Published in final edited form as:
Fertil Steril. 2009 October ; 92(4): 1436–1446. doi:10.1016/j.fertnstert.2008.08.074.

Risk factors for surgically-removed fibroids in a large cohort of teachers

Claire Templeman, M.D.[1], **Sarah F Marshall, M.A.**[2], **Christina A. Clarke, PhD**[3], **Katherine DeLellis Henderson, Ph.D.**[4], **Joan Largent, Ph.D.**[2], **Susan Neuhausen, Ph.D.**[2], **Peggy Reynolds, Ph.D.**[3], **Giske Ursin, M.D., Ph.D.**[5], and **Leslie Bernstein, Ph.D.**[4]

[1] Department of Obstetrics and Gynecology, Keck School of Medicine of the University of Southern California, Los Angeles, California

[2] Department of Epidemiology, University of California, Irvine, California

[3] Northern California Cancer Center, Fremont, California

[4] Department of Cancer Etiology, Division of Population Science, City of Hope Comprehensive Cancer Center, Duarte, CA

[5] Department of Preventive Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, California

Abstract

Objective—To describe reproductive and lifestyle correlates of surgically confirmed fibroids.

Design—Prospective Cohort Study

Setting—The California Teachers Study (CTS), an ongoing prospective study of over 133,000 female teachers and school administrators identified through the California State Teachers Retirement System.

Patients—CTS cohort members reporting no prior history of fibroids were ascertained prospectively for surgical diagnosis of fibroids using hospital patient discharge records.

Main Outcome Measure(s)—Multivariable Cox proportional hazards regression methods were used to assess the association of self-reported menstrual, reproductive, and lifestyle characteristics with fibroids, using ages at the start and end of follow-up (in months) to define time on study. Hazard rate ratios, presented as relative risks (RR) with 95% confidence intervals (CI), were estimated.

Results—The strongest risk factor we identified was African-American race/ethnicity, as compared to non-Latina white women. We observed a reduced risk of fibroids for postmenopausal women in comparison to premenopausal women, but use of hormone replacement therapies (regardless of formulation) were associated with an increased risk. Other risk factors included race, a family history of fibroids, being overweight and drinking alcohol, Smoking and diabetes were associated with a decreased risk of fibroids.

Corresponding author: Dr Claire Templeman Department of Obstetrics and Gynecology, Keck School of Medicine of the University of Southern California, Los Angeles, CA 90033. templeman_c@ccnt.usc.edu. Tel.: 323 865 3979.

Capsule The epidemiologic profile of women with surgically treated fibroids suggests that both sex hormones and lifestyle factors are important factors in determining risk.

Conclusions—These observations provide a more detailed epidemiologic profile of women with surgically managed fibroids

Keywords

Fibroids; epidemiology

Uterine leiomyoma, commonly known as fibroids, are benign smooth muscle tumors of the uterus. They are the most common type of pelvic tumor and may be associated with infertility and menorrhagia (1) Currently fibroids are the leading cause of hysterectomy in the United States (1) (2)African-American women have been reported to have higher prevalence of fibroids compared to non-Latina white women (3) (4) (5). Previous studies have reported an inverse relationship between fibroids and age at menarche, parity and age at first pregnancy (3) (6) (7). Data on the association of physical activity and the incidence of fibroids are limited but suggest that regular exercise may prevent fibroids (8) Prior studies have not provided consistent results regarding risks with oral contraceptive use, smoking, or obesity (9) (10) (3) (11) possibly because of the heterogeneity of case definition across studies, with some relying on self reports of uterine fibroids, and others requiring diagnosis by ultrasound or hysterectomy. The effect of alcohol intake on the risk of fibroids has received scant attention in the literature to date but was associated with an increased risk in the single study that examined this factor (11)

The California Teachers Study (CTS) provides a unique opportunity to investigate surgically-confirmed fibroids because of its routine linkage to the California Office of Statewide Health Planning and Development (OSHPD) database for hospital discharge diagnoses, making possible uniform criteria for continuous ascertainment of surgically-diagnosed fibroids. Taking advantage of this important resource, our objective was to describe the reproductive and lifestyle risk factors for women having surgery for fibroids.

Subjects and Methods

The CTS is an ongoing prospective study of female public school teachers and administrators, designed to investigate breast cancer and other women's health conditions (12). A total of 133,479 women, ranging in age from 22 to over 90 years, completed a self-administered, baseline questionnaire in 1995-1996. In this questionnaire, members of the cohort were asked about their health, including whether they had ever had fibroids, information on reproductive history, use of hormones, physical activity, height and weight, alcohol intake, smoking history, and family history of health conditions including fibroids.

Following institutional review board approval we identified women with a diagnosis of fibroids using OSHPD hospital patient discharge records for the years 1991 to 2006 (13). These records include discharge diagnoses for all inpatients discharged from a California licensed hospital, as required by the California Health and Safety Code. A probabilistic record linkage algorithm using social security number, date of birth and sex, was used to obtain all OSHPD records for the CTS cohort in the 17-year time period. Social security numbers were available for 99 percent of the cohort; these have been validated using a checking algorithm that excludes numbers out of the possible range. Dates of birth were obtained on the baseline questionnaire for all CTS members and verified through comparison with California State Teachers Retirement System records.

Eligibility was limited to the 80,204 women younger than 80 years who were California residents (as OSHPD data are available only for California residents), with no history of fibroids or hysterectomy and with known age at first menstrual period. Women were excluded

sequentially from the original cohort if they were 80 years or older or a non-California resident (n=14,755), reported a history of fibroids on the baseline questionnaire (n=22,521), had a hospital discharge diagnosis of fibroids between 1991 and the date they joined the cohort (n=846), reported a hysterectomy or had a hysterectomy recorded in the OSHPD database between 1991 and the date they joined the cohort (n=13,819), or who did not provide an age at menarche on the baseline questionnaire (n=1,334). Validity of self-reported benign neoplasms by CTS participants exceeded 85 percent (14). After all exclusions, 80,204 women remained eligible for analysis.

Eligible cohort members were followed from the date they completed the baseline questionnaire in 1995 or 1996, until the earliest of the following events: the date of first surgically-confirmed primary diagnosis of fibroids, date of hysterectomy for any reason other than fibroids, date of death, date of move outside of California, or December 31, 2006. The surgical procedure by which fibroids were confirmed was hysterectomy for 92% of women, uterine incision including myomectomy for 7% of women and ovarian surgery for 1% of women. We censored the follow-up of 60 women whose fibroid diagnosis was not surgically-confirmed on the date of that diagnosis, and 1,429 women whose fibroid diagnosis was not the primary discharge diagnosis, at the date of their surgery. Deaths were identified by family report and annual probabilistic record linkage to the California state mortality file, the nationwide Social Security Administration death master file, and the National Death Index. Continued California residence was self-reported on four questionnaires (mailed in 1995, 1997, 2000, and 2005) and was supplemented by information obtained annually from the U.S. Postal Service National Change of Address database.

Variable Definitions

Hospitalization Characteristics—For women with fibroids, age at hospitalization, type of fibroid, and principal and other procedures were obtained from the same OSHPD discharge record as their fibroid diagnosis.

Participant Characteristics—With the exception of socioeconomic status (described below), all characteristics used in the statistical analyses were self-reported by cohort members on the baseline questionnaire. Age at baseline in years was calculated from the date of birth and the date of questionnaire completion. Race/ethnicity was classified as non-Latina white, African American, Latina, Asian/Pacific Islander, or other (including mixed or unknown race). (A positive family history of fibroids was defined as having a mother or sister with fibroids and categorized as no, yes, or adopted/unknown. To adjust for recent screening for fibroids, we included recent Papanicolaou (Pap) test history (yes during the two years before cohort entry or no/unknown). Four indicators of cardiovascular health were used; smoking history divided into four categories (never smoker, former smoker, current smoker and unknown), history of high blood pressure (no, yes), history of heart attack/myocardial infarction (no, yes), and history of stroke (no, yes). We also investigated diabetes history (no, yes) which could be related to fibroids since it is reportedly a risk factor for endometrial cancer. Neighborhood socioeconomic status was obtained by linking the residential street addresses of cohort members at baseline to U.S. Census neighborhood (block group) data (15) A summary index of socioeconomic status for each participant was calculated as previously described (16) (17) and was divided into four equal categories (quartiles).

Average alcohol consumption was measured in grams (g) per day; we assigned a serving of beer (bottle, glass or can) 13.2 g of alcohol, a glass of wine 11.1 g of alcohol and a shot of liquor 15.0 g of alcohol. Daily intake was classified as none, less than 20 g, 20 g or more, or unknown based on previous findings from this cohort (18). Physical activity was measured as the average lifetime strenuous and moderate physical activity per week, and it was grouped

into low activity (no more than 30 minutes of strenuous or moderate physical activity per week), intermediate activity (over 30 minutes but less than 3 hours a week of moderate or strenuous physical activity), high activity (over 3 hours a week of either moderate or strenuous physical activity) and unknown. Body mass index (BMI) was calculated from self-reported height and weight and was categorized as underweight (<18.50 kg/m^2), normal weight (18.50-24.99 kg/m^2), overweight (25.00-29.99 kg/m^2), obese (≥30.00 kg/m^2) or unknown. These definitions are consistent with those of the World Health Organization (19). Change in weight during adult years was measured in kilograms (kg) and was calculated as the difference between weight at age 18 years and baseline weight. The categories used in the statistical analysis were; same weight or weight loss since age 18, weight gain of less than 10 kg, weight gain of 10 to less than 20 kg, weight gain of 20 kg or more and unknown.

The reproductive factors that we investigated included age at menarche (less than 10 years, 11, 12, 13, 14, or 15 years or older). Women were also classified according to their use of oral contraceptives (never, past user, current user, or unknown) and, among those who had used oral contraceptives, we classified duration of use (less than 1 year, 1 to 4, 5 to 9, or more than 10 years) and age at first use(less than 20, 20 to 29, or 30 years or older). We created three pregnancy variables; age at first full-term pregnancy (14 to 19, 20 to 24, 25 to 29, 30 to 34, or 35 years or older, nulliparous), and among parous women, number of full-term pregnancies (1, 2, 3, 4, 5 or more), and years since last pregnancy (0 to 5, 6 to 10, 11 to 20, 21 to 30, 31 years or more) We also considered whether women ever had difficulty becoming pregnant (no, yes, or information not provided); this was defined as having tried unsuccessfully to get pregnant for at least one year. Women who had difficulty becoming pregnant were classified according to whether or not they had ever used fertility drugs for pregnancy (no, yes). We also classified women according to whether they had undergone a tubal sterilization (no, yes, and unknown). Menopausal status at baseline was defined by combining information collected on age, age at last menstrual period, reason for cessation of menstrual periods, and bilateral oophorectomy status. Perimenopausal women were those who had stopped menstruating within 6 months of completing the baseline questionnaire. Women who reported that their menstrual periods had stopped more than 6 months before completing the baseline questionnaire, or who had had a bilateral oophorectomy were defined as postmenopausal. In addition, all women who were not already classified as premenopausal and were 55 years of age or older were considered to be postmenopausal. We also categorized postmenopausal women according to their use of hormone therapy (estrogen alone, combined estrogen with progestin, mixed use of estrogen alone and estrogen in combination with progestin or never).

Statistical Analysis

Multivariable Cox proportional hazards regression methods were used to assess the association of the risk factors associated with surgical treatment of fibroids, using women's ages at the start and end of follow-up (in months) to define time on study. Hazard rate ratios, presented as relative risks (RR) with 95% confidence intervals (CI), were estimated and tested for linear trend across exposure categories where appropriate. To check the proportional hazards assumption we assessed the correlation of the scaled Schoenfeld residuals with time on study. *P* values ranged from 0.10 to 0.98, consistent with hazards that are proportional.

First, explanatory variables were fit in separate regression models, adjusting for race/ethnicity and family history of fibroids, and stratifying by age at baseline (in single years of age). Next, a stepwise selection procedure was used to create a multivariable model. The stepwise selection procedure was based on a likelihood ratio test comparing two models and used a significance level for entry of 0.20 and a significance level to remain of 0.25.

Analyses were performed for all women and then repeated, first excluding women who reported difficulty in getting pregnant, and then restricting the analyses to women who had had a Pap smear in the two years prior to joining the cohort.

We did not adjust the *P* values for multiple comparisons. All analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC).

Results

We identified 1,790 (2.2%) women in our cohort with a surgically-confirmed primary discharge diagnosis of fibroids during follow-up (Table 1). The average annual age-adjusted incidence rate of a surgically-confirmed primary fibroid diagnosis was 217.4 per 100,000 women (standardized using the Year 2000 US population); the age group with the highest incidence was 45 to 49 years, followed by age group 40 to 44 years. The majority of women (1,646 or 92.0%) were treated with hysterectomy.

African-American women had substantially higher risk of fibroid surgery (RR 2.28, 95% CI 1.81-2.87) than non-Latina white women who comprise the majority racial/ethnic group in our cohort (Table 2). Latinas also had significantly greater risk than non-Latina whites (RR 1.34, 95% CI 1.12-1.60). Women with fibroids were more likely than those without to have a mother or sister with fibroids (RR 1.42, 95% CI 1.25-1.61). Pap screening was not statistically associated with a diagnosis of fibroids (RR 1.15, 95% CI 0.97-1.36). Both women with and women without fibroids had extremely high levels of Pap screening in the two years prior to joining the cohort: 90.2% and 88.1% respectively. Women who reported having hypertension were more likely to be diagnosed with fibroids than those who without hypertension (RR 1.26, 95% CI 1.08-1.48), and current smokers were less likely to have fibroids than those who had never smoked (RR 0.68, 95% CI 0.52-0.89). Neither history of heart attack/myocardial infarction nor history of stroke was associated with surgery for fibroids, but diabetic women had a significantly lower risk than women not diagnosed with diabetes (RR 0.54, 95% CI 0.34-0.87). Neighborhood socioeconomic status was not associated with a fibroid diagnosis.

We found no relationship between lifetime physical activity and surgical treatment of fibroids. Drinking 20 g or more of alcohol per day was associated with surgery for fibroids (RR 1.33, 95% CI 1.12-1.58) (Table 3). BMI at entry into the study, and weight change since age 18 years, were both statistically significantly associated with surgery. Compared to women of normal body size (18.5-24.9 kg/m^2), those who were obese ($\geq$ 30.00 kg/m^2) had elevated risk (RR 1.33, 95% CI 1.17-1.52), as did women who were overweight (25.00-29.99 kg/m^2, RR 1.26, 95% CI 1.13-1.41). Similarly, women who gained 20 kg or more since age 18 years were at greater risk of surgery for fibroids than did those with less than 10 kg of weight gain since age 18 years (RR 1.23, 95% CI 1.08-1.41). When we stratified by menopausal status, we observed a statistically significant positive association for BMI and surgical diagnosis of fibroids among premenopausal and perimenopausal women (p-trend<0.001) but not among postmenopausal women (p-trend=0.20) (data not shown).

Age at menarche was inversely associated with surgically-confirmed fibroids (*p* for trend = 0.004); women who reported an age at menarche of 10 years or younger had a greater likelihood of surgery for fibroids than women with menarche at 13 years (RR 1.27, 95% CI 1.06-1.52) (Table 4). There was no association between past or current oral contraceptive use, or age at first oral contraceptive use, and surgery for fibroids. Among oral contraceptive users, those with very short-term oral contraceptive use (<1 year) had greater risk than women who had used oral contraceptives for 1 to 4 years, but we did not observe any trend in risk with duration of use. Women taking hormone therapy for menopausal symptoms, either estrogen alone (RR 2.03, 95% CI 1.17-3.52) or estrogen and progestin combined (RR 2.38, 95% CI 1.66-3.41) had

a higher risk of surgically-treated fibroids in our cohort than women who had never used hormones.

Some aspects of pregnancy history were associated with fibroids in our study. In comparison with women who were aged 25 to 29 years at the time of their first full-term pregnancy, those who had never given birth (nulliparous) had a higher risk of having surgery for fibroids (RR 1.16, 95% CI 1.03-1.31), those who had their first pregnancy at age 35 years or older had lower risk of having surgery for fibroids (RR 0.59, 95% CI 0.45-0.78) and the test for trend was statistically significant (p for trend < 0.001). The total number of full term pregnancies was not associated with surgically treated fibroids; however, a recent pregnancy was associated with a decreased risk of surgery for fibroids in these analyses which compared risk profiles of women of the same age. Tubal ligation was associated with an increased risk for a fibroid diagnosis (RR 1.20, 95% CI 1.06-1.36).

In the multivariable model, menopausal hormone status, age at first full-term pregnancy, race/ethnicity, a family history of fibroids, and BMI were most strongly associated with risk of surgically treated fibroids (Table 5). Alcohol intake, smoking status, difficulty getting pregnant, diabetes, hypertension, history of tubal ligation, and age at menarche also remained statistically significant in the final model. Increasing duration of oral contraceptive use, and weight gain since age 18, were not associated with fibroids in the multivariable model.

We imposed restrictions on the final model to reduce the opportunity for detection bias, first restricting the analysis to women who had a Pap test within two years of joining the cohort and then excluding women who had difficulty conceiving a pregnancy. This was done to reduce any chance of including women with undetected, asymptomatic fibroids. The multivariable model restricted to women with a Pap test within two years of study entry retained all factors except history of tubal ligation with risk estimates that were similar to those in the full model (data not shown). After excluding women who had difficulty becoming pregnant, the model retained all factors except hypertension and history of tubal ligation with risk estimates similar to those obtained in the full model (data not shown).

Discussion

Fibroids are monoclonal smooth muscle tumors (20) that appear and grow during the reproductive years and decrease in size during menopause (21). In addition gonadotrophin releasing hormone agonists (GnRHa), which decrease serum estradiol levels are used in some patients to decrease the size of fibroids prior to surgery (22) These findings support the concept that sex steroids are important regulators of fibroid growth. However the mechanisms by which sex steroids regulate this growth in fibroid cells are not fully elucidated but are thought to be through local growth factors such as epidermal growth factor (EGF) and insulin like growth factor-1 (IGF-1) (23). It has been shown that these growth factors are differentially expressed in fibroid smooth muscle cells compared to normal myometrium (24)

Our study investigated reproductive and lifestyle factors associated with having surgery for a primary diagnosis of fibroids ascertained prospectively in a large cohort of current and former public school teachers and administrators living in California. Our study approach differed from that used in previous cohort studies of fibroid diagnoses which were limited to premenopausal women (6) (3) as we also included perimenopausal and postmenopausal women. This broader age range allowed us to evaluate the association between hormone therapy and surgically treated fibroids. We found an association with use of all types of menopausal hormones (estrogen alone and estrogen in combination with progesterone). This is particularly important considering that fibroids were significantly less common among perimenopausal and postmenopausal women in our study than among premenopausal women.

It is possible that postmenopausal vaginal bleeding, in the setting of known myoma, may be more likely to be managed with hysterectomy. However, in our study, the association persisted in multivariable analysis. These results are also supported by the findings of another prospective study suggesting that women taking combined hormone therapy experienced an increase in fibroid volume that peaked in the first two years of therapy (25) Reed et al demonstrated in a case control study that prior use of estrogen and progestin therapy was associated with an increased risk of subsequent fibroids (26). In particular, the increased risk in this study was confined to a subset of women who had a BMI of less than 24 kg/m^2 suggesting that exogenous sources of estrogen and progestin in patients with low BMI may contribute to the development of fibroids.

We found that increasing BMI and weight gain since age 18 years are associated with an increasing risk of a surgical diagnosis of fibroids. This effect appears to be limited to premenopausal and perimenopausal women. One possible explanation is that increasing BMI in a combination with menopause results not only in a reduction in estradiol levels but also in fibroid growth factors such as IGF-1. Our BMI result is consistent with data for premenopausal women in the Nurses' Health Study II (9) (27) and with results from the Black Women's Health Study (28). In these two studies, the associations between BMI and fibroids were greater for women with surgical diagnoses than for those diagnosed by other means. In these two previously published studies, weight gain was also positively associated with risk of fibroids (27) (28). We cannot exclude the possibility that these observed associations are due to diagnostic bias; heavier women are more likely to undergo transvaginal ultrasound because pelvic examination in the setting of obesity yields limited information (29)

Neither a history of myocardial infarction nor stroke was associated with a surgical diagnosis of fibroids in our study; however we demonstrated reduced risk among women reporting a history of diabetes. Since we were unable to assess details of diabetic treatment and glucose control we could not establish exactly how these patients were being managed. However, it is likely that normalization of glucose levels in diabetics would result in a lowering of insulin levels, an elevation of SHBG, and an effective decrease in circulating estradiol levels. It is also possible that IGF-1 levels, known to be an important growth factor for fibroid cells in vitro are decreased in treated diabetics (30). Therefore the protective effect of diabetes in relation to a diagnosis of fibroids may be related to diabetic treatment. Indeed pioglitazone, a medication currently used in the treatment of type 2 diabetes has been shown *in vivo* to decrease the proliferative effects of fibroid cells in comparison to normal myometrial cells (31)

The likelihood of having surgery for fibroids during the 11 year follow-up was higher for African-American and Latina women than for non-Latina white women in our study. An elevated risk for African American women has been well documented in other epidemiologic studies on fibroids (32) (4) (5). A possible explanation for these racial/ethnic differences in risk is a difference in estrogen metabolism. In particular, estrogen receptor alpha (ERalpha) polymorphisms may play a role; indeed the ER-alpha PP genotype has been associated with an increased risk of fibroids in both non-Latina white and African American women, but the overall prevalence of the genotype is significantly higher among African American women (33). In addition, polymorphisms in catechol-o-methytransferase (COMT), an essential enzyme for estrogen metabolism, have been investigated as a possible mechanism for the racial differences in fibroid prevalence. Al- Hendy et al (34) found a much higher prevalence of the COMT Val158Met polymorphism among African American as compared to non-Latina white or Latina women however this was not confirmed by Gooden et al (35). Clearly more research is required in this area.

Few studies have investigated an association between alcohol use and fibroids. Our results are consistent with those of other studies. Wise et al (11) found that risk was positively associated

with years of alcohol consumption and current consumption of alcohol, particularly beer. Relative to non- drinkers the incidence rate ratios for beer consumption were <1, 1-6 and 7+ drinks/week were 1.11 (95% CI 0.98-1.27), 1.18 (95% CI 1.00-1.40) and 1.57 (95% CI 1.17-2.11) respectively Similarly, current alcohol consumption was positively associated with fibroid risk in the Nurses' Health Study II, a predominately Caucasian population (4). Alcohol has been found to increase estradiol levels in both premenopausal (36) and postmenopausal women (37). The postulated mechanism for this effect is an impairment of hepatic estrogen metabolism along with an enhancement of androgen to estrogen conversion (37)

With respect to pregnancy, a woman's age at first term pregnancy is inversely associated with risk in our study as it has been in other studies (3,6) It is possible that the explanation for this finding is that women who complete their childbearing earlier in life are more likely to accept a hysterectomy as treatment for their symptomatic fibroids. The finding that the risk of being diagnosed with fibroids increases as age at menarche decreases is also in agreement with findings from other studies (3) (32) (6). Early menarche increases overall exposure to circulating steroid hormones and may be associated with higher estrogen levels during reproductive life (38). Alternatively early menarche may be associated with early regular onset of ovulation and hence more prolonged exposure to estrogen and progesterone (39)

The literature on the effect of cigarette smoking and fibroid risk is mixed. Some studies have confirmed our finding of an inverse association between fibroids treated by hysterectomy and smoking (40) (41) (42), while others have not found an association (9) (11) Smoking is known to induce enzymes that promote estrogen metabolism and this is postulated as the potential mechanism for its effect on fibroid risk.

Two strengths of our study are its prospective design and case ascertainment without reliance on self-reporting. Only women with a principal and surgically-confirmed fibroid diagnosis were included as cases, effectively excluding patients in whom fibroids may have been an incidental finding at the time of surgery. We also included menopausal patients who were not included in previous cohort studies.

It is possible that we may have misclassified women with asymptomatic or otherwise undiagnosed fibroids. However, the high level of Pap screening among women without a diagnosis of fibroids suggests frequent physician contact, and makes diagnostic bias less likely. Our reliance on surgical diagnosis for inclusion in this study may produce results for risk factors that are influenced by symptoms and physician treatment preferences. In effect, we are defining the incidence of hospitalization for prevalent fibroids and may be identifying risk factors that predict access to medical care among women with fibroids. However, the cost associated with the management of fibroids is concentrated in the treatment of symptomatic patients; therefore identifying predictors for surgery may be helpful in determining more effective avenues for treatment.

In conclusion, this study identifies a number of important risk factors for a surgical diagnosis of fibroids among women in our cohort. The strongest risk factor we identified was African-American race/ethnicity, with elevated risks also observed for Latina women, as compared to non-Latina white women. We observed a reduced risk of fibroids for postmenopausal women in comparison to premenopausal women, but use of hormone replacement therapies (regardless of formulation) were associated with an increased risk. Other important risk factors in this cohort included race, having a positive family history of fibroids, being overweight or obese, and drinking alcohol, Smoking and a history of type 2 diabetes were associated with a decreased risk of fibroids.

Acknowledgments

This research was supported by grants R01 CA77393 from the National Cancer Institute and contract 97-10500 from the California Breast Cancer Research Fund

References

1. Merrill RM. Hysterectomy Surveillance in the United States, 1997 through 2005. Med Sci Monit 2008;14(1):CR24–31. [PubMed: 18160941]
2. Schwartz SM. Epidemiology of uterine leiomyomata. Clin Obstet Gynecol 2001;44(2):316–26. [PubMed: 11344995]
3. Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, Adams-Campbell LL, et al. Reproductive factors, hormonal contraception, and risk of uterine leiomyomata in African-American women: a prospective study. Am J Epidemiol 2004;159(2):113–23. [PubMed: 14718211]
4. Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol 1997;90(6):967–73. [PubMed: 9397113]
5. Day Baird D, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003;188(1):100–7. [PubMed: 12548202]
6. Marshall LM, Spiegelman D, Goldman MB, Manson JE, Colditz GA, Barbieri RL, et al. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. Fertil Steril 1998;70(3):432–9. [PubMed: 9757871]
7. Baird DD, Dunson DB. Why is parity protective for uterine fibroids? Epidemiology 2003;14(2):247–50. [PubMed: 12606893]
8. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. Association of physical activity with development of uterine leiomyoma. Am J Epidemiol 2007;165(2):157–63. [PubMed: 17090618]
9. Marshall LM, Spiegelman D, Manson JE, Goldman MB, Barbieri RL, Stampfer MJ, et al. Risk of uterine leiomyomata among premenopausal women in relation to body size and cigarette smoking. Epidemiology 1998;9(5):511–7. [PubMed: 9730029]
10. Chiaffarino F, Parazzini F, La Vecchia C, Marsico S, Surace M, Ricci E. Use of oral contraceptives and uterine fibroids: results from a case-control study. Br J Obstet Gynaecol 1999;106(8):857–60. [PubMed: 10453838]
11. Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, Adams-Campbell LL, et al. Risk of uterine leiomyomata in relation to tobacco, alcohol and caffeine consumption in the Black Women's Health Study. Hum Reprod 2004;19(8):1746–54. [PubMed: 15218005]
12. Bernstein L, Allen M, Anton-Culver H, Deapen D, Horn-Ross PL, Peel D, et al. High breast cancer incidence rates among California teachers: results from the California Teachers Study (United States). Cancer Causes Control 2002;13(7):625–35. [PubMed: 12296510]
13. Patient discharge data file documentation: January- December 2006. Sacramento, California: Office of Statewide health planning and development; 2007.
14. Marshall SF, Deapen D, Allen M, Anton-Culver H, Bernstein L, Horn-Ross PL, et al. Validating California teachers study self-reports of recent hospitalization: comparison with California hospital discharge data. Am J Epidemiol 2003;158(10):1012–20. [PubMed: 14607810]
15. Census of population and housing, 1990: modified age/race, sex and hispanic origin (MARS) state and county file (data file). Washinton DC: US Census Bureau; 1992.
16. Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, et al. Regional variations in breast cancer among california teachers. Epidemiology 2004;15(6):746–54. [PubMed: 15475725]
17. Reynolds P, Hurley SE, Goldberg DE, Yerabati S, Gunier RB, Hertz A, et al. Residential proximity to agricultural pesticide use and incidence of breast cancer in the California Teachers Study cohort. Environ Res 96(2):206–18. [PubMed: 15325881]

18. Horn-Ross PL, Canchola AJ, West DW, Stewart SL, Bernstein L, Deapen D, et al. Patterns of alcohol consumption and breast cancer risk in the California Teachers Study cohort. Cancer Epidemiol Biomarkers Prev 2004;13(3):405–11. [PubMed: 15006916]
19. WHO Consultation on Obesity: preventing and Managing the Global Epidemia. Geneva, Switerland: World health oragnization; 2000.
20. Fletcher JA, Morton CC, Pavelka K, JM L. Chromosome aberrations in uterine smooth muscle tumors: potential diagnostic relevance of cytogenetic instability. Cancer Res 1990;(50):4092–7. [PubMed: 2354458]
21. Rein, MS.; RA, N. Biology of uterine myomas and myometrium in vitro. In: Barbieri, RL., editor. Seminars in Reproductive Endocrinology. New York: Thieme; 1992. p. 310-9.
22. West CP, Lumsden MA, lawson S, Williamson J, DT B. Shrinkage of uterine fibroids during therapy with goserelin (Zoladex): a luteinizin hormone-releasing heomone agonist administered as a montly subcutaneous depot. Fertil Steril 1987;48:45–51. [PubMed: 2954863]
23. Maruo T, Ohara N, Wang J, H M. Sex steriod regulation of uterine leiomyoma growth and apoptosis. Hum Reprod Update 2004;10(3):207–20. [PubMed: 15140868]
24. Chandrasekhar Y, Hainer J, Osuamkpe C, Nagamani M. Insulin like growth factor 1 and 11 binding in human myometrium and leiomyomas. Am J Obstet Gynecol 1992;166:64–9. [PubMed: 1310202]
25. Yang CH, Lee JN, Hsu SC, Kuo CH, Tsai EM. Effect of hormone replacement therapy on uterine fibroids in postmenopausal women--a 3-year study. Maturitas 2002;43(1):35–9. [PubMed: 12270580]
26. Reed SD, Cushing-Haugen KL, Daling JR, Scholes D, Schwartz SM. Postmenopausal estrogen and progestogen therapy and the risk of uterine leiomyomas. Menopause 2004;11(2):214–22. [PubMed: 15021452]
27. Terry KL, De Vivo I, Hankinson SE, Spiegelman D, Wise LA, Missmer SA. Anthropometric characteristics and risk of uterine leiomyoma. Epidemiology 2007;18(6):758–63. [PubMed: 17917603]
28. Wise LA, Palmer JR, Spiegelman D, Harlow BL, Stewart EA, Adams-Campbell LL, et al. Influence of body size and body fat distribution on risk of uterine leiomyomata in U.S. black women. Epidemiology 2005;16(3):346–54. [PubMed: 15824551]
29. Padilla LA, Radosevich DM, Milad MP. Limitations of the pelvic examination for evaluation of the female pelvic organs. Int J Gynaecol Obstet 2005;88(1):84–8. [PubMed: 15617719]
30. Clemmons DR. Modifying IGF1 activity: an approach to treat endocrine disorders, atherosclerosis and cancer. Nat Rev Drug Discov 2007;6(10):821–33. [PubMed: 17906644]
31. Loy CJ, Evelyn S, Lim FK, Liu MH, Yong EL. Growth dynamics of human leiomyoma cells and inhibitory effects of the peroxisome proliferator-activated receptor-gamma ligand, pioglitazone. Mol Hum Reprod 2005;11(8):561–6. [PubMed: 16051682]
32. Faerstein E, Szklo M, Rosenshein N. Risk factors for uterine leiomyoma: a practice-based case-control study. I. African-American heritage reproductive history, body size, and smoking. Am J Epidemiol 2001;153(1):1–10. [PubMed: 11159139]
33. Al-Hendy A, Salama SA. Ethnic distribution of estrogen receptor-alpha polymorphism is associated with a higher prevalence of uterine leiomyomas in black Americans. Fertil Steril 2006;86(3):686–93. [PubMed: 16860797]
34. Al-Hendy A, Salama SA. Catechol-O-methyltransferase polymorphism is associated with increased uterine leiomyoma risk in different ethnic groups. J Soc Gynecol Investig 2006;13(2):136–44.
35. Gooden KM, Schroeder JC, North KE, Gammon MD, Hartmann KE, Taylor J, et al. Val153Met polymorphism of catechol-O-methyltransferase and prevalence of uterine leiomyomata. Reprod Sci 2007;14(2):117–20. [PubMed: 17636223]
36. Muti P, Trevisan M, Micheli A, Krogh V, Bolelli G, Sciajno R, et al. Alcohol consumption and total estradiol in premenopausal women. Cancer Epidemiol Biomarkers Prev 1998;7(3):189–93. [PubMed: 9521430]
37. Onland-Moret NC, Peeters PH, van der Schouw YT, Grobbee DE, van Gils CH. Alcohol and endogenous sex steroid levels in postmenopausal women: a cross-sectional study. J Clin Endocrinol Metab 2005;90(3):1414–9. [PubMed: 15572431]

38. Bernstein L, Pike MC, Ross RK, Henderson BE. Age at menarche and estrogen concentrations of adult women. Cancer Causes Control 1991;2(4):221–5. [PubMed: 1873451]

39. Apter D, Vihko R. Early menarche, a risk factor for breast cancer, indicates early onset of ovulatory cycles. J Clin Endocrinol Metab 1983;57(1):82–6. [PubMed: 6222061]

40. Ross RK, Pike MC, Vessey MP, Bull D, Yeates D, Casagrande JT. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. Br Med J (Clin Res Ed) 1986;293(6543):359–62.

41. MacMahon B, Trichopoulos D, Cole P, Brown J. Cigarette smoking and urinary estrogens. N Engl J Med 1982;307(17):1062–5. [PubMed: 7121516]

42. Faerstein E, Szklo M, Rosenshein NB. Risk factors for uterine leiomyoma: a practice-based case-control study. II. Atherogenic risk factors and potential sources of uterine irritation. Am J Epidemiol 2001;153(1):11–9. [PubMed: 11159140]

Table 1

Selected characteristics of California Teachers Study participants with a principal diagnosis of surgically-treated fibroids (*n*=1790) identified in the California Office of Statewide Health Planning and Development patient discharge records, 1995-2006.

	n	%	ASR*
Age at diagnosis (years)			
25-29	2	0.1	51.4
30-34	33	1.8	120.9
35-39	102	5.7	205.4
40-44	285	15.9	412.7
45-49	551	30.8	464.8
50-54	457	25.5	321.3
55-59	175	9.8	181.7
60-64	94	5.3	135.8
65-69	43	2.4	90.7
70-74	22	1.2	63.0
75-79	22	1.2	44.8
80-84	4	0.2	48.7
Type of fibroid			
Intramural fibroid	654	36.5	
Sub serous fibroid	230	12.9	
Sub mucous fibroid	299	16.7	
Unspecified fibroid	607	33.9	
Concurrent hysterectomy			
Yes	1646	92.0	
No[a]	144	8.0	

*Annual age-specific incidence rate per 100,000 women.

[a]Fibroids not treated by hysterectomy were treated with other surgical procedures, primarily other uterine incision including myomectomy (7%), or ovarian surgery (1%).

Table 2

Multivariable-adjusted relative risks for surgically-treated fibroids according to baseline health characteristics among 80,204 women in the California Teachers Study.

	Surgery for fibroids during study follow-up period, 1995-2006	
	Woman years	***n*Multivariable adjusted RR (95% CI)*[a]**
Race/Ethnicity		
Non-Latina white	684164	14481.00
African American	15796	752.28 (1.81, 2.87)
Latina	40647	1321.34 (1.12, 1.60)
Asian/Pacific Islander	33096	791.08 (0.86, 1.36)
Other	22179	561.13 (0.86, 1.47)
Mother or sister had fibroids		
No	698023	14651.00
Yes	83880	2871.42 (1.25, 1.61)
Adopted/unknown	13978	38
Neighborhood socioeconomic status		
Fourth quartile (high)	354780	7261.00
Third quartile	262740	6281.07 (0.96, 1.19)
Second quartile	135250	3261.07 (0.93, 1.22)
First quartile (low)	33629	891.17 (0.94, 1.46)
Unknown	9484	21
p trend		0.42
Pap screen in the last two years		
No	73078	1451.00
Yes	702611	16151.15 (0.97, 1.36)
Unknown	20193	30
Cigarette smoker		
Never	540539	13321.00
Former	211341	3940.89 (0.80, 1.00)
Current	39428	570.68 (0.52, 0.89)
Unknown	4573	7
High blood pressure		
No	699777	16061.00
Yes	96105	1841.26(1.08, 1.48)
Heart attack/Myocardial infarction		
No	790624	17841.00
Yes	5258	61.04 (0.47, 2.34)
Stroke		
No	790301	17821.00
Yes	5581	80.84 (0.42, 1.69)
Diabetes		
No	778905	17721.00
Yes	16976	180.54 (0.34, 0.87)

[*] RR, relative risk; CI, confidence interval.

[a] Adjusted for race/ethnicity, and family history of fibroids, and stratified by age.

Table 3

Multivariable-adjusted relative risks for surgically-treated fibroids according to energy balance related factors in the California Teachers Study.

	Surgery for fibroids during study follow-up period, 1995-2006	
	Woman Years	***n*Multivariable adjusted RR (95% CI)*[a]**
Daily alcohol intake (g)		
None	248237	5610.96 (0.87, 1.07)
<20	444657	10111.00
≥20	61404	1561.33 (1.12, 1.58)
Unknown	41584	63
Lifetime moderate and strenuous physical activity [b]		
Low	83851	1541.02 (0.86, 1.21)
Intermediate	388484	9031.00
High	319080	7250.95 (0.86, 1.05)
Unknown	4466	8
Body mass index (kg/m^2)		
Underweight (<18.50)	22562	450.97 (0.72, 1.31)
Normal weight (18.50-24.99)	468749	9851.00
Overweight (25.00-29.99)	178437	4341.26 (1.13, 1.41)
Obese (≥30.00)	101738	2881.33 (1.17, 1.52)
Unknown	24396	38
p trend		<0.001
Change in weight since age 18 (kg) [c]		
Same weight or weight loss	169149	3430.87 (0.76, 1.01)
Weight gain <10.00	289062	6231.00
Weight gain 10.00-19.99	182750	4411.16(1.02, 1.31)
Weight gain ≥20.00	124919	3391.23 (1.08, 1.41)
Unknown	30002	44
p trend		<0.001

[*] RR, relative risk; CI, confidence interval.

[a] Adjusted for race/ethnicity, and family history of fibroids, and stratified by age.

[b] Low activity is no strenuous or moderate activity with cumulative duration that is more than 30 minutes per week. High activity is over 3 hours a week of either moderate or strenuous physical activity.

[c] Additionally adjusted for body mass index at age 18.

Table 4

Multivariable-adjusted relative risks for surgically-treated fibroids according to baseline reproductive and hormonal characteristics in the California Teachers Study.

	Surgery for fibroids during study follow-up period, 1995-2006	
	Woman years	***n*Multivariable adjusted RR (95% CI)*[a]**
Age at menarche (years)		
≤10	52387	1541.27 (1.06, 1.52)
11	118355	3111.21 (1.05, 1.39)
12	218284	4971.04 (0.92, 1.17)
13	240360	5111.00
14	100540	1950.94 (0.80, 1.11)
≥15	65956	1220.91 (0.75, 1.11)
P trend		0.004
Oral contraceptive use		
No	210369	3301.00
Yes, past user	497482	12591.01 (0.89, 1.15)
Yes, current user	72174	1701.02 (0.84, 1.24)
Unknown	15856	31
Duration of oral contraceptive use (years)[b]		
<1	61107	1761.23 (1.03, 1.47)
1-4	192003	4601.00
5-9	180029	4541.09 (0.96, 1.24)
≥10	125003	3131.10 (0.95, 1.27)
Unknown duration	11514	26
p trend		0.12
Age first used oral contraceptives (years)[b]		
<20	148228	5021.00
20-29	338773	8020.90 (0.80, 1.01)
≥30	67545	850.89 (0.68, 1.16)
Unknown age	15110	40
p trend		0.20
Age at first full-term pregnancy (years)		
Nulliparous	230342	5691.16 (1.03, 1.31)
14-19	22729	571.13 (0.86, 1.48)
20-24	150587	3541.28 (1.12, 1.47)
25-29	236383	5201.00
30-34	113179	2240.76 (0.65, 0.89)
≥35	34818	570.59 (0.45, 0.78)
Unknown	7846	9
p trend		<0.001
Ever had difficulty becoming pregnant		
No	639664	13811.00
Yes	149313	3971.14 (1.02, 1.28)
Unknown	6905	12
Ever used fertility drugs for pregnancy		
No	752840	16531.00
Yes	43041	1371.08 (0.91, 1.29)
Number of full-term pregnancies[c]		
1	127625	2681.00
2	257690	6661.20 (1.04, 1.38)
3	116223	2060.97 (0.81, 1.17)
4	39231	520.91 (0.67, 1.23)
≥5	16779	200.99 (0.62, 1.57)
p trend		0.017
Years since last pregnancy[c]		
0-5	96970	1780.41 (0.33, 0.51)
6-10	64763	2440.76 (0.64, 0.89)
11-20	156419	5121.00
21-30	114940	1901.28 (1.03, 1.58)
≥31	124456	881.61 (1.07, 2.41)
p trend		<0.001
Ever had tubal ligation		
No	679809	14551.00

	Surgery for fibroids during study follow-up period, 1995-2006	
	Woman years	***n*Multivariable adjusted RR (95% CI)*[a]**
Yes	106202	3161.20 (1.06, 1.36)
Unknown	9871	19
Menopausal hormone status		
Premenopausal	436719	14095.31 (3.61, 7.82)
Perimenopausal	21006	322.98 (1.82, 4.87)
Postmenopausal, never used hormone therapy	104875	401.00
Postmenopausal, used estrogen alone	30222	192.03 (1.17, 3.52)
Postmenopausal, used combined estrogen-progestin	126568	1312.38 (1.66, 3.41)
Postmenopausal, mixed hormone therapy use	32378	383.25 (2.08, 5.08)
Unknown menopausal status	44113	121

*RR, relative risk; CI, confidence interval.

[a]Adjusted for race/ethnicity, and family history of fibroids, and stratified by age.

[b]Among oral contraceptive users.

[c]Among parous women.

Table 5

Multivariable model of best predictors of surgically-treated fibroids (presented in order selected by stepwise Cox proportional hazards modeling) in the California Teachers Study.

	Surgery for fibroids during study follow-up period, 1995-2006
	Multivariable adjusted RR (95% CI)*[a]
Menopausal hormone status	
Premenopausal	5.33 (3.62, 7.85)
Perimenopausal	2.89 (1.77, 4.74)
Postmenopausal, never used hormone therapy	1.00
Postmenopausal, used estrogen alone	2.01 (1.16, 3.50)
Postmenopausal, used combined estrogen- progestin	2.34 (1.63, 3.36)
Postmenopausal, mixed hormone therapy use	3.18 (2.03, 4.96)
Age at first full-term pregnancy (years)	
Nulliparous	1.20 (1.06, 1.36)
14-19	1.12 (0.85, 1.47)
20-24	1.28 (1.11, 1.46)
25-29	1.00
30-34	0.77 (0.65, 0.90)
≥35	0.59 (0.45, 0.78)
Race/Ethnicity	
White	1.00
African American	2.14 (1.69, 2.71)
Latina	1.28 (1.07, 1.54)
Asian/Pacific Islander	1.15 (0.91, 1.44)
Mother or sister had fibroids	
No	1.00
Yes	1.37 (1.21, 1.55)
Adopted/unknown	
Body mass index (kg/m^2)	
Underweight (<18.5)	1.00 (0.74, 1.35)
Normal weight (18.5-24.9)	1.00
Overweight (25-29.9)	1.23 (1.10, 1.38)
Obese (≥30)	1.27 (1.11, 1.46)
Daily alcohol intake (g)	
None	0.94 (0.84, 1.04)
<20	1.00
≥20	1.36 (1.14, 1.61)
Ever had difficulty becoming pregnant	
No	1.00
Yes	1.23 (1.10, 1.38)
Cigarette smoker	
Never	1.00
Former	0.87 (0.77, 0.97)
Current	0.65 (0.50, 0.85)
Diabetes	
No	1.00
Yes	0.51 (0.32, 0.82)
High blood pressure	
No	1.00
Yes	1.19 (1.01, 1.40)
Ever had tubal ligation	
No	1.00
Yes	1.19 (1.05, 1.35)
Age at menarche (years)	
≤10	1.21 (1.00, 1.45)
11	1.17 (1.01, 1.35)
12	1.03 (0.91, 1.16)
13	1.00
14	0.95 (0.80, 1.12)
≥15	0.93 (0.76, 1.13)

[*] RR, relative risk; CI, confidence interval.

[a] Stratified by age and adjusted for all the other variables in the table.