Downloaded from https://journals.lww.com/greenjournal by PaiGAmDl1iBWlto1wobQLbbXEjpGPprd9Qk+dUdz/v66UbpPNth/EluMmALaG/DFiVRttbJMTkzxT7pGXPxSWTRbUkiaO2A8oxvG33gXZRvBgACeRKNWLCWBoBDAXHORnCvjUrnLjhAuOklKwgoF5A6cj8xFFGTIlYMGuqZITBYfIBTBDsh1zBg== on 02/07/2019

Cancer: *Original Research*

Human Papillomavirus Genotypes From Vaginal and Vulvar Intraepithelial Neoplasia in Females 15–26 Years of Age

Suzanne M. Garland, MD, *Elmar A. Joura,* MD, *Kevin A. Ault,* MD, *F. Xavier Bosch,* MD, PhD, *Darron R. Brown,* MD, *Xavier Castellsagué,* MD, *Alex Ferenczy,* MD, *Daron G. Ferris,* MD, *Anna R. Giuliano,* PhD, *Mauricio Hernandez-Avila,* MD, *Warner K. Huh,* MD, *Ole-Erik Iversen,* MD, PhD, *Susanne K. Kjaer,* MD, *Robert J. Kurman,* MD, *Joaquin Luna,* MD, *Joseph Monsonego,* MD, *Nubia Muñoz,* MD, *Jorma Paavonen,* MD, *Punnee Pitisuttihum,* MD, *Brigitte M. Ronnett,* MD, *Marc Steben,* MD, *Mark H. Stoler,* MD, *Cosette M. Wheeler,* PhD, *Dorothy J. Wiley,* PhD, MPH, *Gonzalo Perez,* MD, *Alfred J. Saah,* MD, *Alain Luxembourg,* MD, PhD, *Se Li,* PhD, *Mark J. DiNubile,* MD, *Monika Wagner,* PhD, *and Christine Velicer,* PhD

OBJECTIVE: To estimate the proportion of vulvar and vaginal low-grade and high-grade squamous intraepithelial lesions (LSILs and HSILs) in females 15–26 years of age attributable to 14 human papillomavirus (HPV) genotypes (6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59).

METHODS: A post hoc analysis of prospectively diagnosed vulvar and vaginal LSILs and HSILs among females 15–26 years of age enrolled in the placebo arms of two phase 3, randomized HPV vaccine trials assessed 14 prespecified HPV genotypes associated with cervical cancers or anogenital warts using a type-specific multiplex polymerase chain reaction assay. The frequency of lesions associated with specific HPV genotypes was estimated by proportional and other attribution methods.

RESULTS: During approximately 4 years of follow-up in 8,798 females, 40 vulvar LSILs and 46 vulvar HSILs were diagnosed in 68 females, and 118 vaginal LSILs and 33 vaginal HSILs were diagnosed in 107 females. Females developing vulvar (41.2%) or vaginal (49.5%) lesions also had cervical lesions, whereas 6.5% of females with cervical lesions had vaginal or vulvar lesions. At least 1 of the 14 HPV genotypes was detected in females with vulvar LSIL (72.5%), vulvar HSIL (91.3%), vaginal LSIL (61.9%), and vaginal HSIL (72.7%). Considering only HPV-positive lesions, the nine most common genotypes causing cervical cancer and anogenital warts (6, 11, 16, 18, 31, 33, 45, 52, and 58) were

See related editorial on page 259.

From the Department of Microbiology Infectious Diseases, the Royal Women's Hospital, Department of Microbiology, the Royal Children's Hospital, Infection and Immunity, Murdoch Children's Research Institute, Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Australia; the Department of Gynecology and Obstetrics, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; the Department of Obstetrics and Gynecology, University of Kansas Medical Center, Kansas City, Kansas; Institut Catala d'Oncologia, IDIBELL, CIBER-ESP, RTICC, L'Hospitalet de Llobregat, Barcelona, Spain; the Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana; the Department of Pathology, SMBD Jewish General Hospital and McGill University, Montréal, Québec, Canada; the Department of Obstetrics and Gynecology, Augusta University, Augusta, Georgia; the Center for Infection Research in Cancer, Moffitt Cancer Center, Tampa, Florida; the National Institute of Public Health, Cuernavaca, Morelos, Mexico; the Division of Gynecologic Oncology, University of Alabama, Birmingham, Alabama; the Department of Clinical Science, University of Bergen/Haukeland University Hospital, Bergen, Norway; the Danish Cancer Society Research Center, Copenhagen, Denmark and Department of Gynecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; Johns Hopkins University School of Medicine, Baltimore, Maryland; the Department of Obstetrics and Gynecology, Clinica Colsanitas, Fundacion Universitaria Sanitas, Bogota, Colombia; Institut du col, Paris, France; the National Institute of Cancer, Bogotá, Colombia; the Department of Obstetrics and Gynecology, University Central Hospital, Helsinki, Finland; the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; Direction des Risques Biologiques et de la Santé au Travail, Institut National de Santé Publique du Québec, Montréal, Québec, Canada; Robert E. Fechner Laboratory of Surgical Pathology, University of Virginia Health System, Charlottesville, Virginia; the Departments of Pathology and Obstetrics and Gynecology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico; UCLA School of Nursing, Los Angeles, California; Merck & Co, Inc., Kenilworth, New Jersey; Universidad del Rosario, Bogota, Colombia; and Analytica LASÉR, Montréal, Québec, Canada.

© 2018 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. All rights reserved.
ISSN: 0029-7844/18

Copyright © by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

found in 89.4% of vulvar LSILs, 100% of vulvar HSILs, 56.0% of vaginal LSILs, and 78.3% of vaginal HSILs.

CONCLUSION: Most vulvar and vaginal lesions were attributable to at least 1 of the 14 HPV genotypes analyzed. Effective immunization programs could potentially prevent substantial numbers of HPV-related vulvar and vaginal LSILs and HSILs.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT00092521 and NCT00092534.

(Obstet Gynecol 2018;132:261–70)

DOI: 10.1097/AOG.0000000000002736

Many common human papillomavirus (HPV) types have been detected in vulvar and vaginal lesions typically diagnosed in women in the third to sixth decade of life.[1–8] Human papillomavirus-related vulvar intraepithelial neoplasia (VIN) is divided into low-grade squamous intraepithelial lesions (LSIL, VIN 1) and potentially precancerous high-grade squamous intraepithelial lesions (HSIL, VIN 2/3).[9,10] A substantial number of untreated vulvar HSILs (87.5%) progress to cancer.[11] Low-grade and high-grade vaginal intraepithelial neoplasia (VAIN) are also classified as LSIL (VAIN 1) and HSIL (VAIN 2/3), respectively; HSILs variably progress to invasive vaginal cancer.[12] Delayed diagnosis of vulvar and vaginal cancers is common and can adversely affect prognosis.

The research in the current study and the parent studies adhered to Good Publication Practice (GPP3) and was sponsored and funded by Merck & Co, Inc., Kenilworth, New Jersey, the manufacturer of Gardasil and Gardasil9.

Presented in part at EUROGIN 2016, June 15–18, 2016, Salzburg, Austria; AOGIN 2016, August 12–14, 2016, Singapore; EUROGIN 2017, October 8–11, 2017, Amsterdam, The Netherlands; and ISSVD 2017, September 13–15, 2017, Mendoza, Argentina.

The authors thank Jane Liao, Weifeng Xu, and Xingshu Zhu of Merck & Co, Inc. for statistical support; Adrienne Jackson and Karyn Davis of Merck & Co, Inc. for logistic support; and Elizabeth Suarez for analytical support while interning at Merck & Co, Inc. Medical writing and editorial assistance were provided by Emily Cullinan of The Lockwood Group, Stamford, Connecticut, and funded by Merck & Co, Inc.

Xavier Castellsagué is deceased.

Each author has indicated that he or she has met the journal's requirements for authorship.

Received February 5, 2018. Received in revised form April 25, 2018. Accepted May 3, 2018.

Corresponding author: Suzanne M. Garland, MD, Royal Women's Hospital, Locked Bag 300, Cnr Grattan St & Flemington Road, Parkville VIC 3052, Australia; email: suzanne.garland@thewomens.org.au.

Financial Disclosure

All academic authors have been investigators for Merck & Co, Inc., Kenilworth, New Jersey. Dr. Garland reports having received funding through her institution to perform human papillomavirus (HPV) vaccine studies for Merck & Co, Inc., CSL Limited, and GlaxoSmithKline; received payment for board membership on the Merck Global Advisory Board; and received honoraria for lectures including services on a speakers' bureau conducted during her personal time; she also serves as co-chair of the PATRICIA publication steering committee. Dr. Joura reports having received grant support paid to his institution from Merck & Co, Inc. and GlaxoSmithKline; advisory board fees from Merck & Co, Inc. and Sanofi Pasteur MSD, and lecture fees from Sanofi Pasteur MSD, Merck & Co, Inc., GlaxoSmithKline, and Roche. Dr. Ault has received grants to his institution from Merck & Co, Inc. and the National Institutes of Health and advisory committee fees from the American College of Obstetricians and Gynecologists. He also serves on the editorial board for the National Cancer Institute. Dr. Bosch has received institutional research and educational grants from Sanofi Pasteur MSD and GlaxoSmithKline and personal travel grant and speakers' honorarium from Sanofi Pasteur MSD and GlaxoSmithKline. Dr. Brown has served on an advisory board at Merck & Co, Inc. and has lectured on the quadrivalent HPV vaccine (honoraria received from Merck & Co, Inc. are donated to charities). His laboratory has received research funding from Merck & Co, Inc. Indiana University and Merck &Co, Inc. have an agreement that pays the university based on certain landmarks related to vaccine development. Dr. Brown receives a portion of these funds as income. Dr. Castellsagué received institutional research and educational grants from Sanofi Pasteur MSD, Merck & Co, Inc., GlaxoSmithKline, and Genticel and occasional personal travel grants and speakers' honoraria from Sanofi Pasteur MSD and Vianex. Dr. Castellsagué's family has given permission that he may be listed as a coauthor in this article. Dr. Ferenczy is a member of the Pathology Panel for Merck & Co, Inc. randomized controlled vaccine trials. Dr. Ferris has received grants to his institution and lecture fees from Merck Sharp & Dohme, a subsidiary of Merck & Co, Inc., and advisory board and consultant fees from Merck & Co, Inc. Dr. Giuliano has received grant support and advisory board member fees to her institution from Merck & Co, Inc. Dr. Huh has received honoraria for advisory board participation with Merck & Co, Inc. Dr. Iversen has received compensation from Merck & Co, Inc. and GlaxoSmithKline to conduct vaccine clinical trials as well as scientific advisory board fees from Merck & Co, Inc. Dr. Kjaer has received scientific advisory board and speakers' fees from Sanofi Pasteur MSD and Merck & Co, Inc. and unrestricted research grants through her institution from Merck & Co, Inc. and scientific advisory board fees from Becton Dickinson. Dr. Kurman is a member of the Pathology Panel for Merck & Co, Inc. randomized controlled vaccine trials. Dr. Monsonego has received an honorarium as a member of the scientific advisory board of Sanofi Pasteur MSD, Merck & Co, Inc., Roche Diagnostics, Genprobe, and Genticel and compensation from Merck & Co, Inc. and GlaxoSmithKline to conduct vaccine trials. Dr. Muñoz has received an honorarium from Merck & Co, Inc. for being a member of the HPV Global Advisory Board. Dr. Paavonen has received research funding from Merck & Co, Inc. and GlaxoSmithKline through his institution. Dr. Pitisuttithum has received research funding from Merck & Co, Inc. through her institution. Dr. Ronnett has consulted for Merck & Co, Inc. as a member of the Pathology Panel for Merck & Co, Inc. randomized controlled vaccine trials. Dr. Steben has received grants and personal fees from Merck & Co, Inc., BD Diagnostics, Hologic/Gen-Probe, Roche Diagnostics, and Valeant as well as personal fees from Cepheid, Inovio, and Paladin. Dr. Stoler has served or is serving as a consultant in clinical trial design and as an expert pathologist for HPV vaccine and diagnostic trials for Roche, Ventana Medical Systems, Hologic/Gen-Probe, Becton Dickinson, Cepheid, Qiagen, Inovio, and Merck & Co, Inc. Dr. Wheeler has received equipment and reagents for HPV genotyping from Roche Molecular Systems and contracts for HPV vaccine studies from GlaxoSmithKline and Merck & Co, Inc. through her institution, the University of New Mexico. Dr. Wagner is a senior consultant with Analytica LASER, contracted to participate in the analysis, design, and reporting of study findings. Dr. Wiley has received an honorarium as a member of the speakers' bureau and has received industry-sponsored grant support for research from Merck & Co, Inc. Drs. Perez, Saah, Luxembourg, Li, and Velicer are employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc. and hold stock and stock options in the company. Dr. DiNubile was an employee of Merck Sharp & Dohme Corp and held stock and stock options in the company for most of the time this article was in preparation; he continues to hold stock options in the company through 2018 and now is an employee of BioAegis Therapeutics, North Brunswick, New Jersey, where his involvement with the article has continued. The other authors did not report any potential conflicts of interest.

Copyright © by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Cervical cancer is predominately caused by 12 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), and most anogenital warts are caused by two low-risk HPV types (6 and 11).[13] Three highly efficacious HPV vaccines are in widespread worldwide use against genital HPV infection and associated anogenital lesions: bivalent (HPV16/18 [Cervarix]),[14] quadrivalent (HPV6/11/16/18 [GARDASIL]),[15,16] and nonavalent vaccines (HPV6/11/16/18/31/33/45/52/58 [GARDASIL9]).[17]

Estimates for the frequencies of HPV types associated with vulvovaginal lesions remain imprecise.[7,18–21] To delineate the association of HPV genotypes with incident vulvovaginal abnormalities, we estimated the proportion of vulvar or vaginal lesions attributable to the 14 HPV genotypes most frequently linked to cervical cancer and anogenital warts among females 15–26 year old prospectively followed in the placebo arms of two pivotal trials assessing the prophylactic efficacy of the quadrivalent vaccine.[15,16]

MATERIALS AND METHODS

For this post hoc descriptive analysis, we used data to delineate the association of HPV genotypes from females 15–26 years of age in the placebo arms of two already published, randomized, double-blind clinical trials of the quadrivalent HPV vaccine (FUTURE I, NCT00092521,[15] and FUTURE II, NCT00092534[16]) who developed vulvar or vaginal LSILs and HSILs during approximately 4 years of follow-up. Secondary objectives were to compare baseline characteristics of females with and without incident vulvar or vaginal lesions and to explore patterns of lesion development at multiple (vulvar, vaginal, and cervical) sites in the same female. An exploratory, but clinically informative, objective was to estimate the proportion of vulvar or vaginal LSILs or HSILs attributable to genotypes covered by current vaccines.

The study designs, protocols, and results for each study have been previously published.[15,16] Both studies were sponsored by Merck & Co, Inc., conducted in accordance with principles of Good Clinical Practice, and approved by the appropriate institutional review boards and regulatory agencies governing each site. Females reporting a history of abnormal cervical Pap test results or multiple sexual partners (defined as four or greater lifetime partners by most but not all sites) were excluded. These trials enrolled a total of 17,622 healthy, nonpregnant females aged 15–26 years, 8,812 of whom were randomized to the placebo arms. Participants underwent pelvic examinations for cytologic testing with visual inspection of the vulvovaginal and perianal areas and collection of cervical and anogenital swabs for HPV testing by polymerase chain reaction assay at randomization on day 1, at months 7 and 12, and then every 6–12 months for up to 48 months.

The 8,798 placebo recipients who received one or greater study injections and had follow-up data were included in the current descriptive analysis. Individual participants could have more than one lesion of the same or different histologic type. Biopsies were obtained from all external anogenital lesions deemed possibly HPV-related on inspection. If multiple lesions were apparent, each suspicious lesion was sampled. All biopsy specimens were first read for clinical management by pathologists at a central laboratory (Diagnostic Cytology Laboratories, Indianapolis, Indiana) and then adjudicated by a panel of four gynecologic pathologists blinded to central laboratory and clinical diagnoses, treatment group, and HPV status. Specimens were tested for 14 prespecified HPV genotypes (6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) using a type-specific multiplex polymerase chain reaction assay developed by Merck Research Laboratories (Merck & Co, Inc.) to simultaneously amplify and detect the L1, E6, and E7 open reading frames of HPV6, 11, 16, 18, 31, 45, 52, and 58 or the E6 and E7 open reading frames of HPV33, 35, 39, 51, 56, and 59.[22,23] The adjudicated diagnoses of vaginal and vulvar LSILs (not including condylomata) and HSILs were captured for these analyses.

Baseline characteristics of females who did and did not develop vulvar or vaginal lesions were analyzed by lesion location and grade. If a female developed greater than one lesion at a site, the highest grade lesion was used in the analysis. To calculate age-adjusted associations between baseline characteristics and lesion development, odds ratios (ORs) and 95% CIs were computed using a nested case–control approach. Five controls per case were randomly selected from females who did not develop cervical or anogenital lesions throughout the follow-up period. The comparison group was not matched by person-time at risk.

We explored patterns of lesion development at cervical, vulvar, and vaginal sites in individual females. The proportion of females with incident lesions at a specified site who also had lesions at other sites was calculated from females with histologically confirmed cervical, vulvar, or vaginal lesions during follow-up.

Copyright © by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Human papillomavirus types were grouped into bivalent vaccine types (16/18), quadrivalent vaccine types (6/11/16/18), nonavalent vaccine types (6/11/16/18/31/33/45/52/58), the five additional types included in the nine-genotype vaccine, but not in the quadrivalent vaccine (31/33/45/52/58), and the most common nonvaccine high-risk types identified in the quadrivalent HPV vaccine trials (35/39/51/56/59).

Proportional attribution was the primary attribution approach.[18–21,24] The relative proportion of co-infected lesions attributed to each HPV type detected in the lesion corresponded to the relative proportion of lesions from the same population in which that HPV type had been detected as a single infection. Four other approaches[18–21,24] were used as sensitivity analyses (Appendix 1, available online at http://links.lww.com/AOG/B118). For additional interpretative context, we also present the type-specific analyses for only the subset of lesions in which any of the 14 HPV types being tested was identified.

RESULTS

There were 8,812 females aged 15–26 years at baseline randomized to the two placebo arms, but 14 females were excluded from this analysis because of missing data or cross-treatment with vaccine. During approximately 4 years of follow-up in the remaining 8,798 females, a total of 86 vulvar lesions (40 LSILs and 46 HSILs) were diagnosed in 68 females, and 151 vaginal lesions (118 LSILs and 33 HSILs) were diagnosed in 107 females (Appendix 2, available online at http://links.lww.com/AOG/B118).

Females who developed vulvar or vaginal lesions during follow-up tended to have higher numbers of lifetime and recent (last 6 months) sex partners and also tended to test positive for at least one measured HPV genotype at baseline than females who remained lesion-free. Females who developed vaginal lesions during follow-up were more likely to have a Pap test result abnormality at baseline compared with those with no lesions during follow-up (LSIL crude OR 3.1, 95% CI 1.7–5.7; HSIL crude OR 2.3, 95% CI 0.9–6.0); however, development of vulvar lesions during follow-up was not associated with abnormal Pap test results at baseline (Appendix 2, http://links.lww.com/AOG/B118).

By the end of the approximately 4 years of follow-up, 41.2% of females with vulvar lesions and 49.5% of females with vaginal lesions also had cervical lesions, whereas only 6.5% of females with cervical lesions had vaginal or vulvar lesions (Table 1). Overall,

Table 1. Proportion of Young Females Who Developed Lesions at Multiple Sites (Cervical, Vulvar, or Vaginal) During Follow-up

	Subset With Cervical Lesions*			Subset With Vulvar Lesions*			Subset With Vaginal Lesions*			With Lesions at Any Other Site*	With Lesions at Both Other Sites*
	Any Cervical	LSIL	HSIL	Any Vulvar	LSIL	HSIL	Any Vaginal	LSIL	HSIL		
Cervical lesions											
Any (N=1,201)†	—	—	—	28 (2.3)	13 (1.1)	15 (1.3)	53 (4.4)	41 (3.4)	12 (1.0)	78 (6.5)	3 (0.3)
LSIL (n=677)†	—	—	—	16 (2.4)	8 (1.2)	8 (1.2)	36 (5.3)	28 (4.1)	8 (1.2)	50 (7.4)	2 (0.3)
HSIL (n=524)†	—	—	—	12 (2.3)	5 (1.0)	7 (1.3)	17 (3.2)	13 (2.5)	4 (0.8)	28 (5.3)	1 (0.2)
Vulvar lesions											
Any (N=68)†	28 (41.2)	16 (23.5)	12 (17.7)	—	—	—	7 (10.3)	4 (5.9)	3 (4.4)	32 (47.1)	3 (4.4)
LSIL (n=32)†	13 (40.6)	8 (25.0)	5 (15.6)	—	—	—	3 (9.4)	1 (3.1)	2 (6.3)	16 (50.0)	—
HSIL (n=36)†	15 (41.7)	8 (22.2)	7 (19.4)	—	—	—	4 (11.1)	3 (8.3)	1 (2.8)	16 (44.4)	3 (8.3)
Vaginal lesions											
Any (N=107)†	53 (49.5)	36 (33.6)	17 (15.9)	7 (6.5)	3 (2.8)	4 (3.7)	—	—	—	57 (53.3)	3 (2.8)
LSIL (n=81)†	41 (50.6)	28 (34.6)	13 (16.1)	4 (4.9)	1 (1.2)	3 (3.7)	—	—	—	43 (53.1)	2 (2.5)
HSIL (n=26)†	12 (46.2)	8 (30.8)	4 (15.4)	3 (11.5)	2 (7.7)	1 (3.9)	—	—	—	14 (53.9)	1 (3.9)

LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.
Data are n (%).
* Number of females with a specified lesion type in each row who also developed the lesion type indicated in the column.
† Total number of females who developed the lesion type specified in the row during the follow-up.

Copyright © by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

10.3% of females with vulvar lesions had vaginal lesions, whereas 6.5% of females with vaginal lesions also had vulvar lesions. In 47.1% of females who developed vulvar lesions and 53.3% of females who developed vaginal lesions, abnormalities involving cervical and other sites were also present. Females who developed vulvar HSILs had the highest likelihood of having lesions at all three genital sites (8.33%). For females with lesions at multiple sites, no consistent pattern in the relative timing of diagnosis was observed.

In total, 72.5% of vulvar LSILs and 91.3% of vulvar HSILs tested positive for one or greater of the 14 HPV types assayed (Table 2 and Fig. 1A), and coinfections multiple HPV types were present in 24.1% and 45.2% of the HPV-positive LSILs and HSILs, respectively. Using proportional attribution, 87.7% and 89.4% of all HPV-positive vulvar LSILs were attributable to HPV types in the quadrivalent and nonavalent vaccines, respectively (Fig. 1B). Specifically, 52.0% of all vulvar LSILs and 71.7% of HPV-positive vulvar LSILs were associated with HPV6,

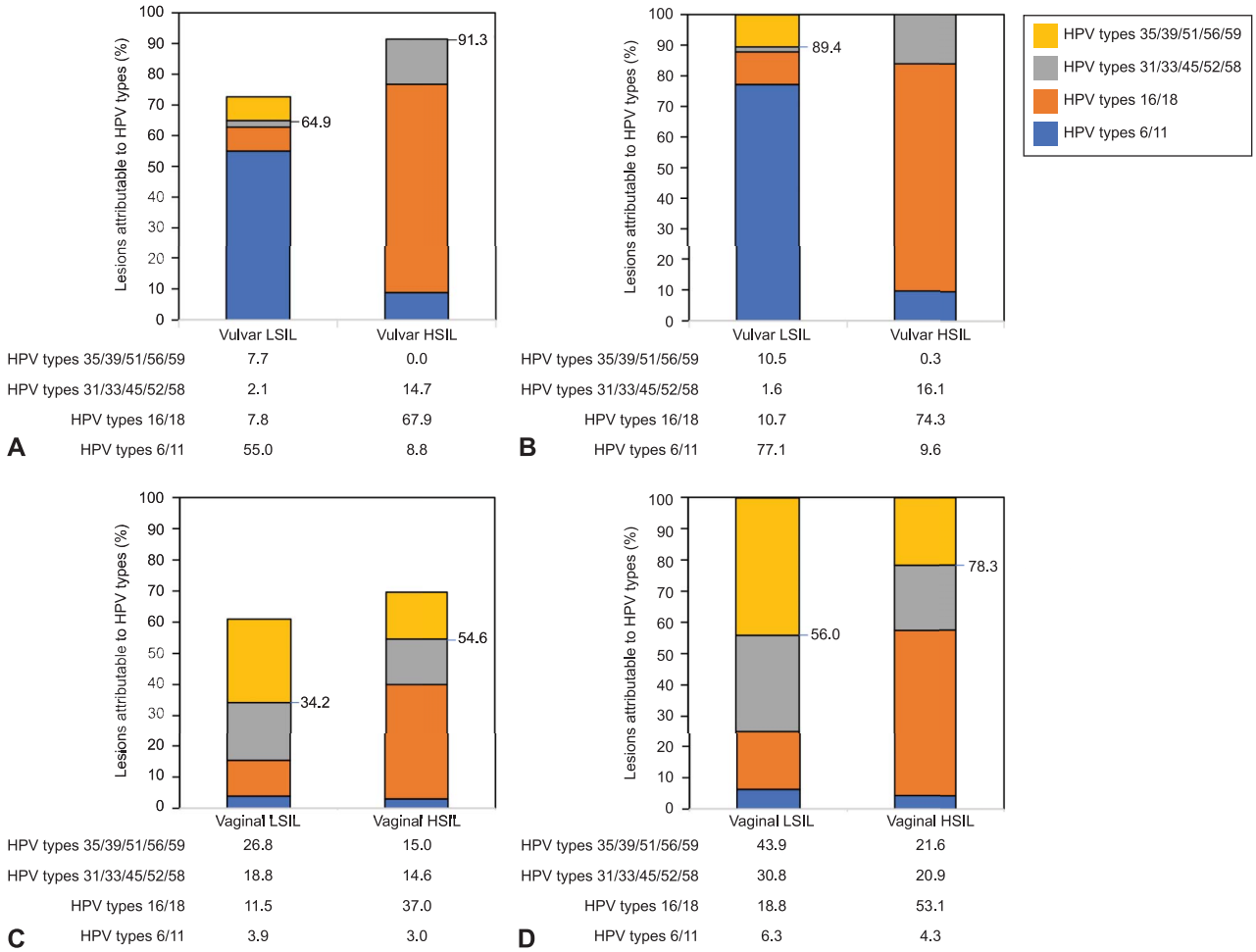

Fig. 1. Vulvar or vaginal lesion attribution in females aged 15–26 years to nonavalent vaccine types (6/11, 16/18, and 31/33/45/52/58) and high-risk nonvaccine types (35/39/51/56/59). **A**. Based on the proportional attribution method, percentage of all human papillomavirus (HPV)–positive vulvar low-grade squamous intraepithelial lesions (LSILs) or high-grade squamous intraepithelial lesions (HSILs) attributable to quadrivalent and nonavalent vaccine types were measured, respectively; denominator includes all lesions (n=40 for vulvar LSILs and n=46 for vulvar HSILs). **B**. Using multitype-adjusted attribution methods; percentage of all vulvar LSIL and HSILs attributable to all HPV vaccine types; denominator includes HPV-positive lesions (n=29 for vulvar LSILs and n=42 for vulvar HSILs). **C**. Based on the proportional attribution method; denominator includes all lesions (n=118 for vaginal LSILs and n=33 for vaginal HSILs). **D**. Using multitype-adjusted attribution methods, percentage of all vaginal LSILs and HSILs attributable to HPV genotypes; denominator includes HPV-positive lesions only (n=72 for vaginal LSILs and n=23 for vaginal HSILs).

Garland. Human Papillomavirus-Related Vulvar and Vaginal Lesions. Obstet Gynecol 2018.

Copyright © by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 2. Type-specific Prevalence and Proportional Attribution of Human Papillomavirus Genotypes in Vulvar Lesions Among Females 15–26 Years of Age

	Vulvar LSIL					
	All Lesions in Denominator (n=40)			Only HPV-Positive Lesions in Denominator (n=29)		
HPV Type(s) Tested	Any*	Single†	Proportion‡	Any*	Single†	Proportion‡
6	21 (53)	17 (43)	20.8 (52)	21 (72)	17 (59)	20.8 (72)
11	3 (8)	1 (3)	1.6 (4)	3 (10)	1 (3)	1.6 (5)
16	4 (10)	2 (5)	3.1 (8)	4 (14)	2 (7)	3.1 (11)
18	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
31	1 (3)	0 (0)	0.5 (1)	1 (3)	0 (0)	0.5 (2)
33	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
45	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
52	2 (5)	0 (0)	0 (0)	2 (7)	0 (0)	0 (0)
58	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
35	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
39	3 (8)	1 (3)	1.6 (4)	3 (10)	1 (3)	1.6 (5)
51	1 (3)	0 (0)	0.5 (1)	1 (3)	0 (0)	0.5 (2)
56	1 (3)	1 (3)	1.0 (3)	1 (3)	1 (3)	1.0 (3)
59	1 (3)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)
6/11/16/18	—	—	25.4 (63.6)	—	—	25.4 (87.7)
31/33/45/52/58	—	—	0.5 (1.3)	—	—	0.5 (1.7)
6/11/16/18/31/33/45/52/58	—	—	25.9 (64.9)	—	—	25.9 (89.4)
35/39/51/56/59	—	—	3.1 (7.7)	—	—	3.1 (10.6)

HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.
Data are number of females with indicated lesion type (%).
* n (%) of all lesions testing positive for the respective HPV type, regardless of co-infections.
† n (%) of lesions testing positive for the respective HPV type only, excluding co-infections.
‡ n (%) of lesions attributable to the respective HPV type, as determined applying the proportional attribution method.

predominantly as single-type infections. Overall, 60.0–67.5% of vulvar LSILs were linked to nonavalent vaccine types, most (60.0–65.0%) of which were quadrivalent vaccine types (Appendix 3, available online at http://links.lww.com/AOG/B118).

In vulvar HSILs, HPV16 was the predominant type detected with proportional attribution rates of 67.9% among all lesions and 74.3% among HPV-positive lesions (Table 2). Using multitype adjusted attribution methods, 76.1–91.3% of all vulvar HSILs were attributable to nonavalent vaccine types and a smaller proportion (65.2–78.3%) to quadrivalent vaccine types, indicating a nontrivial contribution of types 31, 33, 45, 52, and 58 (10.9–14.7%) (Appendix 3, http://links.lww.com/AOG/B118). All HPV-positive vulvar HSILs were attributable to nonavalent vaccine types (Table 2 and Fig. 1B).

In vaginal LSILs (Table 3), HPV31, 56, and 16 were the most prevalent types and only HPV33 went undetected. Overall, 61.9% of vaginal LSILs and 72.7% of vaginal HSILs tested positive for one or greater of the 14 HPV types assayed with co-infections present in 41.1% and 33.3% of the HPV-positive LSILs and HSILs, respectively. By the proportional method, 3.9% of all vaginal LSILs (6.3% of HPV-positive vaginal LSILs) were attributable to the low-risk types (HPV6 [2.2%] and HPV11 [1.7%]) (Fig. 1C, D). Of all HPV-positive vaginal LSILs, 56.0% were attributable to nonavalent vaccine types by the proportional method (Fig. 1D). Adjusting for co-infections, 27.1–43.2% of all vaginal LSILs were attributable to the nonavalent vaccine types and 15.3–21.2% to quadrivalent vaccine types, revealing a substantial contribution of types 31, 33, 45, 52, and 58 (11.9–22.0%; Appendix 4, available online at http://links.lww.com/AOG/B118). An estimated 18.6–26.8% of vaginal LSILs were attributable to the nonvaccine types 35, 39, 51, 56, and 59.

The most common HPV type in vaginal HSILs was HPV16, accounting for 32.5% of all lesions and 46.6% of HPV-positive lesions using the proportional method (Table 3). Most other HPV types tested were also detected (except 11, 45, and 39), but usually as co-infections with HPV16. For all vaginal HSILs, multitype-adjusted attribution estimates ranged from 30.3–48.5% for quadrivalent vaccine types; from 12.1–21.2% for types 31, 33, 45, 52, and 58 (Appendix

Copyright © by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Vulvar HSIL					
All Lesions in Denominator (n=46)			Only HPV-Positive Lesions in Denominator (n=42)		
Any*	Single†	Proportion‡	Any*	Single†	Proportion‡
8 (17)	3 (7)	4.03 (9)	8 (19)	3 (7)	4.03 (10)
2 (4)	0 (0)	0.0 (0)	2 (5)	0 (0)	0 (0)
32 (70)	16 (35)	31.2 (68)	32 (76)	16 (38)	31.2 (74)
1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
8 (17)	4 (9)	6.8 (15)	8 (19)	4 (10)	6.8 (16)
2 (4)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2 (4)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)
2 (4)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
6 (13)	0 (0)	0 (0)	6 (14)	0 (0)	0 (0)
2 (4)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)
—	—	35.2 (76.6)	—	—	35.2 (83.9)
—	—	6.8 (14.7)	—	—	6.8 (16.1)
—	—	42.0 (91.3)	—	—	42.0 (100)
—	—	0 (0)	—	—	0 (0)

4, http://links.lww.com/AOG/B118); and from 42.4–60.6% for all nonavalent vaccine types. Although nonvaccine HPV types were detected in 30.3% of vaginal HSILs, 60% of these lesions were co-infected with quadrivalent HPV types; therefore, only 12.1–15.1% of vaginal HSILs were exclusively attributable to this group (Table 3; Appendix 4 [http://links.lww.com/AOG/B118]). Of all HPV-positive vaginal HSILs, 78.3% were attributable to nonavalent vaccine types (Table 3 and Fig. 1D).

The majority of HPV-positive lesions were attributable to types targeted by the nonavalent vaccine using the proportional method, including 89.4% and 100% of vulvar LSILs and HSILs and 56.0% and 78.3% of vaginal LSILs and HSILs, respectively (Appendix 5, available online at http://links.lww.com/AOG/B118). These estimates compare with 87.7% and 83.9% of vulvar LSILs and HSILs and 25.2% and 57.4% of vaginal LSILs and HSILs, respectively, attributable to the four genotypes (6, 11, 16, and 18) in the quadrivalent vaccine. The nonvaccine high-risk types (35, 39, 51, 56, and 59) measured in the quadrivalent vaccine trials were detected in 10.6% of vulvar LSILs, no vulvar HSILs, 44.0% of vaginal LSILs, and 21.7% of vaginal HSILs.

DISCUSSION

These analyses show 14 high-risk HPV types are detectable more often than not in both vaginal and vulvar LSIL and HSIL. Most HPV-positive lesions were attributable to HPV types targeted by the nonavalent vaccine using the proportional attribution method, including 89.4% and 100% of vulvar LSILs and HSILs and 56.0% and 78.3% of vaginal LSILs and HSILs, respectively. The five additional HPV types in the nonavalent vaccine, but not in the quadrivalent vaccine, were detected in 1.7% of vulvar LSILs, 16.1% of vulvar HSILs, 30.8% of vaginal LSILs, and 20.9% of vaginal HSILs. Nonvaccine HPV types contributed more frequently to vaginal LSIL but less to vaginal HSIL, which is also seen in cervical intraepithelial neoplasia.[24]

Of the 40 vulvar LSILs, 72.5% were positive for one or greater of the 14 HPV types tested. These findings are consistent with several meta-analyses.[3,4] Applying the proportional method to HPV-positive vulvar LSILs, 89.4% were attributed to nonavalent vaccine types with only 1.7% attributed to the five additional HPV types not in the quadrivalent vaccine. The most common type in these lesions was HPV6, identified in 71.7% of HPV-positive vulvar LSILs and targeted by the quadrivalent and nonavalent vaccine.

All HPV-positive vulvar HSILs were attributable to genotypes covered by the nonavalent vaccine, including HPV16 found in 74.3% of lesions by the proportional method. Nonvaccine types were unusual and only identified in co-infections with vaccine types. In close agreement with our findings, a multinational,

Copyright © by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 3. Type-specific Prevalence and Proportional Attribution of Human Papillomavirus Genotypes in Vaginal Lesions Among Females 15–26 Years of Age

	Vaginal LSIL					
	All Lesions in Denominator (n=118)			Only HPV-Positive Lesions in Denominator (n=73*)		
HPV Type(s) Tested	Any†	Single‡	Proportion§	Any†	Single‡	Proportion§
6	4 (3)	2 (2)	2.6 (2)	4 (5)	2 (3)	2.6 (4)
11	4 (3)	1 (1)	2.0 (2)	4 (5)	1 (1)	2.0 (3)
16	14 (12)	6 (5)	9.5 (8)	14 (19)	6 (8)	9.5 (13)
18	7 (6)	2 (2)	4.0 (3)	7 (10)	2 (3)	4.0 (6)
31	18 (15)	9 (8)	14.7 (12)	18 (25)	9 (12)	14.7 (20)
33	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
45	3 (3)	2 (2)	2.5 (2)	3 (4)	2 (3)	2.5 (3)
52	13 (11)	1 (1)	3.3 (3)	13 (18)	1 (1)	3.3 (5)
58	5 (4)	1 (1)	1.7 (1)	5 (7)	1 (1)	1.7 (2)
35	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
39	8 (7)	5 (4)	6.4 (5)	8 (11)	5 (7)	6.4 (9)
51	12 (10)	2 (2)	5.3 (4)	12 (16)	2 (3)	5.3 (7)
56	15 (13)	7 (6)	12.0 (10)	15 (21)	7 (10)	12.0 (17)
59	11 (9)	5 (4)	7.9 (6.7)	11 (15)	5 (7)	7.9 (11)
6/11/16/18	—	—	18.1 (15.4)	—	—	18.1 (25.2)
31/33/45/52/58	—	—	22.2 (18.8)	—	—	22.2 (30.8)
6/11/16/18/31/33/45/52/58	—	—	40.4 (34.2)	—	—	40.4 (56.0)
35/39/51/56/59	—	—	31.7 (26.8)	—	—	31.7 (44.0)

HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.
Data are number of females with indicated lesion type (%).
* As a result of incomplete data for two lesions (one LSIL and one HSIL), these two cases were excluded from the proportional attribution analyses; therefore, the denominator is 72 for LSILs and 23 for HSILs.
† n (%) of all lesions testing positive for the respective HPV type, regardless of co-infections.
‡ n (%) of lesions testing positive for the respective HPV type only, excluding co-infections.
§ n (%) of lesions attributable to the respective HPV type, as determined applying the proportional attribution method.

retrospective analysis reported that 88.7% (509/587) of vulvar HSILs were HPV-positive, 77.3% of the positive lesions were attributable to HPV16, and 94.2% to nonavalent vaccine types.[1] Both HPV positivity exceeding 80% and the predominance of HPV16 in vulvar HSILs have been observed previously.[3,4] Human papillomavirus-31, closely related to type 16,[25] appeared to play a relatively modest role in vulvar HSILs (14.7% in our study using proportional attribution), whereas HPV33 was infrequently detected. In contrast, prior analyses identified HPV33 (10.6%) in vulvar HSILs, whereas type 31 (1.2%) was rare.[1]

Nonavalent HPV types were found in 56.0% of vaginal LSILs in this study, as also observed in cervical intraepithelial neoplasia.[24,26] Other investigators have observed mainly HPV16 associated with vaginal LSILs.[3,4,12] Non-HPV causes of vaginal LSILs may reflect past in utero exposure to diethylstilbestrol in women 40 years of age and older.[27,28]

Of the 33 vaginal HSILs in our study, 72.7% tested HPV-positive, of which 78.3% were attributable to nonavalent vaccine types by the proportional attribution method. A nearly identical attribution of 79.0% was found in 181 HPV-positive vaginal HSILs from a recent multinational, retrospective survey.[5] In contrast to our findings, most previous reports have identified greater than 90% of vaginal lesions as HPV-positive.[29] Differences in assays to detect HPV, variations in the prevalent genotypes, sample storage and handling, age distribution of study participants, sample size, and intraobserver variability in the cytologic or histologic diagnosis may explain some differences across studies.

Approximately 41% and 50% of females with vulvar and vaginal lesions, respectively, also developed cervical lesions in our study, confirming the multifocal nature of anogenital infection and subsequent disease, particularly the association of cervical disease with HPV-related vaginal and vulvar lesions.[30,31] Although the coexistence of HPV-related cervical, vulvar, and vaginal cancers and precancerous lesions has not been well studied, a history of cervical cancer or cervical intraepithelial neoplasia 2/3 has been associated with an increased risk of both vulvar and vaginal cancers.

Copyright © by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Vaginal HSIL					
All Lesions in Denominator (n=33)			Only HPV-Positive Lesions in Denominator (n=24*)		
Any†	Single‡	Proportion§	Any†	Single‡	Proportion§
1 (3)	1 (3)	1.0 (3)	1 (4)	1 (4)	1.0 (4)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
13 (39)	6 (18)	10.7 (32)	13 (54)	6 (25)	10.7 (46)
2 (6)	1 (3)	1.5 (5)	2 (8)	1 (4)	1.5 (7)
2 (6)	1 (3)	1.5 (5)	2 (8)	1 (4)	1.5 (7)
3 (9)	1 (3)	1.3 (4)	3 (13)	1 (4)	1.3 (6)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1 (3)	1 (3)	1.0 (3)	1 (4)	1 (4)	1.0 (4)
1 (3)	1 (3)	1.0 (3)	1 (4)	1 (4)	1.0 (4)
2 (6)	1 (3)	1.2 (4)	2 (8)	1 (4)	1.2 (5)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2 (6)	1 (3)	1.2 (4)	2 (8)	1 (4)	1.2 (5)
5 (15)	1 (3)	1.6 (5)	5 (21)	1 (4)	1.6 (7)
1 (3)	1 (3)	1.0 (3)	1 (4)	1 (4)	1.0 (4)
—	—	13.2 (40.0)	—	—	13.2 (57.4)
—	—	4.8 (14.6)	—	—	4.8 (20.9)
—	—	18.0 (54.6)	—	—	18.0 (78.3)
—	—	5.0 (15.1)	—	—	5.0 (21.7)

Approximately 30% of patients with vaginal cancer had previous premalignant or cancerous cervical lesions.

Our study has several important limitations. This study was a post hoc, descriptive analysis of clinical trial data; the relatively small number of events can affect the precision of the estimated attribution fractions. Applying five attribution approaches may be a better measure of biological variability as opposed to statistical variability. The ideal approach for measuring attribution is laser-capture microdissection. Because our study was limited to females 15–26 years of age, it is possible that older women could differ in HPV type attribution or positivity. Nonetheless, our results were consistent with those reported from recent large multinational studies of vulvar and vaginal HSILs conducted in women over a wider age range with mean (±SD) ages of 50 (±15) years for vulvar HSILs and 50 (±14) years for vaginal HSILs.[1,2]

Vulvar and vaginal lesions are rare but increasing findings in young women.[7] Human papillomavirus infections, including vaccine genotypes, cause the majority of genital abnormalities. Widespread adoption of an efficacious prophylactic vaccine has the potential to prevent a substantial fraction of HPV-related vulvar and vaginal lesions in addition to preventing the majority of cervical lesions.[15–17,24,32]

REFERENCES

1. de Sanjosé S, Alemany L, Ordi J, Tous S, Alejo M, Bigby SM, et al. Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. Eur J Cancer 2013;49:3450–61.
2. Alemany L, Saunier M, Tinoco L, Quirós B, Alvarado-Cabrero I, Alejo M, et al. Large contribution of human papillomavirus in vaginal neoplastic lesions: a worldwide study in 597 samples. Eur J Cancer 2014;50:2846–54.
3. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer 2009;124:1626–36.
4. Smith JS, Backes DM, Hoots BE, Kurman RJ, Pimenta JM. Human papillomavirus type-distribution in vulvar and vaginal cancers and their associated precursors. Obstet Gynecol 2009; 113:917–24.
5. Chao A, Chen TC, Hsueh C, Huang CC, Yang JE, Hsueh S, et al. Human papillomavirus in vaginal intraepithelial neoplasia. Int J Cancer 2012;131:E259–68.
6. Srodon M, Stoler MH, Baber GB, Kurman RJ. The distribution of low and high-risk HPV types in vulvar and vaginal intraepithelial neoplasia (VIN and VaIN). Am J Surg Pathol 2006;30:1513–8.
7. Kurdgelashvili G, Dores GM, Srour SA, Chaturvedi AK, Huycke MM, Devesa SS. Incidence of potentially human papillomavirus-related neoplasms in the United States, 1978 to 2007. Cancer 2013;119:2291–9.
8. Joura EA, Lösch A, Haider-Angeler MG, Breitenecker G, Leodolter S. Trends in vulvar neoplasia. Increasing incidence of vulvar intraepithelial neoplasia and squamous cell carcinoma of the vulva in young women. J Reprod Med 2000;45:613–5.
9. Darragh TM, Colgan TJ, Thomas Cox J, Heller DS, Henry MR, Luff RD, et al. The Lower Anogenital Squamous Terminology Standardization project for HPV-associated lesions: background

Copyright © by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Int J Gynecol Pathol 2013;32:76–115.

10. Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors. WHO classification of tumours of female reproductive organs. 4th ed. Lyon (France): International Agency for Research on Cancer (IARC); 2014.
11. Jones RW, Rowan DM. Vulvar intraepithelial neoplasia III: a clinical study of the outcome in 113 cases with relation to the later development of invasive vulvar carcinoma. Obstet Gynecol 1994;84:741–5.
12. Lamos C, Mihaljevic C, Aulmann S, Bruckner T, Domschke C, Wallwiener M, et al. Detection of human papillomavirus infection in patients with vaginal intraepithelial neoplasia. PLoS One 2016;11:e0167386.
13. Human papillomavirus vaccines: WHO position paper–May 2017. Available at: www.who.int/wer/2017/wer9227/en/. Retrieved July 12, 2017.
14. Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009;374:301–14.
15. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928–43.
16. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915–27.
17. Huh WK, Joura EA, Giuliano AR, Iversen OE, de Andrade RP, Ault KA, et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. Lancet 2017;390:2143–59.
18. Insinga RP, Liaw KL, Johnson LG, Madeleine MM. A systematic review of the prevalence and attribution of human papillomavirus types among cervical, vaginal, and vulvar precancers and cancers in the United States. Cancer Epidemiol Biomarkers Prev 2008;17:1611–22.
19. de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol 2010;11:1048–56.
20. Insinga RP, Perez G, Wheeler CM, Koutsky LA, Garland SM, Leodolter S, et al. Incident cervical HPV infections in young women: transition probabilities for CIN and infection clearance. Cancer Epidemiol Biomarkers Prev 2011;20:287–96.
21. Sahasrabuddhe VV, Castle PE, Follansbee S, Borgonovo S, Tokugawa D, Schwartz LM, et al. Human papillomavirus genotype attribution and estimation of preventable fraction of anal intraepithelial neoplasia cases among HIV-infected men who have sex with men. J Infect Dis 2013;207:392–401.
22. Else EA, Swoyer R, Zhang Y, Taddeo FJ, Bryan JT, Lawson J, et al. Comparison of real-time multiplex human papillomavirus (HPV) PCR assays with INNO-LiPA HPV genotyping extra assay. J Clin Microbiol 2011;49:1907–12.
23. Roberts CC, Swoyer R, Bryan JT, Taddeo FJ. Comparison of real-time multiplex human papillomavirus (HPV) PCR assays with the linear array HPV genotyping PCR assay and influence of DNA extraction method on HPV detection. J Clin Microbiol 2011;49:1899–906.
24. Joura EA, Ault KA, Bosch FX, Brown D, Cuzick J, Ferris D, et al. Attribution of 12 high-risk human papillomavirus genotypes to infection and cervical disease. Cancer Epidemiol Biomarkers Prev 2014;23:1997–2008.
25. Bernard HU. Taxonomy and phylogeny of papillomaviruses: an overview and recent developments. Infect Genet Evol 2013;18:357–61.
26. Fu Xi L, Schiffman M, Ke Y, Hughes JP, Galloway DA, He Z, et al. Type-dependent association between risk of cervical intraepithelial neoplasia and viral load of oncogenic human papillomavirus types other than types 16 and 18. Int J Cancer 2017;140:1747–56.
27. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 1971;284:878–81.
28. Mittendorf R. Teratogen update: carcinogenesis and teratogenesis associated with exposure to diethylstilbestrol (DES) in utero. Teratology 1995;51:435–45.
29. Bruni L, Barrionuevo-Rosas L, Albero G, Serrano B, Mena M, Gómez D, et al; ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human papillomavirus and related diseases in USA. Summary report 27 July 2017. Available at: http://www.hpvcentre.net/statistics/reports/USA.pdf. Retrieved July 11, 2017.
30. Edgren G, Sparén P. Risk of anogenital cancer after diagnosis of cervical intraepithelial neoplasia: a prospective population-based study. Lancet Oncol 2007;8:311–6.
31. Gaudet M, Hamm J, Aquino-Parsons C. Incidence of anogenital and head and neck malignancies in women with a previous diagnosis of cervical intraepithelial neoplasia. Gynecol Oncol 2014;134:523–6.
32. Pitisuttithum P, Velicer C, Luxembourg A. 9-valent vaccine for cancers, pre-cancers and genitals warts related to HPV. Expert Rev Vaccines 2015;14:1405–14.

Copyright © by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.