

Five-Year Experience of Human Papillomavirus DNA and Papanicolaou Test Cotesting

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OBJECTIVE: To estimate the 5-year age group-specific test positives for Pap tests and human papillomavirus (HPV) testing in a large, general screening population of women 30 and older.

METHODS: Using data from Kaiser Permanente Northern California, a large health maintenance organization that introduced cotesting in 2003, we evaluated the cotesting results overall and by 5-year age groups. Women (n=580,289) who opted for and underwent cotesting (n cotests=812,598) between January 2003 and April 2008 were included in the analysis. Pap tests interpreted as atypical squamous cells of undetermined significance (ASC-US) or more severe were considered to be positive. Women were tested for carcinogenic HPV using an assay approved by the U.S. Food and Drug Administration. Binomial exact 95% confidence intervals (CIs) were calculated.

RESULTS: Overall, 6.27% (95% CI 6.21–6.32%) of cotests were carcinogenic HPV positive, and only 3.99% (95% CI 3.94–4.03%) cotests had normal cytology and were carcinogenic HPV positive. By comparison, 5.18% (95% CI 5.13–5.23%) of cotests had ASC-US or more severe cytology, and 2.87% (95% CI 2.84–2.91%) of cotests had ASC-US or more severe cytology and were carcinogenic HPV negative.

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CONCLUSION: In a general screening population, concerns about excessive HPV test positives among women aged 30 years and older are not borne out.

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LEVEL OF EVIDENCE: III

Although it has successfully reduced the burden of cervical cancer by 75% or more in the United States,¹ Pap test/cervical cytology is insensitive for the detection of precancer and cancer of the cervix² and must be repeated frequently to achieve programmatic effectiveness.³ A more efficient and accurate screen could greatly reduce the billions of dollars⁴ spent annually on the U.S. cytology-based system.

Based on the central role of persistent, carcinogenic human papillomavirus (HPV) in cervical carcinogenesis, carcinogenic HPV testing has recently been introduced into cervical cancer screening. Carcinogenic HPV testing has proven greater reproducibility^{5,6} and greater sensitivity for detection of cervical precancer (cervical intraepithelial neoplasia grade 3 [CIN 3]) and cancer (together, abbreviated here as CIN 3 or more severe)^{2,7–10} than cytology.

Carcinogenic HPV testing is now commonly used in the United States to triage equivocal cytology for colposcopic referral. Carcinogenic HPV testing with cytology is also accepted for primary screening of women aged 30 years and older,¹¹ who are past the peak of self-limited infections.¹² Women aged 30 years and older who test negative for carcinogenic HPV and are cytologically normal are at an extremely low risk for incipient precancer and cancer of the cervix for the subsequent 10 years or more.^{13,14} Therefore, the recommended screening interval for these women is no less than 3 years in the United States.

Despite the ability of HPV testing to detect 25–50% of lesions missed by a single cytology screen,



there are concerns about the addition of HPV testing because of the number of women aged 30 years and older who would test carcinogenic HPV positive but cytologic negative and therefore would require increased surveillance and clinical follow-up per current guidelines.¹¹ Recent epidemiologic data^{15,16} have raised concerns that the addition of HPV testing was undesirable because many cytologically normal women will be labeled and therefore stigmatized as being HPV positive, despite the utility of HPV testing to detect the 25–50% of the precancer and cancer missed by a single cytologic screen. To estimate the prevalence of Hybrid Capture 2-positive results in cytologically-normal women aged 30 and older in a representative general screening population with a much larger sample size, we analyzed the data collected at Kaiser Permanente Northern California, which instituted cotesting with Hybrid Capture 2 and conventional cytology in women aged 30 and older in 2003.

PARTICIPANTS AND METHODS

With the permission of Kaiser and National Cancer Institute institutional review boards, results of all Pap tests with HPV DNA tests collected within 7 days of one another (“cotests”) between January 2003 and April 2008 were assembled and tabulated from the laboratory databases. Human papillomavirus DNA testing for 13 carcinogenic HPV genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68) was performed using the U.S. Food and Drug Administration-approved Hybrid Capture 2 (Qiagen Corporation, Gaithersburg, MD) according to the manufacturer’s instructions. Cotests were excluded if the HPV testing was performed in duplicate or no result was available, or the Pap result was unsatisfactory or “other” (the 2001 Bethesda System general categorization used for “exfoliated endometrial cells present in a woman >40”). Pap tests that were interpreted as atypical squamous cells of undetermined significance (ASC-US), the threshold for referral to colposcopy (without an HPV test)^{11,17}, or more severe cytology were considered screen positives.

During the study period, 812,598 cotests were identified in 580,289 women aged 30 years and older, of which 1,376 cotests were excluded for HPV results (none available or duplicate), and 13,295 cotests were excluded for Pap results of “other” or “unsatisfactory,” leaving 797,927 cotests (98.2%) for analysis. These data included multiple cotests from some women, the results of which were included in the analysis because the primary focus was the screening results in the general population over a period of time rather than the point prevalence of carcinogenic HPV.

Individual and paired test results were compared with patient age, categorized into 5-year age groups from age 30 years to 79 years and grouping all women aged 80 years or older into an 80 years and older (80+) category. Cotesting was done according to Kaiser Permanente Northern California cervical cancer screening guidelines,¹⁸ including the screening of a small percentage of women aged 65 years and older (approximately 6.5% of all women cotested), for whom screening is recommended if they have either not had three or more documented, consecutive, technically satisfactory normal/negative cervical cytology tests after the age of 55 years or had an abnormal/positive cytology test for which HPV testing was indicated. Continued screening is also left to the discretion of the clinician if a woman aged 65 years or older tests HPV positive. These guidelines are consistent with national screening guidelines that recommend discontinuing cervical cancer screening above the age of 65 years (<http://www.ahrq.gov/>) or 70 years¹⁸ only when these women have had adequate recent screening with normal Pap tests and are not otherwise at high risk for cervical cancer.

Prevalence ratios (HPV/Pap) with 95% confidence intervals (CIs) were calculated to show the relative contribution of HPV to Pap for screening positive by cotesting. McNemar χ^2 was used to test for significant differences ($P < .05$) for testing HPV positive compared with testing positive by Pap tests for all women and by age group. Binomial exact 95% CIs were calculated for the overall and age group-specific HPV prevalence. We used NCSS 2004 (NCSS, Kaysville, UT) for statistical analyses.

RESULTS

The average and median age of women at the time of undergoing cotesting was 46 years and 44 years, respectively. The mean per capita and household incomes were \$27,869 and \$56,795, respectively. Self-reported race is available for approximately 2% of the reported cotests, and is very similar to the racial distribution in the 2006 census for the counties that Northern California Kaiser facilities serve. Table 1 shows the distribution of self-reported race, with 50.2% of women reported being white, 22.4% reported being Asian or Pacific Islander, 14.9% reported being Hispanic.

The results for Hybrid Capture 2 testing and conventional Pap tests by age are shown in Table 2. Overall, 6.27% (95% CI 6.21–6.32%) of 797,927 cotests were Hybrid Capture 2 positive at Kaiser. Women aged 30–34 years were the most likely (10.82%) to be Hybrid Capture 2 positive, and women aged 60–64 years were the least likely (3.67%) to be



Table 1. Distribution of Self-reported Race at Kaiser Permanente Northern California by 2% of 580,280 Women Aged 30 Years and Older Who Underwent Cotesting With Conventional Pap Tests and Carcinogenic HPV Testing by Hybrid Capture 2 From January 2003 Through April 2008

Self-reported Race	n	%
Asian/Pacific Islander	129,869	22.4
Black/African American	42,477	7.3
Hispanic	86,173	14.9
Native American/Aleutian/Eskimo	2,437	0.4
Other	15,784	2.7
Unknown	12,128	2.1
Total	580,289	100

Hybrid Capture 2 positive. There was a slight rise in testing Hybrid Capture 2 positive among women aged 70 years and older (4.31% in 70- to 74-year olds, 4.36% in 75- to 79-year-olds, and 5.27% in 80-year-olds and older) compared with women aged 60–64 years. Only 3.99% (95% CI 3.94–4.03%) cotests had normal cytology and were Hybrid Capture 2 positive. Cytologically normal women aged 30–34 years were the most likely (6.76%) to test Hybrid Capture 2 positive, whereas women aged 60–64 years were the least likely (2.56%). The age-specific percentages of testing Hybrid Capture 2 positive with 95% confidence intervals are shown in Figure 1.

By comparison, 5.18% (95% CI 5.13–5.23%) of all cotests had ASC-US or more severe cytology. Cotest-

ing women aged 30–34 years were the most likely (6.48%) to have an ASC-US or more severe cytology, and cotesting women aged 60–64 years were the least likely (3.17%) to test Hybrid Capture 2 positive. Of note, 2.87% (95% CI 2.84–2.91%) of cotests in women aged 30 years and older had ASC-US or more severe cytology and tested Hybrid Capture 2 negative. Women aged 45–49 years were the most likely (3.77%) to have ASC-US or more severe cytology and test Hybrid Capture 2 negative.

DISCUSSION

In our experience of 800,000 cotests, we found that the likelihood of testing Hybrid Capture 2 positive was much less than was previously reported in smaller epidemiologic studies or selected populations in the United States.^{15,16} The percentage of carcinogenic HPV test positives, as measured using Hybrid Capture 2, was 6.27%. Not surprisingly, the highest percentage of Hybrid Capture 2 positives was found in women aged 30–34 years (10.82%) and women aged 35–39 years (8.03%), in the age group of Kaiser Permanente Northern California female membership with highest prevalence of CIN 2/3 (data not shown). These data are consistent with the prevalence of HPV in women of those ages participating in the HPV Sentinel Surveillance project,¹⁵ in which more than half of the women enrolled in that study were between the ages of 30 and 39 years and thus partially explaining the observed high HPV prevalence. There was the expected and pronounced decrease in HPV

Table 2. A Summary of Results From Cotesting With Conventional Pap Tests and Carcinogenic Human Papillomavirus Testing by Hybrid Capture 2 by 5-Year Age Groups

Age Group (y)	n	%	Pap+	HPV+	Pap-/HPV-	Pap+/HPV-	Pap-/HPV+	Pap+/HPV+	Prevalence Ratio (95% CI)	P*
30–34	133,835	16.77	6.48	10.82	86.75	2.43	6.76	4.06	1.67 (1.64–1.70)	<.001
35–39	124,673	15.62	5.74	8.03	89.25	2.71	5.01	3.03	1.40 (1.37–1.43)	<.001
40–44	122,384	15.34	5.83	6.31	90.36	3.33	3.81	2.50	1.08 (1.06–1.11)	<.001
45–49	117,776	14.76	5.57	4.89	91.35	3.77	3.08	1.81	0.876 (0.852–0.902)	<.001†
50–54	102,631	12.86	4.77	4.33	92.34	3.33	2.89	1.44	0.908 (0.878–0.939)	<.001†
55–59	85,365	10.70	3.76	3.85	93.52	2.63	2.72	1.13	1.02 (0.983–1.07)	.3
60–64	59,328	7.44	3.17	3.67	94.26	2.06	2.56	1.11	1.16 (1.10–1.22)	<.001
65–69	28,059	3.52	3.28	3.70	94.13	2.17	2.59	1.12	1.13 (1.05–1.21)	<.001
70–74	13,183	1.65	3.46	4.31	93.61	2.09	2.94	1.37	1.25 (1.13–1.38)	<.001
75–79	7,049	0.88	3.89	4.36	93.25	2.40	2.87	1.49	1.12 (0.984–1.28)	.09
80+	3,644	0.46	4.45	5.27	92.54	2.20	3.02	2.25	1.19 (1.02–1.38)	.03
Total	797,927	100	5.18	6.27	90.83	2.90	3.99	2.28	1.21 (1.20–1.22)	<.001

HPV, human papillomavirus; CI, confidence interval.

Data are % except where otherwise specified.

Data are from the Kaiser Permanente Northern California Health Plan from January 2003 through April 2008. Prevalence ratio (HPV/Pap) is the ratio of the prevalence of a positive HPV test to the prevalence of a positive cytologic interpretation.

* McNemar χ^2 test.

† Statistically significantly greater number of Pap positives compared with human papillomavirus positives.



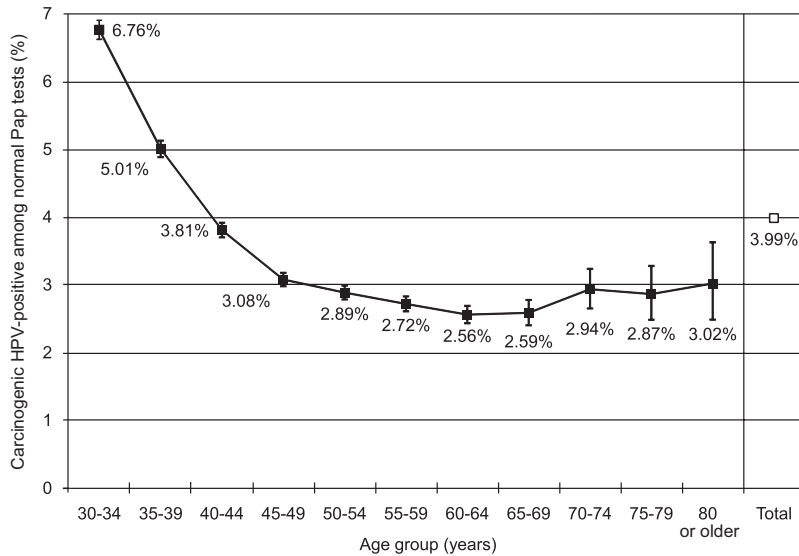


Fig. 1. Percentage of woman with normal Pap tests who tested positive for carcinogenic human papillomavirus (HPV) by Hybrid Capture 2 by age group (black squares) and for all women aged 30 years and older (white squares). Data from the Kaiser Permanente Northern California Health Plan from January 2003 through April 2008. HPV, human papillomavirus.

Castle. Human Papillomavirus DNA and Pap Cotesting. *Obstet Gynecol* 2009.

prevalence in the older Kaiser Permanente Northern California female membership. Thus, the concerns raised about introduction of HPV testing into clinical practice¹⁹ may be seen to have been overstated when population screening data are considered.

Although these are data from a large population, we point out that these data may not be generalizable to all populations worldwide. The likelihood of testing HPV positive in conjunction with cotesting is population specific and depends on the age and risk behaviors in that population.

The percentage of Hybrid Capture 2 positive results among cytologically normal women observed at Kaiser (3.99%) was similar to the percentage (3.7%) of carcinogenic HPV positives in cytologically normal women reported in a population-based study of 44,102 women using a GP5+/6+ polymerase chain reaction assay, which has shown to have comparable clinical performance to Hybrid Capture 2.²⁰ The percentage is also similar to the median percentage of HPV positives (4%) in all women aged 30 years and older as reported in a survey conducted by the College of American Pathologists.²¹ Interestingly, we found that the likelihood of testing carcinogenic HPV positive but cytologic negative to be only slightly more common than the likelihood of testing carcinogenic HPV negative but cytologic positive (3.99% compared with 2.90%), which is primarily (HPV-negative) ASC-US cytology (82.8%) that bears a very low risk of CIN 2/³²² but also requires increased surveillance and clinical follow-up according to current guidelines.¹¹

Although Kaiser uses conventional Pap tests for detection of cytologic abnormalities while approxi-

mately 90% of U.S. clinics rely on liquid-based cytology, a recent meta-analysis²³ indicates that liquid-based cervical cytology is *not* more sensitive and may be less specific for detection of high-grade cervical intraepithelial neoplasia than the Pap test. Thus, the use of liquid-based cervical cytology, widely adopted in advance without evidence of greater screening accuracy compared with conventional Pap tests,²⁴ would be expected to increase the proportion of test positives by cytology, including false positives. Regardless, the use of Pap test (compared with liquid-based cytology) at Kaiser does not alter our observations about HPV testing.

Recognition of cytologically normal, HPV-negative women is important because extension of screening intervals from 1 to 3 years based on negative cytology alone, despite being preceded by three consecutive negative cytology results, triples the risk of invasive cervical cancer.²⁵ Although unfamiliar with the research, many women and providers intuitively understand that fewer Pap tests mean more cancer risk, and the majority of women and medical care providers participating in screening in our population and that of the Southern California Kaiser Permanente Medical Care Plan were unwilling to accept recommendations made by the Kaiser clinicians in the 1980s and 1990s to abandon annual screening with cytology alone in favor of longer screening intervals (data not shown).

As the morbidities associated with the treatment of dysplasia have become more apparent,²⁶⁻²⁸ and it has been recognized that half of CIN 2 (which is routinely treated) regresses in 24 months,^{29,30} the



adverse consequences for the patient of annual screening come into sharper focus. Currently Kaiser Permanente Northern California offers screening with Pap and HPV at 3-year intervals or screening with cytology at more frequent intervals to our female members aged 30 years and older. During the period from December 1, 2006, through February 26, 2007, 91.6% of Kaiser Permanente Northern California members aged 30 years and older who participated in screening elected the cotesting option (screening every 3 years if Pap and HPV were both negative) instead of annual screening. Providing the reassurance required to move away from annual screening is one of the benefits of cotesting that we have observed.


We will be conducting subsequent analyses on the predictive values for CIN 2 or more severe, CIN 3 or more severe, and cancer of all pair-wise cotesting results. However, we already recognize that women who test positive for carcinogenic HPV and negative by cytology are at an elevated risk for cervical precancer and cancer compared with women who test negative on both,^{13,31} and yet the positive predictive value of a single Pap-negative, HPV-positive cotest for CIN 3 or more severe remains less than ideal. Thus, the development of a viable strategy for identifying the subset of Pap-negative; HPV-positive women at highest risk of CIN 3 or more severe would further improve the efficiency of secondary cervical cancer prevention. Future clinical research will need to focus on identifying the best strategies for managing women who test positive for carcinogenic HPV and negative by cytology, which may include HPV genotyping for HPV16, HPV18, and possibly HPV45^{11,32,33} or immunodetection of p¹⁶INK4a.³⁴

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