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Incidence of Laparoscopically Confirmed Endometriosis by Demographic, Anthropometric, and Lifestyle Factors

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The authors investigated the relations of demographic, anthropometric, and lifestyle factors with endometriosis in the Nurses' Health Study II prospective cohort. During 10 years of follow-up (1989–1999), 1,721 cases of laparoscopically confirmed endometriosis were reported among women with no past infertility. The incidence rate was greatest among women aged 25–29 years and lowest among women over 44 years ($p_{trend} < 0.0001$). In multivariate Cox proportional hazards models, African-American women had a lower rate of disease compared with Caucasian women (rate ratio = 0.6, 95% confidence interval: 0.4, 0.9). The authors also observed an inverse relation with body mass index at age 18 years (for body mass index of >30 vs. 19–20.4 kg/m^2: rate ratio = 0.8, 95% confidence interval: 0.6, 1.1; $p_{trend} = 0.004$) and with current alcohol intake (for >10 vs. 0 g/day: rate ratio = 0.7, 95% confidence interval: 0.6, 0.8; $p_{trend} < 0.0001$) but no association with height, waist/hip ratio, or caffeine intake. An inverse relation with current body mass index and current cigarette smoking was observed only when cases were concurrently infertile. The authors conclude that age, race, body mass index, alcohol use, and cigarette smoking are associated with the incidence of endometriosis and that some of these relations may differ by infertility status at the time of laparoscopic diagnosis.

alcohol drinking; anthropometry; cohort studies; continental population groups; endometriosis; incidence; prevalence

Endometriosis, the third leading cause of gynecologic hospitalization in the United States, is defined by the presence of tissue resembling endometrium external to the uterus (1). Signs and symptoms arise from cyclic bleeding into the surrounding tissues, resulting in inflammation and formation of scarring and adhesions. Treatment options include hormonal suppression and surgery, but many women experience unsatisfactory results.

Despite the high associated morbidity and health care costs, the incidence, prevalence, and risk factors of endometriosis remain uncertain. Using data collected from the Nurses' Health Study II, an ongoing, prospective cohort study of US nurses that began in 1989, we have determined the frequency and distribution of laparoscopically confirmed endometriosis by age, race, anthropometry, and lifestyle factors.

MATERIALS AND METHODS

Study population and data collection

Data for these analyses were collected in the Nurses' Health Study II cohort from September 1989 to June 1, 1999. Questionnaires requesting information on incident diseases and demographic, biologic, environmental, and lifestyle risk factors are updated and mailed biennially. A total of 116,678 female registered nurses, ranging in age from 25 to 42 years and residing in one of 14 states in the United States,

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completed the baseline questionnaire. Follow-up of this cohort in each 2-year interval has been consistently 90 percent or more.

Case ascertainment and analytical definition

In 1993, the women were first asked if they had "ever had physician-diagnosed endometriosis." If "yes," they were asked to report when the diagnosis had occurred (before September 1989, September 1989–May 1991, and June 1991–May 1993 which correspond to the follow-up periods) and if the diagnosis had been confirmed by laparoscopy, a standard surgical method for diagnosing endometriosis (2, 3). These questions were asked again in each subsequent questionnaire cycle.

To assess the validity of self-reported endometriosis, we mailed supplementary questionnaires in 1994 to 200 women randomly selected from 1,766 cases who had reported an incident diagnosis (155 of these 200 women (77.5 percent) had reported laparoscopic confirmation). Of the 184 women who responded (92 percent), 78.3 percent had reported laparoscopic confirmation (n = 144/184). Among the nonresponders, 68.5 percent had reported a laparoscopy (n = 11/16). A total of 148 (77.2 percent) of the responders gave permission for review of their clinical and surgical records. Records were received and reviewed for 88.5 percent (n = 131/148) of those who gave permission. A record of performance of laparoscopy was confirmed for all of those who had reported a laparoscopy. A diagnosis of endometriosis was confirmed in 88.6 percent of these women (n = 93/105). Of the 12 who were disconfirmed, either 1) the laparoscopic record stated that extrauterine tissue resembling endometrium was found but the pathology report identified the tissue as not endometrial (most commonly paratubal tissue; n = 4) or 2) the clinical record indicated that, because adhesions were found or symptoms persisted, the woman was told by her physician that, despite lack of direct visualization of endometrial lesions, she most likely had endometriosis (n = 8). Severity data suggested that the majority of laparoscopically confirmed cases (61 percent) had minimal or mild disease. Among those women who did not report a laparoscopic confirmation, no record of a laparoscopy was found, and evidence of a clinical diagnosis was found for only 53.8 percent (n = 14/26).

We sent supplementary questionnaires to all women (n = 665) who in 1993 had reported an incident diagnosis of endometriosis without laparoscopic confirmation. The response rate was 49.2 percent, although the same follow-up methods were used. Requests for permission to review medical records were sent to any woman who indicated that she had had a hysterectomy during the time period of reported diagnosis of endometriosis. Visualization of endometriosis at the time of surgical procedure was confirmed in 79.6 percent (n = 144/181) of the records received. However, endometriosis was the primary indication for hysterectomy in only 5.5 percent (n = 9/163) of women for whom information on indication was available.

Based upon these validation results, self-reported physician-diagnosed endometriosis without laparoscopic confirmation may be substantially misclassified. Indeed, when these cases (n = 1,080 reported from 1989 to 1999) were included in our analyses, all effect estimates were attenuated modestly. In addition, allowing women who report endometriosis and a hysterectomy in the same follow-up period to be cases might yield spurious results, because it would be unclear if the associated risk factors were related to endometriosis or to the pathology for which the hysterectomy was performed. Therefore, analyses of incident diagnosis of endometriosis were restricted to those women who reported laparoscopic confirmation of their diagnosis.

Within this restricted case definition, the relation between endometriosis and infertility status is complex. At baseline, the prevalence of infertility (defined as attempting to become pregnant for >1 year without success) was greater among women with laparoscopic confirmation (20 percent) than among those who were diagnosed without laparoscopic confirmation (4 percent), potentially resulting in oversampling those with "asymptomatic" disease. Approximately 20 percent of all infertile women are found to have endometriosis (4). Had these women not attempted to become pregnant, a large proportion may never have received a laparoscopic diagnosis of endometriosis. We may also assume that cases with no infertility who have had a laparoscopic diagnosis are "symptomatic"; otherwise a surgical evaluation would not have been conducted. Because endometriosis with infertility is typically indicative of asymptomatic disease secondary to other primary causes of infertility, the risk factors for endometriosis with infertility could differ from those for endometriosis without concurrent infertility. Hence, we looked at risk factors separately by these two "subtypes" of endometriosis. Within this cohort, self-reported infertility was validated in a study of 100 randomly selected women who reported ovulatory infertility; 95 percent of the self-reports were confirmed through medical record review (5).

Assessment of exposures

At baseline, 99 percent of participants indicated their race or ethnicity. Women who indicated "Southern European/Mediterranean," "Scandinavian," or "other Caucasian" but not "African American," "Hispanic," or "Asian" were grouped as Caucasians.

Weight at age 18 years and current height were reported at baseline, and current weight was updated every 2 years; these measures were used to calculate body mass index (kg/m^2). The validity of self-reported height and weight at age 18 years was evaluated by comparing the questionnaire responses with information obtained from medical records corresponding to the time of the nurse's entry into college or nursing school. The correlations between reported and measured height and weight were 0.94 and 0.87, respectively (6).

In 1993, women were asked to measure their waist and hip circumferences using a tape measure. The validity of these self-reports was evaluated in the Nurses' Health Study I cohort (another study of female US registered nurses) by comparison with standardized measurements taken 6 months apart by study researchers during home visits. Pearson's

correlations were 0.89 for waist and 0.84 for hip measurements (7).

A detailed cigarette smoking history was obtained at baseline and updated with each biennial questionnaire. At baseline, nurses were also asked to quantify their current and past alcohol consumption. Current intake of alcohol and caffeine (derived from reported consumption of caffeinated beverages) was updated by a food frequency questionnaire in 1991 and 1995.

Statistical analysis

Exclusion criteria. Those who reported the diagnosis of endometriosis or a history of infertility prior to September 1989 were excluded from all analyses. Analyses were also restricted to those who were premenopausal and had intact uteri, because the occurrence of endometriosis after hysterectomy or in postmenopausal women is rare. Women with prior cancer diagnoses other than nonmelanoma skin cancer also were excluded. The diagnosis date was set to the midpoint of the interval between the date of questionnaire receipt in which laparoscopically confirmed endometriosis was reported and the date of receipt of the previous questionnaire.

Person-time calculation. Woman-months at risk were calculated from entry into the cohort until independently confirmed death or cancer diagnosis or until self-reported, laparoscopically confirmed diagnosis of endometriosis, hysterectomy, or the onset of menopause. Women who reported physician-diagnosed endometriosis with no laparoscopic confirmation were censored at the time of that report but were allowed to reenter the analysis population if they reported laparoscopic confirmation on a subsequent questionnaire. In addition, because infertility is so strongly correlated with diagnosis of endometriosis via laparoscopy, we censored at self-report of infertility. Therefore, the person-time denominator for the incidence rate consists of women with neither diagnosed endometriosis nor infertility. Follow-up time was assigned to exposure categories based on the participant's exposure status at the beginning of each questionnaire interval so that women could change exposure status during follow-up.

Relative risk estimation. Incidence rates for each exposure category were computed as the number of incident cases divided by the woman-time accumulated. Time-varying Cox proportional hazards models treating age in months and 2-year questionnaire period as the time scale were used to estimate multivariate incidence rate ratios and to calculate 95 percent confidence intervals, after adjusting simultaneously for confounding variables. To evaluate the incidence of laparoscopically confirmed endometriosis by 5-year age groups while adjusting for confounding factors, we conducted pooled logistic regression across the five 2-year questionnaire intervals (8, 9). Tests for trend in ordinal categorical exposures were calculated by creating an ordinal variable in which the median value or midpoint of each category was assigned to all participants in that group. Tests for heterogeneity comparing the effect estimates among cases having no past or current infertility with effect estimates among cases having concurrent infertility were calculated with a Wald statistic referred to a chi-squared distribution with 1 df (10). In addition, we examined the age-specific incidence rate of laparoscopically confirmed endometriosis by nonparametric regression with restricted cubic splines (11). To evaluate effect modification, we conducted stratified analyses, and likelihood ratio tests comparing the model having both the main effects and the interaction terms with that having the main effects only were performed.

Confounding variables. We considered other possible risk factors for endometriosis as potential confounders if addition of that variable to the model changed the rate ratio by 10 percent or more (12). If a factor was identified as a confounder of any estimated main effect, it was kept in all models. Based on these criteria, only parity, race, and body mass index at age 18 years were adjusted for in multivariate analyses. Other risk factors considered but not included in the final models were age at menarche, age at first birth, time since last birth, if the woman was breastfed as an infant, if she was one of a multiple gestation, current alcohol use, current cigarette smoking status, health care use (a proxy variable created from the answers to several questions that ask if the nurse has had a physical examination, Papanicolaou smear, pelvic examination, or a breast examination by a clinician in the past 2 years), and use of oral contraceptives (coded as never, past, or current).

RESULTS

After baseline exclusions, a total of 90,065 women contributed 726,205 person-years to these analyses; 1,721 incident cases of laparoscopically confirmed endometriosis with no past infertility were reported. These included 1,340 never infertile cases and 361 cases who reported an infertility evaluation during the same follow-up period as laparoscopic confirmation of endometriosis. At baseline, we excluded 6,203 prevalent cases of self-reported endometriosis (laparoscopically confirmed or not) (5.3 percent of Nurses' Health Study II participants).

The incidence of laparoscopically confirmed endometriosis within the entire cohort population (regardless of infertility status) decreased with increasing age (2,518 incident cases; 845,405 person-years; incidence rate = 298/100,000 person-years) (figure 1). The overall incidence rate among women with no past infertility (the population for analysis) was 237/100,000 person-years and did not begin to decrease significantly until women were in their late thirties to early forties (figure 2). Among women with a history of infertility (excluded from subsequent analyses), the age-adjusted incidence rate of diagnosis of laparoscopically confirmed endometriosis was 1,380/100,000 person-years (table 1). The age-related decrease in risk was most modest among cases and comparison women who had never reported infertility, declining only after age 44 years.

Compared with that among Caucasian women, the rate of diagnosis among African Americans or Hispanics was 40 percent lower (table 2). These differences remained when analyses were restricted to those who reported having had a gynecologic examination during the past 2 years. The difference in risk between Asians and Caucasians was not significant. These rate ratios also changed little in multivariate

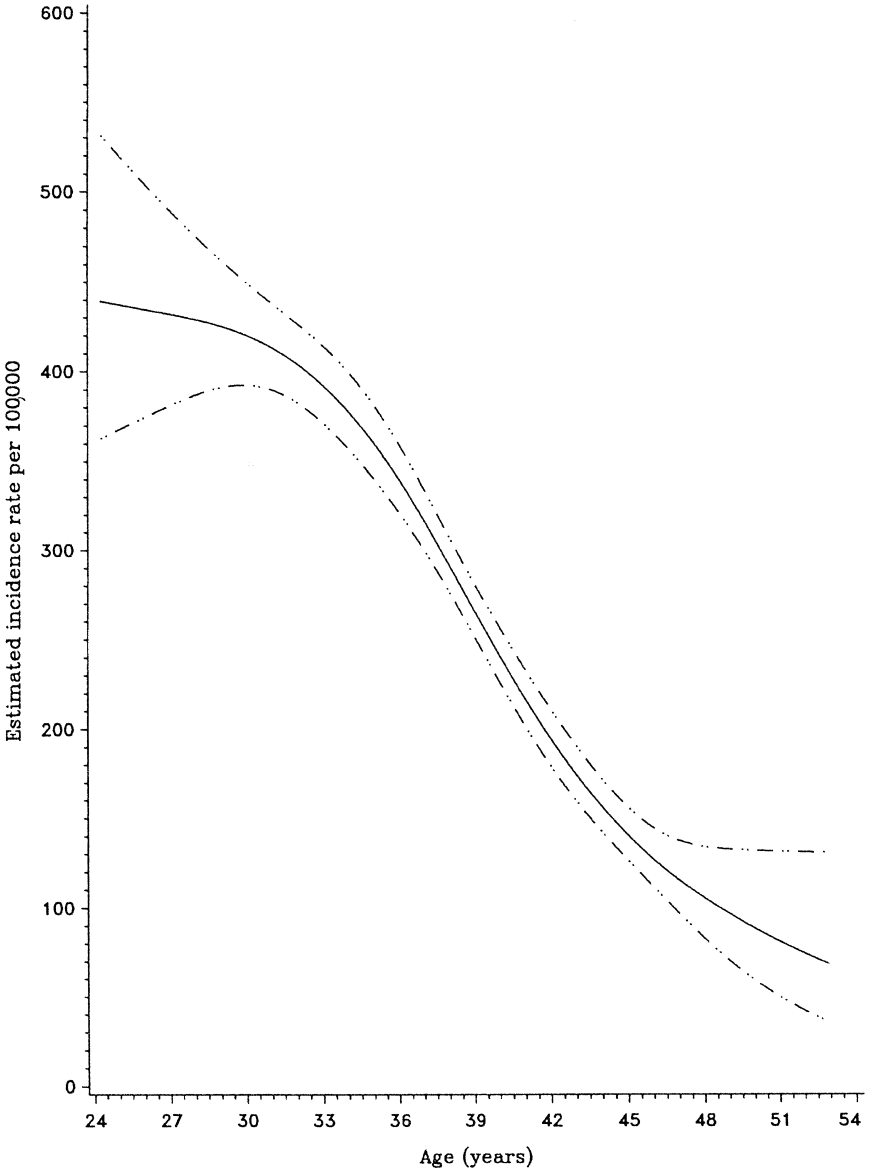

FIGURE 1. Nonparametric regression curve of the age-specific incidence of laparoscopically confirmed endometriosis among premenopausal women in the Nurses' Health Study II (1989–1999), regardless of past or current infertility status and not adjusted for covariates. Dashed and dotted lines, 95% confidence intervals.

analyses, and they did not change appreciably when analyses were restricted to women who had never used oral contraceptives (data not shown).

Among all women, body mass index at age 18 years was inversely associated with the incidence of diagnosis of laparoscopically confirmed endometriosis (table 3). No significant difference by case-infertility status or effect modification by physical examination or use of oral contraceptives was observed (data not shown). A linear trend was not observed for current body mass index among all women or women without infertility within any subgroup. However, when cases were concurrently infertile, we observed a decrease in risk among overweight and obese women. This trend was not confounded by menstrual cycle irregularity (data not shown). Overall, and in subgroups, no trend with height or waist/hip ratio was observed (table 3). In our small sample of women less than 30 years of age, there was the suggestion of an inverse relation with waist/hip ratio, but the age-adjusted association was less than twofold when comparing the lowest with the highest ratio category (data not shown).

In multivariate analyses, women who reported greater current alcohol intake had a lower rate of endometriosis (table 4). This effect was not modified by nulliparity or

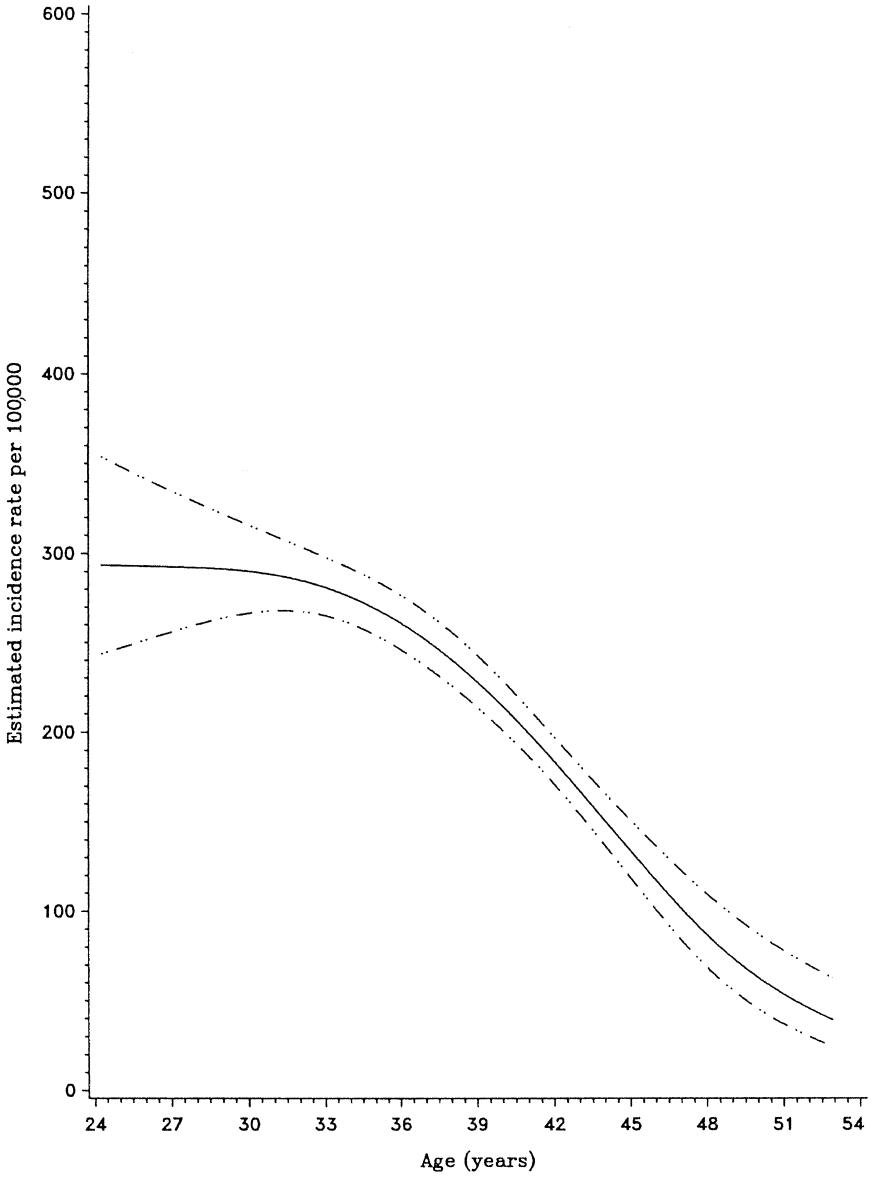

FIGURE 2. Nonparametric regression curve of the age-specific incidence of laparoscopically confirmed endometriosis among premenopausal women *with no past infertility* in the Nurses' Health Study II (1989–1999) (not adjusted for covariates). Dashed and dotted lines, 95% confidence intervals.

having had a recent gynecologic examination (data not shown). To evaluate if the association between alcohol and endometriosis was influenced by alteration of intake because of prediagnosis symptoms, we repeated our analysis using baseline consumption and excluding the first 4 years of follow-up; results did not change substantially (data not shown). In addition, an inverse trend was observed with alcohol consumption between the ages of 15 and 22 years (data not shown). We did not observe an association with milligrams of caffeine consumed per day (table 4) or frequency of coffee or tea consumption independent of caffeine intake (data not shown).

We observed a complex relation with cigarette smoking (table 4). The rate of endometriosis was not linearly associated with past smoking dose. However, the relation with current smoking differed by case-infertility status. Among women who had never reported infertility, cigarette smoking was directly associated with risk. However, when cases were concurrently infertile, current smoking was associated with reduced risk. Effect modification was not observed by use of oral contraceptives or having had a recent physician's exam-

TABLE 1. Age-specific incidence of laparoscopically confirmed endometriosis among premenopausal women, Nurses' Health Study II, 1989–1999

	Women with past infertility					Women with no past infertility*					Case definition									
											No past or concurrent infertility‡					Concurrent infertility‡				
	No. of cases	No. of person-years	Rate/100,000 person-years	Multivariate relative risk	95% confidence interval†	No. of cases	No. of person-years	Rate/100,000 person-years	Multivariate relative risk	95% confidence interval†	No. of cases	No. of person-years	Rate/100,000 person-years	Multivariate relative risk	95% confidence interval†	No. of cases	No. of person-years	Rate/100,000 person-years	Multivariate relative risk	95% confidence interval†
Age (years)																				
25–29	100	2,976	3,360	1.5	1.2, 1.9	177	58,965	300	0.8	0.7, 1.0	109	59,039	185	0.9	0.7, 1.1	65	59,173	110	0.7	0.5, 0.9
30–34	260	13,589	1,913	1.0	Referent	499	172,863	289	1.0	Referent	327	173,060	189	1.0	Referent	163	173,913	94	1.0	Referent
35–39	206	18,035	1,142	0.6	0.5, 0.7	623	239,285	260	1.0	0.9, 1.1	506	239,441	211	1.2	1.0, 1.3	112	21,123	46	0.7	0.5, 0.8
40–44	50	9,585	522	0.3	0.2, 0.4	349	191,208	183	0.7	0.6, 0.8	325	191,261	170	0.9	0.8, 1.1	21	192,539	8	0.1	0.1, 0.2
45–52	4	736	543	0.2	0.1, 0.6	73	63,884	114	0.4	0.3, 0.5	73	63,888	114	0.6	0.5, 0.8	0	64,350	0		
Total*	620	44,922	1,380			1,721	726,205	237			1,340	726,689	184			361	731,097	49		
p_{trend}				<0.0001	<0.0001				<0.0001	<0.0001				0.04					<0.0001	

* The total number of cases among women with no past infertility is greater than the sum of cases among women with no past or concurrent infertility and those with concurrent infertility, because some cases were missing data on infertility evaluation and could not be separated.

† Adjusted for calendar time (2-year questionnaire period), parity (0, 1, 2, 3, ≥4), race (Caucasian, other race/ethnicities (African American, Hispanic, Asian)), and body mass index at age 18 years (<19, 19–20.4, 20.5–21.9, 22–24.9, 25–29.9, >29.9 kg/m^2).

‡ Infertility is defined as attempting to become pregnant for more than 1 year without success. Cases with "no past or concurrent infertility" are women who never reported infertility. Cases with "concurrent infertility" are women who reported an infertility evaluation in the same follow-up cycle as laparoscopic confirmation of endometriosis.

TABLE 2. Race/ethnicity and the incidence of laparoscopically confirmed endometriosis among premenopausal women by infertility status and access to health care, Nurses' Health Study II, 1989–1999

Race	Case definition															
	All women (no past infertility)										No past or concurrent infertility*			Concurrent infertility*			
	No. of cases	No. of person-years	Age-adjusted rate ratio†	Multivariate rate ratio	95% confidence interval‡	No recent physical examination§		Recent physical examination§		*p* value¶	No. of cases	Multivariate rate ratio	95% confidence interval‡	No. of cases	Multivariate rate ratio	95% confidence interval‡	*p* value#
						Multivariate rate ratio	95% confidence interval‡	Multivariate rate ratio	95% confidence interval‡								
Caucasian	1,603	664,070	1.0	1.0	Referent	1.0	Referent	1.0	Referent	0.40	1,253	1.0	Referent	332	1.0	Referent	0.20
Asian	31	14,252	0.9	0.8	0.5, 1.1	0.6	0.2, 2.1	0.8	0.5, 1.2		23	0.8	0.5, 1.2	7	0.7	0.4, 1.5	
African American	17	11,732	0.6	0.6	0.4, 0.9	—**		0.6	0.4, 1.0		15	0.7	0.4, 1.1	1	0.2	0.0, 1.1	
Hispanic	17	11,100	0.6	0.6	0.4, 1.0	0.4	0.1, 2.6	0.7	0.4, 1.2		10	0.5	0.3, 0.9	8	1.1	0.5, 2.3	

* Infertility is defined as attempting to become pregnant for more than 1 year without success. Cases with "no past or concurrent infertility" are women who never reported infertility. Cases with "concurrent infertility" are women who reported an infertility evaluation in the same follow-up cycle as laparoscopic confirmation of endometriosis.

† Adjusted for age (months) and calendar time (2-year questionnaire period). Caucasian age-adjusted rate ratio = 1.0 is the referent.

‡ Adjusted for age (months), calendar time (2-year questionnaire period), parity (0, 1, 2, 3, ≥4), and body mass index at age 18 years (<19, 19–20.4, 20.5–21.9, 22–24.9, 25–29.9, >29.9 kg/m^2).

§ As a proxy measure for access to health care, all women were stratified by whether they reported having had a clinical screening breast or pelvic examination during the past 2 years.

¶ *p* value, test for heterogeneity comparing the effect of race among women who have not had a recent physical examination with those who have had a recent examination.

p value, test for heterogeneity comparing the effect of race among women having no past or current infertility with those having concurrent infertility.

** —, no cases.

ination (data not shown). When the age-specific smoking dose was evaluated among ever smokers, the smoking dose before age 20 years was not associated with risk (data not shown). We did not observe an effect of pack-years, age when quit smoking, or time since quitting smoking (data not shown).

DISCUSSION

In this prospective study among premenopausal women, we observed the incidence rates of diagnosis of laparoscopically confirmed endometriosis to be inversely associated with age and 20–40 percent lower among women of other races/ethnicities compared with Caucasian women. The excess rates among younger, Caucasian women were not explained by infertility status at the time of diagnosis or by measures of routine health care utilization. Body mass index at age 18 years was modestly inversely associated with the rate of diagnosis, but when cases were concurrently infertile, current obesity was strongly associated with decreased risk. We observed no significant relation with height or waist/hip ratio.

Prevalence estimates of endometriosis in clinic populations vary by diagnosis. In four of the largest studies (13–16), the prevalence of mainly asymptomatic endometriosis found in women undergoing tubal ligation ranged from 1 to 7 percent. In a multicenter study of infertility, endometriosis was diagnosed in 17 percent of women with primary infertility (17), and in other series the prevalence varied from about 9 percent to 50 percent (18, 19). Among women with pelvic pain, the prevalence of endometriosis ranged from about 5 percent to 21 percent (18, 20–22). The baseline prevalence of self-reported, physician-diagnosed endometriosis in our cohort was 5 percent.

The only study to report general population incidence rates of histologically confirmed endometriosis was conducted among White women in Rochester, Minnesota, from 1970 to 1979 (23, 24). The National Hospital Discharge Survey suggested that the incidence of endometriosis requiring hospitalization peaked between the ages of 40 and 44 years (25), the same as that observed a decade earlier in Rochester. Our data suggest a greater incidence rate with a younger peak. Diagnostic criteria, disease recognition and definition, access to health care, and utilization of invasive procedures have improved substantially in the decade between the baseline of this study and ours. In addition, our population consists of health professionals and therefore may be more likely than women in the general population to seek and receive an earlier and more accurate diagnosis.

Studies have suggested that Asian women are at higher risk of endometriosis compared with women of other races, while African-American women are at lower risk (1, 16, 23). Asian women in our cohort were not at greater risk than were Caucasian women, but African-American women had a lower incidence of laparoscopically confirmed endometriosis. It has been argued that the relation with African-American ancestry is spurious because of decreased access to health care and misclassification of the outcome, because racial minority women are often misdiagnosed as having pelvic inflammatory disease rather than endometriosis. However, in our cohort, the lower diagnosis rate of endometriosis was evident even among those who had had a clinical examination during the past 2 years. In addition, within this same cohort, we observed an increased risk of uterine leiomyomata among African-American women of from two- to threefold compared with the risk among Caucasians (26). Thus, detection and diagnostic bias are not likely to explain missed diagnoses of endometriosis and overdiagnosis of leiomyomata. The biologic basis for the decreased incidence rates among racial minority women remains unclear, particularly given data that suggest that African-American women experience greater exposure to endogenous estrogens (27).

Several studies of anthropometric characteristics have observed weak inverse associations (17, 28, 29). We observed an inverse relation with body mass index at age 18 years, but a relation between current body mass index and endometriosis was found only when cases were concurrently infertile. Perhaps these case women represent a leaner subset of this cohort as they were leaner than those cases who had never reported infertility. There may, however, be a synergy between obesity and the underlying cause of infertility, as the greater prevalence of oligomenorrhea among obese women may explain both their increased risk of infertility and decreased risk of endometriosis. For example, this relation may represent patients with polycystic ovarian syndrome who tend to be obese and anovulatory. However, adjusting for menstrual cycle regularity did not alter the observed relation. Our results fail to confirm a previously reported direct relation between taller height and endometriosis (17, 29).

In one previous case-control study (n = 88 cases, 88 controls), in women aged 30 years or less, the odds of endometriosis were inversely related to waist/hip ratio (for women with a waist/hip ratio of 0.61–0.72 compared with women with a waist/hip ratio of 0.76–1.01: odds ratio = 6.18, 95 percent confidence interval: 2.01, 19.01) (30). However, we observed no relation overall and a small, nonsignificant difference between the lowest and highest waist/hip ratio categories in our small sample of women less than 30 years of age (data not shown).

Studies of endometriosis within infertile populations have suggested a direct relation with both caffeine (31, 32) and moderate (one drink or less per day) alcohol consumption (33), while another study comparing cases with both fertile and infertile controls observed no association with alcohol (29). The inverse association that we observed for alcohol contradicts these findings. Moderate alcohol intake has been shown to increase total and bioavailable estrogen levels (34, 35), and therefore we would expect an increase not a decrease in risk. As average current alcohol intake within this cohort population is low, we had limited power to examine consumption of more than one drink per day.

Cigarette smoking is known to have an effect on the hormonal milieu. Studies of the effect of smoking on endometriosis have produced conflicting results (17, 28, 36, 37). In two prior case-control studies, an inverse association with smoking that began in adolescence was reported (17, 28). However, neither a case-control study conducted among parous women (16) nor a cohort study of 17,302 women

TABLE 3. Body mass index, height, waist/hip ratio, and the incidence of laparoscopically confirmed endometriosis among premenopausal women by infertility status, Nurses' Health Study II, 1989–1999

	Case definition													
	All women (no past infertility)					No past or concurrent infertility*				Concurrent infertility*				
	No. of cases	No. of person-years	Age-adjusted rate ratio†	Multivariate rate ratio	95% confidence interval‡	No. of cases	No. of person-years	Multivariate rate ratio	95% confidence interval‡	No. of cases	No. of person-years	Multivariate rate ratio	95% confidence interval‡	*p* value§
Body mass index (kg/m^2) at age 18 years														
<19	185	63,387	1.2	1.2	1.0, 1.4	138	63,449	1.2	1.0, 1.4	45	63,975	1.3	0.9, 1.9	0.12
19–20.4	431	184,836	1.0	1.0	Referent	340	184,947	1.0	Referent	86	186,103	1.0	Referent	
20.5–21.9	341	150,729	1.0	1.0	0.8, 1.1	271	150,811	1.0	0.8, 1.1	65	151,712	0.9	0.7, 1.3	
22–24.9	319	134,320	1.0	1.0	0.8, 1.1	249	134,412	1.0	0.8, 1.2	68	135,201	0.9	0.7, 1.3	
25–29.9	128	55,254	1.0	0.9	0.7, 1.1	102	55,280	0.9	0.8, 1.2	26	55,599	0.7	0.4, 1.0	
>29.9	46	17,628	1.1	0.8	0.6, 1.1	39	17,641	1.0	0.7, 1.5	6	17,783	0.4	0.2, 0.8	
p_{trend}			0.37	0.004				0.30				0.0003		
Current body mass index (kg/m^2)¶														
<19	97	31,035	1.1	1.0	0.8, 1.2	71	31,072	1.1	0.8, 1.4	23	31,288	0.7	0.5, 1.2	0.006
19–20.4	239	83,425	1.0	1.0	Referent	167	83,499	1.0	Referent	68	83,940	1.0	Referent	
20.5–21.9	292	122,564	0.9	0.9	0.8, 1.1	213	122,649	0.9	0.7, 1.1	78	123,348	1.0	0.7, 1.4	
22–24.9	461	187,208	0.9	1.0	0.8, 1.2	356	187,333	1.0	0.8, 1.3	99	188,413	1.0	0.7, 1.3	
25–29.9	337	143,659	0.9	1.0	0.9, 1.2	278	143,730	1.1	0.9, 1.3	54	144,753	0.8	0.5, 1.1	
>29.9	211	101,066	0.8	0.9	0.7, 1.1	190	101,099	1.1	0.8, 1.3	20	101,815	0.4	0.2, 0.7	
p_{trend}			0.14	0.78				0.27				0.008		
Current height (m)¶														
<1.60	320	136,535	1.0	1.0	0.9, 1.2	249	136,635	1.0	0.9, 1.2	65	137,460	1.0	0.8, 1.4	0.27
1.60–1.63	451	197,145	1.0	1.0	Referent	352	197,280	1.0	Referent	92	198,416	1.0	Referent	
1.65–1.68	438	100,549	1.0	0.9	0.8, 1.1	336	199,663	0.9	0.8, 1.1	102	200,861	1.0	0.8, 1.4	
1.70–1.73	362	135,372	1.2	1.1	1.0, 1.3	281	135,478	1.1	1.0, 1.3	75	136,336	1.0	0.7, 1.4	
>1.73	145	56,441	1.1	1.0	0.8, 1.2	118	56,468	1.1	0.9, 1.4	26	56,856	0.8	0.5, 1.2	
p_{trend}			0.19	0.78				0.35				0.31		

Current waist/hip ratio¶,#														
<0.70	29	14,240	1.0	0.9	0.6, 1.4	20	14,249	0.8	0.5, 1.3	9	14,425	1.5	0.7, 3.1	0.36
0.70–0.79	225	107,751	1.0	1.0	Referent	190	107,806	1.0	Referent	35	108,845	1.0	Referent	
0.80–0.89	104	53,521	0.9	1.0	0.8, 1.2	86	5,354	0.9	0.7, 1.2	18	53,881	1.2	0.7, 2.2	
>0.89	23	12,286	0.9	1.0	0.6, 1.5	18	12,291	0.9	0.5, 1.4	5	12,407	1.6	0.6, 4.2	
p_{trend}			0.34	0.87				0.82				0.79		

* Infertility is defined as attempting to become pregnant for more than 1 year without success. Cases with "no past or concurrent infertility" are women who never reported infertility. Cases with "concurrent infertility" are women who reported an infertility evaluation in the same follow-up cycle as laparoscopic confirmation of endometriosis.
† Adjusted for age (months) and calendar time (2-year questionnaire period). Age-adjusted rate ratios = 1.0 for the second category under each heading are the referent values.
‡ Adjusted for age (months), calendar time (2-year questionnaire period), race (Caucasian, other race/ethnicities (African American, Hispanic, Asian)), and parity (0, 1, 2, 3, ≥4).
§ *p* value, test for heterogeneity comparing the effect of anthropometry among women having no past or current infertility with those having concurrent infertility.
¶ Also adjusted for body mass index at age 18 years (<19, 19–20.4, 20.5–21.9, 22–24.9, 25–29.9, >29.9 kg/m^2).
# Waist/hip data were collected in 1993; therefore, the prospective follow-up time period for these analyses is from 1993 to 1999.

attending family clinics (36) found an association. Our observation of an inverse relation with current smoking when cases were concurrently infertile is consistent with studies by Cramer et al. (17) and Darrow et al. (28). However, in contrast, among women with no infertility, we observed an increase in risk with a greater number of cigarettes currently smoked per day. Smoking dose before age 20 years was not associated with risk.

These complex findings could result from the fact that, while smokers are relatively estrogen deficient, they are also exposed to higher levels of dioxin or other components of cigarette smoke that have hormone-like activities (38, 39). However, human epidemiologic studies, based on serum levels of dioxin or polychlorinated biphenyls, have been contradictory (40–43).

As for strengths and limitations, the large sample size and prospective design of the Nurses' Health Study II offer a unique opportunity to add to the limited knowledge of the epidemiology of endometriosis. In case-control studies, appropriate control selection is difficult, because factors that might influence which affected women are diagnosed could be related to exposures of interest (44, 45). As a result of the invasive nature of diagnosis, studies have often chosen controls from among groups of women who have had surgical pelvic investigation for other reasons (e.g., tubal ligation); however, this procedure may result in overmatching and attenuation of the relative risks for some exposures. In addition, detection bias may exist, because the thoroughness of examination may differ between cases identified during a work-up for infertility or pelvic symptoms and controls who were declared to be free of endometriosis during a tubal ligation or other surgical procedure not initiated by symptoms (29). In addition, when the study population comprises only infertile women, comparing infertile cases with a comparison or control group comprising infertile women without endometriosis may yield results very different from those that would be observed when comparisons are made with fertile women without endometriosis (29). We have accounted for these concerns by censoring women who have reported infertility prior to endometriosis diagnosis and subsequently separating analyses between cases who did and did not report an evaluation for infertility during the same follow-up period in which endometriosis was laparoscopically confirmed.

By limiting our case definition to those with laparoscopic confirmation of disease, we substantially decrease misclassification of the outcome. It is possible that patients with consistently more frequent utilization of the medical system (a strength of using Nurses' Health Study II data where access to health care is more homogeneous than in the general population), those of higher socioeconomic class, or those with more severe/aggressive disease may be more likely to undergo investigative laparoscopy. However, within strata of health care utilization as measured by exposure to a recent gynecologic examination, we observed similar results. It is also possible that our cases represent women with more severe disease, as all underwent laparoscopy. However, in several studies, the severity of endometriosis among women with laparoscopic confirmation does not

TABLE 4. Alcohol and caffeine consumptions, cigarette smoking, and the incidence of laparoscopically confirmed endometriosis among premenopausal women by infertility status, Nurses' Health Study II, 1989–1999

	Case definition													
	All women (no past infertility)					No past or concurrent infertility*				Concurrent infertility*				
	No. of cases	No. of person-years	Age-adjusted rate ratio†	Multivariate rate ratio	95% confidence interval‡	No. of cases	No. of person-years	Multivariate rate ratio	95% confidence interval‡	No. of cases	No. of person-years	Multivariate rate ratio	95% confidence interval‡	*p* value§
Current alcohol (g/day)¶														
None	608	256,700	1.0	1.0	Referent	495	256,824	1.0	Referent	110	258,518	1.0	Referent	0.77
>0–5.00	655	251,591	1.1	1.0	0.9, 1.1	494	251,768	1.0	0.9, 1.1	155	253,307	1.1	0.8, 1.4	
5.01–10.00	162	66,778	1.0	0.9	0.7, 1.1	118	66,824	0.8	0.7, 1.0	39	67,174	0.9	0.6, 1.3	
>10.00	118	60,646	0.8	0.7	0.6, 0.8	84	60,683	0.6	0.5, 0.8	32	6,095	0.8	0.5, 1.2	
p_{trend}			0.03	<0.0001				0.0001				0.05		
Current caffeine, quintiles (mg/day)														
<46.3	219	96,486	1.0	1.0	Referent	171	96,539	1.0	Referent	48	97,316	1.0	Referent	0.78
46.3–130.7	218	96,629	1.0	1.0	0.8, 1.2	176	96,680	1.0	0.8, 1.3	42	97,458	0.8	0.5, 1.2	
>130.7–228.2	221	96,365	1.1	1.0	0.8, 1.2	172	96,429	1.0	0.8, 1.2	47	97,185	0.9	0.6, 1.4	
>228.2–391.6	189	97,043	0.9	0.9	0.7, 1.1	151	97,083	0.9	0.7, 1.1	40	97,765	0.9	0.6, 1.3	
>391.6	213	94,918	1.0	1.0	0.8, 1.2	173	94,976	1.0	0.8, 1.3	41	95,678	1.0	0.6, 1.5	
p_{trend}			0.61	0.85				0.65				0.76		
Current smoking status¶														
Never smoker	1,150	480,872	1.0	1.0	Referent	872	481,218	1.0	Referent	266	484,112	1.0	Referent	0.07
Past, any dose (cigarettes/day)	332	141,340	0.9	0.9	0.8, 1.0	265	162,425	0.9	0.8, 1.1	60	163,311	0.8	0.6, 1.1	
1–14	189	90,665	0.9	0.9	0.8, 1.1	150	90,707	0.9	0.8, 1.1	37	91,208	0.9	0.6, 1.2	
15–24	89	28,174	0.8	0.8	0.7, 1.0	74	49,199	0.9	0.7, 1.1	13	49,455	0.6	0.4, 1.1	
25–34	31	15,273	0.9	0.9	0.6, 1.3	23	15,288	0.8	0.6, 1.3	8	15,366	1.3	0.7, 2.7	
≥35	23	7,228	1.5	1.4	0.9, 2.2	18	7,231	1.5	0.9, 2.4	2	7,282	0.7	0.2, 2.8	
p_{trend}			0.38	0.46				0.64				0.31		
Current, any dose (cigarettes/day)	235	81,964	1.2	1.2	1.0, 1.4	199	82,017	1.3	1.2, 1.6	34	82,641	0.7	0.5, 1.0	
1–14	87	36,608	1.0	1.0	0.8, 1.2	70	36,629	1.1	0.8, 1.4	18	36,901	0.8	0.5, 1.3	
15–24	104	32,778	1.3	1.3	1.1, 1.6	88	32,806	1.5	1.2, 1.9	13	33,048	0.7	0.4, 1.2	
25–34	34	9,021	1.6	1.6	1.1, 2.2	32	9,024	1.9	1.3, 2.7	2	9,105	0.4	0.1, 1.7	
≥35	10	3,557	1.2	1.2	0.6, 2.2	9	3,558	1.4	0.7, 2.7	1	3,587	0.6	0.1, 4.2	
p_{trend}			0.0006	0.002				<0.0001				0.05		

* Infertility is defined as attempting to become pregnant for more than 1 year without success. Cases with "no past or concurrent infertility" are women who never reported infertility. Cases with "concurrent infertility" are women who reported an infertility evaluation in the same follow-up cycle as laparoscopic confirmation of endometriosis.

† Adjusted for age (months) and calendar time (2-year questionnaire period). Age-adjusted rate ratios = 1.0 for the first category under each of the three main headings are referent values.

‡ Adjusted for age (months), calendar time (2-year questionnaire period), race (Caucasian, other race/ethnicities (African American, Hispanic, Asian)), parity (0, 1, 2, 3, ≥4), and body mass index at age 18 years (<19, 19–20.4, 20.5–21.9, 22–24.9, 25–29.9, >29.9 kg/m^2).

§ *p* value, test for heterogeneity comparing the effect of alcohol use among women having no past or current infertility with those having concurrent infertility.

¶ Also adjusted for current smoking status or current alcohol, respectively.

appear to be skewed to more extensive disease (16, 28, 30, 42). Our validation study data support this.

Nurses' Health Study II participants are not a random sample of US women, so findings may not be directly generalizable to the entire population. However, it is unlikely that the biologic relations among women in this cohort will differ from those among women in general.

Our prospective analyses among premenopausal US registered nurses suggest that endometriosis is most often diagnosed among Caucasian women between the ages of 25 and 35 years. Infertility status may alter the effect of hypothesized risk factors and must be considered carefully in study design and analysis. Further analyses within this cohort and others will help to clarify the risk factors that underlie this prevalent, poorly understood disease.

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