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Effect of Several Negative Rounds of Human Papillomavirus and Cytology Co-testing on Safety Against Cervical Cancer

An Observational Cohort Study

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Background: Current U.S. cervical cancer screening and management guidelines do not consider previous screening history, because data on multiple-round human papillomavirus (HPV) and cytology "co-testing" have been unavailable.

Objective: To measure cervical cancer risk in routine practice after successive negative screening co-tests at 3-year intervals.

Design: Observational cohort study.

Setting: Integrated health care system (Kaiser Permanente Northern California, Oakland, California).

Patients: 990 013 women who had 1 or more co-tests from 2003 to 2014.

Measurements: 3- and 5-year cumulative detection of (risk for) cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ, and cervical cancer (≥CIN3) in women with different numbers of negative co-tests, overall and within subgroups defined by previous co-test results or baseline age.

Results: Five-year ≥CIN3 risks decreased after each successive negative co-test screening round (0.098%, 0.052%, and 0.035%). Five-year ≥CIN3 risks for an HPV-negative co-test, regardless of the cytology result, nearly matched the performance (reassurance) of a negative co-test for each successive round of screening (0.114%, 0.061%, and 0.041%). By comparison, ≥CIN3 risks for the cytology-negative co-test, regardless of the HPV result, also decreased with each successive round, but 3-year risks were as high as 5-year risks after an HPV-negative co-test (0.199%, 0.065%, and 0.043%). No interval cervical cancer cases were diagnosed after the second negative co-test. Independently, ≥CIN3 risks decreased with age. Length of previous screening interval did not influence future ≥CIN3 risks.

Limitation: Interval-censored observational data.

Conclusion: After 1 or more negative cervical co-tests (or HPV tests), longer screening intervals (every 5 years or more) might be feasible and safe.

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Human papillomavirus (HPV) causes virtually all cases of cervical cancer and its precursors. Vaccination against HPV is the definitive preventive strategy but will take decades to reduce cancer rates; thus, screening remains very important. Testing for HPV is more sensitive than cytology for detecting treatable cervical cancer and precancer, including cervical intraepithelial neoplasia grade 3 (CIN3) and adenocarcinoma in situ (AIS) (1–6). On the basis of that evidence, current U.S. guidelines for cervical cancer screening recommend concurrent high-risk HPV and cytology testing (that is, "co-testing") at 5-year intervals, with cytology every 3 years as an acceptable alternative (7–9). An interim guidance proposed HPV testing every 3 years as an alternative to cytology every 3 years (10). The U.S. Preventive Services Task Force (USPSTF) now has draft recommendations for HPV testing every 5 years for cervical cancer screening starting at age 30 years (11). However, the length of experience with strategies incorporating HPV testing has been short.

See also:

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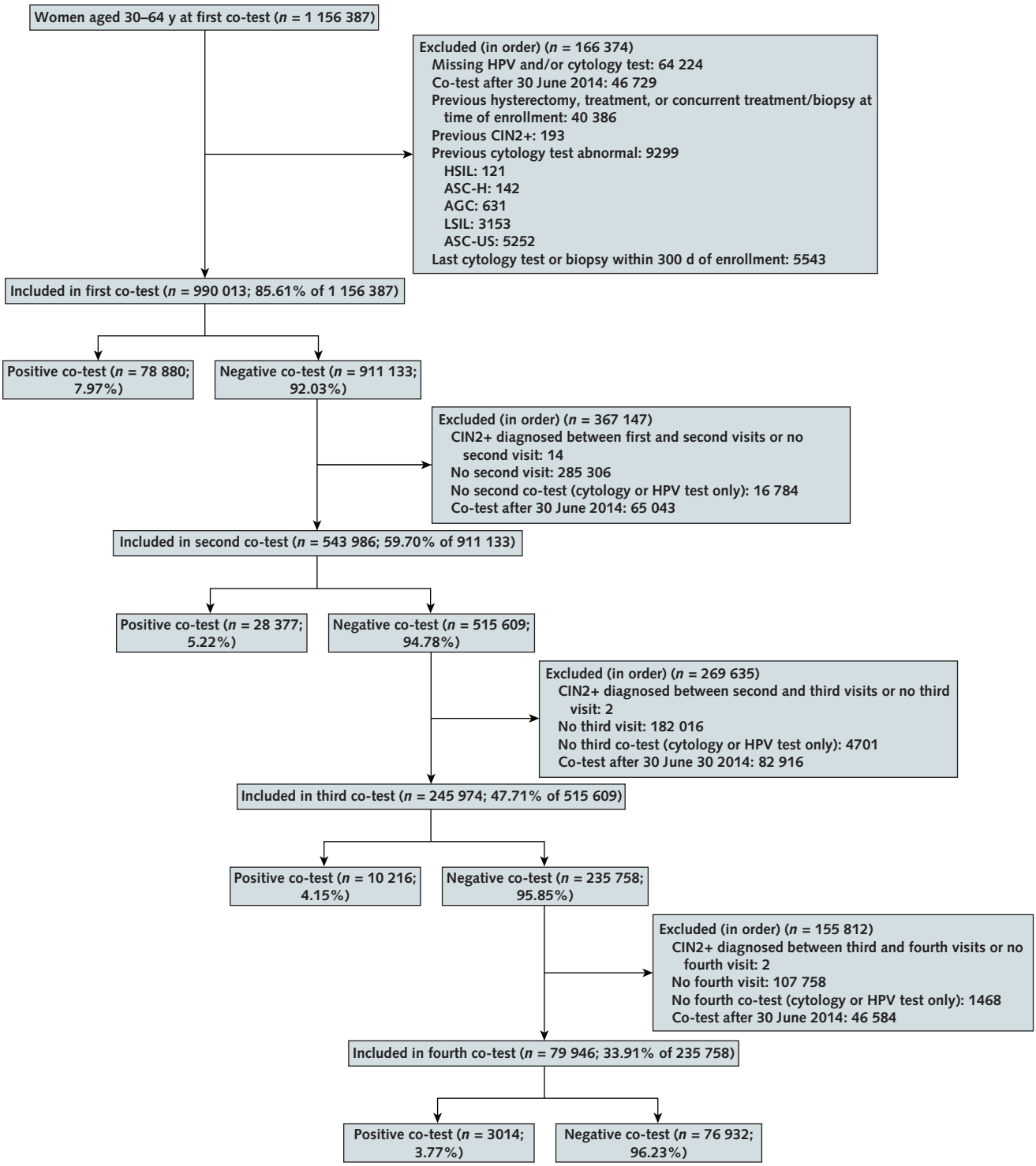
It is accepted that the greater sensitivity of cervical screening for CIN3, AIS, and invasive cervical cancer (grouped together here as ≥CIN3) when HPV testing is included translates into greater reassurance against subsequent ≥CIN3 or invasive cervical cancer after a negative screening result (6, 12, 13), allowing screening intervals to be extended without compromising safety. However, most of the published evidence on HPV-based screening is from a single round of cervical cancer screening. Some randomized controlled trials have used several screening rounds, but very few cancer cases are diagnosed after the first round (14–16). Longer-term, multiple-round follow-up in actual clinical practice is required to calculate the risk for ≥CIN3 or invasive cervical cancer after a series of negative screens that include HPV testing in routine practice.

Data from routine practice are now available from Kaiser Permanente Northern California (KPNC), where co-testing for women aged 30 years or older, with the screening interval extended to 3 years after a negative co-test, was implemented in 2003 and 2004. More than 1 million women aged 30 years or older had at least 1 co-test during 12 years at KPNC, and a small but clinically meaningful number of women (~80 000) had up to 4 rounds of co-testing, allowing the safety of 3 consecutive screening intervals to be evaluated.

Figure 1. CONSORT diagram of study inclusions and exclusions, by screening round.



AGC = atypical glandular cells; ASC-H = atypical squamous cells, cannot exclude HSIL; ASC-US = atypical squamous cells of undetermined significance; CIN2+ = cervical intraepithelial neoplasia grade 2 positivity; CONSORT = Consolidated Standards of Reporting Trials; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.

Although KPNC currently uses co-testing every 3 years rather than standalone HPV testing every 3 years (10) or co-testing every 5 years (8), strong evidence suggests that the 3-year risk for ≥CIN3 or invasive cervical cancer after negative HPV and cytology tests (that is, a negative co-test) is only slightly more reassuring than the 3-year risk for ≥CIN3 after a negative HPV test or the 5-year risk for ≥CIN3 after a negative co-test, because the negative HPV test is what effectively rules out disease (15). Moreover, analysis of co-testing results may be used to infer the safety of HPV testing every 3 years. Because not all women return exactly at 3 years, these data also may be used to estimate risks for co-testing every 5 years. We therefore analyzed KPNC data to determine the effect of a history of negative co-tests, at 3 or 5 years, on safety against ≥CIN3 or invasive cervical cancer after negative co-test, HPV test, or cytology results.

METHODS

Population

The cohort study within KPNC was described previously (17). From 1 January 2003 to 31 December 2015, a total of 1 156 387 women aged 30 to 64 years underwent co-testing. For each woman, we considered the first available co-test in this study period as "enrollment." Cervical histopathology outcomes were collected for women through 31 December 2015. The KPNC institutional review board approved use of the data, and the institutional review boards of the National Institutes of Health Intramural Research Program's Human Research Protections Program and Albert Einstein College of Medicine deemed the use of these de-identified data exempt from review.

Screening and Clinical Management

Women underwent co-testing as previously described (15). Cytologic interpretations were based on the Bethesda System for cytology classification (18). Hybrid Capture 2 (Qiagen) was used for HPV testing. Women were followed according to internal Kaiser guidelines that were broadly concordant with national standards at the time (19–22). Women with HPV- and cytology-negative (HPV−/Cyto−) co-test results were offered screening again in 3 years. Women with definite cytologic abnormalities were referred to colposcopy in accordance with national recommendations (19, 22, 23). The KPNC management of women with HPV-positive and Cyto− (HPV+/Cyto−) or HPV− equivocal ("atypical squamous cells of undetermined significance") results led to retesting at 1 to 3 years, with intervals that evolved over time, as previously described (17). Observation with repeated colposcopy was elected for some younger women with cervical intraepithelial neoplasia grade 2 (CIN2), as nationally recommended (23, 24).

Statistical Analyses

The CONSORT (Consolidated Standards of Reporting Trials) diagram of inclusions and exclusions, by screening round, is shown in **Figure 1**. Starting with a cohort of 1 156 387 women aged 30 to 64 years at the time of the first co-test, 990 013 were included in the analysis of the first co-test, 543 986 for the second co-test, 245 974 for the third co-test, and 79 946 for the fourth co-test after 0, 1, 2, and 3 previously negative co-tests. **Appendix Table 1** (available at Annals.org) provides details regarding prevalent and incident disease, censoring, and losses to follow-up. **Appendix Table 2** (available at Annals.org) shows the number of women at risk at each time point for each co-test. Mean and median ages, respectively, were 43.9 and 42 years for the first, 47.7 and 47 years for the second, and 50.1 and 50 years for the third co-test. Mean and median screening intervals, respectively, were 3.1 and 3.0 years between the first and second, 2.9 and 3.0 years between the second and third, and 2.8 and 2.9 years between the third and fourth co-tests.

Risks were estimated by using a logistic regression model for prevalent disease and a Weibull survival model for incident disease (logistic-Weibull prevalence–incidence mixture model) (**Appendix**, available at Annals.org). The Weibull assumption makes smoother and more accurate risk estimates than nonparametric methods analogous to Kaplan–Meier, naturally handles interval censoring of disease outcomes between screening tests, and allows for easy interpretation of covariate effects (25). Parameters for the logistic regression and Weibull survival model were estimated jointly to allow for the possibility that some disease found in follow-up actually may have been missed prevalent disease. We estimated variance on the complementary log–log survival scale to calculate 95% CIs and then transformed the intervals back to the cumulative risk scale.

Primary end points were 3- and 5-year cumulative detection of ("risk for") cervical cancer (3- and 5-year cervical cancer risk) and 3- and 5-year cumulative detection of ≥CIN3 (3- and 5-year ≥CIN3 risk). We focused on 3- and 5-year risks for an HPV−/Cyto− co-test, 3- and 5-year risks for an HPV− test, and 3-year risks for a Cyto− test, because current KPNC, national, and international guidelines recommend these intervals (8, 10, 26). Although a negative screen should provide reassurance against overt invasive cervical cancer, the numbers of cervical cancer cases were insufficient to conduct subgroup-specific analyses to evaluate confounding and effect modification by covariates. We therefore used ≥CIN3, the best surrogate for cervical cancer risk, for subgroup analyses. Only 5-year risks were reported for subgroup analyses. However, similar results for subanalyses were observed for 3-year risks (data not shown). Case ascertainment was done through electronic medical records and a KPNC-wide cancer registry.

We calculated 3- and 5-year cervical cancer and ≥CIN3 risks for an HPV−/Cyto− co-test after increasing numbers of negative co-tests, that is, after 0, 1, and 2 negative co-test(s), respectively. We also assessed the relative contributions of the HPV and cytology components of co-testing by repeating the analyses for each, regardless of the other: an HPV− co-test regardless of

Table 1. Cumulative Detection of (Risk for) Cervical Cancer at 3 and 5 Years After Screening, by HPV Testing and Cytologic Evaluation Based on Screening History and Negative Test Results

Co-test Number	Patients, *n*	Invasive Cervical Cancer					
		End Point, *n*	Noninformative Results, *n*	3 Years		5 Years	
				Risk (95% CI), %	*P* Value*	Risk (95% CI), %	*P* Value*
HPV−							
1†	931 567	61	295 200	0.0081 (0.0062–0.0106)	–	0.0092 (0.0071–0.0118)	–
2‡	527 014	13	186 682	0.0038 (0.0022–0.0066)	0.010	0.0038 (0.0022–0.0066)	0.003
3§	239 684	2	109 876	0.0015 (0.0004–0.0062)	0.143	0.0015 (0.0004–0.0062)	0.143
P for trend				<0.001		<0.001	
Cyto−							
1†	945 152	107	298 309	0.0140 (0.0115–0.0171)	–	0.0160 (0.0132–0.0193)	–
2‡	525 221	15	186 343	0.0043 (0.0026–0.0072)	<0.001	0.0045 (0.0027–0.0074)	<0.001
3§	239 209	3	109 474	0.0023 (0.0007–0.0072)	0.43	0.0023 (0.0007–0.0072)	0.186
P for trend				<0.001		<0.001	
HPV−/Cyto−‖							
1†	911 133	42	291 571	0.0054 (0.0039–0.0075)	–	0.0064 (0.0047–0.0086)	–
2‡	515 609	10	184 964	0.0030 (0.0016–0.0056)	0.077	0.0030 (0.0016–0.0056)	0.024
3§	235 758	2	109 032	0.0015 (0.0004–0.0060)	1.00	0.0015 (0.0004–0.0060)	1.00
P for trend				0.014		0.004	

Cyto− = negative results on cytologic evaluation; HPV = human papillomavirus; HPV− = negative results on HPV testing.
* For the difference in risk between this risk and the risk for the previous result (that is, the second co-test vs. the first co-test and the third co-test vs. the second co-test).
† Not preceded by a negative co-test.
‡ Preceded by 1 negative co-test.
§ Preceded by 2 negative co-tests.
‖ Negative co-test.

the cytology result and a Cyto− co-test regardless of the HPV test result. In other words, an HPV− result includes both HPV−/Cyto− and HPV−/Cyto+ results, and a Cyto− result includes both HPV−/Cyto− and HPV+/Cyto− results. Five-year ≥CIN3 risks for each round of screening were calculated for age at first co-test (baseline): 30 to 39 years, 40 to 49 years, and 50 years or older. Five-year ≥CIN3 risks for second and third co-tests also were calculated for the preceding screening interval ("gap" time): less than 2.5 years, 2.5 to less than 3.5 years, or 3.5 years or longer. Age- and gap time–specific risks were estimated by adding age or gap time to the logistic-Weibull mixture model as a covariate. Statistical significance ($P < 0.050$) was assessed by using the likelihood ratio test.

Role of the Funding Source

The National Cancer Institute's Intramural Research Program partially supported the conduct of these analyses, and program members (N.W., J.C.G., L.C.C., and M.S.) contributed to the collection, analysis, and interpretation of the data.

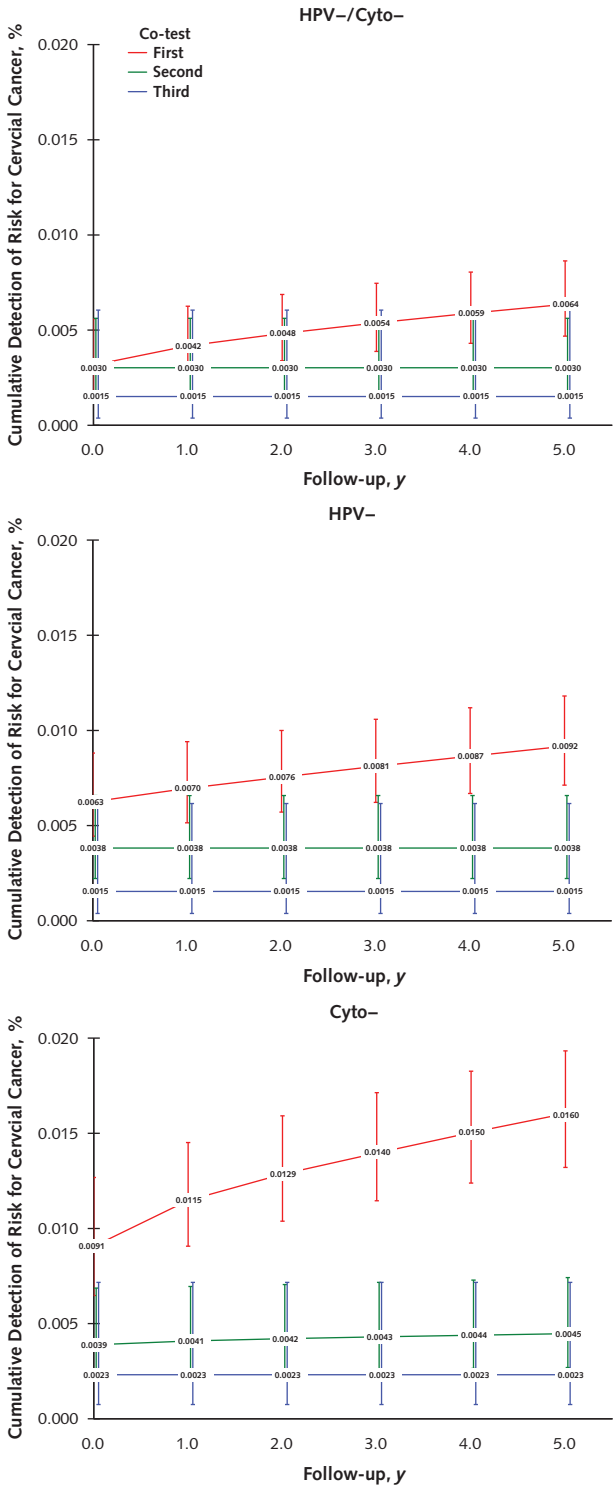
RESULTS

Invasive cervical cancer and ≥CIN3 risks decreased with each co-testing round, with a greater absolute decrease in risks occurring between the first and second than between the second and third co-tests. Table 1 and Figure 2 show risks for invasive cervical cancer for HPV−/Cyto−, HPV−, and Cyto− results for the first, second, and third co-testing rounds. Five-year risk decreased with each successive HPV−/Cyto− result, from 0.0064% (6.4 per 100 000) for the first co-test to 0.0015% (1.5 per 100 000) for the third. Three-year risk decreased with each successive HPV−/Cyto− result, from 0.0054% (5.4 per 100 000) for the first co-test to 0.0015% (1.5 per 100 000) for the third.

The 5-year risk for invasive cervical cancer after an HPV− result decreased from 0.0092% (9.2 per 100 000) for the first HPV− result (no preceding negative co-tests) to 0.0015% (1.5 per 100 000) for an HPV− result on the third co-test after 2 negative co-tests. The 3-year risk for invasive cervical cancer after an HPV− result decreased from 0.0081% (8.1 per 100 000) for the first HPV− result to 0.0015% (1.5 per 100 000) for an HPV− result on the third co-test after 2 negative co-tests. By comparison, the 3-year risk for invasive cancer after a Cyto− result decreased from 0.0140% (14 per 100 000) for the first Cyto− result to 0.0023% (2.3 per 100 000) for a Cyto− result on the third co-test after 2 negative co-tests.

Table 2 and Figure 3 show 3- and 5-year ≥CIN3 risks after HPV−/Cyto−, HPV−, and Cyto− results from the first, second, and third co-tests, which followed patterns similar to those of the invasive cervical cancer end point. The 5-year ≥CIN3 risk after an HPV−/Cyto− result decreased with each successive testing round, from 0.098% for the first co-test to 0.035% for the third. The 3-year ≥CIN3 risk after an HPV−/Cyto− result decreased from 0.070% for the first co-test to 0.020% for the third. The 3-year ≥CIN3 risk after an HPV− result decreased with each successive testing round, from 0.085% for the first co-test to 0.024% for the third. The 3-year ≥CIN3 risk after a Cyto− result decreased from

Figure 2. Cumulative detection of (risk for) cervical cancer for a negative co-test (HPV−/Cyto−) (*top*), a negative HPV test (HPV−) (*middle*), and negative cytology (Cyto−) (*bottom*) for the first, second, and third co-test after 0, 1, and 2 negative co-tests, respectively.



Error bars indicate 95% CIs. Data from second and third co-tests are shifted (jittered) to the right to show the CIs. Cyto = cytology; HPV = human papillomavirus.

0.199% for the first co-test to 0.043% for the third. Age-standardized 3- and 5-year ≥CIN3 risks (**Appendix Table 3**, available at Annals.org) were very similar to crude risks; therefore, the age differences among the first, second, and third co-tests cannot explain the differences in risk. For each age group, risks decreased substantially (2- to 3-fold on a relative scale) for each screening round (**Table 3**).

Finally, we examined whether the length of the preceding interval substantially influenced future ≥CIN3 risks (**Appendix Table 4**, available at Annals.org). Five-year ≥CIN3 risks for the second and third co-tests were greater for women who received their previous HPV−/Cyto− result at least 3.5 years earlier than for those who received it less than 2.5 years or 2.5 to less than 3.5 years earlier; however, these differences were not statistically significant.

DISCUSSION

We investigated how low cervical cancer risk can become by screening with 1 or more rounds of HPV and cytology co-testing. We found that women with a screening history showing an increasing number of negative co-tests have a steadily decreasing risk for future cancer or ≥CIN3, although the first negative co-test had the greatest effect on risk reduction. Within a given co-testing round, the reassurance against cancer and cancer risk were similar for an HPV− result alone, regardless of cytology results, and an HPV−/Cyto− co-test result. We infer that similar patterns of risk would have been observed if standalone HPV testing had been used instead of co-testing but acknowledge that HPV testing alone missed a few cases of CIN3 and AIS (**Appendix Table 1**), some of which may have developed into cancer eventually. Women aged 50 years or older who had their third consecutive negative co-test had a 5- to 6-fold lower risk than women aged 30 to 39 years who had their first negative co-test, suggesting that screening intervals might be assigned on the basis of both age and number of previous negative screens.

One of the barriers to adopting HPV testing into routine practice is simply a lack of long-term, longitudinal data on safety. Most clinical trials have been limited practically to 1 or 2 screening rounds, whereas screening is done for women aged 21 to 64 years in the United States, stopping at age 65 years or older only in those with a 10-year history of negative test results (8). In the context of routine screening, we demonstrated that reassurance of an HPV− or HPV−/Cyto− co-test result is superior to that of negative cytology. However, the ability to see the true absolute differences between cytology and HPV or co-test screening in subsequent rounds was likely muted because of accumulated censoring of HPV-detected ≥CIN2 (CIN2, CIN3, AIS, and cervical cancer) among women with a Cyto− result. The 5-year cumulative detection of ≥CIN2 after an HPV+/Cyto − result for each round was 8.50% in round 1, 5.38% in round 2, and 4.24% in round 3.

Some clear patterns emerge from these KPNC data that are consistent with our understanding of the natu-

Table 2. Cumulative Detection of (Risk for) ≥CIN3 at 3 and 5 Years After Screening, by HPV Testing and Cytologic Evaluation Based on Screening History and Negative Test Results

Co-test Number	Patients, *n*	≥CIN3					
		End Point, *n*	Noninformative Results, *n*	3 Years		5 Years	
				Risk (95% CI), %	*P* Value*	Risk (95% CI), %	*P* Value*
HPV−							
1†	931 567	790	295 200	0.085 (0.079–0.092)	–	0.114 (0.106–0.122)	–
2‡	527 014	196	186 682	0.043 (0.037–0.051)	<0.001	0.061 (0.053–0.070)	<0.001
3§	239 684	39	109 876	0.024 (0.017–0.033)	0.001	0.041 (0.029–0.056)	0.016
P for trend				<0.001		<0.001	
Cyto−							
1†	945 152	1689	298 309	0.199 (0.189–0.210)	–	0.248 (0.236–0.260)	–
2‡	525 221	281	186 343	0.065 (0.058–0.074)	<0.001	0.089 (0.079–0.100)	<0.001
3§	239 209	65	109 474	0.043 (0.034–0.056)	0.003	0.063 (0.049–0.081)	0.015
P for trend				<0.001		<0.001	
HPV−/Cyto−‖							
1†	911 133	664	291 571	0.070 (0.065–0.076)	–	0.098 (0.090–0.105)	–
2‡	515 609	161	184 964	0.036 (0.030–0.042)	<0.001	0.052 (0.045–0.061)	<0.001
3§	235 758	32	109 032	0.020 (0.014–0.028)	0.004	0.035 (0.024–0.050)	0.023
P for trend				<0.001		<0.001	

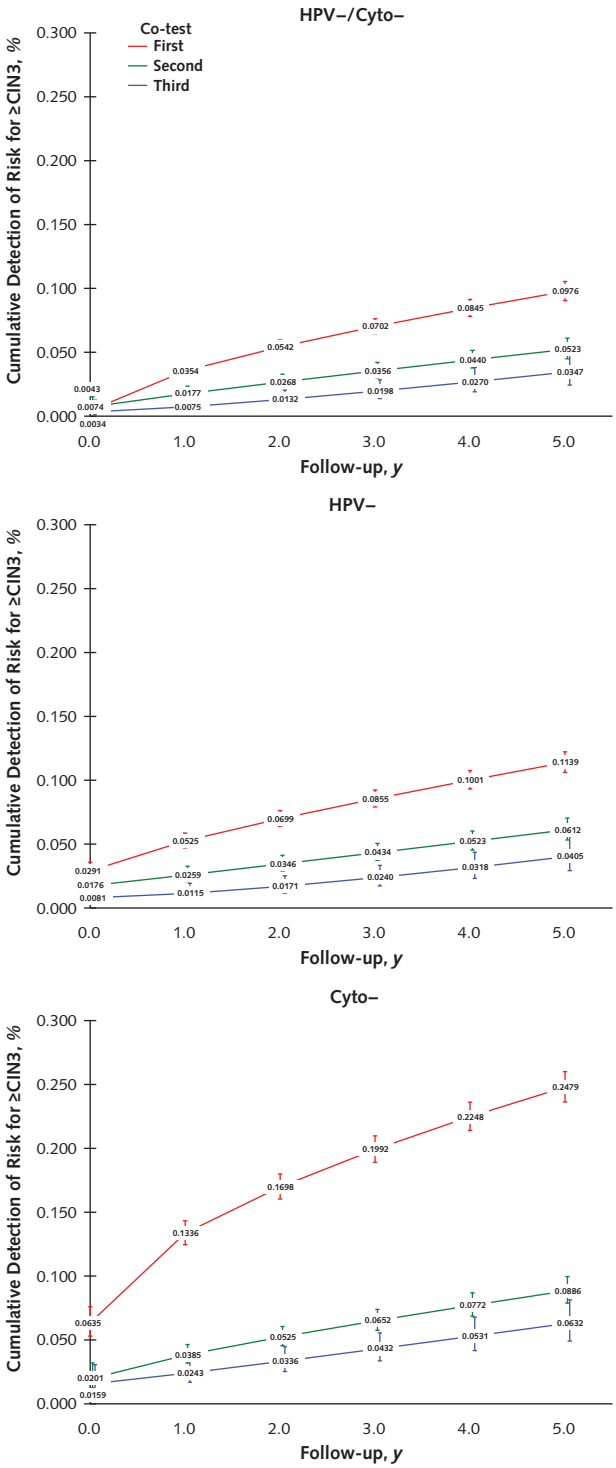
≥CIN3 = cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ, and cervical cancer; Cyto− = negative results on cytologic evaluation; HPV = human papillomavirus; HPV− = negative results on HPV testing.
* For the difference in risk between this risk and the risk for the previous result (that is, the second co-test vs. the first co-test and the third co-test vs. the second co-test).
† Not preceded by a negative co-test.
‡ Preceded by 1 negative co-test.
§ Preceded by 2 negative co-tests.
‖ Negative co-test.

ral history of HPV and cervical cancer (27). Modeling has shown that most HPV infections that eventually cause cervical cancer are acquired before the age of 30 years (28). Therefore, cervical cancer screening in women aged 30 years or older would be predicted to diagnose and treat precancer and cancer due primarily to those early exposures, and relatively few precancer or cancer cases would be the result of truly incident HPV infection acquired after the age of 30 years. In the context of those modeling data and the greater sensitivity of screening that includes HPV testing, one may reasonably expect a precipitous drop in cervical cancer risk (≥CIN3) after the first HPV− co-test. In other words, screening that includes HPV testing can effectively rule out prevalent cancer, CIN3 or AIS, and HPV infections that will subsequently develop into ≥CIN3. Incident CIN3 developing from an incident HPV infection during the screening interval is very uncommon compared with the point prevalence of ≥CIN3 in the population at the time of the first co-test.

Indeed, a single negative co-test was so effective at ruling out ≥CIN3 and cervical cancer that after the second co-test, no interval cancer cases occurred among women with an HPV− result. We also observed that negative cytology in a screening round after a previous negative co-test was almost as reassuring as a negative co-test or HPV test, most likely because of censoring of HPV-detected ≥CIN2, especially ≥CIN3. Of note, the risk difference between the first and second co-tests was greater than the differences between an older and a younger age group undergoing their first co-test, with older women likely having had several cytology screens in the decade before their first co-test (for example, women aged 40 to 49 years had cytology screening during their 30s). One may speculate that 1 round of screening that includes HPV testing finds some ≥CIN3 cases that may have been systematically missed by cytology. This may be especially true of AIS, an immediate precursor of adenocarcinoma, as was inferred previously from secular trends in cervical cancer incidence by histologic type (29–33). For screening programs that are thinking of remaining cytology based, at least 1 round of screening that includes HPV testing may be worth considering. More generally, these data support new international recommendations that all adult women have HPV screening at least once in their lifetime (34, 35). Conversely, if cost-effective, a single round of co-testing might be considered before standalone HPV testing to detect the few early cancer and precancer cases that are systematically or randomly missed by HPV testing alone.

These data also support extending the screening interval further after 2 or possibly 1 negative co-tests or HPV tests. Current international guidelines recommend HPV testing at intervals of 5 years or longer (26, 34), because shorter-interval testing tends to find more transient, benign infections and related abnormalities (for example, CIN2) that might be treated unnecessarily. Resource availability and the acceptable level of cancer risk inform decisions about screening frequency and method (such as HPV testing alone vs. co-testing) (15, 36–38). Shortening the screening interval incre-

Figure 3. Cumulative detection of (risk for) ≥CIN3 for a negative co-test (HPV−/Cyto−) (*top*), a negative HPV test (HPV−) (*middle*), and negative cytology (Cyto−) (*bottom*) for the first, second, and third co-test after 0, 1, and 2 negative co-tests, respectively.



Error bars indicate 95% CIs. Data from the second and third co-tests are shifted (jittered) to the right to show the CIs. Cyto = cytology; ≥CIN3 = cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ, and cervical cancer; HPV = human papillomavirus.

mentally decreases cancer risk—but, practically speaking, can never achieve zero risk—while becoming more cost-ineffective and increasing the risk for treating CIN2 that, if undetected, would regress on its own (39, 40). Excisional treatments for CIN2, CIN3, and AIS have been linked to a greater risk for pregnancy complications, such as preterm delivery (41–43). For example, overscreening in the United States is estimated to have increased the likelihood of preterm delivery compared with the Netherlands (44).

We acknowledge several limitations to our analysis. First, we did not have complete ascertainment of women who had a total hysterectomy, thereby effectively censoring them from getting cervical cancer; therefore, we could not entirely correct for this reduction in the number of women at risk with increasing age. Women who are known to have had a hysterectomy do not undergo cervical screening at KPNC unless clinical indications are present. During any screening interval, only a few women (<0.1%) were likely to have had a hysterectomy, and those who did were excluded from analyses of subsequent screening rounds. Second, we also acknowledge that our analysis on the effect of preceding screening intervals on future risk was biased, that is, the group that had screening every 3.5 years or more is truncated because of limited follow-up, so shorter durations in that group are overrepresented. We did not observe enough events to evaluate whether longer preceding intervals (such as those greater than 5 years) influence future risks. Third, we did not have the women's screening history before they underwent co-testing, which would have informed us about future risks. Fourth, because of the small number of cancer cases, it was necessary to use ≥CIN3 as an imperfect proxy of cancer risk. Cancer is preceded by CIN3 and AIS; therefore, the age distributions of patients with CIN3 or AIS differ greatly (27). In addition, not all cases of CIN3 or AIS develop into cancer (45).

Finally, our analysis was limited in that we could only infer the performance of HPV testing from co-testing results. Co-testing is a few percent more sensitive than HPV testing alone, as has been otherwise observed (46); as a consequence, some abnormalities were censored before they could develop into cancer. However, as shown in **Appendix Table 1**, only a few ≥CIN3 cases were found by cytology alone (HPV−/Cyto+); therefore, we suggest that the patterns observed in the co-testing results might reasonably approximate what might be expected for multiple-round HPV testing alone.

In conclusion, we present the effect of several rounds of cervical screening including HPV testing on the population risks for cervical cancer. We found a substantial decline in cervical cancer risk after 1 or more negative co-tests. Following the principle of equal management for equal risk (47), these data support extending screening intervals further after 1 or more negative co-tests to optimize the benefit-to-harm ratio of screening. The rationale for further extending the screening interval differs by age. For women in their 30s who have a history of negative co-tests or HPV

Table 3. Baseline Age Stratification of the 5-Year Cumulative Detection of ≥CIN3 for a Negative Result on HPV Testing, Cytologic Evaluation, and HPV Testing and Cytologic Evaluation Co-testing for the First, Second, and Third Co-test After 0, 1, and 2 Negative Co-tests, Respectively

Co-test Number	Risk (95% CI), %*		
	Age 30–39 Years	Age 40–49 Years	Age ≥50 Years
HPV−			
1	0.154 (0.141–0.167)	0.108 (0.109–0.119)	0.073 (0.065–0.083)
2	0.092 (0.076–0.111)	0.064 (0.053–0.078)	0.042 (0.034–0.052)
3	0.067 (0.041–0.109)	0.045 (0.030–0.068)	0.027 (0.017–0.044)
Cyto−			
1	0.387 (0.365–0.411)	0.201 (0.185–0.218)	0.129 (0.117–0.144)
2	0.157 (0.133–0.185)	0.087 (0.073–0.104)	0.052 (0.043–0.064)
3	0.119 (0.079–0.179)	0.067 (0.047–0.096)	0.040 (0.027–0.061)
HPV−/Cyto−†			
1	0.137 (0.125–0.150)	0.090 (0.043–0.066)	0.060 (0.052–0.069)
2	0.081 (0.066–0.100)	0.053 (0.023–0.059)	0.036 (0.029–0.046)
3	0.060 (0.036–0.101)	0.037 (0.020–0.134)	0.024 (0.014–0.039)

≥CIN3 = cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ, and cervical cancer; Cyto− = negative results on cytologic evaluation; HPV = human papillomavirus; HPV− = negative results on HPV testing.
* Risks decreased significantly with each round of screening for a given age group (P for trend < 0.001) and with older age groups for a given round of screening (P for trend < 0.001).
† Negative co-test.

tests and may be considering having children, extending the screening interval may reduce the preterm delivery risk. For women aged 50 years or older with a sufficient history of negative co-tests or HPV tests, continued screening may prove inefficient and cost-ineffective, even at 5-year intervals, given the very low probability of subsequent cervical cancer prevented by screening. However, whether abnormalities are mostly absent in these older women or are missed by the screening tests or colposcopy is unclear. Thus, evidence for safely extending screening intervals after negative co-tests or HPV tests at any age must be established.

To optimize cervical cancer screening by balancing the cancer prevention benefits with the potential harms of overscreening, it will be necessary to consider the effect of a negative screening history on the cervical cancer risk of a negative screen, as presented here, and on an (incident) positive screen, which will be addressed in a companion paper. Given the large number of possible screening strategies and combination of results longitudinal as well as integrating important risk modifiers, such as HPV vaccination status, into risk-based cervical screening and management, a risk calculator, in the form of a smartphone application, might be helpful, if not necessary, for clinicians to advise women when they need their next screening (48).

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Appendix

Cervical cancer screening data from routine clinical practice, such as KPNC, have features that must be taken into account to produce unbiased absolute and relative risk estimates for onset of clinically detectable disease. First, the time of disease onset, T, for a woman is unobserved and known only to fall between screens in which disease is definitively ascertained (interval censoring). We considered disease to have been definitively ascertained if the woman had a colposcopy visit or a follow-up screen that was HPV−/Cyto− or equivocal. Baseline screens and other follow-up screening results without a colposcopy visit were considered uninformative for the presence or absence of disease.

Second, prevalent disease may be present at the baseline screen. Third, prevalent disease is not always immediately diagnosed (for example, in those with negative screening results); thus, some disease found at later screens is actually missed prevalent disease (**Appendix Figure**).

We estimated the risk for disease onset by using a logistic-Weibull prevalence–incidence mixture model (25). Given covariate values x, the cumulative risk at time t (where $t = 0$ is baseline) can be modeled as the sum of the probability of having prevalent disease at baseline and the probability of incident disease developing after baseline:

$$P(T \le t;x,\theta) = P(T = 0;x,\beta) + \{1 - P(T = 0;x,\beta)\}\{1 - S(t;\gamma,\tau|T > 0,x)\},$$

where P is a logistic regression model with regression coefficients β,

$$P(T = 0;x,\beta) = \frac{\exp(x'\beta)}{1 + \exp(x'\beta)},$$

and S is a Weibull survival model with regression coefficients γ and shape parameter τ,

$$S(t;\gamma,\tau|T > 0,x) = \exp\left[-\left\{\frac{t}{\exp(x'\gamma)}\right\}^{\frac{1}{\tau}}\right].$$

We call the combined model a logistic-Weibull prevalence–incidence mixture model.

The observed data log-likelihood is

$$l(y^{obs};\theta) = + \sum_{i\epsilon K_2}\{\log(1 - P(T = 0;x,\beta)) + \log S(L_i;\gamma,\tau|T > 0,x) - \log S(R_i\gamma,\tau|T > 0,x)\} + \sum_{i\epsilon K_3}\log[P(T = 0;x,\beta) + \{1 - P(T = 0;x,\beta)\}\{1 - S(R_i;\gamma,\tau|T > 0,x)\}],$$

where K_1, K_2, and K_3 are the populations known to have prevalent disease, known to not have prevalent disease, and with unknown prevalent disease status (disease found in follow-up that might have been missed prevalent disease), respectively.

The parameters $\theta = (\beta, \gamma, \tau)$ that maximized the log-likelihood can be jointly estimated by using an expectation–maximization algorithm (49). The Weibull survival model is a proportional hazard model with a Weibull baseline distribution, which is suggested by the multistage model for carcinogenesis (50) and naturally handles interval censoring of disease onset. By jointly fitting the logistic regression and Weibull survival model components as a mixture model, we can account for unknown prevalent disease status.

Cumulative risk predictions were made by plugging estimated parameters and covariate values into equations (1) to (3). The variance for the cumulative risk is derived by using the multivariate delta method as

$$\widehat{Var}\{P(T \geq t; x, \theta)\} = \nabla' I(\theta)^{-1} \nabla,$$

where ∇ is the gradient of P and $I(\theta)$ is the observed Fisher information.

Confidence limits for the cumulative risk were constructed on the complementary log–log scale and then converted to the cumulative risk scale. The complementary log–log of the cumulative risk is asymptotically normal via the multivariate delta method (51), because maximum likelihood estimators are asymptotically normal (52).

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Appendix Table 1. Outcomes of Women in the Screening Cohort*

Variable	Patients	All ≥CIN3	Prevalent ≥CIN3	Unsure Prevalent/Incident ≥CIN3	Incident ≥CIN3	Right Censored†	CIN2	Loss to Follow-up‡	Noninformative§
Co-test 1‖									
HPV−/Cyto−¶	911 133	664	7	352	305	618 898	1556	617 342	291 571
HPV+/Cyto−	34 019	1025	59	627	339	26 256	1425	24 831	6738
HPV−/Cyto+	20 434	126	54	35	37	16 679	218	16 461	3629
HPV+/Cyto+	24 427	2354	1855	122	377	20 228	2957	17 271	1845
Co-test 2**									
HPV−/Cyto−¶	515 609	161	6	96	59	330 484	461	330 023	184 964
HPV+/Cyto−	9612	120	2	73	45	8113	266	7847	1379
HPV−/Cyto+	11 405	35	11	11	13	9652	70	9582	1718
HPV+/Cyto+	7360	275	201	3	71	6854	641	6213	231
Co-test 3††									
HPV−/Cyto−¶	235 758	32	2	14	16	126 694	119	12 675	109 032
HPV+/Cyto−	3451	33	2	21	10	2976	67	2909	442
HPV−/Cyto+	3926	7	4	0	3	3075	24	3051	844
HPV+/Cyto+	2839	65	50	1	14	2699	181	2518	75

≥CIN3 = cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ, and cervical cancer; CIN2 = cervical intraepithelial neoplasia grade 2; Cyto− = negative results on cytologic evaluation; Cyto+ = positive results on cytologic evaluation; HPV = human papillomavirus; HPV− = negative results on HPV testing; HPV+ = positive results on HPV testing.

* Values are numbers.

† Censored because of development of CIN2 or loss to follow-up.

‡ Includes the end of data collection because they left Kaiser Permanente's managed care, moved away, or died (we cannot differentiate among these because we do not have membership data).

§ Indicates that we do not have any information whether they developed ≥CIN3 during the entire follow-up.

‖ Not preceded by a negative co-test.

¶ Negative co-test.

** Preceded by 1 negative co-test.

†† Preceded by 2 negative co-tests.

Appendix Table 2. Number at Risk at Each Time Point*

Co-test Number	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
1	686 230	673 183	651 017	590 965	446 346	394 154
2	355 694	352 022	340 275	291 965	165 487	138 456
3	135 581	134 128	127 719	103 423	35 684	25 444

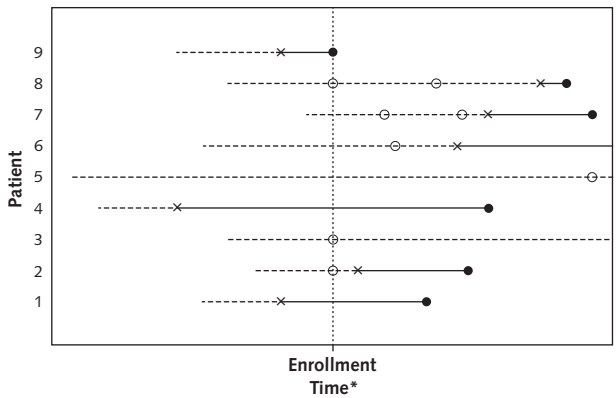
* Values are numbers.

Appendix Table 3. Age-Standardized Cumulative Detection of (Risk for) ≥CIN3 at 3 and 5 Years After Screening, by HPV Testing and Cytologic Evaluation Based on Screening History and Negative Test Results

Co-test Number	Risk (95% CI), %	
	3 Years	5 Years
HPV−		
1*	0.079 (0.075–0.084)	0.106 (0.100–0.112)
2†	0.044 (0.039–0.049)	0.063 (0.055–0.070)
3‡	0.026 (0.019–0.032)	0.044 (0.031–0.056)
Cyto−		
1*	0.179 (0.171–0.187)	0.223 (0.213–0.233)
2†	0.068 (0.061–0.075)	0.092 (0.082–0.102)
3‡	0.048 (0.037–0.075)	0.070 (0.053–0.102)
HPV−/Cyto−§		
1*	0.079 (0.075–0.084)	0.104 (0.098–0.109)
2†	0.042 (0.037–0.047)	0.058 (0.052–0.065)
3‡	0.026 (0.019–0.033)	0.042 (0.030–0.054)

≥CIN3 = cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ, and cervical cancer; Cyto− = negative results on cytologic evaluation; HPV = human papillomavirus; HPV− = negative results on HPV testing.
* Not preceded by a negative co-test.
† Preceded by 1 negative co-test.
‡ Preceded by 2 negative co-tests.
§ Negative co-test.

Appendix Figure. Screening data from electronic health records for 9 women.



Women became susceptible to disease (start of dashed lines) at some point before enrollment (vertical dotted line), may have acquired clinically detectable disease (denoted with ×), and then may have received a diagnosis (solid circles). Disease status was known only at specific times (unfilled circles represent known disease-free status, solid circles known diseased status).
* The time frame from susceptibility to detectable cervical precancer or cancer is in years; however, to make the example generalizable to any screened disease, a unit of time is not given here.

Appendix Table 4. 5-Year Cumulative Detection of (Risk for) ≥CIN3 for a Negative Result on HPV Testing, Cytologic Evaluation, and HPV Testing and Cytologic Evaluation Co-testing for the Second and Third Co-test, by Preceding Screening Interval Time*

Co-test Number	Risk (95% CI), by Interval Time Between the Previous Screen, %		
	<2.5 Years	≥2.5 to <3.5 Years	≥3.5 Years
HPV−			
2	0.062 (0.051–0.077)	0.059 (0.051–0.069)	0.073 (0.052–0.102)
3	0.043 (0.027–0.067)	0.039 (0.027–0.056)	0.073 (0.021–0.239)
Cyto−			
2	0.096 (0.080–0.116)	0.083 (0.073–0.096)	0.105 (0.076–0.145)
3	0.063 (0.042–0.095)	0.062 (0.046–0.083)	0.097 (0.032–0.300)
HPV−/Cyto−†			
2	0.060 (0.049–0.074)	0.055 (0.047–0.065)	0.063 (0.049–0.089)
3	0.041 (0.026–0.065)	0.037 (0.026–0.054)	0.063 (0.019–0.210)

≥CIN3 = cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ, and cervical cancer; Cyto− = negative results on cytologic evaluation; HPV = human papillomavirus; HPV− = negative results on HPV testing.
* The differences in risk by preceding screening interval were not significant ($P = 0.11$ for the second co-test and $P = 0.64$ for the third co-test).
† Negative co-test.