Vaccino vs HPV dopo trattamento



Azienda USL Toscana NordOvest
Ospedale ss.ti Giacomo e Cristoforo
Massa
Dr. A. Ghelardi

REGIONE TOSCANA

Review 2006-2017

- *Conoscenze immunologiche*
  - *Infezione naturale*
  - *Risposta evocata dal vaccino*

- *Conoscenze epidemiologiche*
  - *Review dei dati 2006-2017*

- *Studi retrospettivi*
  - *Review dei dati 2006-2017*
- *Dati prospettici*

Stanley MA. Human papillomavirus vaccines.Rev Med Virol. 2006 May-Jun;16(3):139-49. Review.

Carter JJ, Koutsky LA, Hughes JP, Lee SK, Kuypers J, Kiviat N, Galloway DA.Bachmann MF, Rohrer UH, Kundig TM, Burki K, Hengartner H, Zinkernagel RM.Comparison of human papillomavirus types 16, 18, and 6 capsid antibody responses following incident infection. J Infect Dis. 2000 Jun;181(6):1911-9.

Ho GY, Studentsov YY, Bierman R, Burk RD.Natural history of human papillomavirus type 16 virus-like particle antibodies in young women. Cancer Epidemiol Biomarkers Prev. 2004 Jan;13(1):110-6.

Olsson S-E, Kjaer SK, Sigurdsson K, Iversen O-E, Hernandez-Avila M, Wheeler CM, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. Human Vaccines 2009;5:696-704

Villa LL, Ault K, Giuliano AR, Costa RLR, Petta CA, Andrade RP, et al. Immunologic responses following administration of a vaccine targeting human papillomavirus types 6, 11, 16 and 18. Vaccine 2006;24:5571-83.

Olsson S-E, Villa LL, Costa R, Petta C, Andrade R, Malm C, et al. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like-particle vaccine. Vaccine 2007;25:4931-9.

The FUTURE II Study Group. Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virologic evidence of HPV infection. J Infect Dis 2007;196:1438-46.

Munoz N, Kjaer SK, Sigurdsson K, Iversen O-E, Hernandez-Avila M, Wheeler CM, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst 2010;102:325-39.

Munoz N, Kjaer SK, Sigurdsson K, Iversen O-E, Hernandez-Avila M, Wheeler CM, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst 2010;102:325-39.

Munoz N, Manalastas R, Pitisuttithum P, Tresukosol D, Monsonego J, Ault K, et al. Safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women between 24 and 45 years of age: a randomized, double-blind trial. Lancet 2009;373:1949-57.

Castellsague X, Munoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Cancer 2011;105:28-37.

COI

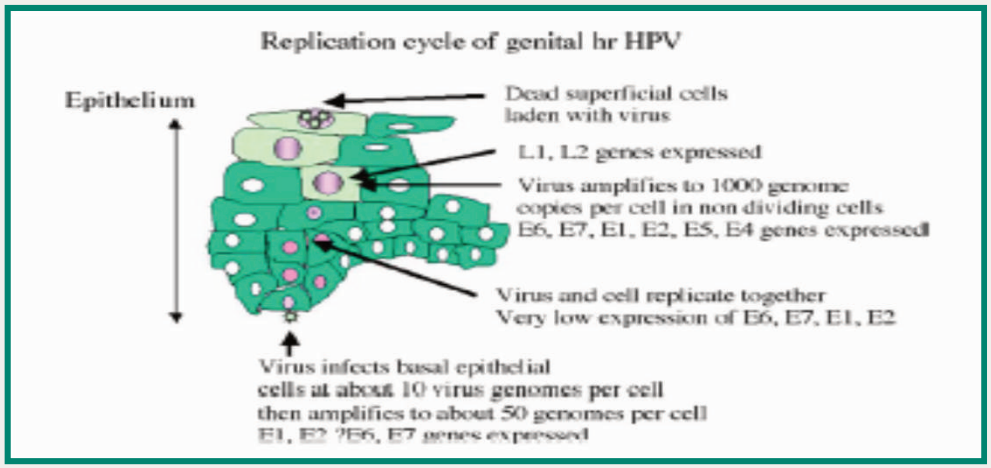
Dichiaro di non avere conflitti di interesse riguardo all' argomento trattato in questa relazione

Current data show that HPV vaccination does not reduce progression to cervical precancers in women with ongoing infections at the time of vaccination…

Le conoscenze attuali dimostrano che il vaccino non è in grado di ridurre i tassi di progressione della lesioni pretumorali in pazienti con infezione corrente al tempo della vaccinazione…

CONOSCENZE IMMUNOLOGICHE
LE BASI DELLA RICERCA CLINICA

Si evidenzia come i meccanismi di riconoscimento adattativi del sistema immunitario siano a volte inefficaci nella risposta naturale all'esposizione del Papilloma virus. Il breve ciclo vitale dei cheratinociti evita la necessità da parte del virus di lisare la cellula e ciò impedisce l'innesco della risposta infiammatoria e pone le basi per l'escape immunologico.



Stanley MA. Human papillomavirus vaccines.Rev Med Virol. 2006 May-Jun;16(3):139-49. Review.

EVIDENZE CLINICHE: INFEZIONE NATURALE E RISPOSTA IMMUNOLOGICA

L' infezione naturale infatti non sempre evoca una risposta immunitaria sierologicamente rilevabile ed è noto come dal 30% al 40% delle donne con infezione da HPV 16 non sviluppi una siero conversione pur in presenza di DNA virale rilevato in PCR

Carter JJ, Koutsky LA, Hughes JP, Lee SK, Kuypers J, Kiviat N, Galloway DA.Bachmann MF, Rohrer UH, Kundig TM, Burki K, Hengartner H, Zinkernagel RM.Comparison of human papillomavirus types 16, 18, and 6 capsid antibody responses following incident infection. J Infect Dis. 2000 Jun;181(6):1911-9. Ho GY, Studentsov YY, Bierman R, Burk RD.Natural history of human papillomavirus type 16 virus-like particle antibodies in young women. Cancer Epidemiol Biomarkers Prev. 2004 Jan;13(1):110-6.

EVIDENZE CLINICHE RIATTIVAZIONE - REINFEZIONE

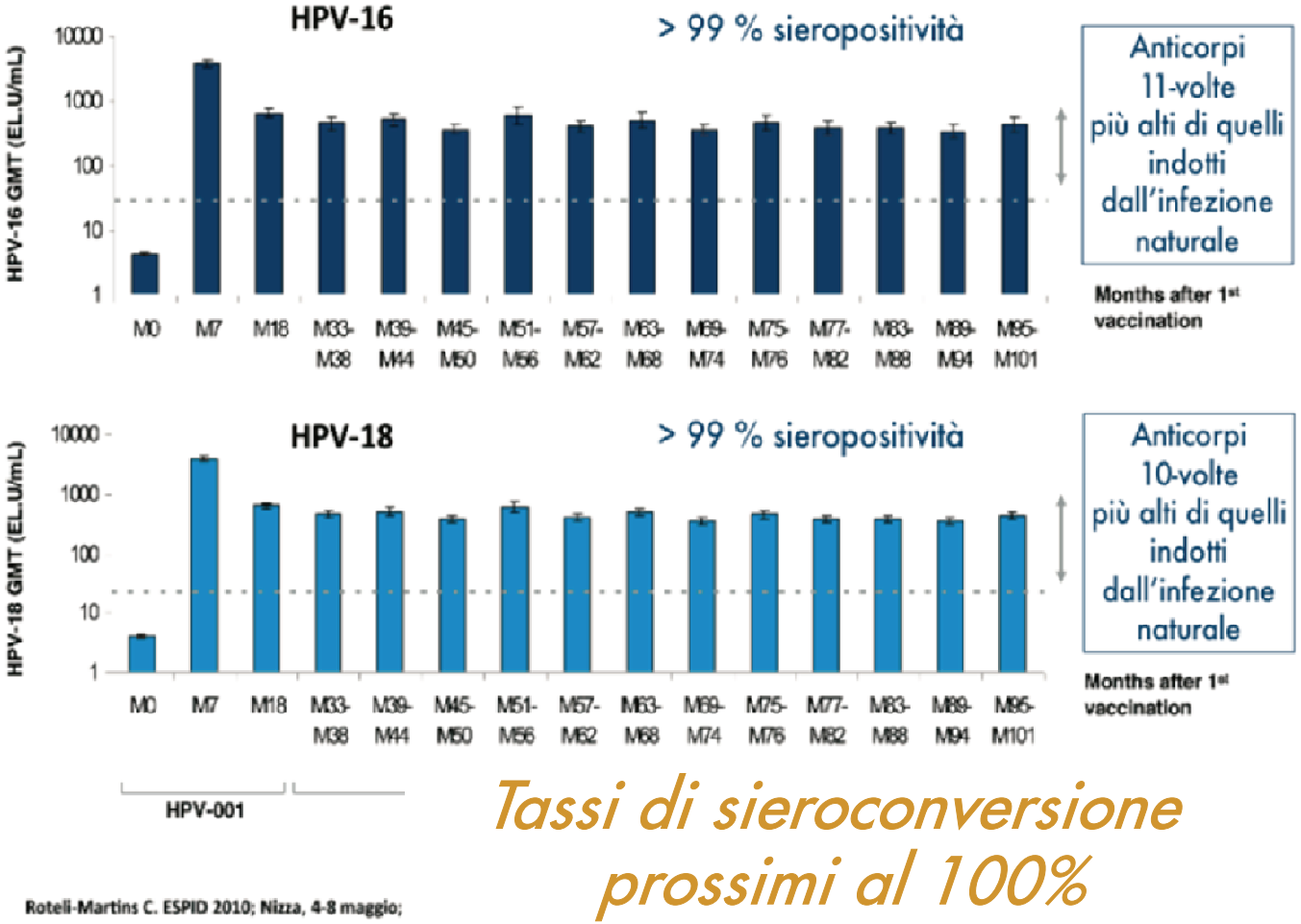
Gli Ab evocati dall'infezione naturale possono
NON PROVVEDERE ad una protezione duratura:

L'immunità naturale non sembra avere un ruolo nel controllo delle reinfezioni virali sia anche in caso di riattivazioni con lo stesso virotipo (H.Trottier & E.Franco 2010)

Fino al 19% delle infezioni tipo specifiche divenute non rilevabili sono nuovamente positive entro 1 anno (R. Winer 2011)

Nell'infezione naturale la sieropositività non è associata ad un decremento del rischio di infezione con lo stesso virotipo (R.Viscidi 2004; B.Lu 2012)

EVIDENZE CLINICHE RISPOSTA IMMUNITARIA EVOCATA DA VACCINO



Tassi di sieroconversione prossimi al 100%

Roteli-Martins C. ESPID 2010; Nizza, 4-8 maggio;

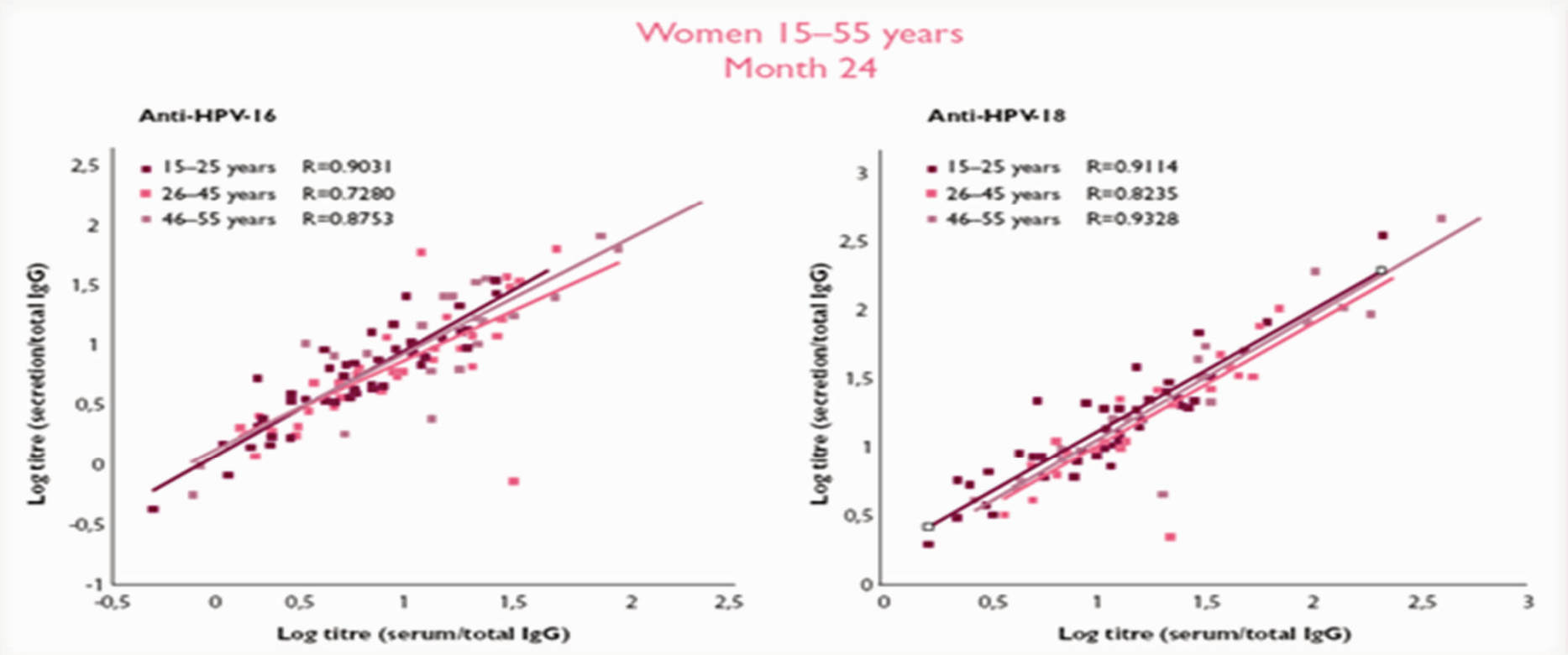
EVIDENZE CLINICHE
RIATTIVAZIONE - REINFEZIONE

Antibody titers	PY	No. of new HPV16/18 infections	Univariate, RR (95% CI)	Multivariable,RR (95% CI)†
Enrollment HPV16 titers				
Negative	5886	231	1	1
0–33rd ptl (8–16 EU/mL)	627	20	0.81 (0.50 to 1.25)	0.79 (0.48 to 1.22)
33–66th ptl (17–59 EU/mL)	749	28	0.95 (0.63 to 1.38)	0.83 (0.53 to 1.25)
≥66th ptl (≥60 EU/mL)	581	12	0.53 (0.28 to 0.90)	0.50 (0.26 to 0.86)
Enrollment HPV18 titers				
Negative	6352	136	1	1
0–33rd ptl (7–10 EU/mL)	620	19	1.43 (0.86 to 2.25)	1.36 (0.81 to 2.15)
33–66th ptl (11–27 EU/mL)	760	17	1.04 (0.61 to 1.68)	1.01 (0.59 to 1.65)
≥66th ptl (≥28 EU/mL)	675	6	0.42 (0.16 to 0.86)	0.36 (0.14 to 0.76)

Women with higher Ab titres were at reduced risk of subsequent new HPV16 (-50%) and HPV18 (-64%) infection.

(M. Safaeian, 2010)

IPOTESI DI MECCANISMI DI PROTEZIONE EVIDENZE CLINICHE LIVELLI AB SIERO- CERVICE PZ VACCINATE



S. Poncele et al. 24th International Papilomavirus Conference and Clinical Workshop 2007

"..and that the quadrivalent HPV vaccine prevents reinfection or reactivation of disease that is related to vaccine HPV types."

Donne esposte ad infezione virale sieroconvertite (presenza di IgG anti HPV) senza evidenza di malattia e PCR negative per la ricerca di DNA virale, cioè con pregressa infezione naturale, successivamente vaccinate → non evidenza di malattia a 40 mesi

Olsson S-E, Kjaer SK, Sigurdsson K, Iversen O-E, Hernandez-Avila M, Wheeler CM, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. Human Vaccines 2009;5:696-704

"..quadrivalent HPV vaccine generates an anamnestic response (renewed rapid production of an antibody on a subsequent encounter with the same antigen) in women aged 15–26 who are seropositive before vaccination."

Rinnovata rapida produzione di Ab contro lo stesso antigene incontrato anche nelle donne già esposte (età 15-26)

Villa LL, Ault K, Giuliano AR, Costa RLR, Petta CA, Andrade RP, et al. Immunologic responses following administration of a vaccine targeting human papillomavirus types 6, 11, 16 and 18. Vaccine 2006;24:5571-83.
Olsson S-E, Villa LL, Costa R, Petta C, Andrade R, Malm C, et al. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like-particle vaccine. Vaccine 2007;25:4931-9.

"..women who are infected with one or more vaccine HPV types derive residual benefit by the quadrivalent HPV vaccine's prevention of infection and disease from HPV type(s) to which the woman has not yet been exposed".

Vantaggio della vaccinazione contro successive infezioni non ancora acquisite.

The FUTURE II Study Group. Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virologic evidence of HPV infection. J Infect Dis 2007;196:1438-46.

"..Intention to treat analysis that measured the impact of the quadrivalent HPV vaccine in a mixed population of HPV naïve and HPV infected women, vaccination significantly reduced the number of abnormal smear test results and procedures such as colposcopy, biopsy examination, and definitive therapy irrespective of the causal HPV type."

Analisi popolazione ITT pazienti non necessariamente naïve, il vaccino riduce significativamente il numero di citologie anomale e approfondimenti di secondo livello fino a terapia indipendentemente dal virotipo HPV

Munoz N, Kjaer SK, Sigurdsson K, Iversen O-E, Hernandez-Avila M, Wheeler CM, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst 2010;102:325-39.

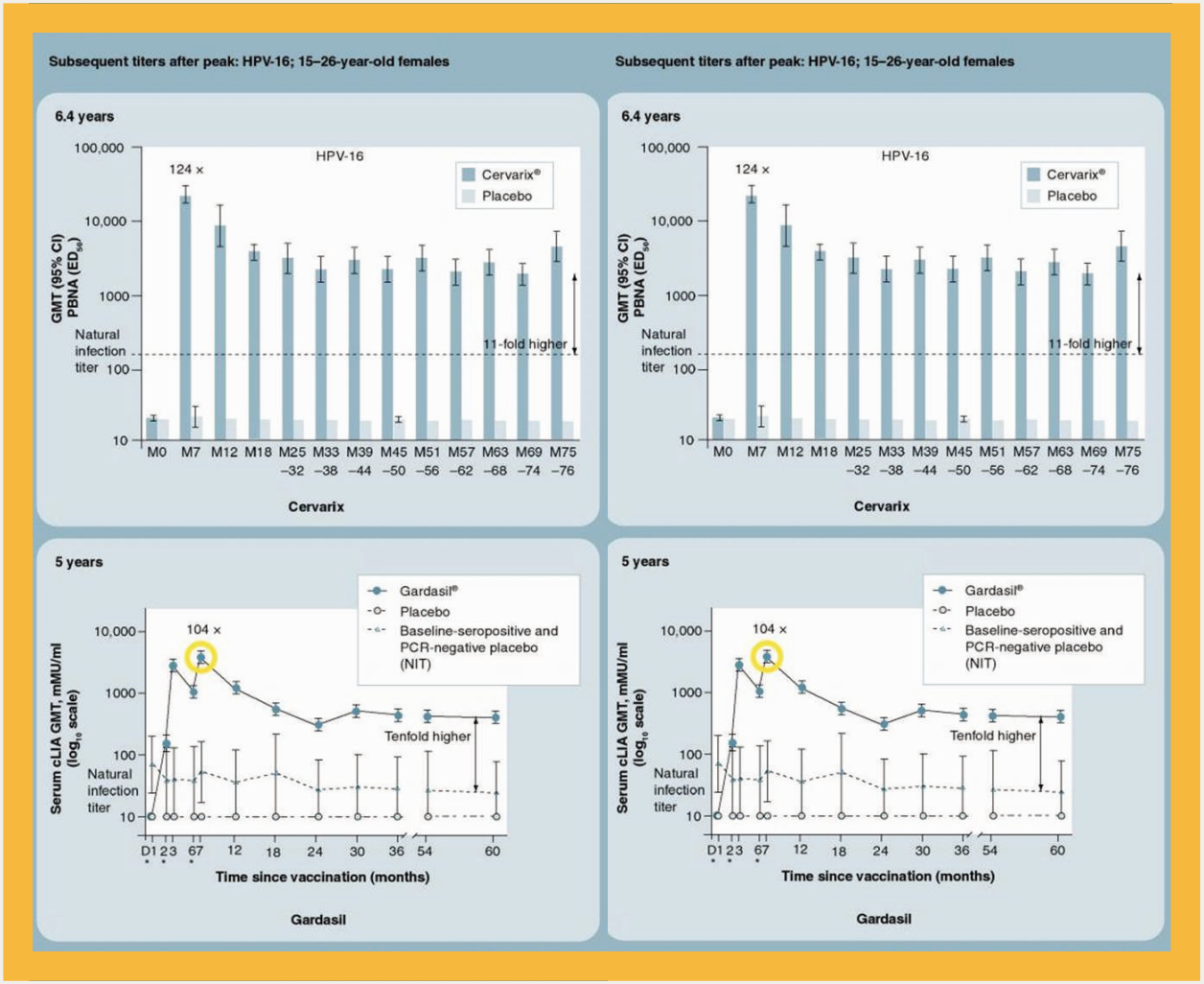
"..the vaccine is also effective in women up to the age of 45, whereby prophylactic vaccine efficacy against disease related to vaccine HPV types was 92.4% (49.6% to 99.8). "

Il vaccino è efficace fino a 45 anni, dove la sua prevenzione clinica nei confronti delle successive malattie HPV correlate è stata del 92.4%

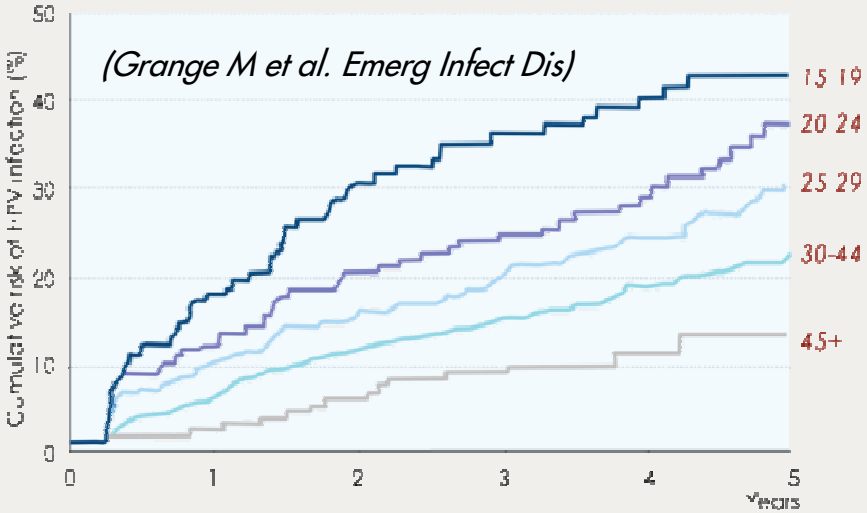
Munoz N, Manalastas R, Pitisuttithum P, Tresukosol D, Monsonego J, Ault K, et al. Safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women between 24 and 45 years of age: a randomized, double-blind trial. Lancet 2009;373:1949-57.

Castellsague X, Munoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Cancer 2011;105:28-37.

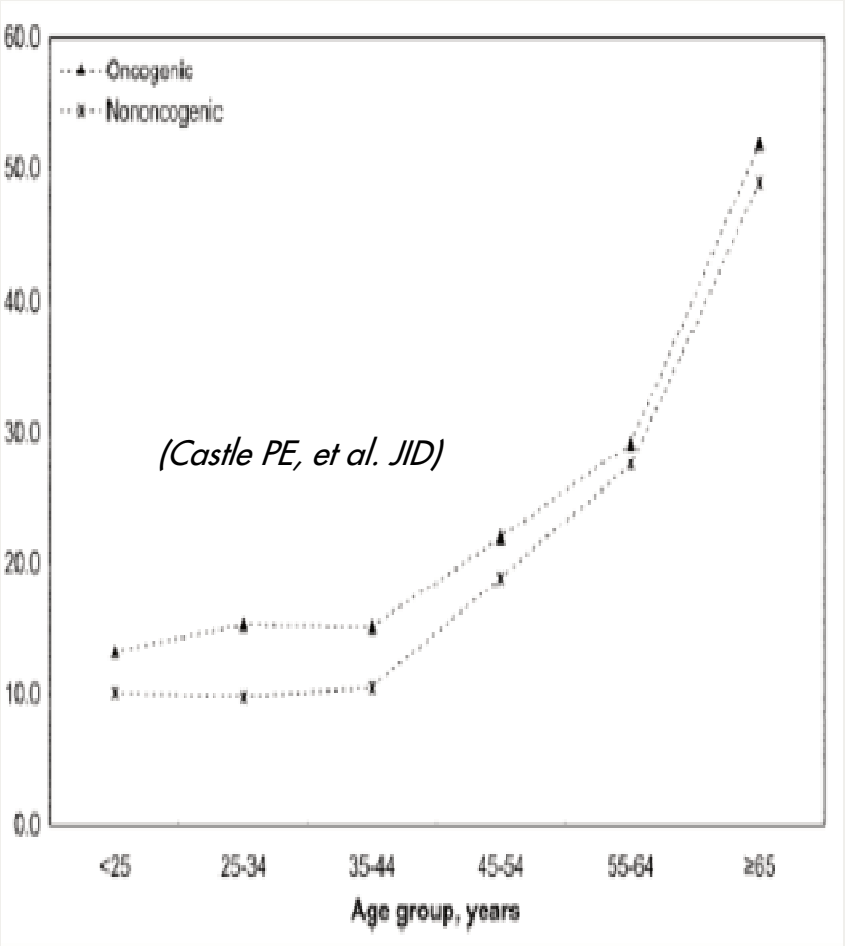
EVIDENZE CLINICHE LIVELLI AB VACCINO VS INF. NATURALE



INCIDENZA NUOVE INFEZIONI



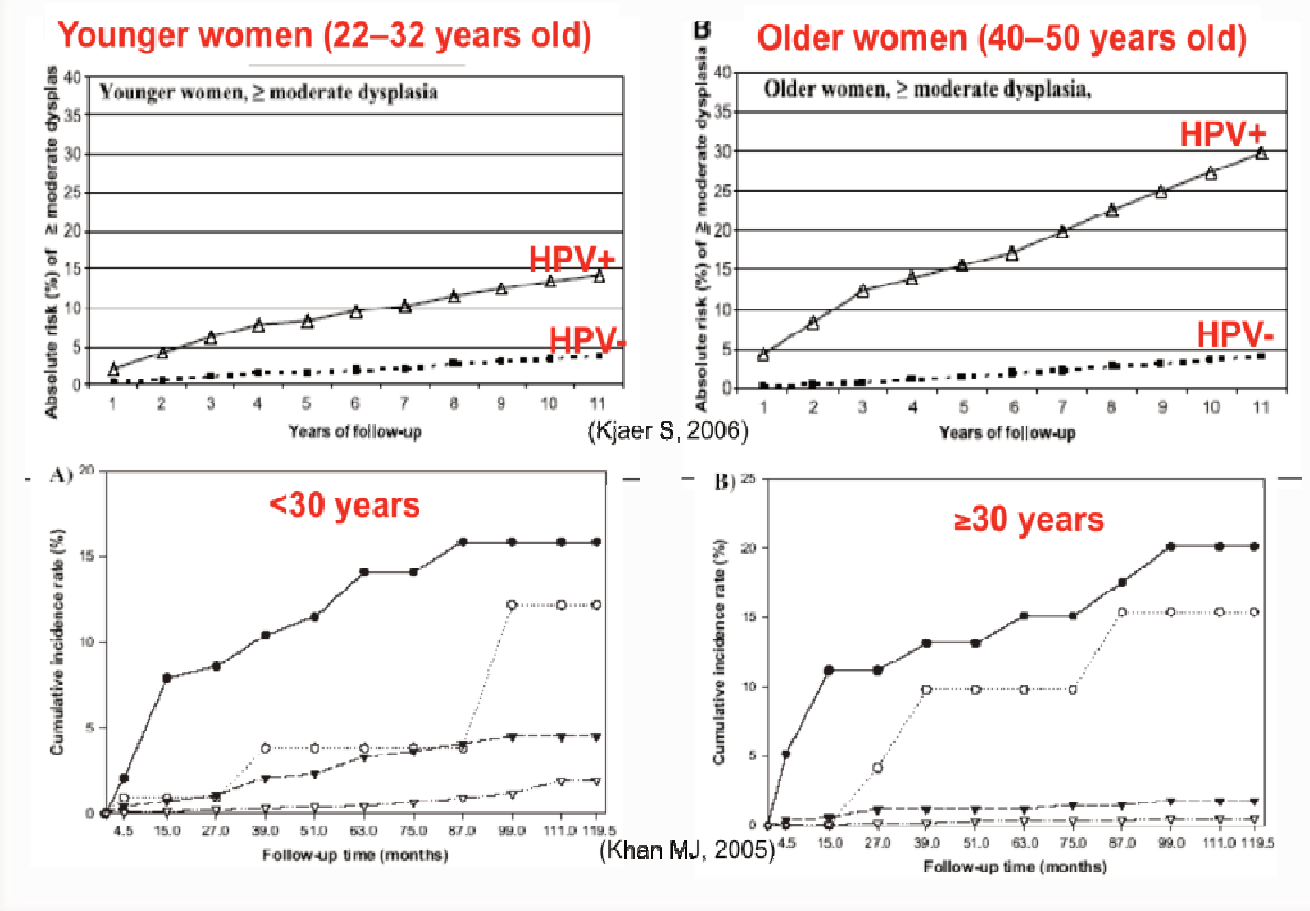
	% acquisizione nei 3 aa	
Età	HPV 16	HPV 18
21	3.7	2.5
31	3.1	5.3
41	3.1	3.1
51	3.0	3.8

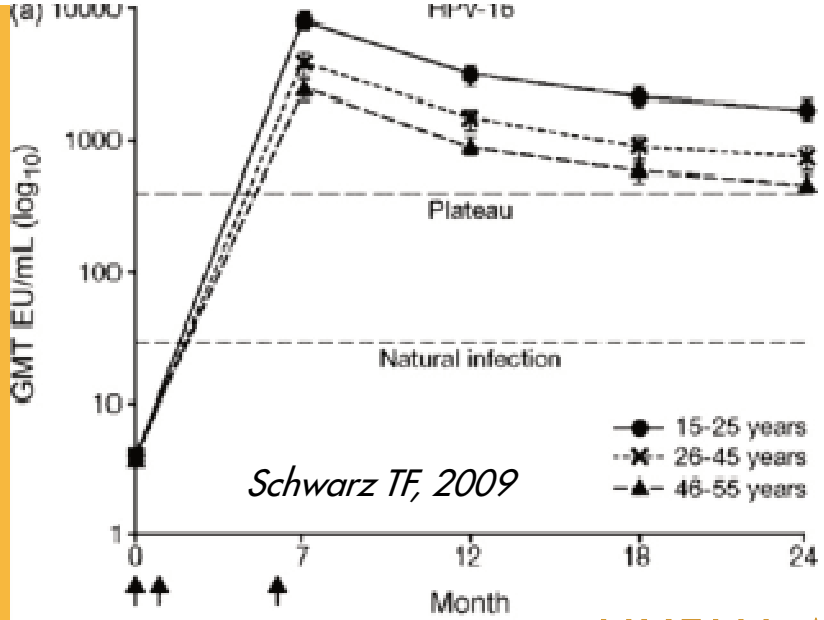


PERSISTENZA IN ETÀ ADULTA

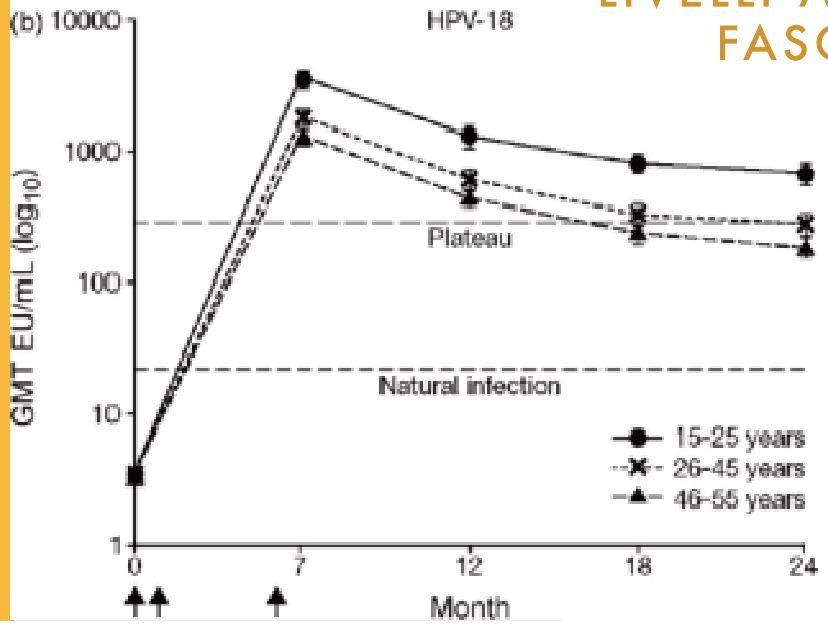
PROGRESSIONE PER FASCE D'ETÀ



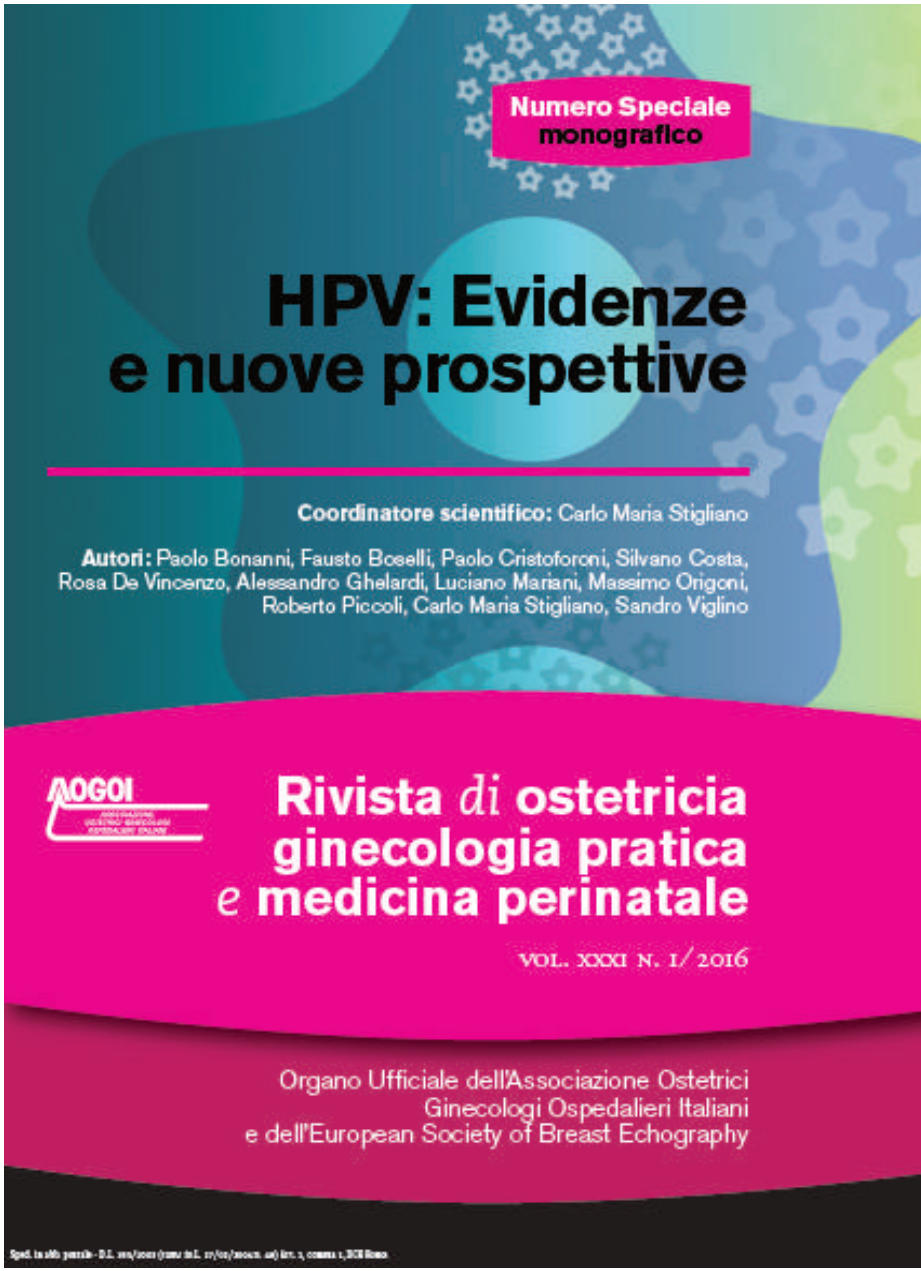




Schwarz TF, 2009



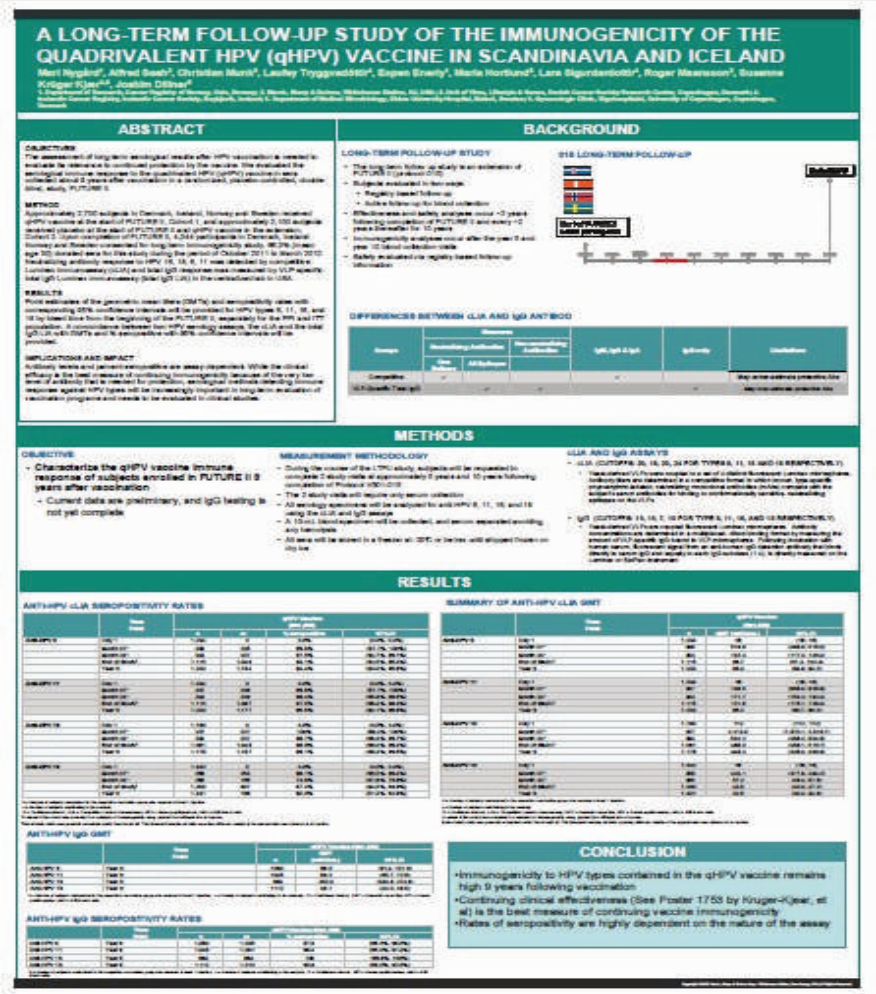
LIVELLI AB EVOCATI PER FASCIA DI ETA'



Long Term Follow Up Study di qHPV in Scandinavia e Islanda

Immunogenicità dopo oltre 10 anni attraverso raccolta di sieri (~14 anni post-vaccinazione)

- Immunogenicità verso i 4 tipi di HPV rimane elevata a negli anni dalla vaccinazione
- Nessun caso di "breakthrough" di CIN2 HPV 16/18 correlate è stato rilevato in PPP con vaccinazione con qHPV



A LONG-TERM FOLLOW-UP STUDY OF THE IMMUNOGENICITY OF THE QUADRIVALENT HPV (qHPV) VACCINE IN SCANDINAVIA AND ICELAND

ABSTRACT

BACKGROUND

METHODS

RESULTS

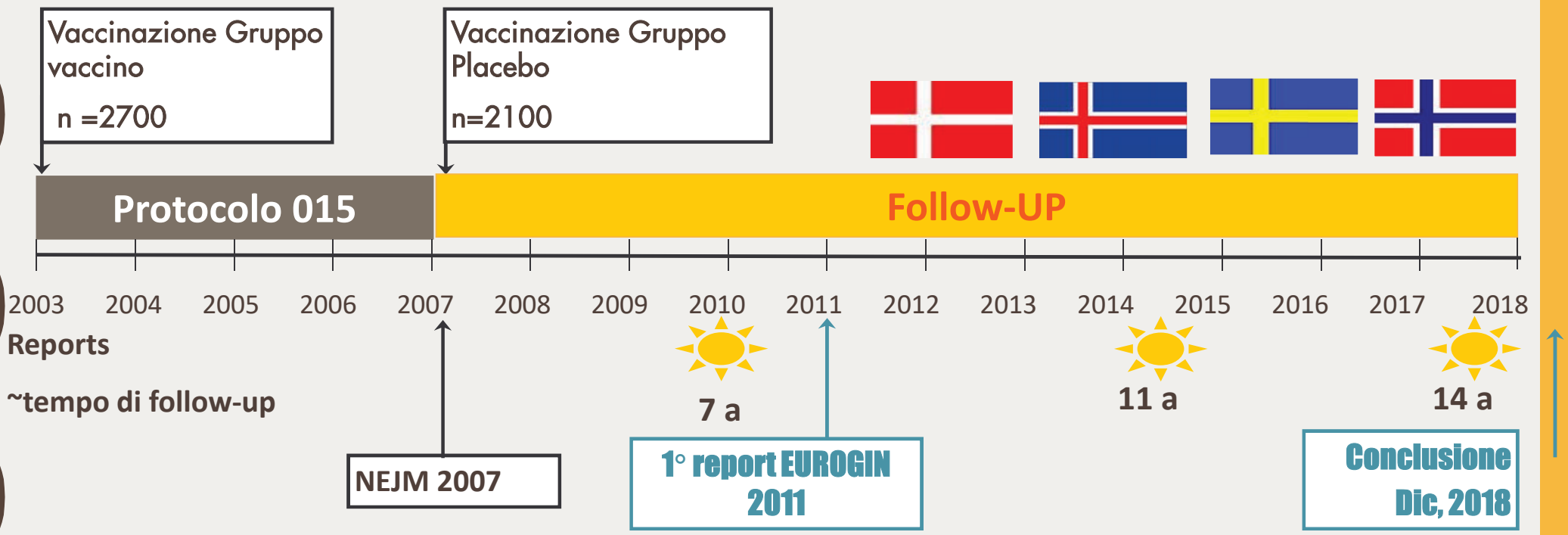
CONCLUSION

FOLLOW UP DELLO STUDIO FUTURE II

Durata di efficacia (CIN 2/3, AIS, cancro cervicale, VIN 2/3, Cancro della vulva, VaIN 2/3, cancro vaginale)

Potenziale protezione crociata o type-replacement

Durata di efficacia nel lungo termine



INFEZIONE NATURALE

- *Escape immunologico, con mancato innesco risposta infiammatoria locale*
- *Fino al 40% di mancata sieroconversione*
- *Qualora in presenza di sieroconversione possibile riattivatizione/reinfezione*
- *20% delle infezioni naturali si riattivano entro 1 anno dalla clearance del test HPV*

RISPOSTA AL VACCINO

- *Escape immunologico, pressoché assente risposta Ab direttamente proporzionale alla risposta locale*
- *sieroconversione prossima al 100%*
- *Risposta anticorpale persistente a 9 anni dalla vaccinazione*
- *Persistenza clinica di mancata riattivazione virale*

Review Retrospettivi

- Conoscenze immunologiche
  - Infezione naturale
  - Risposta evocata dal vaccino
- Conoscenze epidemiologiche
  - Review dei dati 2006-2017

- Studi retrospettivi
  - Review dei dati 2006-2017
- Dati prospettici

Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males.
N Engl J Med. 2011 Feb 3;364(5):401-11 Giuliano AR et al.
Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2–3)?Woo Dae Kang, Ho Sun Choi, Seok Mo Kim Gynecologic Oncology Volume 130, Issue 2, Pages 264-268 (August 2013)
Int J Cancer. 2016 Dec 15;139(12):2812-2826. doi: 10.1002/ijc.30391. Epub 2016 Sep 9.
Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: Post-hoc analysis from a randomized controlled trial.
Garland SM[1], Paavonen J[2], Jaisamrarn U[3], Naud P[4], Salmerón J[5], Chow SN[6], Apter D[7], Castellsagué X[8], Teixeira JC[9], Skinner SR[10,11], Hedrick J[12], Limson G[13], Schwarz TF[14], Poppe WA[15], Bosch FX[8], de Carvalho NS[16], Germar MJ[17], Peters K[18], Del Rosario-Raymundo MR[19], Catteau G[20], Descamps D[20], Struyf F[20], Lehtinen M[21], Dubin G[22]; HPV PATRICIA Study Group.
J Voice. 2017 Jan;31(1):104-106. doi: 10.1016/j.jvoice.2016.01.008. Epub 2016 Apr 8.
Gardasil Vaccination for Recurrent Laryngeal Papillomatosis in Adult Men: First Report: Changes in HPV Antibody Titer.
Makiyama K[1], Hirai R[2], Matsuzaki H[2].
Author information
Abstract
BACKGROUND:
Patients with human papillomavirus (HPV) DNA-positive recurrent laryngeal papillomatosis commonly have repeated recurrences following surgery. The reason is suspected to be a mechanism by which latent HPV infection in the surrounding healthy mucosa reinfects the surgicalsite. It may be that production of HPV antibodies in the laryngeal mucosa with Gardasil injection could inhibit postoperative recurrence.
STUDY DESIGN:
This is a case series study.
PURPOSE:
The purpose of this study was to examine whether Gardasil injection effectively inhibits recurrence. However, as a first report, we describe the antibody titers before and after vaccination.
METHODS:
Gardasil was injected in 12 men (aged 32-74 years; mean age 47.9 years) with HPV-positive laryngeal papillomatosis. Serum antibody titers of HPV-6, -11, -16, and -18 were measured by a competitive Luminex-based immunoassay before the vaccination and 7 months after the start of the vaccination.
RESULTS:
Each of the antibody titers was very low before vaccination, and they rose in all patients after the vaccination.
CONCLUSIONS:
This finding demonstrates that antibody titers increase with Gardasil injection in post-adolescent males

J Voice. 2017 Aug 30. pii: S0892-1997(17)30139-X. doi: 10.1016/j.jvoice.2017.07.017. [Epub ahead of print]
Gardasil Vaccination for Recurrent Laryngeal Papillomatosis in Adult Men Second Report: Negative Conversion of HPV in Laryngeal Secretions.
Hirai R[1], Makiyama K[2], Matsuzaki H[2], Oshima T[3].
Author information
Abstract
BACKGROUND:
In our first report on antibody levels in middle-aged and older men with recurrent laryngeal papillomatosis (RLP), we reported increases in human papillomavirus (HPV) antibody levels similar to those seen in adult women and young men. We posited that HPV antibodies produced in laryngeal mucus by Gardasil would prevent postoperative reinfection in patients with RLP.
STUDY DESIGN:
This is a case series study.
PURPOSE:
The purpose of this study was to examine whether Gardasil injection effectively inhibits recurrence of RLP. Specifically, in this second report, whether HPV antibodies produced in laryngeal secretions by Gardasil are capable of causing negative conversion of HPV-DNA (deoxyribonucleic acid) in laryngeal mucosa was investigated.
METHODS:
A total of 11 patients for whom antibodies were measured in the first report were studied. Before vaccination and after 1 year Post-vaccination, HPV screening tests were performed on laryngeal secretions, and whether HPV-DNA negative conversion had occurred was evaluated. At the time of collection of laryngeal secretions, the presence or absence of laryngeal papillomas was examined.
RESULTS:
Before vaccination, all patients were HPV low-risk positive on laryngeal secretion screening tests. After vaccination, three patients were positive. Laryngeal papillomas remained in five patients.
CONCLUSIONS:
The HPV-DNA test showed negative conversion in eight of 11 (72.7%) patients after vaccination. Residual laryngeal papillomas were found in five of 11 (45.5%) patients. The serum HPVantibody titer did not differ significantly between the group in which laryngeal secretions showed HPVnegative conversion and the group in which conversion did not occur. The serum antibody titer did not differ significantly as a function of whether there were residual tumors.

Eur Arch Otorhinolaryngol. 2014 Dec;271(12):3255-62. doi: 10.1007/s00405-014-3143-y. Epub 2014 Jun 26.
Human papilloma virus vaccination in patients with an aggressive course of recurrent respiratory papillomatosis.
Hočevar-Boltežar I[1], Matičič M, Seneg-Bahar M, Gale N, Poljak M, Kocjan B, Zargi M.
Author information
Abstract
In the case of an aggressive course of recurrent respiratory papillomatosis (RRP), adjuvant therapy can be used besides surgery. The aim of the study was to investigate the influence of vaccination with a quadrivalent vaccine against human papilloma viruses (HPV) types 6, 11, 16 and 18 on the course of RRP. Eleven subjects aged 13-46 years with a rapid growth of laryngeal papillomas were included in the study. They were vaccinated with three doses of the quadrivalent prophylactic HPV vaccine(Silgard®, MSD) and followed up for 12-52 months. The intervals between the successive surgical procedures, the extension of the disease (Derkay score) at each surgery, and the number of surgical procedures per year before vaccination and after its completion were compared. The mean interval between the surgical procedures was 271.2 days before the vaccination and 537.4 days after it (p = 0.034). The mean number of surgeries per year was 2.16 before the vaccination and 0.93 after it (p = 0.022). The Derkay score did not change significantly after vaccination. Complete remission of the disease was observed in one patient, partial response to the vaccination was observed in seven patients and no response was observed in three patients. In conclusion, vaccination with the quadrivalent HPV vaccine can favorably influence the course of RRP in patients with the rapid growth of the papillomas. It significantly prolongs the intervals between the surgical procedures and reduces the number of procedures needed in the majority of patients. The present investigation can serve as a pilot study for further research. For a final conclusion a longer follow-up and studies on more patients are necessary.

J Voice. 2015 Mar;29(2):223-9. doi: 10.1016/j.jvoice.2014.08.003. Epub 2015 Jan 22.
The use of the quadrivalent human papillomavirus vaccine (gardasil) as adjuvant therapy in the treatment of recurrent respiratory papilloma.
Young D[1], Moore MW[2], Halstead LA[2].
Author information
Abstract
OBJECTIVE:
To examine the effect of the quadrivalent human papillomavirus vaccine, Gardasil, on the disease course of patients with recurrent respiratory papillomatosis (RRP).
METHODS:
A retrospective chart review of patients with RRP was conducted and 20 patients were selected who had received the Gardasil vaccine as part of their treatment. Efficacy was assessed by calculating the intersurgical interval (ISI) before and after receiving the vaccine, as well as number of complete and partial remissions.
RESULTS:
Analysis of all patients found a significant increase in the ISI of 3.1 months (95% confidence interval [CI]: 1.02-5.19, P=0.0061). Male patients experienced an increase in the ISI of 4.2 months (95% CI: 1.6-6.7, P=0.0048). Female patients had a nonsignificant increase in ISI of 1.2 months (95% CI: 3.1-5.4, P=0.51). Eight patients (40%; six male and two female) experienced complete remission. Five patients (25%) overall (three male and two female) experienced partial remission. In total, complete or partial remission was achieved in a total of 13 (65%) patients (nine male and four female).
CONCLUSIONS:
The Gardasil vaccine can modulate the severity of RRP and induce remission in some patients. The effect was much greater in males and in females in low estrogen states

Laryngoscope. 2018 Jan;128(1):E16-E20. doi: 10.1002/lary.26772. Epub 2017 Sep 4.
Prophylactic immunization with human papillomavirus vaccines induces oral immunity in mice. Ahn J[1], Peng S[2], Hung CF[2], Roden RBS[2], Best SR[1].

Laryngoscope Investig Otolaryngol. 2017 May 28;2(4):184-186. doi: 10.1002/lio2.80. eCollection 2017 Aug.**Recurrent respiratory papillomatosis (RRP)-time for a reckoning?** Kin Cho Goon P[1], Scholtz LU[2], Sudhoff H[2].
We found a >7-fold decrease in the incidence rates of papillomatosis requiring surgical intervention from the pre-vaccination period (47.44/1000 patient-months) compared to the post-vaccination period (6.71/1000 patient-months).
JAMA Otolaryngol Head Neck Surg. 2017 Jun 1;143(6):614-622. doi: 0.1001/jamaoto.2016.4736. **Adjuvant Human Papillomavirus Vaccination for Secondary Prevention: A Systematic Review.** Dion GR[1], Tang SI, Boyd LR[2], Northam A[1], Mason-Appa C[1], Vieira D[3], Amin MR[1], Branski RC[1]. Nineteen studies with 22 474 unique patients were included in the review. When HPV vaccination was used as an adjuvanttreatment for active clinical disease, 9 of 12 studies reported decreased disease recurrence, decreased disease burden, or increased intersurgical interval. In contrast, none of the 7 studies of vaccination in individuals with HPV DNA positivity and/or seropositivity without clinical disease reported improved outcomes.
Urologiia. 2016 Nov;(5):47-51.
[Anogenital warts: a new way of solving the common problem of urology (results of long-term follow-up)].
[Article in Russian]
Protasov AD[1], Lipatov IS[1], Kostinov MP[2], Tezikov YV[1], Shmitko AD[2], Pokhomov DV[2], Blagovidov DA[2], Zheslkov AV[1], Ryzhov AA[2], Vekhova EV[3].
Author information
Abstract
AIM:
To evaluate the effectiveness of combined use of the imiquimod 5% cream and vaccination against human papillomavirus (HPV) using a quadrivalent recombinant vaccine to achieve long-term clinical remission of chronic HPV infection manifested by anogenital warts.
MATERIAL AND METHODS:
The study comprised 36 patients, including 22 men, aged 26.4+/-4.1 years, who had from 1 to 5 anogenital warts. Participants of the study were vaccinated by quadrivalent recombinant vaccine under a 3-dose scheme 0-2-6 months co-administered with imiquimod 5% cream three times per week up to 16 weeks. The follow-up period was 2 years.
RESULTS:
Complete disappearance of genital warts within 1 year from baseline was observed in 34 (94.4%) patients. Two patients with anogenital warts after 1 year were treated for 1 year 3 months and 1 year and 4 months with Solcoderm which lead to the complete disappearance of genital warts. There were no recurrences of genital warts during the 2 years of follow-up.
CONCLUSION:
Vaccination with a recombinant quadrivalent vaccine concurrently with using imiquimod 5% cream results in prolonged clinical remission of chronic HPV infection manifested by anogenital warts in at least 94.4% of the cases (2 year follow-up)

Review immunologia

- *Conoscenze immunologiche*
  - *Infezione naturale*
  - *Risposta evocata dal vaccino*

- *Conoscenze epidemiologiche*
  - *Review dei dati 2006-2017*

- *Studi retrospettivi*
  - *Review dei dati 2006-2017*
- *Dati prospettici*

Front Immunol. 2017 Mar 6;8:226. doi: 10.3389/fimmu.2017.00226. eCollection 2017.

Adjusted Particle Size Eliminates the Need of Linkage of Antigen and Adjuvants for Appropriated T Cell Responses in Virus-Like Particle-Based Vaccines.

Gomes AC[1], Flace A[2], Saudan P[2], Zabel F[3], Cabral-Miranda G[1], Turabi AE[1], Manolova V[2], Bachmann MF[4].
Author information

Abstract

Since the discovery of the first virus-like particle (VLP) derived from hepatitis B virus in 1980 (1), the field has expanded substantially. Besides successful use of VLPs as safe autologous virus-targeting vaccines, the powerful immunogenicity of VLPs has been also harnessed to generate immune response against heterologous and even self-antigens (2-4). Linking adjuvants to VLPs displaying heterologous antigen ensures simultaneous delivery of all vaccine components to the same antigen-presenting cells. As a consequence, antigen-presenting cells, such as dendritic cells, will process and present the antigen displayed on VLPs while receiving costimulatory signals by the VLP-incorporated adjuvant. Similarly, antigen-specific B cells recognizing the antigen linked to the VLP are simultaneously exposed to the adjuvant. Here, we demonstrate in mice that physical association of antigen, carrier (VLPs), and adjuvant is more critical for B than T cell responses. As a model system, we used the E7 protein from human papilloma virus, which spontaneously forms oligomers with molecular weight ranging from 158 kDa to 10 MDa at an average size of 50 nm. E7 oligomers were either chemically linked or simply mixed with VLPs loaded with DNA rich in non-methylated CG motifs (CpGs), a ligand for toll-like receptor 9. E7-specific IgG responses were strongly enhanced if the antigen was linked to the VLPs. In contrast, both $CD4^+$ and $CD8^+$ T cell responses as well as T cell-mediated protection against tumor growth were comparable for linked and mixed antigen formulations. Therefore, our data show that B cell but not T cell responses require antigen-linkage to the carrier and adjuvant for optimal vaccination outcome.

Clin Nucl Med. 2017 May;42(5):329-334. doi: 10.1097/RLU.0000000000001603.

Lymph Node Activation by PET/CT Following Vaccination With Licensed Vaccines for Human Papillomaviruses.

Coates EE[1], Costner PJ, Nason MC, Herrin DM, Conant S, Herscovitch P, Sarwar UN, Holman L, Mitchell J, Yamshchikov G, Koup RA, Graham BS, Millo CM, Ledgerwood JE; VRC 900 Study Team.
Author information

Abstract

BACKGROUND:

While PET using F-FDG is most commonly used for imaging malignant tumors, vaccination is known to cause transient inflammation of lymph nodes inducing positive findings on F-FDG PET scans. The pattern, magnitude, and duration of lymph node activation following vaccination have not been clearly defined. Furthermore, the addition of adjuvants to vaccines can further enhance the immune response. The presented study was designed to define lymph node activation following administration of the Food and Drug Administration-licensed human papillomavirus vaccines, Cervarix and Gardasil, which contain similar antigens with different adjuvants.

METHODS:

Twenty-seven women aged 18 to 25 years were randomized to receive either Cervarix or Gardasil in the clinical trial VRC 900. Fifteen subjects participated in the PET/CT portion of the trial and received scans of lymph node activation at prevaccination and "1 week" (8-14 days) and "1 month" (23-36 days) after the first or third vaccination.

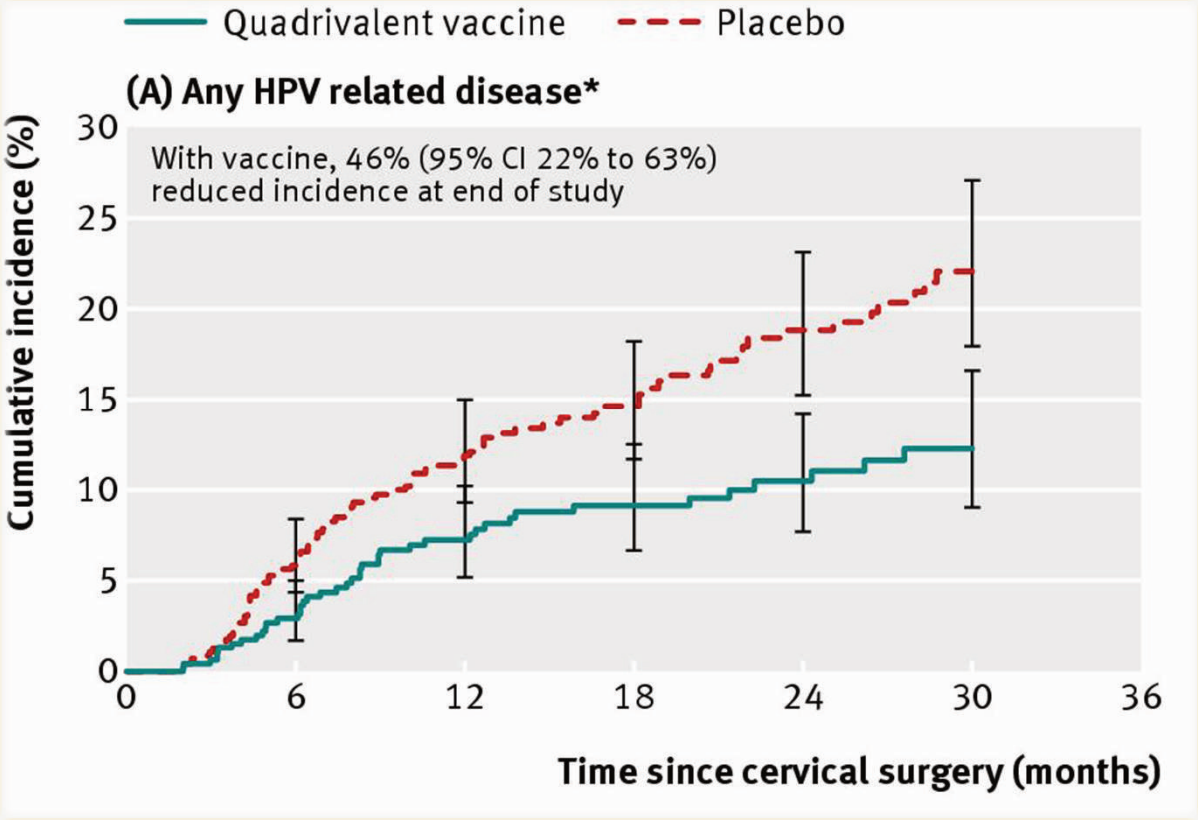
RESULTS:

PET/CT scans revealed that all vaccine recipients had ipsilateral axillary lymph node activity. Three of 4 Cervarix recipients also showed contralateral lymph node activity 1 month after the first vaccination. For both Cervarix and Gardasil, the SUV activity resolved over time, with activity extended up to day 37 after the first and third vaccinations.

CONCLUSIONS:

Following intramuscular vaccination, there were no major differences between duration of uptake and intensity of SUV between Cervarix and Gardasil recipients in ipsilateral axillary lymph nodes. Contralateral node activation was detected up to 1 month after the first vaccination in Cervarix recipients only, possibly reflecting differences in vaccine adjuvant formulation.

STUDI RETROSPETTIVI



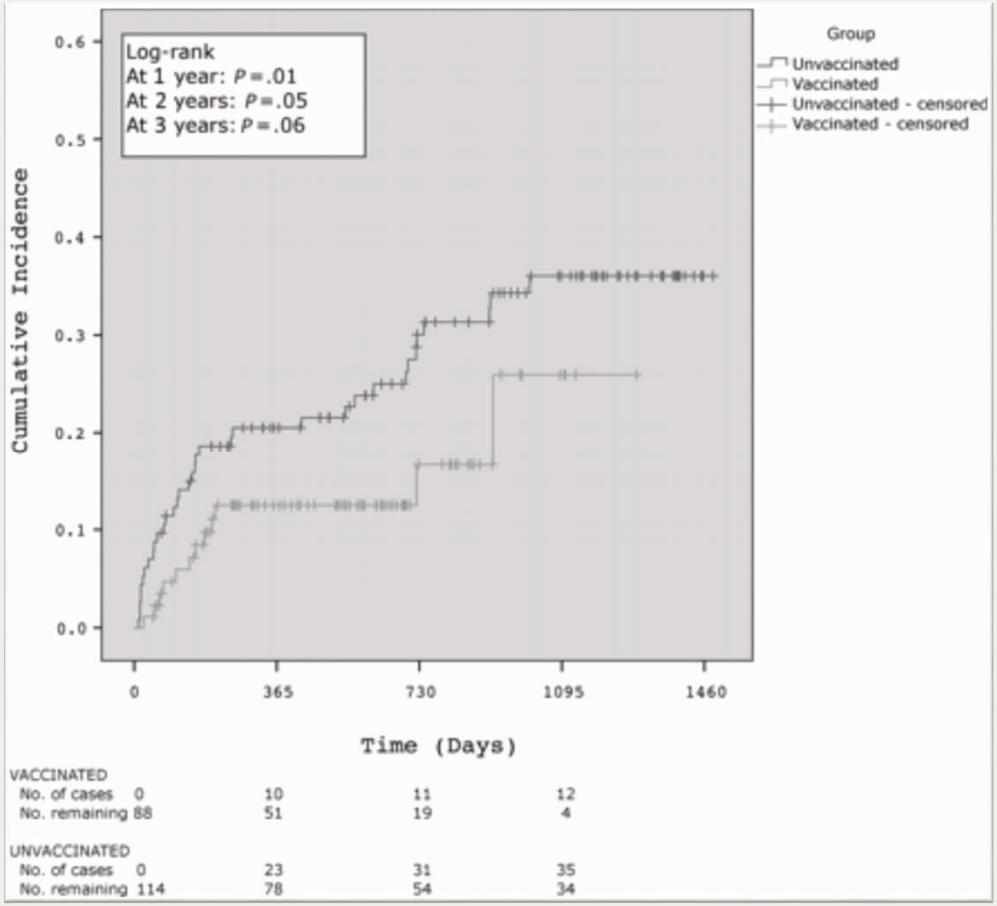
FUTURE I – II 17.622 PAZIENTI ARRUOLATE:

1350 SVILUPPATO PATOLOGIA HPV CORRELATA - 587 GRUPPO VACCINATE RIDUZIONE DEL 46% DOPO PATOLOGIA DA HPV CERVICALE O VULVO-VAGINALE DI ALTRE LESIONI HPV- CORRELATE

65% RIDUZIONE DI RECIDIVE CERVICALI DI ALTO GRADO

(JOURA ET AL. 2012)

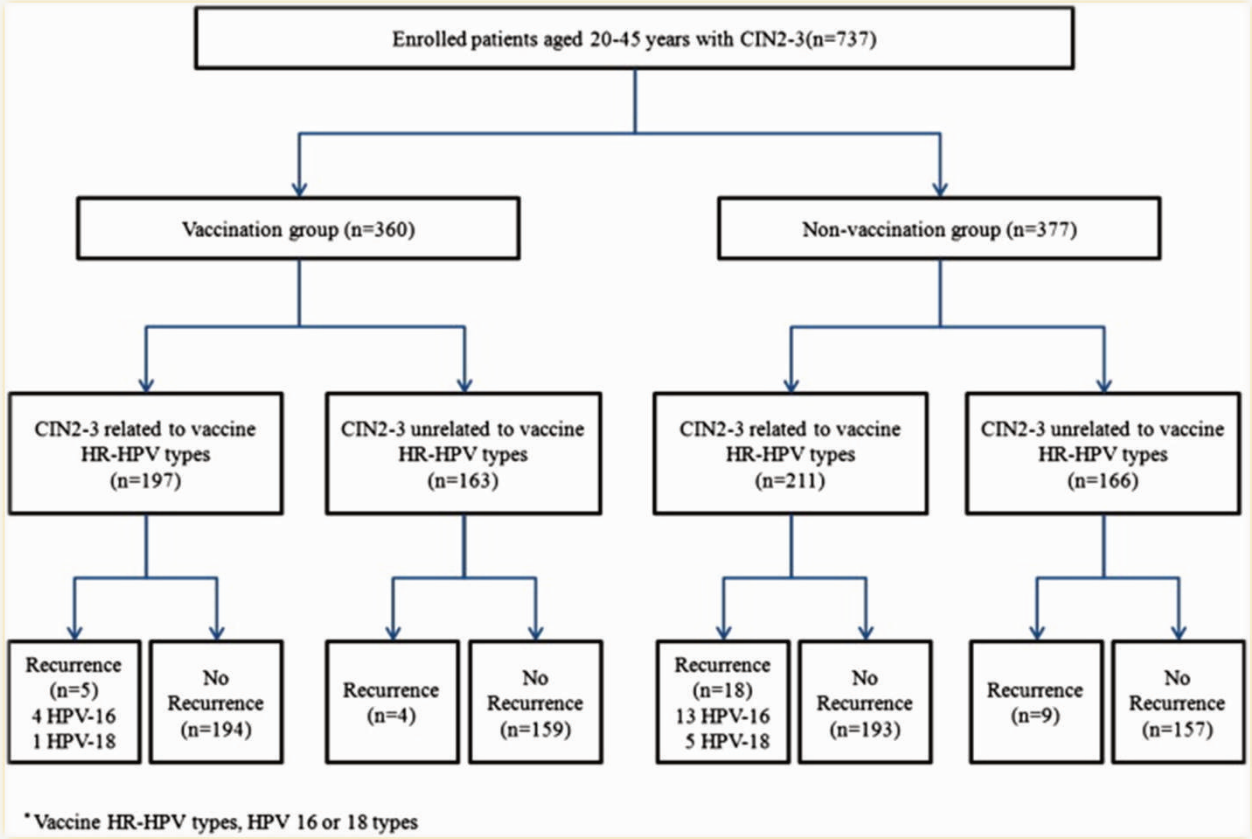
STUDI RETROSPETTIVI



TASSI DI RICORRENZA DI NEOPLASIA ANALE INTRAEPITELIALE HG IN MASCHI TRATTATI (HGAIN). LO STUDIO CONFRONTA PAZIENTI PRECEDENTEMENTE SOTTOPOSTI A CHIRURGIA PER HGAIN DI CUI 88 VACCINATI E 114 NON VACCINATI.

IL GRUPPO VACCINATO PRESENTA UN'INCIDENZA DI RECIDIVA DI 13.6% CONTRO IL 30.7% DEI SOGGETTI NON VACCINATI (SWEDISH 2012)

STUDI RETROSPETTIVI

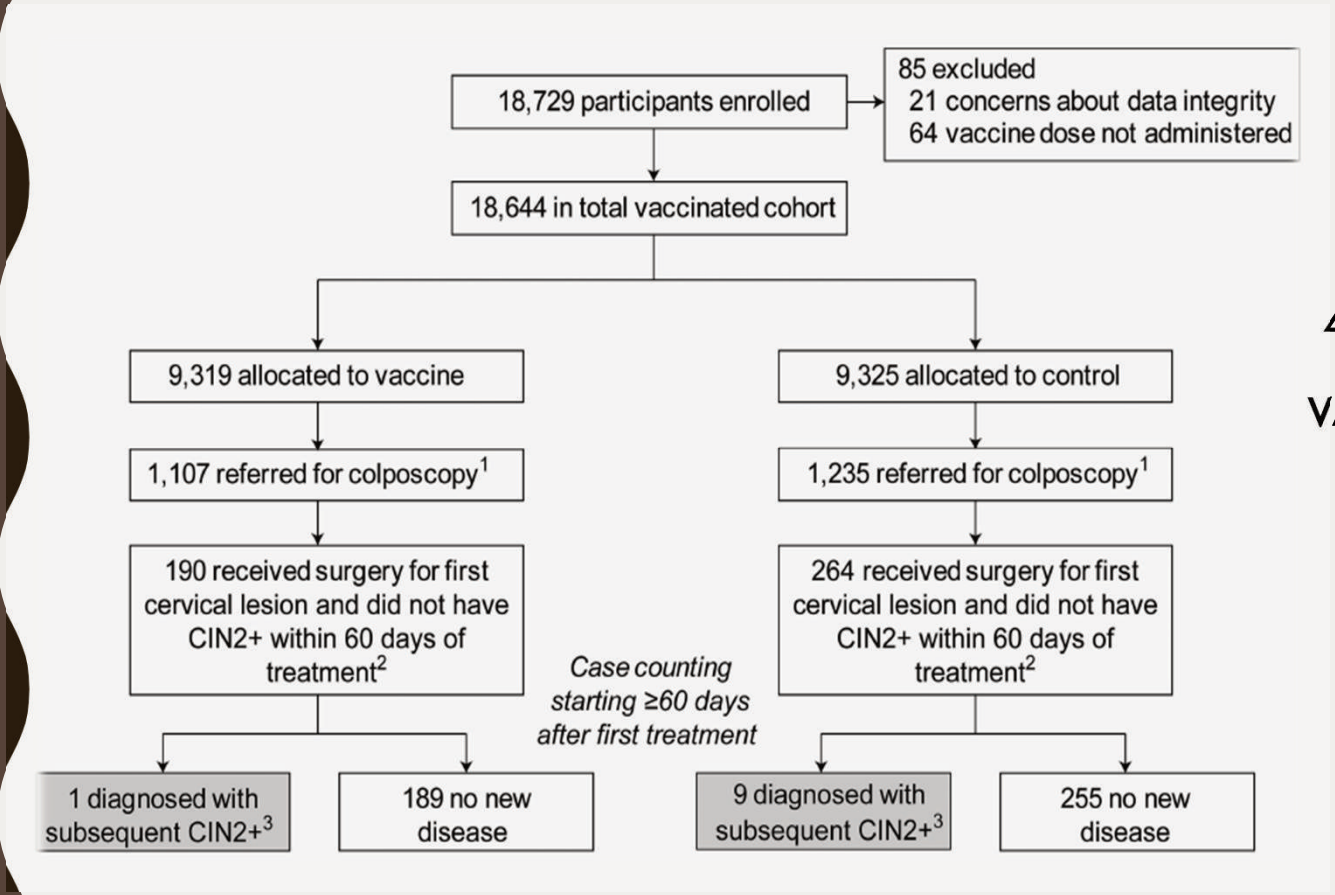


IS VACCINATION WITH QUADRIVALENT HPV VACCINE AFTER LOOP ELECTROSURGICAL EXCISION PROCEDURE EFFECTIVE IN PREVENTING RECURRENCE IN PATIENTS WITH HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN2–3)?

WOO DAE KANG, HO SUN CHOI, SEOK MO KIM

GYNECOLOGIC ONCOLOGY
VOLUME 130, ISSUE 2, PAGES 264-268 (AUGUST 2013)

STUDI RETROSPETTIVI



HPV PATRICIA STUDY GROUP
18,729 PAZIENTI ARRUOLATE:

454 SVILUPPATO PATOLOGIA HPV CORRELATA - 190 GRUPPO VACCINATE RIDUZIONE A >60 GG. DI CIN2+ RECIDIVANTE

-42.6% CIN1

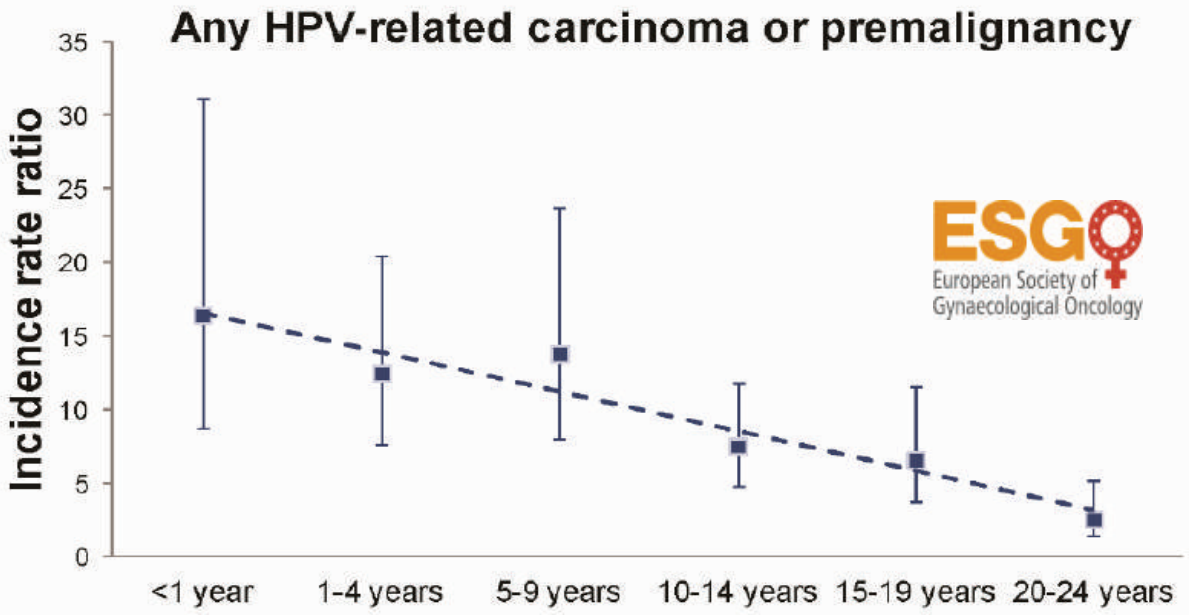
88.2% RIDUZIONE DI RECIDIVE CERVICALI DI ALTO GRADO

(GARDLAND ET AL. 2016)

Long-Lasting Increased Risk of Human Papillomavirus-Related Carcinomas and Premalignancies After CIN3

R.M.F. Ebisch[1,2], D. Rutten[1], J. IntHout[3], W.J.G. Melchers[4], L.F.A.G. Massuger[1], J. Bulten[5], R.L.M. Bekkers[1,2], A.G. Siebers[5].

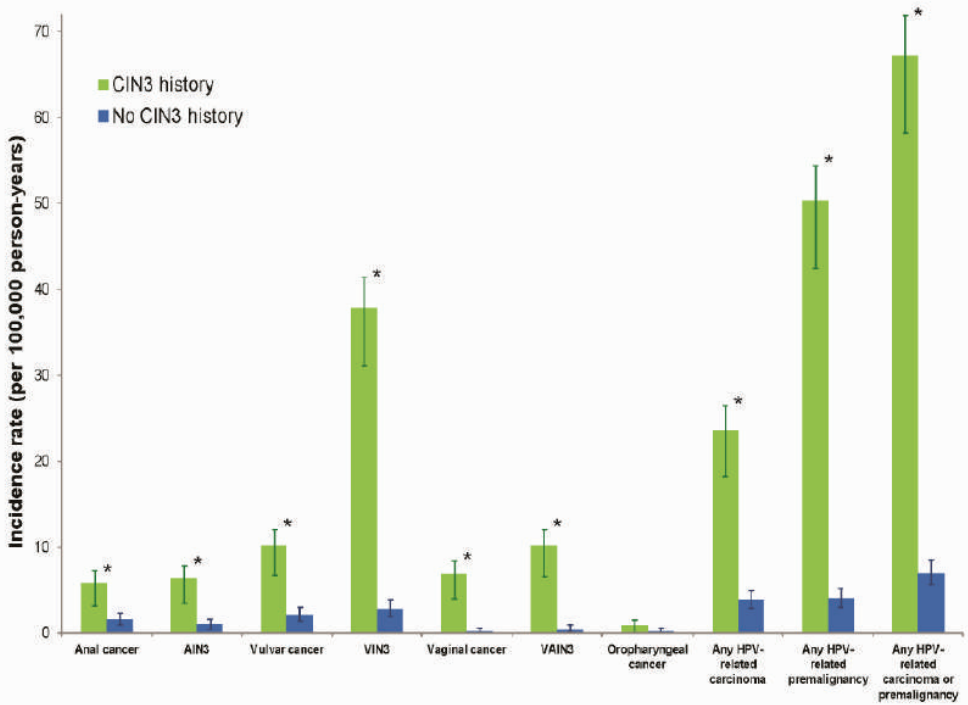
The incidence rate ratio of any HPV–related carcinoma or premalignancy is still increased 20 years after the CIN3 diagnosis.



Results

incidence rate ratios:

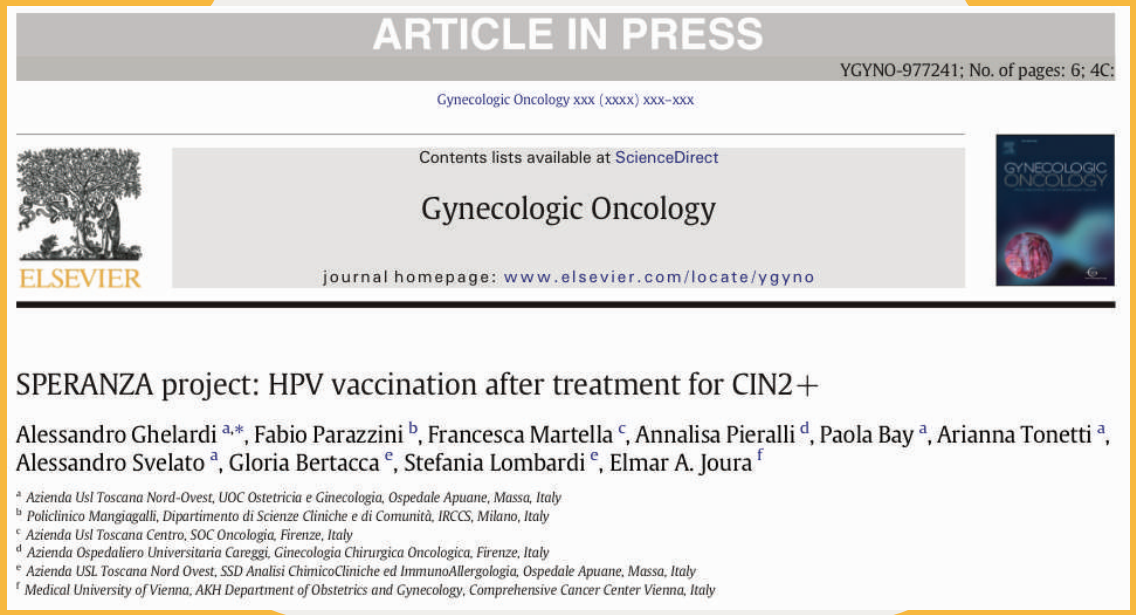
3.85	(95% CI, 2.32 to 6.37) anal cancer
6.68	(95% CI, 3.64 to 12.25) HG-AIN
4.97	(95% CI, 3.26 to 7.57) vulvar cancer
13.66	(93% CI, 9.69 to 19.25) HG-VIN
86.08	(95% CI, 11.98 to 618.08) vaginal cancer
25.65	(95% CI, 10.50 to 62.69) HG-VAIN
5.51	(95% CI, 1.22 to 24.84) orophar. cancer



Error bars indicate 95% CIs of estimated incidence rates. The asterisks indicate a significant difference in incidence rates of the group with a history of CIN3 compared with the group without a history of CIN3.

SPERANZA PROJECT

RESULTS OF HPV VACCINATION AFTER SURGICAL TREATMENT FOR HPV RELATED DISEASES



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YGYNO-977241; No. of pages: 6; 4C:

Gynecologic Oncology xxx (xxxx) xxx–xxx

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journal homepage: www.elsevier.com/locate/ygyno

SPERANZA project: HPV vaccination after treatment for CIN2+

Alessandro Ghelardi [a,*], Fabio Parazzini [b], Francesca Martella [c], Annalisa Pieralli [d], Paola Bay [a], Arianna Tonetti [a], Alessandro Svelato [a], Gloria Bertacca [e], Stefania Lombardi [e], Elmar A. Joura [f]

[a] Azienda Usl Toscana Nord-Ovest, UOC Ostetricia e Ginecologia, Ospedale Apuane, Massa, Italy
[b] Policlinico Mangiagalli, Dipartimento di Scienze Cliniche e di Comunità, IRCCS, Milano, Italy
[c] Azienda Usl Toscana Centro, SOC Oncologia, Firenze, Italy
[d] Azienda Ospedaliero Universitaria Careggi, Ginecologia Chirurgica Oncologica, Firenze, Italy
[e] Azienda USL Toscana Nord Ovest, SSD Analisi ChimicoCliniche ed ImmunoAllergologia, Ospedale Apuane, Massa, Italy
[f] Medical University of Vienna, AKH Department of Obstetrics and Gynecology, Comprehensive Cancer Center Vienna, Italy

ALESSANDRO GHELARDI

GYNECOLOGY AND OBSTETRIC UNIT

AZIENDA ASL TOSCANA NORD OVEST - ITALY

STUDIO SPERANZA

CIN 2+ study: Clinical recurrence of disease (HG SIL- FIGO Ia1 cervical cancer)

174 patients recruited SURGERY+QHPV FOLLOW-UP

176 patients recruited SURGERY FOLLOW-UP ALONE

2 excluded*

4 excluded *

4 years follow-up

172 patients → 2 recurrences (1,16%)

172 patients → 11 recurrences (6,39 %)

536 women enrolled
6 *excluded for persistence*
12 *excluded for low compliance*
73 *lost to follow-up*
101 *follow-up <6 months*

344 with at least 6 months FU

SPERANZA STUDY 536 PAZIENTI ARRUOLATE:

GRUPPO VACCINATE VALUTAZIONE RIDUZIONE A 4 ANNI FOLLOW-UP DI CIN2+ RECIDIVANTE

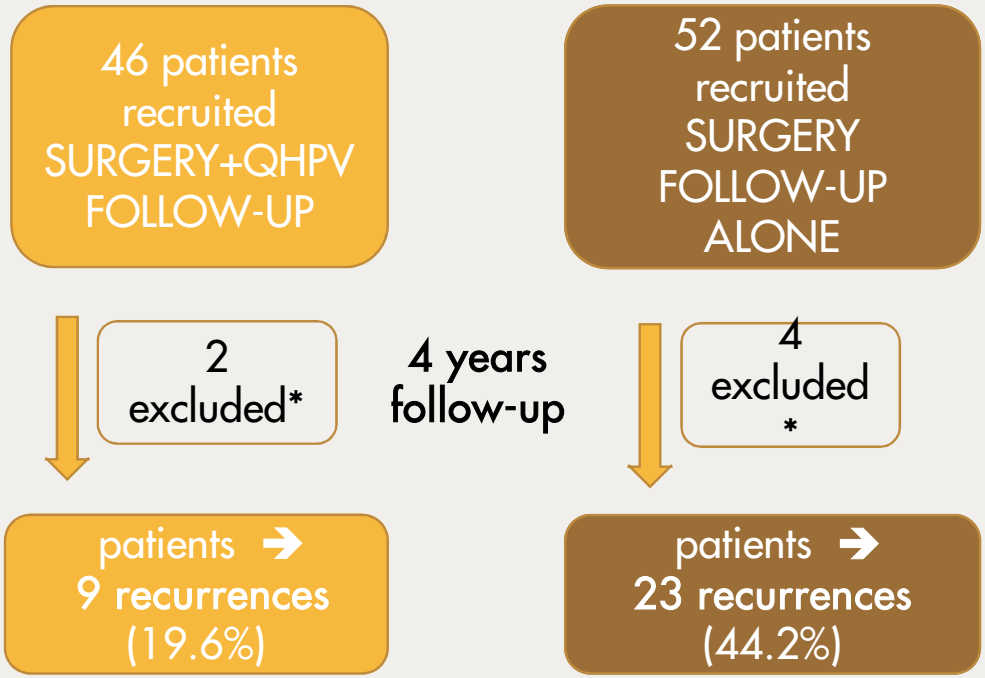
81.2% RIDUZIONE DI RECIDIVE CERVICALI DI ALTO GRADO

The rate of recurrence was significantly higher in the unvaccinated group, with a p=0.0139 by Pearson's chi squared test

ANOGENITAL WARTS STUDY

ESGO
European Society of Gynaecological Oncology

Ano-genital warts study: Clinical recurrence of disease AGW



536 women enrolled
6 *excluded for persistence*
12 *excluded for low compliance*
73 *lost to follow-up*
101 *follow-up <6 months*

344 with at least 6 months FU

SPERANZA STUDY 536 PAZIENTI ARRUOLATE:

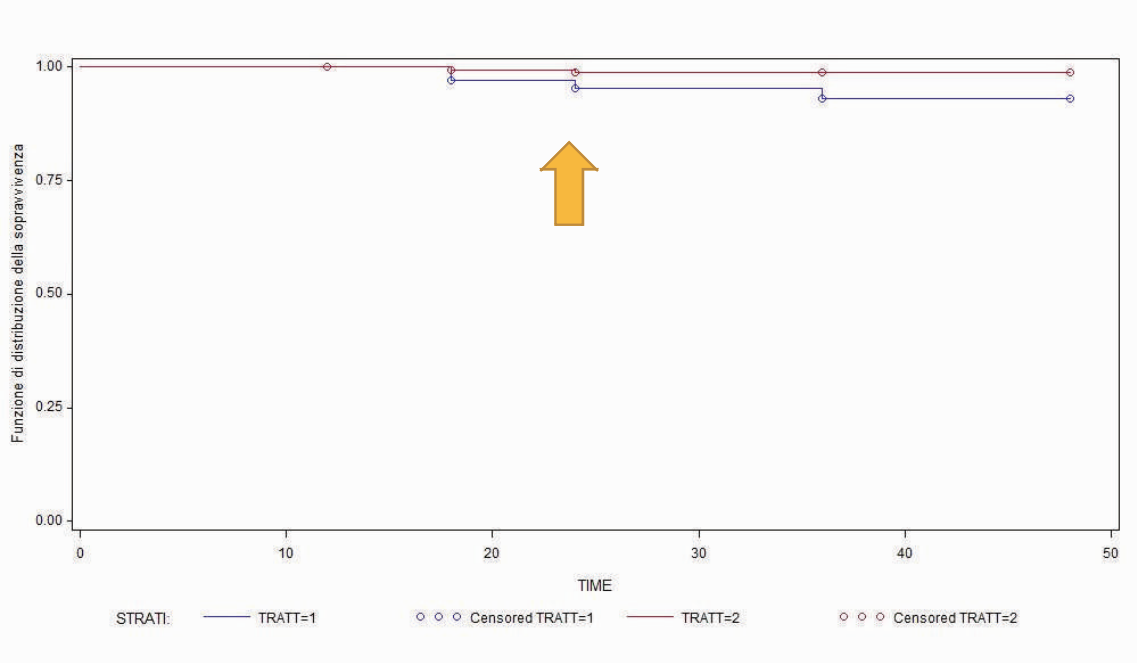
GRUPPO VACCINATE VALUTAZIONE RIDUZIONE A 2 ANNI FOLLOW-UP DI

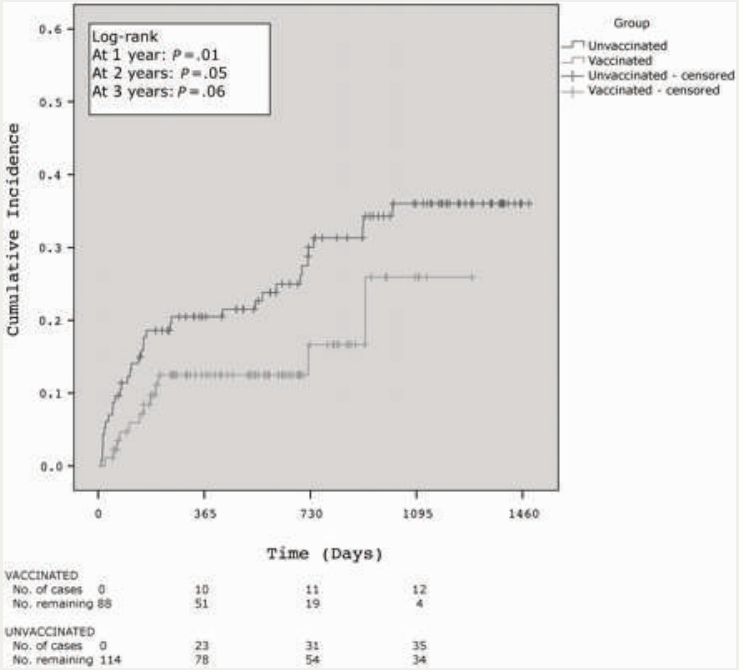
60.8% RIDUZIONE DI RECIDIVE CONDILOMATOSI ANO-GENITALE

(SUBMITTED UNPUBLISHED)

The rate of recurrence was significantly higher in the unvaccinated group, with a p=0.0105 by Pearson's chi squared test

Our results.. what's new ? Time factor





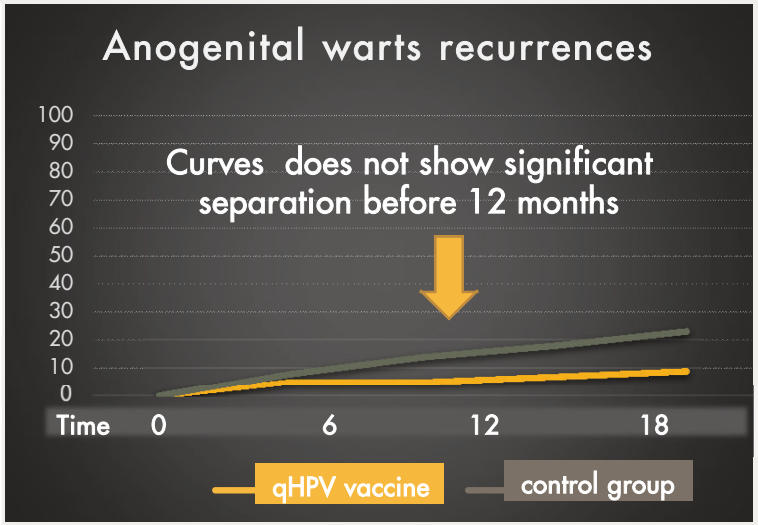
- qHPV decrease the risk CIN2+ clinical recurrence in vaccinated group compared to those who did not received the vaccine showing a CRP
  - The groups are not significantly different until 24 months

THE VACCINE EFFECTIVENESS BECOMES STATISTICALLY SIGNIFICATIVE AFTER 24 MONTHS OF FOLLOW-UP

ESGO
European Society of Gynaecological Oncology

Our results.. what's new? Time factor

	SUB GROUP ANALISYS	ANOGENITAL WARTS	(AGW)	
TIME	6 MOTHS	12 MONTHS	18 MONTHS	24 MONTHS
NOT VACCINATED				
NO. OF CASES	26	29	46	52
NO. OF RECURRENCES	8	14	18	23
NO. OF RECURRENCES	5	5	7	9
TWO-TAILED p VALUE	0.21 NOT SIGNIFICATIVE	0.01 SIGNIFICATIVE	0.05 NOT QUITE SIGNIFICATIVE	0.01 SIGNIFICATIVE



- qHPV decrease the risk of developing GW in vaccinated group compared to those who did not received the vaccine showing a CRP
- The groups are not significantly different until 12 months

THE VACCINE EFFECTIVENESS BECOMES STATISTICALLY SIGNIFICATIVE AFTER 12 MONTHS OF FOLLOW-UP

ESGO
European Society of Gynaecological Oncology

MULTICENTRICO

TRIPLE NEGATIVE Study

(submitted)

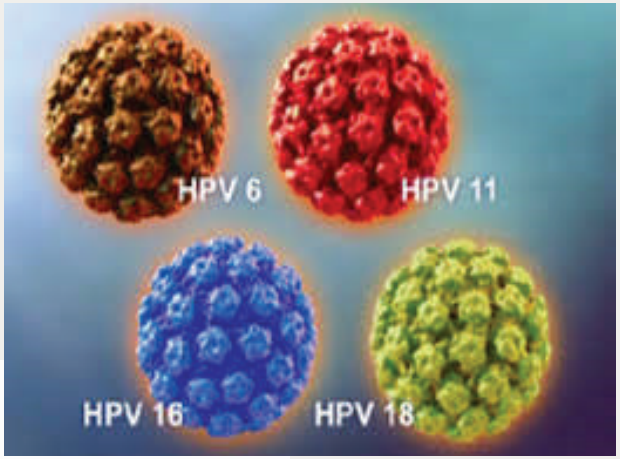
Abstract

BACKGROUND:
Indagine circa la possibilità acquisizione di nuove infezioni HPV in pazienti adulte non naive con infezione non rilevabile al tempo zero di inclusione post cono.

METODI:
Pazienti triplo negative : colposcopia- Paptest - HPV test. Pazienti randomizzate post chirurgia a ricevere o meno vaccino quadrivalente. Studio prospettico randomizzato caso controllo arruolate 187 pazienti 2013-2014.

END POINT PRIMARIO: tempo libero da infezione HPV clinicamente rilevabile. Interazione del vaccino in adiuvante con la storia naturale della patologia HPV clinica; analizzando intervallo libero da infezione.

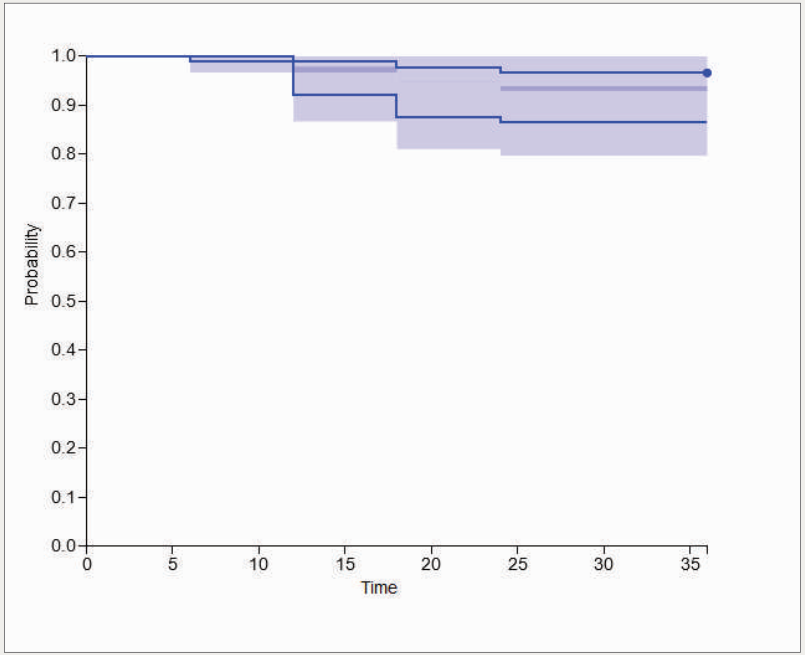
CONCLUSIONS:
Può la vaccinazione HPV post trattamento di lesioni CIN2+ favorire un più rapido rientro a screening?

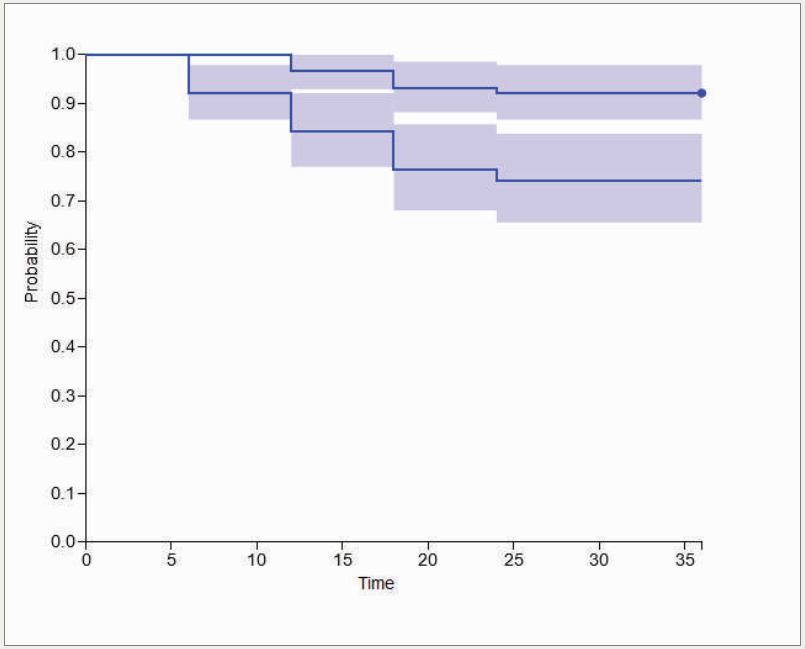




TRIPLE NEGATIVE Study

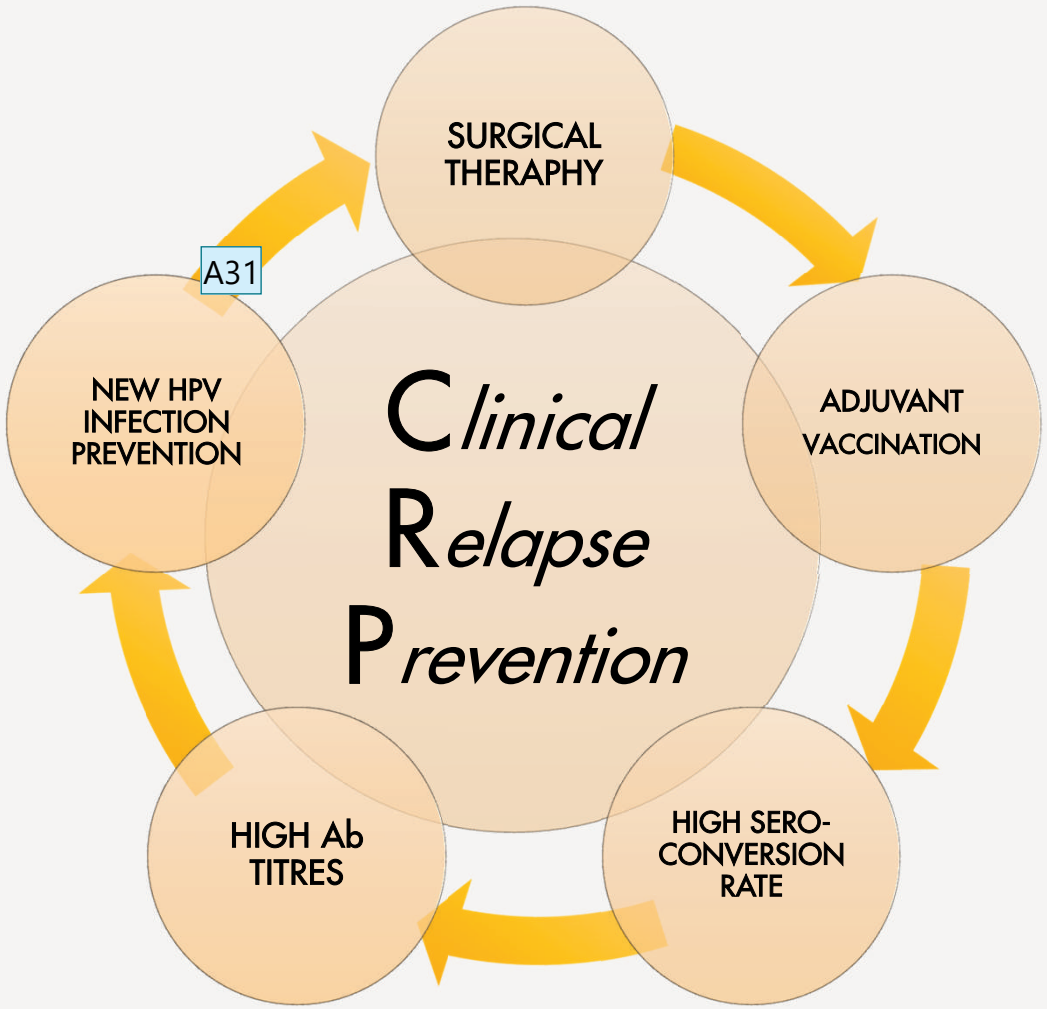
Kaplan Meier's curves show the difference during the follow-up period for the **overall free of disease time** in two groups. The comparison between the two groups, done with the log rank test, was statistically significant (z=2.44, p=0.0147).





Kaplan Meier's curves show the difference in **the intervals free from positive Pap smears** in the two groups during the 3 years of follow-up, The comparison between the two groups, done with the log rank test, was statistically significant (z=3.26, p=0.00113).

CONCLUSIONI - CRP



What's new?

Persistent infection with oncogenic human papillomavirus (HPV) is a pre-requisite for cervical cancer, with women who have already undergone treatment for related cervical lesions representing a high-risk group for the subsequent development of cervical cancer and HPV-related diseases.

To date, HPV vaccination is not thought to alter the course of disease in women with prevalent type-specific infections or pre-existing lesions at the time of vaccination.

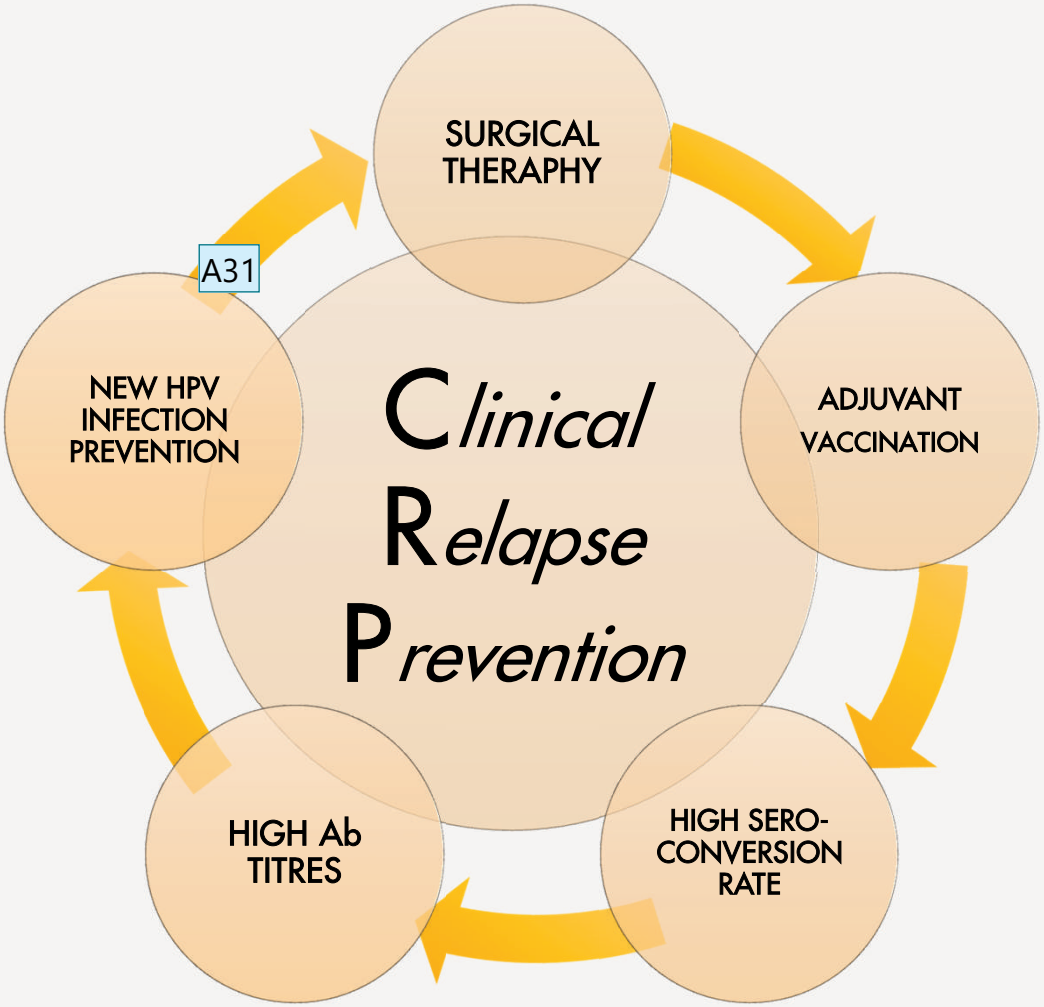
- *Prevenzione della riattivazione*
- *Prevenzione vs infezioni de novo*

HPV – adjuvanted vaccine may continue to benefit from vaccination, with a reduced risk of developing subsequent

Diapositiva 37

A31 i think it would be useful to clarify that this is not treatment, but prevention of recurrence. 'Relapse' could give the impression that the HPV vaccine is acting as a treatment and we do not have the indication for treatment, but the vaccine is indicated for the prevention of new HPV disease.
One of the keay learnings from all these studies, including yours, is that women that are being treated can benefit from HPV vaccination as they are at risk of recurrence of new disease.
This is the main point of your studies, and a key one for this women.
Autore; 23/10/2017

CONCLUSIONI - CRP



What's new?

Women treated for high grade cervical lesions and microinvasive cervical cancer, while compared to general population, represent **an high-risk group for HPV persistent infection, cervical disease recurrence and obstetrical complication due to surgical repeated treatments**. Even if HPV vaccine is not able to alter a pre-surgical prevalent HPV infection, this perspective study demonstrate that post surgical quadrivalent HPV vaccine in women who undergo to LEEP for cervical high grade lesions (CIN2+) has an important:

- ***clinical effectiveness***, *showing a reduced risk of developing recurrent cervical disease by 81.2%*

- ***overall free disease time***
vantaggio temporale di circa 2 anni – riduzione delle recidive con incidenza quattro volte inferiore

- ***free interval from positive Pap smears***

Diapositiva 38

A31 i think it would be useful to clarify that this is not treatment, but prevention of recurrence. 'Relapse' could give the impression that the HPV vaccine is acting as a treatment and we do not have the indication for treatment, but the vaccine is indicated for the prevention of new HPV disease.
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This is the main point of your studies, and a key one for this women.
Autore; 23/10/2017