

Incidence of Cervical Cytological Abnormalities With Aging in the Women's Health Initiative

A Randomized Controlled Trial

Shagufta Yasmeen, MD, MRCOG, Patrick S. Romano, MD, MPH, Mary Pettinger, MS, Susan R. Johnson, MD, MS, F. Allan Hubbell, MD, MSPH, Dorothy S. Lane, MD, MPH, and Susan L. Hendrix, DO

OBJECTIVE: To estimate the incidence of cytological abnormalities and cervical cancer and to determine the effect of oral estrogen and progestin on cervical cytology among postmenopausal women participating in a multi-institution clinical trial.

METHODS: The study was a longitudinal analysis of a prospective cohort of 16,608 postmenopausal women (aged 50–79 years) participating in the Women's Health Initiative (WHI) clinical trial of estrogen plus progestin. Eligible participants had a cervical smear within 1 year before randomization and at 3- and 6-year follow-ups. Outcomes measured were low-grade and high-grade squamous intraepithelial lesions (LSIL, HSIL) and cervical cancer at follow-up years 3 and 6.

RESULTS: Of 15,733 eligible participants with a uterus, 7,663 were assigned to placebo and 8,070 to estrogen plus progestin. At baseline, 318 women (2%) had low-grade abnormalities on cervical cytology. The annual incidence rate of any new cytological abnormality in the estrogen plus progestin group was significantly higher than that in the placebo group (hazard ratio 1.4, 95% confidence interval [CI] 1.2–1.6). Independent risk factors for HSIL and cervical cancer over a 6-year follow-up (after stratifying for baseline cytologic abnormalities)

included sexual activity in the past year while not being married or living as married (hazard ratio 3.5, 95% CI 1.5–8.3). Risk factors did not include age or use of estrogen plus progestin.

CONCLUSION: Use of estrogen plus progestin was associated with increased incidence of any cytologic abnormality, although it had no impact on the incidence of HSIL or cervical cancer. Sexually active older women who are not married or living as married may benefit from continued cervical cancer screening.

CLINICAL TRIAL REGISTRATION: Clinicaltrials.gov, www.clinicaltrials.gov, NCT00000611

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LEVEL OF EVIDENCE: I

In the United States, 25% of new cases and 41% of deaths from cervical cancer occur among the 13% of the female population aged 65 years or older.¹ However, few prior studies provide data on cervical cancer screening from large numbers of women aged 65 years and older. Sigurdsson² reported that the frequency of high-grade intraepithelial lesions in women aged 60–69 years decreased as the number of prior normal cytology tests increased. Sawaya et al³ observed low rates of low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) among women aged 65 years and over with at least one previous normal cytology within the last 3 years. Accordingly, current recommendations by professional groups range from discontinuing screening at 65 years of age in previously screened women with a history of normal cervical cytology⁴ to lifelong screening at less frequent, but undefined, intervals.⁵ The American Cancer Society based its recommendation to cease screening at age

From the University of California, Davis, Davis, California; Women's Health Initiative Clinical Coordinating Center, Fred Hutchinson Cancer Research Center, Seattle, Washington; University of Iowa, Iowa City, Iowa; University of California Irvine, California; State University of New York, Stony Brook, New York; Wayne State University School of Medicine, Detroit, Michigan.

Wyeth-Ayerst Research provided the study medication (active and placebo).

Corresponding author: Shagufta Yasmeen, MD, MRCOG, Assistant Professor, University of California, Davis, Department of Obstetrics/Gynecology and Internal Medicine, 4860 Y Street, Suite 2500, Sacramento, CA 95817; e-mail: syasmeen@ucdavis.edu.

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70 on mathematical modeling and demographic trends that may decrease the likelihood of older women having new sexual partners and thus new exposures to human papillomavirus (HPV).^{6,7}

The objective of this paper was to estimate the incidence of cytological abnormalities and cervical cancer on routine cytology among postmenopausal women, using data from the Women's Health Initiative (WHI) randomized, controlled trial of estrogen plus progestin. In addition, we estimated the effects of independent risk factors for acquiring HSIL and cervical cancer in this population.

MATERIALS AND METHODS

The WHI is a prospective study of 161,808 postmenopausal women aged 50–79 years who were enrolled from 1993 to 1998 at 40 U.S. clinical centers. Our study population included 16,608 postmenopausal women with a uterus who enrolled in the estrogen plus progestin clinical trial. Study methods have been published in detail elsewhere.⁸ Briefly, postmenopausal women were eligible for enrollment if they had no history of breast, endometrial, or nonmelanoma skin cancer and no history of other cancers within 10 years, and if they were unlikely to move or die within 3 years and not currently participating in any other clinical trial. Women with a prior diagnosis of invasive cervical cancer were excluded from our analysis. Eligible women were randomized in equal proportions, using a permuted-block algorithm stratified by clinical center and age group, with block sizes of 10, to either placebo or to 0.625 mg/d of conjugated equine estrogen plus 2.5 mg/d of medroxyprogesterone acetate, which was administered in a single tablet (Prempro, Wyeth, St. Davids, PA).^{8,9} At baseline, women completed screening and enrollment questionnaires by interview and self-report, a physical examination, and blood specimen collection. Special efforts were made to recruit a diverse sample that represented the population of community-dwelling, postmenopausal women in the United States. The study was reviewed and approved by the Human Subjects Review Committee at each participating institution. This report includes outcomes and procedures occurring before the estrogen plus progestin trial closure on July 8, 2002.

All cervical cytology reports were collected and recorded at the individual clinical centers on a "Pap test" data collection form and entered into the Clinical Coordinating Center study-wide database. Women were eligible for randomization in the estrogen plus progestin trial if they had normal findings or LSIL, either at baseline or within 1 year before

enrollment. Women with HSIL at baseline screening were required to have follow-up, and if the results were normal or LSIL, they were given clearance to enroll in the trial. The Women's Health Initiative introduced a separate form for "Pap test" results in 1995, consistent with 1991 Bethesda System categories.¹⁰ For the purpose of our study, LSIL included atypical squamous cells of unknown significance (ASCUS), human papillomavirus (HPV), and mild dysplasia/cervical intraepithelial neoplasia grade 1 (CIN I), whereas HSIL included moderate or severe dysplasia/CIN II–CIN III, and cytological features suspicious for invasion.

All women had at least one cervical smear within 1 year before randomization and follow-up cervical cytology at years 3 and 6 in conjunction with routine pelvic examination. Women with LSIL had repeat cervical cytology within 6 months. If the repeat smear was normal, then further follow-up was recommended within 6 months per protocol. If the abnormal smear persisted, then women were referred to their health care professional for further diagnostic evaluation and treatment. Participants with HSIL or cervical cancer were taken off study medication for the remainder of the clinical trial unless these abnormalities were treated and the follow-up cervical cytology was normal or LSIL.

Semiannual self-reports of new diagnoses were recorded and all associated medical records were obtained from local health care professionals. The records were reviewed and outcomes were classified by blinded physician adjudicators at each clinical center. All gynecological cancers were forwarded to the Clinical Coordinating Center for centralized adjudication by specialists who were blinded to randomization assignment and reported symptoms. Histological codes were based on the International Classification of Disease for Oncology, second edition. All follow-up results on cervical cytology were entered in the WHI database. Although cervical cancer was not a primary endpoint in the WHI, central adjudication and coding of histology and extent of disease were performed at the WHI Clinical Coordinating Center using the Surveillance, Epidemiology, End Results (SEER) coding system.

The WHI did not centrally collect information on colposcopic findings and treatments such as cryosurgery and loop electrosurgical excision procedure (LEEP). Only local clinical centers were required to collect this information before dispensing study medications.

Information on potential cervical cancer risk factors, including age, ethnicity, history of smoking (past,



current), age at first birth, parity, previous abnormal cervical cytology, history of hormone use (estrogen and progestin), alcohol use, education, family income, medical insurance, and marital status (married, never married, divorced or separated, widowed, living in a marriage-like relationship), was collected at baseline. At baseline and year 1, all women were asked questions on marital status and sexual activity in the past year. We recoded the responses to these questions as 1) currently married or living as married; 2) not currently married or living as married, and not sexually active; and 3) not currently married or living as married, and sexually active. For statistical analysis, women who were married or “living in a marriage-like relationship” were combined into one group. Among all study participants, baseline characteristics were compared between women with LSIL and women with normal cytology at baseline. The *t* test was used to compare the means of continuous variables, while the χ^2 was used to compare the distributions of categorical variables.

We looked at the incidence of all cytological abnormalities (LSIL, HSIL) and in situ or invasive cervical cancer during the study. Incidence rates of cytological abnormalities and cervical cancer were also estimated based on marital status and sexual activity. We present Kaplan-Meier estimates of the cumulative hazard of abnormal cytology (expressed as rates per 10,000 person-years of follow-up), stratified by abnormal cytology at baseline (LSIL versus normal) and by estrogen plus progestin randomiza-

tion assignment (estrogen plus progestin versus placebo). We also substratified the former life table analysis by age at screening (50–59, 60–69, and 70–79 years). Women were censored at the date of their last cervical smear or at hysterectomy. Women with a diagnosis of cervical cancer were censored at the date of diagnosis.

We used unadjusted (univariable) Cox proportional hazard models to estimate hazard ratios (HRs), with 95% confidence intervals (CIs), for new cervical cytologic abnormalities among postmenopausal women with normal cytology, and separately among women with LSIL at baseline. The time to occurrence of the first event after baseline screening was used to calculate the estimated HR. The risk factors with either statistically significant or clinically meaningful effects in these univariable models were entered into a multivariable Cox proportional hazards model. Participants with missing results were excluded only from analyses using the relevant variables. For all analyses, we considered unadjusted 2-sided *P* values less than .05 to be significant. All tests were performed using SAS 8.2 (SAS Institute, Cary, NC).

RESULTS

Of 16,608 WHI estrogen plus progestin participants, 875 (5%) were excluded based on exclusion criteria (Fig. 1). Among the 15,733 included women, 7,663 were assigned to placebo and 8,070 to estrogen plus progestin. At baseline, 15,415 (98%) women had normal findings, and 318 (2%) had abnormal cervical

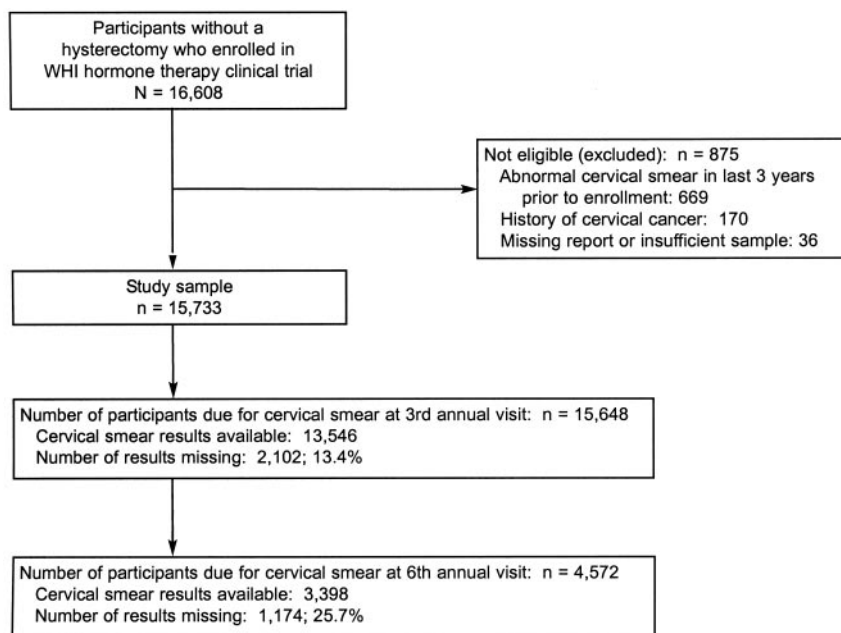


Fig. 1. Flow chart showing number of participants with baseline, 3-, and 6-year follow-up cervical cytology.

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cytology. Although 15,648 and 4,572 participants were due for cervical smears at the third and sixth annual visit, respectively, results were available for only 13,546 participants at year 3 and 3,398 participants at year 6 (Fig. 1).

Mean age, body mass index, waist-to-hip ratio, ethnicity, marital status, hormone use, smoking, alcohol intake, age at menarche, number of pregnancies, age at first birth, and education were compared between women with abnormal and normal baseline cervical cytology. Women with abnormal cytology at baseline (predominantly LSIL) were younger, with a mean age of 62 years (standard deviation 6.8), had a slightly higher mean waist-to-hip ratio, were marginally more likely to be nonwhite, and likely to be older at menarche (13–15 years versus 10–12 years) and younger at first birth (less than 20 years versus other age categories) (Table 1). Marital status, hormone therapy, smoking, alcohol intake, number of pregnancies, education, and body mass index were not significantly associated with abnormal cytology at baseline. Baseline cervical smear abnormalities included LSIL (n=313, 2%) and HSIL (n=5, 0.03%).

The observed annual incidence of newly diagnosed cervical smear abnormalities was significantly higher (HR 4.6, 95% CI 3.6–5.8) for women with abnormal baseline cytology compared with women with normal baseline cytology (653 versus 146 per 10,000 person-years). The annual incidence rates of HSIL and cervical cancer were also significantly higher (HR 9.0, 95% CI 4.3–19.2 and HR 13.8, 95% CI 2.9–66.0, respectively) among women with abnormal cytology at baseline (62 and 11.7 cases per 10,000 person-years, respectively) than among women with normal baseline cytology (7.1 and 0.9 cases per 10,000 person-years, respectively) (Table 2). The incidence of new cervical smear abnormalities in the hormone therapy group was significantly higher than that in the placebo group (HR 1.4, 95% CI 1.2–1.6).

The incidence of any abnormal cytology decreased with advancing age among women with both normal and abnormal (predominantly LSIL) cervical cytology at baseline (Table 2). However, among women aged 70–79 years with normal cervical cytology at baseline, the incidence of HSIL was slightly but significantly higher (7.8 per 10,000 person-years) than that among women 50–59 and 60–69 years of age (7.0 and 6.8 per 10,000 person-years, respectively). The overall annual incidence rate of HSIL or cervical cancer (not shown) was significantly higher (19.5 per 10,000 person-years) among sexually active women who were neither married nor living as married than among either unmarried women who were not sexu-

ally active (11.3 per 10,000 person-years) or married women (4.6 per 10,000 person-years). The same ordering of risk was seen among the subset of postmenopausal women with normal cervical cytology at baseline (16.1, 10.4, and 3.6 per 10,000 person-years, respectively).

In univariable Cox proportional hazard regression models (not shown), the statistically significant predictors of any abnormal cytology after a normal baseline cervical smear were Hispanic ethnicity (HR 1.4, 95% CI, 1.0–1.8); new sexual partner in past year (HR 1.4, 95% CI 1.2–1.8); age at first birth less than 20 years (HR 1.8, 95% CI, 1.3–2.4), 20–24 years (HR 1.7, 95% CI 1.3–2.3), 25–29 years (HR 1.8, 95% CI 1.3–2.4); and hormone therapy (HR 1.4, 95% CI, 1.2–1.6). After adjusting for significant covariates in a multivariable model, the statistically significant predictors of abnormal cytology after a normal baseline smear still included not being married or living as married and being sexually active at baseline or year 1 (HR 1.4, 95% CI 1.1–1.8), age categories less than 30 years at first birth (HR 1.7, 95% CI 1.3–2.3 to HR 1.8, 95% CI 1.3–2.4), and hormone therapy (HR 1.4, 95% CI 1.2–1.6; number needed to harm 285.5, 95% CI 206.1–464.3). The Kaplan-Meier cumulative hazard of any abnormal cytology is shown graphically in Figure 2A (stratified by baseline cervical smear result) and Figure 2B (stratified by randomization to hormone therapy).

A total of 54 participants had HSIL abnormalities during the 6-year follow-up period. Of those women, 46 had normal and 8 had abnormal cervical cytology at baseline screening. Because the number of participants who developed HSIL among those with baseline abnormalities was small, a single multivariable Cox proportional hazard regression model was used to adjust for significant covariates, stratified by the baseline cervical smear result (normal or abnormal) to adjust for any difference in the risk for development of HSIL. As displayed in Table 3, sexual activity in the past year (before the baseline or first annual visit) was associated with a significantly increased risk for development of HSIL on follow-up among women who were neither married nor living as married. Neither estrogen plus progestin therapy nor the interaction between combined hormone therapy and baseline cytologic abnormalities was a significant predictor of high-grade abnormalities. The Kaplan-Meier cumulative hazard of HSIL or cancer is shown graphically in Figure 3A (stratified by baseline cervical smear result) and Figure 3B (stratified by randomization assignment). Ten invasive cervical cancers were diagnosed over the entire follow-up period (1.15 cases



Table 1. Demographic and Clinical Characteristics of Women by Baseline Cervical Smear Results, Among Women's Health Initiative Hormone Therapy Clinical Trial Participants With a Uterus

	Baseline Cervical Smear Result				P*
	Normal (n=15,415)		Abnormal (n=318)		
	n	%	n	%	
Ethnicity					.06
White	13,029	84.5	248	78.0	
Black	1,000	6.5	28	8.8	
Hispanic	787	5.1	23	7.2	
American Indian	49	0.3	1	0.3	
Asian/Pacific Islander	337	2.2	11	3.5	
Unknown	213	1.4	7	2.2	
Marital status					.39
Never married	644	4.2	10	3.1	
Divorced/separated	2,533	16.5	62	19.5	
Widowed	2,921	19.0	63	19.8	
Presently married/living as married	9,255	60.3	183	57.5	
History of HT use					.25
Never used	11,447	74.3	234	73.6	
Past user	3,035	19.7	58	18.2	
Current user	926	6.0	26	8.2	
Smoking					.43
Never smoked	7,595	49.8	170	53.5	
Past smoker	6,061	39.8	116	36.5	
Current smoker	1,582	10.4	32	10.1	
Alcohol intake					.13
Nondrinker	1,772	11.6	43	13.7	
Past drinker	2,584	16.9	64	20.4	
Less than 1 drink per week	5,128	33.5	104	33.1	
1 drink or more per week	5,817	38.0	103	32.8	
Age at menarche (y)					.004
9 or less	197	1.3	4	1.3	
10–12	6,915	45.0	113	35.6	
13–15	7,541	49.0	188	59.3	
16 or more	723	4.7	12	3.8	
Number of pregnancies					.17
None	1,220	7.9	15	4.8	
1–3	6,885	44.8	146	46.3	
4–6	5,847	38.0	120	38.1	
7 or more	1,415	9.2	34	10.8	
Age at first birth (y)					.02
Never pregnant	1,220	8.7	15	5.3	
No term pregnancy	382	2.7	5	1.8	
Less than 20	2,058	14.7	48	17.1	
20–24	5,844	41.9	128	45.6	
25–29	3,177	22.8	61	21.7	
30–34	939	6.7	17	6.0	
35–39	273	2.0	6	2.1	
40 or more	62	0.4	1	0.4	
Education					.27
0–8 years	327	2.1	7	2.2	
Some high school	653	4.3	18	5.7	
High school diploma/GED	3,029	19.8	54	17.0	
Some school after high school	5,931	38.7	137	43.2	
College degree or higher	5,378	35.1	101	31.9	
Age (n, mean years±SD)	15,415	63±7.1	318	62±6.8	.002
BMI (n, mean±SD)	15,332	29±5.9	317	29±6.2	.13
Waist/hip ratio (n, mean±SD)	15,343	0.82±0.08	318	0.83±0.07	.02

HT, hormone therapy; GED, general equivalency diploma; SD, standard deviation; BMI, body mass index (kg/m²).

Data are presented as number and percentage or number and mean±SD, as indicated.

* Comparison between participants with normal and abnormal baseline results. Chi-square test for categorical and *t* test for continuous variables.



Table 2. Incidence Rates of Cytological Abnormalities Among Women With Normal and Abnormal Cervical Cytology by Age at Baseline Screening and Hormone Treatment Randomization Assignment in the Women's Health Initiative Clinical Trial

Cervical Cytology by Age at Baseline Screening (y)	Any Abnormality*		HSIL [†]		Cervical Cancer [‡]	
	Number of Events	Rate per 10,000 Person-Years [§]	Number of Events	Rate per 10,000 Person-Years [§]	Number of Events	Rate per 10,000 Person-Years
Normal at baseline (n=15,415)	922	146.2	46	7.1	8	0.94
50–59 (n=5,024)	341	154.2	16	7.0		
60–69 (n=6,999)	410	144.2	20	6.8		
70–79 (n=3,392)	171	136.6	10	7.8		
Abnormal at baseline (n=318)	72	653.0	8	62.1	2	11.68
50–59 (n=118)	32	722.0	6	115.0		
60–69 (n=155)	34	644.5	2	32.6		
70–79 (n=45)	6	454.8	0	0		
By HT randomization assignment						
E+P (n=8,070)	591	178.9	23	6.7	6	1.34
Placebo (n=7,663)	403	129.5	31	9.7	4	0.95

HSIL, high-grade squamous intraepithelial lesion; HT, hormone therapy; E+P, estrogen plus progestin.

* First occurrence of “abnormal, mild dysplasia,” “abnormal, LSIL, atypia,” ASCUS, “abnormal, moderate dysplasia,” “abnormal, severe dysplasia,” “abnormal, HSIL,” or cancer.

[†] First occurrence of “abnormal, moderate dysplasia,” “abnormal, severe dysplasia,” “abnormal, HSIL,” or cancer.

[‡] Locally confirmed outcomes data.

[§] Person-years were censored at the date of hysterectomy or last pap test (follow-up year 7).

^{||} Person-years were censored at the date of hysterectomy.

per 10,000 person-years); 8 women had normal and 2 had abnormal cervical smears at baseline. We had no information about ASCUS cervical cytology at baseline because WHI introduced Bethesda System categories in 1995.¹⁰ The prevalence of ASCUS cytology was 0.2% (28 cases) and 0.9% (31 cases) at 3-year and 6-year follow-ups, respectively. Women randomized to estrogen plus progestin had 60% higher risk for ASCUS cytology compared with women in the placebo group.

DISCUSSION

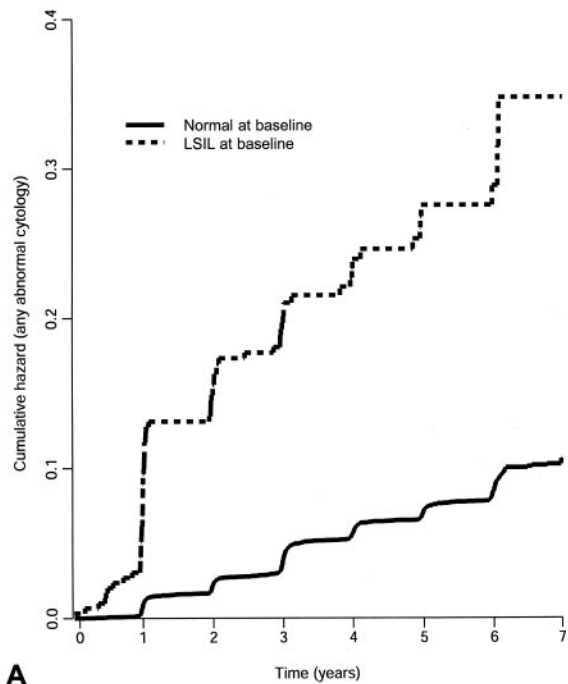
Our results show that use of conjugated equine estrogen and medroxyprogesterone acetate over a 6-year period did not affect the incidence of high-grade cytological abnormalities and cervical cancer, although it did increase the incidence of overall cytological abnormalities among postmenopausal women with normal baseline cytology. The annual incidences of new cervical smear abnormalities (LSIL and HSIL) and cervical cancer were much lower among women with a normal cervical smear at baseline than among women with an abnormal smear at baseline. Postmenopausal women with normal baseline cervical cytology had a relatively low risk of developing new cytological abnormalities, and the cumulative incidence of HSIL over a follow-up period of 3–6 years was less than 0.01%. Consistent with previous studies, our results show a modest age-related decrease in the

incidence of any cytological abnormality,^{3,11,12} but we found no age-related decrease in the incidence of high-grade abnormalities or cancer. Additionally, past hormone use did not have any significant effect on the incidence of cytological abnormalities and cancer among postmenopausal women in our univariable and multivariable analyses.

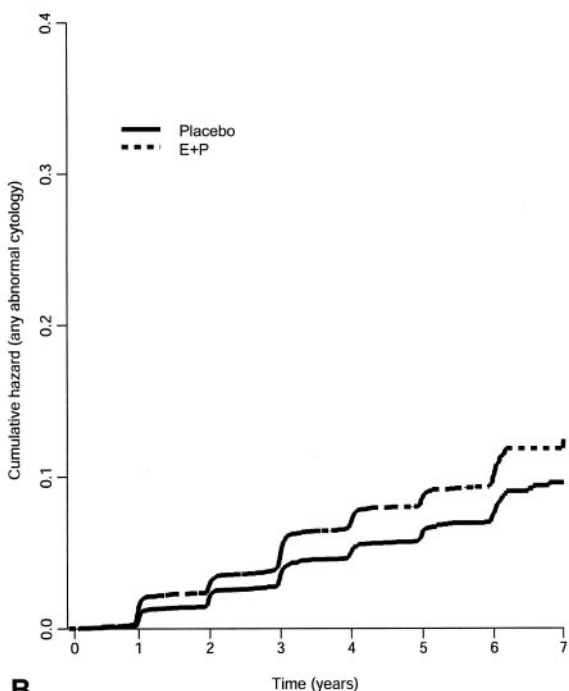
Our estimate of the incidence of squamous-cell cervical cancer after negative cytology (0.93 cases per 10,000 person-years) was generally consistent with estimates reported from a racially, ethnically, and geographically diverse population-based study from the United States (prevalence 0.06%)¹³ and from a prospective study of an unselected female population from Sweden (0.8 cases per 100,000 person-year).¹⁴ At baseline screening, the prevalence of abnormal cervical cytology in our study sample was 2%, which is lower than the 5–7% reported from other studies of women aged 50 years and older.^{11,15} These differences in prevalence are likely due to selection bias because women participating in this trial may be at lower risk for abnormal cervical cytology because of regular screening histories before enrollment.

Postmenopausal women with normal cervical cytology at baseline who were randomly assigned to receive estrogen plus progestin had a significantly higher risk of low-grade cytological abnormalities than women who were assigned to receive placebo. However, estrogen plus progestin therapy did not





A



B

Fig. 2. Kaplan-Meier estimates of cumulative incidence of abnormal cytology on cervical cytology (censored at date of hysterectomy or last cervical smear), among women in the Women's Health Initiative Hormone Therapy Clinical Trial. **A.** Cumulative hazard by baseline cervical smear result. **B.** Cumulative hazard by hormone trial randomization assignment. LSIL, low-grade squamous intraepithelial lesion; E+P, estrogen plus progestin.

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increase the incidence of HSIL and cervical cancer among women with normal cervical cytology at baseline. Another important observation noted during 3–6 years of follow-up was an increase in the risk of ASCUS cytology among women assigned to estrogen and medroxyprogesterone acetate compared with placebo. A nonsignificantly higher incidence of any cytologic abnormality (relative hazard 1.36, 95% CI 0.93–1.99) due to 58% greater incidence of ASCUS (relative hazard 1.58, 95% CI 0.99–2.52) among women in the hormone group was also reported by HERS investigators.³

The observed increase in the incidence of cytological abnormalities among participants assigned to estrogen plus progestin may be due to estrogen. Estrogen has been shown to affect dysplastic cells, because they have more estrogen receptors in their cytoplasm than malignant cells.¹⁶ In addition, the cytological changes are preserved due to cellular maturation and less drying artifact after estrogen administration, which may decrease the number of false-negative cytologies.^{17–19} The observed association between exogenous hormones and cervical dysplasia may also be mediated by the progesterone component because progesterone enhances the ability of viral DNA to transform cells that are infected with human papillomavirus.²⁰ Observational studies have demonstrated an increased risk of cervical cancer among younger women with human papillomavirus who are on oral contraceptives or pregnant, presumably due to progesterone effects,^{21,22} but this relationship remains unclear.^{23,24} However, menopausal hormone therapy has not been shown to increase the prevalence of HPV among postmenopausal women.²⁵

With regard to risk factors for cervical cancer, smoking and a history of hormone use were not significantly associated with abnormal cytology at baseline. However, women who reported sexual activity at baseline and at year 1 and not married or living as married had a significantly increased risk for development of HSIL on follow-up, independent of baseline cervical cytology. This risk is likely due to the increased chance for new exposure to HPV and a new sexual partner. The WHI did not collect information on acquiring a new sexual partner, the number of sexual partners, age at first intercourse, frequency of intercourse, or the presence of human papillomavirus infection. Additionally, information on sexual activity after year 1 was available on a small subsample (8%) of participants. For this reason, we were not able to identify women who acquired a new sexual partner, and we cannot determine the impact



Table 3. Results of Multivariable Cox Proportional Hazard Regression Model to Predict New Findings of HSIL or Cancer on Follow-up, Stratified by Baseline Cervical Smear Results (Normal, Abnormal)*

Variables	Hazard Ratio	95% CI	P
Race/ethnicity			
White	1.0		
Black	1.4	0.5–3.8	.50
Hispanic	1.2	0.3–5.3	.78
Other (Asian/PI, Am Indian, Unknown)	2.3	0.7–7.7	.17
Marital status/sexual activity			
Married or living as married	1.0		
Not married or living as married and no sexual activity	2.3	1.1–4.7	.02
Not married or living as married and sexual activity	3.5	1.5–8.3	.005
History of HT use			
Never used	1.0		
Past user	1.4	0.7–2.7	.39
Current user (at baseline)	0.4	0.0–2.7	.32
Smoking			
Never smoked	1.0		
Past smoker	1.8	0.9–3.8	.09
Current smoker	2.3	0.9–5.7	.08
Age at first birth (y)			
Never pregnant/ no term pregnancy	1.0		
Less than 20	2.1	0.5–8.0	.28
20–24	1.9	0.6–6.5	.31
25–29	2.4	0.7–8.7	.19
30 or more	1.0	0.2–6.2	.98
HT randomization assignment			
Placebo	1.0		
E+P	0.9	0.5–1.7	.75

CI, confidence interval; PI, Pacific Islander; HT, hormone therapy; E+P, estrogen plus progestin.

* This stratification allows for a different baseline hazard function in those with and without a normal baseline smear. Model also adjusted for age (linear term), alcohol use, and age at menarche.

of these traditional risk factors on HSIL or cervical cancer incidence rates.

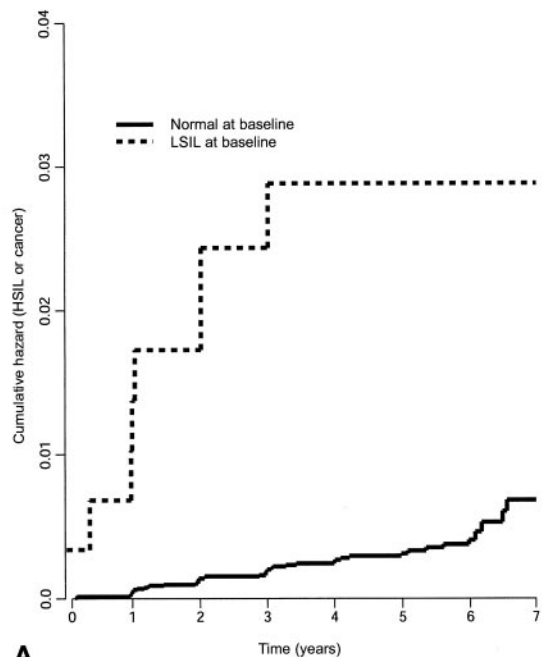
Our study results are derived from a large prospective cohort of postmenopausal women with long-term follow-up of cervical cytology. Our results confirmed the findings of previous studies on cervical cytology among postmenopausal women,^{3,13,26} but contribute new information on follow-up of abnormal cervical cytology among postmenopausal women, the risks associated with use of oral estrogen plus progestin, and the risk associated with continuing sexual activity among women who are not married or living as married. The size and geographic distribution of the sample and the completeness of data collection at each WHI study center are important strengths of this study. The WHI has 40 centers in a wide range of academic and community settings that were selected to maximize generalizability.

The main limitations of our study are that women participating in this trial may be at low risk for cervical cancer, and the study may be underpowered to estimate the differences in risk of HSIL and cervical cancer between women randomized to estrogen plus

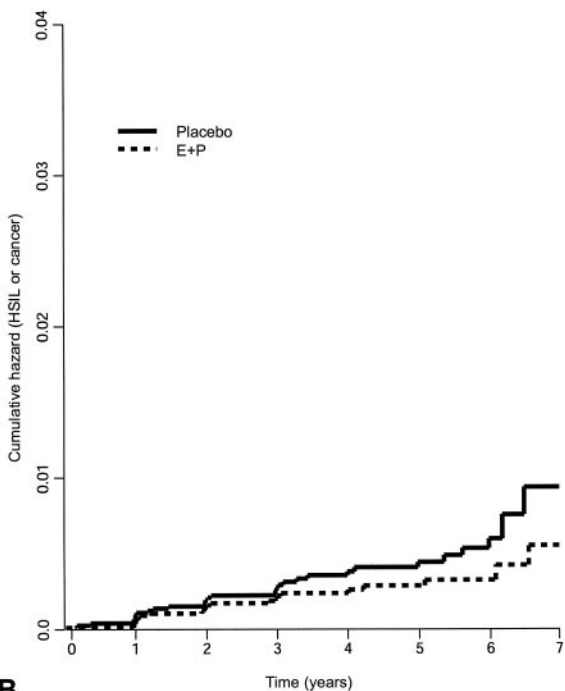
progestin and placebo. In general, the vast majority of cervical cancer cases occur among women who have not been previously screened or who have not had three consecutive normal cytology results.^{13,27,28} All women in the WHI Clinical Trial were screened and judged to be free of cervical cancer at or within 1 year before entry into the trial. Second, the results of interim steps in diagnostic evaluation and treatment, especially for LSIL, are risk-based and considered optional and sometimes inconsistent.¹¹

Our estimates of the risk of cervical cancer after negative results on cytological testing appear to be somewhat lower than estimates from other population-based studies.^{3,13,14} The low prevalence of cervical smear abnormalities at baseline is likely because the volunteers participating in the WHI clinical trial were healthier and at lower risk for cervical disease than women in the general population. Use of combined hormone therapy over a 6-year period increased the incidence of any cytologic abnormalities, but not the incidence of high-grade abnormalities, among postmenopausal women with normal baseline cytology. This study also confirms that traditional risk





A



B

Fig. 3. Kaplan-Meier estimates of cumulative incidence of abnormal cytology on cervical cytology (censored at date of hysterectomy or last cervical smear), among women in the Women's Health Initiative Hormone Therapy Clinical Trial. **A.** Cumulative hazard by baseline cervical smear result. **B.** Cumulative hazard by hormone trial randomization assignment. HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; E+P, estrogen plus progestin.

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factors such as sexual activity continue to play a role in the development of cervical dysplasia and cancer in older women. These results are generalizable to postmenopausal women who have recently had a normal cervical smear or a smear with low-grade abnormalities, but they are not applicable to postmenopausal women who have never been screened or have not recently been screened.

Annual screening provides little if any benefit over triennial screening because the absolute risk of undiagnosed cervical cancer within 3 years after a normal cervical smear is very low.²⁶ Our findings support the appropriateness of recommending triennial screening among low-risk women who are married or living as married and have previously normal cervical cytology.¹³ Although there is an age-related decrease in the incidence of cytological abnormalities, the incidence drops neither fast enough nor low enough to ignore the risk of high-grade cytologic abnormalities and cervical cancer in all women over the age of 70 years. Current recommendations to discontinue screening for elderly women do not take into account risk factors such as continuing sexual activity (which may involve new partners) and associated exposure to human papillomavirus. Our study suggests that sexually active unmarried elderly women may benefit from continued cervical cancer screening, even if they have previously had normal cervical cytology.

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