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A European Society of Gynaecological Oncology (ESGO) accredited Centre for Gynaecological Oncology Training

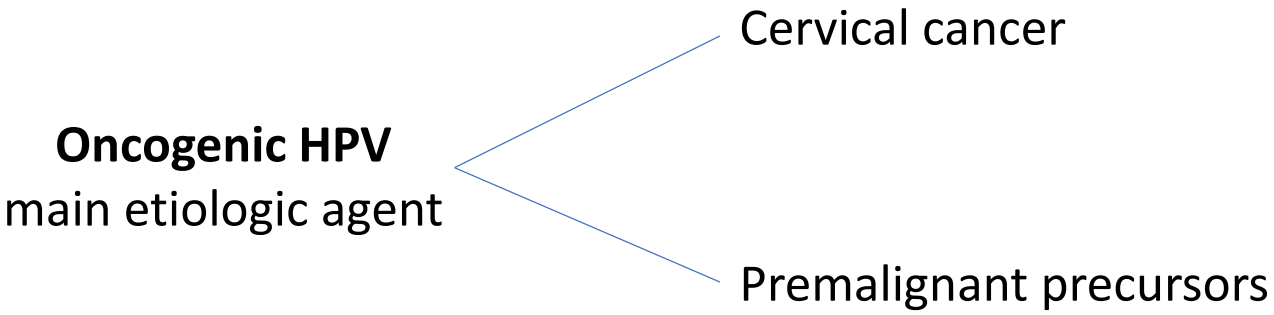
CIN : Prevention of reccurence
Efficacy and timing of HPV vaccination

Alexandros Rodolakis MD , PhD

Athens University , Greece

VERBAL DISCLOSURE

- I have nothing to disclose



Primary prevention : Prophylactic vaccines

Secondary prevention : Primary HPV nucleic acid testing as screening

treatment of High-Grade SIL (CIN2/3)

Global burden of cervical cancer for 2018

* 569,847 new cases

* 311,365 deaths

Globocan Cancer Fact Sheets, Cervical cancer Feb 2019

Cervical cancer: A preventable disease

* WHO 2018 global coordination action

Comprehensive approach:

- Vaccination
- Screening
- Early treatment of precancerous lesions
- Early diagnosis, treatment and palliative of invasive Ca

WHO all to action, Feb. 2019

HPV vaccines
Prophylactic rather than therapeutic

* Regulatory indications to use up to 45 years
- Highest immune response among 9-15 years old
- Highest efficacy in unexposed girls

Block SC, Pediatrics 2006.
Schiller JT, Vaccine 2012.

* Routine vaccination in early adolescence prior to HPV infection
- Long-term impact on cervical cancer incidence
- Short term impact on CIN2/3 detection rate

Thamshorg LH, Int J Cancer 2018.
Herweijen E, Int J Cancer 2016.

HPV vaccines

HPV-naïve women

Sufficient evidence of protection against HPV related disease

HPV-previously infected women

Potential benefit debatable

- Prevent type-specific new infection
- Unclear the prevention of reactivation of latent previous infections

Munoz N, Lancet 2009.
Geravitt PE. Viruses 2017.

Recurrence after treatment for High Grade CIN

Excisional or Ablative modalities with comparable safety

Martin-Hirsh PP, Cochrane Database Syst, 2013.

Excisional treatment

- Histologic confirmation
- Better clearance of HPV infections within 12 months

Hoffmann SR, Int J Cancer 2017..

INCOMPLETE EXCISION CAN OCCUR

Martin-Hirsh PP, Cochrane Database Syst, 2013.

Recurrence after treatment for High Grade CIN

* Incomplete excisions after treatment of (CIN2+) of 23.1%

* Failure of treatment as recurrent (CIN2+) within 2 years up to 7% (2,5% to 18%)

Arbyn M. A systematic review of metanalysis. Cancer Oncol 2017.
Tan JH, J Low Genit Tract Dis 2013.
Arbyn M, Vaccine 2012.

Recurrence after treatment for High Grade CIN

Recurrence: could be

- Residual disease following incomplete excision
- Persistent infection from the same HPV type
- Reactivation of a latent HPV infection
- Newly acquired infection

Hoffmann SR, Int J Cancer 2017.
Grarland SM, Int J Cancer 2016.

Recurrence after treatment for High Grade CIN
Predictors of recurrence

- Margin involvement
- Oncogenic HPV types in excised cervical tissue persisting after treatment

Arbyn M. A systematic review of metanalysis. Cancer Oncol 2017.

- 28% positive for oncogenic HPV, 3 months after treatment
- Subsequent persistence during longer follow up correlated with increasing age

Hoffmann SR, Int J Cancer 2016.

Post CIN treatment surveillance

•To detect residual / recurrent disease

- HPV testing
- Cytology
- Co-testing (HPV and cytology)

* Observational data only

* No RCTs

Van der Heijden E. Cochrane Database 2015.

Post CIN treatment surveillance

* 5-year cumulative risk of CIN2+

After 2 negative post-treatment results at 6 & 12-18 months

- 1.5%: Co-testing
- 2.7%: HPV testing
- 2.7%: Cytology

After 1 negative test at 6months

- 3.0%: Co-testing
- 4.4%: HPV testing
- 5.8%: Cytology

After 2 negative tests at 6 and 24 months

- 1.0%: Co-testing
- 2.3%: HPV testing

Kafki HA, J Low Genit Tract Dis 2013.
Kocken M, Cancer Oncol 2011.
Uijterwaal MH, J Low Genit Tract Dis 2011.

Post CIN treatment surveillance

Women previously treated for CIN2+

Increased risk of developing HG CIN

* 8-year risk: For treated and co-testing negative: 2.9%
  General population: 1.92%

* 10-year risk: For treated and co-testing negative: 6.05%
  General population: 2.67%

CONTINUING SURVEILLANCE 5 YEARS POST TREATMENT

Gehaen-Maghmi S, BJOG 2011.

Post CIN treatment surveillance

Co-testing at 2 separate time points

The most common strategy as “test of cure”

- Highest sensitivity 95% than HPV testing and cytology
- Lower specificity (more women to triage)

Cushieri K, J Clin Vird 2016.

Compliance necessary of long term follow up

Morelli S, J Med Screen 2014.
Leyood R, Sentinel Site Study BMJ, 2012.

HPV vaccination after treatment for pre-cancer

- High levels of type-specific vaccine targeted HPV antibodies

  Protection against new cervical infections (new partner or self inoculation)

- Newly detected HPV types after treatment

  Oncogenic HPV types:
  up to 24% at 3-11 months
  up to 21% at 12-36 months

Rositch AF, Gynecol Oncol 2014.

Observational Study

Medicine®

OPEN

Persistent HPV-16 infection leads to recurrence of high-grade cervical intraepithelial neoplasia

Jung Mi Byun, MD, PhD[a,b,*], Dae Hoon Jeong, MD, PhD[a,b,*], Young Nam Kim, MD, PhD[a,b], Eun Jung Jung, MD[a], Kyung Bok Lee, MD, PhD[a,b], Moon Su Sung, MD, PhD[a,b], Ki Tae Kim, MD, PhD[a,b]

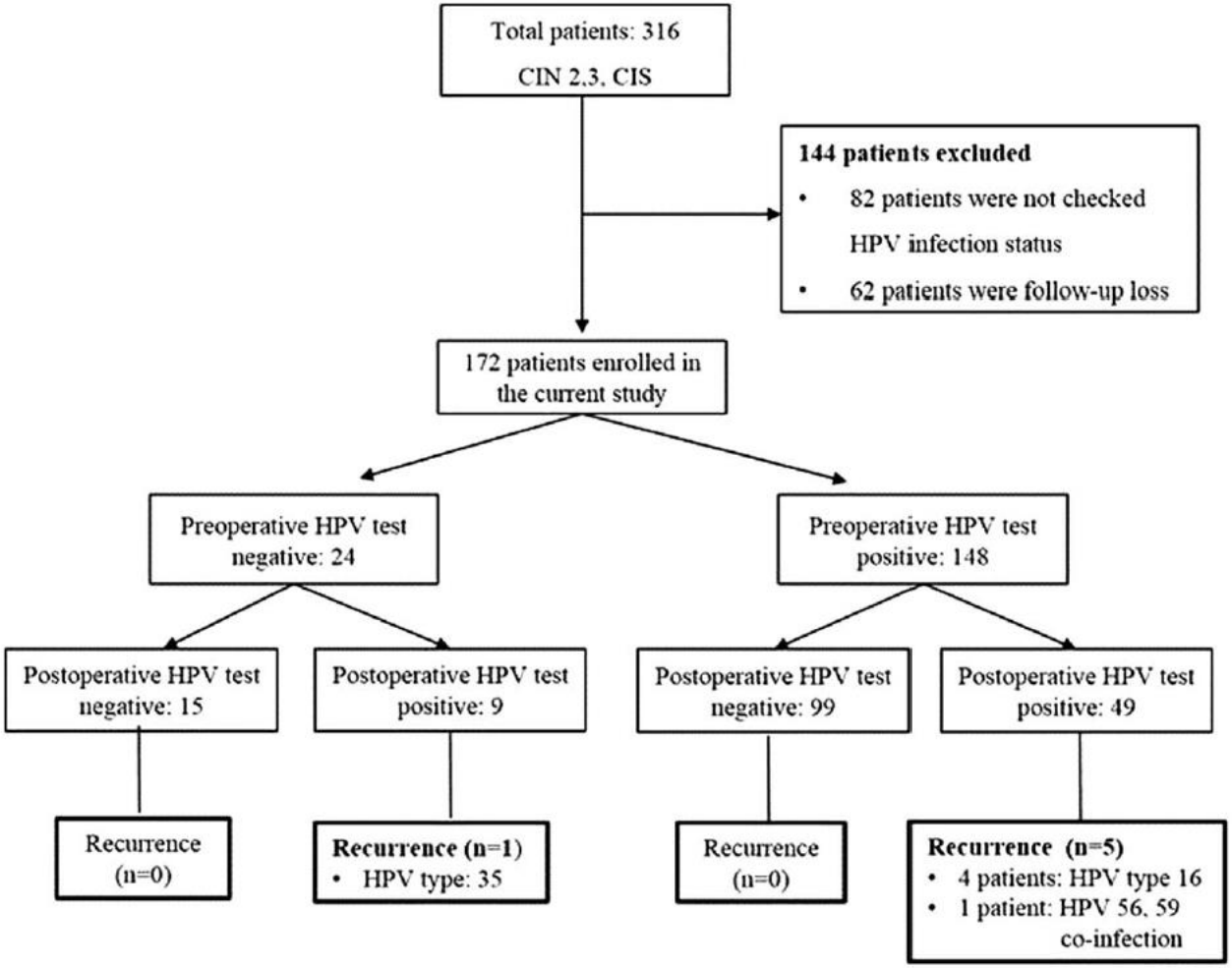


Figure 1. Flow chart showing patient recruitment. CIN=cervical intraepithelial neoplasia, CIS=carcinoma in situ, HPV=human papillomavirus.

Observational Study

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Multivariate evaluation of factors affecting recurrence after treatment (n = 58).

Variable	Odds ratio (95% CI)	*P*
Margin involvement	2.03 (0.19–21.32)	.553
Method of operation	1.35 (0.16–11.74)	.783
HPV 16 infection after treatment	19.4 (1.89–198.79)	.012
Number of HPV infection after treatment	13.34 (0.84–210.94)	.065

CI = confidence interval, HPV = human papillomavirus.

Observational Study

Medicine®

OPEN

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- The recurrence of high-grade CIN was related to HPV infection after treatment
- Persistent HPV 16 infection was the most important risk factor for recurrence.
- The majority of patients who were positive for HPV 16 type after treatment had persistent infection.

HPV vaccination for HPV 16 type may be useful in preventing recurrence of CIN2/3 and CIS.

Prophylactic vaccines after CIN treatment

Lack of protective effect against:

- Incident disease in women already infected with HPV

No therapeutic effect on existing infection and associated lesions

*ORIGINAL RCTs

Hildesteim A, JAMA, 2007
Hangot RM, Int J Cancer 2011
Szazewski A, Int J Cancer, 2012

Prophylactic vaccines after CIN treatment

Post hoc analysis of vaccine trials (bivalent & quadrivalent)

- Women infected at baseline and developed a lesion

    - Women who received HPV vaccine had lower rates of subsequent/recurrent CIN than placebo

- Women not randomized to vaccine receipt according to
    - baseline HPV status
    - presence of a lesion

(observational and not randomized data)

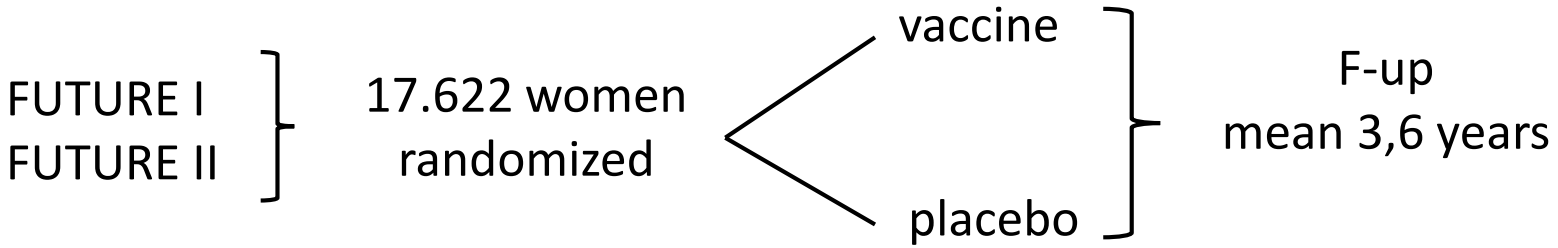
The BMJ
BMJ. 344: e1401

Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data

Elmar A Joura, associate professor[1], Suzanne M Garland, director, professor[2], Jorma Paavonen, professor, physician in chief[3], Daron G Ferris, professor[4], Gonzalo Perez, professor[5], Kevin A Ault, associate professor[6], Warner K Huh, associate professor[7], Heather L Sings, director of Global Scientific and Medical Publications[8], Margaret K. James, senior biometrician[8], Richard M Haupt, executive director of clinical research[8]for the FUTURE I and II Study Group

Prophylactic vaccines after CIN treatment

Quadrivalent vaccine trials



Vaccine Efficacy (VE) against recurrence ≥ 60 days post surgery

- VE against subsequent CIN_2+: 64.9% (95% CI 20.1%, 86.3%)
- VE against subsequent CIN_1+: 48.3% (95% CI 19.1%, 67.6%)

Joura EA, BMJ 2012

Prophylactic vaccines after CIN treatment

- *Bivalent vaccine trial*

  18.664 Women aged 15-25 years – f-up for 4 years

  Examining CIN_2+ & CIN_1+ at ≥60 days post treatment

454 women
- 190 vaccinated
- 264 placebo

HPV-vaccinated women

- Recurrent CIN_2+ lesions significant lower (VE 88.2% [95% CI 14.8, 99.7])
- Recurrent CIN_1+ lesions **not** significant lower (VE 42.6% [95% CI 14.8, 99.7])

Garland SM, Post-hoc analysis from a RCT, Int J Cancer 2016

Prophylactic vaccines after CIN treatment

- Bivalent HPV vaccine trial – COSTARICA TRIAL post-hoc analysis

Non significant results

(lower No of women limiting power)

Published in final edited form as:

Am J Obstet Gynecol. 2016 August ; 215(2): 212.e1–212.e15. doi:10.1016/j.ajog.2016.02.021.

Impact of human papillomavirus (HPV) 16 and 18 vaccination on prevalent infections and rates of cervical lesions after excisional treatment

Dr. Allan Hildesheim, PhD, **Dr. Paula Gonzalez, MD**, **Dr. Aimee R. Kreimer, PhD**, **Dr. Sholom Wacholder, PhD**, **Mr. John Schussler**, **Dr. Ana C. Rodriguez, MD**, **Dr. Carolina Porras, PhD**, **Dr. Mark Schiffman, MD**, **Ms. Mary Sidawy**, **Dr. John T. Schiller, MD**, **Dr. Douglas R. Lowy, MD**, and **Mr. Rolando Herrero for the Costa Rica HPV Vaccine Trial (CVT) Group**

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Drs Hildesheim, Kreimer, Wacholder, Schiffman); Proyecto Epidemiológico Guanacaste, Fundación INCIENSA, San José, Costa Rica (Drs Gonzalez, Rodriguez, and Porras, and Mr Herrero); Information Management Services, Silver Spring, Maryland (Mr Schussler); Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC (Ms Sidawy); and 6 Center for Cancer Research, National Cancer Institute, Bethesda, Maryland (Drs Schiller and Lowy)

Prophylactic vaccines after CIN treatment

- *Hildesheim A, Am J Obstet Gynecol 2016*

311 women LEEP for CIN

- 142 vaccinated
- 169 control vaccine

F-up median 27,3 months

- 34% with HPV infection post treatment
- Only 1.68% with recurrent CIN_2+

NO consistent evidence of VE against:

- infection
- recurrence overall

(Predominance of pre-existent infections continuing)

When incident infections

- VE was consistently positive

(although very low numbers and wide CI)

Gynecologic Oncology 130 (2013) 264–268

Contents lists available at SciVerse ScienceDirect

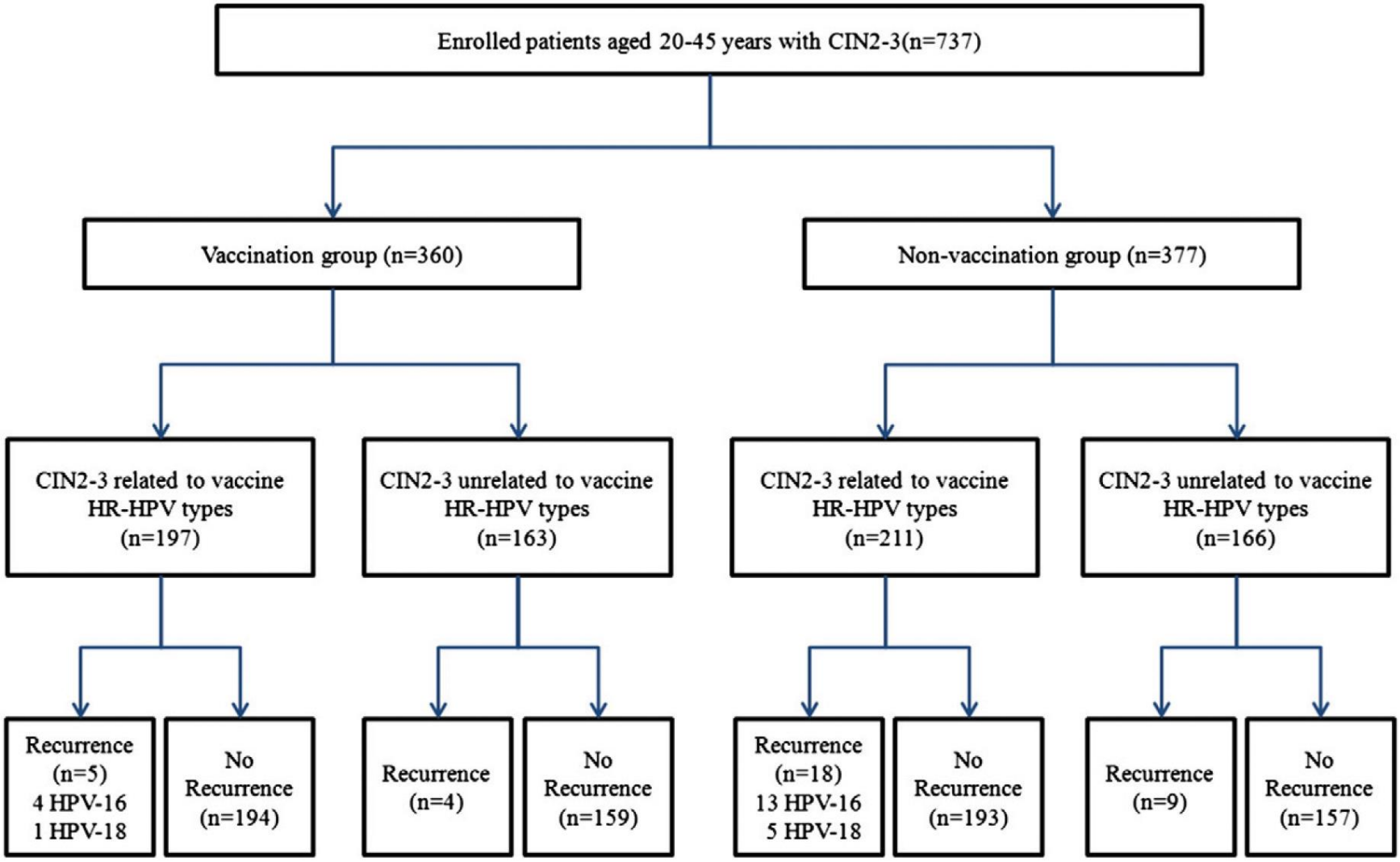
Gynecologic Oncology

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

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 *

Department of Obstetrics and Gynecology, Chonnam National University Medical School, Gwangju, Republic of Korea



*Vaccine HR-HPV types, HPV 16 or 18 types

Prophylactic vaccines after CIN treatment

- *Kang WD, Gynecol Oncol 2013*
  A non-randomized observational study

737 women with CIN_{2-3}
Aged 20-45 years → LEEP treatment

Routine counseling for HPV quadrivalent vaccine
- 360 vaccinated
- 377 not vaccinated

F-up of 3,5 years – co-testing (Colposcopy ij positive test)

Prophylactic vaccines after CIN treatment

- *Kang WD, Gynecol Oncol 2013*

No significant difference between vaccinated and unvaccinated women in:

- age
- CIN grade 2 vs 3 distribution
- HPV 16/18 positivity
- Margin status

Overall recurrence rate 4.9%

- 360 vaccinated
- 377 not vaccinated

* **Non vaccination was a significant predictor of reccurence**

(Hazard ratio 2.8 [25% CI 1.3, 6.0])

IT MAY BE A BENEFIT IN OFFERING HPV VACCINATION TO WOMEN POST CIN TREATMENT

Prophylactic vaccines after CIN treatment

Ghelardi A, Gynecol Oncol 2018

- *Non randomized observational study*

Women aged 18 – 45 years with CIN_2+ to stage IA1 CaCx
Intensively counseled about HPV vaccination
30 days post LEEP
quadrivalent vaccine

* Follow up by co-testing (colposcopy for test positive)
(36 months)

536 women treated by LEEP
- 174 vaccinated
- 176 unvaccinated
- rest lost to F-up

Prophylactic vaccines after CIN treatment

Ghelardi A, Gynecol Oncol 2018

* No difference on
  - marginal status
  - age

* Recurrence rate
  - 6.4% unvaccinated women
  - 1.2% vaccinated women

p=0.01 VE=81.2% (95% CI 34.3, 25.7%)

IT MAY BE A BENEFIT IN OFFERING HPV VACCINATION TO WOMEN POST CIN TREATMENT

Prophylactic vaccines after CIN treatment

Available evidence

Potential reduction in risk of recurrent disease if women treated for CIN are vaccinated

Biological plaucible:

- Vaccine induced antibodies
  - Can prevent infection
  - Women failed to clean HPV infection at risk for new infection

- Lack of randomized trials

Prophylactic vaccines
to reduce CIN recurrence

Pathway – Cervix modeling

Evaluation of the potential effectiveness and cost effectiveness of vaccinating women treated for CIN_2 + (either HPV vaccine)

Velentzis LS , Gynecol Oncol 2019

Gynecologic Oncology 152 (2019) 465–471

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Pathways to a cancer-free future: A protocol for modelled evaluations to maximize the future impact of interventions on cervical cancer in Australia

Louiza S. Velentzis [a,b,*], Megan A. Smith [a,c], Kate T. Simms [a,d], Jie-Bin Lew [a,d], Michaela Hall [a,d], Suzanne Hughes [a], Susan Yuill [a], James Killen [a], Adam Keane [a], Katherine Butler [a], Jessica Darlington-Brown [a], Harriet Hui [a], Julia M.L. Brotherton [b,e], Rachel Skinner [f,g], Alison Brand [h,i], Lara Roeske [e], Stella Heley [e], Jonathan Carter [j], Deborah Bateson [k,l], Ian Frazer [m], Suzanne M. Garland [n,o,p], Rebecca Guy [q], Ian Hammond [r], Paul Grogan [s], Marc Arbyn [t], Philip E. Castle [u], Marion Saville [e,p], Bruce K. Armstrong [c,v], Karen Canfell [a,c,d]

Priority evaluations for cervical cancer control recommended by the SAC: obtaining maximum impact[a] from existing approaches.

Evaluation	Approach/broad intervention category[a]
Impact of achieving 100% vaccination coverage compared to current vaccination coverage.	Improving vaccination uptake
Impact of maintaining vaccine coverage in girls and boys at current levels of ~80%.	Improving vaccination uptake
Impact of vaccinating women aged 35+ with HPV4 or HPV9 compared to no adult vaccination.	Vaccinating older women (HPV FASTER)
Impact of increasing attendance for on-time screening to 100% at five years.	Increasing screening participation rates
Impact of all women initiating screening by the age of 30 (no unscreened women).	Increasing screening participation rates
Impact of eliminating under-screening (i.e. the proportion of women who have not attended for screening for ≥7 years).	Increasing screening participation rates
Impact of using HPV assays/HPV genotyping assays that are not clinically-validated.	Ensuring quality assurance in screening
Impact of regular screening using a self-collected samples offered to i) all women and ii) selectively offered to never screened and under-screened.	Increasing screening participation rates
Impact of 100% attendance for women under surveillance for a recent abnormality.	Improving the diagnosis of CIN and cancer
Impact of increasing colposcopy attendance rates to 100% when recommended.	Improving the diagnosis of CIN and cancer
Impact of improving colposcopy performance to 100% sensitivity at CIN2+.	Improving the diagnosis of CIN and cancer
Impact of reduction in colposcopy sensitivity by an absolute magnitude of 20%.	Improving the diagnosis of CIN and cancer
Impact of reducing the rate of unsatisfactory colposcopy procedures.	Improving the diagnosis of CIN and cancer
Impact of improving the effectiveness of treatment for cervical pre-cancer while reducing its harms.	Improving pre-cancer treatment
Impact of HPV16/18 positive women receiving an alternative treatment for HPV-related infection or disease (such as a therapeutic HPV vaccine) after cancer is ruled out.	Treatment for HPV infections, LSIL (CIN1), HSIL (CIN2/3)
Impact of treatment options for women with CIN2/3 and women with HPV/CIN1 separately.	Treatment for HPV infections, LSIL (CIN1), HSIL (CIN2/3)
Impact and threshold costs of a cervical cancer treatment that increases 5 and 10-year survival for each stage (or a specific stage) by reducing cumulative mortality (1-cumulative survival) by 10%, ii) 50% and iii) 80%.	Cervical cancer treatment and guidelines in Australia
Impact of improved quality of life in women being treated for cancer on quality-adjusted life-years saved.	Cervical cancer treatment and guidelines in Australia

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Priority evaluations for cervical cancer control recommended by the SAC: exploring the potential of new approaches.

Evaluation	Approach
Optimal screening regime for unvaccinated women (based on birth cohort) and vaccinated women based on their vaccination history and type of vaccine received.	Tailored screening based on vaccination status (HPV4 or HPV9)
Longer interval screening schedules following two consecutive negative HPV test results within routine screening.	Tailored screening based on vaccination and screening history.
Impact of partial genotyping for oncogenic HPV types other than 16/18 with direct colposcopy referral for select types compared to cytology triage.	Methods for Triage
Impact of triaging oncogenic HPV positive (non 16/18 types) women with dual-staining (p16 ki67) cytology, compared to LBC.	Methods for Triage
Impact of methylation markers in HPV positive self-collected samples testing compared to clinician-collected cytology test.	Methods for Triage
Impact of vaccinating women treated for CIN2/3 with HPV4/HPV9 if the vaccine reduces recurrence by 50% (for pre-existing HPV types) or 80% (naïve for HPV types).	Vaccine to prevent CIN2/3 recurrence
Impact of vaccinating women treated for CIN2/3 with HPV4/HPV9 if the vaccine prevents or reduces recurrence of CIN2+ after treatment.	Vaccine to prevent CIN2/3 recurrence

Prophylactic vaccines to reduce CIN recurrence

- Absence of RCTs data for secondary vaccination from prophylactic vaccines

- Necessary use of existing observational studies

Garland SM, Int J Cancer 2016
Joura CA, BMJ 2012
Kang WD, Gynecol Oncol 2013

Prophylactic vaccines to reduce CIN recurrence

Modeling the impact of vaccinating HPV-FASTER concept

mid – adult women & men up to 45 years

(Bivalent, quadrivalent, nonavalent vaccine)

Vs

No adult vaccination

Bosch X, Nat Rev Clin Oncol 2016

Prophylactic vaccines to reduce CIN recurrence

Simms KT, Lancet Oncol 2019

A modelling study

A global -in 181 countries- of various vaccination scenarios on future incidence rates and the burden of cervical cancer on the next 50 years (2020 – 2069)

Prophylactic vaccines to reduce CIN recurrence

Simms KT, Lancet Oncol 2019

- Vaccination of girls and boys 12 – 15 years
- Vaccination of men and women 16 – 49 years
  - One-off catch-up phase in 2020 (Nonavalent vaccine)
  - If high coverage was to be achieved

14.0 – 14.3 million cancers could be averted worldwide on next 50 years

Prophylactic vaccines to reduce CIN recurrence

The cost – effectiveness of HPV-FASTER scenario have to be evaluated carefully

Effectiveness based on:

- Vaccine 90% effective at preventing new infection in uninfected individuals older than 26 years

- The price of vaccine

Bosch X, Nat Rev Clin Oncol 2016
Simms KT, Lancet Oncol 2019

Prophylactic vaccines to reduce CIN recurrence

Despite the reduction of HPV vaccine prices population-wide vaccination to 45 years of age is unlikely to be affordable or cost – effective

Unless:

- Vaccine price is substantially reduced
- One dose is effective

Simms KT, Lancet Oncol 2019

Prophylactic vaccines to reduce CIN recurrence

Alternatively

Vaccination of a targeted High-Risk subgroup

like women previous treated for CIN_{2-3}

is more likely to be cost-effective

Prophylactic vaccines
to reduce CIN recurrence

Available evidence

Potential reduction in risk of recurrent CIN disease

if women diagnosed and treated for CIN are offered prophylactic HPV vaccination