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

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Abstract

Objective—To estimate the 5-year age group-specific test positives for Papanicolaou (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 (CI) were calculated.

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

Conclusions—In a general screening population, concerns about excessive HPV test positives among women 30 and older are not borne out.

Introduction

While it has successfully reduced the burden of cervical cancer by 75% or more in the U.S. (1), Papanicolaou (Pap) smear/cervical cytology is insensitive for the detection of precancer and cancer of the cervix (2) and must be repeated frequently to achieve programmatic effectiveness (3). A more efficient and accurate screen could greatly reduce the billions of dollars (4) spent annually on the U.S. cytology-based system.

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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 [CIN3]) and cancer (together, abbreviated here as $\geq$ CIN3)(2;7–10) than cytology.

Carcinogenic HPV testing is now commonly used in the U.S. to triage equivocal cytology for colposcopic referral. Carcinogenic HPV testing with cytology is also approved 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 30 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 epidemiological data (15;16) has 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 hc2 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 co-testing with hc2 and conventional cytology in women aged 30 and older in 2003.

Methods

With the permission of Kaiser and National Cancer Institute Institutional Review Boards, results of all Pap smears 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. HPV DNA testing for 13 carcinogenic HPV genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68) was performed using the Food and Drug Administration-approved Hybrid Capture 2 (hc2; Qiagen Corporation, Gaithersburg, MD, USA) 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”). Paps 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 ($\geq$ ASC-US) were considered screen positives.

During the study period 812,598 cotests were identified in 580,289 women age 30 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.

Individual and paired test results were compared to patient age, categorized into 5-year age groups from age 30 to 79 and grouping all women 80 and older into an 80 and older (80+) category. Cotesting was done according to KPNC cervical cancer screening guidelines (18), including the screening of a small percentage of women 65 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 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 65 or older tests HPV positive. These guidelines are consistent with national screening guidelines that recommend discontinuing cervical cancer screening above the age of 65 (<http://www.ahrq.gov/>) or 70 (18) only when these women have had adequate recent screening with normal Pap smears and are not otherwise at high risk for cervical cancer.

Prevalence ratios (HPV/Pap) with 95% confidence intervals (95%CI) were calculated to show the relative contribution of HPV to Pap for screening positive by cotesting. McNemar's chi square test was used to test for statistical differences ($p < 0.05$) for testing HPV positive versus testing positive by Pap smears for all women and by age group. Binomial exact 95%CI were calculated for the overall and age group-specific HPV prevalence. NCSS 2004 (Kaysville, Utah) was used for statistical analyses.

Results

The average and median age of women at the time of undergoing cotesting were 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 hc2 testing and conventional Pap smears by age are shown in Table 2. Overall, 6.27% (95%CI = 6.21%–6.32%) of 797,927 cotests were hc2 positive at Kaiser. Women aged 30–34 were the most likely (10.82%) to be hc2 positive, and women aged 60–64 were the least likely (3.67%) to be hc2 positive. There was a slight rise in testing hc2 positive among women aged 70 and older (4.31%–5.27%) compared to women aged 60–64. Only 3.99% (95%CI = 3.94%–4.03%) cotests had normal cytology and were hc2 positive. Cytologically normal women aged 30–34 were the most likely (6.76%) to test hc2 positive while women aged 60–64 were the least likely (2.56%). The age-specific percentages of testing hc2 positive with 95% confidence intervals are shown in Figure 1.

By comparison, 5.18% (95%CI = 5.13%–5.23%) of all cotests had $\geq$ ASC-US cytology. Cotesting women aged 30–34 were the most likely (6.48%) to have an $\geq$ ASC-US cytology, and cotesting women aged 60–64 were the least likely (3.17%) to test hc2 positive. Of note, 2.87% (95%CI = 2.84%–2.91%) of cotests in women 30 and older had $\geq$ ASC-US cytology and tested hc2 negative. Women aged 45–49 were the most likely (3.77%) to have $\geq$ ASC-US cytology and test hc2 negative.

Discussion

In our experience of eight hundred thousand cotests, we found that the likelihood of testing hc2 positive was much less than was previously reported in smaller epidemiological studies or selected populations in the U.S. (15;16). The percentage of carcinogenic HPV test positives, as measured using hc2, was 6.27%. Not surprisingly, the highest percentage of hc2 positives was found in women 30–34 (10.82%) and women 35–39 (8.03%), in the age group of KPNC female membership with highest prevalence of CIN2/3 (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 30–39 and thus partially explaining the observed high HPV prevalence. There was the expected and pronounced decrease in HPV prevalence in the older KPNC female membership. Thus, the concerns raised about introduction of HPV testing into clinical practice (19) 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 hc2 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+ PCR assay, which has shown to have comparable clinical performance to hc2 (20). The percentage is also similar to the median percentage of HPV positives (4%) in all women 30 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% vs. 2.90%), which is primarily (HPV-negative) ASC-US cytology (82.8%) that bears a very low risk of CIN2/3 (22) but also requires increased surveillance and clinical follow-up according to current guidelines (11).

Although Kaiser uses conventional Pap smears for detection of cytologic abnormalities while ~90% of U.S. clinics rely on liquid-based cytology, a recent meta-analysis (23) 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 smear. Thus, the use of LBC, widely adopted in advance without evidence of greater screening accuracy versus conventional Pap smears (24), would be expected to increase the proportion of test positives by cytology, including false positives. Regardless, the use of Pap smear 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 one to three years based on negative cytology alone, despite being preceded by three consecutive negative cytology results, triples the risk of invasive cervical cancer (25). While unfamiliar with the research, many women and providers intuitively understand that fewer Paps 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 CIN2 (which is routinely treated) regresses in 24 months (29;30), the adverse consequences for the patient of annual screening come into sharper focus. Currently KPNC offers screening with Pap and HPV at 3-year intervals or screening with cytology at more frequent intervals to our female members age 30 and above. During the period from December 1, 2006 through February 26, 2007, 91.6% of KPNC members age 30 and older who participated in screening elected the cotesting option (screening every three 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 $\geq$ CIN2, $\geq$ CIN3, 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 to women who test negative on both (13;31), and yet the positive predictive value of a single Pap-negative HPV-positive cotest for $\geq$ CIN3 remains less than ideal. Thus, the development of a viable strategy for identifying the subset of women at highest risk of $\geq$ CIN3 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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Figure 1.

Percentage of woman with normal Papanicolaou (Pap) tests who tested positive for carcinogenic human papillomavirus (HPV) by Hybrid Capture 2 (hc2+) by age group (black squares) and for all women 30 and older (white squares). Data from the Kaiser Permanente Northern California Health Plan from January 2003 through April 2008.

Table 1

Distribution of self-reported race at KPNC by 2% of 580,280 women 30 and older who underwent cotesting with conventional Pap smears 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%
White	291,363	50.2%
total	580,289	100%

Table 2

A summary of results from cotesting with conventional Pap smears and carcinogenic HPV testing by Hybrid Capture 2 by 5-year age groups. Data are from the Kaiser Permanente Northern California Health Plan from January 2003 through April 2008. Prev. Ratio (HPV/Pap), ratio of the prevalence of a positive HPV test to the prevalence of a positive cytologic interpretation

Age Group (Years)	N	%	%Pap+	%HPV+	%Pap−/HPV−	%Pap+/HPV−	%Pap−/HPV+	%Pap+/HPV+	Prev. Ratio HPV/Pap) (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)	<0.001
35–39	124,673	15.62%	5.74%	8.03%	89.25%	2.71%	5.01%	3.03%	1.40 (1.37–1.43)	<0.001
40–44	122,384	15.34%	5.83%	6.31%	90.36%	3.33%	3.81%	2.50%	1.08 (1.06–1.11)	<0.001
45–49	117,776	14.76%	5.57%	4.89%	91.35%	3.77%	3.08%	1.81%	0.876 (0.852–0.902)	<0.001*
50–54	102,631	12.86%	4.77%	4.33%	92.34%	3.33%	2.89%	1.44%	0.908 (0.878–0.939)	<0.001*
55–59	85,365	10.70%	3.76%	3.85%	93.52%	2.63%	2.72%	1.13%	1.02 (0.983–1.07)	0.3
60–64	59,328	7.44%	3.17%	3.67%	94.26%	2.06%	2.56%	1.11%	1.16 (1.10–1.22)	<0.001
65–69	28,059	3.52%	3.28%	3.70%	94.13%	2.17%	2.59%	1.12%	1.13 (1.05–1.21)	<0.001
70–74	13,183	1.65%	3.46%	4.31%	93.61%	2.09%	2.94%	1.37%	1.25 (1.13–1.38)	<0.001
75–79	7,049	0.88%	3.89%	4.36%	93.25%	2.40%	2.87%	1.49%	1.12 (0.984–1.28)	0.09
80+	3,644	0.46%	4.45%	5.27%	92.54%	2.20%	3.02%	2.25%	1.19 (1.02–1.38)	0.03
Total	797,927	100%	5.18%	6.27%	90.83%	2.90%	3.99%	2.28%	1.21 (1.20–1.22)	<0.001

‡ McNemar’s chi-square test.

* Statistically significantly greater number of Pap positives vs. HPV positives.