Variation in the Incidence of Uterine Leiomyoma Among Premenopausal Women by Age and Race

LYNN M. MARSHALL, ScD, DONNA SPIEGELMAN, ScD, ROBERT L. BARBIERI, MD, MARLENE B. GOLDMAN, ScD, JOANN E. MANSON, MD, GRAHAM A. COLDITZ, MBBS, WALTER C. WILLETT, MD, AND DAVID J. HUNTER, MBBS

Objective: **To quantify the incidence of uterine leiomyoma confirmed by hysterectomy, ultrasound, or pelvic examination according to age and race among premenopausal women.**

Methods: **From September 1989 through May 1993, 95,061 premenopausal nurses age 25–44 with intact uteri and no history of uterine leiomyoma were followed to determine incidence rates of uterine leiomyoma. The self-reported diagnosis was confirmed in 93% of the medical records obtained for a sample of cases. Using pooled logistic regression, we estimated relative risks (RRs) of uterine leiomyoma according to race and examined whether adjustment for other potential risk factors could explain the variation in the race-specific rates.**

Results: **During 327,065 woman-years, 4181 new cases of uterine leiomyoma were reported. The incidence rates increased with age, and the age-standardized rates of ultrasound- or hysterectomy-confirmed diagnoses per 1000 woman-years were 8.9 among white women and 30.6 among black women. After further adjustment for marital status, body mass index, age at first birth, years since last birth, history of infertility, age at first oral contraceptive use, and current alcohol consumption, the rates among black women were significantly greater for diagnoses confirmed by ultrasound or hysterectomy (RR 3.25; 95% confidence interval [CI] 2.71, 3.88) and by hysterectomy (RR 1.82; 95% CI 1.17, 2.82) compared with rates among white women. We observed similar RRs when the cohort was restricted to participants who reported undergoing a screening physical examination within the 2 years before baseline.**

Conclusion: **A higher prevalence of known risk factors did not explain the excess rate of uterine leiomyoma among premenopausal black women. (Obstet Gynecol 1997;90:967–73. © 1997 by The American College of Obstetricians and Gynecologists.)**

Among US women age 15–44, uterine leiomyoma is the fifth leading cause of hospitalizations for gynecologic disorders unrelated to pregnancy.[1] Moreover, this condition is the most frequent reason for hysterectomy among US women of all ages, accounting for 33% of the approximately 567,000 procedures performed annually.[2] Despite this major contribution to gynecologic morbidity, information regarding the distribution of uterine leiomyoma is limited. The incidence rate of hysterectomy for uterine leiomyoma was estimated to be 1.9 per 1000 woman-years in the US National Hospital Discharge Survey[2] and 2.7 per 1000 woman-years in a cohort of white, married women from the United Kingdom.[3] In the United States, the rate of hospitalization for uterine leiomyoma was 3.0 per 1000 woman-years.[1] However, incidence rates of uterine leiomyoma diagnosed at other gynecologic procedures, such as ultrasound, have not been quantified.

Descriptive studies suggest that black women appear to be disproportionately affected by this condition. The prevalence of hysterectomy for uterine leiomyoma was observed to be greater among black women than among white women,[4,5] and in the US National Hospital Discharge Survey,[2] the incidence rates of hysterectomy for this condition were 3.8 per 1000 woman-years among black women and 1.6 per 1000 woman-years among

From the Departments of Epidemiology, Biostatistics, and Nutrition, and the Center for Cancer Prevention, Harvard School of Public Health, Boston, Massachusetts; the Channing Laboratory and the Division of Preventive Medicine in the Department of Medicine, and the Department of Obstetrics and Gynecology, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts.

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white women. Epidemiologic studies among whites undergoing hysterectomy for uterine leiomyoma have demonstrated a significant positive association with obesity,[3] and significant inverse associations with parity, late age at last birth, and cigarette smoking.[3,6] Whether the racial disparity in rates of uterine leiomyoma is attributable to a different prevalence of these characteristics among black women has not been examined.

Therefore, to assess more completely the distribution of uterine leiomyoma according to age and race, we determined the incidence rate of diagnoses confirmed by hysterectomy, ultrasound, or pelvic examination reported in a prospective cohort of 95,061 premenopausal, female registered US nurses. We also examined the extent to which race was associated independently with the incidence of this condition, after accounting for other potential risk factors.

Materials and Methods

The Nurses' Health Study II cohort formed in September 1989 when 116,678 registered female nurses age 25–42 years from 14 states in the United States returned mailed questionnaires regarding age, race, height, weight at age 18, current weight, age at menarche, pregnancy history, history of oral contraceptive use, menopausal status, history of cigarette smoking, current alcohol consumption, and leisure-time physical activity. New questionnaires are mailed every two years to update this information. In 1993, we first asked about past diagnoses of uterine leiomyoma. Physical activity, oral contraceptive use, infertility due to ovulatory disorder, weight at age 18, current weight, height, and menopausal status are observed to be reported with reasonable accuracy in this cohort[7–10] or in the Nurses' Health Study,[11,12] another cohort of female registered US nurses. Follow-up of this cohort in each 2-year interval is over 90%.

At baseline, participants indicated their ethnic origin as "African-American," "Hispanic," "Asian," "Southern European/Mediterranean," "Scandinavian," "other Caucasion," or "other." We classified a participant as black if she indicated "African-American" ethnicity regardless of any other group she may also have marked. Of the black women, 91% indicated "African-American" ethnicity only. Participants who indicated "Hispanic," but not "African-American," were classified as Hispanic. Those who marked "Asian," but not "African-American" or "Hispanic," were considered as such. Participants indicating "Southern European/Mediterranean," "Scandinavian," or "other Caucasion," but not "African-American," "Hispanic," or "Asian," were classified as white. The remaining participants who marked "other" or did not answer the question were classified as unknown race.

In 1993, we asked participants for the first time to report if they "ever had physician-diagnosed uterine fibroids," whether that diagnosis was confirmed by "pelvic exam" or by "ultrasound/hysterectomy" and for the date of the first diagnosis in one of three intervals ("before September 1989," "September 1989–May 1991," or "June 1991–May 1993"), which correspond to the biennial follow-up periods.

We assessed the accuracy of this self-report in a sample of women who reported a new diagnosis confirmed by ultrasound or hysterectomy after September 1989. From among all white women who met this criteria, 100 were chosen randomly by a computerized random number generator. An additional 143 black women who met the same criteria and who had not been selected previously for other validation studies in this cohort were identified. These 243 participants were mailed supplemental questionnaires regarding symptoms and asked for permission to review their medical records. Of the 216 (89%) who responded, 12 (6%) denied the diagnosis, and 74 (34%) confirmed the diagnosis but did not release their medical record. For the remaining 130, we obtained records for 116 and confirmed the self-report in 108 (93%). The proportion confirmed was 92% (45 of 49) among black participants and 94% (63 of 67) among white participants. Similar proportions of white (71%) and black participants (63%) reported at least one symptom on the supplemental questionnaire; there were no material differences in the proportions of each group reporting unusually heavy bleeding, intermenstrual bleeding, pelvic pain, dyspareunia, lower back pain, or abdominal swelling. However, in comparison to white women, black women were more likely to have multiple lesions (74% of black and 54% of white participants), a larger median diameter of the largest leiomyoma (5.0 cm and 3.8 cm), and higher median uterine weight (excluding adnexa) recorded at hysterectomy (391 g and 168 g). Among those who did not release their medical record, the proportion who reported that their diagnosis was first confirmed at hysterectomy, myomectomy, examination under anesthesia, or ultrasound was the same as that among those who gave permission (88%). Among all medical records that we obtained, 59% of the recorded dates were within the self-reported diagnosis interval, 38% of the recorded dates fell into a later interval, and 4% were earlier than the reported interval. For the hysterectomy-confirmed cases, these proportions were 91%, 9%, and 0%, respectively. We were unable to obtain information regarding the recorded date of first clinical diagnosis for each participant, which may ex-

plain why the recorded dates are systematically later than the self-reported dates.

At baseline, the study population was restricted to premenopausal women with intact uteri. We excluded participants who reported being naturally menopausal because the development of uterine leiomyoma is rare after menopause.[2,3,6] Participants also were excluded if they did not answer the 1993 questionnaire on which we asked about diagnosed uterine leiomyoma, if they reported any diagnosis of uterine leiomyoma before September 1989 or provided no information about the date of their diagnosis or the confirmation type, or if they reported any diagnosis of cancer (other than nonmelanoma skin cancer). The resulting population for analysis comprised 95,061 women who were followed from the return of the 1989 questionnaire through May 1993.

During follow-up, we defined incident cases as participants who reported on the 1993 questionnaire a first diagnosis of uterine leiomyoma confirmed by pelvic examination, ultrasound, or hysterectomy in the intervals September 1989–May 1991 or June 1991–May 1993. The diagnosis date was set to the midpoint of the interval in which it was reported. Thus, incident refers to a first diagnosis rather than to the actual onset of uterine leiomyoma, which cannot be ascertained (this condition may be present before a leiomyoma becomes palpable or symptomatic). We further classified the diagnoses into three mutually exclusive categories according to the reported method of confirmation. A diagnosis was classified as hysterectomy-confirmed if the participant reported a hysterectomy[12] and a uterine leiomyoma diagnosis confirmed by ultrasound or hysterectomy in the same time interval. A diagnosis was classified as confirmed by ultrasound if no hysterectomy was reported in the same interval as a diagnosis confirmed by ultrasound or hysterectomy. Finally, a diagnosis was classified as made by pelvic examination if only that method of confirmation was reported.

Time at risk in each category of age or race was assigned as the number of months between the return of the 1989 questionnaire and May 1993, death, the onset of menopause, diagnosis of cancer other than nonmelanoma skin cancer, or date of uterine leiomyoma diagnosis, whichever occurred first. Age was updated in these analyses. Incidence rates of uterine leiomyoma were computed as the number of incident cases divided by the woman-time at risk. In analyses restricted to cases confirmed by ultrasound or hysterectomy or to hysterectomy only, the remaining cases were censored at the diagnosis date. The race-specific incidence rates were standardized to the age distribution of the study population.[13,14]

We used pooled logistic regression for grouped failure times[15] to estimate relative risks (RRs) of uterine leiomyoma associated with race and to calculate 95% confidence intervals (CIs), after controlling simultaneously for other potential risk factors. These analyses were restricted to cases confirmed at ultrasound or hysterectomy in order to reduce misclassification of the diagnosis. Initially, we fit a logistic model containing indicator terms for 11 potential risk factors along with terms for age and race. We considered a characteristic to be independently associated with the incidence of uterine leiomyoma if deleting the variable from the model resulted in a statistically significant likelihood ratio test.[16] We considered a characteristic to confound the association between black race and incidence if deleting that variable from the model containing all other independent predictors resulted in a change of 1% or more in the RR for black race.[17] We used a lower cutoff than the frequently used 10% change in the point estimate[17] because we wanted to obtain the most precise RR estimates and to minimize possible confounding.

Results

During 327,065 woman-years of follow-up, 4181 incident cases of uterine leiomyoma were reported. Of these, 667 (16%) were confirmed at hysterectomy, 2339 (56%) at ultrasound, and 1175 (28%) at pelvic examination only. The crude incidence rates per 1000 woman-years were 12.8 for all diagnoses of uterine leiomyoma, 9.2 for diagnoses confirmed at ultrasound or hysterectomy, and 2.0 for diagnoses confirmed at hysterectomy. Incidence rates increased with age (Table 1).

The incidence rates of uterine leiomyoma among black women were nearly always significantly greater than rates among others (Table 1); the rates among white, Hispanic, and Asian women were similar. The rate of uterine leiomyoma confirmed by ultrasound or hysterectomy increased with age in each racial group (Figure 1), but the age-specific rate among black women appeared to peak earlier than rates in the other groups. Small numbers of cases among Hispanic and Asian women made the age-specific rates unstable, and no ultrasound- or hysterectomy-confirmed cases were reported by Asian women age 25–29 years.

The age-standardized distributions at baseline of potential risk factors for uterine leiomyoma are shown according to race in Table 2. There was little difference in the proportions of women who were nulliparous or of low parity, or in mean levels of physical activity. Black women were older on average and more likely never to have married, to have been younger at their first term birth, to have last given birth in the more distant past, to be current users of oral contraceptives, and to have a higher current body mass index.

Table 1. Incidence of Uterine Leiomyoma Among Premenopausal Women

		Confirmation type					
		Any*		Ultrasound or hysterectomy		Hysterectomy	
	Woman-years	Cases	Rate† (95% CI)	Cases	Rate† (95% CI)	Cases	Rate† (95% CI)
Age							
25–29	49,730	212	4.3 (3.7, 4.8)	165	3.3 (2.8, 3.8)	10	0.2 (0.1, 0.3)
30–34	104,521	941	9.0 (8.4, 9.6)	706	6.8 (6.3, 7.3)	89	0.9 (0.7, 1.0)
35–39	110,730	1630	14.7 (14.0, 15.4)	1144	10.3 (9.7, 10.9)	273	2.5 (2.2, 2.8)
40–44	62,084	1398	22.5 (21.3, 23.7)	991	16.0 (15.0, 17.0)	295	4.8 (4.3, 5.3)
Age-standardized rates by race‡							
White	300,899	3785	12.5 (12.1, 12.9)	2679	8.9 (8.6, 9.2)	609	2.0 (1.9, 2.2)
Black	4367	174	37.9 (32.3, 43.6)	140	30.6 (25.5, 35.7)	21	4.5 (2.5, 6.4)
Hispanic	4654	66	14.5 (11.0, 18.0)	50	11.0 (8.0, 14.1)	6	1.3 (0.3, 2.4)
Asian	6007	65	10.4 (7.9, 13.0)	50	8.0 (5.8, 10.3)	12	1.9 (0.8, 3.0)

CI = confidence interval.
* Cases confirmed by hysterectomy, by ultrasound, or by pelvic examination only.
† Rate per 1000 woman-years.
‡ Incidence rates were standardized to the age-distribution of the woman-years at risk in the entire study population. The 11,139 woman-years and 118 cases occurring among women with unknown race are not included.

In multivariate analyses, we observed significant positive associations of incidence of uterine leiomyoma with age, race, body mass index, years since last term birth, history of infertility, and current alcohol consumption and significant inverse associations with age at menarche, age at first term birth, age at first oral contraceptive use, and being never married. Cigarette smoking and leisure-time physical activity were not associated. We observed similar relations between these variables and hysterectomy-confirmed cases, as well as in analyses conducted separately among white and black participants. After adjustment for these nine variables, the rate of uterine leiomyoma confirmed at ultrasound or hysterectomy among black women remained significantly elevated compared with rates among white women (RR 3.25; 95% CI 2.71, 3.88) as did the rate of hysterectomy-confirmed cases (RR 1.82; 95% CI 1.17, 2.82) (Table 3).

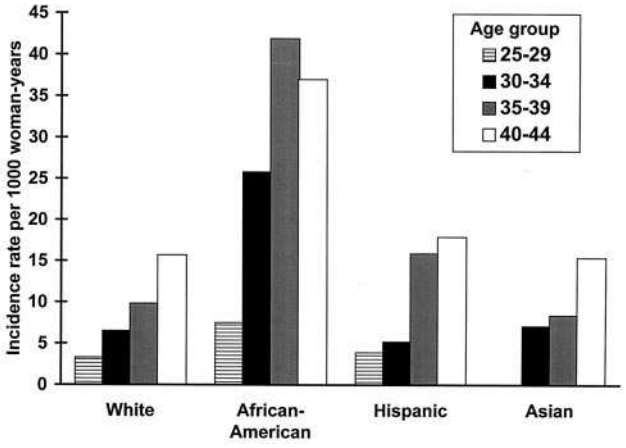

Figure 1. Incidence rates of uterine leiomyoma confirmed by ultrasound or hysterectomy according to age and race among premenopausal women in the Nurses' Health Study II, 1989–1993.

We identified body mass index, years since last term birth, age at first term birth, age at first oral contraceptive use, and marital status to be confounders of the association between race and the incidence of uterine leiomyoma. Together these five variables accounted for the modest attenuation in the age-adjusted RR for black race. To examine whether residual confounding by these variables might be present, we conducted separate analyses in which we modeled body mass index with indicator terms for deciles or as a continuous variable, modeled the interaction between weight change since age 18 and body mass index at age 18, replaced terms for years since last birth with terms for age at last birth, and replaced terms for age at first oral contraceptive use with terms for duration of use and years since last use. The multivariate RRs in these analyses were virtually identical to those shown in Table 3.

Population-based survey data from 1989 indicate that a greater proportion of US black women report a Papanicolaou smear in the previous 12 months (73%) than do white women (61%).[18] Because pelvic examinations frequently are conducted when a Papanicolaou smear is obtained, we wished to assess whether differences in gynecologic screening practices might influence our results. However, we had no information on past pelvic examinations for the entire study population, so we used the report of a physical examination for

Table 2. Potential Risk Factors for Uterine Leiomyoma According to Race

Characteristic	Race* White (n = 87,437)	Black (n = 1309)	Hispanic (n = 1345)	Asian (n = 1727)
Age (mean ± SD)	34.6 ± 4.6	35.3 ± 4.5	34.3 ± 4.6	34.8 ± 4.6
Ever married (%)	87	72	82	77
Age at menarche (%)				
≤11 y	24	33	35	24
≥14 y	18	16	13	20
Nulliparous (%)	30	33	34	42
Parity 1 or 2 (%)	52	53	50	48
Age at first birth (%)†				
≤24 y	38	57	42	23
≥30 y	16	11	16	28
Years since last birth (%)†				
<5	55	42	53	62
≥10	20	28	20	14
History of infertility (%)	17	14	17	14
Oral contraceptive use (%)				
Never	17	15	18	40
Current	14	18	15	11
Smoking (%)				
Never	65	74	75	86
Current	13	13	8	5
Mean BMI at age 18 (kg/m^2)	21.2	21.5	21.1	19.4
Mean current BMI (kg/m^2)	23.9	26.2	24.3	22.0
Mean current alcohol intake (g/d)	3.2	2.0	2.5	1.1
Mean physical activity (mets/d)	22.7	21.7	23.2	21.3

SD = standard deviation; BMI = body mass index; mets = metabolic equivalents.

* Percentages and means (except for age) are standardized to the age distribution of the study population in 5-year categories.

† Among parous women (at least one pregnancy of 6 months or more).

screening or a recent Papanicolaou smear as surrogate measures of pelvic examinations. In this cohort, 72% reported a physical examination for screening within the 2 years before baseline (73% of white and 78% of black participants), and 78% reported a Papanicolaou smear between June 1991 and the end of follow-up (78% of white and 70% of black participants). After excluding participants who reported no screening physical examination within the 2 years before baseline, we observed RRs nearly identical to those in the entire cohort (Table 3). After further restricting the cohort to women who reported a Papanicolaou smear since June 1991 and to cases first diagnosed after June 1991, we again observed a significant excess in the rate of uterine leiomyoma among black participants (RR 2.73; 95% CI 2.05, 3.64).

Discussion

In these prospective data, we observed the incidence rates of uterine leiomyoma among premenopausal women to be associated strongly with age and approximately two to three times greater among black women than among white women. The excess rates were not attributable to a higher prevalence of risk factors among black women, nor were they attributable to differences in health screening practices, as measured by a recent physical examination or Papanicolaou smear, among the racial groups in this study.

The educational and occupational similarity of the study participants enhances the validity of this study by reducing differences in socioeconomic status and health care use that could potentially confound this association.[19] Furthermore, biased reporting is unlikely because information on risk factors was collected before the diagnosis and confirmation of uterine leiomyoma. As we noted previously, this information is reported

Table 3. Incidence Rate of Uterine Leiomyoma Confirmed by Ultrasound or Hysterectomy Among Premenopausal Women

Confirmation type	Race White	Black	Hispanic	Asian
Ultrasound or hysterectomy				
Age-adjusted RR (95% CI)*	1.00	3.59 (3.01, 4.27)	1.24 (0.94, 1.65)	0.92 (0.70, 1.22)
Multivariate RR (95% CI)†	1.00	3.25 (2.71, 3.88)	1.19 (0.89, 1.58)	1.04 (0.78, 1.38)
Multivariate RR (95% CI)‡	1.00	3.24 (2.61, 4.02)	1.23 (0.86, 1.74)	1.01 (0.71, 1.42)
Hysterectomy				
Age-adjusted RR (95% CI)*	1.00	2.18 (1.41, 3.37)	0.66 (0.30, 1.48)	0.97 (0.55, 1.72)
Multivariate RR (95% CI)†	1.00	1.82 (1.17, 2.82)	0.65 (0.29, 1.45)	1.37 (0.77, 2.45)
Multivariate RR (95% CI)‡	1.00	1.83 (1.05, 3.20)	0.75 (0.28, 2.00)	1.57 (0.80, 3.08)

RR = relative risk; CI = confidence intervals.

* Adjusted for age in 5-year categories.

† Adjusted by pooled logistic regression for time period, age, marital status, age at menarche, body mass index, age at first term birth, years since last term, history of infertility, age at first oral contraceptive use, and current alcohol consumption.

‡ Restricted to 68,071 participants who had a physical examination for screening no more than 2 years before completing the 1989 questionnaire. Adjusted for the variables listed directly above.

with a reasonable degree of accuracy in this cohort,[7–10] so random errors in the report of potential risk factors are unlikely to have diminished our ability to control adequately for these variables. Moreover, residual confounding did not seem to affect our results because we observed no material changes in the RRs when we modeled the confounding variables in several ways.

Standardized pelvic or ultrasound examinations by the study investigators of this large cohort were not feasible. Therefore, we defined cases of uterine leiomyoma from diagnoses reported by the participants, after observing that the self-report was confirmed in 93% of the medical records that we obtained for a samples of cases. We attempted to reduce potential misclassification of case status by categorizing diagnoses according to confirmatory procedures. The medical records study provided evidence that accuracy in the self-report was similar among white and black participants, so the true difference in rates may be even greater than what we observed. Alternatively, the use of self-reported diagnoses could have resulted in an underascertainment of cases because some women with asymptomatic lesions may not have been diagnosed during the study period. However, for under-reporting of cases status to explain our results, white participants would have to be much less likely than black participants to undergo gynecologic screening procedures by which a diagnosis of uterine leiomyoma could be made. Such a bias seems unlikely because more than 70% of the study population reported a physical examination for screening at baseline or a Papanicolaou smear after June 1991 and restriction on these two surrogate measures of pelvic examinations resulted in RRs similar to those observed in the entire study population.

Although documentation has been limited to survey data, it has been accepted widely among clinicians that black women are at higher risk for uterine leiomyoma. Thus, if physicians are more likely to call a pelvic mass a uterine leiomyoma or to perform surgery for a pelvic mass among black women because of their race, then both the incidence rate and the RR of this condition could be overestimated in this group. However, in a case series[20] of 281 white and 301 black women undergoing hysterectomy for uterine leiomyoma, the two groups had similar symptomatology, and the black participants had significantly larger uteri, more numerous lesions, and a longer interval between the initial diagnosis and surgery than white women. In our validation study, we observed a similar tendency for black cases to have multiple lesions, larger leiomyomas, and greater uterine weight, providing evidence that the significantly greater rate of uterine leiomyoma in this group is unlikely to result from diagnostic bias.

The biologic basis for the elevated incidence rates of uterine leiomyoma among black women is unclear. Some have hypothesized that black women experience greater exposure to endogenous estrogens unopposed by progesterone[21] and that higher estrogen levels are associated with an increased incidence of uterine leiomyoma.[3] Follicular phase levels of estrone, estradiol, and free estradiol may be higher[22] and estrogen metabolism may differ (Taioli E, Garte SJ, Trachman J, Garbers S, Sepkovic DW, Osborne MP, et al. Ethnic differences in estrogen metabolism in healthy women [Letter]. J Natl Cancer Inst 1996;88:617) among young black and white women, but associations between the development of uterine leiomyoma and steroid hormone levels or markers of hormone metabolism have not been investigated prospectively.

This study confirms previous observations that the incidence of uterine leiomyoma increases with age[2,3] and that black women are disproportionately affected by uterine leiomyoma compared with white women.[2] The high incidence rate that we observed in the entire study population, equivalent to approximately 1% per year, suggests that preventive measures aimed at reducing the burden of gynecologic morbidity caused by this condition would benefit all premenopausal women. Identifying the factors—possibly hormonal or genetic—that underlie the racial difference may be valuable in guiding such efforts.

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Address reprint requests to:
David J. Hunter, MBBS
Channing Laboratory
181 Longwood Avenue
Boston, MA 02115

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