Latest recommendations regarding anal screening in women

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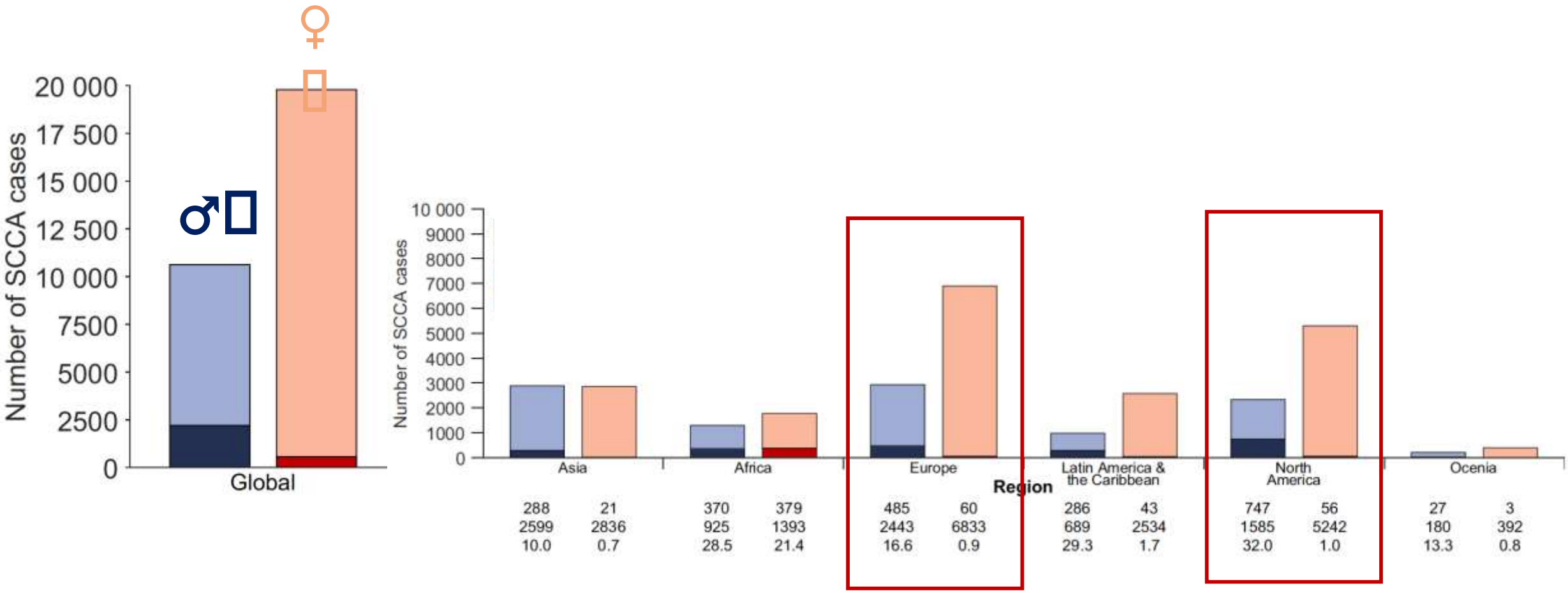
Why do we need to talk about women?

Anal cancer in women



Deshmukh A A and Damgacioglu H et al. Int. J. Cancer. 2023

Anal cancer in women

EXPERT REVIEW OF GASTROENTEROLOGY & HEPATOLOGY
https://doi.org/10.1080/17474124.2020.1775583

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REVIEW

A 2020 update of anal cancer: the increasing problem in women and expanding treatment landscape

Caroline Lum[a], Hans Prenen[a,b], Amy Body[a], Marissa Lam[a] and Eva Segelov[a,c]

Article highlights

- Anal cancer incidence has been rising for 40 years. It is more common in women than men, apart from selected high-risk populations such as HIV co-infection.

The incidence of anal cancer in women has increased during the past 30 years and is more pronounced in high-income countries.

The mortality rate from anal cancer has also increased by 3.1% per year, with higher rates over 50 years of age, highlighting elderly females as a high-risk group

C. Lum et al. *Expert Rev Gastroenterol Hepatol*. 2020

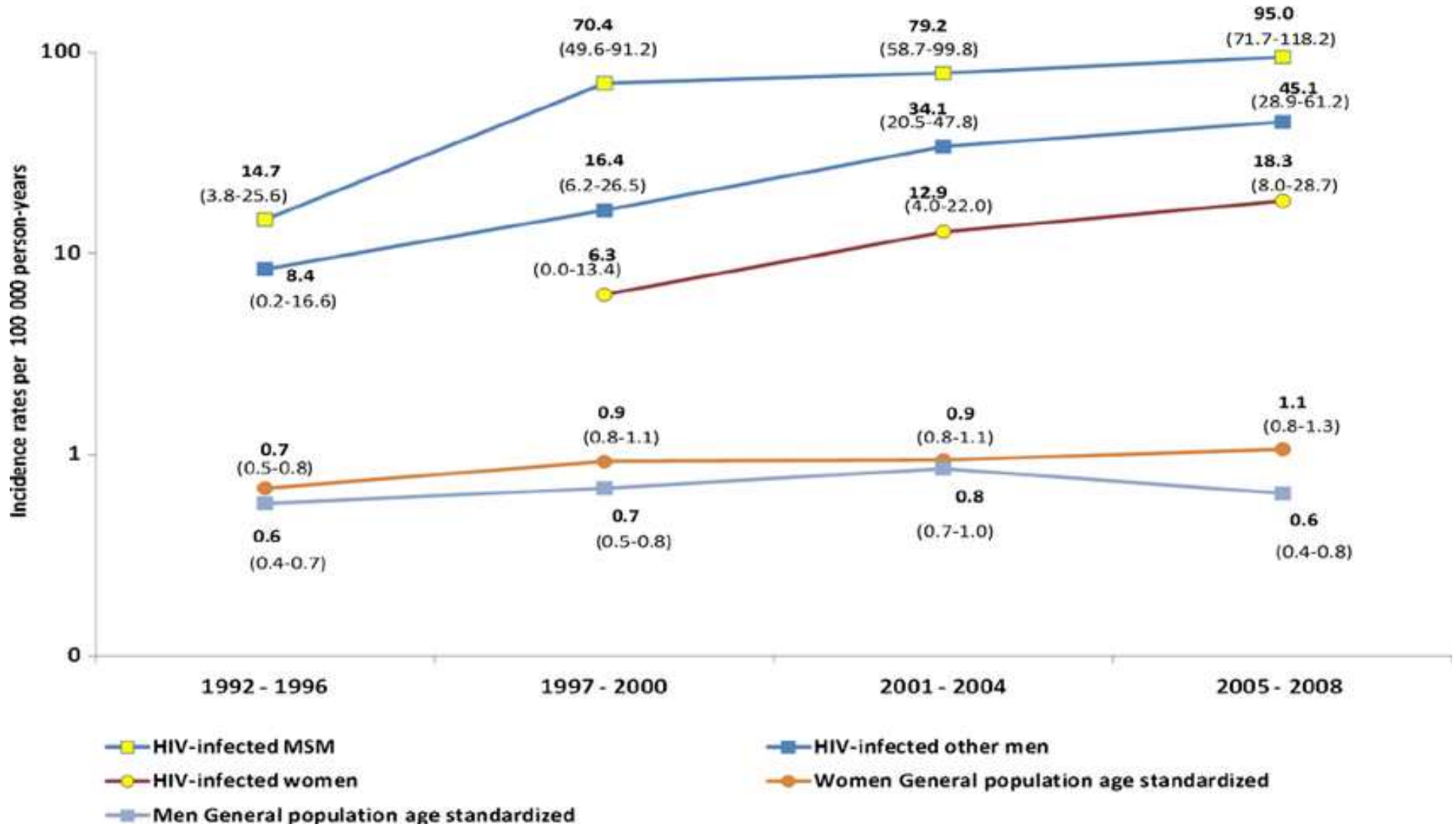
Anal cancer in women

“Women contributed **two-thirds of the global anal cancer** burden, and the majority of the cases, in both men and women, occurred in **highest-resource countries”**

“However, studies of anal HPV infection, anal lesions, and **anal cancer have focused largely on men**, notably men who have sex with men, due to their high relative risk”

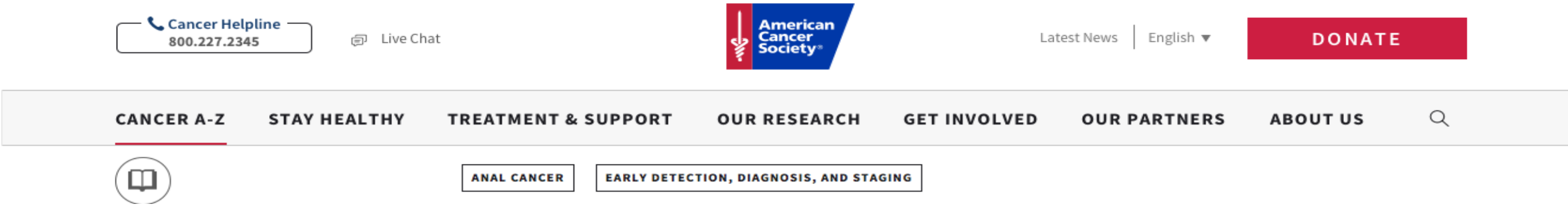
Deshmukh A A and Damgacioglu H et al. Int. J. Cancer. 2023
Wei F. et alJID 2023

Anal cancer & high risk groups



Van del Loeff M, et al. *HPV and anal cancer in HIV-infected individuals: a review.* Current HIV/AIDS Reports. 2014

Anal cancer & high risk groups



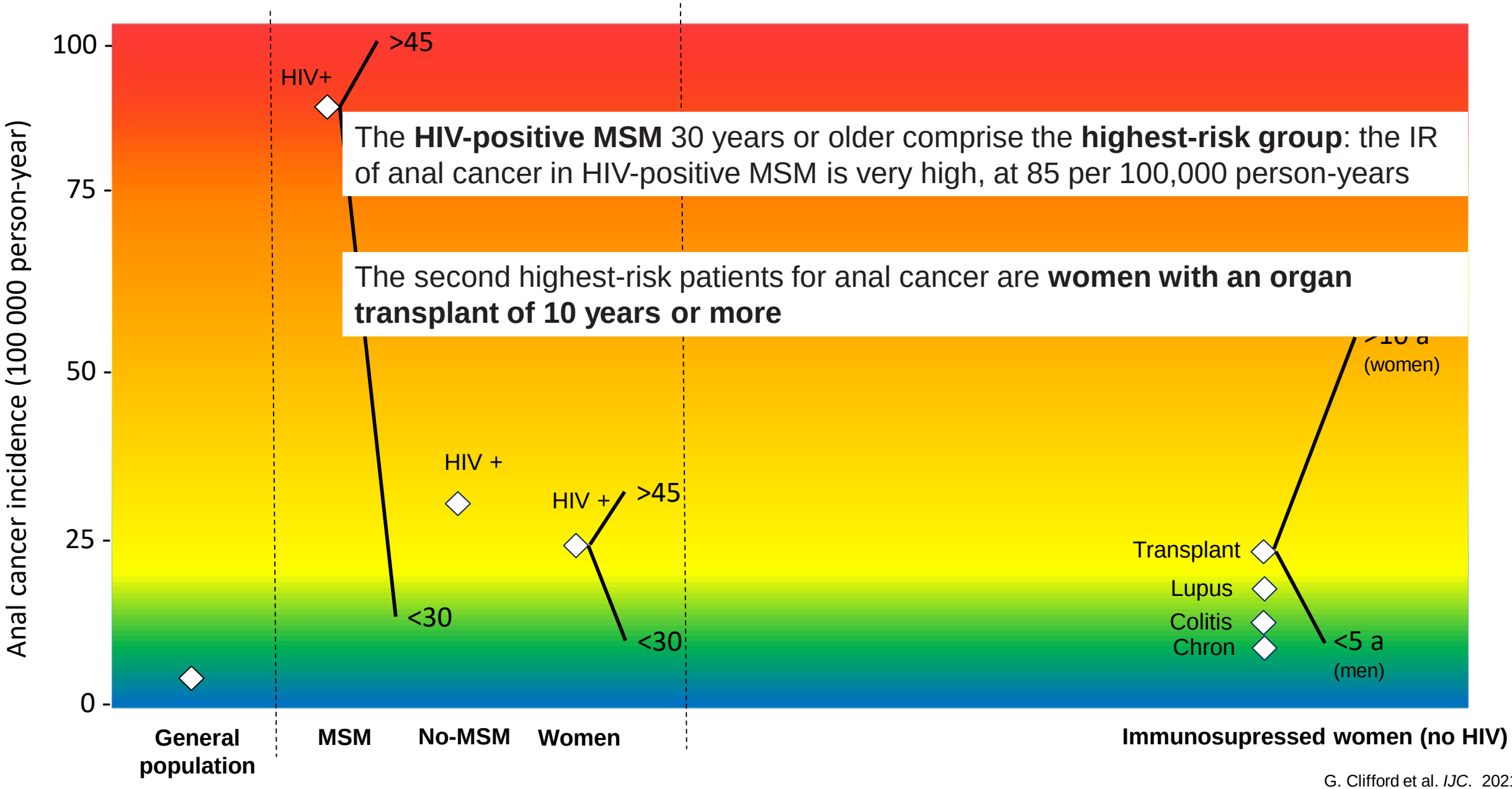
Screening in people at high risk

Anal cancer is not common in the United States, so screening the general public for anal cancer is not widely recommended at this time.

Still, some people at increased risk for anal intraepithelial neoplasia (AIN, a potentially pre-cancerous condition) and anal cancer might benefit from screening. This includes men who have sex with men (regardless of HIV status), women who have had cervical cancer or vulvar cancer, anyone who is HIV-positive, and anyone who has received an organ transplant. Some experts also recommend screening for anyone with a history of anal warts.

https://www.cancer.org/cancer/anal-cancer.html

Anal cancer risk



The **HIV-positive MSM** 30 years or older comprise the **highest-risk group**: the IR of anal cancer in HIV-positive MSM is very high, at 85 per 100,000 person-years

The second highest-risk patients for anal cancer are **women with an organ transplant of 10 years or more**

G. Clifford et al. *IJC*. 2021
Vegunta S et al. *Am J Gastroenterol* 2021

Anal cancer screening in women

Recommendations from the scientific societies

Guideline	Population	Recommendation
European AIDS Clinical Society 2021	WLWHIV with HPV-associated dysplasia	Digital exam ± cytology /1-3 years
Grupo de estudio SIDA/SEIMC (GeSIDA) 2020	WLWHIV with genital warts or receptive anal sex WLWHIV with HPV-associated dysplasia	Cytology (optative) HRA and biopsy
New York State Department of Health AIDS Institute (NYSDHAI) 2020	WLWHIV ≥35 years	Annual cytology
Infectious disease society of America (IDSA)/HIV medicine association (hivma) 2020	WLWHIV with abnormal cytology, genital warts or receptive anal sex	Annual cytology/anoscopy
Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (ASTIDCP) 2019	Transplant women with HPV-associated dysplasia or anal intercourse	Annual cytology

European AIDS Clinical Society. EACS guidelines version 11.1. 2021. https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf

Guía de práctica clínica sobre los tumores no definitorios de sida e infección por el VIH (2020). https://gesida-seimc.org/wp-content/uploads/2020/07/TAR_GUIA_GESIDA_2020_COMPLETA_Julio.pdf

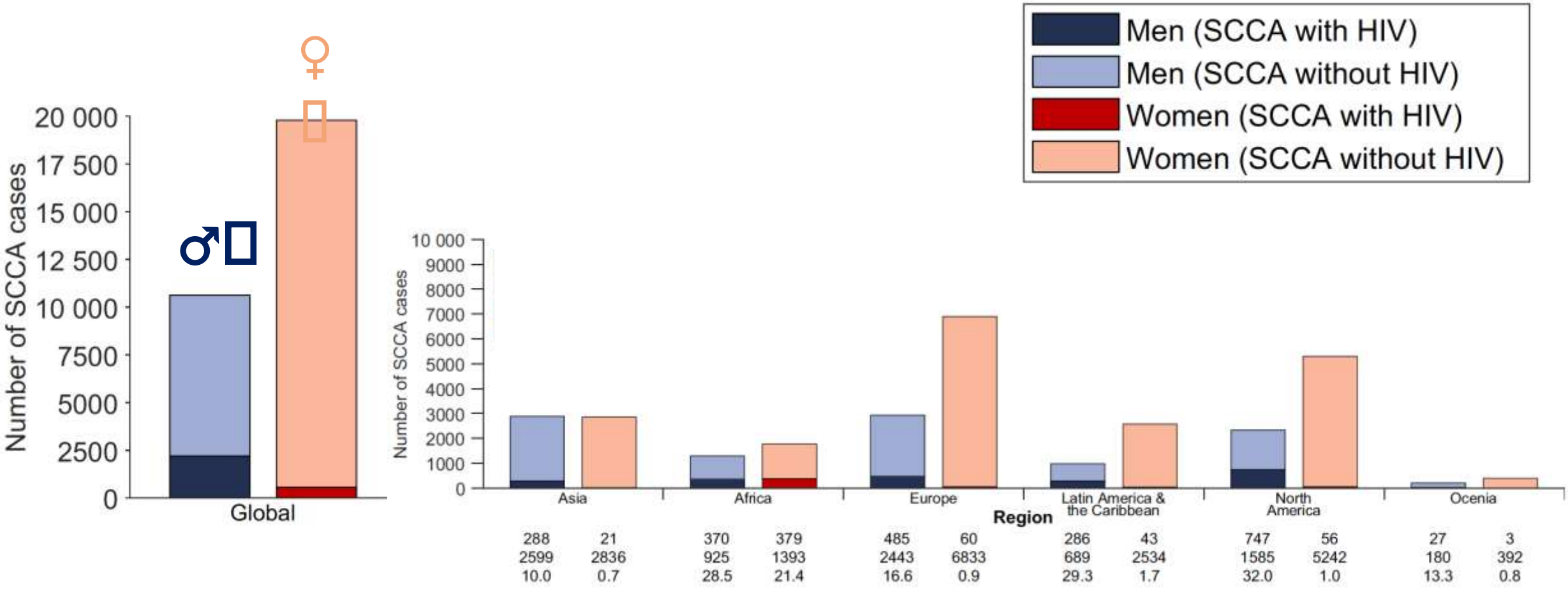
NYSDHAI: New York State Department of Health AIDS Institute. Anal dysplasia and cancer, March 2020. https://www. hivguidelines.org/hiv-care/anal-dysplasia-cancer

HIVMA/IDSA: HIV Medicine Association of the Infectious Diseases Society of America. Thomson MA. Clin Infect Dis 2020

Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Chin-Hong PV et al. Clin Transplant 2019

Why do we need to talk about immunocompetent women?

Anal cancer in women according to HIV

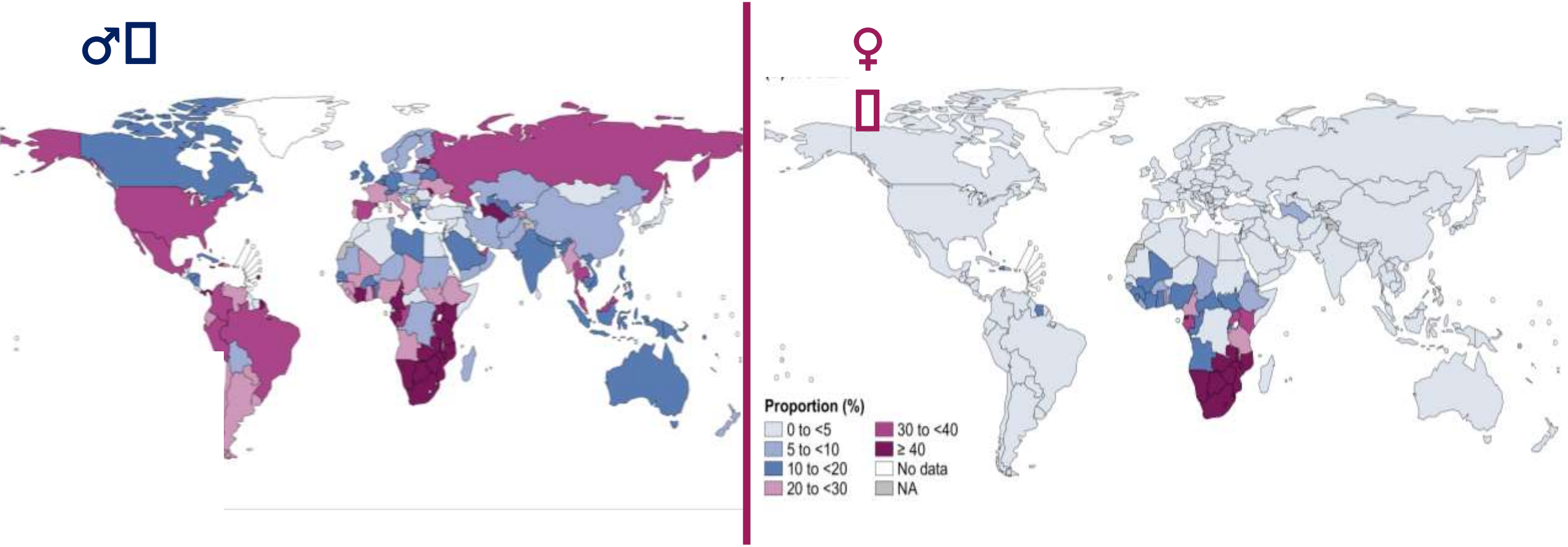


Among women, the proportion of anal cancer in WLHIV was 24.6% in sub-Saharan Africa, but ≤ 2% in other subregion

Deshmukh A A and Damgacioglu H et al. Int. J. Cancer. 2023

Anal cancer in women according to HIV

Proportions of anal cancer in persons living with HIV for men and for women



Deshmukh A A and Damgacioglu H et al. Int. J. Cancer. 2023

Anal cancer in women according to HIV

The Journal of Infectious Diseases

EDITORIAL COMMENTARY

Hopes for Prevention of Anal Cancer in Women

Gary M. Clifford and Jean-Damien Combes

International Agency for Research on Cancer, Lyon, France

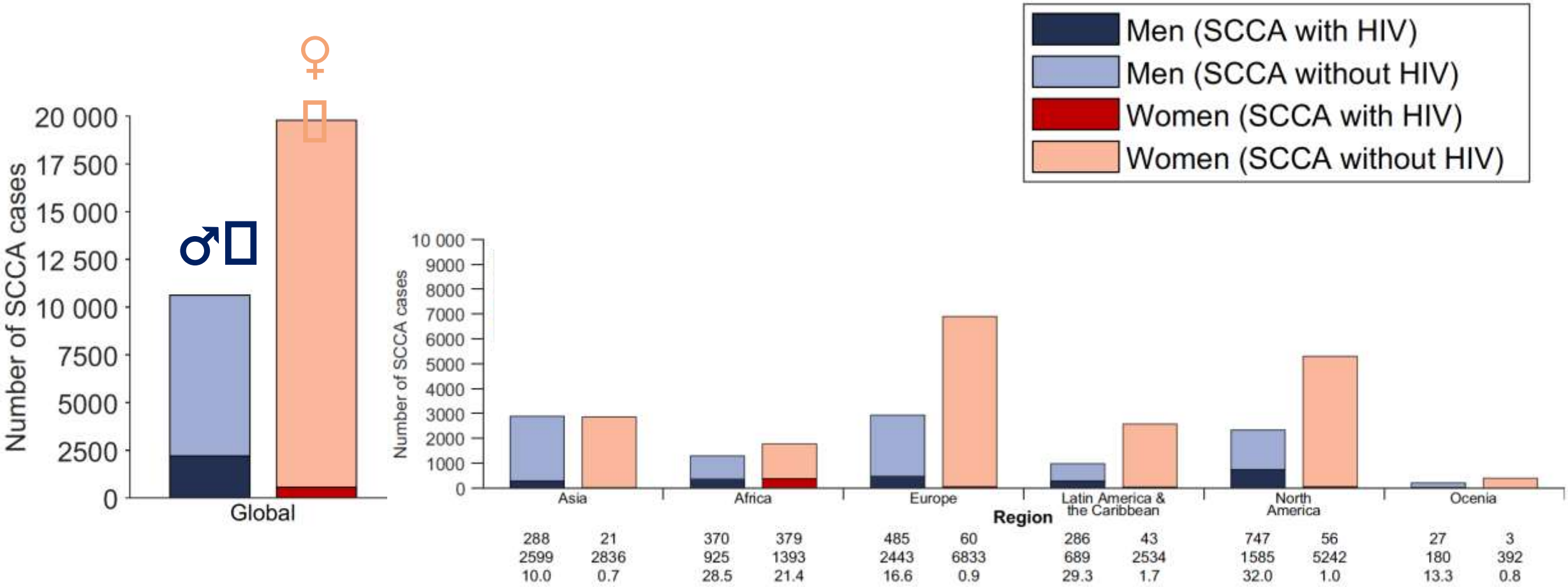
Research into primary and secondary prevention of anal cancer has understandably tended to focus on highest risk groups, most notably human immunodeficiency virus (HIV)–infected persons and/or men who have sex with men. Hence, it is sometimes easy to forget that the burden of anal cancer falls predominantly on immunocompetent women. In the general population, anal cancer in women tends to be 1.5- to 2-fold more frequent than in men [1], with little contribution from HIV [2]. Furthermore, anal HPV-16 infection and anal cancer [3], this can be expected to translate into a huge proportional impact on future anal cancer risk in this vaccinated female population.

For reasons of timeliness and statistical efficiency, Woestenberg and colleagues [4] wisely chose to evaluate population-level vaccine effectiveness (VE) in 16–24-year-old visitors to sexually transmitted infection clinics, expected to represent the leading edge of HPV infection in this age group of genital HPV-16/18 in unvaccinated men, particularly those with a vaccine-eligible partner [6], and the proportional impact of herd immunity should be even higher in women in the general population with a lower risk of HPV infection.

When considering prevention of anal cancer, it makes sense to focus on HPV-16, given that it causes the large majority (86%) [3] of all anal cancer cases. Nevertheless, Woestenberg and colleagues [4] also establish population-level vaccine impact beyond HPV-16.

GM. Clifford and JD Combes J Infect Dis 2

Anal cancer in women according to HIV



Deshmukh A A and Damgacioglu H et al. Int. J. Cancer. 2023

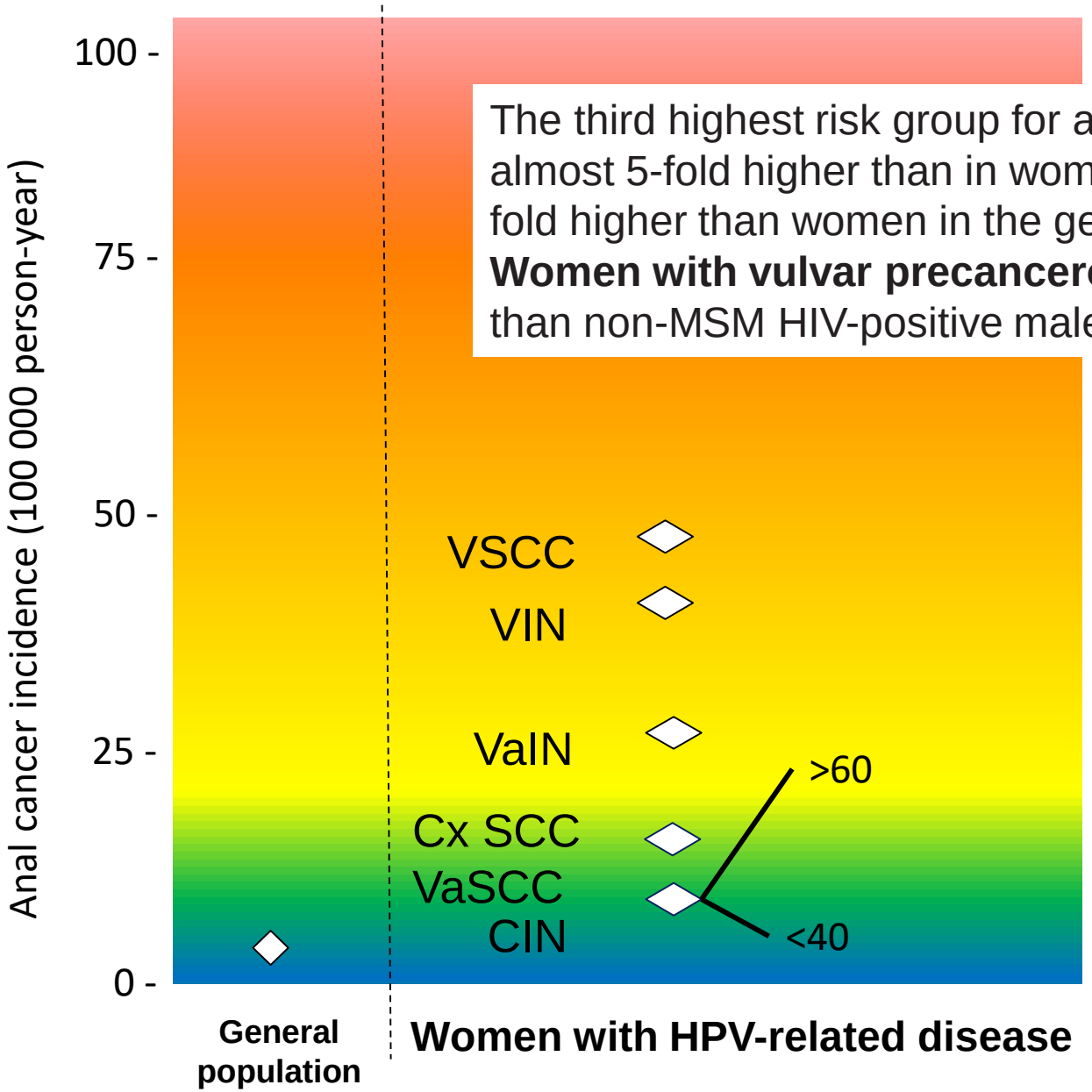
Anal cancer in immunocompetent women. Other risk groups

Type of HPV-Related Gynecological Disease	Risk of AC Mean SIR (95% CI) [1]	Risk of AC Mean IR (95% CI) [2]	Risk of AC Mean IR per 100,000 PY (95% CI) [3]	Risk of AIN Mean SIR (95% CI) [1]	Risk of AIN Mean IR (95% CI) [2]	Risk of AIN Mean IR per 100,000 PY (95% CI) [3]
Cervical cancer	3.814 (1.21–6.41)	0.086% (0.07–0.102)	9.73 (8.03–11.43)			
Vulvar cancer	14.55 (0.15–24.4)	0.265% (0.17–0.36)	37.98 (22.64–53.32)			
Vaginal cancer	1.8 (0.2–5.3)	0.096% (0.009–0.183)	11.78 (0–29.15)			
CIN 3	5.701 (2.23–19.2)	0.084% (0.076–0.092)	5.78 (4.85–5.89)	6.68 (3.64–12.25)		6.34 (5.10–7.90)
CIN (1–3)	4.563 (0.12–19.2)	0.066% (0.06–0.072)	5.37 (4.85–5.89)		16.45% (13.25–19.65)	
VIN 3		0.810% (0.59–1.03)				
VIN (1–3)					36.4% (28–44.8)	
VaIN 3		0.342% (0.037–0.647)				
VaIN (1–3)					18.2% (7.8–28.6)	

SIR: Standardized incidence ratio; IR: incidence rate

Brzezinski M et al. J. Clin. Med. 2023
Wang M et al. Cancer Epidemiolo 2020
Papatla K et al. AJOG 2019

Anal cancer risk in women with HPV related lesions



The third highest risk group for anal cancer is **women with vulvar cancer** (risk almost 5-fold higher than in women with previous vaginal or cervical cancer and 25-fold higher than women in the general population).
Women with vulvar precancerous lesions have an anal cancer risk higher than than non-MSM HIV-positive males and HIV-positive female.

G. Clifford et al. *IJC*. 2021
Vegunta S et al. *Am J Gastroenterol* 2021

Equal anal cancer risk

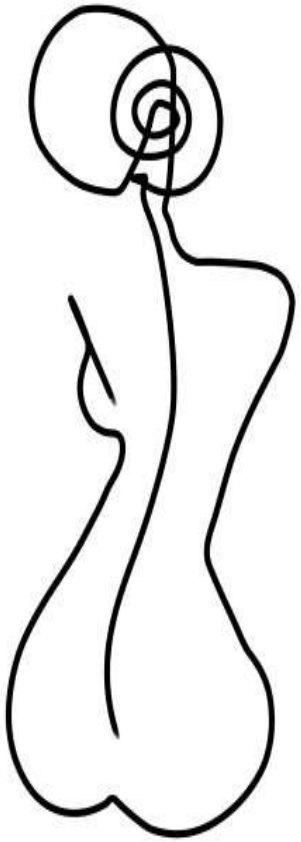
Equal risk. Equal management

- Women with HIV >45 y (IR: 30 / 100000 women-year)
- Women with organ transplant >10 years ago (IR: 50/ 100000 women-year)

- Women with **vulvar cancer** (IR: 48 / 100000 women-year)
- Women with **HSIL vulvar (VIN)** (IR: 42 / 100000 women-year)

G. Clifford et al. *IJC*. 2021
Vegunta S et al. *Am J Gastroenterol* 2021
Albuquerque, A *JGTD* 2022

Anal cancer risk in women with HPV related lesions

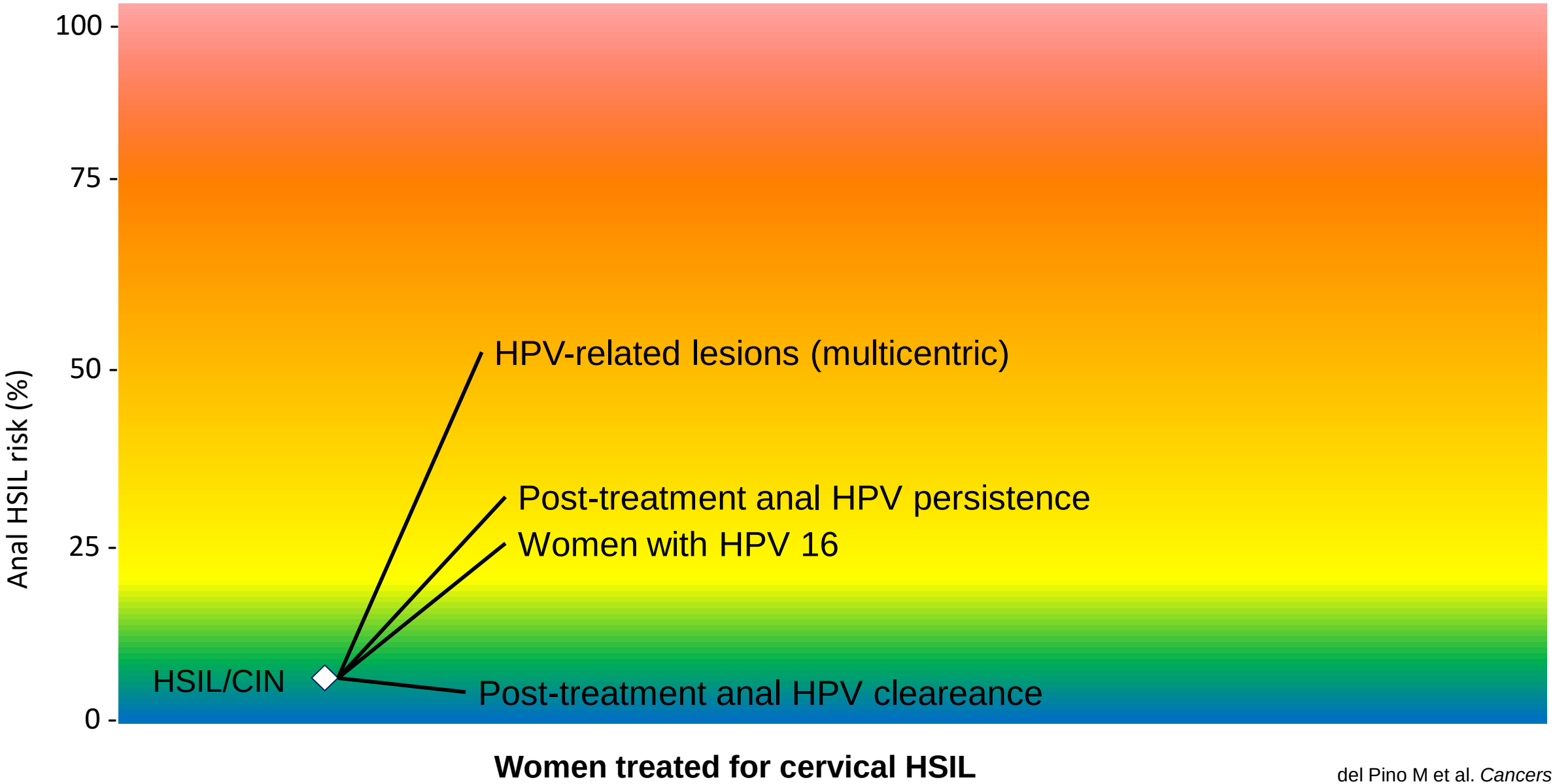


Risk group	SIR for anal cancer	95% CI
HSIL(VIN)	**22,2**	(16,7-28,4)
Vulvar cancer	**17,4**	(11,5–24,4)
HSIL (CIN)	**16,4**	(13,7–19,2)
Cervical cancer	**6,2**	(4,1– 8,7)
HSIL (VaIN)	**7,6**	(2,4 –15,6)
Vagina cancer	**1,8**	(0,2–5,3)

SIR: standarized incidence ratio

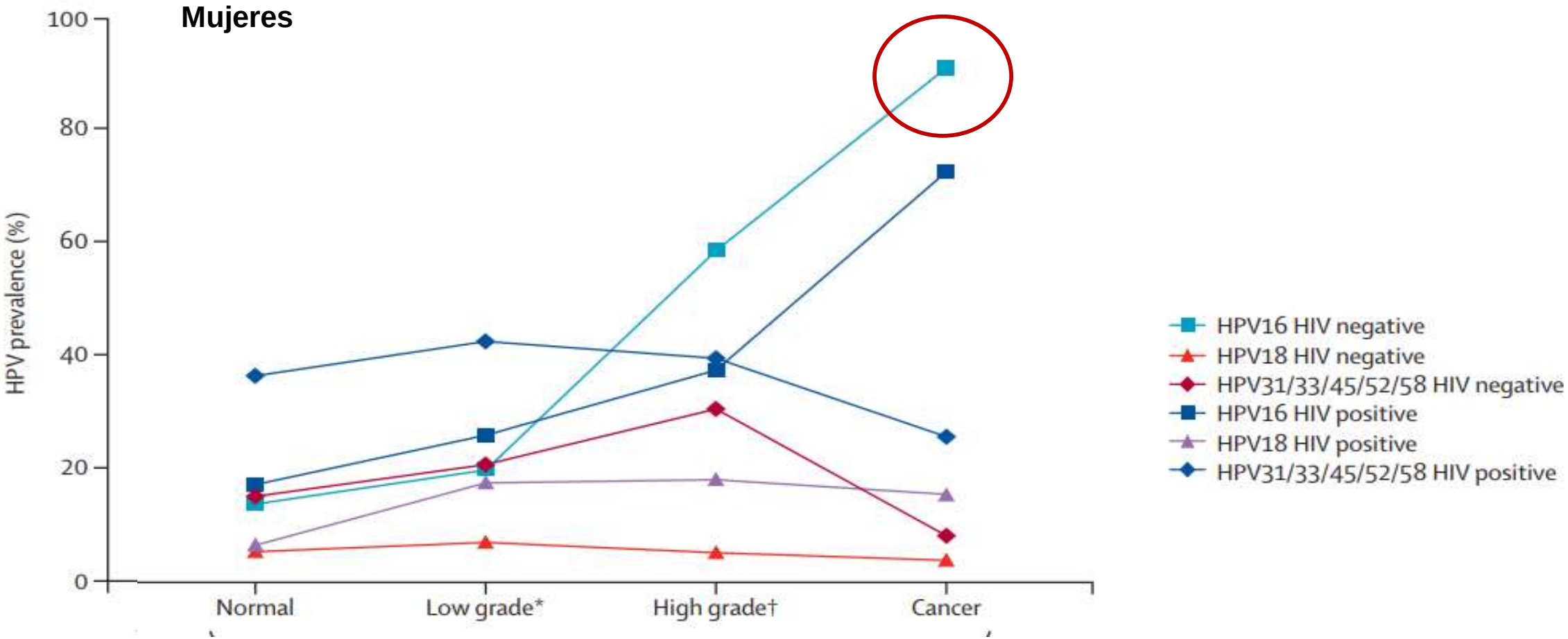
Stier E. *Women with prior HPV-associated disease.* Eurogin 2018
Acevedo-Fontanez AI, et al.. *J Low Genit Tract* Dis. 2018
Pan J et al, *IJC* 2019
J. Fokom Domgue et al.Gynecol Oncol 2019

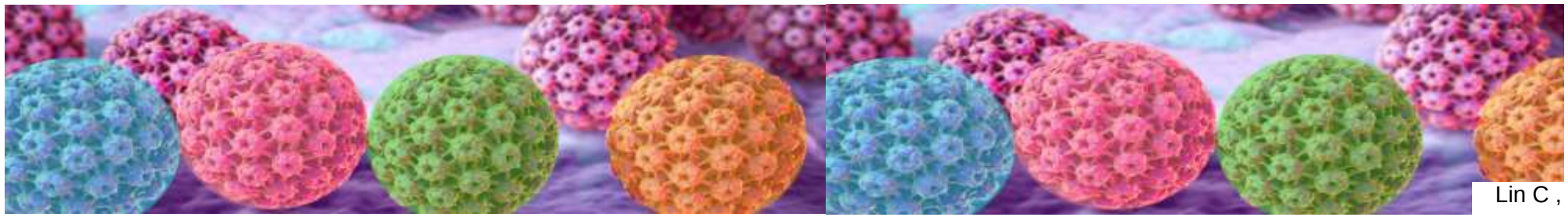
Anal HSIL in women with cervical HSIL



del Pino M et al. *Cancers* 2023
Vegunta S et al. *Am J Gastroenterol* 2021

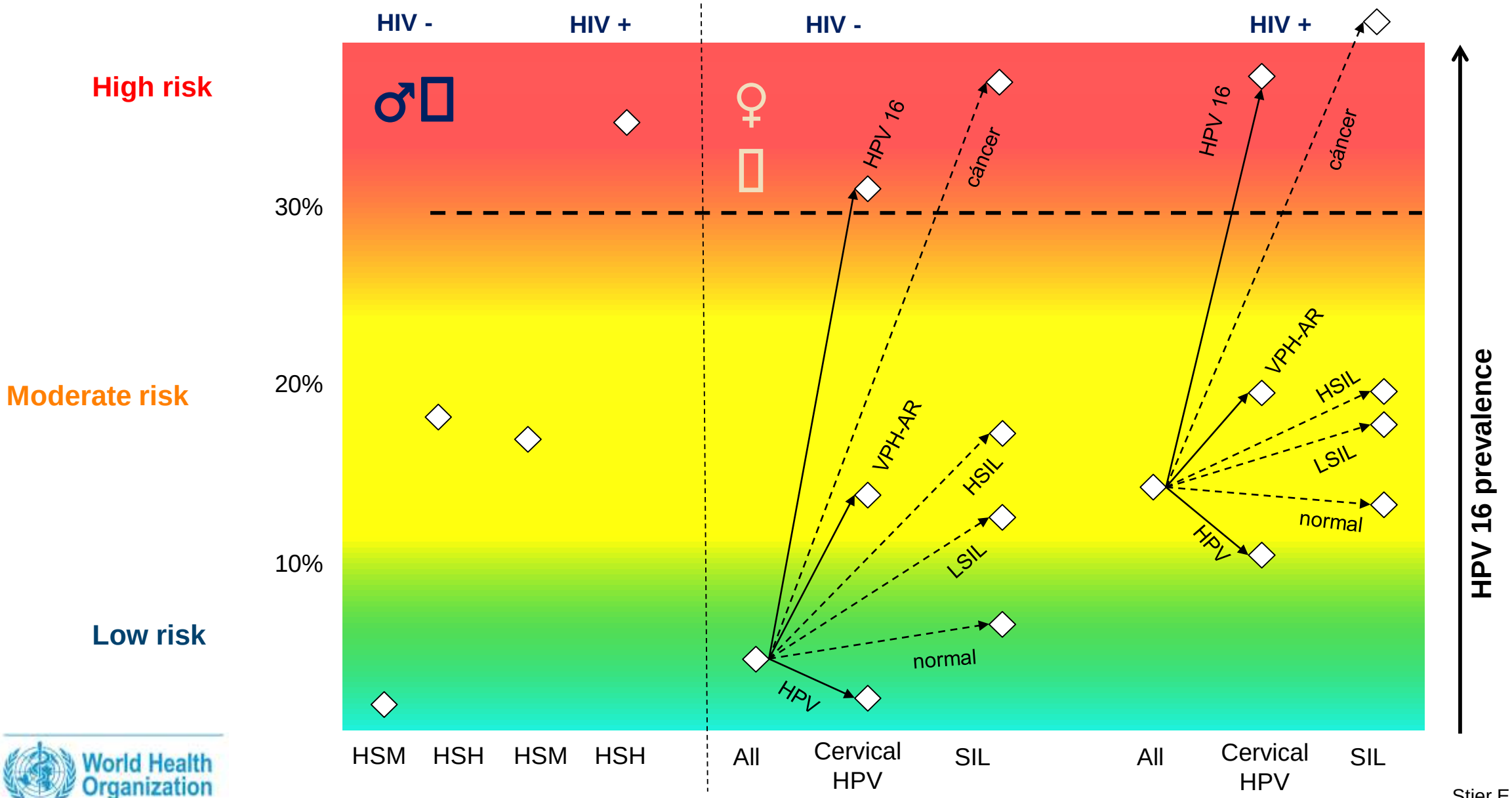
HPV 16 and anal disease





Lin C , et al. L*ancet Infect Dis.* 2018
Stier E. Eurogin 2018

Anal HPV 16 risk according to cervical status



World Health Organization

Stier E.. Eurogin 2018

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- Women with **vulvar cancer** (IR: 48 / 100000 women-year)
- Women with **HSIL vulvar (VIN)** (IR: 42 / 100000 women-year)
- Women with **persistent cervical HPV (16) ???**

G. Clifford et al. *IJC*. 2021
Vegunta S et al. *Am J Gastroenterol* 2021
Albuquerque, A *JGTD* 2022

Anal cancer screening in women

Recommendations from the scientific societies for immunocompetent women with HPV infection or HPV-related lesions

Guideline	Population	Recommendation

Anal cancer screening in women

Published in final edited form as:

J Low Genit Tract Dis. 2015 July ; 19(3 0 1): S26–S41. doi:10.1097/LGT.0000000000000117.

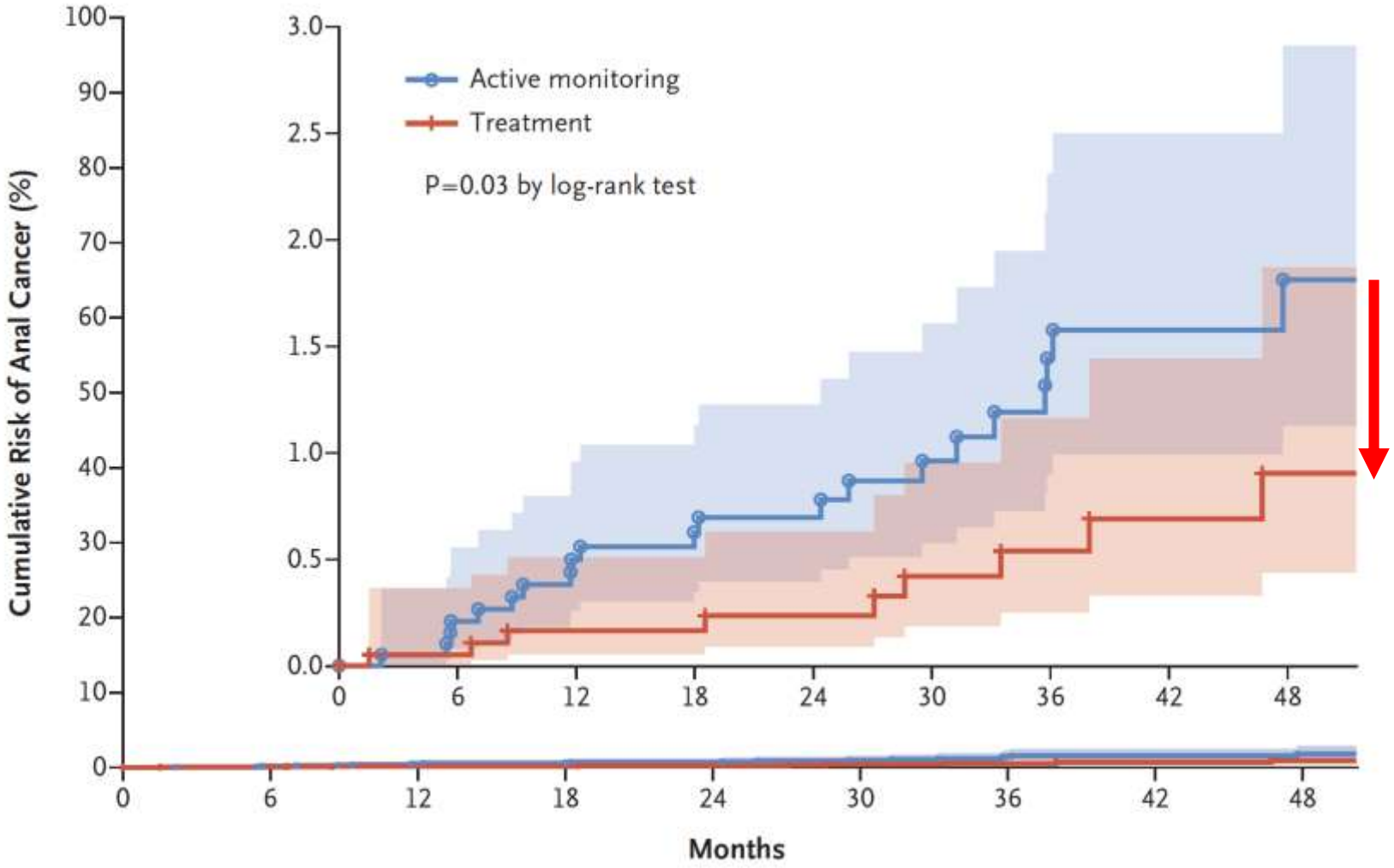
Screening for Anal Cancer in Women

Methods—A group of experts convened by the ASCCP and the International Anal Neoplasia Society reviewed the literature on anal HPV infection, anal SIL and anal cancer in women.

Conclusions—While there are no data yet to demonstrate that identification and treatment of anal HSIL leads to reduced risk of anal cancer, women in groups at the highest risk should be queried for anal cancer symptoms and have digital anorectal examinations to detect anal cancers. HIV-infected women and women with LGTN, may be considered for screening with anal cytology with triage to treatment if HSIL is diagnosed. Healthy women with no known risk factors or anal cancer symptoms do not need to be routinely screened for anal cancer or anal HSIL.

Moscicki B et al. *J Low Genit Tract Dis.* 2015

Anal cancer screening: one answer, many questions…



Different in the risk of progression: 57%

Palefsky J. et al. *NEJM*. 2022

Anal cancer screening in women. How?

Screening method	Sensitivity	Specificity	Comments
Anal cytology conventional staining	47%–90%	16%–92%	Similar to cervical cytology on average and better sensitivity and specificity in higher risk populations.
Anal HPV testing	94%	Low, by itself	HPV testing alone has good sensitivity, but poor specificity. For high-risk groups, cytology plus hrHPV better predicts AIN compared with cytology alone. (Strength in NPV)
p16 staining of anal cytology	72%	100% (tissue specimens)	High specificity in biopsy specimens. Needs more study for anal cytology thin prep/anal pap and not widely available at this time.
HPV mRNA E6/E7 testing	TBD	TBD	For cervical cancer, the mRNA E6/E7 has better specificity than hrHPV testing, more study needed for anal specimens. Testing for mRNA E6/E7 is becoming more widely available.

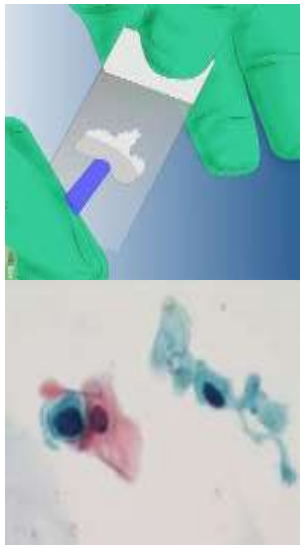
See text for references.
AIN, anal intraepithelial neoplasia; hrHPV, high-risk human papillomavirus; mRNA, messenger RNA; NPV, negative predictive value.

Vegunta S et al. *Am J Gastroenterol* 2021

Anal cytology in women

Sensitivity for **anal HSIL in men (MSM) living with HIV 76%** (68% - 93%)
Si CD4 ≤ 400 90%
Si CD4 > 400 67%

Sensitivity for **anal HSIL in men (MSM) no HIV 59%** (38%-82%)



Sensitivity for **anal SIL in women with vuvar HSIL o cancer 57%** (95%CI 46%-67%)
Specificity for **anal SIL in women with vuvar HSIL o cancer 70%** (95%CI 42%-88%)

Sensitivity for **anal HSIL in women with vuvar HSIL o cancer 71%** (95%CI 61%-79%)
Specificity for **anal HSIL in women with vuvar HSIL o cancer 73%** (95%CI 66%-79%)

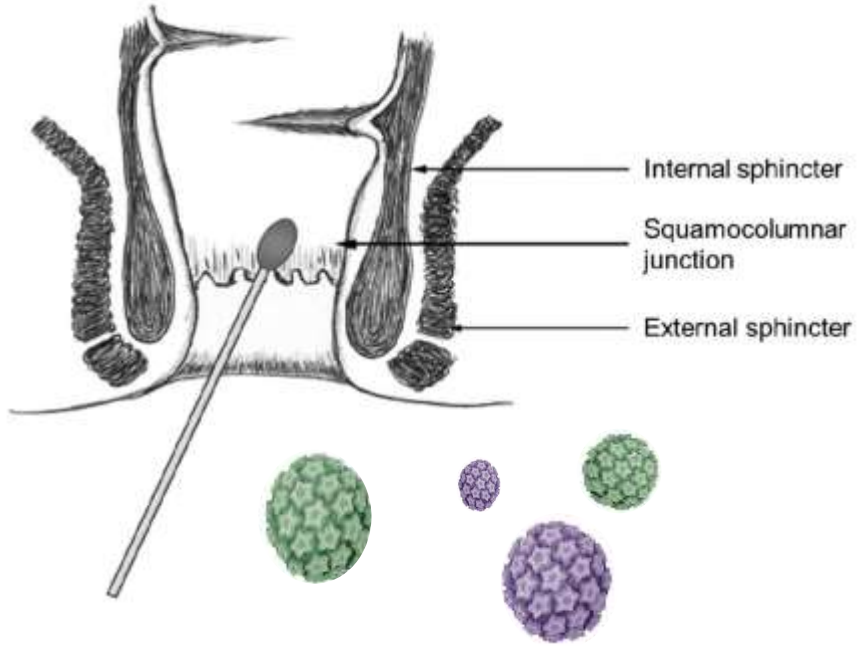
If anal lesion <2 quadrants : 57%
If anal lesion ≥ 2 quadrants: 86%

The sensitivity of anal cytology in non-immunosuppressed women with vulvar HSIL/cancer seems to be low. In women with lower genital tract neoplasia, anal cytology performs better in those who are immunosuppressed or have wide lesions.

Anal HPV test

Anal HPV testing

The US Food and Drug Administration has not approved any HPV tests for the anus, and clinical laboratories must validate their tests for this anatomical site. HPV has been identified in women who do not participate in receptive anal intercourse, but the prevalence of HPV infection varies considerably with the population being tested (42).



Anal HPV testing has not been routinely recommended as part of the screening because of the high positivity in the high-risk group of MSM living with HIV

Vegunta S et al. *Am J Gastroenterol* 2021
Albuquerque, A et al. J Low Genit Tract Dis 2022; (review)

Anal cancer screening in women. When?

Primary Gynecologic Neoplasm	Anal Cancer Cases	Mean (Median) Time Between Diagnoses (y)	Minimum Time Between Diagnoses (y)	Maximum Time Between Diagnoses (y)
Cervical neoplasm				
Invasive	28	11.4 (13)	0	29
In situ	137	15.7 (16)	0	30
Vulvar neoplasm				
Invasive	28	7.1 (4.5)	0	23
In situ	55	8.9 (8)	0	23
Vaginal neoplasm				
Invasive	<5†	4.5 (4.5)	3	6
In situ	5	11 (11.5)	1	16

Edad media al diagnóstico de cáncer anal: 50-62 años

Saleem AM et al. *Obstet Gynecol.*2011
Albuquerque, A et al. J Low Genit Tract Dis 2022; (review)

Anal cancer screening in women …..Some proposals…

At-risk population	Commence anal cancer screening	Minimal screening modality	Schedule
HIV positive	At age 35 y	• History • Visual inspection • DRE Consider annual anal cytology (anal HPV)	Annually For HIV-positive patients, screening can be less frequent, depending on initial screening results and CD4 count
History of VIN3, VaIN3, or vulvar or vaginal cancer	At diagnosis		
Immunosuppression (transplant recipient or ≥2 immunosuppressive medications) AND Positive for HPV-16 or HPV-18 or history of CIN3+ (VIN3+ or VaIN3+, per above)			
Women with history of CIN3+	At age 50 y or within 2-3 years of CIN3+ diagnosis	• History • Visual inspection • DRE Consider anal cytology (anal HPV) • Annually for 3 y and then every 2 y • If positive for HPV-16 or HPV-18, refer for HRA	Annually
Immunosuppression (transplant recipient or ≥2 immunosuppressive medications) AND Positive for hrHPV (HPV-16 or HPV-18, per above)	At age 35 y or at diagnosis if age ≥35 y		

A grading of these recommendations was not provided in the article, and these guidelines were not formally endorsed by any society.

Vegunta S et al. *Am J Gastroenterol* 2021

Conclusions

- Anal cancer **screening** is **not considered in non-immunocompromised women**. Since anal cancer incidence is increasing, **we are missing something important**…. BUT WHAT ??

- There is evidence about some **high-risk groups among non-immunocompromised women** (besides the already considered high-risk groups in WLWHIV and women with organ trasplants)

- The problem is: **WHO, HOW and WHEN?**

Conclusions

- **WHO?** Women with HPV-related lesions are probably an heterogeneous group. Women with vulvar HSIL/cancer and/or women with persistent HPV 16 infection in the genital tract and/or multicentric lesions are those at highest risk

- **HOW?** Cytology is probable not the best approach (low sensitivity). Anal HPV testing has not been recommended as screening test because of the high positivity in the immunocompromised high-risk groups. However, it can be different in non-immunocompetent risk groups

- **WHEN?** Anal cancer lesions develop later tan HPV-lesions in the lower genital tract. Despite no formal recommendations can be done, it should be considered in anal cancer screening strategies


Muchas gracias por su atención!