



Condylomas in women



Marta del Pino

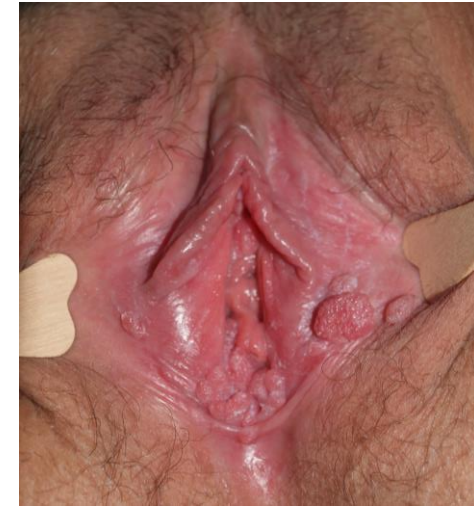
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Genital warts: really an important issue?

- Related with low-risk HPV (HPV 6 and 11, mainly)
- Benign lesions (exception of Buschke-Loewenstein)
- No life-threatening disease

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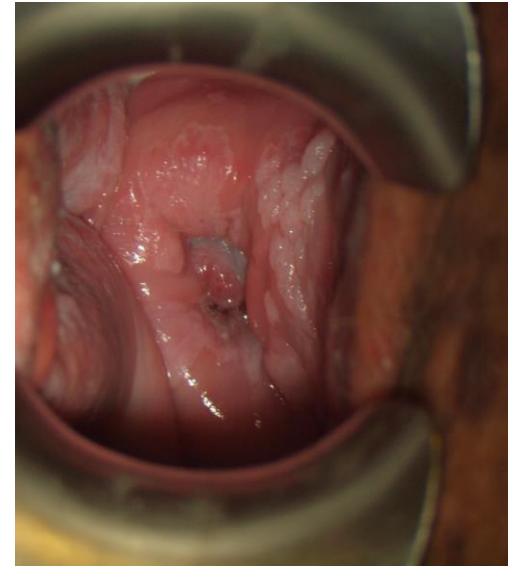
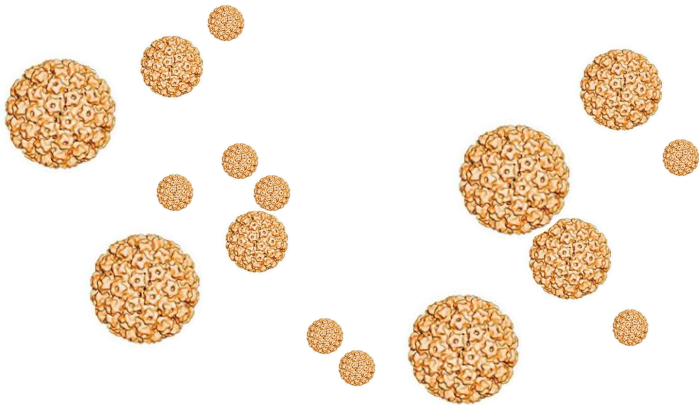
- No new diagnosis methods
- No new treatment approaches



Genital warts: really an important issue?

BUT.....

- Most common sexually transmitted disease
- Trend to increase in high income countries (in the pre-vaccine era)
- They can be difficult to treat and recurrence is frequent
- Remarkable psychological burden and loss in quality of life
- Considerable economic cost on health care system



Genital warts: really an important issue in Spain?

	Number of GWs cases	Annual cost in Spain (million €)	
		NHS perspective	Societal perspective
Men	31 833	21.42	29.51
Women	24 613	25.59	30.10
Total	56 446	47.01	59.61

	New cases	Recurrent cases	Resistant cases
Males			
Annual no. of cases	21 397	7313	3123
Rate per 100 000	136.58	46.68	19.93
Females			
Annual no. of cases	15 168	5872	3573
Rate per 100 000	99.59	38.55	23.46
Total			
Annual no. of cases	36 565	13 185	6 696
Rate per 100 000	117.86	42.57	21.72

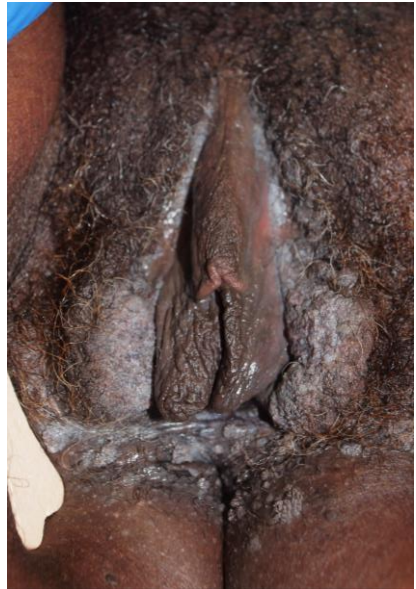


General issues

- Highly contagious and will develop in 65% of individual with infected partner
- Manifestation of acute infection (time between infection and development shorter in women [2.6 months] than men [11.0 months])
- Annual incidence: 85-205 cases per 100 000 (77-560 in men; 76-790 in women)
- Higher incidence in people younger than 30-y
- Most important risk factors: related to sexual habits, immunosuppression
- Genital warts in HIV women tend to be florid and long lasting lesions (related to low CD4+ counts)

General issues

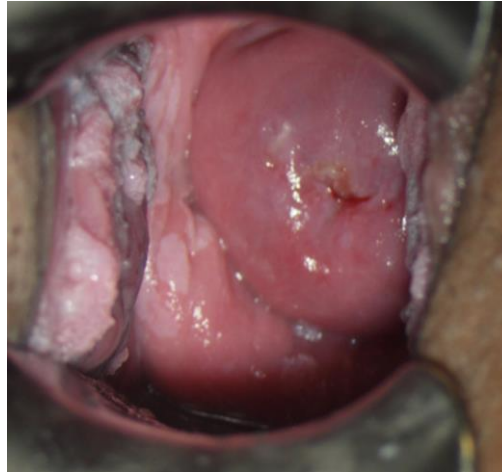
Vulva



Cervix



Vagina



Anus/perianal



Uretra



Head & Neck



Genital warts: the dark side

- Coexistence of other HPV (non-oncogenic and oncogenic) and sexually transmitted pathogens is frequent

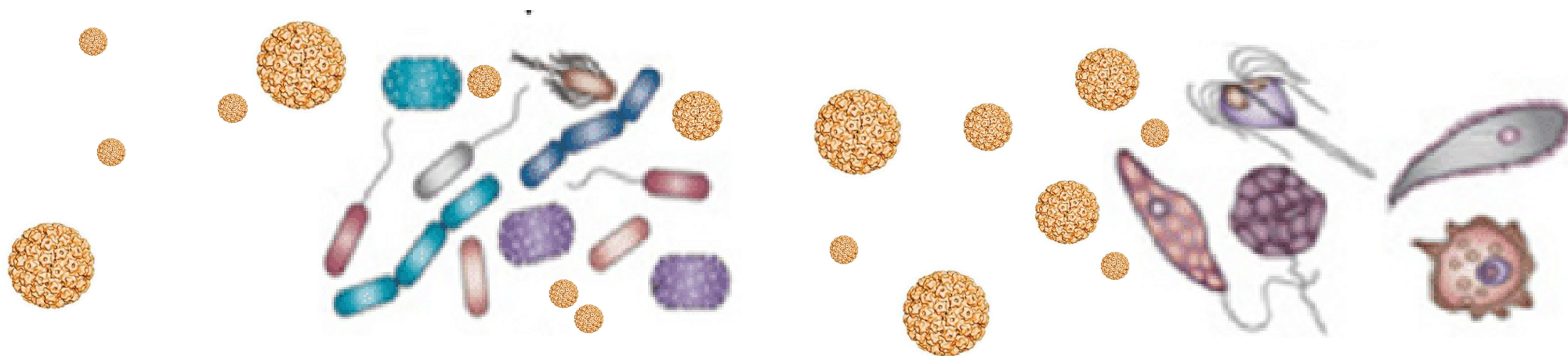
n= 689 women

Three study groups:

1) women with AGWs (“AGWs group”) : 196

2) women with a history of cervical HPV infection within the last year (“Cervical HPV group”) 315

3) women who visited the hospital for their routine gynecological check-up (“Control group”) 178



Genital warts: relation with hr-HPV

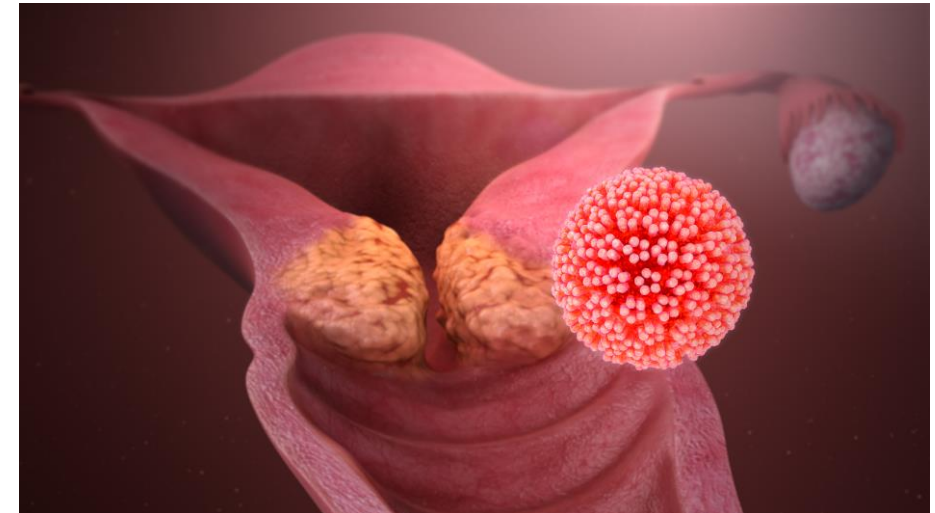
Cases (n=689)	AGWs group (n=196)	Cervical HPV group (n=315)	Control group (n=178)	<i>p</i> -Value
Mycoplasma genitalium				0.005
Positive (n=11)	8 (4.1%)	2 (0.6%)	1 (0.6%)	
Negative (n=678)	188 (95.9%)	313 (99.4%)	177 (99.4%)	
Mycoplasma hominis				0.005
Positive (n=62)	32 (16.3%)	19 (6%)	11 (6.2%)	
Negative (n=627)	164 (83.7%)	296 (94%)	167 (93.8%)	
Ureaplasma spp				0.005
Positive (n=250)	90 (45.9%)	117 (37.1%)	43 (24.2%)	
Negative (n=439)	106 (54.1%)	198 (62.9%)	135 (75.8%)	
Chlamydia				0.652
Positive (n=27)	9 (4.6%)	13 (4.1%)	5 (2.8%)	
Negative (n=662)	187 (95.9%)	302 (95.9%)	173 (97.2%)	
HR-HPV				0.0049
Positive (n=174)	67 (34.2%)	92 (29.2%)	15 (8.4%)	
Negative (n=515)	129 (65.8%)	223 (70.8%)	163 (91.6%)	

Cases (n=196)	Single episode (n=150)	Recurrent AGWs (n=46)	<i>p</i> -Value
HR-HPV			0.001
Positive (n=67)	38 (25.3%)	29 (63%)	
Negative (n=129)	112 (74.7%)	17 (37%)	

Genital warts: relation with hr-HPV

n= 562 patients (162 women)

	Number (%) of Patients			P value
	Total (n = 530)	Male (n = 375)	Female (n = 155)	
Negative	25 (4.7)	12 (3.2)	13 (8.4)	0.010
Any HPV	505 (95.3)	363 (96.8)	142 (91.6)	
LR-HPV	489 (92.3)	354 (94.4)	135 (87.1)	0.004
Only LR-HPV	289 (54.5)	229 (61.1)	60 (38.7)	<0.001
HR-HPV	216 (40.8)	134 (35.7)	82 (52.9)	<0.001
Only HR-HPV	17 (3.2)	10 (2.7)	7 (4.5)	0.271
Single infection	293 (55.3)	225 (60.0)	68 (43.9)	<0.001
Multiple infections	237 (44.7)	150 (40.0)	87 (56.1)	<0.001
HPV 6/11	464 (87.5)	336 (89.6)	128 (82.6)	0.026



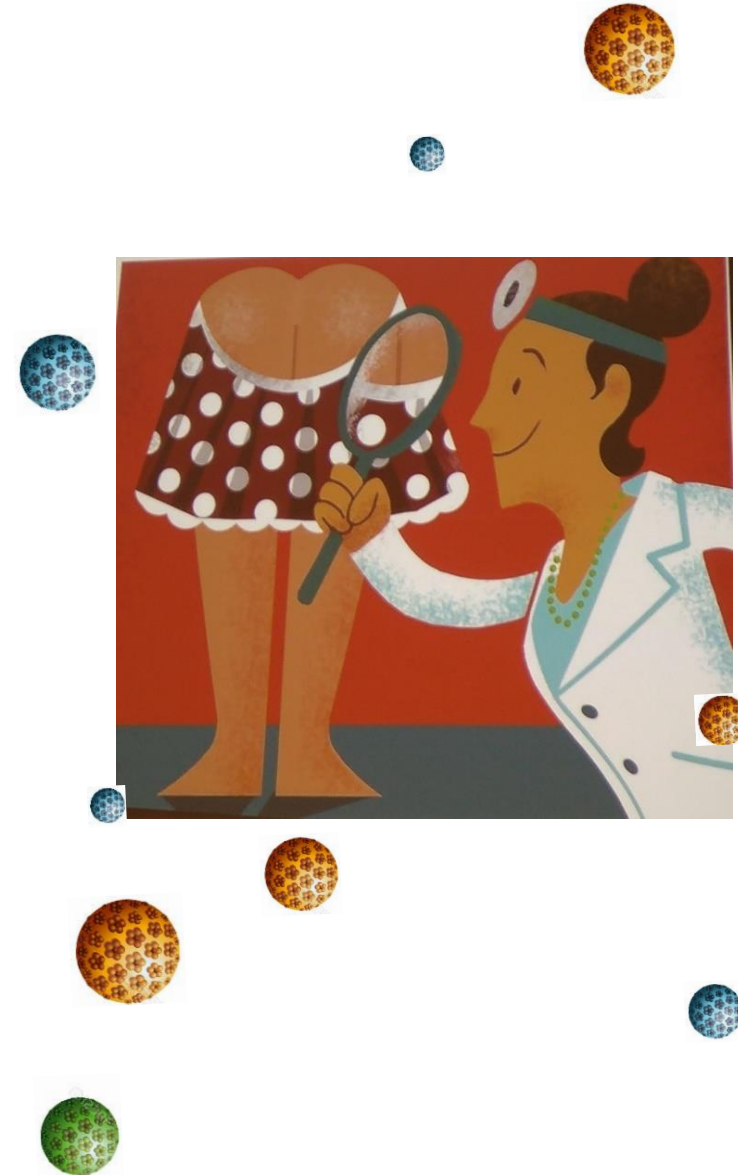
high prevalence of HR-HPVs, particularly of HPV 16 in patients (specially in women) with AGWs

Genital warts: relation with hr-HPV

n= 200 (58 women) with genital warts

To assess the frequency of anal and oral HPV in patients with genital warts

Variable	Male n (%)	Female n (%)	Total n (%)	<i>p</i> ^e
<i>Genital HPV types</i>				
Single low-risk	67 (54.0)	14 (24.1)	81 (44.5)	<0.001
Single high-risk	5 (4.0)	6 (10.3)	11 (6.0)	0.11
Multiple low-risk	11 (8.9)	4 (6.9)	15 (8.2)	0.78
Multiple incl. ≥1 high-risk type	41 (33.1)	34 (58.6)	75 (41.2)	0.001
<i>Extra genital HPV</i>				
<u>Anal</u>				
Low-risk only	26 (21.0)	11 (19.0)	37 (20.3)	0.84
≥1 high-risk type	15 (12.1)	32 (55.2)	47 (25.8)	<0.001
With perianal warts ^a	31 (72.1)	14 (77.8)	45 (73.8)	0.75
Without perianal warts ^b	10 (12.3)	29 (72.5)	39 (32.3)	<0.001
MSM and WSW ^c	16 (66.7)	0 (0.0)	16 (61.5)	0.14
Hetero ^d	25 (25.0)	43 (76.8)	68 (43.6)	<0.001
<u>Oral</u>				
Low-risk only	5 (4.0)	2 (3.4)	7 (3.8)	1.0
≥1 high-risk type	10 (8.1)	2 (3.4)	12 (6.6)	0.34
No extra genital infection	76 (61.3)	14 (24.1)	90 (49.5)	<0.001



Genital warts & hr-HPV infection

n= 541 (160 ♀) included in the HERCOLES (HPV Epidemiological Research on COndyloma LESions) study

To assess the type-specific prevalence of HPV in the anal canal and oral mucosa from patients with AGWs

HPV prevalence
(overall)

Variable	Total n (%)	Women n (%)	Men n (%)	p-value
Anal canal	n = 509	n = 154	n = 355	<0.001
Any HPV ^b	305 (59.9)	131 (85.1)	174 (49.0)	
95% CI	[55.6–64.1%]	[78.6–89.8%]	[43.9–54.2%]	
Negative ^c	62 (12.2)	12 (7.8)	50 (14.1)	
Undetermined ^d	142 (27.9)	11 (7.1)	131 (36.9)	
Oral mucosa	n = 538	n = 160	n = 378	0.348
Any HPV ^b	78 (14.5)	27 (16.9)	51 (13.5)	
95% CI	[11.8–17.7%]	[11.8–23.4%]	[10.4–17.3%]	
Negative ^c	443 (82.3)	130 (81.3)	313 (82.8)	



Anogenital warts represent a clinical marker for both anal and oral HPV infections, including anal high risk-HPV infections, particularly among women

high-risk HPV
prevalence

HR-HPV	157 (51.5)	77 (58.8)	80 (46.0)	0.012
Single LR	130 (42.6)	45 (34.4)	85 (48.9)	
Single HR	38 (12.5)	13 (9.9)	25 (14.4)	
Multiple LR	18 (5.9)	9 (6.9)	9 (5.2)	
Multiple with ≥ 1 HR	119 (39.0)	64 (48.9)	55 (31.6)	
Oral mucosa	n = 78	n = 27	n = 51	0.348
LR-HPV	38 (48.7)	11 (40.7)	27 (52.9)	
HR-HPV	40 (51.3)	16 (59.3)	24 (47.1)	
Single LR	36 (46.2)	11 (40.7)	25 (49.0)	
Single HR	18 (23.1)	5 (18.5)	13 (25.5)	
Multiple LR	2 (2.6)	0 (0.0)	2 (3.9)	0.277
Multiple with ≥ 1 HR	22 (28.2)	11 (40.7)	11 (21.6)	

Genital warts & HPV-related disease

HPVWorld

The newsletter on Human Papillomavirus

n° 39

HPV infections in High-Risk groups

As most HPV infections are transient, subjects who develop genital warts may represent a vulnerable group of individuals in whom HPV infections tend to become persistent. Hence, this group would have – in theory – an increased risk of developing HPV-related high-grade lesions or cancers, such as anogenital cancers and some specific types of head and neck cancer.



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Genital warts & premalignant lesions

n= 9552 ♀ with genital warts in the Danish Hospital Discharge Register. Follow-up: 7.4-y

Cancer type	Observed	Expected	SIR	95% CI
CIN III				
By age* (years)				
<40	292	114.1	2.6	2.3–2.9
≥40	16	3.5	4.6	2.6–7.4
By time of follow-up (years)				
<1	58	10.7	5.4	4.1–7.0
1–4	128	50.6	2.5	2.1–3.0
5–9	100	43.5	2.3	1.9–2.8
10–15	22	12.9	1.7	1.1–2.6
Total	308	117.6	2.6	2.3–2.9



SIR: Standardised incidence ratio. CI: Confidence Interval.

Genital warts & HPV-related cancers

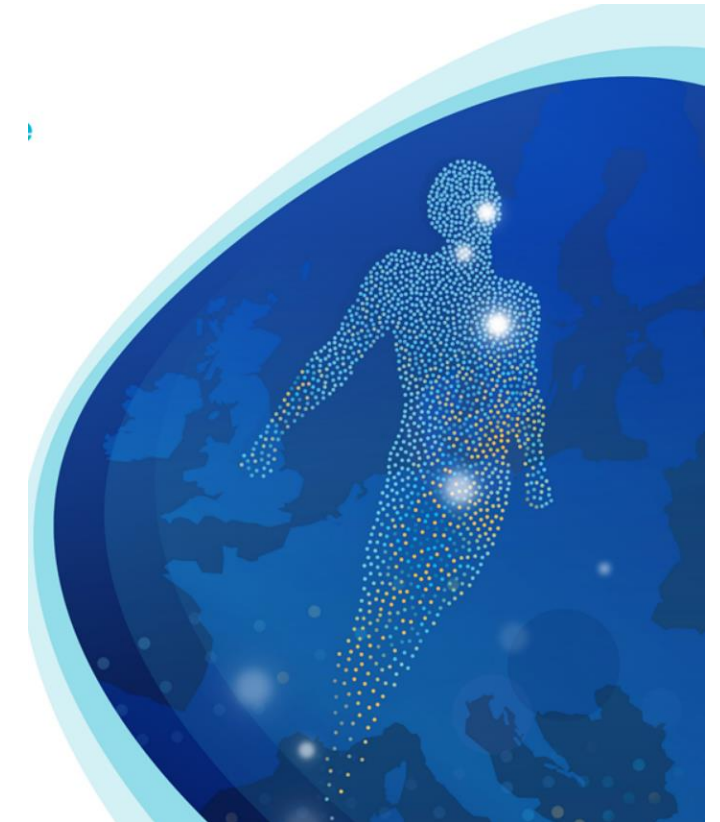
Cancer type	Observed	Expected	SIR	95% CI
Anal	2	0.24	8.5	0.9–30.5
Vulvar				
By age* (years)				
<40	6	0.14	42.4	15.6–92.3
≥40	5	0.13	37.6	12.2–87.8
By time of follow-up (years)				
<1	1	0.02	42.8	0.6–238
1–4	6	0.11	56.2	20.5–122
5–9	4	0.10	39.6	10.7–102
10–15	0	0.04	—	—
Total	11	0.27	40.1	20.0–71.7
Cervical				
By age* (years)				
<40	16	9.0	1.8	1.0–2.9
≥40	6	2.0	3.0	1.1–6.5
By time of follow-up (years)				
<1	2	1.0	2.1	0.2–7.5
1–4	5	4.4	1.1	0.4–2.7
5–9	10	4.1	2.5	1.2–4.5
10–15	5	1.5	3.2	1.0–7.5
Total	22	11.0	2.0	1.3–3.0

Genital warts & HPV-related cancers

Risk of genital cancer among women who received a diagnosis of genital warts in Denmark from 1978–2009 according to likelihood of HPV relationship (n= 32,933 ♀ followed for 30-y)

Cancer site	Women		
	Observed	SIR	95 % CI
All HPV-related cancers ^b	245	2.8	2.4–3.1
Anogenital			
Cervix uteri	117	1.5	1.3–1.8
Vagina	6	5.9	2.2–12.9
Anus	33	7.8	5.4–11.0
Vulva	74	14.8	11.7–18.6

SIR: Standardised incidence ratio. CI: Confidence Interval.

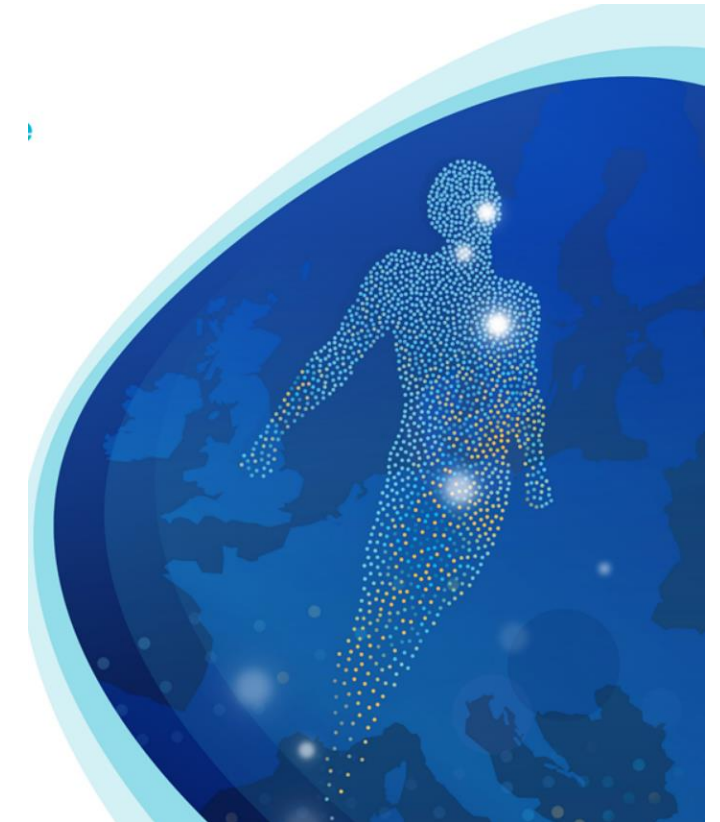


Genital warts & HPV-related cancers

Risk of head and neck cancer among women who received a diagnosis of genital warts in Denmark from 1978–2009 according to likelihood of HPV relationship (n= 32,933 ♀ followed for 30-y)

HEAD AND NECK CANCER	WOMEN	
	Observed number	SIR (95 % CI)
HPV-associated	15	4.8 (2.7-8.0)
Potentially HPV-associated	24	3.3 (2.1-4.8)
No or weakly HPV-associated	1	0.5 (0.0-3.0)

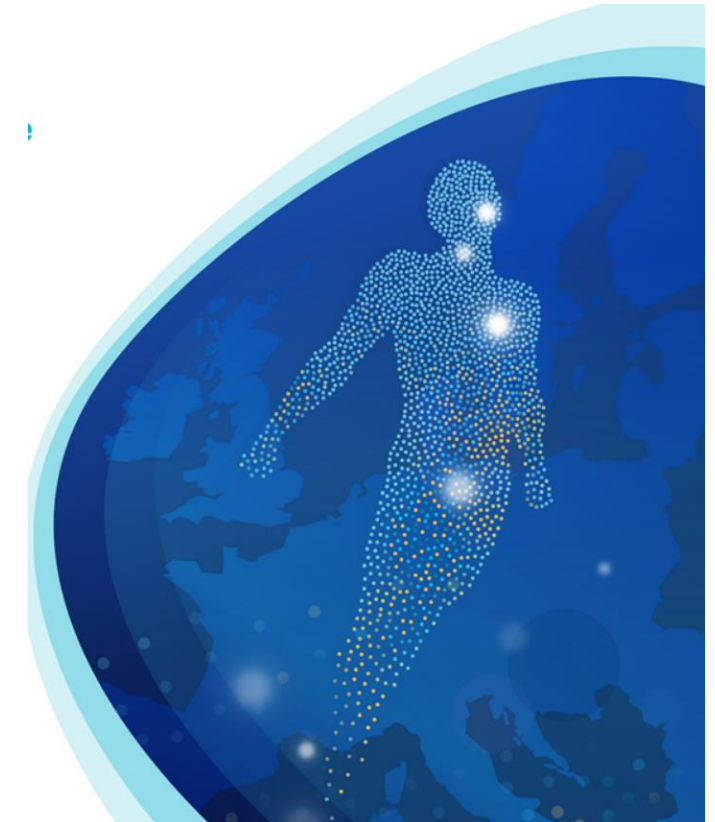
SIR: Standardised incidence ratio. CI: Confidence Interval.



Genital warts & HPV-related cancers

cancer among women who received a diagnosis of genital warts in Denmark from 1978–2009

FOLLOW-UP TIME BY CANCER TYPE	WOMEN	
	Observed number	SIR (95 % CI)
Anal cancer		
< 1y	10	66.5 (31.9-122.4)
1-4y	10	14.5 (7.0-26.7)
5-9y	14	14.1 (7.7-23.7)
> 10y	28	7.5 (5.0-10.8)
Tonsillar cancer		
< 1y	0	0 (0-68.5)
1-4y	0	0 (0-14.5)
5-9y	2	5.4 (0.6-19.5)
> 10y	9	5.4 (2.5-10.2)



The subsequent risk of cancer amongst individuals that suffered from genital warts remains high after 10 years of follow up.

Genital warts & cervical HPV lesions screening

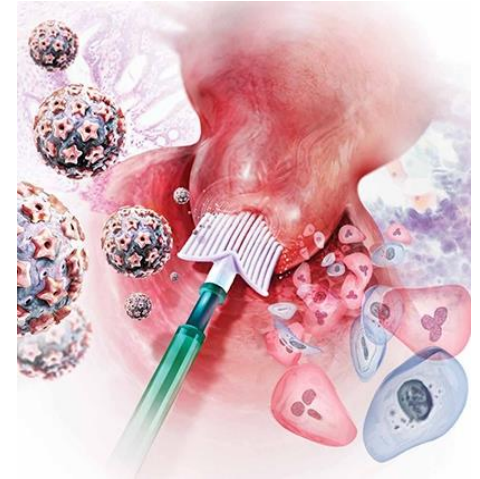


Women with AGWs should undergo thorough **anal and gynecologic examinations** (including cervical cytologic smear) at regular intervals, in order **to identify anogenital neoplasias** at an early stage.

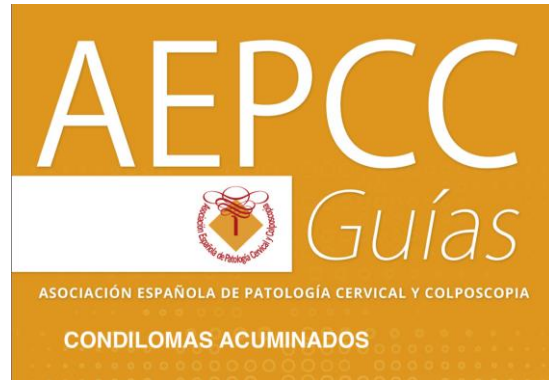
Genital warts & cervical HPV-(cervical) lesions screening



When a patient is diagnosed with genital warts, she should undergo testing for other sexually transmitted infections (gonorrhea, chlamydia, HIV, syphilis, hepatitis B/C) as well as cervical cancer screening based on available published guidelines.¹⁶



Genital warts & cervical HPV-(cervical) lesions screening



A pesar de que la evidencia publicada hasta la fecha sugiere que los condilomas acuminados son marcadores de lesiones premalignas del tracto genital, y hasta no disponer de más datos al respecto, las mujeres que presentan o han presentado en el pasado condilomas acuminados deben realizarse los controles de cribado del cáncer de cuello uterino de acuerdo a la guía de cribado del cáncer de cuello de útero en España publicada en el año 2014¹³¹.

Despite genital condylomata are markers of the premalignant lesions. women with GW should follow regular cervical cancer screening programs

Genital warts & HPV lesions screening




GUIDELINES

2019 IUSTI-Europe guideline for the management of anogenital warts

Grade	Recommendation
1	A strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. Most clinicians and patients would want to follow a strong recommendation unless there is a clear rationale for an alternative approach
2	A weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values
Quality of evidence	
A	High-quality evidence that comes from consistent results from well-performed randomized controlled trials (RCTs), or overwhelming evidence from another source (such as well-executed observational studies with consistent strong effects and exclusion of all potential sources of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect
B	Moderate-quality evidence from randomized trials that suffers from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with specific strengths such as observational studies with consistent effects and exclusion of the majority of the potential sources of bias
C	Low-quality evidence from controlled trials with several serious limitations, or observational studies with limited evidence on effects and exclusion of most potential sources of bias
D	Evidence based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there can be little confidence in the effect estimate

- In female patients presenting with anogenital warts, vaginal or cervical warts are present in an estimated 15% and 6% of individuals respectively.¹⁴ Speculum examination should be offered at initial assessment if cervical or vaginal lesions are suspected, such as when lesions are found at the introitus or when the patient reports being aware of possible internal lesions (1D).
- Perianal inspection should be offered for both sexes at initial assessment or if there are symptoms (e.g. lesions or anal irritation are reported) (1D); digital rectal examination and proctoscopy should be offered if anal canal warts are suspected (e.g. external lesions extending into the anal canal; anal bleeding or discharge) (1D).
- Human papillomavirus detection or typing does not influence management and is not recommended

Genital warts & HPV-(anal) lesions screening in HIV

Guideline	Population	Recomendation
New York State Department of Health's (NYSDOH) AIDS Institute (2007)		<p>Updated 2020: Anal cancer screening for all HIV ≥ 35 years old, regardless of HPV status. For HIV <35 years old only if anal dysplasia or history of anal cancer.</p>
HIV Medical Association (HIVMA) of the Infectious Diseases Society of America (IDSA) (2013)	<p>HIV-infected MSM HIV-infected persons with a history of anogenital condylomata HIV-infected men CIN, VIN HIV-infected women with a history of receptive anal sex</p>	Annual anal cytology screening
Grupo de Estudio del SIDA (GeSIDA) (2019)	<p>HIV-infected MSM HIV-infected persons with a history of anogenital condylomata HIV-infected women CIN, VIN</p>	Annual anal cytology screening

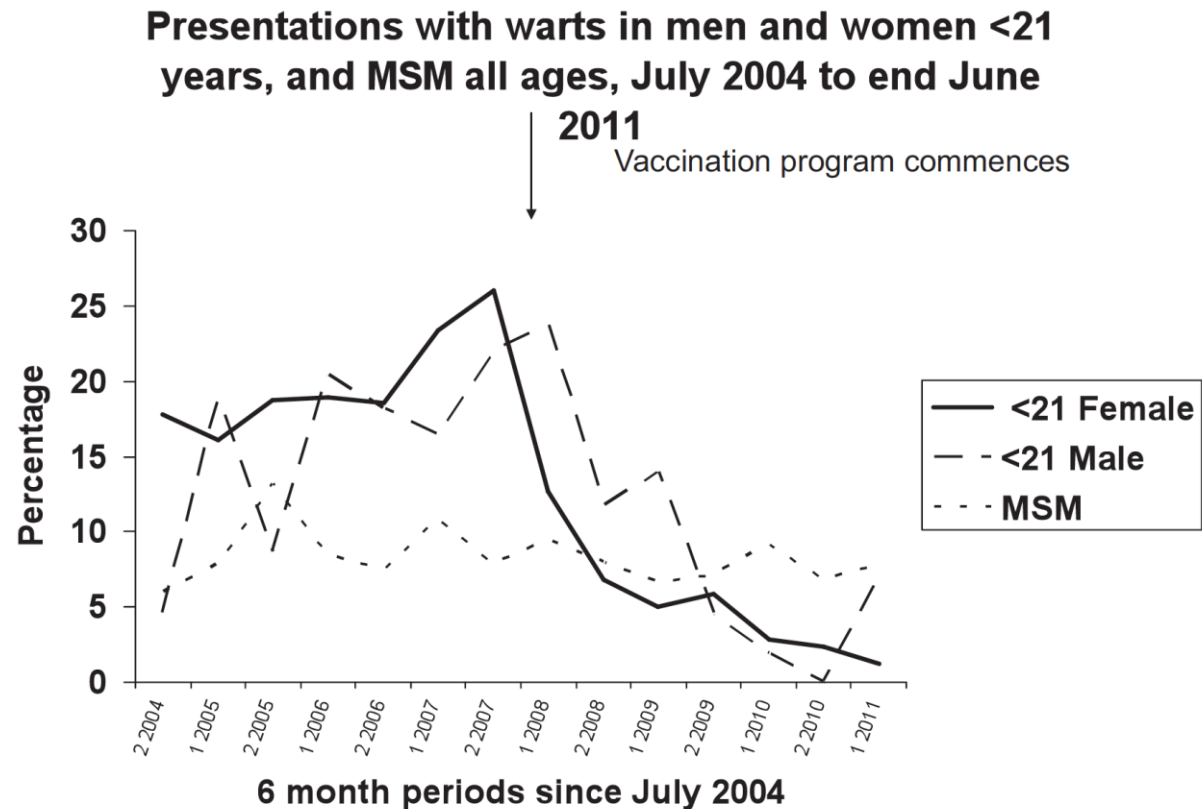
HIV + women (& men) with genital warts are considered high-risk groups for anal (pre-)malignancies

New York State Department of Health AIDS Institute. Anal dysplasia and cancer, 2007. Available at: <http://www.hivguidelines.org/clinicalguidelines/adults/anal-dysplasia-and-cancer/>
 New York State Department of Health AIDS Institute. Anal dysplasia and cancer, 2020. Available from: <https://www.hivguidelines.org/hiv-care/anal-dysplasia-cancer/>
 Roberg JA, Gallant JE, Ghanem KG, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2014
 GeSIDA: Grupo de Estudio del SIDA-SEIMC Guía de práctica clínica sobre los tumores no defintorios de sida e infección por el VIH (Actualización Marzo 2019). Available from: http://gesida.seimc.org/wp-content/uploads/2019/05/gesida_DC_TumoresNoDefintorios_Marzo_2019_14_05_19.pdf

Genital warts: a message of hope

Australian national HPV vaccination program commenced in April 2007 (using 4v: free vaccination to 12-13 year-old **girls** + 3-year catch-up program for 13-26 year-old girls & in 2013, **boys** were added to the program)

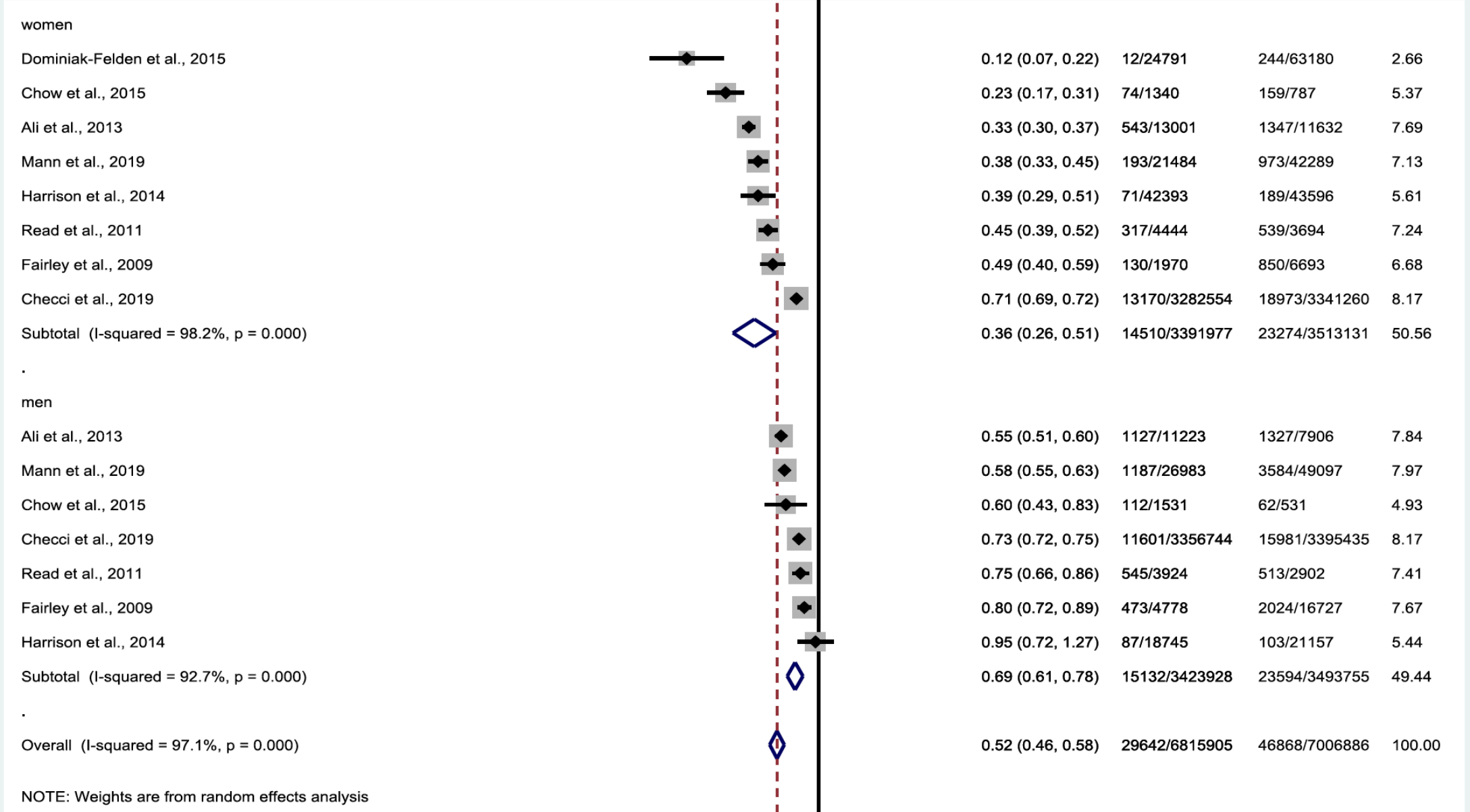
High coverage rates among vaccine-eligible girls: 73% had received all three doses in 2010.



Meta-

nts)

study	OR (95% CI)	Events, post vaccinated	Events, pre vaccinated	% Weight
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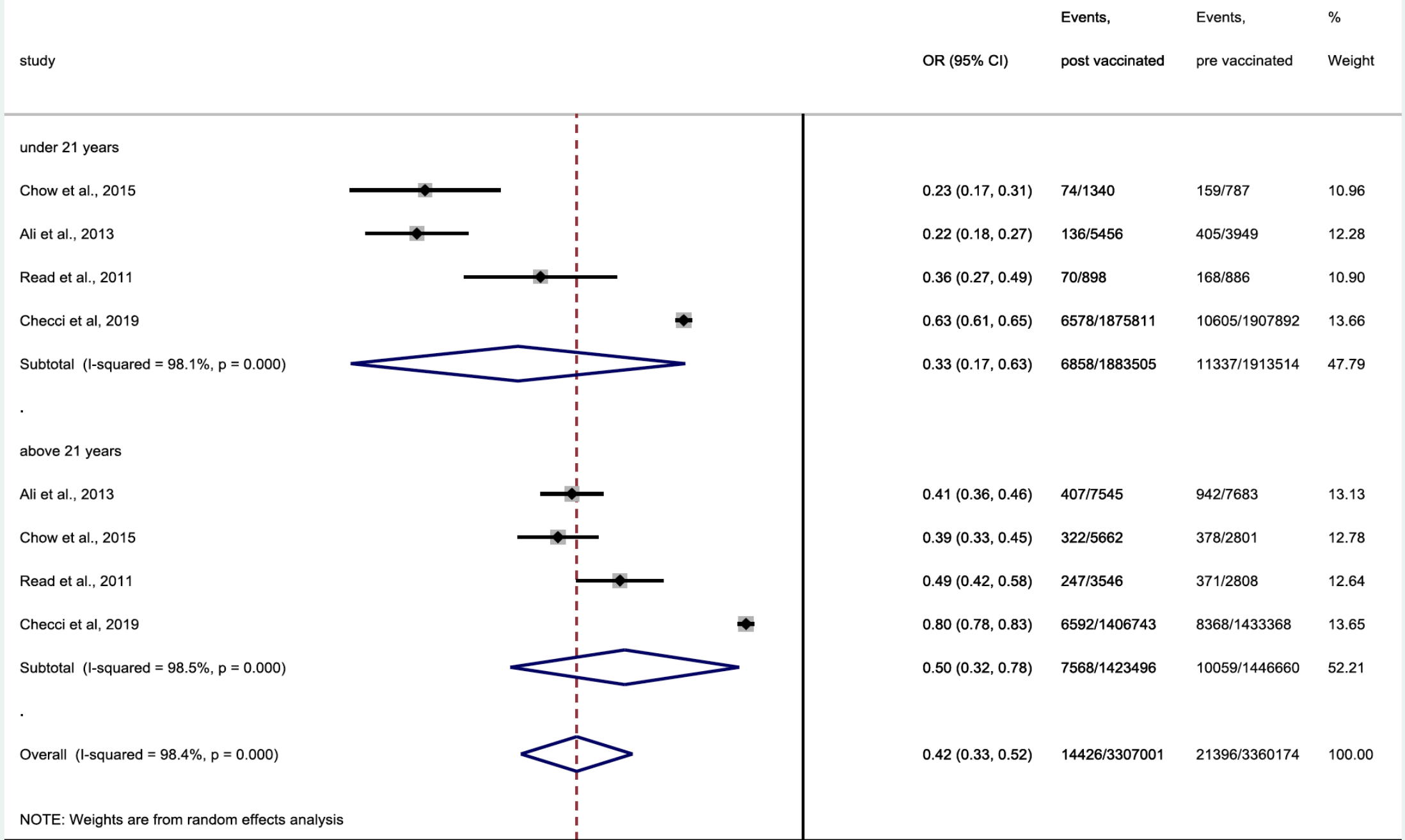


NOTE: Weights are from random effects analysis

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Meta-

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NOTE: Weights are from random effects analysis

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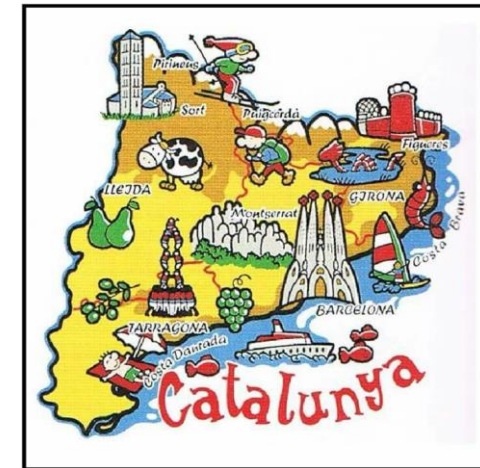
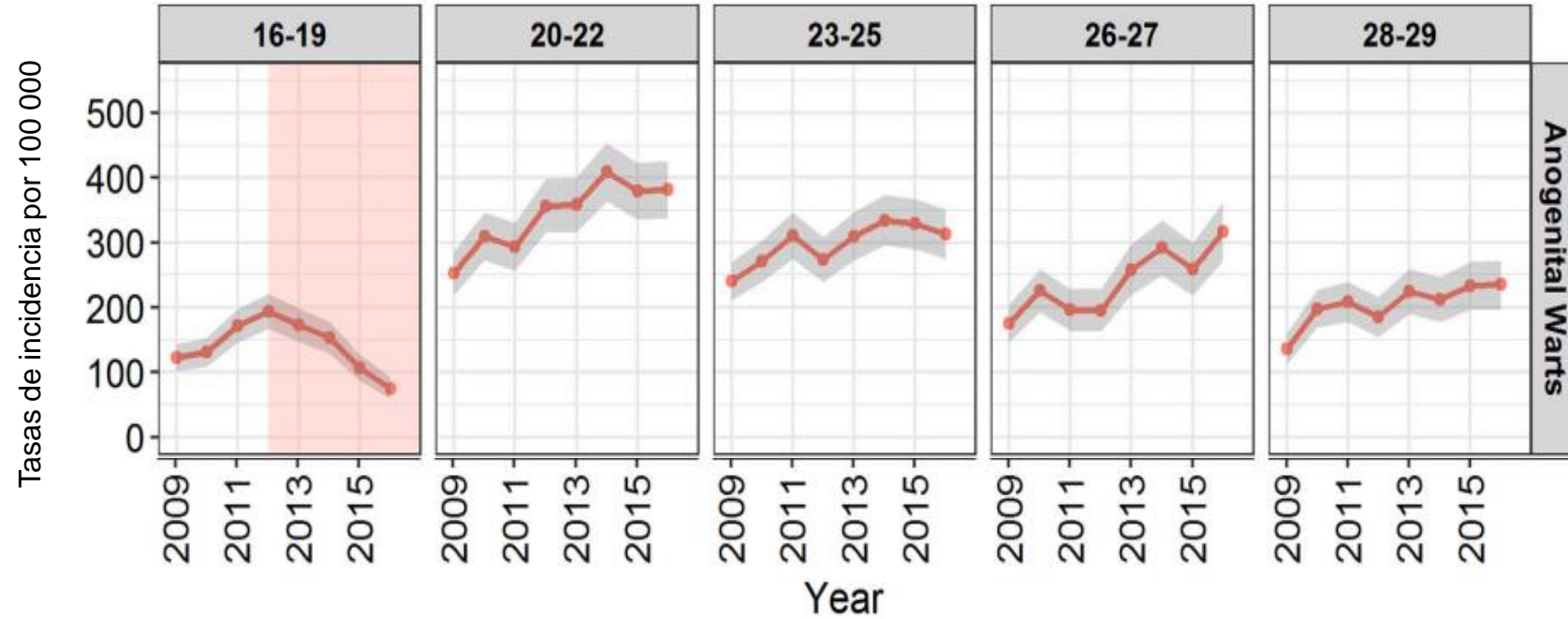
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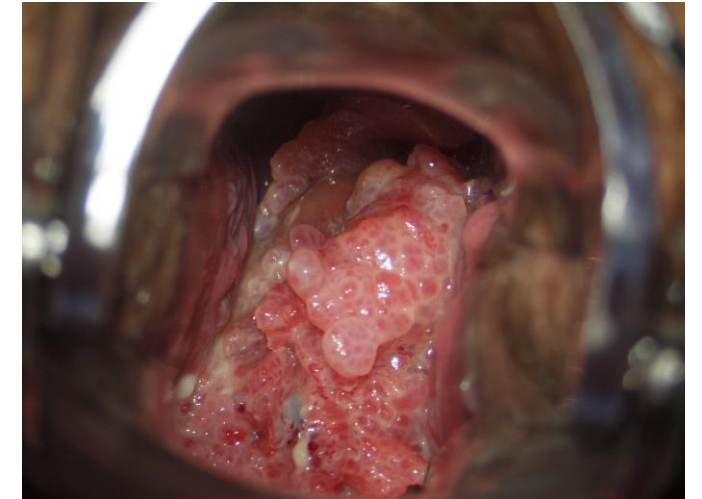
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Genital warts: a message of hope in Catalonia



Conclusions

- Most common sexually transmitted disease
- Manifestation of acute infection
- GW are a benign lesions BUT....
- DARK SIDE:



Shall we do any HPV-cancer screening to women with GW????

- GOOD NEWS
 - ✓ Vaccination has (very) significantly reduced the prevalence and incidence

Many thanks for your attention

