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Risk of uterine leiomyomata in relation to tobacco, alcohol and caffeine consumption in the Black Women's Health Study

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BACKGROUND: Tobacco, alcohol and caffeine consumption may influence risk of uterine leiomyomata via changes in ovarian function or hormone metabolism. METHODS: We prospectively assessed the relation of these exposures to risk of self-reported uterine leiomyomata in the Black Women's Health Study. From 1997 to 2001, we followed 21 885 premenopausal women with intact uteri and no prior myoma diagnosis. Cox regression models were used to estimate incidence rate ratios (IRRs) and 95% confidence intervals (CIs). RESULTS: During 73 426 person-years of follow-up, 2177 incident cases of uterine leiomyomata confirmed by ultrasound ($n = 1920$) or hysterectomy ($n = 257$) were reported. Cigarette smoking was not associated with risk of uterine leiomyomata. Risk was positively associated with years of alcohol consumption and current consumption of alcohol, particularly beer. Relative to non-drinkers, multivariate IRRs for beer consumption of <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. Heavy coffee and caffeine consumption were not associated with risk overall, but IRRs were increased among women aged <35 years. CONCLUSIONS: In US black women, risk of uterine leiomyomata was positively associated with current consumption of alcohol, particularly beer. Cigarette smoking and caffeine consumption were unrelated to risk overall.

Key words: African–Americans/female/premenopausal/risk factors/uterine neoplasms

Introduction

Uterine leiomyomata (fibroids) are the most common tumours of the female reproductive tract and the leading indication for hysterectomy among US women (Farquhar and Steiner, 2002). Black women are more likely than white women to be diagnosed with uterine leiomyomata (Brett *et al.*, 1997; Marshall *et al.*, 1997; Baird *et al.*, 2003), develop them at earlier ages (Baird *et al.*, 2003), and have more numerous and symptomatic tumours at the time of diagnosis (Kjerulff *et al.*, 1996). The observation that uterine leiomyomatas develop during the reproductive years and regress after menopause suggests that ovarian hormones play a critical role in their aetiology.

Tobacco, alcohol and caffeine consumption are modifiable risk factors that may affect endogenous levels of hormones via changes in ovarian function or alterations in hormone metabolism. Smoking is associated with lower serum and urinary estrogen levels in some (MacMahon *et al.*, 1982; Westhoff *et al.*, 1996), but not all (Longcope and Johnston, 1988; Zumoff *et al.*, 1990; Daniel *et al.*, 1992), studies. Alcohol consumption is associated with higher endogenous levels of estradiol (E_2) and estrone (Katsouyami *et al.*, 1991; Reichman *et al.*, 1993; Hankinson *et al.*, 1995), but other studies show no such associations (Cauley *et al.*, 1989; London *et al.*, 1991; Dorgan *et al.*, 1994; Newcomb *et al.*, 1995). Coffee and caffeine consumption are associated with increased levels of early follicular phase E_2, independent of alcohol or tobacco use (Lucero *et al.*, 2001), and may enhance sex steroid production (Leonard *et al.*, 1987).

Many epidemiological studies have shown an inverse relationship between current cigarette smoking and risk of uterine leiomyomata (Ross *et al.*, 1986; Romieu *et al.*, 1991; Lumbiganon *et al.*, 1996; Parazzini *et al.*, 1996; Faerstein *et al.*, 2001), but no association was found in the Nurses' Health Study II (Marshall *et al.*, 1998), a US prospective cohort study. The latter study found a positive association for

current alcohol consumption (Marshall *et al.*, 1997). A case–control study of Italian women (Chiaffarino *et al.*, 1999) found no association with alcohol, tea or coffee consumption. Since previous study populations comprised mostly white women (Schwartz and Marshall, 2000), little is known about the impact of these factors in black women. With evidence that premenopausal black women have higher ovarian hormone levels than white women (Woods *et al.*, 1996; Haiman *et al.*, 2002), risk factors for uterine leiomyomata may differ by race. The present study prospectively examines the association of tobacco, alcohol and caffeine consumption with risk of uterine leiomyomata in a large cohort of premenopausal US black women. Results on reproductive and hormonal risk factors for uterine leiomyomata in this cohort have been published previously (Wise *et al.*, 2004).

Patients and methods

Study population

The Black Women's Health Study (BWHS) is an ongoing prospective cohort study, established in 1995, when ~59 000 US black women aged 21–69 years were enrolled through questionnaires mailed mainly to subscribers of *Essence* magazine (Rosenberg *et al.*, 1995). The baseline questionnaire elicited information on demographic and behavioural characteristics, reproductive history, healthcare utilization, and medical conditions. The cohort is followed every 2 years by postal questionnaire and >80% of the original cohort completed a questionnaire in each follow-up cycle.

Follow-up for the present analysis began in 1997, the start of the second questionnaire cycle, because data on method of confirmation for uterine leiomyomata were first obtained in 1999. Of the 53 322 women who completed the 1997 questionnaire, we restricted the sample to premenopausal women with intact uteri ($n = 36\ 618$) and excluded women who reported a diagnosis of leiomyomata before 1997 ($n = 10\ 455$), women who did not complete any follow-up questionnaires in 1999 or 2001 ($n = 2193$), 'cases' who provided no information about year of diagnosis ($n = 99$) or confirmation type ($n = 208$), and women with incomplete data on smoking, alcohol or caffeine ($n = 1015$). After these exclusions, 21 885 women remained and were followed for incidence of leiomyomata in the subsequent 4 years.

Assessment of outcome

Because studies limited to histologically confirmed cases of uterine leiomyomata may spuriously identify risk factors associated with large tumour size, symptoms or treatment preference (Schwartz *et al.*, 2000), our outcome definition included confirmation by ultrasound or hysterectomy. This is the same definition as employed by the Nurses' Health Study II, a prospective study with similar methodology to the BWHS (Marshall *et al.*, 1997). Ultrasound has high sensitivity (99%) and specificity (91%) relative to histological evidence (Loutradis *et al.*, 1990; Dueholm *et al.*, 2002).

On the 1999 and 2001 follow-up questionnaires, women were asked if they had been diagnosed with 'fibroids' in the previous 2-year interval and, if 'yes', the calendar year in which they were first diagnosed and whether their diagnosis was confirmed by 'pelvic exam' and/or by 'ultrasound/hysterectomy'. A diagnosis was considered 'hysterectomy-confirmed' if the woman reported hysterectomy on the same questionnaire.

Incident cases were defined as women who self-reported a first diagnosis of 'fibroids' confirmed by ultrasound or hysterectomy. Women with diagnoses confirmed only by pelvic exam ($n = 394$) were treated as non-cases in primary analyses, because their diagnoses may have represented other pathology (Loutradis *et al.*, 1990). Since their diagnosis may have influenced a change in lifestyle factors, their exposure information was not updated beyond the time of diagnosis.

We assessed the accuracy of self-reported uterine leiomyomata in a random sample of 248 ultrasound- or hysterectomy-confirmed cases. These women were mailed supplemental questionnaires regarding their method of confirmation, symptoms and treatment, and were asked for permission to review their medical records. We obtained medical records for 123 of the 128 women who gave us permission and confirmed the self-report in 118 (96%). The proportion of cases reporting on the supplemental questionnaire the presence of symptoms at the time of diagnosis (71%) was similar among those who did ($n = 128$) and did not ($n = 50$) release their medical record (73% versus 60%).

Assesment of exposures and covariates

Data on smoking history were first obtained in 1995 and were updated in 1997 and 1999. Ever-smokers were asked about the age at which they started to smoke regularly, the number of cigarettes they smoked and the cumulative number of years they had smoked. Former smokers were asked how many years ago they quit. Current exposure to environmental tobacco smoke was measured in 1997 and was defined as being 'in the same room with a smoker for at least 1 h a day for 12 consecutive months or more, at home or in the workplace'.

Alcohol intake was derived mainly from the 1995 questionnaire, because this was the only questionnaire on which we asked about type of alcoholic beverage. Current drinkers were asked to report the average frequency of beer [12 oz (360 ml) can or bottle], wine [4 oz (120 ml) glass] and liquor [1 oz (30 ml) shot] consumption during the previous year. We computed the average daily intake of each beverage by multiplying the frequency of consumption by the alcoholic content in the specified portion size; per drink, beer contains 12.8 g of alcohol, wine 11.0 g and liquor 14.0 g (Department of Agriculture, 1982). Total alcohol intake was the sum of values for all three beverages. In 1997 and 1999, participants were asked about frequency of alcohol consumption.

The 1995 questionnaire included a 68-item Block NCI food frequency questionnaire to assess the consumption of specified foods during the previous year, including caffeinated items (coffee, decaffeinated coffee, tea, soft drinks and chocolate candy), with frequencies ranging from 'never or <1 per month' to '6 + per day', and portion sizes of 'small', 'medium' [8 oz (250 ml) for coffee or tea, 12 oz (360 ml) for soft drinks and 1 oz (31 ml) for chocolate candy] or 'large' (Block *et al.*, 1986). This questionnaire was validated in 408 cohort members against three non-consecutive 24-h recalls and a 3-day food diary (Kumanyika *et al.*, 2003). We calculated a summary caffeine score for each subject based on estimates that there are 137 mg per cup of coffee, 47 mg per cup of tea, 46 mg per 12 oz soft drink, 7 mg per serving of chocolate candy and 5 mg per cup of decaffeinated coffee (Willett *et al.*, 1987). These quantities were then multiplied by portion size.

Age at menarche and education were ascertained on the baseline survey. Data on parity, age at each birth, oral contraceptive (OC) use and body mass index (BMI) were obtained on the baseline and follow-up surveys, and were treated as time-dependent variables in the analysis, as was smoking.

Data analysis

Each participant contributed person-time from March 1997 until the diagnosis of uterine leiomyomata, menopause, death, loss to follow-up or end of follow-up (March 2001), whichever came first. Analyses were carried out using SAS statistical software (SAS Institute, 2002). We used multivariate Cox regression to estimate incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for tobacco, alcohol and caffeine consumption (Cox and Oakes, 1984). To control for age, calendar time and any two-way interactions between these two time scales, we stratified our analyses jointly by age in 1-year intervals at the start of follow-up and calendar year of the questionnaire cycle (Hertzmark and Spiegelman, 2001). The Anderson–Gill data structure was used to update time-varying covariates (Therneau, 1997) and exact methods were used to handle tied event times (Kalbfleisch and Prentice, 1980).

A covariate was included in multivariate analyses if the literature supported its role as a risk factor or if adding it to a model containing all other predictors of uterine leiomyomata changed the IRR by 10% or more (Greenland, 1989). Based on these criteria, we adjusted for age at menarche, parity, age at first birth, years since last birth, OC use, education and BMI, and mutually adjusted for smoking, alcohol and caffeine.

Departures from the proportional hazards assumption (i.e. effect modification by age and time) were tested by the likelihood ratio test comparing models with and without cross-product terms for exposures (in their categorical form) with age (<35 versus 35 + years) and time period (1997–1999 versus 1999–2001). In addition, we conducted stratified analyses and computed likelihood ratio tests to evaluate effect modification by education, BMI, parity and OC use, risk factors by which BWHS participants may differ from the general population of black women. Finally, we used Robins' methods of 'inverse probability of censoring weighting' (Robins *et al.*, 2000) to evaluate the impact of differential loss to follow-up. This method constructs a regression model that weights women who were not lost to follow-up more heavily to account for those who were, given the same exposure and covariate history.

Results

At the start of follow-up, the prevalence of current and former smoking in the cohort was 14% and 13%, respectively (Table I). Relative to never smokers, current smokers consumed more alcohol and caffeine, and were older, less educated and less likely to report a recent Pap smear. Current alcohol drinkers (25%) were older than never drinkers, and were more likely to smoke, consume caffeine and have greater energy intake. Median caffeine consumption was 64 mg/day, equivalent to half a cup of caffeinated coffee (data not shown). Heavy consumers of caffeine [500 + mg/day (5%)] were older than light consumers, and were more likely to smoke, consume alcohol, be less educated, and have higher BMI and energy intake.

During 73 426 person-years of follow-up, 2177 new cases of uterine leiomyomata confirmed by ultrasound ($n = 1920$) or hysterectomy ($n = 257$) were reported. There was little evidence of an association between smoking and uterine leiomyomata (Table II). The IRR was slightly reduced for current smokers, but there was no trend across pack-years of smoking, number of cigarettes smoked per day, years of smoking or age first smoked. None of the IRRs varied appreciably by age or by exposure to environmental tobacco smoke (data not shown). To assess differences according to method of confirmation, we repeated our analyses among hysterectomy-confirmed cases only. In this case group,

Table I. Characteristics of 21 885 women according to tobacco, alcohol and caffeine consumption at the start of follow-up: the Black Women's Health Study, 1997[a]

Characteristic	Cigarette smoking			Alcohol consumption			Caffeine consumption (mg/day)		
	Current	Former	Never	Current	Former	Never	<50	150–299	500 +
Number studied	3055	2945	15 885	5367	2684	13 834	9199	3150	1106
Mean of characteristic									
Pack-years of cigarette smoking	9.1	5.3	–	3.9	3.9	1.3	1.5	2.9	5.3
Current alcohol consumption (drinks/week) (1995)									
Beer	1.5	0.9	0.2	2.0	–	–	0.4	0.6	0.8
Wine	0.7	0.8	0.3	1.7	–	–	0.3	0.5	0.7
Liquor	1.2	0.6	0.2	1.6	–	–	0.3	0.5	0.6
Current alcohol from beer, wine, liquor (g/week) (1995)	43.9	28.5	9.6	67.1	–	–	11.7	20.8	27.2
Caffeine consumption (mg/day) (1995)	212	176	112	179	145	115	22	204	752
Caffeinated coffee (cups/day) (1995)	1.0	0.8	0.4	0.8	0.6	0.4	0.1	0.6	4.2
Energy intake (kilocalories/day) (1995)	1638	1636	1512	1637	1642	1495	1334	1838	1918
Body mass index (kg/m^2)	28.2	29.1	27.8	28.0	29.3	27.7	27.4	28.7	29.4
Education (years) (1995)	14.2	14.7	15.1	14.7	14.6	15.1	15.0	14.8	14.7
Age at menarche (years)	12.4	12.3	12.3	12.4	12.3	12.3	12.4	12.3	12.2
Percentage with characteristic									
Age (years)									
<30	15.3	10.9	33.9	22.7	22.2	31.5	34.3	22.1	12.9
30–39	48.0	43.9	45.0	46.6	43.4	45.2	43.8	46.7	42.8
40 +	36.7	45.2	21.1	30.7	34.4	23.3	21.8	31.2	44.3
Current exposure to environmental tobacco smoke	67.1	18.7	13.7	31.7	27.8	16.5	16.1	26.7	35.8
Parous	62.6	63.2	54.4	55.6	64.5	55.2	54.9	57.9	58.7
Current oral contraceptive use	15.4	21.8	24.7	24.0	19.6	23.6	24.3	21.7	19.4
Pap smear within past 2 years	87.4	91.0	91.0	91.0	89.2	90.5	91.3	89.2	86.7

[a]Data from 1997 (start of follow-up) unless otherwise noted. Means and percentages (with exception of age) are standardized to the age distribution of women free of uterine leiomyomata at the start of follow-up. Percentages may not add to 100% due to rounding errors.

Table II. Risk of ultrasound- or hysterectomy-confirmed uterine leiomyomata in relation to cigarette smoking: the Black Women's Health Study, 1997–2001

	Person-years	Cases	Age-adjusted IRR[a]	Multivariate IRR (95% CI)[b]
Smoking status				
Never smoker	53 799	1549	1.00[c]	1.00[c]
Former smoker	9927	329	0.97	0.95 (0.84–1.08)
Current smoker	9700	299	0.94	0.88 (0.77–1.01)
Pack-years of smoking[d]				
Never smoker	53 799	1549	1.00[c]	1.00[c]
<2.0	4884	146	0.98	0.94 (0.79–1.12)
2.0–5.9	4461	144	1.00	0.97 (0.81–1.16)
6.0–12.4	4679	148	0.91	0.88 (0.73–1.04)
12.5+	4716	169	0.99	0.93 (0.79–1.11)
Cigarettes per day				
Non-smoker	63 726	1878	1.00[c]	1.00[c]
<10	2722	94	1.11	1.06 (0.86–1.30)
10–19	4922	139	0.86	0.82 (0.68–0.98)
20+	2045	66	0.94	0.87 (0.78–1.12)
Years of smoking[d]				
Never smoker	53 799	1549	1.00[c]	1.00[c]
<10	7947	235	0.98	0.94 (0.82–1.09)
10–19	6661	222	0.97	0.93 (0.80–1.08)
20+	4267	152	0.95	0.89 (0.74–1.06)
Years since quitting[e]				
Never smoker	53 799	1549	1.00[c]	1.00[c]
<5	13 091	395	0.92	0.87 (0.78–0.99)
5–9	2710	98	1.10	1.08 (0.88–1.34)
10+	3662	129	0.98	0.95 (0.79–1.15)
Age at first smoke[f]				
Never smoker	53 799	1549	1.00[c]	1.00[c]
<16	4178	138	1.00	0.94 (0.78–1.13)
16–17	4282	123	0.86	0.82 (0.68–1.00)
18–20	6216	197	0.93	0.90 (0.77–1.06)
21+	4671	162	1.06	1.02 (0.86–1.20)

[a]Adjusts for age at start of questionnaire cycle (1-year intervals) and time period (1997–1999 versus 1999–2001).
[b]Adjusts for age, time period, age at menarche (years), parity (ever versus never), age at first birth (years), years since last birth (four-knot restricted cubic spline), use of oral contraceptives (current, past, never), education (≤12, 13–15, 16, 17+), smoking (never, former, current), caffeine intake (ordinal) and BMI (kg/m^2, four-knot restricted cubic spline).
[c]Reference group.
[d]Omits 21 cases and 887 person-years among ever smokers with missing data.
[e]Omits six cases and 164 person-years among ever smokers with missing data.
[f]Omits eight cases and 280 person-years among ever smokers with missing data.

the IRR was 0.65 (95% CI 0.46–0.94) for former smoking and 0.92 (95% CI 0.66–1.29) for current smoking. Results for all other smoking variables were similar to those presented in Table II (data not shown).

There was a small positive association between current alcohol consumption and uterine leiomyomata (Table III). Among ever drinkers, risk was positively associated with years of alcohol consumption. In models that controlled for other sources of alcohol, the IRR increased monotonically with increasing current consumption of beer, but not wine or liquor. The elevated risk among beer drinkers remained when the alcohol variables were assessed in their continuous form: for each additional beer consumed per week, holding other sources of alcohol constant, the multivariate IRR was 1.02 (95% CI 1.01–1.04). The association for beer differed significantly from liquor ($P = 0.02$), but not wine ($P = 0.10$) (data not shown). Additional control for variables that distinguished beer drinkers from other drinkers—e.g. occupation and marital status—did not alter these findings. Results were not notably different when we stratified by age, when we repeated analyses among hysterectomy-confirmed cases only, when we updated status or frequency of consumption in 1997 and 1999, or when we used a cumulative average measure for alcohol consumption (data not shown).

No association was detected for coffee or caffeine consumption overall (Table IV). Since the caffeine data indicated a departure from the proportional hazards assumption, we presented these data within strata of age. The IRRs were significantly elevated in the highest category of coffee and caffeine consumption among women <35 years of age, but there was no evidence of a monotonic dose–response relation for either of these measures. When analyses were confined to hysterectomy-confirmed cases only, findings remained similar overall; small numbers of cases precluded us from assessing differences according to age.

Effect modification was not observed by BMI, education, parity or OC use on any of the associations of interest, nor was there any evidence that smoking modified the IRRs for alcohol or caffeine consumption. Because current smokers, alcohol drinkers and heavy consumers of caffeine were less likely to report a recent Pap smear (Table I), a marker of pelvic exam, we restricted analyses to the 90% of women who reported this practice in the prior 2 years. None of the results changed materially. Results were also unchanged when

Table III. Risk of ultrasound- or hysterectomy-confirmed uterine leiomyomata in relation to alcohol consumption in 1995: the Black Women's Health Study, 1997–2001

	Person- years	Cases	Age-adjusted IRR[a]	Multivariate IRR (95% CI)[b]
Alcohol consumption status				
Never drinker	46 835	1319	1.00[c]	1.00[c]
Former drinker	8804	263	0.99	1.05 (0.91–1.20)
Current drinker	17 786	595	1.12	1.13 (1.01–1.25)
Current alcohol consumption, drinks per week				
None	55 639	1582	1.00[c]	1.00[c]
1–6	14 207	462	1.09	1.09 (0.98–1.21)
7–13	2322	86	1.21	1.21 (0.97–1.51)
14+	1257	47	1.22	1.23 (0.92–1.66)
Current alcohol consumption, grams per day				
None	55 639	1582	1.00[c]	1.00[c]
<5	7200	223	1.03	1.03 (0.90–1.19)
5–14	7760	265	1.16	1.15 (1.00–1.31)
15–24	1590	60	1.22	1.22 (0.94–1.59)
25+	1236	47	1.24	1.25 (0.93–1.68)
Years of alcohol consumption[d]				
Never drinker	46 835	1319	1.00[c]	1.00[c]
<10 years	7034	189	1.00	1.03 (0.92–1.17)
10–19 years	7402	260	1.10	1.12 (0.98–1.27)
20+ years	3237	144	1.27	1.32 (1.11–1.58)
Type of alcohol[e]				
Beer, drinks per week				
None	55 639	1582	1.00[c]	1.00[c,e]
<1	11 042	359	1.08	1.11 (0.98–1.27)
1–6	5559	183	1.12	1.18 (1.00–1.40)
7+	1185	53	1.44	1.57 (1.17–2.11)
Wine, drinks per week				
None	55 639	1582	1.00[c]	1.00[c,e]
<1	9520	329	1.15	1.16 (1.01–1.33)
1–6	7657	244	1.07	1.05 (0.91–1.21)
7+	609	22	1.19	1.15 (0.74–1.78)
Liquor, drinks per week				
None	55 639	1582	1.00[c]	1.00[c,e]
<1	11 587	378	1.08	1.08 (0.95–1.23)
1–6	5441	194	1.21	1.18 (1.00–1.39)
7+	758	23	1.00	0.95 (0.61–1.48)

[a]Adjusts for age at start of questionnaire cycle (1-year intervals) and time period (1997–1999 versus 1999–2001).
[b]Adjusts for age, time period, age at menarche (years), parity (ever versus never), age at first birth (years), years since last birth (four knot restricted cubic spline), use of oral contraceptives (current, past, never), education (≤12, 13–15, 16, 17+), smoking (never, former, current), caffeine intake (ordinal) and BMI (kg/m^2, four knot restricted cubic spline).
[c]Reference group.
[d]Omits two cases and 113 person-years among current drinkers with missing data.
[e]Multivariate models further adjust for other sources of alcohol.

cases confirmed by pelvic examination only ($n = 394$) were included as part of the outcome definition, censored at the time of diagnosis or excluded from the analysis.

Discussion

The BWHS is the first prospective cohort study to examine risk factors for uterine leiomyomata in a large population of US black women. Although uterine leiomyomata represent a major public health problem among black women of reproductive age, most epidemiological studies have been conducted in white women. In the BWHS, risk was positively associated with current consumption of alcohol, particularly beer. Cigarette smoking and caffeine consumption were unrelated to risk overall.

While some studies show an association between smoking and lower endogenous estrogen levels (MacMahon *et al.*, 1982; Westhoff *et al.*, 1996), others show no such association (Longcope and Johnston, 1988; Zumoff *et al.*, 1990; Daniel *et al.*, 1992). Tobacco components may inhibit aromatase, an enzyme that synthesizes estrogen in granulosa cells (Barbieri *et al.*, 1986), or shift E_2 metabolism toward 2-hydroxylation pathways, thereby decreasing estrogen bioavailability (Michnovicz *et al.*, 1986; Bradlow, 1994).

In the epidemiological studies that show an inverse association between current smoking and uterine leiomyomata, decreases in risk range from 20% to 50% (Ross *et al.*, 1986; Romieu *et al.*, 1991; Lumbiganon *et al.*, 1996; Parazzini *et al.*, 1996; Faerstein *et al.*, 2001). The null association for cigarette smoking in the BWHS is consistent with the Nurses' Health Study II (Marshall *et al.*, 1998). The counteracting effects of tobacco smoke components could explain the lack of association. While smoking may have an anti-estrogen effect on the endogenous hormonal milieu (MacMahon *et al.*, 1982; Westhoff *et al.*, 1996), components of cigarette smoke (e.g. dioxin) may also exert estrogen-related effects on the uterus that could promote cell proliferation (Ohtake *et al.*, 2003).

Table IV. Risk of ultrasound- or hysterectomy-confirmed uterine leiomyomata in relation to caffeine consumption in 1995, according to age at start of questionnaire cycle: the Black Women's Health Study, 1997–2001

	Age <35 years				Age 35+ years				All women	*P*-value, test for age interaction
	Cases	Person-years	Age-adjusted IRR[a]	Multivariate IRR (95% CI)[b]	Cases	Person-years	Age-adjusted IRR[a]	Multivariate IRR (95% CI)[b]	Multivariate IRR (95% CI)[b]	
Coffee (caffeinated), cups/day										0.04
Almost never	598	17 592	1.00[c]	1.00[c]	751	21 106	1.00[c]	1.00[c]	1.00[c]	
<1	134	5197	1.13	1.11 (0.92–1.34)	240	6262	1.07	1.04 (0.90–1.20)	1.06 (0.95–1.20)	
1	61	2200	1.15	1.11 (0.85–1.45)	165	4230	1.08	1.04 (0.88–1.23)	1.07 (0.92–1.23)	
2	26	1104	0.98	0.89 (0.60–1.32)	108	2745	1.10	1.06 (0.86–1.30)	1.03 (0.86–1.24)	
3 or more	31	768	1.67	1.53 (1.06–2.22)	63	2223	0.80	0.77 (0.59–1.00)	0.93 (0.75–1.15)	
Coffee (decaffeinated), cups/day										0.69
Almost never	774	34 032	1.00[c]	1.00[c]	1108	30 663	1.00[c]	1.00[c]		
<1	56	2073	1.12	1.12 (0.86–1.48)	128	3613	0.97	0.96 (0.80–1.15)	1.01 (0.87–1.18)	
1 or more	20	756	1.05	1.07 (0.69–1.68)	91	2290	1.12	1.11 (0.89–1.38)	1.11 (0.92–1.35)	
Tea, cups/day										0.75
Almost never	372	17 571	1.00[c]	1.00[c]	631	17 698	1.00[c]	1.00[c]	1.00[c]	
<1	313	13 112	1.12	1.10 (0.94–1.27)	438	12 026	1.02	1.01 (0.89–1.14)	1.05 (0.95–1.15)	
1	88	3354	1.19	1.16 (0.93–1.47)	133	3446	1.10	1.09 (0.90–1.31)	1.12 (0.97–1.30)	
2	34	1352	1.16	1.09 (0.76–1.54)	54	1590	0.95	0.94 (0.71–1.24)	0.99 (0.80–1.23)	
3 or more	43	1471	1.36	1.27 (0.93–1.75)	71	1806	1.11	1.12 (0.88–1.43)	1.18 (0.97–1.43)	
Soft drinks, cans/day										0.66
Almost never	350	15 651	1.00[c]	1.00[c]	657	17 812	1.00[c]	1.00[c]	1.00[c]	
<1	333	13 947	1.09	1.16 (1.00–1.35)	431	12 190	0.96	0.97 (0.86–1.10)	1.04 (0.95–1.14)	
1	84	3380	1.14	1.25 (0.98–1.59)	122	3276	1.00	1.04 (0.86–1.27)	1.11 (0.96–1.30)	
2	45	2107	0.96	1.07 (0.78–1.46)	62	1666	1.03	1.04 (0.80–1.35)	1.04 (0.85–1.27)	
3 or more	38	1776	1.00	1.14 (0.81–1.60)	55	1620	0.92	0.93 (0.70–1.22)	0.99 (0.80–1.23)	
Caffeine, mg/day										0.01
<50	359	17 799	1.00[c]	1.00[c]	470	13 422	1.00[c]	1.00[c]	1.00[c]	
50–149	300	11 382	1.27	1.27 (1.09–1.49)	408	10 974	1.06	1.05 (0.92–1.20)	1.14 (1.03–1.26)	
150–299	107	4528	1.12	1.13 (0.91–1.41)	235	5964	1.12	1.11 (0.94–1.30)	1.12 (0.99–1.28)	
300–499	42	2085	0.94	0.92 (0.67–1.28)	135	3689	1.03	1.00 (0.82–1.22)	1.00 (0.85–1.18)	
500 +	42	1068	1.79	1.70 (1.23–2.36)	79	2516	0.90	0.87 (0.68–1.11)	1.07 (0.88–1.30)	

'Almost never' = <0.14 servings per day.

[a]Adjusts for age at start of questionnaire cycle (1-year intervals) and time period (1997–1999 versus 1999–2001).

[b]Adjusts for age, time period, age at menarche (years), parity (ever versus never), age at first birth (years), years since last birth (four knot restricted cubic spline), use of oral contraceptives (current, past, never), education (≤12, 13–15, 16, 17 +), smoking (never, former, current), current alcohol consumption (<1, 1–6, 7+ per week) and BMI (kg/m^2, four knot restricted cubic spline). Estimates for decaffeinated coffee, tea and soft drinks are additionally adjusted for caffeinated coffee (cups per day).

[c]Reference group.

High levels of estrogens, prolactin and insulin-like growth factor (IGF) may promote growth of uterine leiomyomata (Mora *et al.*, 1995; Andersen, 1996). Several studies have shown associations between alcohol intake and high levels of plasma or urinary E_2 (Katsouyami *et al.*, 1991; Reichman *et al.*, 1993; Hankinson *et al.*, 1995), estrone, androstenedione, IGF-I and prolactin (Soyka *et al.*, 1991; Singletary and Gapstur, 2001), as well as lower levels of FSH (Singletary and Gapstur, 2001), while others have shown no such associations (Cauley *et al.*, 1989; London *et al.*, 1991; Dorgan *et al.*, 1994; Newcomb *et al.*, 1995).

In the present study, risk of uterine leiomyomata was positively associated with years of alcohol consumption and current consumption of alcohol, particularly beer. The BWHS is the first study to examine risk in relation to type of alcoholic beverage. The Nurses' Health Study II also found a positive association for current alcohol consumption, but did not report effect estimates (Marshall *et al.*, 1997), while an Italian case–control study found no association (Chiaffarino *et al.*, 1999). In the latter study, subjects were interviewed after the diagnosis of uterine leiomyomata, and no data on portion size were elicited.

In the BWHS, there appeared to be a stronger association for beer consumption than for wine or liquor consumption. This finding requires confirmation by future studies. It is possible that beer exerts a different effect than other types of alcohol on hormone-dependent neoplasms. In the Italian case–control study, wine accounted for >90% of the alcohol consumed (Chiaffarino *et al.*, 1999), which could explain the lack of association between alcohol and uterine leiomyomata in that study. A meta-analysis of cohort studies showed that beer drinkers have the largest relative risk of breast cancer, although the beverage-specific risks were not significantly different (Smith-Warner *et al.*, 1998). Moreover, a recent study showed that the phytoestrogen in beer, 8-prenylnarigenin, stimulates the growth of MCF-7/6 breast cancer cell lines *in vitro*, and may mimic the effects of 17β-E_2 (Rong *et al.*, 2001).

Few studies have examined the effect of caffeine on ovarian hormones. In a cross-sectional study, coffee and total caffeine consumption were associated with increased levels of early follicular phase E_2, independent of alcohol or tobacco use (Lucero *et al.*, 2001). By inhibiting phosphodiesterase, caffeine may decrease clearance of cAMP and enhance steroid production (Leonard *et al.*, 1987). Moreover, in high doses, caffeine can induce stress-like effects in the pituitary–adrenal axis (Spiller, 1998), which could raise risk of uterine leiomyomata via increased secretion of prolactin (Reichlin, 1988; Mora *et al.*, 1995; Andersen, 1996).

The one previous study to examine caffeine consumption as a risk factor for uterine leiomyomata was a case–control study, and no association was found (Chiaffarino *et al.*, 1999). In the BWHS, no overall association was observed for coffee or caffeine consumption, but an increased risk was found for heavy consumption in younger women. This latter finding should be interpreted with caution, because there is no evidence that caffeine metabolism differs by age in humans (Arnaud, 1993). It is also possible that unmeasured factors related both to heavy consumption of caffeine and risk of leiomyomata confounded the results, or that reverse causality played a role (e.g. subclinical cases could have experienced anemia and fatigue, leading to heavy caffeine consumption). There was no evidence that differential screening by age and caffeine consumption accounted for the observed effect modification. Pap smear screening levels were similar for both younger (88%) and older (85%) heavy caffeine consumers, and within age groups, the heavy consumers were consistently less likely than the light consumers to report a recent Pap smear.

BWHS participants were not systematically screened for uterine leiomyomata. Owing to the high cumulative incidence of these tumours and their tendency to be asymptomatic (Baird *et al.*, 2003), true cases may have been misclassified as non-cases. If misclassification was unrelated to tobacco, alcohol or caffeine consumption, the IRRs would have been biased towards the null, unless there was perfect specificity, in which case the IRR would be unbiased (Greenland, 1998). Since we were able to confirm 96% of self-reported cases in the BWHS validation study, specificity of outcome classification was high. In contrast, if exposure status influenced the likelihood of detection, over- or underestimation of the IRR could have occurred. Since restriction of the analytic sample to women with a recent Pap smear yielded similar results, detection bias is unlikely to account for our findings. Moreover, 71% of validation study cases had symptoms prior to their initial diagnosis, suggesting that the proportion of incidentally detected cases was low.

One strength of the present study is that exposure data were collected before the diagnosis and confirmation of uterine leiomyomata, thereby avoiding recall bias. In addition, low loss to follow-up in the BWHS reduced the potential for selection bias. While mean length of follow-up was similar for current and never smokers, current and never alcohol drinkers, and heavy and light caffeine consumers, significant differences existed for educational attainment (40 versus 43 months of follow-up for <13 versus 17 + years of education; $P < 0.001$). As education was inversely associated with smoking and alcohol consumption, and positively associated with risk of uterine leiomyomata, differential loss to follow-up may have produced a downward bias of the IRRs. However, use of Robins' methods (Robins *et al.*, 2000) did not change the results appreciably.

Prevalence estimates for smoking and drinking in the BWHS were slightly lower than those documented in nationwide representative studies of black women (US Department of Health and Human Services, 2001; Centers for Disease Control, 2002). Because we did not find effect modification by any factor, with the exception of age, BWHS findings should be generalizable to other black women.

At present, few modifiable risk factors for uterine leiomyomata have been identified. Observations from the present study regarding smoking and alcohol consumption are consistent with another large US prospective study (Marshall *et al.*, 1998). Future studies are needed to evaluate whether the BWHS findings for beer, coffee and caffeine consumption can be replicated. As the associations are modest,

and the prevalence of these risk factors low, they are unlikely to explain a large fraction of the disease burden among US black women.

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