

The Positive Predictive Value of Cervical Smears in Previously Screened Postmenopausal Women: The Heart and Estrogen/progestin Replacement Study (HERS)

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Background: The benefits and risks of performing annual cervical smears on postmenopausal women are not well defined. The independent effect of hormone replacement therapy on development of cytologic abnormalities is unknown.

Objective: To determine the positive predictive value of cervical smears in previously screened postmenopausal women and to determine the effect of oral estrogen plus progestin on incident cervical cytologic abnormalities.

Design: Prospective cohort study (incidence) and randomized, double-blind, placebo-controlled trial (hormone therapy).

Setting: 20 U.S. outpatient and community clinical centers.

Participants: 2561 women with a uterus and normal cytologic characteristics at baseline.

Interventions: Annual smears; oral conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, or identical placebo.

Measurements: Incident cytologic abnormalities (atypical squamous cells of undetermined significance, atypical glandular cells of undetermined significance, low-grade squamous epithelial lesion, and high-grade squamous epithelial lesion) and final histologic diagnoses.

Results: The incidence of new cytologic abnormalities in the 2 years following a normal smear was 110 per 4895 person-years (23 per 1000 person-years [95% CI, 18 to 27 per 1000 person-years]). Among the 103 women with known histologic diagnoses, one had mild to moderate dysplasia. The positive predictive value of any smear abnormality identified 1 year after a normal smear, therefore, was 0% (CI, 0% to 5.0%) (0 of 78 women); the positive predictive value of abnormalities found within 2 years was 0.9% (CI, 0.0% to 3.0%) (1 of 110 women). In hormone-treated compared with non-hormone-treated women, the incidence of cytologic abnormalities was nonsignificantly higher (relative hazard, 1.36 [CI, 0.93 to 1.99]), largely because of a nonsignificant 58% greater incidence of atypical squamous cells of undetermined significance (relative hazard, 1.58 [CI, 0.99 to 2.52]).

Conclusions: Because of a poor positive predictive value, cervical smears should not be performed within 2 years of normal cytologic results in postmenopausal women. Therapy with oral estrogen plus progestin does not significantly affect the incidence of cytologic abnormalities.

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In the United States, there is no consensus about screening postmenopausal women for cervical neoplasia. Current recommendations by professional groups range from discontinuing screening at 65 years of age in previously screened women with a history of normal cervical smears (1) to lifelong screening at less frequent, but undefined, intervals (2). Since women spend one third of their lives in the postmenopausal period, the issue of cervical screening has great public health importance. Although the benefits of screening are clear in unscreened women, benefits of frequent repeated screening in postmenopausal women with a history of normal cytologic results in terms of “true-positive” test results have not been well defined. Recent studies have demonstrated a low incidence of important cervical disease in

previously screened women older than 50 years of age (3, 4). Since the likelihood that a positive test result is “false positive” increases as disease incidence decreases, cervical smears may have a poor positive predictive value in previously screened postmenopausal women. These false-positive smears are related to the risks associated with screening because they lead to needless patient concern, follow-up diagnostic testing, and invasive procedures. Because few previous studies have comprehensively defined these risks, many women have had limited information on which to base an informed decision about screening.

Data are conflicting regarding the effect of exogenous hormone therapy on cervical cytologic conditions in postmenopausal women. A report from a National

Cancer Institute–sponsored workshop advocates therapeutic use of topical estrogen creams in postmenopausal women with atypical squamous cells of undetermined significance (ASCUS) (5) on the basis of supporting evidence suggesting that the treatment may ameliorate atrophy that can be mistaken for cytologic atypia (6). No controlled trials of this intervention have been performed. That oral hormonal replacement therapy may prevent cervical smears interpreted as ASCUS is biologically plausible; a recent observational study, however, reported that women older than 55 years of age with ASCUS were three times more likely to be users of hormone replacement therapy than women of a similar age with normal cervical cytologic characteristics (7). Because the study was observational, causation could not be determined. Since ASCUS is the most common cytologic abnormality in postmenopausal women, occurring in up to 3.5% of all cervical smears and accounting for more than 70% of cytologic abnormalities in women older than 50 years of age (8), any effect of hormone replacement therapy on cytologic abnormalities, regardless of the direction of effect, would be substantial on a population level.

The main objective of this study was to determine the predictive value of an abnormal cervical smear in postmenopausal women with recent normal smears. Specifically, we determined the risk for false-positive test results compared with that for true-positive test results. Using data from a randomized, controlled trial of oral estrogen plus progestin, we also determined the independent effect of oral estrogen plus progestin on development of cytologic abnormalities.

METHODS

The Heart and Estrogen/progestin Replacement Study

We used cervical smears collected prospectively during the Heart and Estrogen/progestin Replacement Study (HERS). This study was a randomized, double-blind, placebo-controlled trial of oral estrogen plus progestin in postmenopausal women with a uterus and coronary artery disease. Details of the study have been published elsewhere (9). Briefly, screening interviews were performed on 68 561 women, and 2763 women younger than 80 years of age at 20 participating clinical centers were randomly assigned to receive hormones or placebo and were followed for an average of 4.1 years. As part of

the study protocol, cervical smears were performed at annual visits to the study gynecologists. All smears were evaluated at the same central pathology laboratory (Empire Pathology Medical Group, Garden Grove, California). Smear results were reported by using the Bethesda system.

Participants

We identified women who had normal cervical smears at study entry and an abnormal cervical smear at the first or second annual visit. We focused on smears performed only in the first 2 years of the 4-year study to allow at least 2 years for a final diagnosis to be determined. To avoid counting a woman with several abnormal smears more than once, we censored women with abnormal smears at year 1. We defined “abnormal” as ASCUS, atypical glandular cells of undetermined significance (AGCUS), low-grade squamous intraepithelial lesion, or high-grade squamous intraepithelial lesion.

Data Collection

We obtained information on the follow-up of abnormalities from two sources: a questionnaire sent to clinical personnel at each study site and data collected as part of the trial protocol. We used two sources for data abstraction because the main study protocol did not provide a standardized way to follow-up, encode, or report outcomes of abnormal smears. The questionnaire requested specific information on all procedures and therapies that were performed within 2 years of the abnormal smear and were a direct result of the smear abnormality. The HERS database included results of all study cervical smears after the abnormal smear and descriptions of diagnostic and therapeutic cervical procedures performed to evaluate abnormal smears.

All study participants gave informed consent to have medical records reviewed. Personnel at clinical sites reviewed medical records. In cases in which the participant received follow-up care from a physician not related to the study, attempts were made to obtain information from the outside physician. If participants underwent any additional diagnostic tests, such as colposcopy, endocervical curettage, or endometrial biopsy (for the evaluation of AGCUS), we obtained copies of original test results and pathology reports confirming histologic diagnoses.

Table 1. Criteria for Defining Final Status as “Normal” in 110 Women with Abnormal Cytologic Results at the First or Second Annual Visit*

Cytologic Result	Criteria for “Normal” Status
ASCUS	The next smear and all other smears performed within the subsequent 2 years were normal, or The next smear showed ASCUS but was followed by two normal smears performed within the subsequent 2 years, or Colposcopy performed at any time within the subsequent 2 years was normal†
Low-grade squamous intraepithelial lesion	The next smear and all other smears performed within the subsequent 2 years were normal, or The next smear revealed ASCUS or a low-grade squamous intraepithelial lesion but was followed by two normal smears within the subsequent 2 years, or Colposcopy performed at any time within the subsequent 2 years was normal†
AGCUS	The next smear and all other smears performed within the subsequent 2 years were normal, or Colposcopy performed within the subsequent 2 years was normal†
High-grade squamous intraepithelial lesion	Colposcopy performed at any time within the subsequent 2 years was normal†

* AGCUS = atypical glandular cells of undetermined significance; ASCUS = atypical squamous cells of undetermined significance.

† Colposcopy with normal biopsy, endocervical curettage, or both, or colposcopy with no biopsy performed if no lesion is seen.

We determined the date and type of initial procedure performed in evaluation of the abnormal smear and enumerated all procedures secondary to the abnormal smear, including repeated smears. We classified cervical smears as “extra” if they were performed within 9 months of an abnormal smear and were not performed as part of the annual evaluation. We included endometrial biopsies only if supporting documentation indicated that the smear result was the primary reason for the test. In addition, we enumerated additional procedures and therapies, such as cone biopsies, loop electro-surgical excision procedures, and hysterectomies.

We classified the final histologic status of each woman in one of four diagnostic categories: normal (a nondysplastic process, such as atrophy, cervicitis, or inflammation), low-grade histologic condition (human papillomavirus effect or grade I cervical intraepithelial neoplasia), high-grade histologic condition (cervical intraepithelial neoplasia, grades II to III, or vaginal intraepithelial neoplasia, grades II to III), and unknown. For each cytologic abnormality, we considered the final histologic diagnosis to be “normal” only if participants met the criteria outlined in **Table 1**. We considered all other participants, including those who did not meet the cri-

teria for a normal diagnosis and those whose results could not be located, to have “unknown” final histologic diagnoses. We considered high-grade cervical intraepithelial neoplasia (grades II to III) and invasive cervical cancer to be the most important histologic outcomes because identification and treatment of these lesions are the goals of cervical cytologic screening.

Study participants were randomly assigned to receive one tablet of conjugated equine estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, or placebo. Randomization was done by using computer-generated random numbers at each clinical center. The placebo pill was identical in appearance to the active medication. Tablet composition and the accuracy of the blinded medication assignment were confirmed by chemical analysis. Cytotechnologists and pathologists at the laboratory evaluating the cervical smears were blinded to the study group assignment.

Demographic data, including information on risk factors for cervical neoplasia (for example, current smoking and parity), were collected at two baseline clinic visits. In addition, we distributed a pretested questionnaire that included information about traditional risk factors for cervical neoplasia, such as age at first intercourse, previous screening frequency, previous cervical smear abnormalities, recency of sexual activity, and history of sexually transmitted infections. Seventeen of 20 sites, involving 2417 enrollees, agreed to distribute the questionnaire, and 1603 questionnaires (66.3%) were returned. Questionnaires were designed to be self-administered, although clinical personnel at some sites assisted participants in completing the forms. We collected this information to provide an overview of the risk status of the HERS sample, which allowed us to address the issue of generalizability of the results to other groups of women.

Statistical Analysis

We determined the incidence rates of cervical smear abnormalities for each year by dividing the number of women with abnormal smears by the number of women screened. We computed incidence rates for the first 2 years of the study by dividing the total number of women with abnormal smears at the end of the second year by the number of person-years of observation. We calculated the positive predictive value of each smear

Table 2. Incidence Rates of Smear Abnormalities in All Women according to Treatment Assignment (Univariate Analyses)*

Cytologic Outcomes	Time Period	Treatment Assignment				Relative Hazard (95% CI)
		Estrogen plus Progestin		Placebo		
		Patients, <i>n</i>	Rate per 1000 Person-Years	Patients, <i>n</i>	Rate per 1000 Person-Years	
ASCUS	Year 1	27	21.2	19	14.7	1.44 (0.81–2.57)
	Year 2	18	15.6	10	8.5	1.84 (0.86–3.92)
	Years 1 and 2	45	18.5	29	11.8	1.58 (0.99–2.52)
AGCUS, low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion	Year 1	16	12.6	16	12.4	1.02 (0.51–2.02)
	Year 2	2	1.7	2	1.7	1.02 (0.14–7.24)
	Years 1 and 2	18	7.4	18	7.3	1.02 (0.53–1.95)
Any cytologic abnormality requiring follow-up†	Year 1	43	33.8	35	27.1	1.25 (0.80–1.93)
	Year 2	20	17.3	12	10.2	1.70 (0.84–3.44)
	Years 1 and 2	63	26.0	47	19.1	1.36 (0.93–1.99)

* AGCUS = atypical glandular cells of undetermined significance; ASCUS = atypical squamous cells of undetermined significance.

† ASCUS, AGCUS, low-grade squamous intraepithelial lesion, or high-grade squamous intraepithelial lesion.

abnormality by dividing the number of women with high-grade cervical histologic conditions (defined as grade II cervical intraepithelial neoplasia or worse) by the number of women with any cervical abnormality (defined as ASCUS, AGCUS, low-grade squamous intraepithelial lesion, or high-grade squamous intraepithelial lesion). We used an unadjusted Cox proportional hazards model to determine relative hazards and 95% CIs for the incident rates of cervical smear abnormalities between the two groups (SAS, version 6.12 [SAS, Inc., Cary, North Carolina]). With the chi-square test, we tested the hypothesis that the incidence rates of smear abnormalities did not differ by study site. The assumption of proportionality for the Cox model was tested and met. We adjusted for potential differences between the two groups in terms of traditional risk indicators for cervical neoplasia by using a multivariate model. For all analyses, we considered an α value less than 0.05 to be statistically significant.

Role of the Funding Sources

The Heart and Estrogen/progestin Replacement Study was designed and carried out by the co-investigators and was funded by Wyeth-Ayerst Research. Investigators at the HERS Coordinating Center at the University of California, San Francisco, collected all outcome data, supervised adjudication of outcome events, and performed all data analysis.

RESULTS

Our study was made up of 2561 women with normal baseline smears. The mean age of the cohort was 66.7 years. Approximately 11% of patients were of non-white ethnicity, 60% had 12 or fewer years of education, 20% had had five or more children, 20% were 18 years of age or younger at the birth of their first child, and 13% currently smoked cigarettes. One year after the normal baseline smear, 78 women (3.0%) had an abnormal smear; an additional 32 of 2346 women (1.4%) had an abnormal smear 2 years later (Table 2). The incidence of new cytologic abnormalities in the 2 years following a normal smear, therefore, was 110 per 4895 person-years (23 per 1000 person-years [95% CI, 18 to 27 per 1000 person-years]). Most abnormalities were reported as ASCUS (67.3%) and AGCUS (21.0%). In-

Table 3. Total Interventions Performed on 110 Women within 2 Years of an Abnormal Smear

Type of Intervention	Interventions Performed, <i>n</i>
Extra cervical smear	112
Colposcopy	33
Cervical or vaginal biopsy	30
Endocervical curettage	35
Endometrial biopsy	8
Dilatation and curettage	4
Loop electrosurgical excision procedure	7
Cone biopsy	2
Hysterectomy	0
Total	231

idence rates of abnormalities did not vary by study site ($P = 0.12$). Most smears were of satisfactory quality for interpretation; in the first year following a normal smear, the incidence of smears reported as wholly unsatisfactory was 0.16%.

We obtained follow-up information on the 110 women with cervical smear abnormalities in the first 2 years. These data were obtained from questionnaires and supporting documentation sent from the clinical sites in 67.3% of women ($n = 74$), from the questionnaire with supplemental information from the study database in 25.0% of women ($n = 27$), and from the study database alone in the remainder of the women (8.2% [$n = 9$]). Two women (1 with ASCUS and 1 with AGCUS) left the study or died before the abnormal smear could be evaluated. Repeated smears were the most common initial procedure performed in women with ASCUS (91.9%) and AGCUS (65.2%). Most women with dysplastic smears—low-grade squamous intraepithelial lesion (8 of 12 women [66.7%]) and high-grade squamous intraepithelial lesion (1 of 1 woman [100%])—were evaluated by colposcopy. A total of 231 interventions were performed, and 48.5% (112 of 231) were cervical smears (Table 3). Twenty-six women had 33 colposcopies, and 21 women had cervical biopsies.

Final diagnoses were obtained for all women except for the 2 described above and 5 others: 3 with ASCUS and 2 with low-grade squamous intraepithelial lesion. Of the 3 women with ASCUS, the first had another ASCUS smear followed by only one normal smear

within the 2-year follow-up period. The second, who had a normal subsequent smear followed by an AGCUS smear and a normal smear, was included in the “unknown” category because her test results did not meet the definition of normal outlined in Table 1. The third had two subsequent normal smears followed by a normal colposcopy and a loop electrosurgical excision procedure, the results of which are unknown. Of the 2 women with low-grade squamous intraepithelial lesion, 1 had cryotherapy and a loop electrosurgical excision procedure followed by two normal cervical smears; we were unable to obtain the pathology report from her loop electrosurgical excision procedure. The other woman with low-grade squamous intraepithelial lesion had a normal subsequent smear but died before undergoing further evaluation.

Most of the final diagnoses (94 of 110 [85.5%]) were normal (Table 4). No woman had grade II to III cervical intraepithelial neoplasia or invasive cervical cancer. Three women had potentially important final histologic diagnoses: one cervical finding (cervical intraepithelial neoplasia, grade I to II) and two noncervical findings (grade III vaginal intraepithelial neoplasia and endometrial hyperplasia without atypia). The woman with grade I to II cervical intraepithelial neoplasia was in the hormone group and had a normal cervical smear at baseline and at year 1, followed by an ASCUS smear at year 2; on cervical and cone biopsy, her final diagnosis was reported as “mild to moderate dysplasia.” The positive predictive value for any cervical smear abnormality

Table 4. Final Diagnoses in 110 Women with Abnormal Cervical Smears*

Results of Cytologic Examination	Women Who Received Each Final Diagnosis					Total <i>n</i>
	Normal or Nondysplastic Process†	Low-Grade Histologic Condition‡	High-Grade Histologic Condition§	Endometrial Hyperplasia without Atypia	Unknown	
	← <i>n</i> (%) →					
ASCUS	66 (89.2)	2 (2.7)	1 (1.4)	1 (1.4)	4 (5.4)¶	74
AGCUS	20 (87.0)	2 (8.7)	–	–	1 (4.3)¶	23
Low-grade squamous intraepithelial lesion	8 (66.7)	2 (16.7)	–	–	2 (16.7)	12
High-grade squamous intraepithelial lesion	–	–	1 (100)**	–	–	1
Total	94	6	2	1	7	110

* AGCUS = atypical glandular cells of undetermined significance; ASCUS = atypical squamous cells of undetermined significance.

† Atrophy, cervicitis, inflammation.

‡ Human papillomavirus effect, grade I cervical intraepithelial neoplasia.

§ Cervical intraepithelial neoplasia, grades II to III, or vaginal intraepithelial neoplasia, grades II to III.

|| Reported as cervical intraepithelial neoplasia, grade I to II.

¶ One participant left the study or died before initial evaluation.

** Reported as grade III vaginal intraepithelial neoplasia.

Table 5. Risk Factors for Developing Cytologic Abnormalities over the First 2 Years of the Study Period (Multivariate Analyses)*

Variable	Relative Hazard (95% CI)		
	ASCUS	Low-Grade Squamous Intraepithelial Lesion, High-Grade Squamous Intraepithelial Lesion, or AGCUS	Any Abnormality Requiring Additional Test†
Age per 5-year interval	0.90 (0.77–1.10)	0.86 (0.66–1.10)	0.90 (0.77–1.05)
Nonwhite ethnicity	0.81 (0.38–1.73)	1.39 (0.56–3.44)	0.99 (0.56–1.76)
≥12 years of education	0.98 (0.61–1.58)	1.10 (0.55–2.20)	1.02 (0.69–1.51)
Parity ≥5	1.42 (0.84–2.40)	1.83 (0.90–3.73)	1.56 (1.02–2.37)
≤18 years of age at birth of first child	1.59 (0.95–2.65)	0.96 (0.43–2.14)	1.36 (0.88–2.09)
Current smoker at baseline	1.29 (0.70–2.39)	0.98 (0.37–2.58)	1.19 (0.71–2.00)
Oral estrogen plus progestin	1.58 (0.99–2.51)	0.99 (0.51–1.90)	1.35 (0.92–1.97)

* AGCUS = atypical glandular cells of undetermined significance; ASCUS = atypical squamous cells of undetermined significance.

† ASCUS, AGCUS, low-grade squamous intraepithelial lesion, or high-grade squamous intraepithelial lesion.

(ASCUS, AGCUS, low-grade squamous intraepithelial lesion, and high-grade squamous intraepithelial lesion) in the first year following a normal smear was 0% (CI, 0% to 5.0%) (0 of 78 women). On the basis of the one observed outcome in the second year, the positive predictive value for any cervical smear abnormality in the 2 years following a normal smear was 0.9% (CI, 0.0% to 3.0%) (1 of 110 women). The incidence of an important cervical histologic finding within 2 years of a normal smear, therefore, was 1 per 4895 person-years (0.2 per 1000 person-years [CI, 0 to 1.0 per 1000 person-years]).

We found no significant differences in the baseline prevalence of traditional risk factors for cervical neoplasia between the group receiving estrogen plus progestin and the group receiving placebo. Women in the hormone group had a nonsignificantly higher incidence of any cytologic abnormality over the 2-year period (relative hazard, 1.36 [CI, 0.93 to 1.99]), largely because of a nonsignificant 58% greater incidence of ASCUS among hormone-treated women (relative hazard, 1.58 [CI, 0.99 to 2.52]) (Table 2). We found no increased incidence of low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, or AGCUS combined among women in the hormone group (relative hazard, 1.02 [CI, 0.53 to 1.95]). In multivariate analyses, women who had had five or more children had an increased incidence of all cytologic abnormalities (relative hazard, 1.56 [CI, 1.02 to 2.37]) (Table 5). The incidence of ASCUS associated with hormone use was unchanged in multivariable analyses (relative hazard, 1.58 [CI, 0.99 to 2.51]). Because we observed only a

small number of outcomes, we did not perform stratified analyses by study site.

From the questionnaire, we found that the mean age at first intercourse was 20.1 years and that 38.2% of women reported first intercourse at or before 18 years of age. One third of women (551 of 1603 [34.4%]) had been screened less often than every 1 to 2 years before entering the HERS trial. Ten percent (162 of 1603) reported having had at least one previous abnormal smear, and 7.1% (114 of 1603) reported previous treatment for a cervical abnormality (cryotherapy, laser therapy, loop electrosurgical excision procedure, or cone biopsy). About half (759 of 1603 [47.4%]) had been sexually active within the past 5 years, and 31% (500 of 1603) had been sexually active within the past year. Forty-five percent (723 of 1603) reported more than one lifetime male sexual partner; 50 of 1603 women (2.9%) reported having new male partners within the past 5 years. Fewer than 5% of women reported ever having a sexually transmitted infection (59 of 1603 [3.6%]).

DISCUSSION

Important histologic cervical lesions are uncommon in previously screened postmenopausal women. Within 2 years of a normal smear, 110 women in the trial (23 per 1000 person-years) had a cytologic abnormality. Of these, all but 1 were false positive. Thus, these women were many times more likely to have a false-positive smear than a true-positive smear. The risks in terms of false-positive test results have not been well defined and are therefore not often discussed with women. While the

evaluation of false-positive tests is costly, the risks for overscreening go beyond costs. Women who receive abnormal cytologic results may become anxious and depressed and develop low self-esteem (10, 11). Given these adverse effects on quality of life, practitioners should be cautious about applying tests that have a high likelihood of yielding false-positive results because such tests can lead to needless patient concern, follow-up diagnostic testing, and invasive procedures. In our study, interventions for cervical smear abnormalities were not uncommon. We found that 231 additional interventions were performed to find one potentially important cervical lesion (cervical intraepithelial neoplasia, grade I to II).

We were unable to determine a final outcome for five women with abnormal smears, two of whom underwent loop electrosurgical excision procedures. If these two women had significant cervical histologic abnormalities, the positive predictive value of an abnormal cervical smear may be as high as 3 of 110 (2.7% [CI, 0.0% to 6.2%]) or 5 of 110 (4.6% [CI, 0.0% to 8.8%]) if other outcomes, such as grade III vaginal intraepithelial neoplasia and endometrial hyperplasia without atypia, are included. We do not consider the latter two noncervical findings important in cervical cancer screening. Alternatively, the positive predictive value may be as low as 0% (CI, 0.0% to 2.6%) if these women had low-grade lesions and if the single diagnosis of mild to moderate cervical dysplasia identified is considered not clinically significant. In any case, the range of possible positive predictive values is low, especially given the relatively high risk for a false-positive result. We were unable to calculate negative predictive value because we could not be sure that women with normal cytologic characteristics did not have false-negative smears.

We also found that daily use of oral conjugated equine estrogens and medroxyprogesterone acetate over a 2-year period in postmenopausal women with normal cervical smears did not affect the incidence of cytologic abnormalities or clinically important cervical disease. The independent effect of estrogen plus progestin on risk for ASCUS, however, remains unclear. We found a 58% increased risk for ASCUS in hormone-treated women. However, this risk was not statistically significant ($P = 0.06$), and findings of marginal significance are difficult to interpret. Either hormone treatment does not increase risk for ASCUS, or it increases risk and we

had insufficient power to demonstrate this conclusively. If estrogen plus progestin increases risk, the mechanisms by which it may do so are enigmatic. Associations between exogenous hormones in the form of oral contraceptive pills and cervical neoplasia have been demonstrated in observational studies (12, 13). This association may be mediated by an effect of estrogen (14), progesterone (15), or both on human papillomavirus, the agent strongly associated with cervical neoplasia (16). Previous studies in postmenopausal women, however, do not support associations between hormone replacement therapy and prevalence of human papillomavirus (17, 18) or cervical cancer (19–21). Regardless of hormone use, most ASCUS in postmenopausal women is not associated with underlying cervical neoplasia.

Our investigation is a large prospective study of previously screened postmenopausal women and quantifies the risk for false-positive test results related to cervical smear screening and use of oral estrogen plus progestin. Since all women were screened annually solely because they were enrolled in the trial and not because of individual risk factors, our estimates of the incidence of cytologic abnormalities in this sample should be unbiased. Not all women screened at the first annual visit were screened at the second annual visit because of dropout or death; however, these women represented less than 5% of the eligible cohort.

Women in the HERS trial were volunteers with coronary artery disease, and generalizability of our results to other groups of women may not be appropriate. However, we know of no evidence linking heart disease to cervical neoplasia and therefore have no reason to believe that these results are not applicable to postmenopausal women without heart disease. Volunteers in clinical trials may be healthier than other women and may be at generally lower risk for cervical disease. From our questionnaire, these women seemed to be at low risk in general, although how they compare to other women of a similar age is not known. Screening periodicity, however, should not depend on the risk status of individual women but only on test sensitivity and the length of the preinvasive stage of cervical neoplasia (22). We have no reason to believe that either of these factors was different in our study sample from those in other postmenopausal women. It is important to emphasize that our results are generalizable to postmenopausal women with a cervix who have had a recent normal cervical smear; they do

not apply to postmenopausal women who have never been screened or those not recently screened. In addition, we assessed only those outcomes that occurred during the 2 years following a normal smear and therefore could not assess the utility of screening beyond this period.

Future studies should focus on determining the optimal screening strategy in postmenopausal women with a history of normal smears by obtaining quantitative estimates of benefits and risks and taking into account cost-effectiveness and individual patient preferences. Until more information is available, we recommend not performing cervical smears within 2 years of a normal smear in postmenopausal women. Women choosing to be screened within that interval should be informed that they are far more likely to undergo further diagnostic testing secondary to a false-positive result than to have clinically important cervical disease.

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A childlike innocence, unaffected by age with its maddening mutilations—remains still her virtue. To some it is childish, all the characteristics of a spoiled child—which she was—with her bad temper, fears, vindictiveness of an undisciplined infant. To others an indestructibility, a permanence in defiance of the offensive discipline which is only a virtue to those who wish to flatten out every rebellious instinct down to a highway levelness for their own crazy facility. Be that as it may she has not given in. And is still, as a child, amused.

William Carlos Williams
Yes, Mrs. Williams
 New York: New Directions; 1982:130

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