Published in final edited form as:
J Low Genit Tract Dis. 2013 April ; 17(5 0 1): S64–S68. doi:10.1097/LGT.0b013e3182854399.

Estimating 5-year risk of CIN3+ to guide the management of women aged 21–24

Hormuzd A. Katki, Ph.D.[1,*], **Mark Schiffman, M.D., M.P.H.**[1], **Philip E. Castle, Ph.D., M.P.H.**[2], **Barbara Fetterman, SCT (ASCP)**[3], **Nancy E. Poitras, P.M.P.**[3], **Thomas Lorey, M.D.**[3], **Li C. Cheung, M.S.**[4], **Tina Raine-Bennett, M.D., M.P.H.**[5], **Julia C. Gage, Ph.D., M.P.H.**[1], and **Walter K. Kinney, M.D.**[6,*]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, DHHS, Bethesda, MD, USA

[2]Visiting Professor, Albert Einstein College of Medicine, The Bronx, NY, USA

[3]Regional Laboratory, Kaiser Permanente Northern California, Berkeley, CA, USA

[4]Information Management Services, Inc., Calverton, MD, USA

[5]Women's Health Research Institute, Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA

[6]Division of Gynecologic Oncology, Kaiser Permanente Medical Care Program, Oakland, CA, USA

Abstract

Objective—Current US national guidelines recommend beginning screening at age 21 using Pap tests only, with cotesting starting at age 30. To inform the management of Pap test abnormalities among women aged 21–24, who have extremely low cancer risks, we compared risks of CIN3+ for women aged 21–24 versus 25–29 or 30–64.

Methods—We estimated 5-year risks of CIN3+ for Pap test results, with HPV triage of ASC-US, for 133,947 women aged 21–24, compared with 135,382 women age 25–29 and 965,360 women age 30–64, between 2003–2010 at Kaiser Permanente Northern California.

Results—There were 3 cancers diagnosed during follow-up in women aged 21–24. Following high-grade Pap results (0.6% of Pap results), 5-year CIN3+ risks for women aged 21–24 were comparable to those aged 25–29 and 30–64 (AGC: 6.9% vs. 14% vs. 8.5%, p=0.8; ASC-H: 16% vs. 24% vs. 18%, p=0.8; HSIL: 28% vs. 28% vs. 47%, p=0.4). Following LSIL, 5-year CIN3+ risk was lower for ages 21–24 (3.0%) than ages 25–29 (5.0%, p=0.01) or ages 30–64 (5.2%, p=0.0002). Although 5-year CIN3+ risk for HPV-negative/ASC-US was similar across all 3 groups (0.57% vs. 0.59% vs. 0.43%, p=1), risk for HPV-positive/ASC-US was lower for age 21–24 (4.4%) than 25–29 (7.1%, p<0.0001) or 30–64 (6.8%, p<0.0001).

[*]Corresponding authors: HAK: Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd. Room 8014, EPS MSC 7244, Bethesda, MD 20882, Phone: 301-594-7818, Fax: 301-402-0081, katkih@mail.nih.gov. WKK: Kaiser Permanente Northern California, Sacramento Medical Center, 1650 Response Road, Sacramento, CA 95815, Phone: 916-614-4120, walter.kinney@kp.org.

Conflicts of Interest: Dr. Schiffman and Dr. Gage report working with Qiagen, Inc. on an independent evaluation of non-commercial uses of CareHPV (a low-cost HPV test for low-resource regions) for which they have received research reagents and technical aid from Qiagen for free. They have received HPV testing for research at no cost from Roche. Dr. Castle has received compensation for serving as a member of a Data and Safety Monitoring Board for HPV vaccines for Merck. Dr. Castle has received HPV tests and testing for research at a reduced or no cost from Qiagen, Roche, MTM, and Norchip. Dr. Castle is a paid consultant for BD, GE Healthcare, and Cepheid, and has received a speaker honorarium from Roche. No other authors report any conflicts of interest.

Conclusions—Women aged 21–24 had almost zero cancer risk, and positive Pap test results predicted low CIN3+ risk except for the 0.6% of Pap results that were high-grade. The generally low risk supports conservative management of women aged 21–24.

Keywords

Human Papillomavirus (HPV); cancer prevention; Pap; cervical intraepithelial neoplasia (CIN); Hybrid Capture 2 (HC2); young women

Introduction

Young women comprise a special group with regard to cervical screening and management of positive screening results. They have high incidence of HPV infection and related minor Pap test abnormalities but extremely low cancer risk(1). Deep excisional treatment can increase preterm birth (2, 3). Therefore, current US national consensus guidelines are conservative, recommending that women under age 21 not be screened at all(1, 4). For women aged 21–29, the current national recommendations are to use Pap testing alone at 3-year intervals, without HPV testing except for triage of ASC-US(4).

The natural history of HPV infection among young women is extremely dynamic, with a sharp peak and decline in HPV prevalence followed by a rise in CIN2 and CIN3. Therefore, young women do not necessarily form a homogeneous group and screening may be less effective for women aged 21–24 than women aged 25–29. In the US, most CIN2 and CIN3 diagnoses occur between ages 25–35. Women aged 21–24 are likely to have higher HPV incidence but have had less time on average for a new HPV infection to produce treatable CIN2 or CIN3 lesions. Accordingly, guidelines for management of abnormal screening results in Kaiser Permanente Northern California, an integrated health care delivery system that utilizes HPV-Pap cotesting, recommend more conservative management of women ages 21–24 compared to women ages 25–29 (5). In 2010 KPNC recommended follow-up in 1 year as opposed to colposcopy for women 21–24 with HPV-positive/ASC-US and LSIL because of the low immediate risk of CIN3+ (6). A comprehensive examination of risk following different screening results in this age group has not been reported.

This report is based upon data on 133,947 women aged 21–24 undergoing screening between 2003–2010 at Kaiser Permanente Northern California (KPNC). Using this exceptionally large data source, we calculate risks of CIN3+ for each screening Pap result (and HPV testing only for triage of ASC-US). We compare these risks to those derived for women aged 25–29 and those aged 30–64.

Methods

The design of our cohort study from KPNC has been described previously(7); in this report we enlarged the dataset to include all women age 21–64 between 2003–2010, and to include data on HPV triage of ASC-US in women 21–29. As a result of the data expansion, we were able to examine 965,360 women aged 30–64, 135,382 women aged 25–29, and 133,947 women aged 21–24, screened from 2003 to 2010. Biopsy and cancer information was collected on all women through December 31, 2010. The Kaiser Permanente Northern California Institutional Review Board (IRB) approved use of the data, and the National Institutes of Health Office of Human Subjects Research deemed this study exempt from IRB review.

Pap tests were performed at KPNC regional and facility labs. HPV tests were performed only at the regional lab. Conventional Pap slides were manually reviewed following processing by the BD FocalPoint Slide Profiler (BD Diagnostics, Burlington, NC, USA)

primary screening and directed quality control system, in accordance with FDA-approved protocols. Starting in 2009, KPNC transitioned to liquid-based Pap testing using BD SurePath (BD Diagnostics, Burlington, NC, USA). Conventional or liquid-based Pap tests are reported according to the 2001 Bethesda System(8). Hybrid Capture 2 (HC2; Qiagen, Germantown, MD, USA) was used to test for high-risk HPV types according to manufacturer's instructions.

The Permanente Medical Group (TPMG) develops Clinical Practice Guidelines for cervical cancer screening and management of abnormal tests in partnership with the KP National Guideline Program, Care Management Institute, to support clinical decisions of their providers. The guidelines recommend less aggressive initial evaluation of cervical screening abnormalities among women aged 21–24 than those aged 25–29.

Cumulative risk of CIN2+, CIN3+, or cervical cancer for each Pap result was calculated as the sum of risk at baseline test (plotted at time zero on each figure) and the incidence after baseline (9). Risk at the baseline screen is the risk of CIN2+, CIN3+, or cancer for Pap results or cotest results where women are immediately referred to colposcopy and was estimated using logistic regression, stratified by age groups 21–24, 25–29, and 30–64, separately for each cotest result or Pap results. We included in the logistic regression analyses the very small numbers of women testing HPV-negative/ASC-US or Pap-negative at their baseline test who underwent colposcopy. We used Weibull survival models(10) to estimate risks over time strictly after the baseline test, among women for whom CIN2+ was not found at the baseline test. Weibull models can make smoother and more accurate risk estimates than non-parametric methods analogous to Kaplan-Meier(11) and naturally handle interval-censoring of disease outcomes between screening tests. Separate Weibull models were fit for each cotest result or Pap result, with age group as a covariate. When risk was calculated for a cytology result without regard to HPV testing, we refer to those risks as "Pap-alone".

Results

Table 1 shows the distribution of the worst histologic findings by Pap results and cotest result through 2010, for women aged 21–24. Although 1,078 CIN2 and 421 CIN3/AIS were diagnosed, only 3 cancers were diagnosed. The 3 cancers, 1 squamous and 2 adenocarcinoma, were diagnosed in women with an HPV-positive/ASC-US result, a high grade Pap test (AGC), and a negative Pap result respectively at baseline.

Table 2 shows the extremely low 5-year cancer risks in women age 21–24. Women aged 25–29 had high 5-year cancer risk only for high-grade Paps, but still less risk than for women age 30–64 (AGC: 1.1% vs. 2.7%, p= 0.3; ASC-H: 1.5% vs.2.6%, p=0.8; HSIL: 2.0% vs. 7.3%, p=0.0004).

Table 2 also shows 5-year risks of CIN3+ after various Pap results in this age group. After high-grade Pap results, 5-year CIN3+ risks for women age 21–24 were high and roughly comparable to risks for age 25–29 and 30–64 (AGC: 6.9% vs. 14% vs. 8.5%, p=0.8; ASC-H: 16% vs. 24% vs. 18%, p=0.8; HSIL: 28% vs. 28% vs. 47%, p=0.4). For LSIL, 5-year CIN3+ risk was lower for age 21–24 (3.0%) than age 25–29 (5.0%, p=0.01) and age 30–64 (5.2%, p=0.0002). For Pap-negative, 5-year CIN3+ risk was lower for age 21–24 (0.20%) than age 25–29 (0.36%, p=0.0002) and age 30–64 (0.26%, p=0.051).

Furthermore, the data in Table 2 permit an examination of the value of HPV triage of ASC-US by age. Five-year CIN3+ risk for HPV-negative/ASC-US was similar across all 3 groups (0.57% vs. 0.59% vs. 0.43%, p=1). However, CIN3+ risk after HPV-positive/ASC-US was lower for age 21–24 (4.4%) than 25–29 (7.1%, p<0.0001) or 30–64 (6.8%, p<0.0001). As a

result, the difference in risks for HPV-positive/ASC-US vs. HPV-negative/ASC-US varied by age. HPV triage of ASC-US provided less risk stratification for ages 21–24 (with a difference of 4.4% – 0.57%, or 3.8%) than for ages 25–29 (6.6%, $p<0.0001$) or 30–64 (6.4%, $p<0.0001$).

Table 3 benchmarks the 5-year risks of CIN3+ in women age 21–24 to implicit risk thresholds for women age 30–64(9). For women age 21–24, only the uncommon (0.6% of total) high-grade Pap tests (HSIL, ASC-H, AGC) achieved the implicit 5.2% risk threshold for colposcopy. For ages 21–24, HPV-positive/ASC-US and LSIL, which were relatively common (12% in aggregate), predicted CIN3+ risks similar to ASC-US in women age 30–64, for which a 6–12 month return is recommended. Finally, HPV-negative/ASC-US and Pap-negative predicted CIN3+ risks similar to a negative Pap-alone in women age 30–64, for which a 3-year return is recommended.

Discussion

In our data, among 130,000 women aged 21–24, we observed near zero cancer risk, the least risk following a negative Pap result for any age group, low CIN3+ risk following LSIL and HPV-positive/ASC-US, and high CIN3+ risk only for those with high-grade Pap results. The near zero cancer risk in women aged 21–24 underscores the low yield of screening women under age 25, at least in this population. Although immediate treatment of cases of CIN2 or CIN3 diagnosed at ages 21–24 might reduce cancer risk at ages 25–29, even at ages 25–29, the cancer risks are high only for the <1% of these women who have high-grade Pap results, and their cancer risks are far lower than those for women aged 30–64 with high-grade Paps.

Even if risk were equivalent, women aged 21–24 should be managed more conservatively than women aged 30–64 (at least the subset that has not completed desired childbearing) because of the potential for excisional treatments to increase risk of future premature delivery. Benchmarking risks at ages 21–24 to implicit risk thresholds at ages 30–64 means that, in this instance, instead of “equal management of equal risks”(9), we must have “more conservative management of equal risks”. For example, the 5-year CIN3+ risk from LSIL in women aged 21–24 of 3.0% is close to the 2.6% risk from ASC-US in women age 30–64. For women aged 30–64 with ASC-US, who do not undergo colposcopy, the recommended initial evaluation is a 6–12 month return. Therefore, women aged 21–24 with LSIL should be managed *at least as conservatively* with a 6–12 month return. The low risk seems to support a 12-month return.

HPV triage of ASC-US in women aged 21–24 proved less worthwhile than for women aged 25–29 or 30–64. For women aged 30–64 with ASC-US, colposcopic referral is recommended for an HPV-positive result, while in the new guidelines retesting in 3 years is recommended for an HPV-negative test (4). This is a substantial difference in management. However, women aged 21–24 with HPV-positive/ASC-US had lower CIN3+ risk than for older women. The difference between risk in the HPV-positive versus HPV-negative groups is a measure of risk stratification, i.e., an indication of how worthwhile it is to use HPV testing to triage ASC-US. As a general rule, the larger the difference in risk observed between HPV-positive and HPV-negative/ASC-US, the greater the value of triage. The post-test risk difference was not as great for the 21–24 age group as for older women. Furthermore, the 4.4% 5-year CIN3+ risk for women aged 21–24 who were HPV-positive/ASC-US did not reach the 5.2% implicit threshold for colposcopy in women aged 30–64 with LSIL, suggesting instead that women aged 21–24 with HPV-positive/ASC-US should return in 6–12 months (compared to 3-year return for HPV-negative/ASC-US). The smaller risk discrimination of HPV triage calls into question its utility for women aged 21–24.

There were important limitations to this analysis. The results may not be generalizable outside of the KPNC setting (9). Importantly, at KPNC, guidelines recommend less aggressive management of Pap test abnormalities for women aged 21–24 than for women aged 25–29, or older. Less aggressive initial evaluation of abnormalities could reduce measured risk of CIN2 and CIN3, especially to the extent that such lesions regress when not found. We attempted to minimize this bias by restricting our evaluation to an extended period and less frequently regressing endpoint, i.e., 5-year risk of CIN3+.

Limitations aside, we clearly observed that screening was less effective in women aged 21–24 than in those aged 25–29 or 30–64. Because excisional treatments can increase the risk of premature delivery, which is an especially important issue for younger women, our findings support efforts to manage women aged 21–24 with abnormal Pap results more conservatively than older women.

Acknowledgments

Role of the funding source

The funding sources did not review or approve the study design and were not involved in data collection, analysis, interpretation, or in writing the paper. The Intramural Research Program of the US National Institutes of Health/ National Cancer Institute and Kaiser Permanente Northern California reviewed the final manuscript for publication. The Kaiser Permanente Northern California Institutional Review Board (IRB) approved use of the data, and the National Institutes of Health Office of Human Subjects Research deemed this study exempt from IRB review.

References

1. Moscicki AB, Cox JT. Practice improvement in cervical screening and management (PICSM): symposium on management of cervical abnormalities in adolescents and young women. J Low Genit Tract Dis. 2010; 14(1):73–80. [PubMed: 20043357]
2. Arbyn M, Kyrgiou M, Simoens C, Raifu AO, Koliopoulos G, Martin-Hirsch P, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. BMJ. 2008; 337:a1284. [PubMed: 18801868]
3. Khalid S, Dimitriou E, Conroy R, Paraskevaidis E, Kyrgiou M, Harrity C, et al. The thickness and volume of LLETZ specimens can predict the relative risk of pregnancy-related morbidity. BJOG. 2012; 119(6):685–91. [PubMed: 22329499]
4. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain JM, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. J Low Genit Tract Dis. 2012; 16(3):175–204. [PubMed: 22418039]
5. Massad LS, Einstein M, Huh WK, Katki H, Kinney W, Schiffman M, et al. Updating guidelines for the management of abnormal cervcial cancer screening tests and cancer precursors. J Low Genit Tract Dis. in press.
6. Moore G, Fetterman B, Cox JT, Poitras N, Lorey T, Kinney W, et al. Lessons from practice: risk of CIN 3 or cancer associated with an LSIL or HPV-positive ASC-US screening result in women aged 21 to 24. J Low Genit Tract Dis. 2010; 14(2):97–102. [PubMed: 20354416]
7. Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol. 2011; 12(7):663–72. [PubMed: 21684207]
8. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002; 287(16):2114–9. [PubMed: 11966386]
9. Katki HA, Schiffman M, Castle PE, Fetterman B, Poitras NE, Lorey T, et al. Benchmarking CIN3+ risk as the basis for incorporating HPV and Pap cotesting into cervical screening and management guidelines. J Low Genit Tract Dis. In press.

10. Lawless, JF. Statistical models and methods for lifetime data. 2. Hoboken, N.J: Wiley-Interscience; 2003.

11. Turnbull B. The empirical distribution function with arbitrarily grouped, censored and truncated data. J Roy Stat Soc B. 1976; 38:290–5.

Table 1

Distribution of worst histologic diagnosis over 2003–2010 among women aged 21–24 at baseline by baseline Pap result (with HPV test triage of ASC-US).

	Total	Worst histologic diagnosis during follow-up								
Baseline Pap and HPV test result	**n**	**<CIN1, n**	**CIN1, n**	**CIN2, n**	**CIN3, n**	**AIS, n**	***Total CIN3 or AIS, n***	**Squamous carcinoma, n**	**Adeno-carcinoma, n**	***Total cancers, n***
Total	133,947	128,608	3,840	1,078	406	11	*418*	1	2	*3*
HSIL	251	114	33	60	43	0	*44*	0	0	*0*
ASC-H	454	232	91	84	46	1	*47*	0	0	*0*
AGC	87	57	17	7	4	1	*5*	0	1	*1*
LSIL	4,810	3,325	1,149	259	77	0	*77*	0	0	*0*
ASC-US	11,280	8,647	1,953	499	176	4	*180*	1	0	*1*
HPV-positive/ASC-US	6,976	4,611	1,750	451	159	4	*163*	1	0	*1*
HPV-negative/ASC-US	3,680	3,517	125	31	7	0	*7*	0	0	*0*
HPV-unknown/ASC-US	624	519	78	17	10	0	*10*	0	0	*0*
Pap-negative	117,065	116,233	597	169	60	5	*65*	0	1	*1*

Footnote: Total cancers also includes adenosquamous carcinoma, cervical cancer of unknown histology, and cervical cancer histology unrelated to HPV infection. The category “Total CIN3 or AIS” also includes 1 woman with a diagnosis that did not differentiate between CIN3 and AIS. “<CIN1” means either that no biopsy was taken, or a biopsy was taken but only normal or metaplastic histology was diagnosed.

J Low Genit Tract Dis. Author manuscript; available in PMC 2014 April 01.

Table 2

Cumulative 5-year risks of CIN3+ and cancer for women aged 21–24, 25–29, and 30–64 given Pap result and HPV test result for ASC-US. The overall ASC-US risks are for all ASC-US alone (regardless of HPV test result).

	CIN3+ risk (%)			Cancer risk (%)		
Baseline Pap and HPV test result	**21–24**	**25–29**	**30–64**	**21–24**	**25–29**	**30–64**
HSIL	28	28	47	0	2	7.3
ASC-H	16	24	18	0	1.5	2.6
AGC	6.9	14	8.5	1.1	1.1	2.7
LSIL	3	5	5.2	0	0	0.16
ASC-US	3	3.9	2.6	0.032	0.12	0.18
HPV-positive/ASC-US	4.4	7.1	6.8	0.055	0.16	0.41
HPV-negative/ASC-US	0.57	0.59	0.43	0	0.018	0.05
Pap-negative	0.2	0.36	0.26	0.004	0.027	0.011

J Low Genit Tract Dis. Author manuscript; available in PMC 2014 April 01.

Table 3

Benchmarking CIN3+ risks for Pap results and HPV test result for ASC-US among women aged 21–24 to risk thresholds implicitly used to determine clinical management options based on screening Pap tests among women aged 30–64.

Current recommended management strategy based on Pap-alone	Implicit risk threshold: 5-year CIN3+ risk by baseline Pap result alone (regardless of HPV result) among women aged 30–64[1]			5-year CIN3+ risk by baseline Pap result and HPV test result for ASC-US among women aged 21–24		
	Management defining result	***Frequency in women aged 30–64***	**CIN3+ risk**	**HPV/Pap result**	***Frequency in women aged 21–24***	**CIN3+ risk**
Immediate Colposcopy	LSIL	*0.97%*	5.2%	HSIL	*0.18%*	28%
				ASC-H	*0.34%*	16%
				AGC	*0.06%*	6.9%
6–12 month return	ASC-US	*2.8%*	2.6%	HPV+/ ASC-US	*5.2%*	4.4%
				LSIL	*3.6%*	3.0%
				ASC-US	*8.4%*	3.0%
3-year return	Pap-	*95.6%*	0.26%	HPV-/ ASC-US	*2.7%*	0.57%
				Pap-	*87.4%*	0.20%

[1] Data presented in: Katki HA, Schiffman M, Castle PE, Fetterman B, Poitras NE, Lorey T, et al. Benchmarking CIN3+ risk as the basis for incorporating HPV and Pap cotesting into cervical screening and management guidelines *J Low Genit Tract Dis* In press.