



Baština Akademije nauka i umjetnosti Bosne i Hercegovine

**Simpozij Učestalost, dijagnostika i terapija
genitalnog karcinoma u Bosni i Hercegovini,
Sarajevo, 08. 06. 2007.**

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AKADEMIJA NAUKA I UMJETNOSTI BOSNE I HERCEGOVINE
АКАДЕМИЈА НАУКА И УМЈЕТНОСТИ БОСНЕ И ХЕРЦЕГОВИНЕ
ACADEMY OF SCIENCES AND ARTS OF BOSNIA AND HERZEGOVINA

POSEBNA IZDANJA
KNJIGA CXXV

Odjeljenje medicinskih nauka
Knjiga 34

SIMPOZIJ
UČESTALOST, DIJAGNOSTIKA
I TERAPIJA GENITALNOG KARCINOMA
U BOSNI I HERCEGOVINI

Sarajevo, 08.06.2007.

Uredili

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Senad Mehmedbašić

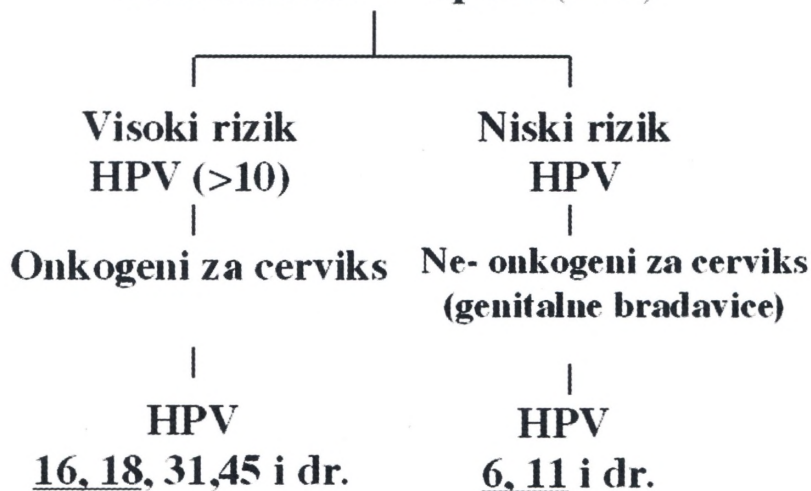
SARAJEVO, 2007.

Genitalna HPV infekcija u žena - liječenje i prevencija

S. Mehmedbašić



Genitalni HPV tipovi (>35)

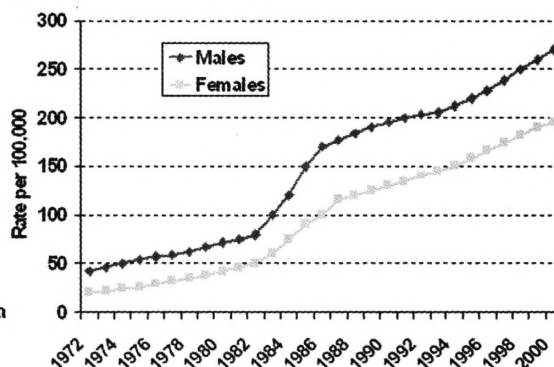


HPV uzrokuje anogenitalne bradavice

- Genitalne bradavice- teško i bolno se liječe, česta ponavljanja^{1,2}
- Predviđeni rizik tijekom života za razvoj genitalnih bradavicač 10%^{3,4}

Podaci o
dijagnozi
genitalnih
bradavica
(Engleska i
Wales)⁵

Rastuća incidencija



1. Maw RD, et al. *Int J STD AIDS*. 1998;9:571-578. 2. Kodaer CM, Naraty S. *Am Fam Physician*. 2004;70:2335-2342. 3. Franco EL, et al. In: *Prasco E, Monsonego J. New Developments in Cervical Screening and Prevention*. Oxford: Blackwell Science, 1997:14-22. 4. Tomolero-Luis G. *Hematol Oncol Clin North Am*. 1999;13:245-257. 5. *CDR Weekly*. 2001;11(35). Available at <http://www.hpa.org.uk/cdr/PDFfiles/2001/cdr13501.pdf>. Accessed April 8, 2005.

As you have heard, HPV causes benign and malignant tumors of the anogenital tract. The most common lesions are cervical cancers and their precursor lesions, as well as benign genital warts.

While Pap testing has reduced cervical cancer rates in developed countries, there are significant drawbacks to this intervention:

First, women must be tested throughout their lives. The health system must either rely on women's awareness of testing, or it must invest in an expensive infrastructure to ensure compliance.

Second, screening has limited sensitivity and specificity, even with the expensive Thin Prep + HPV Testing method

Third, women are negatively affected by a pre-cancer diagnosis - they worry, they miss work, and there is damage to their intimate relations.

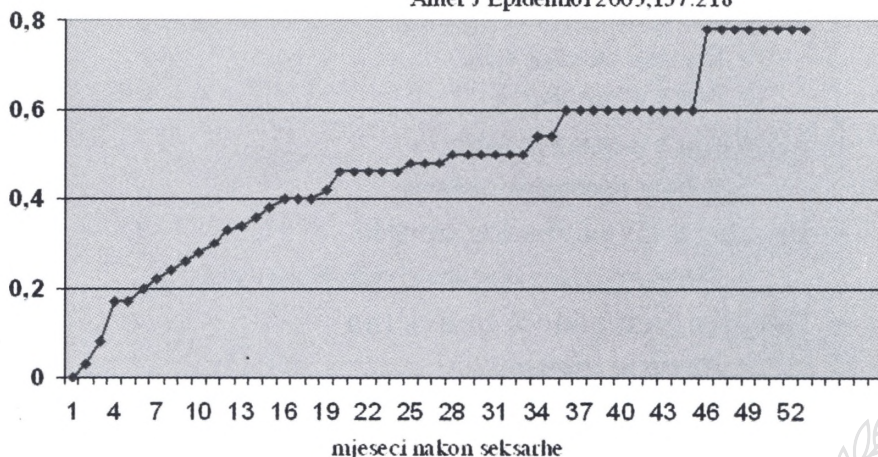
Fourth, the cost of screening is very high - over \$6 Billion per year in the U.S..

In the developing world, this cost makes screening difficult to implement.

A safe and effective vaccine is more efficient.

Rizik za genitalnu HPV infekciju od seksarhe (dob 18-23 godine)

Amer J Epidemiol 2003;157:218



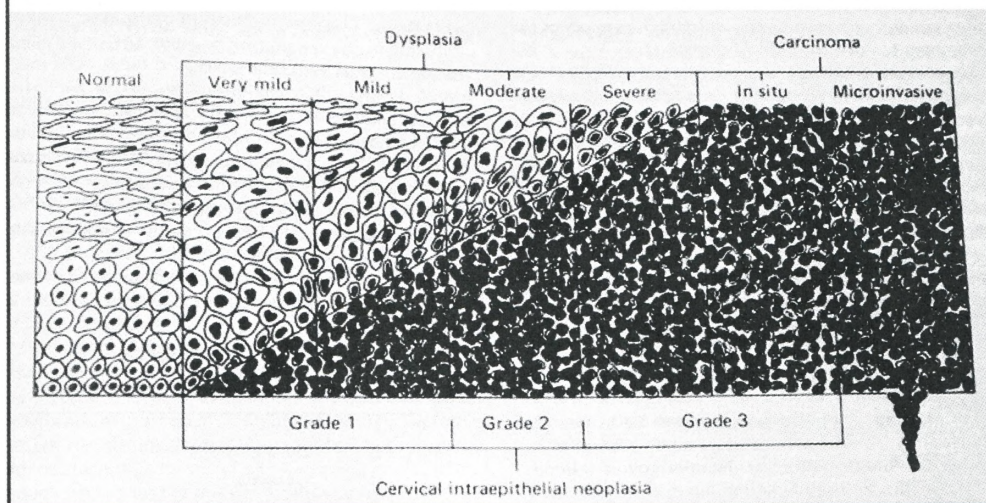
Rizik tijekom života za HPV genitalnu infekciju i posljedice HPV

- genitalna HPV infekcija >50%
- genitalne bradavice >5%
- žene bez redovitog PAPA skrininga
 - do 4% invazivni karcinom cerviksa
- žene s redovitim PAPA skriningom
 - abnormalan nalaz >35%
 - invazivni karcinom cerviksa <1%
- ostali anogenitalni karcinomi <1%
 - karcinom anusa u MSM do 4%

Patogeneza HPV genitalne infekcije

- Mikrotrauma
 - Infekcija bazalnog sloja
 - Rast u gornje slojeve
- Latentna virusna infekcija
 - Stabilni neintegrirani episomi
- Prolifracija pločastog epitela
 - Bradavice i šiljati kondilomi (vegetativna replikacija)
- Integracija u genom domaćina
 - Aktivacija onkogeni
 - Inaktivacija tumor supresorskih gena

Cervikalna Intraepitelna Neoplazija



Dijagnostika genitalnog HPV u žena

- Vizualno
 - Genitalne bradavice i kondilomi
- Eksfolijativna citologija
 - Skvamozna intraepitelna lezija
 - Niski stupanj
 - Visoki stupanj
 - Koilocitoza, diskarioza, atipične bazalne stanice
- Kolposkopija
 - Acidobijeli epitel, ravni kondilomi, punktacije, baza, atipična vaskularizacija
- Histologija
 - Hiperplazija bazalnih stanica, akantoza, papilomatoza, koilocitoza, parakeratoza

Liječenje genitalne HPV infekcije

Nema odgovarajućeg lijeka za eradikaciju genitalnog HPV!

Učinkovitim liječenjem uklanjamo tjelesne simptome i psihičke simptome prouzročene lezijom

Liječenje genitalnog HPV u žena

- Liječenje upale donjeg genitalnog sustava
 - Vulvitis, kolpitis, cervicitis
- Kondom
- Specifično liječenje HPV lezija

Načini liječenja

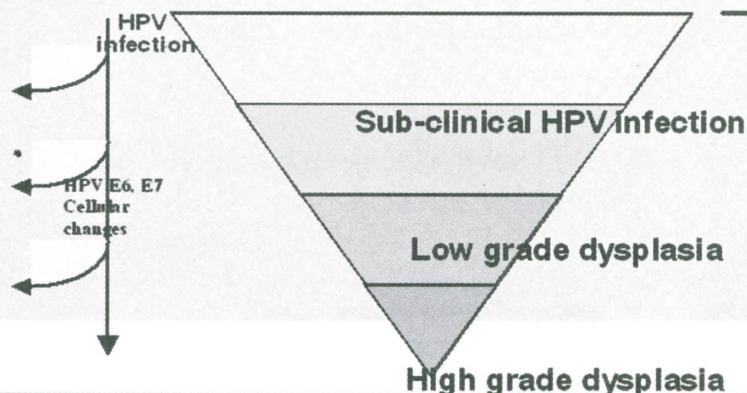
Podofilox	Ekskohleacija
Podofilin	Kiretaža
Imiquimod	Ekscizija hladnim nožem
TCA, BCA	Krioterapija
Interferon	Elektrokauterizacija
	Laser

Što će se dogoditi ako ništa ne poduzmemo?

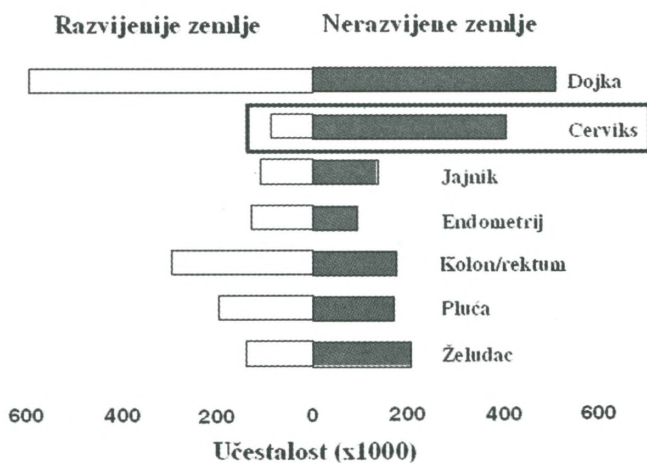
- Samoizlječenje?
- Dobroćudna bolest?
- Rak vrata maternice?



Natural History of Cervical HPV Infection



Najčešći karcinomi u žena



Parkin et al, Eur J Cancer 2001; 37:54

IARC slides from Nubia Munoz, Year 2000 IARC

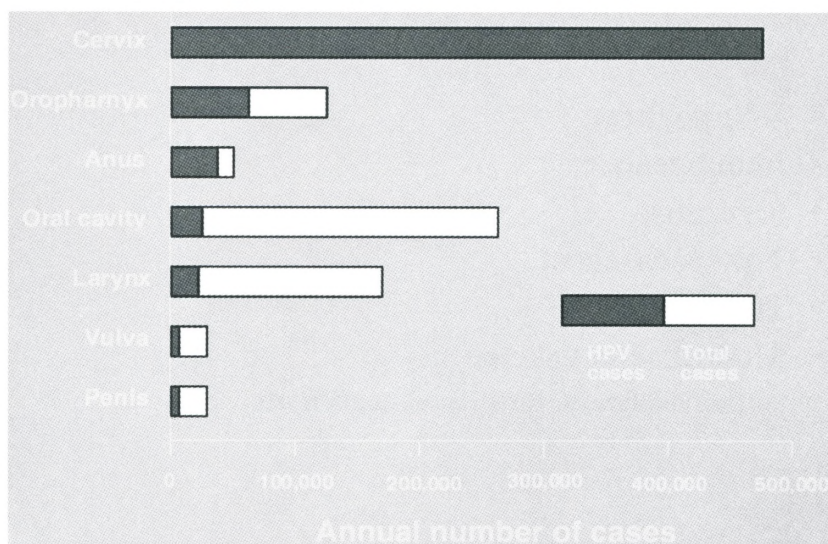
HPV i karcinom

- HPV infekcija je etiološki faktor u karcinomu cerviksa i nekim drugim karcinomima
- Karcinomi povezani s HPV infekcijom su 1/3 svih karcinoma povezanih s infektivnim uzročnicima
- > 600.000 novih slučajeva karcinoma godišnje pripisani HPV infekciji

Izvor: International Agency for Research on Cancer (IARC)

IARC slides from Nubia Munoz, Year 2000 IARC

Učestalost i raspodjela karcinoma pripisanih HPV infekciji



IARC slides from Nubia Munoz, Year 2000 IARC

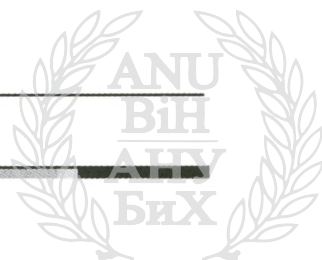


Rak vrata maternice u svijetu

- 5. najčešći karcinom u ljudi
- 2. najčešći karcinom u žena
- Najčešći karcinom u zemljama u razvoju
- životna dob u vrijeme smrti
 - rak vrata maternice **57 godina**
 - svi karcinomi **72 godine**

Humano Cjepivo za HPV

- Učinkovitost
- Imunogenost
- Sigurnost
- Tip-specifičnost
- Trajanje zaštite
- Modifikacija vakcine
 - polivalentnost, terapijske mogućnosti



Profilaktičko HPV cjepivo

- **Četverovalentno HPV cjepivo GARDASIL™**
 - (tip 6, 11, 16, 18)
- VLPs na *Saccharomyces cerevisiae*
 - Osnova: kvasac koja služi za cjepiva korištena u milijunima ljudi do sada.
- Aluminum dodatak 225 µg po dozi
- 0.5 mL injiciranog volumena
- 3 doze unutar 6 mjeseci (0,2,6)



GARDASIL is a trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA.

*VLP = Virus-like particle.

1. Villa LL, Costa RL, Petta CA, et al. *Lancet Oncol.* 2005;6:271–278.

Key Point

GARDASIL™ is Merck's quadrivalent HPV L1 VLP vaccine. It is produced in recombinant yeast, like the hepatitis B vaccine, and adsorbed on a proprietary aluminum adjuvant, like the tetanus vaccine.

Background

Merck's quadrivalent vaccine has the advantage that it targets 4 HPV types (6, 11, 16 and 18).¹ Together, HPV Types 16 and 18 account for about 70% of cervical cancer and high-grade lesions, whereas HPV Types 6 and 11 are associated with approximately 90% of anogenital warts.¹ Together, these 4 types are responsible for over 40% of low-grade cervical lesions,² and HPV 16 and 18 account for over 50% of high-grade lesions.³

The active quadrivalent vaccine is a mixture of 4 recombinant HPV type-specific VLPs consisting of the L1 major capsid proteins of HPV 6, 11, 16, and 18 synthesized in *Saccharomyces cerevisiae*.¹ Expression of the L1 protein in yeast generates noninfectious VLPs that resemble HPV virions.¹ A similar method is used for hepatitis B vaccine.⁴

The 4 VLP types were purified and absorbed onto amorphous aluminum hydroxyphosphate sulfate adjuvant.¹ The adjuvant dose was 225 micrograms per dose, and the vaccine injection volume was 0.5 mL, given by intramuscular injection at Day 1, Month 2, and Month 6.¹

GARDASIL is a trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA.

References

1. Villa LL, Costa RLR, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: A randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol*. 2005;6:271-278.
2. Clifford GM, Rana RK, Franceschi S, Smith JS, Gough G, Pimenta JM. Human papillomavirus genotype distribution in low-grade cervical lesions: Comparison by geographic region and with cervical cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14:1157-1164.
3. Clifford GM, Smith JS, Plummer M, Muñoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: A meta-analysis. *Br J Cancer*. 2003;88:63-73.
4. Recombivax HB® Hepatitis B Vaccine (Recombinant) prescribing information. Merck & Co, Inc. Whitehouse Station, NJ. 1998.

Cilj: Prevenција najvažnijih bolesti povezanih s HPV infekcijom

- Smanjenje rizika:
 - Raka vrata maternice
 - Cervikalne intraepitelne neoplazije (CIN)
 - Vulvarne intraepitelne neoplazije (VIN) i karcinoma
 - Vaginalne intraepitelne neoplazije (VaIN) i karcinoma
 - Kondiloma
- proporcionalno broju cijepljenih žena u općoj populaciji

Key point

The development of GARDASIL™ aims at demonstrating efficacy against HPV related diseases.

GARDASIL is a trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA.

Zašto četverovalentno HPV (Tip 6, 11, 16, and 18) cjepivo?

- Profilaktičkim davanjem očekuje se bitan utjecaj na bolesti koje se povezuju s HPV infekcijom.¹

Tip	Žene	Muškarci
6/11	• >90% kondiloma^{2a} • -10-25% SIL niskog stupnja^{3b} • Transplacentarni prijenos na dijete uzrokuje respiratornu papilomatozu	• >90% kondiloma^{2a} • Prenosanje na žene⁹
16/18	• -25% SIL niskog stupnja^{3b} • -50% SIL visokog stupnja^{4c} • -70% karcinoma cerviksa^{3h,5d,6e} • -70% ostalih genitalnih karcinoma^{7,6g}	• 60% analnih karcinoma^{10h} • Prenosanje na žene⁹

1. FUTURE II Study Group. A phase III randomized controlled trial of the efficacy of the quadrivalent human papillomavirus (HPV) vaccine in preventing HPV-related diseases in women. *N Engl J Med*. 2005;352:1905-1917. 2. O'Connell J, et al. *Proc Natl Acad Sci USA*. 1993;90:5560-5563. 3. Cuzick D, et al. *Br J Cancer*. 2003;89:101-105. 4. Hooton M, et al. *Sex Transm Dis*. 2003;82:19-27. 5. Cuzick D, et al. *Br J Cancer*. 2003;89:101-105. 6. Cuzick D, et al. *Br J Cancer*. 2003;89:101-105. 7. Cuzick D, et al. *Br J Cancer*. 2003;89:101-105. 8. Cuzick D, et al. *Br J Cancer*. 2003;89:101-105. 9. Cuzick D, et al. *Br J Cancer*. 2003;89:101-105. 10. Cuzick D, et al. *Br J Cancer*. 2003;89:101-105.

6 i 11 su odgovorni za...
16 i 18 su odgovorni za...

Key Point

Due to the morbidity associated with HPV types 6, 11, 16, and 18, a prophylactic quadrivalent HPV vaccine targeting these 4 HPV types is expected to substantially reduce the burden of HPV-related disease.

Background

Although many HPV types are known, only a few of them cause the vast majority of disease.¹ For example, low-risk HPV Types 6 and 11 are responsible for >90% of all anogenital warts in women and men.^{1,2} HPV 16 and 18 are the 2 HPV types most commonly identified in patients with cervical cancer.³ Together, HPV 16 and 18 are responsible for at least 70% of cervical cancers.³⁻⁵ HPV infection also has been closely linked to several other tumors.⁶⁻⁸ Together HPV Types 6, 11, 16 and 18 are responsible for approximately 35% of low-grade lesions of the cervix,⁴ and HPV 16 and 18 for at least 50% of high-grade lesions.⁹

Although some men may experience anal or genital lesions associated with HPV 16 and 18,¹⁰ most men generally serve as "carriers" or "vectors" of oncogenic HPVs. In fact, male partners may be important contributors to the risk of cervical cancer in their female partners.¹¹

Because most HPV-related disease is associated with HPV Types 6, 11, 16, and 18, a quadrivalent vaccine that targets these HPV types is expected to substantially reduce the burden of HPV-related disease.¹²

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5. Clifford GM, Smith JS, Plummer M, Muñoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: A meta-analysis. *Br J Cancer.* 2003;88:63-73.
6. Daling JR, Madeleine MM, Schwartz SM, et al. A population-based study of squamous cell vaginal cancer: HPV and cofactors. *Gynecol Oncol.* 2002;84:263-270.
7. Bjorge T, Dillner J, Anttila T, et al. Prospective seroepidemiological study of role of human papillomavirus in non-cervical anogenital cancers. *BMJ.* 1997;315:646-649.
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