk populations to prevent anal cancer. He is the chair of the HPV Working Group of the AIDS Malignancy Consortium. He is co-chair of the Special Populations Committee for and member of the board of the American Society for Colposcopy and Cervical Pathology. He is the author of more than 200 publications.

Conflicts of interest

Dr Palefsky has made the following disclosure:
Research support and advisory board member: Merck and Co.



Marshall Posner

The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA

Dr Posner is a professor of medicine and the director of the human monoclonal antibody laboratory in the department of cell and gene therapy at Mount Sinai School of Medicine. He is also the medical director of the clinical trials office for the Tisch Cancer Institute in New York. He is a current or past member of the editorial boards of the *Journal of Clinical Oncology*, *American Journal of Clinical Oncology*, *Oral Oncology*, *The Oncologist*, the *Annals of Oncology*, and *Head and Neck*, and he serves as an ad hoc reviewer for *The New England Journal of Medicine*, *Cancer*, *Journal of Immunology*, *Clinical Cancer Research*, *Cancer Research*, *British Journal of Cancer*, and *Oncology*. Dr Posner has been a member of several NIH Health review committees. He has published more than 180 peer-reviewed laboratory and clinical studies and multiple reviews and has been the principal investigator on numerous clinical and translational research trials in head and neck cancer. Dr Posner has reported on antibody based immunotherapy in pemphigus and HIV, and adoptive immunotherapy in nasopharynx cancer. He holds patents for Human Monoclonal Antibodies to viral and bacterial antigens.

Conflicts of interest

Dr Posner has made the following financial disclosures with pharmaceutical firms and oncology agencies for the past 12 months:
Honoraria: Sanofi Aventis, Merck
Clinical research support (no salary): Abraxis, Sanofi Aventis, Astra Zeneca, Bristol Myers Squibb, Amgen, NCI, NIAID, Imclone, Novartis, Actogenix
Consultant: Amgen, Glaxo-Smith-Kline, NCI, BMS, Sanofi Aventis, Oxigene, Imclone, Onc-Q-Ity, Biovex, Novartis, Merck, EMD Serono,
Member: ASCO, AACR, ASH, AAI, NCCN, RTOG, ESMO
Stock: None
Significant income from above: None
Financial relationship: None



Amanda Psyrri

University of Athens, Greece

Dr Amanda Psyrri is an assistant professor of medicine at the University of Athens in Greece, and an attending physician at Attikon University Hospital. She gained her medical degree from the University of Patras, Greece, and completed her medical oncology training at Yale University in 2002. She joined the faculty of medicine at Yale University as an assistant professor in 2003. She is Translational Research Chair of the European Organization for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Group and an Associate Editor of the *Annals of Oncology*. Her research interests include the molecular mechanisms of human papillomavirus-associated head and neck carcinogenesis and molecular epidemiology of head and neck cancers. Dr Psyrri is also mentor and educator for a large number of trainees.



John Andrew Ridge

Fox Chase Cancer Center, Pennsylvania, USA

John Andrew 'Drew' Ridge is Past-President of the American Head and Neck Society. At Fox Chase he is chief of the head and neck surgery section, a professor of surgery and developmental therapeutics, and a senior member in the department of surgical oncology. With PhD thesis work in structural biology and an extensive background in clinical research and trial design, he co-directs the Head and Neck Keystone Programme with Erica Golemis and Barbara Burtneis. He has been a member of numerous federal advisory groups, including NCI programme project grant review panels, special emphasis panels for the National Institute of Dental and Craniofacial Research, the NIH/NCI Institutional Review Group SPORE committee, and head and neck cancer 'think tanks' for the NCI and NIDCR. Ridge has also been a member of several CTEP committees (including Common Data Elements and Surgical Effects). A former ECOG Head and Neck Committee co-chair, he currently serves as co-chair of the Previously Untreated, Locally Advanced Task Force of the NCI Head and Neck Steering Committee. A member of many professional organisations, he has authored more than 100 peer-reviewed articles and book chapters.

Conflicts of interest

Dr Ridge has disclosed no significant conflicts of interest.



Guglielmo Ronco

Centre for Cancer Prevention, Turin, Italy

Dr Guglielmo Ronco, an epidemiologist, is responsible for the unit for cervical cancer screening at the Centre for Cancer Prevention in Turin, Italy, where he has worked since 1987. From 1990, his main interest has been in screening for cervical cancer. He has undertaken surveys for the evaluation of cervical screening at the national and European level and has participated in the preparation of national and international guidelines for cervical cancer screening. Dr Ronco has also studied new methods for cervical screening and related fields. In particular, he is the principal investigator of the NTCC study, a large (about 100 000 women enrolled), multicentre, randomised trial for the evaluation of new technologies as primary tests for cervical cancer screening—these include testing for HPV DNA, liquid-based cytology, and biomarkers for improving the specificity of HPV testing.

Conflicts of interest

Dr Ronco has made the following disclosure:
Participation in internal Scientific Advisory Board (March 2008):
Gen-Probe (San Diego, CA, USA).



John W Sellors

McMaster University, Canada

John is a clinical epidemiologist and Clinical Professor of Family Medicine at McMaster University after serving for 8 years as Senior Medical Advisor of the Reproductive Health Program at PATH in Seattle. At PATH he led a public-private partnership project with funding from the Bill & Melinda Gates Foundation and private industry to research and develop new cervical cancer screening tests that are affordable, rapid, and appropriate for public-health programmes in low resource regions. As a result, two new molecular tests, one for HPV DNA and another for E6 oncoprotein, are promising. Projects with the Alliance for Cervical Cancer Prevention and with the HPV Vaccine project at PATH have provided him with an understanding of strategies to prevent cervical cancer. He is an advisor to projects on HPV vaccination in Canada and female genital schistosomiasis in Africa and a member of the board of Grounds for Health, a non-profit organisation working to prevent cervical cancer among coffee plantation workers.

Conflicts of interest

Professor Sellors has disclosed no conflicts of interest.



Peter J F Snijders

VU University Medical Center, Amsterdam

Peter Snijders is a professor of molecular pathology and head of the molecular pathology unit in the department of pathology at VU University Medical Center, Amsterdam. Since 1988, he has worked on HPV-related topics. He was involved in the development of the HPV GP5+/6+ consensus PCR method and was among the first to establish a plausible etiological role of mucosal HPV in tonsillar cancer. He is currently using both in-vitro models and clinically well-defined patient material to investigate HPV-induced oncogenic progression, in particular the identification and characterisation of genes involved in this process and candidate markers for risk assessment. He is also undertaking clinical trials to test viral and host markers for their capability to assess the risk of cervical cancer and identify high-grade precursor stages during screening. He is (co)author of more than 200 international, peer-reviewed articles in his area of expertise.

Conflicts of interest

Professor Snijders has made the following declaration:
Work is funded in part by the Dutch Cancer Society (NKB) and the Netherlands Organization for Health and Development (ZonMW). He provided occasional consultation to companies involved in HPV diagnostics. He has a relationship with Self-screen.



Margaret Stanley

University of Cambridge, Cambridge, UK

Professor Stanley is Professor of Epithelial Biology in the University of Cambridge. She attended the Universities of London, Bristol, and Adelaide, is a Fellow of the Academy of Medical Sciences and Honorary Fellow of the Royal College of Obstetricians and Gynaecologists. She has served on several research council committees and was a member of the Biology and Biotechnology Science Research Council from 2000 to 2003. She is currently a member of the Spongiform Encephalopathies Advisory Committee that advises the UK government on prion diseases, and in 2004 was awarded the OBE for services to Virology. Her current research focuses on mechanisms of host defence and the development of vaccines and immunotherapies against human papillomaviruses, the cause of cervix cancer. She has published extensively and is at present on the editorial board of *Sexually Transmitted Infections*, *Journal of Clinical Virology*, and *Reviews in Medical Virology*. She is a council member of the International Papillomavirus Society.

Conflicts of interest

Professor Stanley has made the following disclosure:

Consultant/SAB member: Merck Corp, New Jersey, USA; SPMSD, Lyon, France. Consultant/Phase IV Steering Group Member: GSK Biologicals, Rixensart, Belgium.



Cornelia L Trimble

Center for Cervical Disease, Johns Hopkins, Baltimore, USA

Dr Connie Liu Trimble is a translational researcher whose work focuses on immune therapies for disease caused by human papillomavirus (HPV). At Johns Hopkins, she has established a multidisciplinary programme—the Center for Cervical Dysplasia—to provide patient care and education, faculty and student mentoring, and to support translational research to improve the care of patients with HPV. In addition to the design and implementation of clinical trials to test immune-based therapies for women with preinvasive HPV disease, her lab studies the mechanisms of immune-cell recruitment, activation, and homeostasis in the genital mucosa, and mechanisms of immune evasion by HPV. She is double-boarded in both obstetrics and gynaecology and in anatomic pathology, with specialty training in gynaecological pathology.

Conflicts of interest

Dr Trimble has disclosed no conflicts of interest.



Nicolas Wentzensen

National Cancer Institute, USA

Dr Wentzensen is an investigator for the division of cancer epidemiology and genetics at the National Cancer Institute (NCI). His area of expertise is research on the etiology of gynaecological cancers and biomarker discovery, especially for cervical and ovarian cancer. Dr Wentzensen has worked on HPV-associated cancers for more than a decade and has focused on the development of biomarkers for cervical cancer screening from basic research to translation in clinical and epidemiological studies. His clinical training and his experience in running a diagnostic service laboratory for cervical cancer screening are important assets for conducting epidemiological studies with translational impact. Currently, he is the principal investigator for a large cervical cancer biomarker research and discovery effort being undertaken at NCI. He recently initiated a new study to analyse the accuracy of cervical colposcopy and biopsy in women with abnormal screening results; this is currently extended to a world-wide network of studies on colposcopy performance and harmonisation. Apart from his work on cervical cancer, Dr Wentzensen is interested in the etiological heterogeneity of ovarian cancer. Dr Wentzensen earned his MD and a PhD in applied tumour biology from the University of Heidelberg and a Master of Epidemiology from the University of Mainz. He joined the National Cancer Institute in 2007. Dr Wentzensen serves as an expert in the *Cochrane Gynaecological Cancer Review Group*, section 'Prevention of Cervical Cancer', and in the *Practice Improvement in Cervical Screening and Management (PICSM) Group* that is working on new guidelines for cervical cancer screening incorporating new molecular assays.

Conflicts of interest

Dr Wentzensen has disclosed no significant conflicts of interest.

Speaker Abstracts

HPV associated cancers on the rise —a growing problem

Margaret Stanley

University of Cambridge, Department of Pathology, Cambridge, UK

Viral infections cause at least 15% of human cancers. One of the most important oncogenic viruses is human papillomavirus (HPV); a causal agent in about 5% of all cancers. HPVs are a large group of viruses that infect both cutaneous and mucosal squamous epithelia and have an exclusively intra-epithelial infectious cycle. About 15 mucosal types are high risk or cancer-causing HPVs, with HPV type 16 and HPV type 18 the most important. Infection with one of these oncogenic HPVs can cause carcinoma of the cervix in women, which is the third most common cancer in women worldwide. Secondary intervention by screening effectively controls this disease in developed countries, but not in the developing world—which bears 86% of the cervical cancer burden. Projections of population growth indicate that without primary or secondary intervention such inequality in disease burden will increase in the coming 3 to 4 decades.

HPV-associated cancers are not confined to the cervix and HPV infection is implicated in the development of vaginal, vulval, anal, penile, and head and neck cancers. Importantly, the incidence of HPV-related cancers in these sites, particularly anal carcinomas and tonsillar carcinomas, is increasing.

Cervical-cancer screening following prophylactic human papillomavirus vaccination

Jack Cuzick

Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK

The recognition that infection with certain types of human papillomavirus (HPV) is a necessary cause of cervical cancer has opened new fronts for the prevention of this disease. Primary prevention is now possible via immunisation with highly efficacious HPV vaccines, and secondary prevention has gained impetus with the advent of sensitive HPV DNA testing to improve traditional cytology-based screening programmes. Although universal vaccination of teenagers and young women is desirable, cost remains a key obstacle. Even with high uptake, a statistically detectable reduction in the burden of cervical cancer via HPV vaccination is unlikely to be observed for at least 10–15 years. To achieve cost-effective reductions in the burden of cervical-cancer prevention, initiatives must consider screening and immunisation as integrated and organised approaches that take advantage of HPV testing as primary screening tests, followed by triage with cytology. On the basis of preliminary findings from the vaccination trials, as successive cohorts of vaccinated young women reach screening age, reduction in cervical lesions will lead to a decrease in rates of colposcopic referral to about 40–60% of the current case loads in most Western countries. These reductions are likely to translate into initial savings for the health-care system, but the vaccine-induced decrease in cervical lesions might lead to a degradation of performance characteristics of cytology because of a decreased rate of abnormalities. The positive predictive value of cytology will decline in vaccinated women because clinically relevant lesions will become less common. A decline in performance will occur because of a decrease in the signal (squamous abnormalities) to noise (inflammation and reactive atypias) ratio that will have a negative impact due to the subjective and tedious nature of reading and interpreting smears.

Another issue is whether screening algorithms can be different for vaccinated versus unvaccinated individuals; this will be particularly important where vaccine coverage is intermediate (30–70%). Knowledge of vaccine status, and registries and other mechanisms are needed if the attendant savings associated with reduced screening are to be realised.

Vaccination for boys: the paediatrician's perspective

Hal B Jenson

Tufts University School of Medicine, USA

In studies of boys and young men, the type-specific immunogenicity of quadrivalent human papillomavirus (HPV) vaccine for HPV types 6, 11, 16, and 18 is 97.4–99.9%, which is non-inferior (and for some segments, numerically superior) to the response in girls and young women. Across all groups, anti-HPV geometric mean titres peak at 7 months, decline through 24 months, and then stabilise through at least 60 months. The prophylactic efficacy of the HPV vaccine in boys and young men 16–26-years of age has been shown in several studies to prevent HPV 6, 11, 16, and 18 related external genital warts; penile, perineal, or perianal intraepithelial dysplasia grades 1, 2, or 3; and penile, perineal, and perianal cancer. Efficacy of the quadrivalent vaccine for the prevention of genital warts in young men has been shown to be 94.3% (95% CI 63.9–99.9%) in 16–20-year-old men, 85.1% (33.2–98.4%) in 21–26 year-old men, and 89.4% (69.2–98.1%) in 16–26 year-old men. Clinical efficacy of the quadrivalent vaccine in 9–15 year-old girls and boys is based on supportive immunogenicity bridging data. Cost-effectiveness analyses (cost per quality-adjusted life year) of the quadrivalent vaccine confirm less effect and less cost-effectiveness of vaccination in men compared with vaccination in women only. Vaccination of men has high efficacy for prevention of anal intraepithelial neoplasias in men who have sex with men. The quadrivalent vaccine might be given to boys and men aged 9 to 26 year of age to reduce their likelihood of acquiring genital warts, and is most effective when given before exposure to HPV through sexual contact. Paediatricians must consider vaccine types, immunogenicity, efficacy, cost effectiveness, public health effects, and impact on public acceptance in formulating recommendations for HPV vaccine for boys and young men.

Community-randomised phase 4 vaccination effectiveness trial: baseline characteristics and trial deliverables

Matti Lehtinen, Dan Apter, Jorma Paavonen

University of Tampere, Family Federation Finland, University of Helsinki, Finland

Genital infections with oncogenic human papillomaviruses (HPV) are common in both men and women. The most important disease associated with oncogenic HPV infection is cervical cancer—currently the second leading cause of cancer-related death in women worldwide—but other HPV positive anogenital cancers and tonsillar cancer occur not infrequently in women and men. A prophylactic virus-like particle based on the cervarix vaccine (GSK Biologicals, Rixensart), containing HPV16 and 18 L1 proteins, which self-assemble to form virus-like particles, formulated with the adjuvant AS04 has been shown to be highly effective in preventing cervical infections with HPV16 and 18 and associated cervical neoplasia.

Since the protection of adolescent girls before the onset of sexual activity and exposure to oncogenic HPVs is vital, the primary target group for implementation of national HPV vaccination programmes will be early adolescents. Our phase 4 study was designed as a community-randomised trial, and will enable assessment of the overall effect (direct effectiveness, indirect effectiveness, or both) of HPV immunisation in a community setting when early adolescents (12–15 years of age) are targeted for vaccination. Effectiveness will be assessed in the girls once they are 18.5 years of age, who live in communities in which both girls and boys have received HPV16 and 18 vaccination (A-arm), or in communities in which girls only have received HPV16 and 18 vaccination (B-arm) in comparison with girls who live in communities that have received only hepatitis B-vaccination (C-arm). Among unvaccinated adolescents, our trial will also assess the effectiveness of the two HPV16 and 18 vaccination strategies (girls and boys versus girls only) in arm A versus B.

Recruitment took place during three school years: 2007–08, 2008–09, and 2009–10, which resulted in equal enrolment of four birth cohorts (born 1992–95) comprising more than 32 000 (40%) early adolescents: 22 000 girls (50% per arm) and 10 000 boys (20–30% per arm) with few adverse effects.

Although men are known to play a crucial part in the transmission of oncogenic HPV to women, the effect of vaccination of early adolescent boys has so far only been estimated in modelling studies. Our community-randomised trial will assess the effect of different vaccination strategies in a randomised setting.

Vaccine development in the developing world

John Sellors

McMaster University, Canada

The most comprehensive approach to cervical cancer prevention in low-resource regions would be based on both prophylactic vaccination of girls and screening of women at about 35 years of age, since current vaccines provide protection against only about 70% of infections causing cervical cancer.

The WHO position paper on human papillomavirus (HPV) vaccines states: "WHO ...recommends that routine HPV vaccination should be included in national immunization programmes, provided that: prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost effectiveness of vaccination strategies in the country or region is considered. HPV vaccines are most efficacious in females who are naïve to vaccine-related HPV types; therefore, the primary target population should be selected based on data on the age of initiation of sexual activity and the feasibility of reaching young adolescent girls through schools, health-care facilities or community-based settings...".

Pilot projects addressing issues associated with the introduction of HPV vaccines are being done in low-resource regions of low-income and middle-income countries, including Uganda, Peru, India, and Vietnam. Cost of vaccines will influence availability in poor settings, and help from the GAVI Alliance and the Pan American Health Organization is anticipated to play a part to facilitate vaccine purchase by poor countries. Preparation for a vaccination programme should include dissemination and discussion of influential messages with girls, parents, health providers, community leaders, religious leaders, teachers, and members of the press. Access to the vaccine through the school system has given good coverage, and acceptance by girls and their families has been high.

Management of women with screen-detected human papillomavirus

Guglielmo Ronco

Centre for Cancer Prevention, Turin, Italy

Human papillomavirus (HPV) testing has a lower positive predictive value than cytology. Therefore, referring all women infected with HPV to colposcopy causes many unneeded colposcopies. The most studied approach is testing women infected with HPV for cytology and immediately referring those who show cytological abnormalities to colposcopy. The remaining women are retested after 6–18 months and referred to colposcopy only if HPV infection persists. This approach, denoted as cytological triage, is based on the knowledge that only persistent infections are relevant for carcinogenesis. From 35 years of age, the reduction of cervical intraepithelial neoplasia 3 (CIN3) in HPV-screened women versus cytology-screened women at round two was similar in randomised trials that applied cytological triage and in trials that referred all women to colposcopy, suggesting that protection against cancer is similar. Instead, the positive predictive value of HPV testing with cytological triage is similar to that of cytology, whereas with direct referral it is markedly less. Infection by HPV type 16 or type 18 has a higher risk of high-grade CIN than infection with other HPV types. Therefore immediate referral to colposcopy, independent of cytology, is suggested by some experts for women with such infections. One drawback of methods that are based on the assessment of persistence of infection is loss to follow up. Other biomarkers—such as viral load, E6 and E7 mRNA, and p16-INK4A overexpression—are under study. A study nested in a randomised trial showed that triaging women infected with HPV by a single p16-INK4A test has 50% higher sensitivity than cytology, while resulting in a similar number of colposcopies. Preliminary data also show that women aged 35 years or older who are infected with HPV, but did not express p16-INK4A, have very low probability of new CIN3.

Risk of high-grade cervical intraepithelial neoplasia in women with human papillomavirus infection—role of persistence and genotyping

Nicolas Wentzensen

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

Carcinogenic human papillomavirus (HPV) infections are the cause of almost all cervical cancers. HPV type 16 and 18 are identified in about 73% of cancers worldwide, followed by HPV type 58, 33, 45, 31, and 52. Prospective studies have shown a substantially higher risk of developing cervical intraepithelial neoplasia (CIN) grade 3 for infections with HPV type 16 and 18 than for other carcinogenic types. Although most cancers are associated with HPV infections with single carcinogenic types only, multiple HPV infections are very common in CIN and complicate HPV type attribution. In a large cross-sectional study, we reported a wide range of potential attribution of HPV type 16 to CIN3, from 25% in single infections to 75% including all women positive for HPV type 16. HPV infections are very common and most infections regress spontaneously within a few months. Only few infections persist over a long period and might develop to CIN3. Thus, testing for presence and persistence of individual genotypes could offer important additional risk stratification beyond simple high-risk HPV-DNA testing. However, implementation of these approaches into screening programmes is not trivial. Only few well-validated HPV genotyping assays are available. Testing for HPV type persistence requires women to return to follow-up testing at appropriate time intervals, and management decisions based on repeat testing require easy access to previous test results. For both HPV genotyping and testing for type persistence, the gain in risk stratification needs to be high enough to influence management so that implementation can be justified.

Organisation of human papillomavirus based screening

Ahti Anttila

Finnish Cancer Registry, Helsinki, Finland

Cytological screening for cervical cancer has been used in Western countries since the 1950s and 1960s. Substantial variation in the organisation and policy of screening exists; however, this has led to variation in the coverage, cost-effectiveness, and impact. In the EU, an organised population-based cervical screening programme has extended to about a third of the women in the potential target population; the rest are either opportunistically screened, or unscreened. About ten times variation in the cervical-cancer burden exists between these countries. Countries without any screening have generally the highest burden of cervical cancer. New methods, such as HPV screening, enable large-scale benefits and efforts are continuing in order to develop feasible, affordable, and sustainable cancer screening programmes in these settings.

Screening is a multistep process, however, and European recommendations propose solutions for the whole chain, from planning, decision-making, piloting, and gradual rollout, up to monitoring and assessment of the performance and outcome. From an organisational perspective, extensive efforts are required to introduce changes in health services within and outside the programmes, and to enable women to make informed choices.

So far, the integration of HPV tests, mainly in secondary screening, has been easier. Introduction of primary HPV screening—with the biggest benefit—is a slow process. In many countries, a transition from non-population-based activity to population-based organised cancer screening programmes is essential. This transition has started as an increasing number of countries are planning or piloting primary HPV screening.

Age issues in human papillomavirus screening

Guglielmo Ronco

Centre for Cancer Prevention, Turin, Italy

In industrialised countries human papillomavirus (HPV) prevalence peaks at about 20 years of age and subsequently decreases. An increase in clinical sensitivity and loss in specificity versus cytology is high in young people. High-grade cervical intraepithelial neoplasia (CIN) occurs very frequently at short intervals after HPV infection in young women, but its clinical relevance is not clear. A randomised trial comparing HPV-based cervical screening with cytology-based cervical screening separately studied women aged 25–34 and 35–60 years. In women aged 25–34 years, a substantial increase in the detection of CIN3 at the first screening round and decrease at the second round was recorded with HPV testing and direct referral of all HPV positives to colposcopy versus cytology. However, no significant difference between colposcopy and cytology was identified with HPV testing and cytological triage. With both strategies, HPV testing in women below the age of 35 years resulted in a three-fold increase of CIN2 detection over the first two screening rounds compared with cytology, suggesting relevant over-diagnosis of regressive CIN2 in young women with HPV testing. Unneeded treatment of regressive lesions is a problem because excisional treatment of cervical lesions is associated with increased risk of pregnancy-related morbidity. This problem is particularly relevant at young ages in view of the high probability of subsequent pregnancy. A pooled analysis of individual data from randomised trials will be useful in establishing at what age HPV screening should start. In the meantime, routine HPV-based screening should not start too early. With HPV testing there is a potential to stop screening at an earlier age than with cytology. However, to date, evidence does not seem sufficient to recommend a change.

HPV and incidence trends for head and neck cancer

Anil Chaturvedi

National Cancer Institute, USA

The causal relationship of HPV infection with a subset of head and neck cancers could be leading to substantial changes in the population-level epidemiology of head and neck cancers. In the USA, incidence rates for head and neck cancer sites without a causal relationship with HPV infection (oral cavity) have significantly declined since 1984, consistent with declining tobacco use. By contrast, incidence rates for HPV-related head and neck cancer sites (oropharynx, including tonsils and base of the tongue) have notably increased during the past two decades, particularly among young males. Analogous data of increasing incidence for HPV-related head and neck cancer sites are emerging from other parts of the world, including Australia, Canada, Denmark, Finland, Japan, the Netherlands, Sweden, and the UK. The increasing incidence for HPV-related head and neck cancer sites in recent calendar periods draws attention to increasing exposure to oral HPV infection among recent birth cohorts. Presumably, changes in oral sex behaviours among recent birth cohorts may have led to an increase in oral HPV exposure, and as a consequence, increasing incidence rates for HPV-related head and neck cancers. Consistent with this hypothesis, recent data from Sweden show a three-fold increase from the 1980s to the 2000s in the proportion of oropharynx cancers attributable to HPV infection. These observations underscore the increasing burden of HPV-related head and neck cancers worldwide, and highlight the need for targeted prevention and treatment strategies.

The new era of targeted agents in head and neck cancer

James A Bonner

University of Alabama at Birmingham, Birmingham, Alabama

Head and neck cancers are known to have high levels of epidermal growth factor receptor (EGFr) expression. Also, radiation therapy is known to cause an increase in EGFr expression. Previous studies revealed that head and neck cancer patients with high levels of EGFr did poorly, compared with those with low levels, when conventional treatments were employed. Therefore, preclinical studies were undertaken and showed radiosensitisation with the combination of anti-EGFr antibodies and radiation. The combination of an anti-EGFr antibody (cetuximab) and radiation showed promising early clinical results for patients with locoregionally advanced disease. Subsequently, a large international phase 3 study compared the combination of radiation and cetuximab with standard radiation alone for patients with locoregionally advanced head and neck squamous cell carcinoma. This study revealed that patients who received cetuximab demonstrated a locoregional control and survival benefit compared with patients treated with radiation alone. At the same time, investigators were exploring the use of cetuximab for patients with metastatic or recurrent head and neck cancer. Cetuximab was found to be an effective agent for these patients and recent studies demonstrated that cetuximab in combination with cisplatin enhanced survival compared with cisplatin alone. Over the past few years, investigators have identified a new role for induction chemotherapy in locoregionally advanced head and neck cancer. Regimens using taxanes in combination with cisplatin have demonstrated significant efficacy for these patients. Additionally, investigators have begun to use anti-EGFr therapies at the time of induction chemotherapy and during radiotherapy. Cetuximab will be reviewed as an example of targeted therapy.

Side effects of new targeted drugs in head and neck cancer

Jean-Pierre Armand

Institut Claudius Regaud, Toulouse, France

The most common head and neck cancer is head and neck squamous cell carcinoma (HNSCC), which is the sixth most common cause of cancer worldwide. The most extensively studied pathway for targeted treatment in HNSCC is the epidermal growth factor receptor (EGFR) pathway. Molecular classification is a very important research area since the traditional clinical-pathological factors do not provide accurate prognostic information. EGFR family members human epidermal growth factor receptor (HER; or ERBB1) 1–4, the vascular endothelial growth factors (VEGF) A, B, C, and D, and their receptors VEGFR 1, 2, and 3 AKT. In addition to EGFR pathway, important research efforts concentrate on the identification of other treatment targets in HNSCC. For each of these targets, new compounds—eg, monoclonal antibodies and tyrosine kinase inhibitors—have been developed, some of which are already registered for treatment of head and neck cancer—cetuximab. Others are under investigation. These new compounds have shown very different toxic effects compared with existing cytotoxic drugs—eg, cutaneous, cardiovascular, gastrointestinal, and tiredness. These systemic side effects have to be accounted for to apply such long-term chronic treatments. Combined radiotherapy has very specific local toxic effects compared with cetuximab in head and neck cancer. Reported benefits of these new compounds are largely superior to the toxic effects; oncologists should find the best way to manage this fragile balance.

Critical assessment of the role of chemotherapy, surgery, and radiotherapy in human papillomavirus-related oropharyngeal cancer and future clinical trials

Marshall Posner

The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA

Identification of human papillomavirus related oropharyngeal carcinoma (HPVOPC) as a distinct clinical entity in head and neck cancer (HNC) is a major advance. The extremes in prognosis identified through human papillomavirus (HPV) analysis of oropharyngeal carcinoma tumours in clinical trials has created an opportunity and an obligation to examine the biology and therapeutic implications of HPVOPC in past, present, and future clinical trials. Past studies of multimodality and monotherapy have been reassessed by retrospective HPV and p16 immunohistochemistry (as a surrogate for specific HPV testing) among many sites in several trials, and specifically in the populations at risk with oropharyngeal carcinoma in selected studies. Several large trials have focused on p16 immunohistochemistry in the absence of available HPV-specific data. p16 analysis is not equivalent to HPV positivity and is a heterogeneous prognostic factor. Up to 20% of p16 positive tumours are HPV negative. HPV data are retrospectively available in three large randomised trials and prospectively in a phase 2 trial; all studies have demographic data that HPVOPC patients are healthier, have a better performance status, and are less prone to secondary environmental cancers than environmentally related cancers, and that HPV positive tumours respond more completely to treatment. All trials show improved local and regional control as the main difference in outcome. Surgical resection alone also results in an improved outcome in patients with HPVOPC. Current trials and treatment algorithms must be re-examined in view of the importance of stratification or selection for HPV and p16 expression, as well as the effect of smoking behaviour on outcome of treatment for HPVOPC. Trials have been initiated to assess reductions in treatment of patients with HPVOPC. The challenge we face will be the analysis of retrospective studies—wherein surgery, chemoradiotherapy, and sequential therapy all result in very high survival outcomes—to establish the future direction of research and the current standards of care for HPVOPC. Integral to our analysis, we will want to make careful assessments of: patient-selection criteria and trial design and protocol adherence; the short-term outcomes of surgery, chemoradiotherapy, and sequential therapy; and long-term survival, patterns of failure, morbidity, mortality, and overall risk for disease and treatment-related events.

Tumour human papillomavirus status as a predictor of survival

Maura Gillison

Johns Hopkins Medical Institutions, USA

Tumour human papillomavirus (HPV) status is a strong and independent predictor of survival for patients with head and neck cancer. The relative survival for HPV-positive versus HPV-negative patients seems independent from the therapeutic approach, as long as that approach is within the current standard of care. Absolute difference in survival between HPV-positive and HPV-negative patients is consistently 30% or greater at 3–5 years for therapeutic approaches that would be considered aggressive (eg, induction followed by concurrent chemoradiation) or less aggressive (radiation alone). Although clearly a significant prognostic factor the field is struggling with the fact that we do not understand to what extent the survival benefit for the HPV-positive patient depends on the therapeutic approach. Are we exposing a young population largely expected to survive cancer to treatment-related long-term morbidity without true therapeutic benefit? What do we know about treatment response and HPV-status interactions? How should we use this information to determine the optimum treatment approach while factoring in the effect of treatment on both survival and quality of life?

The importance of 'window of opportunity' studies

Amanda Psyrrri

University of Athens, Greece

The optimal evaluation of HPV-targeted therapies requires the integration of pharmacodynamic assays into early clinical investigations. Phase '0' trials can provide a platform to investigate immune correlates of treatment failure in vaccine studies, evaluate biomarkers for drug effects, and provide pharmacokinetic data. Monitoring HPV vaccine impact on biological outcomes is a challenging task and plays an essential part in establishing the benefit of vaccination, monitoring the progress of vaccination programmes, and yielding data to inform vaccination and disease prevention policies. For this purpose, the US National Cancer Institute has transferred technology to Costa Rica, such as state-of-the-art laboratories and a biorepository to support a phase 3 clinical trial evaluating the efficacy of HPV 16/18 vaccine. Indeed, the kinetics and phenotype of induced T-cell responses have been associated with success or failure of vaccination. For example, HPV16-specific proliferative responses such as cytokine levels and HPV16-specific CD4(+)CD25(+)Foxp3(+) T cell population have been correlated with the clinical efficacy of therapeutic vaccination. Particularly, a high ratio of HPV16-specific vaccine-prompted effector T cells to HPV16-specific CD4(+)CD25(+)Foxp3(+) T cells has been shown to predict for clinical success.

To summarise, 'window of opportunity' studies could identify therapeutic failures early, and might compress timelines for development of HPV-targeted approaches. We expect that such trials will become a routine part of early-phase therapeutic vaccine development in the future.

Long-term efficacy of human papillomavirus vaccination against hard end-points: cancer-registry-based follow-up of phase 3 efficacy trials

Jorma Paavonen, Mohsin Rana, Eero Pukkala and Matti Lehtinen

University of Helsinki, University of Tampere, Finnish Cancer Registry, Helsinki, Finland

While phase 3 studies have shown that vaccination against human papillomavirus (HPV) types 16 and 18 prevents persistent HPV type 16 and 18 infections and most high-risk HPV type positive cervical intraepithelial neoplasia (CIN) grade 2+ lesions, long-term follow-up of the phase 3 cohorts is important to prove that HPV type 16 and 18 vaccination prevents cervical carcinoma in situ and invasive carcinoma.

We used data from the Finnish cancer registry for passive follow up of cluster (age cohort) and individually randomised cohorts of women born in 1984–89 to assess incidence rates of cervical carcinoma in situ and invasive carcinoma in HPV-vaccinated cohorts in the FUTURE II (Merck & Co. Inc.) (N=874) and PATRICIA (GSK Biologicals) (N=2404) trials, and a reference cohort (N=7049) from the same communities. After completion of the trials the cohorts were linked with the Finnish cancer registry using personal identifiers. A pilot study in 2009 showed that the baseline incidence of CIN3+ was 41 per 100000 women years. Assuming that incidence increases as the cohorts age, the baseline incidence yields 80% power to show 70% vaccine efficacy against cervical carcinoma in situ and invasive carcinoma in less than 10 years. Because the phase 3 trials included intensive clinical follow-up and health education, which might have modified subsequent risk of cervical neoplasia, validation of incidence rates of cervical carcinoma in situ and invasive carcinoma in the HPV vaccine cohorts and the reference cohort, not exposed to clinical intervention, will be critical. For such validation, comparison of the incidence rates in the FUTURE II and PATRICIA study participants who received placebo or control (hepatitis A) vaccine at the baseline, and received no cross-vaccination at the study end, will be made.

Initial results from cancer-registry linkage of the randomised cohorts, which produced up to 400000 women years of follow-up data for HPV vaccine cohorts and reference cohorts, will be reported.

These findings will be important to establish passive follow up for the determination of HPV-vaccine efficacy against the hard end-points.

Ecological competition of vaccine and non-vaccine type human papillomaviruses before and after mass vaccination

Matti Lehtinen, Marjo Kaasila, Marko Merikukka, Proscovia Namujju, Heljä-Marja Surcel, Johanna Palmroth, Jorma Paavonen

Universities of Tampere and Oulu; National Institute for Health & Welfare, Oulu; University of Helsinki, Finland

Replacement of multivalent vaccine covered serotypes of a microbe by non-vaccine serotypes of the same microbe is abolishing effectiveness of, for example, pneumococcal mass vaccination. To understand likelihood of type-replacement following vaccination against human papillomavirus (HPV) types 16 and 18 we studied competition of genital HPV types by assessing occurrence of multiple infections caused by the seven most common genital HPV types 6, 11, 16, 18, 31, 33, and 45 in fertile-aged Finnish women between 1995–2004. Paired first trimester serum samples, from two consecutive pregnancies (mean 2.5 years apart) were retrieved for a random 3100 subsample of 123 000 women belonging to the Finnish Maternity Cohort. 42% had antibodies to at least one HPV type at the baseline. Highly significant increases in incidence rate ratios (IRR), indicating an increased risk of seroconversion to another HPV type, were consistently noted for HPV33 in both baseline HPV16 and HPV18 antibody-positive women: HPV16 antibodies→16 and 33 antibodies (IRR 3.2, 95% CI 2.0–5.2) and HPV18 antibodies→18 and 33 antibodies (3.6, 2.1–5.9); irrespective of the presence of antibodies to other HPV types at baseline, HPV16 antibodies only→16 and 33 antibodies (2.9, 1.6–5.4) and HPV18 antibodies only→18 and 33 antibodies (2.5, 1.1–6.0), but not for the other HPV types. This suggests a competitive advantage for HPV33 over other common HPV types before the era of HPV mass vaccination.

To explore type replacement related to HPV mass vaccination using a prophylactic HPV type 16 and 18 virus-like particle vaccine (GSK Biologicals, Rixensart), with documented cross-protective efficacy against HPV types 31 and 45, we are assessing whether the IRR of non-vaccine high-risk HPV types is significantly different in the HPV type 16 and 18 vaccinated women as compared with hepatitis A-vaccine recipients. In a sizeable phase 3 trial sub-cohort of initially 4808 16–17 year-old Finnish women, the HPV type 16 and 18 vaccine coverage ranged between 1% and 20% by age cohort in the 18 study site communities. Our study is the first attempt to assess the likelihood of HPV type-replacement following HPV mass vaccination in a randomised setting.

Human papillomavirus testing in the developing world

John Sellors

McMaster University, Canada

A WHO meeting of experts concluded that the use of human papillomavirus (HPV) DNA testing for primary screening will be at least as effective as cytology, and consequently an affordable HPV screening test, which is appropriate for public health programmes in low-resource settings, should be achieved. PATH, a non-profit global health organisation has led a project to develop and then clinically assess two simple, rapid, and portable biochemical tests that are inexpensive, acceptable to women and health-care providers, safe, accurate, reliable, and appropriate for use in low-resource settings. The careHPV test (Qiagen, Gaithersburg, MD) detects oncogenic HPV DNA, and a strip test (Arbor Vita Corporation, Sunnyvale, CA) detects the E6 oncoprotein biomarker. The careHPV test performed adequately in a large clinical study. Although the strip test is still in field testing, the E6 biomarker might allow providers to differentiate between women who are only infected with HPV and those who are developing cervical neoplasia.

In developing countries, there are several challenges to widespread adoption of such molecular tests and maximizing their effect on cervical cancer. Before incorporating a test into national or regional cervical cancer prevention strategies, policy makers need evidence that this new test is feasible, cost-effective, and appropriate for their health-system infrastructure and their geographical, cultural, and economic circumstances (compared with other screening approaches). Additionally, private industry needs help navigating the complexities of product introduction to the public sector of developing countries, which is generally perceived as a high-risk, low-return market. The results of research on introduction of molecular tests in low-resource regions will be presented.

Use of biomarkers in human papillomavirus screening programmes

Nicolas Wentzensen

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

Randomised trials have shown that human papillomavirus (HPV) DNA testing can be efficiently used in primary cervical cancer screening. Several challenges need to be addressed when restructuring current cytology-based screening programmes: first, although HPV DNA testing has very good sensitivity for detection of cancers and cancer precursors, and its high negative predictive value allow extended screening intervals, it cannot discriminate between an innocuous transient infection and a prevalent high-grade lesion. A good triage strategy needs to be developed to decide which women with HPV need to undergo further assessment. Second, up to 50% of prevalent precancers might be missed using conventional colposcopy-biopsy procedures. New clinical algorithms and biomarker discovery and validation studies need to address these limitations of disease ascertainment. Third, vaccination against HPV type 16 and 18 greatly reduces the number of cancer precursors, whereas low grade abnormalities, frequently caused by other types, are less affected. As the signal-to-noise ratio is reduced, identification of new biomarkers with strong discriminatory values is important. Currently, several biomarker candidates are being investigated in clinical trials. The most widely studied markers are HPV mRNA and p16. Recently, several promising host gene-methylation markers have been proposed. Biomarker validation studies need to focus on the effect of biomarkers on risk stratification in the study population early on during the assessment process.

Is human-papillomavirus infection prognostic, predictive, or both?

Lisa Licitra

Head and Neck Medical Oncology Unit, Fondazione IRCCS Istituto nazionale dei Tumori, Via Venezian 1, Milano, Italy

HPV positivity is recognised to be a biomarker for oropharyngeal cancer. Biomarkers can be broadly classified as prognostic (associated with disease outcome) or predictive (associated with tumour response). A prognostic marker is able to separate a certain population according to the outcome of interest in the absence of treatment or despite standard non-targeted treatment. A predictive marker, on the contrary, separates a population according to outcome in response to a targeted treatment. Survival of patients with HPV-associated head and neck tumours has been analysed in a meta-analysis, which showed a low risk of dying (hazard ratio 0.85) and a low risk of recurrence (0.62) in patients with HPV-positive tumours. Different reasons of favourable survival outcome have been postulated, which include intact apoptotic machinery in response to radiation and possibly chemotherapy, absence of field-related secondary cancer, immune-system activation by viral specific tumour-associated antigens, and effects of radiotherapy or chemotherapy. In patients with HPV-positive tumours, those able to mount a serological immune response against viral E6 or E7 have improved outcomes. Improved outcome has been reported for patients undergoing primary surgery for oropharyngeal cancer. Moreover, improved outcome has been reported for most measures of outcome, including overall survival, progression-free survival, local-regional control, and second primary tumours—except for distant metastases for more than 400 patients with oropharyngeal cancer undergoing primary concomitant chemoradiation in a randomised phase 3 study, which showed that treatment intensification might be useless, especially in HPV-positive oropharyngeal tumours. Despite improved outcome, studies reported a trend towards advanced N-stage HPV-positive tumours. This finding confirmed, together with advanced T-stage HPV-positive tumours, possible effects on the risk of distant metastases. HPV-positive tumours showed a statistical improvement of response rates with chemotherapy and organ preservation data, disease-free survival, and improved survival. One study pointed out that response rate to induction chemotherapy is associated with HPV16 gene copies quantified in the single tumour. The same observation was made in p16 tumour staining, which is now recognised as an effective and reliable marker of HPV positivity in head and neck cancer. Indeed, p16 immunohistochemical expression has been strongly correlated with in-situ hybridisation and HPV-gene expression through PCR analysis.

Smoking status—categorised as never smoked, past smoker, current smoker, or by packs smoked per year—has been associated with the outcome of patients with HPV-positive oropharyngeal cancer. An inverse correlation between epidermal growth factor receptor (EGFR) expression and smoking exists, suggesting a role of the EGFR pathway in determining prognosis. Association between HPV positivity and tumour response to EGFR inhibitors has not been reported.

Therapeutic human papillomavirus vaccines

Cornelia Trimble

Center for Cervical Disease, Johns Hopkins, Baltimore, USA

Human-papillomavirus (HPV) associated intraepithelial neoplasias are lesions that should be susceptible to an HPV-specific T-cell immune response. Indeed, a substantial percentage of cervical intraepithelial neoplasias (CIN) grade 2 or 3 regress, and findings from clinical trials testing therapeutic vaccination and also topical imiquimod for vulvar intraepithelial neoplasia (VIN) show that a subset of VIN can also regress. However, immune responses to HPV antigens required for disease initiation and persistence, measured in the blood, do not reliably predict regression of intraepithelial lesions, either in unvaccinated or vaccinated cohorts. Memory T cells preferentially circulate in the tissue in which they encountered their cognate antigen. Tissue-resident T cells are antigen-experienced, are predominantly effector memory cells, and have a partially activated phenotype. Immediate challenges for development of therapeutic HPV vaccines include eliciting HPV-specific effector cell responses that are capable of trafficking to and accessing the target tissues; questions that remain to be answered include how T cells home to the genital tract and head and neck mucosae, how they are retained, how they are functionally polarised at the initial antigenic exposure, the degree of elasticity of polarisation of tissue T cells, and how lesion-mediated mechanisms of immune evasion can be identified and circumvented. Clinical trials testing immune therapies for HPV disease should incorporate the study of tissue measures of immunological parameters, and systemic measures of immune response.

Prevalence, natural history, and transmission of oral human papillomavirus in relation to oropharyngeal cancer

Gypsyamber D'Souza

Johns Hopkins Bloomberg School of Public Health, USA

Oral human papillomavirus (HPV) infection is recognised as an important cause of head and neck cancer, primarily oropharyngeal cancers. While the overall incidence of head and neck cancers has declined in the past few decades, the incidence rates for oropharyngeal cancers has increased, especially in men under the age of 60 years. Despite this risk, oral HPV infection has not been well studied, and risk factors for infection and the natural history of these infections are not well understood.

Initial studies suggest oral HPV prevalence in the general population is low (4-5%), with oral HPV type 16, responsible for 95% of HPV-associated head and neck cancers, prevalent in 1-3% of adults. Oral HPV infection is detected in 1-2% of children, supporting some non-sexual transmission. Prevalence increases with age and is higher in women with genital HPV infection and individuals infected with HIV than in the general population. The natural history of oral HPV infection is unknown, and whether the well established natural history of cervical HPV is similar for HPV in the oral cavity, which has a distinct immunological environment, is unclear.

Evidence strongly supports the sexual transmission of HPV to the oral region; however, because sexual behaviours are colinear (related), establishing which behaviours are involved in transmission and the level of risk each might pose is difficult. Initial studies suggest that oral HPV can be sexually transmitted between couples and that spouses of cervical cancer patients have increased rates of oropharyngeal cancer.

Human-papillomavirus-specific genetic markers in human-papillomavirus-associated head and neck and cervical cancers

Peter J F Snijders

Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands

In addition to cervical carcinomas, a subset of head and neck squamous cell carcinomas (HNSCC), particularly those of the oropharynx, can be attributed to high-risk human papillomavirus (HPV), predominantly HPV type 16. However, not all HNSCCs with PCR-detectable HPV DNA display E6 and E7 mRNA expression. Expression of E6 and E7 mRNA is a sign of a biologically relevant infection. HPV type 16 DNA positive HNSCCs with E6 and E7 transcripts can be genetically distinguished as a specific subgroup, whereas those without E6 and E7 transcripts have a similar genetic signature as HPV DNA negative HNSCCs. To detect biologically relevant HPV infections in tumour tissue specimens, p16INK4A immunostaining, a highly sensitive but not 100% specific marker for transforming HPV infections, followed by high-risk HPV PCR or in-situ hybridisation assays, seem most promising.

To establish whether HPV-associated squamous cell carcinomas arising from different organs have specific chromosomal alterations in common, array comparative genome hybridisation profiles of cervical squamous cell carcinomas and HPV (DNA and RNA) positive and negative HNSCCs were compared. Unsupervised hierarchical clustering resulted in one mainly HPV-positive cluster and one mainly HPV-negative cluster. Generally, HPV-negative HNSCCs showed more altered regions. Chromosomal gains of 3q24-29 and losses of 11q22.3-25 were common throughout, irrespective of HPV presence or organ. Loss at 13q21 and gain at 20q were more common in HPV-positive squamous cell carcinomas of both organs. Within the group of HPV-positive carcinomas, HNSCCs frequently showed gains of multiple regions at 8q, whereas cervical squamous cell carcinomas often showed loss at 17p. The existence of HPV-specific alterations in squamous cell carcinomas of different anatomical origins, suggests that these alterations are crucial for HPV-mediated carcinogenesis.

Neck dissection in the surgical management of oropharyngeal cancer: controversies and outstanding questions

Ian Martin

National Confidential Enquiry into Patient Outcome and Death, London, UK

This presentation reviews published works to examine the evidence for and against the use of neck dissections in the management of oropharyngeal squamous cell carcinoma. The primary aim of this review is to establish whether there is any difference in outcome between treatment strategies in terms of survival and local control or functional outcome and quality of life. The question of whether HPV status is of value in determining the treatment regimen will be addressed.

There is wide variation in the range of primary sites and stages of disease. Most studies are retrospective reports of small unmatched samples, and followed up over short periods. Bias is often present in case selection. With the recent increase in popularity of function sparing chemoradiation, temporal bias might also occur. Where neck dissection has been used, there is wide variation in the extent of nodal dissection, and no clear definition of the selective techniques used. Wide variation also exists in histopathological methods and reporting, and in the application of adjuvant management strategies and the ordering and timing of adjuvant treatments.

Taking account of all the limitations of this review, there does appear to be evidence for the balance of probability that neck dissections are an effective treatment modality, and that the selective neck dissection confers substantial benefit over comprehensive neck dissection in terms of functional outcome without compromising disease control.

Human papillomavirus infection in pregnancy: issues related to prophylactic and treatment strategies

Jorma Paavonen, Matti Lehtinen

University of Helsinki; University of Tampere, Finland

Organised mass screening programmes have been effective in reducing cervical cancer incidence rates. However, screening policies are highly variable, mirrored by highly variable incidence rates. With screening programmes, the disease burden has shifted to cervical intraepithelial neoplasia (CIN). Cervical procedures for management of CIN increase the risk for adverse pregnancy outcomes (APO), ie, preterm birth. Phase 3 studies have shown that vaccination against human papillomavirus (HPV) types 16 and 18 prevents most persistent HPV type 16 and 18 infections and high-risk HPV type related high grade cervical intraepithelial neoplasia (CIN2 and 3) lesions. HPV vaccines significantly decrease abnormal cytological findings, colposcopy referrals, colposcopy biopsies, and cervical excisional procedures. This has a serious effect on reproductive health, since patients with CIN are generally young. Prophylactic virus like particle HPV vaccines do not contain live virus, but the safety of vaccinating pregnant women has not been established. Neither of the currently available HPV vaccines are recommended for use in pregnancy. Because the main target population of prophylactic HPV vaccination is young women of reproductive age, and to minimise the risk of exposure during pregnancy, all clinical trial participants have been asked to use effective birth control during the vaccination phase, and a pregnancy test has been done before vaccination. Those with a positive test have not been vaccinated. However, many women were or became pregnant during the vaccination phase. We now provide an updated analysis of the pregnancy outcomes for such women enrolled in the phase 3 trials of the two HPV vaccines.

For active follow up regarding APO, we combined data from five phase 3 trials (N=20551) of the quadrivalent HPV type 6, 11, 16, and 18 vaccine (Gardasil, Merck & Co., Inc, Philadelphia), and two phase 3 trials (N=26130) of the bivalent HPV type 16 and 18 vaccine (Cervarix, GSK Biologicals, Rixensart). In the Gardasil trials, a total of 3620 women became pregnant—1796 women in the vaccine arms and 1824 women in the placebo arms. In the Cervarix trials 4710 women became pregnant, and 3599 had intrauterine pregnancies eligible for analysis—1786 in the vaccine arms and 1813 in the hepatitis A vaccine (control) arms. For passive follow up regarding APO, we linked the registries of the vaccination trial participants from Finland receiving either Gardasil (N=874) or Cervarix (N=2408) and the Finnish birth registry.

The HPV vaccines were generally well tolerated by pregnant women, and no association was found between the vaccines and APO. Active follow up in the clinical trials overall showed no evidence of association between HPV vaccination and risk of miscarriage or other adverse pregnancy outcomes. The pregnancy outcomes in general did not vary between the study arms. Similarly, congenital anomalies detected were evenly distributed between the study arms, and were diverse and consistent with those reported in the general population. The first birth registry linkage results of the passive follow-up of cohorts of the HPV vaccinated and reference cohorts, which produced up to 40 000 women years of follow-up data, will be presented.

Systematic reviews and meta-analyses have shown an association between excisional procedures to treat CIN and APO. Thus, counselling and caution in the treatment of young women for cervical abnormalities is recommended, and unnecessary treatment should be avoided. Established pregnancy registries and postmarketing surveillance will provide further long-term data which is critical when millions of young women will be vaccinated against HPV.

Racial survival disparity in head and neck cancer is attributable to low prevalence of human papillomavirus in black patients with oropharyngeal cancer—University of Maryland experience.

K J Cullen, S S Patel, L M Schumaker, K Settle, S Iqbal, Tan Ming, S Strome Scott, M Suntha, O Goloubeva

University of Maryland Marlene and Stewart Greenebaum Cancer Center, USA

We recently showed that the reported racial survival disparity in head and neck cancer is limited to the site of oropharyngeal cancer and this is due to a much lower incidence of favourable human papillomavirus (HPV)-positive oropharyngeal cancer in blacks than in whites.

To confirm the difference reported in the prevalence of HPV infection between blacks and whites, we did a retrospective analysis of 305 patients with oropharyngeal cancer treated at our institution between 1995 and 2007. Of the 305 patients identified for this study, 176 (58%) were white and 129 (42%) were black. 253 (83%) patients were men. 238 (78%) of patients had stage 4 cancers. HPV type 16 status is known for 166 (54%) of 305 patients. Median survival for white patients was 47 months (95% CI 34-8-69.5) versus 24 months in blacks (15.0-29.1; p=0.003). Of patients with known HPV status, 49 of 100 white patients were HPV positive, whereas only 11 (17%) of 66 black patients were HPV positive (p<0.0001). Median survival for all HPV-negative patients was 14 months (10.3-27.1), whereas median survival for all HPV-positive patients was 93 months (37-NR; p<0.0001). In a multivariable Cox analysis, HPV status had the most substantial effect on survival, but race remained an important independent prognostic indicator.

This study confirms, in an independent data set, our findings that the prevalence of HPV-positive oropharyngeal cancers is much lower in blacks than in whites, and that this difference contributes significantly to overall racial survival disparities in head and neck cancer.

Prevention and treatment approaches to anal intraepithelial neoplasia and anal cancer

Joel Palefsky

UCSF School of Medicine, USA

Like cervical cancer, anal cancer is strongly associated with human papillomavirus (HPV) infection. Anal cancer is preceded by high-grade anal intraepithelial neoplasia (HGAIN, AIN 2+). There is no routine AIN screening and treatment programme to prevent anal cancer that is similar to the cervical intraepithelial neoplasia screening programme to prevent cervical cancer. Treatment of HGAIN is primarily ablative through methods such as infrared coagulation, and is associated with high recurrence rates. In the long-term, reduction of anal cancer might therefore be best achieved through prevention of anal HPV infection and AIN through prophylactic HPV vaccination.

In the Merck 020 trial, 598 men who have sex with men (MSM) aged 16–26 years were randomised to receive quadrivalent HPV (types 6, 11, 16, and 18) vaccine or placebo at enrolment, month 2, and month 6. Efficacy analyses were done in a per-protocol population (seronegative at day 1 and DNA-negative from day 1 through month 7 to the relevant vaccine HPV type). Median follow-up was 2.5 years (post-dose 3). Vaccine efficacy against HPV types 6, 11, 16, and 18 related AIN in MSM was 77.5% (95% CI 39.6–93.3; five vaccine cases versus 24 placebo cases). Efficacy against AIN1 was 73% (16.3–93.4), and efficacy against anal warts was 100% (8.2–100). Efficacy against AIN 2+ was 74.9% (8.8–95.4).

These results show that the quadrivalent HPV vaccine is efficacious in preventing AIN, including AIN 2+ related to HPV types 6, 11, 16, and 18, in MSM naïve to vaccine HPV types at enrolment. HPV vaccination might be an important tool for anal cancer prevention in at-risk individuals.

Circumcision, or human papillomavirus vaccination, or both, in men for prevention of anogenital and oral cancers: possible justification for a future trial of second generation human papillomavirus vaccines

RTD Oliver, L Battery

Institute of Cancer, Barts and The London Medical School, Queen Mary University of London, UK

Vaccination of boys against human papillomavirus (HPV) will never be economical in its own right if assessed from the point of view of the health economics of cervical cancer. However, if such vaccination prevented other cancers, even if only a subset, and were able to alter a surrogate endpoint within less than 5 years of vaccination, the balance of the economical case will swing more strongly towards a changing view of vaccination for both sexes. Given the longstanding relationship between circumcision and prevention of cervical cancer, this review examines the geographical incidence and mortality statistics for prostate and cervical cancers and the results from recent successful randomised trials of circumcision preventing HIV infection. We also consider possible surrogate endpoints in their natural history that could be assessed in future trials of second generation HPV vaccines.

Though deaths from cervical cancer are lower in Saudi Arabia, Israel, and the USA (0.9, 2.1, 1.7 × 105) compared with Brazil and India (10.9, 15.2 × 105), other low circumcising nations—Denmark, Japan, and China (2.5, 2.6, 4.9 × 105)—have lower death rates than high circumcising nations, such as Bangladesh and Pakistan (17.9, 12.9 × 105). For prostate cancer, the lowest death rates are in Denmark, Japan, and China (2.5, 5, 1.8 × 105) compared with high circumcising nations, such as Saudi Arabia, Israel, and the USA (5.1, 7.6, 9.7 × 105). India, Bangladesh, and Pakistan (2.5, 1.2, 4 × 105) show similar low death rates from prostate cancer despite differing policies on circumcision, whereas Brazil with a low circumcision policy has one of the highest death rates (16.3 × 105). A meta-analysis of circumcision and prostate cancer incidence from five studies (1621 cases and 1499 controls) showed an odds ratio of 0.86, whereas three papers comparing Jewish versus non-Jewish prostate cancer incidence in 2878 Jewish versus 40 768 non-Jewish patients showed an odds ratio of 0.25. Although the WHO/IARC report on vitamin D and cancer failed to show a correlation between a single spot vitamin D level and later occurrence of prostate cancer, four studies that recruited 1748 cases and 8939 controls found consistently significant association between an index of long-term sun exposure and prostate cancer risk (OR 3.03, 3.31, 1.41, and 1.24). Pre-existing HPV infection increases while Muslim cultural background decreases HIV acquisition in the African circumcision trials. Access to sanitation is shown to decrease cervical and penile cancer in Denmark, Brazil, India, and China.

These data suggest that by including males in global trials to demonstrate the value of the second generation HPV vaccines, that also sub-randomise the trial subjects to differing policies regarding genital hygiene and that use PSA at the age of 18 years as a surrogate for later prostate cancer occurrence, we could begin to better understand and reduce the differences identified by this analysis. The data could be further enhanced by including questionnaires regarding circumcision status and sun exposure as well as taking blood samples for vitamin D level at enrolment and at 18 years.

Radiotherapy in human papillomavirus infected head and neck and oral pharyngeal cancers

Pernille Lassen

Department of Experimental Clinical Oncology, DK-8000 Aarhus C, Denmark

During the past 30 years the incidence of oropharyngeal cancers in the Western world has increased by five times, and infection with HPV seems to be the predominant cause for this development. Most patients with oropharyngeal cancers are treated with radiotherapy and tumour HPV-positivity is a favourable prognostic factor for radiotherapy outcome. When treated with primary radiotherapy alone the 5-year risk of locoregional tumour failure in HPV-positive tumours is reduced to a third compared with that of HPV-negative tumours. Likewise, for disease-specific survival and overall survival the benefit in favour of HPV-positivity is of similar scale, and the outcome in HPV-positive tumours is substantially improved compared with HPV-negative tumours. Thus, tumour HPV status is the strongest known independent prognostic factor determining tumour control and survival in single-modality primary radiotherapy of head and neck cancer. Response to intensive treatment schedules that combine radiotherapy and chemotherapy is also strongly influenced by tumour HPV status, again with a substantial benefit in favour of HPV positivity. Apparently treatment-related benefits and risks could be used separately on the basis of tumour HPV-status to secure optimum treatment outcome and to avoid unnecessary treatment-induced morbidity in both HPV-positive and HPV-negative tumours.

Rationale for reduction of radiation dose in human papillomavirus-related oropharyngeal cancer

Marshall R Posner

The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA

Human papillomavirus related oropharyngeal cancer (HPVOPC) is epidemic in North America and Europe. HPVOPC is a unique disease with a different prognosis, affecting a different population than previously encountered in head and neck cancer. Patients are young, without significant co-morbidities and risks. Survival at 5 years approaches 70–80% with aggressive treatment. Improved survival is related to improved local-regional control. Although acute treatment-induced morbidity and mortality are important, the long-term consequences of chemotherapy, surgery, and radiotherapy are increasingly critical in assessing the ultimate risks and benefits of treatment. Late side-effects of chemotherapy are varied and are determined by drug selection. Commonly used drugs such as taxanes, platinum, and fluoropyrimidines have few long-term side-effects and an established record from which to extract data. For new compounds and biologics, particularly when used with other modalities or drugs, late consequences have not had time to become apparent. Consequences of surgery as monotherapy seem to be almost fully vested in the initial encounter. Radiotherapy, with or without chemotherapy, is a mainstay of current curative treatment and has substantial, cumulative, late consequential mortality and morbidity. Late radiation toxic effects are dose and volume dependent hence a reduction of dose and volume would be expected to reduce late morbidity. Based on results from phase 3 clinical trials, chemoradiotherapy increases local-regional control out of proportion to the cost in additional late morbidity. Consideration of radiation as a drug that can be synergistic when combined with other drugs is a key paradigm shift. Reduction of the dose of radiation during chemoradiotherapy and administration of additional drugs with non-overlapping acute and minimal late toxicity to balance radiotherapy reductions can be tested as a means to increase survival and moderate morbidity. Induction chemotherapy and sequential chemotherapy improve local-regional control compared with radiotherapy. Across phase 3 trials there is improved late mortality and morbidity when induction chemotherapy is compared with full dose chemoradiotherapy. We can use the gains in survival and local-regional control from different components of multimodal treatment to plan radiotherapy as part of a combined modality treatment—with surgery and chemotherapy—and increase or decrease radiotherapy, depending on patient and tumour factors, to maximise disease control while minimising late morbidity in HPVOPC.

HPV infection in HIV-positive host: molecular interactions and clinical implications

Joel Palefsky

UCSF School of Medicine, USA

The incidence and persistence of anogenital human papillomavirus (HPV) infection and HPV-associated precancerous lesions are increased in HIV-seropositive individuals compared with the general population. Consistent with this, the incidence of HPV-related anal cancer is increased in HIV-seropositive men and women, as is cervical cancer in HIV-seropositive women. However, the incidence of HPV-related cancers in HIV-seropositive individuals has not declined since the introduction of antiretroviral treatment and might instead be increasing as they live longer.

Multiple mechanisms might underlie such an increase. The systemic and local immune response to HPV could be affected by HIV-mediated immune attenuation, and local cytokine perturbations might play a part at the tissue level. However, the lack of response to antiretroviral-treatment-associated immune reconstitution suggests that this is not the entire explanation.

Direct molecular interactions at the tissue level might occur between HIV and HPV. HIV might upregulate early region HPV gene expression; and HPV and HIV infection might both disrupt tight junctions of mucosal epithelium and facilitate infection with the other viruses. Recent reports show that anogenital HPV infection is associated with increased risk of HIV infection. Clearance of HPV was implicated in HIV acquisition, suggesting that the influx of immune cells associated with HPV clearance might be involved. HPV might therefore cause morbidity and mortality through causation of squamous cell cancers, but also by increasing the risk of HIV infection. If confirmed, HPV vaccination might be useful for reducing the risk of both HIV infection and HPV-associated cancers.

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

B. Balaiah*, R. Lakshmi, D. Meenakshi, K. Vinaykumar, M. Kamatchi, S. Vijayakumar, et al

Tamil Nadu Health Systems Project, India

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

P. Bayo*¹, M. Cascella², M. Roccio², A. Spinillo²

¹St. Mary's Hospital, Gulu University, Uganda,

²IRCCS-Fondazione Policlinico San Matteo, University of Pavia, Italy

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

M.A. Broglie*, M. Pawlita, R. Schoenegg, W. Jochum, S.J. Stoeckli

¹Department of Otorhinolaryngology, Head and Neck Surgery Kantonsspital St.Gallen, Switzerland, ²Department of Genome Modifications and Carcinogenesis, German Cancer Research Centre (DKFZ), Heidelberg, Germany, ³Institute of Pathology, Kantonsspital St. Gallen, St. Gallen, Switzerland

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

S. Videla*¹, M-P. Cañadas^{2,3}, L. Darwich^{2,4}, G. Sirera^{1,5}, F. Alameda⁶, B. Clotet^{1,5} et al

¹Lluita Contra La SIDA Foundation, Spain, ²Retrovirology Laboratory-IrsiCaixa Foundation, Spain, ³General Lab, Barcelona, Spain, ⁴Department of Sanitat i Anatomia Animal, Autonomous University of Barcelona, Spain, ⁵HIV Clinical Unit, Department of Medicine, University Hospital Germans Trias i Pujol, Badalona, Spain, ⁶Department of Pathology, Hospital del Mar, Barcelona, Spain

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

C.M. Chivu*¹, D.D. Reidpath²

¹Brunel University, United Kingdom, ²Monash University, Malaysia

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

Y.S. Choi*, W.D. Kang, S.M. Kim, J.H. Nam, C.S. Park, H.S. Choi

Chonnam National University Medical School, Republic of Korea

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

J.S.Y. Chor*, K. Ngai, H. Lam, P.K.S. Chan

The Chinese University of Hong Kong, Hong Kong

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

A. Clad*¹, J. Weinschenk¹, J. Rahmsdorf¹, F. Schaffrath¹, N. Freudenberg^{1,2}

¹Universitaets-Frauenklinik, Freiburg, Germany,

²Institute of Pathology, University of Freiburg, Germany

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

A. del Toro Arreola*¹, S.F. Velasco Ramirez¹, A. Quintero Ramos¹, S.A. Gutierrez Rubio¹, L. Flores Romo², A. Daneri Navarro¹ et al.

¹Universidad de Guadalajara, Departamento de Fisiologia. Guadalajara, Jal, Mexico, ²Centro de Investigacion y Estudios Avanzados del Instituto Politecnico Nacional. Mexico, DF, Mexico, ³Clinica de Colposcopia, Hospital General Regional No. 45, Instituto Mexicano del Seguro Social. Guadalajara, Jal, Mexico, ⁴Universidad de Guadalajara, Salud Publica. Guadalajara, Jal, Mexico, ⁵Centro de Estudios Especializados ARG, Instituto para el Fortalecimiento de las Capacidades en Salud. Mexico, Mex, Mexico, ⁶Servicio de Patologia, OPD Hospital Civil de Guadalajara. Guadalajara, Jal, Mexico

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

E. Deutsch*, M-C. Vozenin

Institut Gustave Roussy, France

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

E. Draper^{*1}, S. L. Bissett¹, D. Edwards², G. Munslow², K. Soldan¹, S. Beddows¹

¹Health Protection Agency, United Kingdom, ²NHS Bolton, United Kingdom

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

E. Hamsikova^{*}, V. Ludvikova, J. Smahelova, M. Salakova, J. Stasikova, R. Tachezy

Institute of Hematology and Blood Transfusion, Czech Republic

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

S. Hussain^{*1}, A. C. Bharti², I. Salam³, M. A. Bhat⁴, M. M. Mir⁵, S. Hedau⁵ et al.

¹Division of Molecular Oncology, Institute of Cytology & Preventive Oncology (ICMR), I-7, Sector-39, Noida, India, ²Department of Clinical Biochemistry, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India, ³Department of Cardiovascular and Thoracic Surgery, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India, ⁴Department of Immunology and Molecular Medicine Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India, ⁵Department of Biosciences, Jamia Millia Islamia; New Delhi, India, ⁶Dr. B.R. Ambedkar Research Centre for Biomedical Research (ACBR), University of Delhi (North Campus), Delhi, India, India

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

J-Y. Kim^{*1}, J-W. Roh², J-A. Lee¹, H-J. Shin¹

¹Research Institute and Hospital, National Cancer Center, Korea, Republic of, ²Department of Obstetrics and Gynecology, Dongguk University Ilsan Hospital, College of Medicine, Dongguk University, Republic of Korea

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

L. Lorenzon*¹, M. Bononi², M. R. Torrisi¹, A. Ciardi², D. French¹, A. Frega¹

¹Sant'Andrea Hospital, II faculty of medicine and Surgery, University of Rome "La Sapienza", Italy, ²Policlinico Umberto I, I Faculty of Medicine and Surgery, University of Rome "La Sapienza", Italy

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

A.T. Lorincz*¹, E. Lazcano-Ponce², A. Cruz-Valdez², J. Salmeron³, P. Uribe⁴, M. Hernandez Avila⁵ et al.

¹Wolfson Institute of Preventive Medicine, Queen Mary University of London, Barts and The London School of Medicine, London, United Kingdom, ²Centro de Investigación en Salud Poblacional. Instituto Nacional de Salud Pública, Cuernavaca, Morelos, Mexico, ³Unidad de Investigación Epidemiológica y en Servicios de Salud, Instituto Mexicano del Seguro Social, Cuernavaca, Morelos, Mexico, ⁴Centro Nacional de Equidad y Género, Secretaría de Salud, México, D.F., Mexico, ⁵Subsecretaría de Prevención y Control de Enfermedades, Secretaría de Salud, México, D.F., Mexico

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

L.G.T. Morris*¹, A.G. Sikora², P.N. Vila², R.B. Hayes³, I. Ganly¹

¹Memorial Sloan-Kettering Cancer Center, United States, ²Mount Sinai School of Medicine, United States, ³New York University School of Medicine, United States

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

M. Nathan*¹, N. Hickey¹, N. Singh², M. Sheaff²

¹Homerton University Hospital NHS Foundation Trust, United Kingdom, ²Barts and the London NHS Trust, United Kingdom

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

G. Orlando*¹, S. Bianchi², F. Mazza¹, M. Fasolo¹, A. Amendola², E. Tanzi² et al.

¹STD Unit Infect Dis II; L Sacco University Hosp, Italy, ²Dipartimento di Sanità Pubblica-Microbiologia-Virologia, Università di Milano, Italy

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

P. Rahal*¹, M.T.O. Mota¹, E. Babeto¹, M.F. Calmon¹, J.L. Bonilha², R.V.D. Silvestre³ et al.

¹Laboratory of Genomics Studies, São Paulo State University, Brazil, ²Department of Pathology, College of Medicine, FAMERP, Brazil, ³Papillomavirus and Respiratory Virus Laboratory, Institute Evandro Chagas/SVS/MS, Brazil, ⁴Department of Pathology, Antonio Prudente Foundation, Brazil, ⁵Department of Pathology, State University of Campinas, Brazil

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

R. Semrau*¹, H. Duerbaum², S. Temming¹, C. Huebbers³, J. P. Klussmann⁴, S. F. Preuss²

¹Department of Radiation Oncology, University of Cologne, Germany, ²Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital of Cologne, Germany, ³Jean-Uhrmacher Institute, University of Cologne, Germany, ⁴Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital of Giessen, Germany

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

E. Tanzi*¹, E.R. Frati¹, S. Bianchi¹, A. Zappa¹, F. Mazza², G. Orlando²

¹Università di Milano, Dip Sanità Pubblica-Microbiologia-Virologia, Italy, ²L Sacco University Hospital, STD Unit Infectious Diseases II, Milan, Italy

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

A.G. Renehan^{*1}, J. Bohlius², K.M. Clough-Gorr², N. Low², M. Zwahlen², M. Egger²

¹The Christie NHS Foundation Trust, School of Cancer and Enabling Sciences, University of Manchester, United Kingdom, ²Institute for Social and Preventive Medicine, University of Bern, Switzerland

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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Abridged Prescribing Information for use in the European Area **GARDASIL**[®] (Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)). Refer to Summary of Product Characteristics for full product information. **Presentation:** Gardasil is supplied as a single dose pre-filled syringe containing 0.5 ml of suspension. **Active ingredients:** Each dose contains L1 protein of HPV type 6 (20 µg), type 11 (40 µg), type 16 (40 µg) and type 18 (20 µg), adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant. **Indications:** Gardasil is a vaccine for use from the age of 9 years for the prevention of premalignant genital lesions (cervical, vulvar and vaginal), and cervical cancer and external genital warts (condyloma acuminata) causally related to certain oncogenic Human Papillomavirus (HPV) types 6, 11, 16 and 18; and external genital warts (condyloma acuminata) causally related to specific HPV types. The indication is based on the demonstration of efficacy of Gardasil in adult females 16 to 26 years of age and on the demonstration of immunogenicity of Gardasil in 9- to 15-year old children and adolescents. Protective efficacy has not been evaluated in males. The use of Gardasil should be in accordance with official recommendations. **Dosage and administration:** The primary vaccination series consists of 3 separate 0.5ml doses administered according to the following schedule: 0, 2, 6 months. If an alternate schedule is necessary the second dose should be administered at least one month after the first and the third dose at least three months after the second. All three doses should be given within a 1 year period. The need for a booster dose has not been established. Paediatric population: there is no experience with the use of Gardasil in children below 9 years of age. The vaccine should be administered by intramuscular injection. It is recommended that individuals who receive a first dose of Gardasil complete the 3-dose vaccination course with Gardasil. **Contraindications:** Hypersensitivity to any component of the vaccine. Hypersensitivity after previous administration of Gardasil. Acute severe febrile illness. **Warnings and precautions:** The decision to vaccinate an individual woman should take into account her risk for previous HPV exposure and her potential benefit from vaccination. As with all vaccines, appropriate

medical treatment should always be available in case of rare anaphylactic reactions. Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Vaccinees should be carefully observed for approximately 15 minutes after administration of Gardasil. As with any vaccine, vaccination with Gardasil may not result in protection in all vaccine recipients. Gardasil will only protect against diseases that are caused by HPV types 6, 11, 16 and 18 and to a limited extent against diseases caused by certain related HPV types. Gardasil has not been shown to have therapeutic effect. Vaccination is not a substitute for routine cervical screening. There are no data on the use of Gardasil in individuals with impaired immune responsiveness. The vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals. **Interaction:** Administration at the same time as hepatitis B vaccine did not interfere with the immune response to the HPV types. Gardasil may be concomitantly administered with a combined booster vaccine containing diphtheria (d) and tetanus (T) with either pertussis [acellular, component] (ap) and/or poliomyelitis [inactivated] (IPV) (dTap-IPV vaccines) with no significant interference with antibody response to any of the components of either vaccine. Use of hormonal contraceptives did not appear to affect the immune response to Gardasil. **Pregnancy and lactation:** There is insufficient data to recommend the use of Gardasil during pregnancy. Gardasil can be given to breastfeeding women. **Undesirable effects:** Very common: pyrexia and at the injection site, erythema, pain and swelling. Common: bruising and pruritus at the injection site, pain in extremity. For a complete list of undesirable effects, including post-marketing undesirable effects, please refer to the Summary of Product Characteristics. **Marketing authorisation**

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