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Age-Stratified 5-Year Risks of Cervical Precancer among Women with Enrollment and Newly Detected HPV Infection

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Abstract

It is unclear whether a woman's age influences her risk of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) upon detection of HPV. A large change in risk as women age would influence vaccination and screening policies. Among 972,029 women age 30-64 undergoing screening with Pap and HPV testing (Hybrid Capture 2, Qiagen, Germantown, MD, USA) at Kaiser Permanente Northern California (KPNC), we calculated age-specific 5-year CIN3+ risks among women with HPV infections detected at enrollment, and among women with "newly detected" HPV infections at their second screening visit. 57,899 women (6.0%) had an enrollment HPV infection. Among the women testing HPV negative at enrollment with a second screening visit, 16,724 (3.3%) had a newly detected HPV infection at their second visit. Both enrollment and newly detected HPV rates declined with age ($p < .001$). Women with enrollment vs. newly detected HPV infection had higher 5-year CIN3+ risks: 8.5% vs. 3.9%, ($p < .0001$). Risks did not increase with age but declined slightly from 30-34 years to 60-64 years: 9.4% vs. 7.4% ($p = 0.017$) for enrollment HPV and 5.1% vs. 3.5% ($p = 0.014$) for newly detected HPV. Among women age 30-64 in an established screening program, women with newly detected HPV infections were at lower risk than women with enrollment infections, suggesting reduced benefit vaccinating women at older ages. Although the rates of HPV infection declined dramatically with age, the subsequent CIN3+ risks associated with HPV infection declined only slightly. The CIN3+ risks among older women are sufficiently elevated to warrant continued screening through age 65.

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Keywords

Human Papillomavirus (HPV); cancer prevention; cytology; cervical intraepithelial neoplasia (CIN); Hybrid Capture 2 (HC2); age

Introduction

Persistent cervical infection with carcinogenic human papillomavirus (HPV) is the necessary cause of cervical cancer¹⁻³. Consequently, the two main ways to prevent cervical cancer are primary prevention using prophylactic human papillomavirus (HPV) vaccines and screening based detection of HPV DNA, RNA, or HPV-associated cytologic (Pap) abnormalities^{4,5}.

The natural history of sexually transmitted HPV infection and cervical precancer dictates that HPV-based strategies for cervical cancer prevention change as women age. Vaccines are prophylactic and, thus, best targeted at girls several years before the median age of sexual initiation. Screening for HPV infection must be adapted to fit a woman's age as well. HPV testing is not suited to very young populations (under age 25 or 30) because the newly acquired HPV infections (incident infections) that are most common among young women are typically benign; these infections generally clear and become undetectable within a year or two. After an initial peak of HPV acquisition at younger ages, women are less likely to have an incident HPV infection⁶⁻⁸. Thus, prevalent HPV infections in younger women tend to be newly acquired whereas HPV infections detected in older women at screening (prevalent infections) tend to represent a longer-duration, persistent infection^{6,9,10}. Because persistent HPV infection is associated with progression to cervical precancer and cancer, HPV-based screening targets older women (i.e., age 25 or 30 and older)⁵.

The age-specific risks of cervical precancer and cancer among older women with prevalent HPV infection are not entirely understood. Because persistent infection with carcinogenic HPV is the true risk factor for cervical precancer and cancer, and because the proportion of prevalent infections that are persistent increases incrementally with age, it might be expected that a woman's risk of precancer following prevalent HPV detection would continue to increase with age (i.e., higher positive predictive value). Although logical, this simple model has not been consistently supported by data from cohort studies^{9,11-13}. It is possible that in a well-screened population, the aggressive persistent HPV infections are removed when women are screened at younger ages. The remaining persistent HPV infections found in older women would then be less aggressive. Limited evidence does support the related expectation that the occurrence of an incident HPV infection in an older woman, as in a woman of any age, has low risk of progression to precancer^{9,11,12,14}.

To understand better the effect of age on the meaning of prevalent and incident HPV infection, and to inform the discussion of the comparative benefits of HPV vaccination and screening as women age, we analyzed data from Kaiser Permanente Northern California (KPNC). Since 2003, women at KPNC have been screened with concurrent HPV and Pap testing ("cotesting"), allowing us to examine risk after HPV detection in a very large established screening program. We specifically examined the age-specific risk of cervical cancer or precancer over 5 years of follow-up among two cohorts of women with prevalent

and/or incident infections: 1) 57,899 women who were HPV-positive at enrollment into cotesting (prevalent infection that includes both persistent and/or incident HPV infections) and 2) 16,724 women with a “newly detected” HPV infection because they tested HPV-positive at their second screening visit after testing HPV negative at enrollment (more likely incident infection although re-appearing latent infection cannot be ruled out).

Material and Methods

The design of our cohort study within KPNC has been described previously^{15, 16}. Briefly, we assembled a cohort of 972,029 women aged 30–64 who enrolled in cotesting (concurrent HPV and Pap screening) in 2003–2012. We excluded women under age 30 and women age 65 and older, for whom routine cotesting is not recommended at KPNC, as well as 1.0% of women with unknown Pap results. For each woman, we considered as the enrollment screen the first available cotest in the study period. Biopsy and cancer information was collected from all women through December 31, 2012. 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.

Cotesting was performed on two separate specimens, with Pap tests performed on the first of the two co-collected specimens. Pap tests were evaluated at KPNC regional and facility labs. HPV tests were performed at the single 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 using BD SurePath (BD Diagnostics, Burlington, NC, USA) while continuing to test for HPV out of the FDA-approved standard transport medium. Conventional or liquid-based Pap tests are reported according to the 2001 Bethesda System¹⁷. Hybrid Capture 2 (hc2; Qiagen, Germantown, MD, USA) was used to test for high-risk HPV types according to manufacturer's instructions. Women were followed according to routine local practice: 1) HPV-positive/atypical squamous cells of undetermined significance (ASC-US) Pap or low-grade squamous intraepithelial lesion (LSIL) or more severe Pap regardless of the HPV result were referred to colposcopy; 2) HPV-negative/ASC-US Pap were rescreened in one year; and 3) women who tested HPV and Pap negative (cotest negative) were rescreened in three years. Of note, from 2003–2005, HPV-positive/Pap-negative women at KPNC were generally monitored annually for cytologic evidence of disease. Since 2006, women with two consecutive HPV-positive/Pap-negative results were offered colposcopy.

Among women with cotesting we defined two exclusive cohorts to distinguish between women with HPV infection detected at enrollment (presumed *a priori* to have a higher chance of being a higher risk persistent infection) and those with a newly detected HPV infection (presumed *a priori* to have a higher chance of being a lower risk incident infection). Women with an enrollment HPV infection were identified as women testing HPV positive upon enrollment into cotesting (considered their baseline test). Women with a newly detected HPV infection were identified as women testing HPV negative at enrollment, with a subsequent HPV positive result at their second screening visit (considered their baseline test). We excluded from the analysis of women with a newly detected

infection, those with LSIL or more severe Pap abnormalities at enrollment because these results are a sign of HPV infection, suggesting the possibility of a false-negative HPV DNA test. Thus, women in the analysis of newly detected HPV infection had Pap-negative or ASC-US Pap result at enrollment.

We focused primarily on risk of cervical intraepithelial neoplasia grade 3 (CIN3), adenocarcinoma *in situ* (AIS) or cancer (CIN3+) rather than CIN2+ because CIN2 is unreliably diagnosed by pathologists^{18, 19}, often regresses spontaneously^{20, 21}, and may simply reflect uncertainty in distinguishing acute HPV infection (CIN1) from CIN3².

Five-year risks of CIN3+ (and also CIN2+ for completeness) at time of HPV detection were estimated for 5-year age groups 30-34, ..., 60-64. We stratified risk estimates for women with enrollment HPV infection by concurrent Pap result. We grouped together non-negative Pap findings into three categories: low-grade (ASC-US and LSIL), atypical high-grade (atypical glandular cells and atypical squamous cells—cannot exclude HSIL), and high-grade (high-grade squamous intraepithelial lesion [HSIL], and squamous cell carcinoma). Smaller numbers did not allow for reliable Pap-stratified calculations among women with newly detected HPV-infection.

Cumulative 5-year risks of CIN3+ were calculated as the sum of risk at baseline test (whether at enrollment or the second visit, as appropriate for the analysis) and the risk after baseline. Risk at the baseline screen was the risk of CIN3+ for cotest results in which women were referred without further screening to colposcopy and was estimated using logistic regression, separately for women with enrollment and newly detected HPV infection. We used Weibull survival models²² 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-Meier²³, and naturally handle interval-censoring of disease outcomes between screening tests. Separate Weibull models were fit for each concurrent Pap result, with age group as a covariate. To compare 5-year CIN2+ and CIN3+ risks across age groups, we used weighted least squares regression to test for trends based upon the 5-year cumulative risk.

Results

At enrollment, 6.0% (n= 57,899) of 972,029 women tested HPV positive, i.e., had an enrollment HPV infection. HPV positivity declined with age ($p<.0001$) from 10.0% among women age 30-34 to 3.0% among women age 60-64 (Figure 1). Among 503,782 women testing negative (HPV negative and negative or ASC-US Pap) at the enrollment screen with HPV results at the second screening visit and therefore included in the newly detected HPV analysis, the average time between 1st and 2nd visits was 2.9 years (median 3.0 years, standard deviation 0.97 year. At their second screening visit 17,101 women tested HPV positive. Among them, 377 had an LSIL or more severe Pap abnormality at enrollment and were therefore excluded, leaving 16,724 women in the newly detected HPV analysis. Similar to enrollment HPV infections, the proportion of women with newly detected

infections declined with age ($p<.0001$) from 5.9% among women age 30-34 to 1.7% among women age 60-64.

Concurrent Pap results at the time of enrollment and newly detected HPV infection are presented in Table 1. Women with an enrollment HPV infection were more likely to have a concurrent high-grade Pap result compared with women with a newly detected HPV infection (3.5% vs. 1.4%, $p<.0001$). Among women with enrollment HPV infections, the proportion with a concurrent normal Pap result increased slightly from age 30-34 to 60-64 (56.5% vs. 69.3%, $p<0.0001$) as well as the proportion with a concurrent atypical high-grade Pap result (2.9% vs. 4.1%, $p=0.0002$). A similar trend was observed among women with newly detected HPV infections where 53.9% vs. 66.4% of women had a concurrent normal Pap (age 30-34 vs. age 60-64, $p<0.0001$) and 2.0% vs. 3.4% of women had a concurrent atypical high-grade Pap result (age 30-34 vs. age 60-64, $p=0.0046$).

The 5-year cumulative risks were higher among women with an enrollment vs. newly detected HPV infection: 17.7% ($n=7,663$) vs. 12.0% ($n=1,183$) for CIN2+ ($p<.0001$) and 8.5% ($n=3,543$) vs. 3.9% ($n=364$) for CIN3+ ($p<.0001$) (data not presented in figures). Figure 2 presents the 5-year cumulative CIN2+ and CIN3+ risks stratified by age. For both groups of women, the 5-year CIN3+ risks did not increase with age but declined slightly ($p=0.01$ for enrollment HPV infections and $p=0.046$ for newly detected HPV infections).

To assess the age-stratified risks among women with negative vs. low-grade vs. atypical high-grade vs. high-grade Pap, we further stratified 5-year risks of CIN2+ and CIN3+ by concurrent Pap result among women with an enrollment HPV infection (Figure 3). The 5-year risk of CIN3+ did not increase with age, and even declined slightly from 30-34 to 60-64 for all but high-grade Pap results (high-grade Pap: 54.9% to 59.7%, $p=0.63$; atypical high-grade Pap: 37.3 to 11.0%, $p=0.04$; low-grade Pap: 8.4% to 6.6%, $p=0.04$; negative Pap: 6.4% to 5.0%, $p=0.01$).

Discussion

Our data from the very large and long-established KPNC screening program showed that across all age groups from 30-34 to 60-64, the rates of both enrollment and newly detected HPV infections declined dramatically by age while the associated 5-year CIN3+ risk was higher among women with enrollment vs. newly detected HPV infection and did not increase with age, but declined slightly.

Findings from population-based cohort studies (usually among previously unscreened women) have suggested that HPV prevalence rates initially decline and then plateau among older women while HPV incidence rates continue to decline as women age⁶⁻¹⁰. At KPNC the coinciding decline of both enrollment and newly detected HPV infections was likely due to the fact that in this well-screened health services management population, many cases of precancer (and corresponding persistent HPV infections) are detected and removed early in a woman's screening history.

Population-based cohort studies also find that the risk of precancer/cancer among women with prevalently detected HPV infection increases with age^{9, 12, 24}. This is because older

women are more likely to have to a long-duration persistent, and therefore higher-risk, HPV infection^{9, 11-13}. We therefore expected the CIN3+ risk among women with an enrollment HPV infection to increase as well but, in fact, we saw the risks decline. When we considered concurrent Pap result, women screening HPV positive with a high-grade Pap were at similar risk across ages. Whereas, women with a low-grade or negative Pap experienced a slight decline in risk through age 45-59 followed by a small increase in risk after age 55. These small changes in age-associated risk might be caused by initial challenges of colposcopic assessment around menopause, followed by eventual diagnosis of previously undetected disease. It is noteworthy that two analyses from previously screened population-based cohorts found that among women with prevalent HPV infection and a concurrent Pap-negative result, the future risks of CIN3+ and cancer were higher among women over age 40 and 45^{9, 25}. Unlike the other studies, the observed risk among women age 60-64 was no higher than the risk among women age 30-44. It is also possible that women in KPNC had more intensive prior screening compared with these cohorts in Taiwan and Denmark. Repeated screening lowers the risk of invasive cancer among women by detecting and treating precancer early. Indeed, the bulk of CIN2/CIN3 cases are detected in KPNC and in other screened populations at ages 25-35²⁶.

We identified 16,724 women with a newly detected HPV infection and considered them a proxy for incident HPV infections, allowing us to explore possible age modification of both incident HPV infection and its associated risk of precancer or cancer. We expected, *a priori*, that newly detected infections would confer lower risk than enrollment HPV infections because infections detected at enrollment would have a greater chance of being a persistent and therefore at higher risk. We actually observed this lower risk among newly detected vs. enrollment HPV infections across all age groups, confirming that, regardless of age, the duration of an infection is important when determining the risk associated with an HPV infection.

Among women with newly detected HPV infection, we expected the low CIN3+ risk would be similar across ages and we found a slight decrease in risk of borderline statistical significance with lowest risks among women ages 45-49 and 50-54. Several studies suggest a similar decline in cervical cancer risk as women age, perhaps due to hormonal changes around peri-menopause^{27, 28}. Yet, this declining risk has not been observed in underscreened populations. The meaning of a newly detected HPV infection among older women is not entirely straightforward. We are unable to determine whether these newly detected infections resulted from a new sexually-acquired HPV infection or a reactivated latent infection acquired many years earlier^{14, 29}. Studies suggest that incident infections are most likely associated with not only new sexual activity but also lifetime number of sexual partners^{14, 29, 30}, supporting the possibility of the latent activation theory. Whether the few cases of precancer and cancer found among women in KPNC with newly detected HPV infection came from latent or newly acquired infection is unknown, but women with a newly detected HPV infection at KPNC were at very low risk of precancer and cancer in the subsequent 5 years. Because older women had few newly detected infections and those with a newly detected HPV infection were at low risk of cervical precancer, it is very unlikely that most older women would benefit from prophylactic HPV vaccination^{4, 31, 32}.

The KPNC cohort is from real-life clinical practice and is not a prospective natural history study where women are systematically followed to ascertain disease status across multiple time points. Subsequently, our analyses are subject to possible biases worth mentioning. First, the majority of women in this analysis (~60%) have a concurrent Pap result that is normal and (per KPNC guidelines) are not referred for immediate colposcopy, but instead return for screening in 1 year. To address this limitation, we present the cumulative risk of CIN2+ and CIN3+ at 5 years. We examined the risks at enrollment and 1 year and saw that age trends were similar to that observed at 5 years. Out of concern of an age-associated difference in detection of CIN2+, we also examined whether the follow-up rates (repeat screen and/or biopsy) varied by age and found no evidence of differential follow-up by age. A final age-related bias that we were unable to examine is the possible lower sensitivity of the colposcopically-guided biopsy exam itself in older women due to the inability to completely visualize and sample the transformation zone as women age³³. A recent study has suggested that the decline in cervical cancer incidence at older ages is an artifact of the higher prevalence of hysterectomy among older women³⁴.

Our data from one of the largest cohorts examining enrollment and newly detected HPV infection showed that women with newly detected HPV infections were at lower risk than women with enrollment infections, suggesting reduced benefit vaccinating women at older ages. Although the rates of HPV infection declined dramatically with age and the subsequent CIN3+ risks associated with HPV infection also declined slightly, the risks among older women are sufficiently elevated, even among women with a negative Pap, to warrant continued screening through age 65.

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Novelty and impact

In an established program screening of 1+ million women age 30-64 with HPV and Pap cotesting, women HPV positive at enrollment were at a higher 5-year risk of cervical precancer and cancer than women with newly detected HPV infection. HPV infection rates declined with age while associated risks did not rise with increasing age.

Figure 1.

(a) Among all women screened, the proportion of women with an HPV infection at enrollment and (b) among women testing HPV-negative and Pap negative or ASC-US at enrollment with a subsequent screening visit, the proportion with a newly detected HPV infection at the 2nd screening visit. For each age group the number of women tested at enrollment and at the second screening visit (HPV negative and Pap negative or ASC-US at enrollment) are presented. Enrollment and newly detected HPV infections declined significantly with age ($p < 0.0001$, and $p < 0.0001$, respectively). Shaded area represents 95% confidence intervals. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 2.

Age-stratified cumulative risk of CIN21 and CIN31 diagnosed up to 5 years after detection of HPV. Women with enrollment detected HPV infection tested HPV-positive at enrollment. Women with newly detected HPV infection tested HPV-positive at their second screening visit after a previously HPV-negative and negative or ASC-US Pap contest result at their enrollment screen. For 5-year risks of CIN21, the p-values for tests of trend across ages were 0.02 and 0.01 among women with prevalent and newly detected HPV infections, respectively. For 5-year risks of CIN31, the p-values for tests of trend across ages were 0.01 and 0.046 among women with enrollment and newly detected HPV infections, respectively. Shaded area represents 95% confidence intervals. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.].

Figure 3.

Age-stratified cumulative incidence of CIN21 and CIN31 diagnosed up to 5 years after enrollment HPV infection given concurrent Pap test result at enrollment. Tests of trend p-values for CIN21 were: 0.75 high-grade, 0.05 atypical high-grade, 0.07 low-grade, 0.03 negative; and for CIN31 were: 0.63 high-grade, 0.04 atypical high-grade, 0.04 low-grade, 0.01 negative. Low-grade Pap includes results of atypical squamous cells of undetermined significance (ASC-US) and low grade squamous intraepithelial lesion. Atypical high-grade includes atypical glandular cells and atypical squamous cells– cannot exclude HSIL. High-grade Pap includes high-grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.].

Table 1
Concurrent Pap result among women with enrollment and newly detected HPV infection

Age	Total enrollment HPV positive	Concurrent pap result			Total newly detected HPV	Concurrent pap result			
		Normal (%)	Low-grade (%)	Atypical high-grade (%)		High-grade (%)	Normal (%)	Low-grade (%)	Atypical high-grade (%)
Total	57,899	59.6	33.7	3.2	16,724	57.2	39.2	2.2	1.4
30–34	23,038	56.5	37.4	2.9	3,522	53.9	42.8	2.0	1.3
35–39	10,845	58.8	34.0	3.2	3,777	54.5	42.0	1.8	1.7
40–44	7,954	59.3	33.3	3.3	2,825	57.2	39.3	2.2	1.3
45–49	6,004	61.0	31.7	3.3	2,426	56.2	40.4	2.2	1.2
50–54	4,566	64.3	28.6	3.6	1,982	60.2	35.5	2.8	1.4
55–59	3,354	68.0	25.2	3.4	1,292	64.9	31.7	2.2	1.2
60–64	2,138	69.3	23.2	4.1	900	66.4	29.0	3.4	1.1

Low-grade Pap includes results of atypical squamous cells of undetermined significance (ASC-US) and low grade squamous intraepithelial lesion. Atypical high-grade includes atypical glandular cells and atypical squamous cells—cannot exclude HSIL. High-grade Pap includes high-grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma.

Newly detected HPV infections were women testing HPV-positive at the 2nd screening visit after testing HPV-negative and Pap negative or ASC-US at enrollment.

Chi-square test of trend for distribution of concurrent Pap results was <0.0001 among enrollment HPV and <0.0001 among newly detected HPV. Women with an enrollment HPV infection were more likely to have concurrent Pap result of high-grade as compared to women with a newly detected HPV infection ($p = <0.0001$).