Značilnosti okužbe s HPV

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Razvrščanje in splošne lastnosti HPV

The PapillomaVirus Episteme (PaVE)
http://pave.niaid.nih.gov/#home
status: October 14, 2014

HPV-199

195 official HPV genotypes

HPV-46, HPV-55, HPV-64 and HPV-79 did not meet the criteria as a unique HPV

Slovenian HPV genotypes

HPV-120
HPV-125
HPV-150
HPV-151
HPV-159
HPV-174
HPV-179
HPV-184
HPV-199

http://www.hpvcenter.se/html/refclones.html

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Characterization of a Novel Cutaneous Human Papillomavirus Genotype HPV-125

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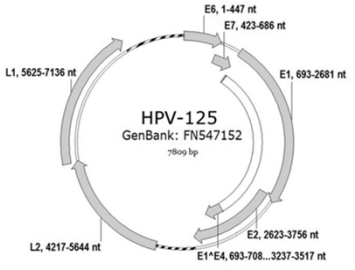
1 Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, 2 Department of Dermatovenereology, University Medical Centre Ljubljana, Ljubljana, Slovenia



Characterization of human papillomavirus type 120: a novel betapapillomavirus with tropism for multiple anatomical niches

Danielle Bottalico,[1]† Zigui Chen,[1]† Boštjan J. Kocjan,[2]† Katja Seme,[2] Mario Poljak[2] and Robert D. Burk[1,3,4,5]

Journal of General Virology (2012), **93**, 1774–1779

Table 1. Prevalence of HPV120 infection from different anatomical sites and lesions

Type of specimen	Total no. of samples*	No. of HPV120-positive samples	Prevalence of HPV120 (%)
Oral cavity (rinse specimens)	446	4	0.9
Oral papillomas	65	0	0
Oral squamous cell carcinomas	65	0	0
Eyebrow hairs (immunocompetent patients)	63	14	22.2
Swab of the anal canal	210	7	3.3
Anal and perianal warts	144	5	3.5
Penile warts	56	2	3.6
Laryngeal papillomas	58	1	1.7
Inverted sinonasal papillomas	60	0	0
Vulvar/vaginal lesions (warts, VIN1-3, VaIN1-3)	80	1	1.3
Cervical squamous cell carcinomas	61	0	0
Total	**1308**	**34**	**2.6**

Global Genomic Diversity of Human Papillomavirus 6 Based on 724 Isolates and 190 Complete Genome Sequences

JVI 2014;88:7307-16.

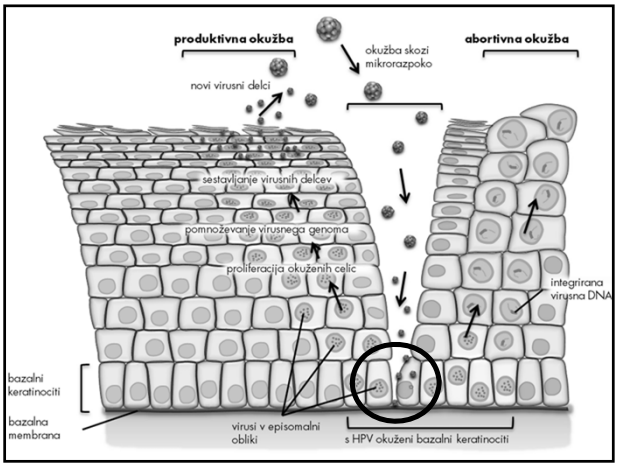
Mateja M. Jelen,[a] Zigui Chen,[b] Boštjan J. Kocjan,[a] Felicity J. Burt,[c] Paul K. S. Chan,[d] Diego Chouhy,[a] Catharina E. Combrinck,[c] François Coutlée,[f] Christine Estrade,[g] Alex Ferenczy,[h] Alison Fiander,[i] Eduardo L. Franco,[j] Suzanne M. Garland,[k,l,m] Adriana A. Giri,[a] Joaquín Víctor González,[n] Arndt Gröning,[o] Kerstin Heidrich,[o] Sam Hibbitts,[i] Lea Hošnjak,[a] Tommy N. M. Luk,[p,q] Karina Marinic,[r] Toshihiko Matsukura,[s] Anna Neumann,[o] Anja Oštrbenk,[a] Maria Alejandra Picconi,[n] Harriet Richardson,[t] Martin Sagadin,[a] Roland Sahli,[g] Riaz Y. Seedat,[u] Katja Seme,[a] Alberto Severini,[v] Jessica L. Sinchi,[r] Jana Smahelova,[w] Sepehr N. Tabrizi,[k,l,m] Ruth Tachezy,[w] Sarah Tohme,[v] Virgilijus Uloza,[x] Astra Vitkauskiene,[y] Yong Wee Wong,[z] Snježana Židovec Lepej,[aa] Robert D. Burk,[ab,b] Mario Poljak[a]

the largest database of globally circulating HPV-6 genomic variants

total of 130 new complete HPV-6 genome sequences (out of 190)

association of HPV-6 variant lineages/sublineages with:
- geographical location
- anatomical site of infection/disease
- gender

Zgradba in pomnoževanje HPV



PNAS | December 1, 2009 | vol. 106 | no. 48

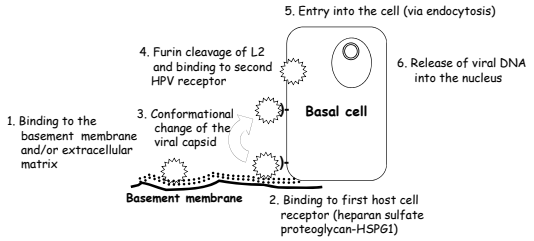
The initial steps leading to papillomavirus infection occur on the basement membrane prior to cell surface binding

Rhonda C. Kines, Cynthia D. Thompson, Douglas R. Lowy, John T. Schiller, and Patricia M. Day[1]

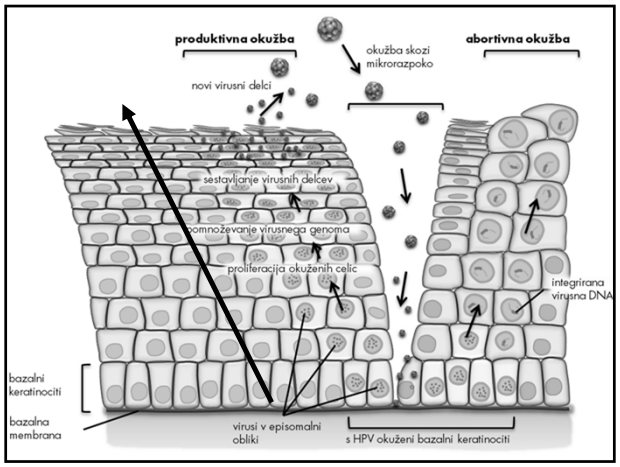
Laboratory of Cellular Oncology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892

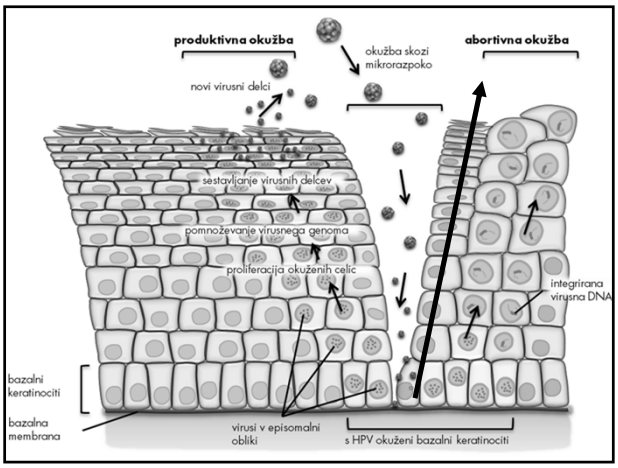
The initial steps of HPV infection take place on the basement membrane, in contrast to the typical viral infection that is initiated by binding to the cell surface.

The basement membrane is the site of a series of conformational changes in the viral capsid that leads to protease digestion of L2 and exposure of its N terminus.



Sapp M, Day PM. Virology 2009;384: 400-9.





Prevalence of Human Papillomavirus in Adolescent Girls Before Reported Sexual Debut

Catherine F. Houlihan,[1,2] Silvia de Sanjosé,[3,4] Kathy Baisley,[5] John Changalucha,[6] David A. Ross,[5] Saidi Kapiga,[2,5] Jose M. Godinez,[3] Ivana Bozicevic,[7] Richard J. Hayes,[5] and Deborah Watson-Jones[1,2]

[1]Clinical Research Department, London School of Hygiene and Tropical Medicine, United Kingdom; [2]Mwanza Intervention Trials Unit, Tanzania; [3]Unit of Infections and Cancer, Institut Català d'Oncologica, IDIBELL, and [4]CIBER, Barcelona, Spain; [5]MRC Tropical Epidemiology Group, London School of Hygiene and Tropical Medicine, United Kingdom; [6]National Institute for Medical Research, Mwanza, Tanzania; and [7]Collaborating Centre for HIV Surveillance, School of Medicine, University of Zagreb, Croatia

The Journal of Infectious Diseases 2014;210:837–45

Background. Human papillomavirus (HPV) vaccines are recommended for girls prior to sexual debut because they are most effective if administered before girls acquire HPV. Little research has been done on HPV prevalence in girls who report not having passed sexual debut in high HPV-prevalence countries.

Methods. Using attendance registers of randomly selected primary schools in the Mwanza region of Tanzania, we enrolled girls aged 15–16 years who reported not having passed sexual debut. A face-to-face interview on sexual behavior and intravaginal practices, and a nurse-assisted self-administered vaginal swab were performed. Swabs were tested for 13 high-risk and 24 low-risk HPV genotypes.

Results. HPV was detected in 40/474 (8.4%; 95% confidence interval [CI], 5.9–11.0) girls. Ten different high-risk and 21 different low-risk genotypes were detected. High-risk genotypes were detected in 5.3% (95% CI, 3.5–7.8). In multivariable analysis, only intravaginal cleansing (practiced by 20.9%) was associated with HPV detection (adjusted odds ratio = 2.19, 95% CI, 1.09–4.39).

Conclusion. This cohort of adolescent Tanzanian girls had a high HPV prevalence prior to self-reported sexual debut, and this was associated with intravaginal cleansing. This most likely reflects underreporting of sexual activity, and it is possible that intravaginal cleansing is a marker for unreported sexual debut or nonpenetrative sexual behaviors.

Journal of Pathology
J Pathol 2012; **227:** 62–71
Published online 17 February 2012 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.3970

ORIGINAL PAPER

One virus, one lesion—individual components of CIN lesions contain a specific HPV type

Wim Quint,[1]*† David Jenkins,[2]†‡ Anco Molijn,[1] Linda Struijk,[1] Miekel van de Sandt,[1] John Doorbar,[3] Johann Mols,[2] Christine Van Hoof,[4] Karin Hardt,[2] Frank Struyf[2] and Brigitte Colau[2]

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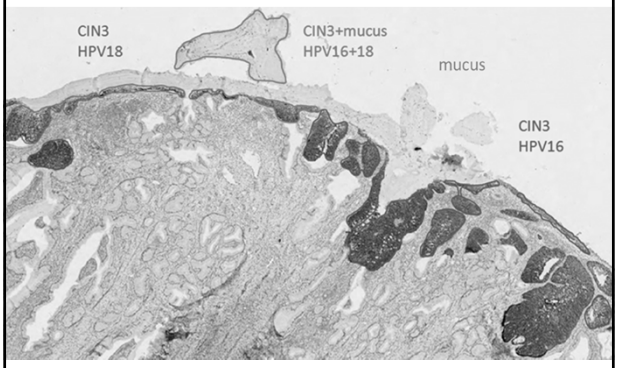
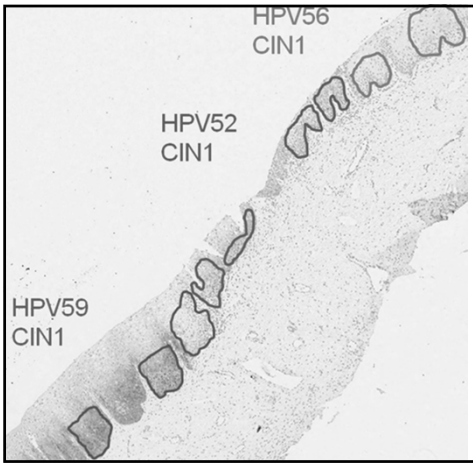
[2] *GlaxoSmithKline Biologicals, Rixensart, Belgium*
[3] *National Institute for Medical Research, London, UK*
[4] *XPePharma and Science, Wavre, Belgium*



J Pathol 2012; 227: 62–71



J Pathol 2012; 227: 62–71

No Evidence for Synergy Between Human Papillomavirus Genotypes for the Risk of High-Grade Squamous Intraepithelial Lesions in a Large Population-Based Study

The Journal of Infectious Diseases 2014;209:855–64

Nicolas Wentzensen,[1] Martha Nason,[2] Mark Schiffman,[1] Lori Dodd,[2] William C. Hunt,[3] and Cosette M. Wheeler,[3] for the New Mexico HPV Pap Registry Steering Committee

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, and [2]Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and [3]Department of Pathology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

Background. Multiple human papillomavirus (HPV) genotypes may be independently or synergistically associated with risk of high-grade squamous intraepithelial lesions (HSILs). We evaluated the risk of HSIL in women concomitantly infected with multiple HPV genotypes.

Methods. A population-based stratified sample of 59 664 cervical cytology specimens from women residing in New Mexico were evaluated for cytologic abnormalities and HPV genotypes. We calculated the risk of HSIL in women infected with a single HPV genotype and the risk in those infected with multiple HPV genotypes.

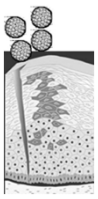
Results. The highest risk of HSIL was observed for HPV-16 (0.036), followed by HPV-33 (0.028), HPV-58 (0.024), and HPV-18 (0.022). For most types, we observed a greater risk of HSIL in women infected with multiple carcinogenic HPV types. In contrast, the risk of HSIL was similar in women infected with HPV-16 and other types, compared with women infected with HPV-16 only. We observed an increased but plateauing risk of HSIL in women infected with multiple types, compared with those infected with a single type, with risk ratios of 1.5 (95% confidence interval [CI], 1.2–1.8), 1.7 (95% CI, 1.3–2.4), and 1.4 (95% CI, 0.83–2.5) for women infected with 2, 3, and ≥4 genotypes, respectively.

Conclusions. In the largest population-based study of HPV genotypes and cytologic outcomes so far, we did not see more than additive effects of HPV types on the risk of HSIL in women infected with multiple types.

Imunologija okužbe s HPV

HPV

Viral characteristics



exclusively intraepithelial pathogens (avoidance of antigen presentation)

do not lyse keratinocytes (no cell death, no inflammation)

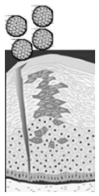
no blood-borne phase of the HPV life cycle

↓

only minimal amounts of replicating virus are exposed to immune system

HPV

Viral characteristics



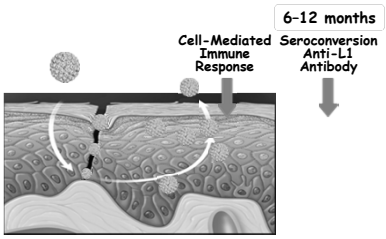
HPV encode proteins that inhibit apoptosis and delay the differentiation program of the infected keratinocyte

HPV downregulate interferon responses and disable the epithelial LCs

↓

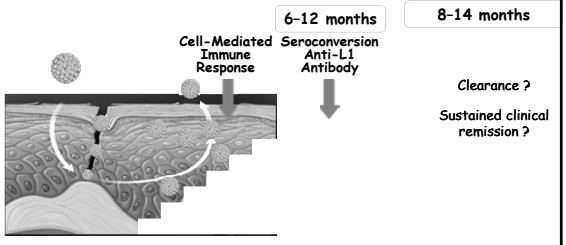
the virus is practically invisible to the host who remains ignorant of the pathogen for long periods of time

Natural History of HPV Infection



- antibody response to HPV infection is slow and weak
- only 54%–69% of women seroconvert within 18 months of incident infection

Natural History of HPV Infection



Natural immunity against HPV

54%–69% of women seroconvert; low-level antibodies

vs.

Vaccine induced immunity against HPV

virtually all women seroconvert; high-level antibodies

Redetection of Cervical Human Papillomavirus Type 16 (HPV16) in Women With a History of HPV16

The Journal of Infectious Diseases 2013;208:403–12

Anna-Barbara Moscicki,[1] Yifei Ma,[1] Sepideh Farhat,[1] Teresa M. Darragh,[2] Michael Pawlita,[4] Denise A. Galloway,[5,6] and Stephen Shiboski[3]

[1]Department of Pediatrics, School of Medicine, [2]Department of Pathology, and [3]Department of Epidemiology and Biostatistics, University of California, San Francisco; [4]Research Program Infection and Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany; [5]Department of Microbiology, University of Washington, Seattle; and [6]Divisions of Human Biology and Public Health Sciences, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Washington

Background. The purpose of this study was to examine the rate of and risks for cervical human papillomavirus type 16 (HPV16) redetection in women with documented or suspected HPV16 infection.

Methods. A convenience sample of women aged 13–21 years were seen at 4-month intervals for HPV DNA testing and cytology. Serum samples were obtained at baseline and annually.

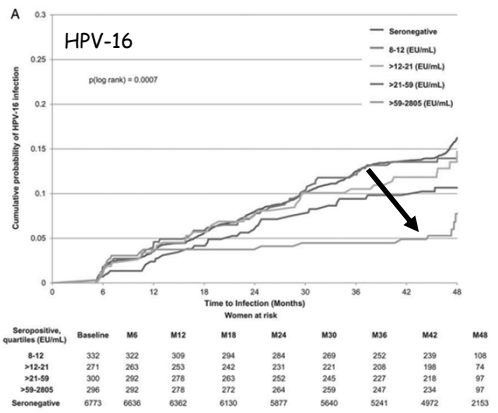
Results. A total of 1543 women entered the study. Of the 295 women with detection of HPV16 DNA and subsequent clearance, 18.1% had HPV16 redetected by 8.5 years (88% cleared this second detection by 3 years). Of the 247 women who had antibodies to HPV16 and were HPV16 DNA negative at baseline, 15.3% had HPV16 redetected by year 5. Risks for redetection included douching, current use of medroxyprogesterone, reporting >1 sex partner or having a new sex partner, and having a sexually transmitted infection. Development of cervical intraepithelial neoplasia 2/3 was rare in women with redetection, except for those with prevalent HPV16 infection.

Conclusions. Reappearance of HPV16 DNA was observed in 18% of women. Most are associated with sexual exposure and appear benign. Interpretation of the studies is more complex in women with prevalent infections as it appears that this small subset reflects women with persistence already present at entry.

Risk of Newly Detected Infections and Cervical Abnormalities in Women Seropositive for Naturally Acquired Human Papillomavirus Type 16/18 Antibodies: Analysis of the Control Arm of PATRICIA

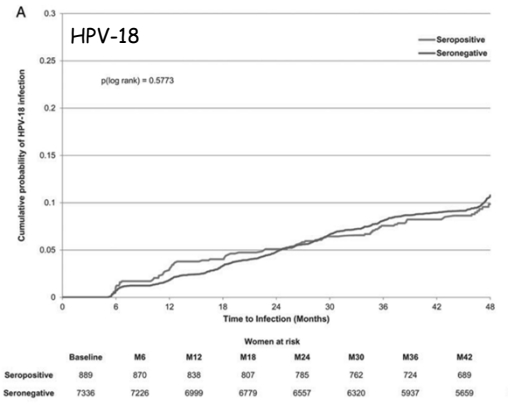
The Journal of Infectious Diseases 2014;210:517–34

Xavier Castellsagué,[1] Paulo Naud,[2] Song-Nan Chow,[3] Cosette M. Wheeler,[4] Maria Julieta V. Germar,[5] Matti Lehtinen,[6] Jorma Paavonen,[7] Unnop Jaisamrarn,[8] Suzanne M. Garland,[9,10,11] Jorge Salmerón,[12] Dan Apter,[13] Henry Kitchener,[14] Julio C. Teixeira,[15] S. Rachel Skinner,[16,17] Genara Limson,[18] Anne Szarewski,[19,a] Barbara Romanowski,[20] Fred Y. Aoki,[21] Tino F. Schwarz,[22] Willy A. J. Poppe,[23] F. Xavier Bosch,[1,24] Newton S. de Carvalho,[25] Klaus Peters,[26] Wiebren A. A. Tjalma,[27] Mahboobeh Safaeian,[28] Alice Raillard,[29] Dominique Descamps,[30] Frank Struyf,[30] Gary Dubin,[31] Dominique Rosillon,[30] and Laurence Barrí[30]



Seropositive, quartiles (EU/mL)	Baseline	M6	M12	M18	M24	M30	M36	M42	M48
8-12	332	322	309	294	284	269	252	239	108
>12-21	271	263	253	242	231	221	208	198	74
>21-59	300	292	278	263	252	245	227	218	97
>59-2805	296	292	278	272	264	259	247	234	97
Seronegative	6773	6636	6362	6130	5877	5640	5241	4972	2153

JID 2014;210:517-34.



	Baseline	M6	M12	M18	M24	M30	M36	M42	M48
Seropositive	889	870	838	807	785	762	724	689	294
Seronegative	7336	7226	6999	6779	6557	6320	5937	5659	2478

JID 2014;209:304-13.

Why are vaccines "better" than nature ??

Why are vaccines "better" than nature ??

Natural infection
- no viraemia, poor access of virus to lymph nodes

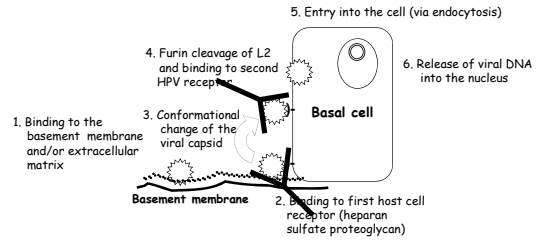
HPV vaccines
- delivered intramuscularly
- rapid access of VLPs to blood vessels and local lymph nodes

BONUS

VLPs are very immunogenic:
- display many neutralising epitopes (more than native virion)
- induce good T-cell helper responses for B-cells
  - important for robust antibody and B-cell memory responses

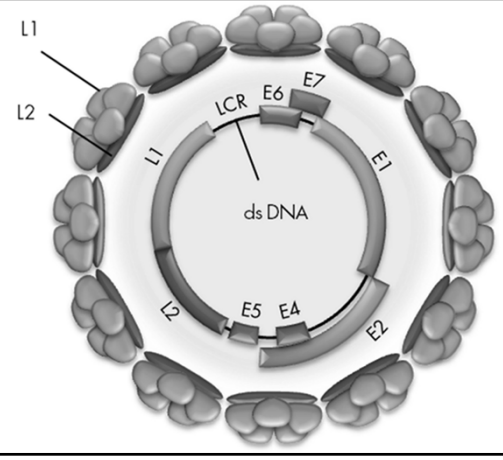
1. Prevent binding to cell surface/basement membrane receptors

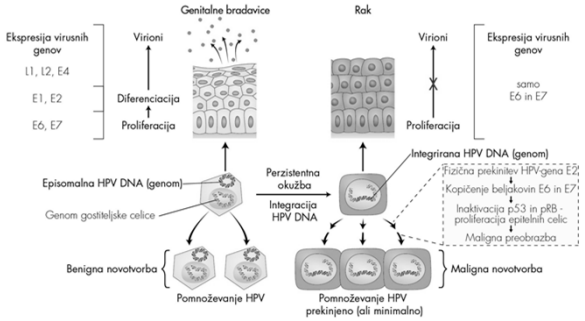
2. Prevent the conformational changes in the virus needed for viral entry



Sapp M, Day PA. Virology 2009;384: 400-9.

Molekularni model karcinogeneze, posredovane z visokorizičnimi genotipi HPV





Type-Dependent Integration Frequency of Human Papillomavirus Genomes in Cervical Lesions

Svetlana Vinokurova,[1] Nicolas Wentzensen,[1] Irene Kraus,[3] Ruediger Klaes,[4] Corina Driesch,[5] Peter Melsheimer,[2] Fjodor Kisseljov,[6] Mattias Dürst,[5] Achim Schneider,[7] and Magnus von Knebel Doeberitz[1]

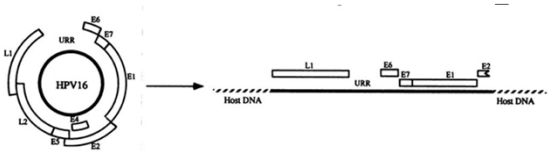
Cancer Res 2008;68(1):307–13

Table 2. Integrated HPV oncogene transcripts in cervical samples

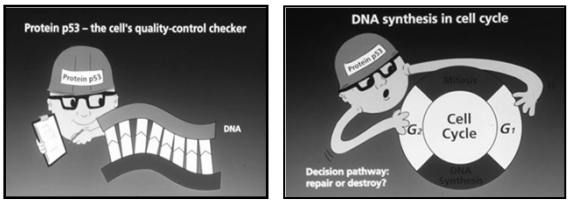
	Normal	CIN 1	CIN 2	CIN 3	CxCa	Total
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n*
HPV16	0/111 (0)	0/61(0)	5/83 (6)	27/141 (19)	33/60 (55)	456
HPV18	0/22 (0)	0/6 (0)	0/13 (0)	0/8 (0)	33/36 (92)	85
HPV31	0/22 (0)	0/16 (0)	0/29 (0)	3/29 (10)	2/14 (14)	110
HPV33	0/23 (0)	0/20 (0)	0/35 (0)	0/28 (0)	7/19 (37)	125
HPV45	0/8 (0)	0/5 (0)	0/12 (0)	6/10 (60)	20/24 (83)	59
	0/186 (0)	0/108 (0)	5/172 (3)	36/216 (17)	95/153 (62)	835

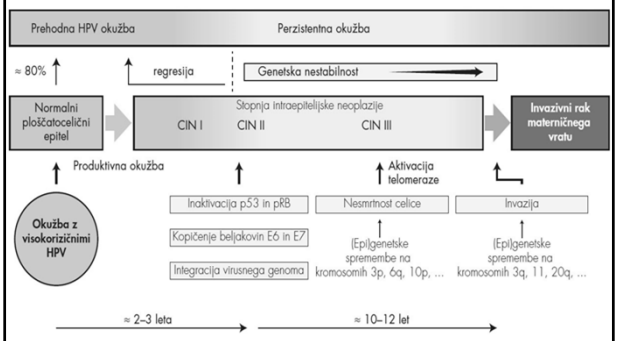
A review of over 190 integration loci confimed that HPV integration sites are randomly distributed over the whole genome.

Wentzensen N et al. Cancer Res 2004; 64: 3878-84.



Vousden K. FASEB J 1993; 7: 872-9.





Genome-wide analysis of HPV integration in human cancers reveals recurrent, focal genomic instability

Keiko Akagi,[1,2,3,10] Jingfeng Li,[1,2,3,10] Tatevik R. Broutian,[2,4] Hesed Padilla-Nash,[5] Weihong Xiao,[2,4] Bo Jiang,[2,4] James W. Rocco,[6,7] Theodoros N. Teknos,[8] Bhavna Kumar,[8] Danny Wangsa,[5] Dandan He,[1,2,3] Thomas Ried,[5] David E. Symer,[1,2,3,4,9,11,12] and Maura L. Gillison[2,4,11,12]

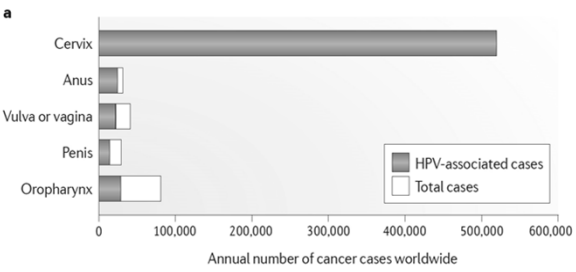
[1]Human Cancer Genetics Program, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio 43210, USA; [2]Viral Oncology Program, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio 43210, USA; [3]Department of Molecular Virology, Immunology and Medical Genetics, The Ohio State University, Columbus, Ohio 43210, USA; [4]Department of Internal Medicine, The Ohio State University, Columbus, Ohio 43210, USA; [5]Cancer Genomics Section, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland 20814, USA; [6]Center for Cancer Research and Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts 02114, USA; [7]Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts 02115, USA; [8]Department of Otolaryngology–Head and Neck Surgery, The Ohio State University Wexner Medical Center, Columbus, Ohio 43210, USA; [9]Department of Biomedical Informatics, The Ohio State University, Columbus, Ohio 43210, USA

Genome Res 2014; 24: 185-99.

Sample name	Gender	Anatomical site of origin	HPV status	Viral variant[a]	Viral copy number, real-time PCR[b]	Viral copy number, WGS[c]	Number of detected viral breakpoints, WGS[d]	Cell line reference
SiHa	F	Cervix	HPV16	EUR	0.397	1.5	2	Friedl et al. 1970
CaSki	F	Cervix	HPV16	EUR	122	831.6	47	Pattillo et al. 1977
UM-SCC-104	M	Oral cavity	HPV16	EUR	2.86	1.1	2	Tang et al. 2012
UD-SCC-2	M	Hypopharynx	HPV16	EUR	14.3	23.4	7	Ballo et al. 1999
UM-SCC-47	M	Tongue	HPV16	AFR2a	21.1	47.0	6	Lamford et al. 1999
UPCI:SCC090	M	Tongue	HPV16	EUR	182.0	483.0	33	White et al. 2007
HMS001	M	Tonsillar fossa	HPV16	ASN	0.81	1.0	2	This study
Tumor A	M	Oral cavity	HPV18	—	41.9	14.3	10	
Tumor B	M	Tonsil	HPV16	EUR	5.7	11.0	2	
C4L 27	M	Tongue	Negative	N/A	0	0	N/A	Gioanni et al. 1988
D562	F	Pharynx	Negative	N/A	0	0	N/A	Peterson et al. 1971
SCC-25	M	Tongue	Negative	N/A	0	0	N/A	Rheinwald and Beckett 1981

High-risk alpha HPV genotypes – related cancers

HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59



Schiller JT, Lowy DR. Nat Rev Microbiol 2012;10:681-92.

Osnovni koncept diagnostike okužbe s HPV

HPV !!!

HPV test ?

Pathogenic role of the eight probably/possibly carcinogenic HPV types 26, 53, 66, 67, 68, 70, 73 and 82 in cervical cancer

Gordana Halec,[1] Laia Alemany,[2,3] Belen Lloveras,[2,4] Markus Schmitt,[1] Maria Alejo,[2] Franz X Bosch,[4] Sara Tous,[2] Jo Ellen Klaustermeier,[2] Nuria Guimerà,[2,7] Niels Grabe,[8,9] Bernd Lahrmann,[8,10] Lutz Gissmann,[1,11] Wim Quint,[7] Francesc X Bosch,[2] Silvia de Sanjose,[2,3] and Michael Pawlita[1] on behalf of the Retrospective International Survey and HPV Time Trends Study Group[†]

eight HPV types which have been rarely but consistently identified as single HPV infections in about 3% of cervical cancers worldwide

55 CxCa tissues harbouring single pHR-HPV infections (2–13 cases per type) and 266 tissues harbouring single HR-HPV (7–40 cases per type) from a worldwide cross-sectional study

in 55 CxCa tissues E6*I mRNA expression was 100%; high p16INK4a, 98%; low pRb, 96%; low CyD1, 93%; and low p53, 84%

individual frequencies of five markers compared to HPV16 as a reference did not differ significantly

eight HPV types, when present as a single infection in CxCa, are biologically active and affect the same cellular pathways as any of the fully recognized carcinogenic HR-HPV types

although this evidence is crucial for HPV-type carcinogenicity classification, per se it is not sufficient for inclusion of these HPV types into population-wide primary and secondary prevention programmes

HPV Test

High genotypes coverage	BALANCED = ARTIFICIALLY REDUCED
High analytical sensitivity	BALANCED = ARTIFICIALLY REDUCED
High analytical specificity	NECESSARY

High clinical sensitivity !!!!

High clinical specificity !!!!

CIN 2+

Ideal HPV Test

optimal balance between clinical sensitivity and clinical specificity for CIN2+

aim to minimize redundant/excessive follow-up procedures for hr-HPV positive women with transient hr-HPV infections and/or without cervical lesions

*****

HPV assay with very high analytical sensitivity yield a large number of clinically insignificant positive results
unnecessary follow-up, diagnostics procedures and treatment of healthy women

Int. J. Cancer: **124,** 516–520 (2009)

FAST TRACK

Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older

Chris J.L.M. Meijer[10], Johannes Berkhof[2], Philip E. Castle[3], Albertus T. Hesselink[1], Eduardo L. Franco[4], Guglielmo Ronco[5], Marc Arbyn[6,7], F. Xavier Bosch[8], Jack Cuzick[9], Joakim Dillner[10], Danielle A.M. Heideman[1] and Peter J.F. Snijders[1]

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Requirements of HPV tests in primary cervical screening

1. A clinical sensitivity for CIN2+ not less than 90% of the clinical sensitivity of the hc2 in women of at least 30 years.

2. A clinical specificity for CIN2+ not less than 98% of the clinical specificity of the hc2 in women of at least 30 years of age.

3. Intra-laboratory reproducibility and inter-laboratory agreement with a lower confidence bound not less than 87%.

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Review

Nucleic Acid Tests for the Detection of Alpha Human Papillomaviruses

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2010 — 70 commercial HPV assays on the market

↓

2012 — 125 commercial HPV assays (and 84 variants) on the market

HPV Tests

- only a small subset of HPV tests has documented clinical performance
- 75% of HPV tests on the market without a single peer-reviewed publication
- several clinically unvalidated HPV assays are used worldwide in daily practice

2010 70 commercial HPV assays on the market

↓

2012 125 commercial HPV assays (and 84 variants) on the market

↓

2014 145+ commercial HPV assays (and 90+ variants) on the market

non-validated HPV tests should not be used in clinical management