

Pelvic organ prolapse in the Women's Health Initiative: Gravity and gravidity

Susan L. Hendrix, DO,^a Amanda Clark, MD,^b Ingrid Nygaard, MD,^c Aaron Aragaki, MS,^d Vanessa Barnabei, MD,^e and Anne McTiernan, MD, PhD^f

Detroit, Mich, Portland, Ore, Iowa City, Iowa, Seattle, Wash, and Milwaukee, Wis

OBJECTIVE: The purpose of this study was to describe the prevalence of and correlates for pelvic organ prolapse.

STUDY DESIGN: This was a cross-sectional analysis of women who enrolled in the Women's Health Initiative Hormone Replacement Therapy Clinical Trial (n = 27,342 women). Baseline questionnaires ascertained demographics and personal habits. A baseline pelvic examination assessed uterine prolapse, cystocele, and rectocele. Descriptive statistics and logistic regression models were used to investigate factors that were associated with pelvic organ prolapse.

RESULTS: In the 16,616 women with a uterus, the rate of uterine prolapse was 14.2%; the rate of cystocele was 34.3%; and the rate of rectocele was 18.6%. For the 10,727 women who had undergone hysterectomy, the prevalence of cystocele was 32.9% and of rectocele was 18.3%. After controlling for age, body mass index, and other health/physical variables, African American women demonstrated the lowest risk for prolapse. Hispanic women had the highest risk for uterine prolapse. Parity and obesity were strongly associated with increased risk for uterine prolapse, cystocele, and rectocele.

CONCLUSION: Pelvic organ prolapse is a common condition in older women. The risk for prolapse differs between ethnic groups, which suggests that the approaches to risk-factor modification and prevention may also differ. These data will help address the gynecologic needs of diverse populations.

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Key words: Pelvic organ prolapse, cystocele, rectocele, uterine prolapse, risk factors, ethnicity

Uterine prolapse, cystocele, and rectocele are among the most common indications for benign gynecologic surgery. Except for urinary incontinence, little is known about the incidence or prevalence of these disorders of pelvic support. The National Center for Health Statistics lists genital prolapse as one of the 3 most common rea-

sons for hysterectomy in women.¹ More than 338,000 procedures for prolapse are performed annually in the United States.¹ The estimated lifetime risk by age 80 years to undergo surgery for urinary incontinence or pelvic organ prolapse was 11.1% in a large managed care population in Oregon.² The Oxford Family Planning Association study followed up 17,032 women who attended family planning clinics between 1968 and 1974 who were aged between 25 and 39 years at study entry.³ The incidence of a hospital admission for the diagnosis of prolapse was 2.04 per 1000 person-years of risk. The incidence of prolapse that required surgical correction after hysterectomy was 3.6 per 1000 person-years of risk. The number of women with pelvic organ prolapse who were treated without hospitalization or surgery or women who did not seek medical care is not known. Incidence and prevalence estimates that are based on hospital admissions or surgical procedure codes undoubtedly underestimate the enormity of the problem.

The functional consequences of pelvic organ prolapse include, but are not limited to, urinary incontinence, voiding dysfunction, symptomatic proctitis, posthysterectomy vaginal prolapse, fecal incontinence, sexual dysfunction, and difficulty with defecation. Although some women treat their symptoms conservatively with pessaries, medications, physiotherapy, or behavioral therapy, others resort to protective undergarments and vagi-

From the Wayne State University School of Medicine,^a Oregon Health Sciences University,^b the University of Iowa College of Medicine,^c the Women's Health Initiative Clinical Coordinating Center, Fred Hutchinson Cancer Research Center,^d the Medical College of Wisconsin,^e and the Cancer Prevention Research Program, Fred Hutchinson Cancer Research Center.^f

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Reprint requests: Susan L. Hendrix, DO, Department of Obstetrics and Gynecology, Wayne State University/Hutzel Hospital, 4707 St Antoine, Detroit, MI 48201. E-mail: shendrix@med.wayne.edu

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Table I. Demographics

<i>Demographic</i>	<i>Any prolapse</i>					<i>Total (No.)</i>
	<i>Data missing (n.)</i>	<i>No n</i>	<i>%</i>	<i>Yes n</i>	<i>%</i>	
Age group at screening (y)						
50-69	72	5,676	34.8	3,085	28.4	8,833
60-69	72	7,137	43.8	5,148	47.4	12,357
70-79	35	3,482	21.4	2,635	24.2	6,152
Total	179	16,295	100.0	10,868	100.0	27,342
Ethnicity						
White	134	13,039	80.0	8,852	81.5	22,025
African American	24	1,910	11.7	805	7.4	2,739
Hispanic	11	812	5.0	720	6.6	1,543
American Indian	1	80	0.5	50	0.5	131
Asian/Pacific Islander	5	256	1.6	266	2.4	527
Unknown	4	198	1.2	175	1.6	377
Total	179	16,295	100.0	10,868	100.0	27,342
Body mass index (kg/m ²)						
Missing	2	95	0.6	58	0.5	155
Normal (≤ 24.9)	58	4,915	30.2	2,289	21.1	7,262
Overweight (25.0-29.9)	66	5,651	34.7	3,814	35.1	9,531
Obese (≥ 30.0)	53	5,634	34.6	4,707	43.3	10,394
Total	179	16,295	100.0	10,868	100.0	27,342
Term pregnancies						
Missing	0	87	0.5	69	0.6	156
Never pregnant/never had term pregnancy	32	2,094	12.9	512	4.7	2,638
1	18	1,509	9.3	650	6.0	2,177
2	36	3,576	21.9	2,194	20.2	5,806
3	41	3,749	23.0	4,616	24.1	6,406
4+	52	5,280	32.4	4,827	44.4	10,159
Total	179	16,295	100.0	10,868	100.0	27,342
Smoking						
Missing	2	184	1.1	131	1.2	317
Never smoked	95	7,806	47.9	5,701	52.5	13,602
Past smoker	56	6,426	39.4	4,111	37.8	10,593
Current smoker	26	1,879	11.5	925	8.5	2,830
Total	179	16,295	100.0	10,868	100.0	27,342
Total hormone replacement usage						
Missing	0	9	0.1	2	0.0	11
Never used	135	10,410	63.9	7,309	67.3	17,854
Past user	22	4,117	25.3	2,501	23.0	6,640
Current user	22	1,759	10.8	1,056	9.7	2,837
Total	179	16,295	100.0	10,868	100.0	27,342
Age at hysterectomy						
Missing	1	32	0.2	17	0.2	50
Never had hysterectomy	146	9,639	59.2	6,831	62.9	16,616
40 y	12	2,740	16.8	1,497	13.8	4,249
40+ y	20	3,884	23.8	2,523	32.2	6,427
Total	179	16,295	100.0	10,868	100.0	27,342
Any incontinence (stress, urge, mixed, nocturnal)						
Missing	15	1,050	6.4	685	6.3	1,750
No	74	5,857	35.9	3,246	29.9	9,177
Yes	90	9,388	57.6	6,937	63.8	16,415
Total	179	16,295	100.0	10,868	100.0	27,342

nal deodorizers to avoid odors. Women who are most impaired seek surgical solutions. Although helpful for many women, 1 in 3 women who undergo operation require further surgical intervention for pelvic floor disorders.² Thus, pelvic floor disorders are not only socially embarrassing and disabling, but the treatments are also costly and may place women at risk. This spectrum of problems creates a social and economic burden on society of enormous magnitude.

Although our information about urinary incontinence increased substantially over the last decade, information about pelvic organ prolapse lags far behind.

Risk factors for and correlates of pelvic organ prolapse are primarily based on expert opinion and are supported by limited epidemiologic and clinical evidence. The epidemiologic reports have been instructive, but they have been small and are not generalizable to the population at large. The number of minority participants in these studies has been too small to produce reliable prevalence estimates.

Existing data suggest that age³ and ethnicity⁴ are associated with pelvic organ prolapse. Of greater interest to clinicians, however, are risk factors that may be amenable to intervention to reduce injury to the pelvic floor. One

such potential risk factor is childbirth and, in particular, vaginal delivery. In the Oxford Family Planning Association prolapse epidemiology study, parity was the strongest risk factor for pelvic organ prolapse, with an adjusted risk ratio of 10.85.³ Although this insult to the pelvic floor cannot be easily avoided, there has been increasing interest in understanding the specific aspects of the labor and delivery process that affect the pelvic floor.

There is scant evidence about other risk factors that are possibly amenable to efforts to prevent pelvic organ prolapse. In 1 study, nursing assistants were more likely to undergo surgery for pelvic floor disorders than the general population, but no adjustment had been made for childbirth.⁵ Neurologic injury to the pelvic floor⁶ and underlying connective tissue disorders⁷ have also been implicated in pelvic organ prolapse. Obesity, cigarette smoking with chronic cough, previous hysterectomy, constipation, and estrogen deficiency have been commonly implicated in the cause of pelvic organ prolapse, largely because of their association with urinary incontinence.⁸⁻¹² However, there is little, if any, evidence that relates these factors directly to pelvic organ prolapse; whether they are risk factors is not known.

The purpose of this study was to measure the prevalence and correlates of uterine prolapse, cystocele, and rectocele in a large population of women after menopause.

Methods

Study population. The study population included women who enrolled in the Women's Health Initiative (WHI) Hormone Replacement Therapy Clinical Trial ($n = 27,342$ women). The WHI is a prospective study of 161,861 women aged 50 to 79 years after menopause in ≥ 1 of 3 clinical trials or an observational study who were enrolled from 1994 through 1998 in 40 clinical centers in the United States. The ethnic distribution includes a diverse population that is 18.3% minority, which represents major ethnic and racial groups across the United States. Study methods have been described in detail elsewhere.¹³ Briefly, women were eligible if they were postmenopausal, unlikely to move or die within 3 years, not currently using hormone replacement therapy (or willing to stop), and not currently participating in any other clinical trial. Demographic characteristics of the women in the hormone trial are shown in Table I. At baseline, women completed screening and enrollment questionnaires by interview and self-report, a physical examination, and blood specimen collection. The study was reviewed and approved by Human Subjects Review Committees at each participating institution.

Baseline assessment. Baseline questionnaires ascertained information on several factors including age, race/ethnicity, education, occupation, overall quality of life (rated 1-10), chronic illnesses, time since menopause, parity, breast-feeding, duration of hormone use, hysterectomy

status, constipation, current and past smoking, coffee consumption (cups per day), and physical activity (episodes per week). Alcohol consumption was estimated from a 120-item food frequency questionnaire.¹⁴ Occupation was grouped into 4 categories (managerial/professional, technical/sales/administration, service/labor, and homemaker only) and analyzed as such. With the exception of hysterectomy, previous therapy for pelvic organ prolapse, which included surgery, was not ascertained. Details of the route of childbirth (vaginal or cesarean) were not recorded.

WHI participants were asked to bring all current prescription medications to their first screening interview. Clinic interviewers entered the names of each medication directly from the medicine containers into the WHI database, which assigned drug codes using Medispan software (First DataBank, San Bruno, Calif).¹⁵ Women reported the duration of use for each current medication. Information on dose was not captured. Current use of thiazide diuretics and anticholinergic medications was recorded. Current and previous use of hormone replacement therapy was ascertained by interview with the use of a detailed questionnaire that measured type, route of administration, number of pills per day per week, and duration for each hormonal preparation ever taken. For the purposes of this report, hormone replacement therapy was defined as current or past use of any oral or transdermal (shots and creams were excluded) estrogen with or without progestin.

Weight was measured to the nearest 0.1 kg on a balance beam scale, with the participant dressed in indoor clothing without shoes. Height was measured to the nearest 0.1 cm with a wall-mounted stadiometer. Body mass index was calculated as weight/height.

Women in the hormone replacement therapy trial ($n = 27,342$) underwent a baseline standardized pelvic examination that was required by the protocol, which included an assessment of uterine prolapse, cystocele, and rectocele (none; grade 1, in vagina; grade 2, to introitus; grade 3, outside vagina). A gynecologist, advanced degree nurse, or physician assistant performed the pelvic examination, with the woman in the supine lithotomy position. The WHI clinic gynecologist certified all midlevel providers to ensure proper performance of the examination. Centralized training provided a review of the elements of the protocol, the definitions of prolapse, and how to record the results on standardized forms. Assessment for prolapse was performed with direct visualization of the external genitalia during Valsalva maneuver. The status of bladder or rectal fullness was not recorded.

Statistical analysis. Descriptive analyses, in the form of frequency tables and cross-tabulations, were performed to examine the associations between the 3 measured forms of prolapse (uterine, cystocele, rectocele) and selected explanatory variables, respectively.

Table II. Regression model for all prolapse

Effect	Uterine prolapse*		Rectocele*		Cystocele*	
	OR	95% CI	OR	95% CI	OR	95% CI
Age compared with 50-59 (y)						
60-69	1.16	1.03-1.30	1.09	1.00-1.19	1.26	1.18-1.35
70-79	1.36	1.19-1.56	1.18	1.07-1.30	1.35	1.25-1.47
Ethnicity compared with white race						
African American	0.63	0.50-0.79	0.50	0.44-0.58	0.65	0.59-0.73
Hispanic	1.24	1.01-1.54	0.95	0.82-1.11	1.20	1.05-1.36
American Indian	0.34	0.11-1.11	0.88	0.55-1.41	0.84	0.56-1.26
Asian/Pacific Islander	0.89	0.64-1.25	1.51	1.21-1.89	2.18	1.80-2.64
Unknown	1.03	0.69-1.54	1.21	0.92-1.58	1.33	1.06-1.68
Waist circumference >88 cm compared with <88 cm						
Apple shape	NS		1.17	1.06-1.29	1.17	1.08-1.27
Body mass index compared with >25 kg/m ²						
Overweight (25-30 kg/m ²)	1.31	1.15-1.48	1.38	1.25-1.53	1.39	1.28-1.51
Obese (>30 kg/m ²)	1.40	1.24-1.59	1.75	1.54-1.99	1.57	1.41-1.74
Constipation	NS		1.08	1.00-1.16	1.10	1.03-1.16
Hysterectomy	NA		0.90	0.83-0.97	0.88	0.83-0.94
Tobacco use compared with never						
Past	0.92	0.83-1.02	0.97	0.90-1.05	0.93	0.87-0.99
Current	0.81	0.68-0.97	0.83	0.73-0.95	0.85	0.77-0.94
Alcohol use compared with nondrinkers						
Past	0.88	0.74-1.06	1.00	0.88-1.13	0.91	0.82-1.01
1 drink/mo	0.90	0.75-1.08	0.96	0.84-1.09	0.87	0.78-0.97
1 drink/wk	0.88	0.74-1.05	0.86	0.76-0.97	0.82	0.74-0.92
≤7 drinks/wk	0.81	0.68-0.96	0.84	0.74-0.95	0.79	0.71-0.88
>7 drinks/wk	0.64	0.52-0.79	0.75	0.65-0.88	0.68	0.60-0.77
Hormone therapy compared with never used						
Past	0.84	0.74-0.96	0.979	0.89-1.05	0.92	0.86-0.99
Current	0.96	0.79-1.16	1.10	0.98-1.24	1.02	0.92-1.12
Childbirth compared with no term birth						
Parity of 1	2.13	1.67-2.72	2.22	1.84-2.68	1.91	1.67-2.19
Each additional birth	1.10	1.05-1.16	1.21	1.17-1.26	1.21	1.17-1.24

NS, Not significant; NA, not applicable.

To further investigate these relationships and to determine the risk of prolapse, logistic regression models were fit. For the purposes of the models, prolapse was considered present if any prolapse was identified, regardless of grade, and was otherwise considered absent. Explanatory variables that were identified as important from the descriptive analyses were included in the regression models; variables that did not appear to be clinically or statistically significant were later removed. Odds ratios (ORs) were calculated with the use of the maximum likelihood parameter estimates from the regression models. ORs were adjusted for the effect of all other explanatory variables in the model. Probability values for the ORs were derived from the Wald χ^2 significance tests that were based on the asymptotic distribution of the parameter estimates.¹⁶ The overall significance of categorical variables, with ≥ 3 levels, was assessed by the likelihood ratio test.

Because uterine prolapse data are collected from participants with an intact uterus only, the modeling for prolapse was restricted to women who had not undergone hysterectomy. Conversely, cystocele and rectocele data were collected for both those with and without hysterectomy. For comparison across each form of prolapse, models for cystocele and rectocele were adjusted for hysterectomy status, and the interactions between hysterectomy status and risk variables were investigated.

Data management and descriptive statistics were completed with the SAS system (SAS Institute, Cary, NC) for Windows version 6.12 (Microsoft Corporation, Redmond, Wash). All regression modeling was done with S-Plus 2000 for Windows, version 3 (Microsoft Corporation).

Results

Of the women with a uterus, 41.1% had some form of prolapse, with 34.3% having cystocele, 14.2% having uterine prolapse, and 18.6% having rectocele. Approximately 1 in 5 participants had prolapse at ≥ 2 sites. Almost 38% of women without a uterus had some form of prolapse, with 32.9% having cystocele and 18.3% having rectocele. The prevalence of uterine prolapse, cystocele, and rectocele by hysterectomy status is shown graphically in Fig 1. Prevalence data were stratified by hysterectomy status because women with a history of hysterectomy may be more likely to have undergone surgery for pelvic organ prolapse. The prevalence for cystocele and rectocele for women with a uterus were slightly higher than for women with a hysterectomy, which suggests that previous prolapse may have been repaired at the time of hysterectomy. The anterior vagina was the most common single site, with the overall prevalence of cystocele in 33.8% of the women.

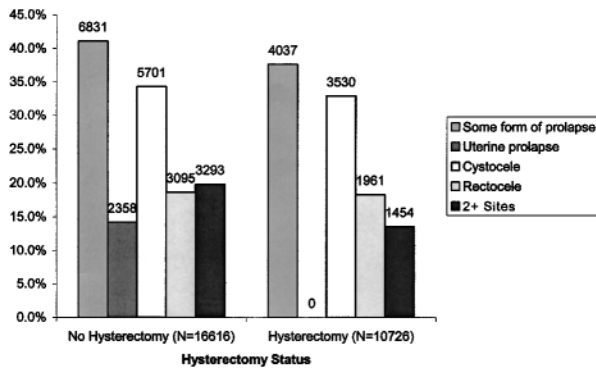


Fig 1. Pelvic organ prolapse prevalence. The *medium gray* bar indicates some form of prolapse; the *dark gray* bar indicates uterine prolapse; the *pale gray* bar indicates cystocele; the *light gray* bar indicates rectocele; the *black* bar indicates ≥ 2 sites.

The multiple logistic regression analysis showed that all sites of pelvic organ prolapse were higher among older women (Table II). Being overweight (body mass index, 25-30 kg/m²) was associated with a significant increase in the occurrence of uterine prolapse by 31%, of rectocele by 38%, and of cystocele by 39%, and obesity (body mass index, >30 kg/m²) was associated with a significant 40%, 75%, and 57% increase, respectively. Waist circumference of ≥ 88 cm had an associated significant increase in risk of 17% for rectocele and cystocele. Current physical activity appeared to have no substantial impact on the risk for any of the forms of pelvic organ prolapse (data not shown).

Compared with white women, African American women had the lowest risk for uterine prolapse, cystocele, and rectocele (Table II). Hispanic women had the highest rate of uterine prolapse and an increased risk for cystocele, but not rectocele. It appeared that American Indian women may have lower risk than white women for all types of pelvic relaxation, but the small sample size precludes us from drawing any statistically meaningful inferences. Asian women had the highest risk of cystocele and rectocele, but not uterine prolapse.

Of the nulliparous women with a uterus, 19.2% had some form of prolapse, with 14.9% having cystocele, 6.3% having uterine prolapse, and 6.5% having rectocele (Fig 2). More than 7% of the women had prolapse at ≥ 2 sites. Almost 20% of the women without a uterus had some form of prolapse, with 18.0% having cystocele and 7.0% having rectocele.

The increased presence of uterine prolapse was associated with parity (OR, 2.13 for first birth and 1.10 for each subsequent birth). No additional risk was conferred for ≥ 5 births. Current smoking and increasing alcohol intake were associated with lower risk.

Modestly increasing risk of both cystocele and rectocele was waist circumference of >88 cm, increasing parity, and constipation. The first birth was associated with an OR of 1.91 for cystocele and 2.22 for rectocele, and each

subsequent birth conferred a risk of 1.21 for both cystocele and rectocele. Current smoking and increasing alcohol intake were associated with a decreased rate of prolapse at both sites. ORs for women with a uterus were slightly higher than for women with a previous hysterectomy, which suggests that previous prolapse may have been repaired at the time of hysterectomy. There were no significant interactions between hysterectomy status and any other risk factors.

There was a strong association between cystocele and incontinence ($P < .001$). Incontinence appeared to be positively associated with cystocele grades, but the data were too sparse to confirm this.

Minimal or no association of pelvic organ prolapse was found with education, occupation, overall quality of life (rated 1-10), chronic illnesses, time since menopause, breast-feeding, duration of hormone use, hysterectomy status, past smoking, coffee consumption (cups per day), and physical activity (episodes per week).

Comment

This study establishes a very high prevalence of pelvic organ prolapse in this cohort of women after menopause. Cystocele was the most common form of prolapse and was present in more than one third of the women, regardless of uterine status. Pelvic organ prolapse was associated with multiple factors in this report, the strongest being parity. Although an increase in cystocele was seen with each subsequent birth, the strongest association was seen with first birth. Cystocele prevalence for women with a uterus were slightly higher than for women with a hysterectomy, which suggests that previous prolapse may have been repaired at the time of hysterectomy.

This study confirms previously reported differences between white and African American women and adds a new dimension about pelvic organ prolapse for other ethnic groups. Hispanic women had the highest rate of uterine prolapse and an increased risk for cystocele, but not rectocele. Asian women had the highest risk of cystocele and rectocele, but not uterine prolapse.

In our study, self-reported constipation was not a risk factor for pelvic organ prolapse. In a previous small case-control study, 61% of women with pelvic organ prolapse reported straining at stool as a young adult compared with 4% of control subjects.¹⁷ However, self-reports of constipation can be inaccurate.

Although we found no association between occupation (as assessed in 4 categories) and prolapse, other studies have linked occupation and strenuous activity to pelvic organ prolapse. Danish nursing assistants who were exposed to repetitive heavy lifting were 1.6 times more likely to undergo surgery for pelvic organ prolapse than population control subjects; however, this study was not able to control for parity.¹⁸ In a German study, 40% of women with uterine prolapse reported a heavy work history compared

to 17% of control subjects.¹⁹ In a recent study, Italian housewives were 3.1 times more likely than professional/managerial women to undergo surgery for pelvic organ prolapse.²⁰ However, occupation was collected as a social class indicator and yielded no information about physical effort. In these studies, activity was assessed as a risk factor for end-stage disease (that is, those women undergoing operation). Risk factors for severe pelvic organ prolapse may differ from those for mild prolapse. The number of women with severe prolapse in our study was too small to draw conclusions about associations that differ with risk.

There are several limitations to this study. First, it was not designed to determine risk factors for pelvic organ prolapse but to evaluate the effects of hormone replacement therapy on incidence and death from cardiovascular disease in women. Second, although all participants were examined with a standard examination, different examiners performed the examinations. Interexaminer reliability was not assessed and may bias the results. Pelvic organ prolapse was assessed only by visual inspection during the Valsalva maneuver with the patient in the supine position. Neither a split speculum examination nor the recently validated POP-Q pelvic organ prolapse grading system was used. In our clinical experience, we would hypothesize that the WHI type of assessment would tend to underestimate the presence of prolapse. Indeed, others have reported an increased risk of detection of pelvic organ prolapse when women were examined in positions other than supine. Barber et al²¹ recently found a higher degree of pelvic organ prolapse when patients were examined in a birthing chair at a 45-degree angle than when they were examined in a supine position. In this study, 70% of the patients had the same stage of prolapse in the 2 positions; 26% of the patients had a higher stage, and 4% of the patients had a lower stage. Of relevance to our study, of patients who were stage 0 or 1 when supine, 36% were stage 2 or greater when examined upright. Third, we lack information on previous surgical procedures for pelvic floor disorders and on the reasons for hysterectomy. This reported prevalence of pelvic organ prolapse is likely to underreport the true prevalence of the sample because it likely includes women who have undergone successful surgical correction. Surgery is usually performed for moderate and severe prolapse and may account for the low prevalence of moderate and severe cases in this cohort. Although the route of delivery is unknown, most participants would have completed childbearing before the dramatic rise in cesarean deliveries in the late 1970s and 1980s. Last, we recognize that these data are cross-sectional and that we cannot assess cause and effect, only identify associations.

However, there are many merits to this study. It is the first study to describe the prevalence of pelvic organ prolapse on the basis of physical examination in a large population of women who are not simply drawn from tertiary

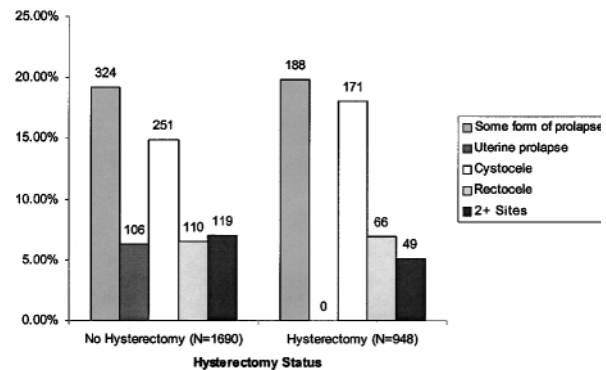


Fig 2. Pelvic organ prolapse prevalence in nulliparous women. The *medium gray bar* indicates some form of prolapse; the *dark gray bar* indicates uterine prolapse; the *pale gray bar* indicates cystocele; the *light gray bar* indicates rectocele; the *black bar* indicates ≥ 2 sites.

care clinics. The few previous reports on the prevalence of these conditions were drawn from clinical populations and used surgical procedure (the proverbial tip of the iceberg) as an indicator of the condition. The WHI clinic gynecologist was required to certify the persons who performed the pelvic examinations to ensure proper performance of the examination. The large study population allowed us to examine numerous associations and to control for potential confounders. Of particular interest is that we were able to describe ethnic variations in the prevalence of pelvic organ prolapse. The examination for prolapse was standardized, as were data recording and entry.

Future studies within WHI will be able to report incident data on pelvic organ prolapse, incident data on pelvic surgical procedure by International Classification of Diseases, 9th Revision, codes from hospitalizations, the effects of hormone therapy on the incidence of pelvic organ prolapse, and the subsequent need for surgical procedures. The effect of pelvic organ prolapse on urinary incontinence and quality of life can also be evaluated. As well, we will be able to compare these effects between racial/ethnic groups.

This is the first description of the prevalence and ethnic variation for pelvic organ prolapse in its various forms. Pelvic organ prolapse, especially cystocele, is a very common condition in women during menopause. The prevalence of prolapse differs between ethnic groups, which suggests that risk factor modification and prevention may differ. Pelvic organ prolapse was consistently related to parity; although no association was found with the number of years since menopause, hormone use, exercise level, or the presence of asthma or emphysema. Our work counters a widely held view by clinicians that the first birth does all of the damage and that subsequent births add little. The prevalence of pelvic organ prolapse probably underestimates the natural history, because the population that was studied presumably includes successfully treated

cases. Future studies with this cohort will have the ability to make comparisons between ethnic groups and to address the risk factors in diverse populations.

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Appendix

Program Office.

National Heart, Lung, and Blood Institute, Bethesda, Md: Jacques E. Rossouw, Linda Pottern, Shari Ludlam, Joan McCowan, Nancy Morris

Clinical Coordinating Center.

Fred Hutchinson Cancer Research Center, Seattle, Wash: Ross Prentice, Garnet Anderson, Andrea LaCroix, Ruth Patterson, Anne McTiernan; Bowman Gray School of Medicine, Winston-Salem, NC: Sally Schumaker, Pentti Rautaharju; Medical Research Labs, Highland Heights, Ky: Evan Stein; University of California at San Francisco, San Francisco, Calif: Steven Cummings; University of Minnesota, Minneapolis, Minn: John Himes; University of Washington, Seattle, Wash: Susan Heckert.

Clinical Centers.

Albert Einstein College of Medicine, Bronx, NY: Sylvia Wassertheil-Smoller; Baylor College of Medicine, Houston, Tex: Jennifer Hays; Brigham and Women's Hospital, Harvard Medical School, Boston, Mass: JoAnn Manson; Brown University, Providence, RI: Annlouise R. Assaf; Emory University, Atlanta, Ga: Lawrence Phillips; Fred Hutchinson Cancer Research Center, Seattle, Wash: Shirley Beresford; George Washington University Medical Center, Washington, DC: Judith Hsia; Harbor-UCLA Research and Education Institute, Torrance, Calif: Rowan Chlebowski; Kaiser Permanente Center for Health Research, Portland, Ore: Cheryl Ritenbaugh; Kaiser Permanente Division of Research, Oakland, Calif: Bette Caan; Medical College of Wisconsin, Milwaukee, Wis: Jane Morley Kotchen; Medstar Research Institute, Washington, DC: Barbara V. Howard; Northwestern University, Chicago/Evanston, Ill: Linda Van Horn; Rush-Presbyterian St Luke's Medical Center, Chicago, Ill: Henry Black; Stanford Center for Research in Disease Prevention, Stanford University, Stanford, Calif: Marcia L. Stefanick; State University of New York at Stony Brook, Stony Brook, NY: Dorothy Lane; Ohio State University, Columbus, Ohio: Rebecca Jackson; University of Alabama at Birmingham, Birmingham, Ala: Cora Beth Lewis; University of Arizona, Tucson/Phoenix, Ariz: Tamsen Bassford; University at Buffalo, Buffalo, NY: Maurizio Trevisan; University of California at Davis, Sacramento, Calif: John Robbins; University of California at Irvine, Orange, Calif: Allan Hubbell; University of California at Los Angeles, Los Angeles, Calif: Howard Judd; University of California at San Diego, LaJolla/Chula Vista, Calif: Robert D. Langer; University of Cincinnati, Cincinnati, Ohio: Margery Gass; University of Florida, Gainesville/Jacksonville, Fla: Marian Limacher; University of Hawaii, Honolulu, Hawaii: David Curb; University of Iowa, Iowa City/Davenport, Iowa: Robert Wallace; University of Massachusetts, Worcester, Mass: Judith Ockene; University of Medicine and Dentistry of New Jersey, Newark, NJ: Norman Lasser; University of Miami, Miami, Fla: Mary Jo O'Sullivan; University of Minnesota, Minneapolis, Minn: Karen Margolis; University of Nevada, Reno, Nev: Robert Brunner; University of North Carolina, Chapel Hill, NC: Gerardo Heiss; University of Pittsburgh, Pittsburgh, Pa: Lewis Kuller; University of Tennessee, Memphis, Tenn: Karen C. Johnson; University of Texas Health Science Center, San Antonio, Tex: Robert Schenken; University of Wisconsin, Madison, Wis: Catherine Allen; Wake Forest University School of Medicine, Winston-Salem, NC: Gregory Burke; Wayne State University School of Medicine/Hutzel Hospital, Detroit, Mich: Susan Hendrix.