

HPV vaccination and risk of HSIL after excisional treatment for HSIL in a cohort of Canadian women

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Disclosures

- I was a site PI for the Merck nonavalent vaccine trial



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Identification and treatment of HSIL/AIS ensures the success of cervical cancer screening

- Large scale quality cervical cancer screening using the Pap test, has contributed to an important reduction in cervical cancer incidence and mortality
- Unlike cervical cancer, HSIL/AIS are most frequent in women of childbearing age
- HSIL/AIS treatment increases the risk of several adverse obstetrical outcomes
- Repeated treatment, necessary in app. 10% of cases, is of particular concern



Best options to limit the adverse consequences of HSIL/AIS treatment

- High coverage vaccination programs targeting young adults before the beginning of sexual activity will translate in a sharp decrease in HSIL/AIS, and consequently the need for treatment
- Vaccination programs typically do not extend free coverage to women past their early twenties, the peak age of HSIL/AIS, based on cost-effectiveness considerations



Objective

- There remains controversy as to the protective effect of HPV vaccines for a second HSIL/AIS after treatment for HSIL/AIS
- A solid evidence-base could convince stakeholders to extend vaccination coverage to women being treated for HSIL/AIS
- **We investigated the association between HPV vaccination and a second HSIL diagnosis in a general screening population of Canadian women treated for a first HSIL.**



Methods (1)

- We conducted a post-hoc analysis of the CoHIPP trial
- Participants were recruited to CoHIPP through 13 colposcopy centers across Canada, between 2010 and 2013, at the time of excisional treatment of HSIL/AIS
- Inclusion criteria:
 - CIN2, CIN3, HSIL or AIS on LEEP or cone pathology; over 18/19 years of age; no immunosuppression
- CoHIPP study procedures
 - Participants were seen after 6, 12, and 24 months
 - Biopsies were taken “as needed” at 6 months, and routinely at 12 and 24 months

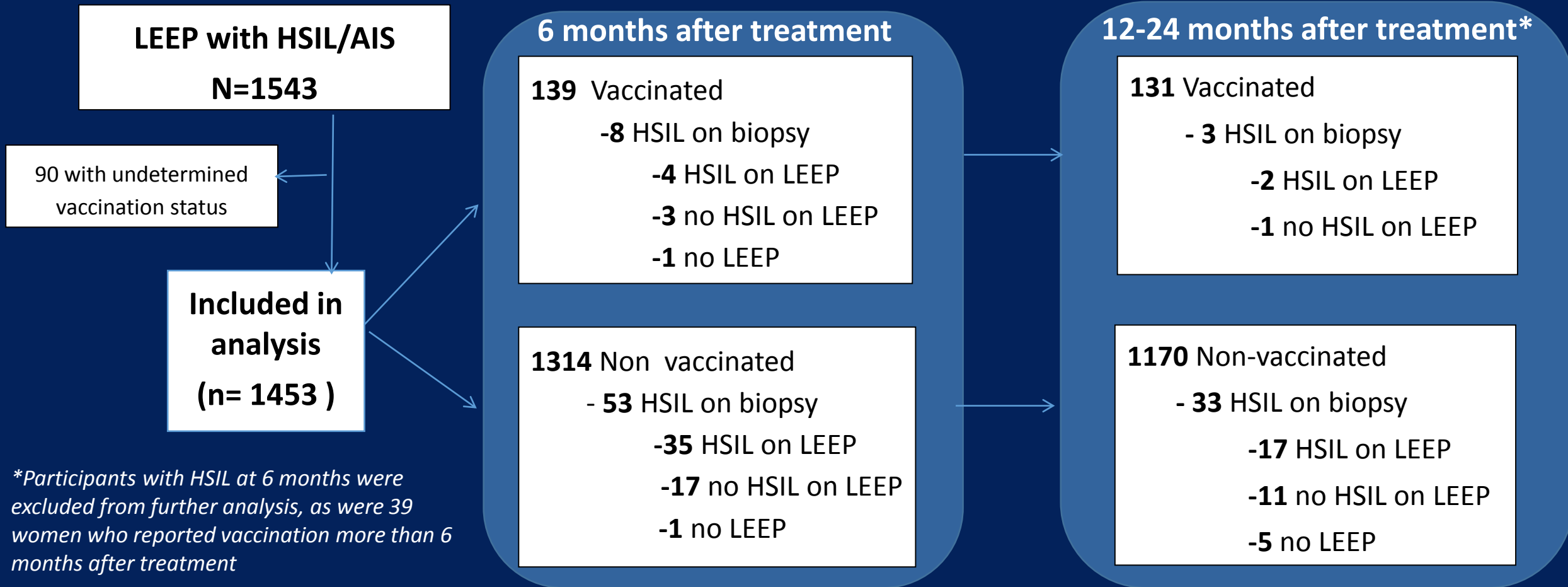


Methods (2)

- Exposure variable:
 - Self-report of HPV vaccination, any HPV vaccine
- Outcome variable:
 - Community pathologist diagnosis of cervical HSIL, AIS or cervical cancer on biopsy and/or ECC at any of the post-treatment study visits
- Confounding variables:
 - Age, self-reported number of sexual partners in the last year, tobacco use
- Analysis:
 - Cox proportional hazards regression analysis



Progression of participants through study visits



Socio-demographic and reproductive characteristics

CHARACTERISTIC	VACCINATED (N=139)	NON-VACCINATED (N=1314)	CHARACTERISTIC	VACCINATED (N=139)	NON-VACCINATED (N=1314)
Age (Median, IQR)	26.6 (23.8 – 31.0)	30.9 (26.8 – 36.5)	Hormonal contraception use*; n (%)		
Education; n (%)			Combined	81 (59.1)	470 (38.4)
Some high-school	7 (5.0)	95 (7.3)	Progestin only	10 (7.3)	101 (8.2)
High-school	24 (17.3)	285 (21.7)	Number of sexual partners in the last year		
College	25 (18.0)	371 (28.3)	0-1	91 (65.5)	930 (72.4)
University	83 (59.7)	560 (42.7)	2 or 3	29 (20.9)	213 (16.6)
Smoking; n (%)			4 or more	19 (13.7)	141 (11.0)
Never	78 (56.9)	511 (39.0)	Frequency of condom use in last year*		
Past	35 (25.6)	402 (30.7)	Never/rarely	73 (53.7)	774 (64.6)
Current	24 (17.5)	397 (30.3)	Some or most of the time	55 (40.4)	302 (25.2)
At least 1 full term pregnancy; n (%)	18 (13.1)	515 (40.43)	Always	8 (5.9)	122 (10.2)

P value less than 0.01 for all variables, except sexual partner: p=0.22

** Denominator includes only participants reporting sexual activity in the last year*



Impact of HPV vaccination on risk of second HSIL

	At 6 months		At 6-24 months	
	Vaccinated	Non-vaccinated	Vaccinated	Non-vaccinated
Number of HSIL on biopsy	8	53	3	33
Women year of follow-up	72.6	699.6	260.1	2281.1
Rate	7.58	11.01	1.15	1.44
Rate ratio	1.45 (0.69-3.08)		0.80 (0.16-2.54)	
Number of HSIL confirmed on LEEP	4	35	2	17
Women year of follow-up	72.6	699.4	260.1	2281.1
Rate	5.50	5.00	0.77	0.75
Rate ratio	1.10 (0.28-3.08)		1.03 (0.12-4.35)	



Exploratory analysis: Could confounders explain the lack of association?

	At 6 months	At 12-24 months
	aHR (95% CI)	aHR (95% CI)
HPV vaccination	1.9 (0.7-5.7)	1.6 (0.3-7.2)
Age (per year)	1.1 (1.0-1.1)	1.1 (1.0-1.1)
Number of sexual partners in last year		
1	referent	referent
2-3	1.4 (0.5-3.7)	0.7 (0.2-3.2)
4 and more	0.9 (0.3-2.4)	0.6 (0.1-4.4)
Current smoker	1.6 (0.8-2.0)	1.0 (0.3-2.7)



Comparison of HPV types identified at the time of LEEP and when 2nd HSIL/AIS diagnosed

	Participants* diagnosed with second HSIL/AIS at 6 months, n=32	
HR-HPV type at the time of second HSIL/AIS diagnosis, n (%)	Vaccinated, n=4	Non-vaccinated, n=28
Same as LEEP only	3 (75%)	23 (82.1%)
Same as LEEP, with new HR-types	1 (25%)	4 (14.3%)
Only new HR-types	0	1 (3.6%)
None	0	0
	Participants* diagnosed with second HSIL/AIS at 12-24 months, n=33	
HR-HPV type at the time of second HSIL/AIS diagnosis, n (%)	Vaccinated, n=2	Non-vaccinated, n=31
Same type(s) as LEEP only	1 (50%)	16 (51.6%)
Same as type(s) LEEP, with new HR-types	0	4 (12.9%)
Only new HR-types	0	6 (19.4%)
None	1 (50%)	5 (16.1%)

*29 participants with HSIL/AIS at 6 months did not have a sample available for genotyping at 6 months; 3 participants with HSIL/AIS at 12/24 months did not have a sample available for genotyping at 12/24 months



Discussion

- Strengths
 - General population, broadly representative of women being treated for HSIL/AIS in Canada
 - 2 year follow-up, several visits with histology
 - Prospective and nearly complete collection of information on confounders
- Limitations
 - Self-report of HPV vaccination



Discussion

- Re-analysis of PATRICIA and FUTURE studies have found vaccination to be prevent 65-88% of HSIL/AIS after treatment *(Joura 2012; Garland, 2016)*
 - Women 15-25/26 y.o, rate of recurrence of 2%-3% in controls
- A retrospective cohort study found a reduction of 65% when vaccination was initiated 1 week after LEEP *(Kang et al, 2013)*
 - Women 20-45, rate of recurrence of 7% over 24 months in unvaccinated
- Re-analysis of Costa Rican trial found no benefit *(Hildesheim et al, 2013)*
 - Women 18-25, rate of recurrence 5-8%
- Re-analysis of CoHIPP found no benefit
 - Women 19-70, rate of persistence/recurrence of 7% over 2 years



Conclusion

- There is no doubt that in women up to 45, including those who have been treated for HSIL/AIS, HPV vaccination is safe and prevents new HPV infections and associated lesions
- It is probable that most HSIL/AIS diagnosed within 2 years after a LEEP in our population represent persistent disease, and as such cannot be prevented by vaccination

