

ORIGINAL ARTICLE

Human Papillomavirus and Papanicolaou Tests to Screen for Cervical Cancer

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ABSTRACT

BACKGROUND

Screening for cervical cancer based on testing for human papillomavirus (HPV) increases the sensitivity of detection of high-grade (grade 2 or 3) cervical intraepithelial neoplasia, but whether this gain represents overdiagnosis or protection against future high-grade cervical epithelial neoplasia or cervical cancer is unknown.

METHODS

In a population-based screening program in Sweden, 12,527 women 32 to 38 years of age were randomly assigned at a 1:1 ratio to have an HPV test plus a Papanicolaou (Pap) test (intervention group) or a Pap test alone (control group). Women with a positive HPV test and a normal Pap test result were offered a second HPV test at least 1 year later, and those who were found to be persistently infected with the same high-risk type of HPV were then offered colposcopy with cervical biopsy. A similar number of double-blinded Pap smears and colposcopies with biopsy were performed in randomly selected women in the control group. Comprehensive registry data were used to follow the women for a mean of 4.1 years. The relative rates of grade 2 or 3 cervical intraepithelial neoplasia or cancer detected at enrollment and at subsequent screening examinations were calculated.

RESULTS

At enrollment, the proportion of women in the intervention group who were found to have lesions of grade 2 or 3 cervical intraepithelial neoplasia or cancer was 51% greater (95% confidence interval [CI], 13 to 102) than the proportion of women in the control group who were found to have such lesions. At subsequent screening examinations, the proportion of women in the intervention group who were found to have grade 2 or 3 lesions or cancer was 42% less (95% CI, 4 to 64) and the proportion with grade 3 lesions or cancer was 47% less (95% CI, 2 to 71) than the proportions of control women who were found to have such lesions. Women with persistent HPV infection remained at high risk for grade 2 or 3 lesions or cancer after referral for colposcopy.

CONCLUSIONS

The addition of an HPV test to the Pap test to screen women in their mid-30s for cervical cancer reduces the incidence of grade 2 or 3 cervical intraepithelial neoplasia or cancer detected by subsequent screening examinations. (ClinicalTrials.gov number, NCT00479375.)

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SCREENING FOR CERVICAL CANCER BY CYTOLOGIC examination (the Papanicolaou [Pap] test) has reduced the incidence of invasive cervical cancer in many countries,^{1,2} yet cervical cancer remains a leading cause of death and illness in women.² Human papillomavirus (HPV) is the major cause of cervical cancer, and in the natural history of the disease, persistent HPV infection precedes the appearance of cytologic abnormalities.^{3,4} Longitudinal cohort studies have shown that combined Pap and HPV testing has better sensitivity and provides better long-term protection (among women with normal results of both tests) against grade 3 cervical intraepithelial neoplasia than does cytologic testing alone.⁵⁻⁸ Grade 3 cervical intraepithelial neoplasia is known to be a precursor of invasive cervical cancer.

In the United States, HPV testing is accepted as an adjunct to cytologic testing for women over 30 years of age.⁹ Increased sensitivity may, however, reflect the inclusion of regressing lesions, and observational cohort studies do not provide information on the effect of an intervention based on the test results. European guidelines recommend that HPV testing not be adopted as a primary screening tool until results are available from randomized trials of the effect of HPV-based cervical screening on the incidence of grade 3 cervical intraepithelial neoplasia or cancer detected by subsequent screening.¹⁰ Several such trials have been started, but so far only baseline data have been reported.¹¹⁻¹⁶

The prevalence of HPV infection peaks in women in their early 20s, but because the infection is usually transient,¹⁷⁻¹⁹ the specificity of HPV screening is higher in women 35 years of age or older than in younger women.²⁰ The age-specific incidence of cervical cancer peaks around the age of 40 years, which suggests that the efficacy of HPV testing should be maximal when it is performed on women between 30 and 40 years of age. We report the results of a population-based, randomized, controlled trial in which women 32 to 38 years of age were screened for cervical cancer either with a Pap test plus a test for HPV infection or with a Pap test alone.

METHODS

STUDY DESIGN

The Swedish cervical-cancer screening program invites women 23 to 50 years of age to undergo cervical-cancer screening at 3-year intervals and wom-

en 51 to 60 years of age to be screened at 5-year intervals. Women invited for screening are chosen from the population registry, which lists all women in Sweden; women who are recorded in cytologic-test registries as having had a recent Pap smear outside the screening program are not invited to participate in the screening program.

All women 32 to 38 years of age who participated in the screening program from May 1997 through November 2000 in five Swedish cities (Gothenburg, Malmö, Uppsala, Umeå, and Stockholm) were eligible; the only exclusion criterion was failure to consent to participation in the study. The number of women who declined participation is unknown, but surveys at screening centers found very few women who did not consent.

A total of 12,527 consenting women were randomly assigned at a 1:1 ratio to the intervention group (a Pap test plus a test for HPV infection; 6257 women) or the control group (a Pap test alone; 6270 women) (Fig. 1). Randomization was performed by an independent institute (the Cancer Registry of Stockholm) with the use of computer-generated random numbers. The women and the clinical personnel were unaware of the women's test assignment, and the laboratory technicians who performed the HPV tests had no personal information about the women. Lists with code numbers specifying which samples should be tested were released to the virus laboratory only after the samples had arrived. Because the proportion of women with a positive HPV test who were found to have grade 2 or 3 cervical intraepithelial neoplasia or cancer was much larger than expected, the steering committee decided to discontinue blinding of the study and inform the women of the results of their HPV tests on August 11, 2003 (3 years after completion of enrollment and 4 months after completion of the first round of study colposcopies in the two groups). The relative numbers of women in the intervention and control groups who had a follow-up HPV test did not change significantly after discontinuation of blinding; while the study was still blinded, 22 women in the intervention group and 24 in the control group had a follow-up test; after discontinuation of blinding, 58 women in the intervention group and 50 in the control group had a follow-up test.

Endocervical and ectocervical samples were taken with a cytologic brush. After a conventional smear had been prepared, the brush was swirled in 1 ml of sterile 0.9% sodium chloride to release

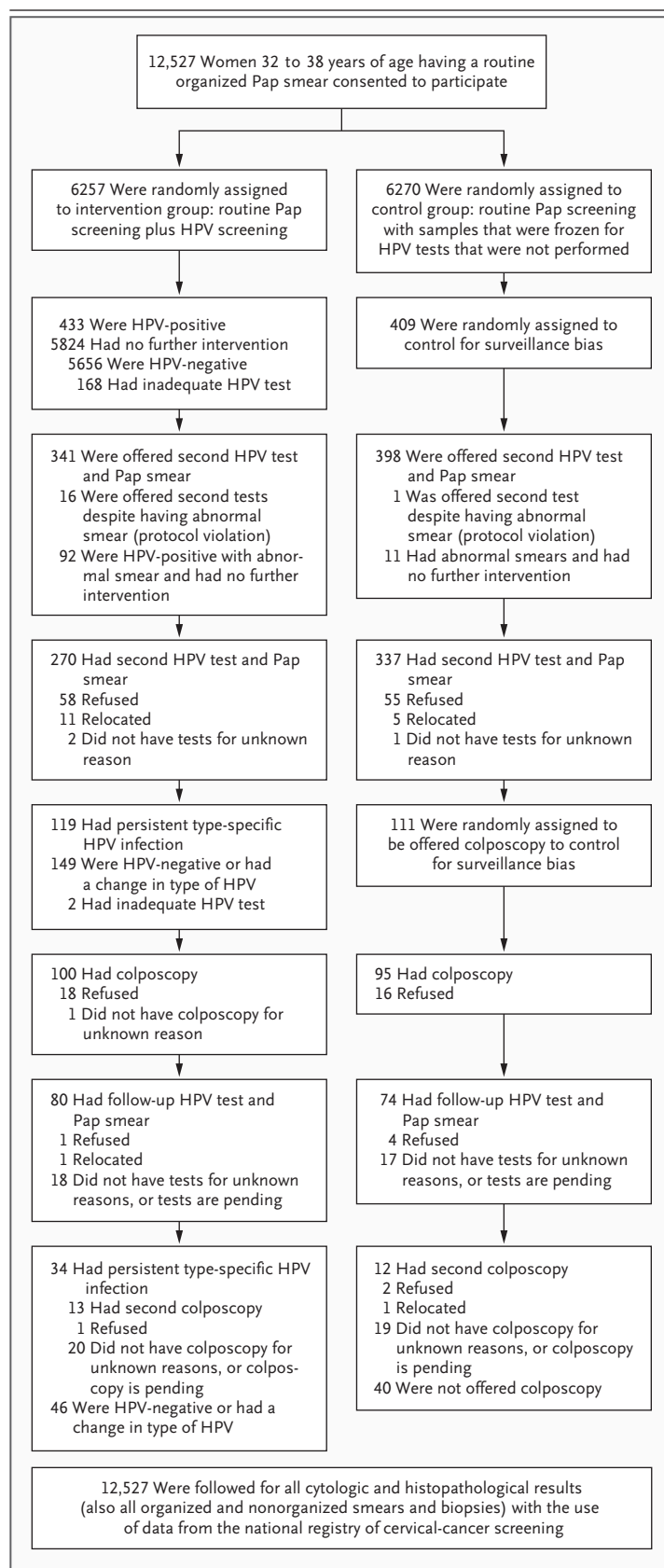
Figure 1. Enrollment and Outcomes.

Lists of women who were positive for HPV were compared with lists in cytologic registries, and women found to have already been referred because of abnormal smears should not have been offered a second HPV or cytologic test. Protocol violations may have occurred because of human error or because the registries contained preliminary or incomplete data at the time. Pending refers to tests not yet taken or colposcopies not yet performed when the follow-up of this study was ended. The study was unblinded 4 months after the first round of colposcopies had been completed, at which time 22 of 80 women in the intervention group and 24 of 74 in the control group had already had a follow-up HPV test or a Pap smear. HPV denotes human papillomavirus.

the remaining cells for analysis of HPV DNA. The samples were transported frozen at -20°C to be tested for HPV DNA.

The nature of the intervention performed as a result of the baseline cytologic test was based on regional routine practice. In Stockholm, all women with an abnormal Pap smear (defined as one with atypical squamous cells of undetermined significance [ASCUS] or more severe cytologic diagnosis [cervical intraepithelial neoplasia; grade 1, 2, or 3 glandular atypia; adenocarcinoma in situ; or cancer]) were immediately referred for colposcopy, whereas in the other cities, a repeat Pap smear was an option in cases of ASCUS or grade 1 cervical intraepithelial neoplasia. Koilocytosis in a normal smear was considered an abnormal cytologic finding in only two cities (Umeå and Gothenburg). Sweden uses the old U.S. cytologic nomenclature,²¹ in which a diagnosis of koilocytosis can be made in addition to any other diagnosis. Only 0.2% of smears were reported as normal, with koilocytosis as an ancillary diagnosis. The regional variation in referral practices is therefore unlikely to have had any effect on the results of the study.

In the intervention group, women with a positive HPV test and no record of referral due to an abnormal Pap test result were offered a second round of HPV and Pap tests at least 12 months later (Fig. 1). After this second round of tests, women who continued to be infected with the same high-risk type of HPV were offered colposcopy. To avoid ascertainment bias, a similar number of randomly selected women from the control group were also offered a second Pap test and colposcopy. Both the women and the clinicians were unaware of the HPV test results and the randomization status of the women.



Ectocervical biopsy specimens were taken from all lesions that turned white when treated with acetic acid and lesions that were not stained by Lugol's iodine solution. If no such lesions were seen, two specimens were obtained at the 12 o'clock and 6 o'clock positions on the ectocervix, close to the squamocolumnar-cell junction.²² In addition to these ectocervical specimens, an endocervical-cell sample was obtained from all women.

The protocol follow-up required annual Pap smears and HPV tests, with colposcopy in cases of persistent high-risk HPV infection, in addition to the following of routine clinical practice for abnormal cytologic, colposcopic, or histopathological findings. High-grade (grade 2 or 3) cervical epithelial neoplasia is always treated by conization, usually with loop excision. The women were followed up by means of personal identification numbers and linkages between regional cytologic, regional pathological, and the national cytologic registries. These registries contain data on all Pap smears and cervical biopsies performed in Sweden, not only those performed in the screening program. The date of the last follow-up was August 31, 2005, for Stockholm and Uppsala and December 31, 2004, for the other cities.

Histologic samples with an abnormal diagnosis and all biopsy specimens obtained during the study colposcopies were reevaluated by an expert pathologist who was unaware of the subject's randomization status. If the second diagnosis differed from the original diagnosis by more than one level of severity, another expert pathologist unaware of the subject's randomization status adjudicated the diagnosis. If the specimen could not be located, the original diagnosis was used. Reevaluation was the basis for 218 of 258 diagnoses of grade 2 or 3 cervical intraepithelial neoplasia or cancer.

The primary outcome of the trial was the incidence of grade 2 or 3 cervical intraepithelial neoplasia lesions or cancers (which include invasive cancers and in situ adenocarcinomas) found by screening that took place after the enrollment screening. The secondary outcomes were the incidence of grade 2 or 3 lesions or cancer at the enrollment screening and outcomes stratified according to grade 2 lesions only and grade 3 lesions or cancer as end points. The study was approved by the ethics review board of the Karolinska Institute, which specified the consent procedure, in

which all participants gave oral consent after receiving written information.

TESTING FOR HPV DNA

Testing for HPV DNA was performed with the use of a polymerase chain reaction (PCR)–enzyme immunoassay, using general primers GP5+ and GP6+, that detects 14 high-risk types of HPV (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).^{23,24} Human β -globin amplification was used to test for sample DNA quality.²⁴ PCR-positive samples were typed with the use of reverse dot blot hybridization with recombinant HPV type-specific plasmids.²⁵ If the result of the reverse dot blot hybridization was negative, the amplicons were cloned and sequenced. Only PCR-positive samples confirmed by reverse dot blot hybridization or sequencing were classified as HPV-positive.

STATISTICAL ANALYSIS

Only women who had had at least one Pap smear or had undergone at least one biopsy after the baseline visit were included in the analyses. No follow-up samples were available for 1568 women; according to population-registry data, 8 of these women had died and 82 had left the country. The mean follow-up time was 4.1 years (range, <0.1 to 7.7) and did not differ significantly between the two groups.

The data from all women were censored at their last testing date except for women whose data were censored at the date of diagnosis of a grade 2 or 3 cervical intraepithelial neoplasia lesion or cancer. When a grade 3 lesion or cancer was used as an end point in a stratified analysis, the data were censored at the date of diagnosis, regardless of a previous diagnosis of a grade 2 lesion.

Lesions were attributed to screening at enrollment and associated follow-up (prevalence screening) if the Pap smear at enrollment triggered immediate referral for colposcopy, according to regional clinical practice; if the Pap smear at enrollment resulted in a follow-up with additional Pap smears; if cervical biopsies had been performed at intervals not exceeding 18 months; or if the lesion was found as a result of protocol procedures in a woman with an HPV-positive test (intervention group) or as a result of the matched, randomly assigned procedures in the subsample of the control group that was followed in order to control for verification bias. The results from the

screening rounds scheduled to take place 3 years later and from all other Pap smears not complying with these definitions (i.e., performed during screening outside the study) were regarded as subsequent (incidence) screening.

The results were analyzed after the screening round at the next 3-year interval had been completed. The study was powered to detect a protection against a grade 2 or 3 cervical intraepithelial neoplasia lesion or cancer at incidence screening of at least 50% at a conventional significance level ($\alpha=0.05$) and power ($1-\beta=0.80$), on the assumption that the 3-year cumulative incidence of grade 2 or 3 cervical intraepithelial neoplasia or cancer in this age group was 1.0%.

Relative rates and 95% confidence intervals were calculated with the use of Poisson regression analysis. Because the primary intention of the study was to reflect a real-life screening program, protocol violations were not excluded from the analysis, and all analyses are reported as intention-to-treat analyses.

RESULTS

STUDY DESIGN

Figure 1 shows the design of the study. The mean age at enrollment, the number of women enrolled at the different screening locations, and the number of women with abnormal Pap smears at enrollment were similar in the intervention and control groups (Table 1).

According to the protocol, women who had already been referred for routine clinical follow-up because of an abnormal Pap smear were not to be offered a second HPV test. However, the protocol was violated for 16 of 341 women in the intervention group and 1 of 398 women in the control group. Those 17 women were offered a second HPV test although they had had an abnormal Pap smear at enrollment. Possible reasons for this protocol violation include human error or preliminary or incomplete data in the cytologic registries at the time the women were offered the second test. Fifteen of the 17 women did have a second HPV test, and 9 of them were found to have a grade 2 or 3 cervical intraepithelial neoplasia lesion or cancer during the trial (5 women before the second HPV test, 3 women at the first colposcopy, and 1 woman in the next screening round). Because the intention of the trial was to refer all HPV-positive women for colposcopy, duplicate referrals could

Table 1. Characteristics of the Women.*

Characteristic	Intervention Group (N=6257)	Control Group (N=6270)
Mean age at enrollment — yr	35.1	35.1
City — no. (%)		
Gothenburg	1368 (21.9)	1376 (21.9)
Malmö	408 (6.5)	403 (6.4)
Stockholm	3022 (48.3)	3040 (48.5)
Umeå	905 (14.5)	893 (14.2)
Uppsala	554 (8.9)	558 (8.9)
Abnormal smear at enrollment — no. (%)†	146 (2.3)	150 (2.4)
No follow-up cytologic or histologic tests — no. (%)	805 (12.9)	763 (12.2)

* Percentages do not total 100 because of rounding.

† An abnormal smear is defined as one with atypical squamous cells of undetermined significance (ASCUS) or more severe cytologic findings.

not have affected the outcome of the study, and 97.7% of the referrals were made according to protocol.

During the entire study, 139 women in the intervention group and 119 in the control group were found to have a grade 2 or 3 cervical intraepithelial neoplasia lesion or cancer ($P=0.20$) (Table 2). Fifty-three cases of grade 2 lesions were detected in the intervention group as compared with 34 in the control group ($P=0.04$), but there was no significant difference between the groups in the rate of detection of grade 3 lesions or cancer (88 cases in the intervention group and 85 in the control group).

Table 2 shows that at the baseline (prevalence) screening round, 51% more cases of grade 2 or 3 cervical intraepithelial neoplasia or cancer were detected in the intervention group than in the control group. Moreover, the incidence of grade 2 or 3 lesions or cancer detected at subsequent screening examinations in the intervention group was reduced by 42% as compared with the control group (all 95% confidence intervals are given in Table 2). After the initial round of screening in the intervention group, there was a statistically significant reduction of 47% in the number of grade 3 lesions or cancer that were found in subsequent screening examinations (Table 2). The increased incidence of grade 2 lesions diagnosed at the initial screening in the intervention group was not followed by a statistically significant reduction in grade 2 lesions at later screenings.

Table 2. Relative Rates of Detection of Cervical Intraepithelial Neoplasia (CIN) or Cancer.*

Variable	Lesions Detected during Entire Study		Lesions Detected by Prevalence Screening†			Lesions Detected by Incidence Screening‡		
	Intervention Group	Control Group	Intervention Group	Control Group	Relative Rate (95% CI)	Intervention Group	Control Group	Relative Rate (95% CI)
	no. (%)		no. (%)			no. (%)		
CIN grade 2 or 3 or cancer	139 (54)	119 (46)	114 (60)	76 (40)	1.51 (1.13–2.02)	25 (37)	43 (63)	0.58 (0.36–0.96)
CIN grade 3 or cancer	88 (51)§	85 (49)	72 (57)	55 (43)	1.31 (0.92–1.87)	16 (35)§	30 (65)	0.53 (0.29–0.98)
CIN grade 2 only	53 (61)	34 (39)	42 (67)	21 (33)	2.01 (1.19–3.40)	11 (46)	13 (54)	0.85 (0.38–1.90)

* CI denotes confidence interval.

† Prevalence screening denotes screening at enrollment and associated follow-up.

‡ Incidence screening denotes screening taking place after the prevalence screening.

§ In two women, grade 2 lesions were detected by prevalence screening and grade 3 lesions were subsequently detected by incidence screening in the next round.

Women persistently infected with the same high-risk type of HPV for whom colposcopy did not show a grade 2 or 3 cervical intraepithelial neoplasia lesion or cancer remained at high risk for a later grade 2 or 3 lesion or cancer. Of the 72 women who had an initial colposcopy because of the persistence of infection with high-risk types of HPV but who did not receive a diagnosis of a grade 2 or 3 lesion or cancer at that time, 17 (24%; 95% confidence interval, 14 to 35%) were subsequently found to have a grade 2 or 3 lesion or cancer (Table 3). Of these 17 women, 11 had a grade 3 lesion or cancer. In 4 of the 17 women, the diagnosis was made at a second colposcopy because of persistent HPV infection; in 12, the diagnosis was made at routine follow-up visits for abnormal findings from the study colposcopy (i.e., abnormal colposcopic findings, abnormal cytologic test results, or histopathological findings of grade 1 cervical intraepithelial neoplasia on the biopsy); and in 1, the diagnosis was made at the subsequent regular 3-year screening. The risk of cervical intraepithelial neoplasia remained elevated for several years: five, four, six, and two cases of grade 2 cervical intraepithelial neoplasia or cancer were found during the first, second, third, and fourth years of follow-up after colposcopy, respectively.

In the intervention group, one woman was found to have invasive squamous-cell carcinoma at incidence screening. She had a positive HPV test and a normal Pap test result at enrollment and was offered, but did not have, the second HPV test. In the control group, invasive squamous-cell carcinoma was found in five women during the study (two had normal Pap test results and all five were

HPV-positive at enrollment). Adenocarcinoma in situ or adenocarcinoma developed in four women in each group. All eight of these women had positive HPV tests at baseline, and four of them had abnormal Pap smear results. In the intervention group, two women with adenocarcinoma in situ had positive HPV tests and normal Pap test results at baseline; in these women, the diagnosis was made at the follow-up colposcopy after the first colposcopy.

DISCUSSION

We found that women in their mid-30s who were screened for HPV in conjunction with Pap smears had a reduction of approximately 40% in the risk of grade 2 or 3 cervical intraepithelial neoplasia or cancer at subsequent screening rounds, as compared with women who were screened with Pap smears alone. A similar reduction in the risk of grade 3 cervical intraepithelial neoplasia or cancer was also observed at subsequent screening rounds; this reduction could allow extended screening intervals, requiring fewer Pap smears and possibly lowering the costs of initial screening. The reduced incidence of grade 3 lesions or cancer associated with HPV testing could reduce mortality from cervical cancer in women who undergo screening less frequently than the recommended interval.

Our trial was designed to produce unbiased estimates of the efficacy of screening with combined HPV testing and cytologic testing, as compared with cytologic testing alone. To ensure high internal validity and generalizability, the trial was conducted within an organized screening pro-

Table 3. Screening History of Women in Whom Histologically Confirmed High-Grade Lesions or Cancer Developed.*

History	Grade 2 or 3 CIN or Cancer		Grade 3 CIN or Cancer	
	Intervention Group	Control Group	Intervention Group	Control Group
No. of lesions detected during entire study	139	119	88	85
ASCUS-positive Pap smear at enrollment — no. (%)	74 (53)	78 (66)	47 (53)	56 (66)
HPV-positive test at enrollment — no. (%)	120 (86)	107 (90)	80 (91)	75 (88)
Offered second HPV test — no.	62†	3	44	3
Offered second HPV test but did not have it — no.	7	—	5	—
Received diagnosis between first and second HPV tests — no.	5	—	4	—
Released from intervention after second HPV test but received diagnosis later — no.‡	3	2	3	2
Offered study colposcopy — no.	47	1	32	1
Offered study colposcopy but did not have it — no.	2	—	2	—
Lesion detected at study colposcopy — no.	28	1	16	1
Underwent study colposcopy but received diagnosis later — no.	17§	—	14¶	—

* High-grade lesions include squamous-cell carcinoma and adenocarcinoma or adenocarcinoma in situ. CIN denotes cervical intraepithelial neoplasia, ASCUS atypical squamous cells of undetermined significance, and HPV human papillomavirus.

† Ten women in whom grade 2 or 3 cervical intraepithelial neoplasia developed were offered a second HPV test despite having had an ASCUS-positive enrollment smear (protocol violation).

‡ The women in the intervention group were infected by different types of HPV in the first and second tests, and the women in the control group were not randomly assigned to be offered colposcopy.

§ Twelve diagnoses were made as a result of clinical follow-up because of abnormal colposcopic, cytologic, or histopathological findings at the first study colposcopy; four diagnoses were made at a second study colposcopy because of persistence of HPV infection; and one diagnosis was made at the subsequent regular 3-year screening.

¶ Three women had received a diagnosis of grade 2 cervical intraepithelial neoplasia at the first study colposcopy.

gram. To avoid ascertainment bias, the number of randomized, double-blinded procedures performed in the control group was similar to that in the intervention group. There was little loss to follow-up, because the women were followed with the use of data from comprehensive registries. Therefore, we believe that our estimates are reliable and are generally applicable to cervical-cancer screening of women in this age group.

Baseline data from other randomized, controlled trials have found that adding HPV testing to cytologic testing increases the detection rate of grade 2 or 3 cervical intraepithelial neoplasia.^{13,15,16} Since HPV infection precedes cytologic abnormalities in the natural history of cervical cancer, it is probable that the increased incidence of grade 2 or 3 lesions or cancer that was observed at prevalence screening, followed by a reduced incidence of grade 2 or 3 lesions or cancer at subsequent screening examinations, represents a gain in lead time

— the early detection of disease due to screening.²⁶ The lack of efficacy data from randomized trials of HPV-based cervical-cancer screening has raised the concern that the increased sensitivity of HPV-based screening represents the diagnosis of lesions that would have regressed spontaneously or that would never have been diagnosed without HPV-based screening.²⁷ Our finding of a statistically significant increase in grade 2 cervical intraepithelial neoplasia lesions detected by prevalence screening in the intervention group, which was not followed by a reduction in grade 2 lesions detected by subsequent screening examinations, suggests that some of the increased sensitivity for grade 2 lesions in HPV-based cervical-cancer screening indeed reflects overdiagnosis. Procedures that result in the diagnosis of regressive lesions will have to be considered in studies of the cost-effectiveness of HPV screening.

A randomized trial of triaging of women with

findings of ASCUS in Pap smears found that HPV-based triaging resulted in the diagnosis of more cases of grade 2 (but not more cases of grade 3) cervical intraepithelial neoplasia than triaging based on repeated Pap smears. This result suggests that HPV-based screening results in overdiagnosis of regressive grade 2 cervical intraepithelial neoplasia lesions, but that the grade 3 lesions detected by HPV testing do not regress.²⁸ Thus, a distinction between the pathological diagnoses of grade 2 and grade 3 cervical intraepithelial neoplasia may be important in future clinical studies of HPV screening and the prevention of cervical cancer.

A limitation of our study is that we followed the women for an average of only 4.1 years. This period covers the next screening round (scheduled to take place 3 years later) in terms of Pap smears and immediate referrals. It does not cover the associated follow-up of low-grade lesions, which may take several years. To evaluate fully the effect of overdiagnosis in the subsequent screening round, a longer follow-up that extends the next screening round for several years will be needed.

We found that women persistently infected with the same high-risk type of HPV who had normal

colposcopic findings, as well as normal histopathological findings on blinded biopsies, were at high risk for grade 2 or 3 cervical intraepithelial neoplasia or cancer for several years after the initial colposcopy. It appears that some high-grade lesions develop without any detectable precursor lesions, even when they have been sought by an extended colposcopy protocol. Additional research will be needed to define the optimal clinical management of persistent HPV infection.

In conclusion, we found that HPV-based cervical-cancer screening protects against grade 2 or 3 cervical intraepithelial neoplasia or cancer and against grade 3 cervical intraepithelial neoplasia or cancer detected in subsequent screening rounds. This result indicates that the improved sensitivity of HPV testing is not merely due to overdiagnosis but is attributable, at least in part, to earlier diagnosis of lesions that do not regress. The extent of overdiagnosis and the long-term duration of protection against grade 3 cervical intraepithelial neoplasia and invasive cancer after a negative test for HPV infection will need additional study.

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CORRECTION

Human Papillomavirus and Papanicolau Tests to Screen for Cervical Cancer

Human Papillomavirus and Papanicolau Tests to Screen for Cervical Cancer . Bo Johansson, Ph.D., should be listed as the ninth author (page 1589, between Drs. Strander and Forslund). The article has been corrected on the *Journal's* Web site at www.nejm.org.