Human Reproduction Vol.18, No.1 pp. 199–206, 2002 DOI: 10.1093/humrep/deg005

Premature menopause in a multi-ethnic population study of the menopause transition*

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BACKGROUND: Premature menopause, also termed premature ovarian failure (POF), is characterized by cessation of menstruation before the age of 40 years. Little information is available on the general prevalence of POF or on the prevalence by ethnic group. There is also a lack of information on the association of POF with health indicators. METHODS: A cross-sectional survey of women aged 40–55 years was conducted at seven sites in the USA to determine eligibility for a community-based, multi-ethnic longitudinal study of the peri-menopause (The Study of Women Across the Nation, SWAN). Interview data were used to (i) determine the prevalence of self-reported POF overall and by ethnic group, and (ii) assess the association of POF with selected self-reported variables related to health. Cases of POF included only women with no discernible cause for POF. RESULTS: POF was reported by 1.1% (126/11 652) of women. By ethnicity, 1.0% (95% CI, 0.7–1.4) of Caucasian, 1.4% (95% CI, 1.0–2.1) of African American, 1.4% (95% CI, 0.8–2.5) of Hispanic, 0.5% (95% CI, 0.1–1.9) of Chinese and 0.1% (95% CI, 0.02–1.1) of Japanese women experienced POF. The differences in frequency across ethnic groups were statistically significant ($P = 0.01$). Only Caucasian, African American and Hispanic women were included in further analyses since too few Asian women had POF. In a multivariate model, POF was independently associated with osteoporosis, female hormone use (excluding oral contraceptives), higher body mass index (BMI) and current smoking after adjustment for education level, ability to pay for basics, site and age at interview. In Caucasian women, use of female hormones, osteoporosis, severe disability and smoking were significantly associated with POF. In contrast, POF in African American women was associated with higher BMI and female hormone use, but not osteoporosis. CONCLUSIONS: The prevalence of POF appears to vary by ethnicity. Health factors associated with POF also vary by ethnicity but because of the cross-sectional study design, it is not possible to determine cause and effect relationships. Health risks of POF would benefit from further study.

Key words: ethnic/health risk/population/premature menopause/premature ovarian failure

Introduction

Premature menopause, also termed premature ovarian failure (POF), is a disorder characterized by cessation of menstruation before the age of 40 years. POF has been studied primarily in selected clinic populations, and rarely in community or population-based studies of women. Based on elevated FSH before the age of 40 years, Coulam *et al*. estimated that 0.9% of women will experience POF (Coulam *et al*., 1986). Likewise, in a population-based study of early ovarian failure, the estimated prevalence of POF was 1.2% (Cramer and Xu, 1996). Thus, only a few prior studies estimated the prevalence of POF. Furthermore, little information exists on the prevalence of POF in different ethnic groups.

The aetiology of POF other than that due to known causes such as surgical intervention (hysterectomy or oophorectomy) or chemical or radiation therapy is not well defined (Hoek *et al*., 1997; Anasti, 1998; Santoro, 2001). Several hypotheses have been proposed to explain the occurrence of POF of unknown cause. Based on evidence of anti-ovarian antibodies and defective antigen processing by immune cells, 50–70% of POF was associated with an autoimmune disease of the ovary (Luborsky *et al*., 1990, 1999; Fenichel *et al*., 1997; Hoek *et al*., 1997; Yan *et al*., 2000). An autoimmune aetiology is consistent with the reported association of POF with other autoimmune diseases (Hoek *et al*., 1997). Genetic defects such as chromosome deletions or translocations, a breakpoint in the human

*The findings of this report were presented in part at the Fourth International Symposium, Women's Health and Menopause, Washington, DC, May 2001.

DIA gene, association with fragile X syndrome (Bondy *et al*., 1998; Christin-Maitre *et al*., 1998; Davison *et al*., 2000) or galactosaemia (Cramer, 1990; Cooper *et al*., 1994) have also been detected in some women with POF. These observations suggest that POF may be the consequence of processes that differ from those leading to natural menopause around the expected age of 50 years.

In addition, POF is associated with a more prolonged low estrogen state than would be observed with natural menopause at an average age of 51 years (McKinlay *et al*., 1992; McKinlay, 1996). Consequently, POF, coupled with an increasing lifespan, is potentially associated with both more severe and different health risks, than natural menopause. Early age at menopause has been reported to be associated with increased risk of mortality (van der Schouw *et al*., 1996; Cooper and Sandler, 1998), cancer (Cramer, 1990; Cooper and Sandler, 1998), cardiovascular disease (Senoz *et al*., 1996; van der Schouw *et al*., 1996; Joakimsen *et al*., 2000; Gold *et al*., 2001), and osteoporosis (Kritz-Silverstein and Barrett-Connor, 1993; Gokmen *et al*., 1995; Ohta *et al*., 1996; Cooper and Sandler, 1997; Harlow and Signorello, 2000). Relatively few of these studies specifically assessed women with POF. For example, although cardiovascular disease risk in women increases around menopause (van der Schouw *et al*., 1996), it was shown that the risk did not differ between women with POF and those with menopause around age 51 years (Senoz *et al*., 1996). In contrast, bone density was lower in women with POF compared with menopausal women (Gokmen *et al*., 1995; Hartmann *et al*., 1997) or regularly cycling women of similar age (Anasti *et al*., 1998). Additional information on potential health risks specifically associated with POF is needed.

In 1995–1997, a cross-sectional survey was conducted to assess eligibility for enrolment into a multi-ethnic longitudinal cohort study of the perimenopause, and to collect health, reproductive, demographic and lifestyle data. The information from this survey provided a unique opportunity to (i) describe the frequency of POF in the overall population, and in specific ethnic groups, and (ii) assess the association of selected medical/biological and lifestyle factors with POF.

Materials and methods

Data were collected in a cross-sectional survey and used to determine eligibility for participation in the longitudinal Study of Women's Health Across the Nation (SWAN), a prospective, multi-ethnic, multi-disciplinary study of the natural history of the menopausal transition. The study included seven locations in the USA: Boston (MA), Chicago (IL), Detroit area (MI), Los Angeles (CA), Newark (NJ), Pittsburgh (PA) and Oakland (CA). Eligibility criteria for the cross-sectional survey were: age 40–55 years, self-designation as Caucasian or in the targeted racial/ethnic group for the site, residence in the geographical area defined by one of the seven study sites, use of English or one of the other selected languages (Spanish, Japanese, Cantonese), and ability to give verbal consent to participate.

A common interview protocol was employed across the seven clinical sites, supported by a written manual of operations, common training, and standardization of research staff. Menopausal status was based on self-report of menstrual characteristics. Menopause was defined as no menses for 12 months. Age and ethnicity were self-reported. Primary race/ethnicity was self-defined as Black or African American, non-Hispanic Caucasian, Chinese, Japanese, or Hispanic (Central American, Cuban or Cuban American, Dominican, Mexican or Mexican American, Puerto Rican, South American, Spanish or other Hispanic). Respondents could also specify 'other', 'mixed', or no primary ethnic affiliation. Of the women that participated in the cross-sectional survey (n = 16 065), 15 605 were a member of one of the primary ethnic groups. The cross-sectional group included 7771 Caucasian women at seven sites, 4393 African American women at four sites, and 1942 Hispanic, 654 Chinese and 845 Japanese women at one site each.

In order to assess premature menopause, women whose menstrual cycles had stopped for known reasons were excluded from analysis. Women who had a hysterectomy (n = 3030), ovariectomy (n = 83), cancer (n = 349), or who were currently pregnant (n = 31) or who stopped menstruating for medical reasons (n = 170), pregnancy or breast-feeding (n = 29), or severe weight loss or other reason (n = 78) were excluded from analysis. In addition, those with missing values for the exclusion criteria (n = 127) or missing information on the year of cessation of menstrual cycles were excluded (n = 56). Of the women screened, 11 652 were included in further analyses. The study group included 9658 women who were still menstruating and 1994 women who had stopped menstruating.

The use of age 40 years to define POF is empirical. An alternative definition of POF is based on a cut-off age that is 2 SD (2×2.5 years) from the expected age of menopause at 50–51 years, or age 45 years (Cramer and Xu, 1996; World Health Organization, 1996; Hoek *et al*., 1997). However, cessation of menstruation before the age of 40 has been customarily used to define premature menopause in research and clinical practice, and was used in this analysis (Hoek *et al*., 1997). Furthermore, women aged ⩾40 years were surveyed and thus all women whose menstrual cycles ceased before the age of 40 years could be identified. Women with POF were defined using the self-reported year that menses stopped and converting the year to the midpoint date (July 1). The estimated date that menses stopped was converted to the age that menses stopped by subtracting the date of birth. Current age was calculated from the difference between the interview date and the birth date. This variable was used to select women who stopped menstruating before the age of 40 years.

Study variables

Variables reported in the literature as significantly related to health, physiology, lifestyle, socioeconomic status, age at menopause or POF were selected. Self-reported history of arthritis, diabetes, heart attack/angina, osteoporosis, ever use of oral contraceptives, use of hormones in the past 3 months, ever use of hormones, ever use of female hormones (excluding oral contraceptives), and ever had a live birth had a 'yes' or 'no' response. Self-reported health had categories of excellent, very good, good, fair and poor. Marital status was categorized as married or living as married, or single (never married/separated/widowed/divorced). Education was categorized as high school or less, high school degree, some college, college degree, or graduate studies. Income category was estimated from a general question on how hard it was to pay for basics (very hard, somewhat hard, not hard). Cigarette smoking was categorized as never, former or current smoker. 'Disability' was calculated from a 10 part question on daily activity (strenuous sports, moderate sports or activity, ability to climb stairs, distance walked comfortably and bathing) and was categorized as limited, limited a little, not limited. Body mass index (BMI) was calculated from self-reported height (cm) and weight (kg) as weight (kg)/height $(m)^2$.

Table I. Menopause status by ethnicity

	Ethnic group					
	Caucasian	Black	Hispanic	Chinese	Japanese	Total
Premature menopause (<40 years)						
Count	61	40	21	3	1	126
% in ethnic group	1.0	1.4	1.4	0.5	0.14	1.1
95% CI	0.7–1.4	1.0–2.1	0.8–2.5	0.1–1.9	0.02–1.1	0.9–1.3
Early menopause (age 40–45 years)						
Count	177	104	60	13	6	360
% in ethnic group	2.9	3.7	4.1	2.2	0.8	3.1
95% CI	2.4–3.5	2.9–4.7	3.0–5.6	1.1–4.3	0.3–2.2	2.7–3.5
Menopause (>45 years)						
Count	791	352	235	54	76	1508
% in ethnic group	13.0	12.5	16.1	9.1	10.5	12.9
95% CI	12.0–14.2	11.0–14.1	13.9–18.7	6.6–12.5	7.9–13.6	12.2–13.7
Premenopausal						
Count	5034	2318	1140	522	644	9658
% in ethnic group	83.0	82.4	78.3	88.2	88.6	82.9
95% CI	81.8–84.2	80.5–84.1	75.5–80.9	84.5–91.1	85.3–91.2	82.0–83.7
Total count	6063	2814	1456	592	727	11 652

The prevalence of women overall and by ethnic group was determined for women with premature ovarian failure (POF). The distribution of women with early menopause between the ages of 40 and 45 years—menopause over the age of 45 years—and pre-menopausal women are shown for comparison. Since the information was obtained from women aged 40–55 years—the prevalence reflects the age and menstrual status at interview. The 95% confidence interval (CI) reflect a Bonferroni adjustment for four proportions within each ethnic group. The prevalence of POF among ethnic groups differed significantly ($P = 0.01$) when compared with women without POF.

Analysis

Based on the concept that the mechanism of the dependent variable, POF, is different than menopause around age 50 years, POF was compared with a 'non-POF' group that included women with and without menses.

The prevalence of POF was calculated and the statistical significance of differences determined by Pearson's χ^2-analysis or Fisher's exact test when expected values were <5. The age at menopause for each ethnic group was displayed using the Kaplan–Meier procedure for estimating survival and hazard rates. Analysis of variance was used to evaluate group means for continuous variables. The selected variables of interest were treated as independent variables to assess associations with POF. Important variables were identified in unadjusted univariate analysis; those significant at the $P < 0.1$ level by χ^2-analysis were included in multivariate analyses. Logistic regression with multiple variables was used to consider the independent relationships of important covariates with POF after adjusting for education and income category (socioeconomic status), site and age at survey. Site was included in all adjusted models since it was a characteristic of the sampling design of the study.

Results

Prevalence

The overall prevalence of POF was 1.1% (Table I). By ethnicity, 1.0% of Caucasian, 1.4% of African American, 1.4% of Hispanic, 0.5% of Chinese and 0.1% of Japanese women experienced POF (Table I). The relative difference in frequency of POF across ethnic groups was statistically significant ($P = 0.01$). POF was significantly more prevalent in Caucasian ($P = 0.02$), African American ($P = 0.004$) and Hispanic ($P = 0.004$) women than in Japanese women (Figure 1). The prevalence of POF was not significantly different between Chinese and Japanese women ($P = 0.2$).

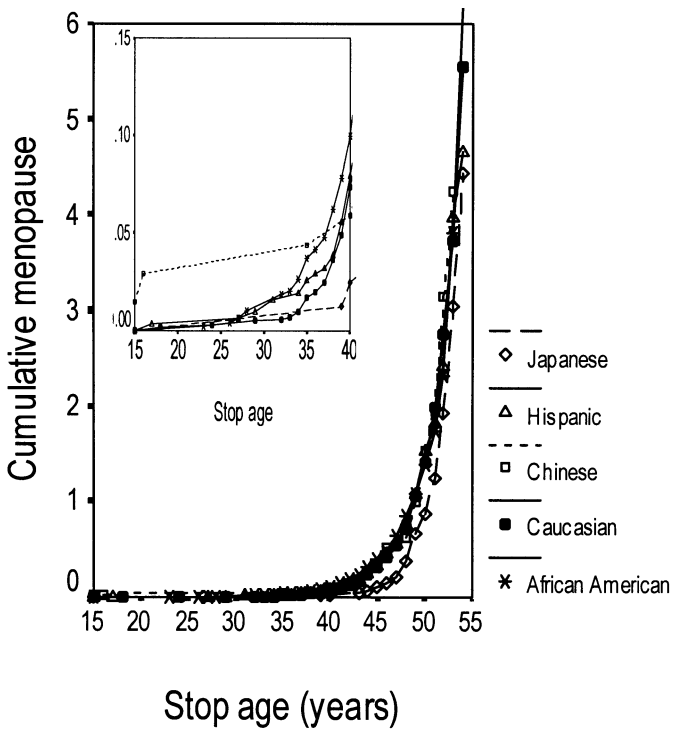

Figure 1. The cumulative rate of menopause by age for each ethnic group. The upper age limit displayed in the graph was determined by the experimental design since only women aged 40–55 years were included in the study. Overall, 1994 were menopausal (17.1% of the sample) and 9658 were pre-menopausal (see Table I) at the time of the interview. Premature ovarian failure (1% of the sample) was defined as cessation of menstruation before the age of 40 years (see inset). Japanese women tended to stop menstruating at later ages.

Table II. Variables associated with premature ovarian failure (POF) compared with women without POF by univariate analysis

		All		Caucasian		African American		Hispanic	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Medical									
Arthritis	no	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	yes	2.4	(1.7–3.4)**	2.2	(1.3–3.7)*	3.2	(1.7–5.9)**	1.4	(0.5–3.5)
BMI (kg/m2)		1.05	(1.02–1.07)**	1.04	(1.0–1.1)*	1.06	(1.02–1.09)**	1.05	(0.94–1.09)
Children	some	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	none	1.3	(0.8–2.1)	1.1	(0.6–2.1)	1.2	(0.4–3.8)	1.9	(0.3–14.2)
Diabetes	no	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	yes	1.8	(1.0–3.2)(1)	2.1	(0.9–5.4)	1.0	(0.4–2.9)	2.9	(0.8–10.0)(1)
Disability	none	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	some	1.1	(0.6–2.2)	1.02	(0.4–2.6)	1.4	(0.4–4.6)	1.5	(0.2–11.2)
	severe	3.2	(2.0–5.0)**	3.9	(2.1–7.6)**	2.3	(1.1–4.8)*	3.3	(1.1–10.1)*
High blood pressure	no	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	yes	1.2	(0.8–1.9)	0.9	(0.5–1.8)	1.6	(0.9–3.0)	0.95	(0.3–2.8)
Heart disease	no	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	yes	1.3	(0.3–5.2)	2.7	(0.7–11.3)	0.01	(0.01–305)	0.01	(0.01–8.2)
Hormone use	no	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
(past 3 months)	yes	1.4	(0.9–2.2)	1.3	(0.7–2.4)	2.7	(1.2–6.3)*	0.7	(0.1–5.4)
Hormone use	never	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	ever	1.1	(0.7–1.7)	1.4	(0.7–2.8)	1.1	(0.5–2.4)	1.0	(0.4–2.4)
Hormone (not oral	no	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
contraceptives)	yes	2.9	(1.98–4.1)**	2.8	(1.7–4.7)**	5.3	(2.8–9.9)**	1.5	(0.5–4.5)
Oral contraceptive use	never	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	ever	0.8	(0.6–1.2)	0.9	(0.5–1.6)	0.8	(0.4–1.6)	0.9	(0.4–2.1)
Osteoporosis	no	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	yes	5.8	(3.2–10.4)**	7.0	(3.3–15.1)**	3.1	(0.7–13.3)	6.6	(1.9–23.6)**
Self-rated health									
	excellent	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	very good	1.6	(0.8–3.1)	2.3	(0.9–5.4)(1)	0.7	(0.2–2.5)	0.6	(0.04–9.8)
	good	2.8	(1.5–5.2)**	3.3	(1.4–7.9)**	1.5	(0.5–4.4)	2.5	(0.3–20.1)
	fair	4.2	(2.1–8.2)**	5.7	(2.1–15.5)**	2.3	(0.7–7.1)	2.9	(0.4–23.6)
	poor	5.5	(2.1–13.9)**	8.9	(2.3–35.1)**	2.1	(0.4–11.6)	4.5	(0.4–50.5)
Lifestyle									
Education attained	graduate	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	college	1.3	(0.6–3.0)	0.9	(0.4–2.7)	4.5	(0.5–37.2)	0.4	(0.02–6.2)
	some college	2.4	(1.2–4.8)*	2.2	(0.9–4.9)(1)	5.9	(0.8–45.5)(1)	0.6	(0.1–5.4)
	high school	3.4	(1.8–0.7)**	2.8	(1.3–6.3)**	9.0	(1.2–67.3)*	1.1	(0.2–8.7)
Paying for basics	not hard	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	somewhat hard	1.5	(1.0–2.3)*	1.2	(0.7–2.2)	1.7	(0.8–3.3)	1.8	(0.5–6.6)
	very hard	2.5	(1.6–4.1)**	3.1	(1.5–6.1)**	2.5	(1.1–5.9)*	1.9	(0.5–7.4)
Marital status	married	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	single	1.5	(1.1–2.2)*	1.8	(1.1–3.1)*	1.4	(0.7–2.6)	0.7	(0.3–1.9)
Smoking	never	1.0	(reference)	1.0	(reference)	1.0	(reference)	1.0	(reference)
	past	1.04	(0.7–1.7)	1.2	(0.6–2,4)	1.2	(0.5–2.8)	0.95	(0.3–2.9)
	current	2.0	(1.4–3.0)**	3.0	(1.7–5.4)**	1.9	(1.0–3.9)(1)	0.5	(0.1–2.2)

*P significant at 0.05 level; **P significant at 0.01 level or greater; (1)P near significance (0.05–0.1)

Unadjusted association of POF with selected medical/ biological and lifestyle variables

Because of the small numbers of Asian women with POF, further analysis was limited to Caucasian, African American and Hispanic women. Arthritis, diabetes, poorer self-reported health, higher BMI, osteoporosis, severe disability, use of female hormones (excluding oral contraceptives), single marital status, lower education level, difficulty paying for basics, and smoking were each significantly associated with POF in univariate analysis (Table II). In subset analyses, the significance of variables differed for Caucasian, African American and Hispanic women (Table II). The prevalence of POF by site also differed significantly, but did not differ for Caucasian or African American women in subset analyses and was likely related to differences in ethnic composition by site. After adjustment for education and paying for basics, site and ethnicity were no longer significant.

The mean ($\pm$ SD) BMI was significantly higher for women with POF (29.3 $\pm$ 8.4) compared with non-POF women (26.7 $\pm$ 6.3; $P = 0.001$). However, the mean BMI differed between African American women with and without POF ($P = 0.03$), but did not differ for Caucasian ($P = 0.1$, non-significant) or Hispanic women ($P = 0.7$, non-significant) with and without POF.

Current smoking was associated with POF (Table II). The association of POF and smoking differed by ethnicity. The

Table III. Multivariate odds ratios (OR) and 95% confidence intervals (95% CI) for factors associated with premature ovarian failure (POF)[a]

		All			Caucasian			African American		
		OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value
BMI (kg/m2)		1.03	(1.01–1.06)	0.011	1.01	(0.98–1.07)	0.3	1.04	(1.0–1.1)	0.028
Hormone (not birth control pills)		2.9	(1.9–4.3)	0.00001	3.0	(1.7–5.2)	0.0001	4.5	(2.3–9.1)	0.0001
Arthritis		1.3	(0.7–2.0)	0.24	1.2	(0.7–2.2)	0.5	1.7	(0.8–3.5)	0.12
Disability	none	1.0	(reference)		1.0	(reference)		1.0	(reference)	
	some	0.9	(0.4–1.9)	0.7	1.0	(0.4–2.7)	0.9	0.8	(0.2–3.3)	0.7
	severe	1.4	(0.8–2.5)	0.1	2.2	(1.1–4.6)	0.04	0.9	(0.3–2.2)	0.7
Osteoporosis		3.7	(1.9–7.0)	0.0006	5.6	(2.5–12.8)	0.0004	1.4	(0.3–6.6)	0.7
Smoking	never	1.0	(reference)		1.0	(reference)		1.0	(reference)	
	past	0.9	(0.5–1.5)	0.7	1.2	(0.6–2.4)	0.7	0.7	(0.3–1.9)	0.5
	current	1.8	(1.1–2.8)	0.01	2.2	(1.2–4.1)	0.02	1.7	(0.8–3.6)	0.2

[a] POF compared with women without POF.
Values were adjusted for site, education, difficulty paying for basics, and age at interview.

trends did not correspond to the prevalence of POF or differences in the frequency of smoking by ethnicity. For example, a similar proportion of African American (29.1%) and Caucasian (23.6%) women but fewer Hispanic (17.1%) women were current smokers ($P = 0.0001$), although the prevalence of POF was similar among Hispanic, African American and Caucasian women.

At interview, the average age of women with POF was significantly different from non-POF women with and without menses (47.9 ± 4.5 versus 46.5 ± 4.3 years respectively; $P < 0.0001$). The average age of women with POF also varied among ethnic groups at interview. Age may have an impact on medical/biological variables. Therefore, an adjustment for age at interview was made in multivariate analyses.

Multivariate models

Variables in univariate analysis with a *P*-value < 0.10 were entered into multi-variate models. For women with POF compared with women without POF in a multivariate logistic regression model, self-reported history of osteoporosis, use of female hormones (excluding oral contraceptives), higher BMI and current smoking were associated with POF, after adjustment for site, socioeconomic status and age at interview (Table III).

The models differed for Caucasian and African American women (Hispanic women were not analysed due to the small numbers of affected women) (Table III). For Caucasian women, osteoporosis, female hormone use (excluding oral contraceptives), severe disability and current smoking were associated with POF after adjustment for site, age and socioeconomic status. For African American women, female hormone use and higher BMI were associated with POF after adjustment for site, age and socioeconomic status.

Discussion

Prevalence

This is the first assessment of the prevalence of POF in a single, multi-ethnic study. We observed that 1.1% of women in our sample experienced POF before the age of 40 years. This result agrees with two previous reports that 0.9% of women under age 40 years have elevated FSH (Coulam *et al*., 1986), and 1.2% of women stopped menstruation before the age of 40 years (Cramer and Xu, 1996). In addition, 4.2% of women experienced an early menopause before age 45 years. This agrees with a previous report of 5.0% (Cramer and Xu, 1996) in a study of Caucasian women in the USA and 3.3% in the current generation of French women (Cassou *et al*., 1997). Furthermore, our data showed that the prevalence of POF varies by ethnicity from 0.1 to 1.4% among Caucasian, African American, Hispanic, Chinese and Japanese women. In this study, significantly fewer Japanese women experienced POF. This is consistent with another report from SWAN that menopause occurred significantly later in Japanese women (Gold *et al*., 2001). This is also consistent with the report that the slope of the age of menstrual cycle cessation increases sharply around the age of 50 years with a smaller skew toward younger ages for Japanese women (Kono *et al*., 1990).

The age of menopause, and the accompanying loss of functional follicles (Faddy *et al*., 1992), may be influenced by genetic determinants (de Bruin *et al*., 2001), and modified 1–2 years from the average by various lifestyle and environmental factors (Vermeulen, 1993; Cramer and Xu, 1996; van Noord *et al*., 1997). Interestingly, the distribution of age at which menses cease is skewed with a long left tail. Using mathematical curve fitting, the distribution of age at menopause in Finnish women was resolved into three curves with mean values at 36.3, 42.9 and 50.5 years representing 3, 19 and 78% of the study population respectively (Luoto *et al*., 1994). This is consistent with the possibility that different processes are involved in ovarian failure, or that selected processes differentially accelerate ovarian ageing in some women.

Demographic/lifestyle associations

The variables selected for examination in this study were reported in the literature as significantly associated with POF. In univariate analysis, difficulty paying for basics, lower educational level attained, single marital status, and smoking were significantly associated with POF in agreement with earlier reports. The association of POF, or an earlier meno-

pause, with a tendency to be single was reported by others (Gokmen *et al*., 1995; Cassou *et al*., 1997; Gold *et al*., 2001). However, after adjustment for socioeconomic status in multivariate analysis, marital status was no longer associated with POF. Although low parity was related to earlier natural menopause in other reports (Luoto *et al*., 1994; Torgerson *et al*., 1994; Do *et al*., 1998; Frohlich *et al*., 2000; Gold *et al*., 2001), it was not specifically associated with POF in this study. Lower socioeconomic status is also associated with a younger age at natural menopause (Luoto *et al*., 1994; Cramer *et al*., 1995; Do *et al*., 1998; Gold *et al*., 2001). In this study, two variables were used as indicators of socioeconomic status, difficulty paying for basics and educational level attained. Both variables were associated with POF consistent with previous studies of an earlier natural menopause in women of low socioeconomic status (Luoto *et al*., 1994; Torgerson *et al*., 1994; van Noord *et al*., 1997).

Smoking has been suggested as a significant risk factor for POF (Luoto *et al*., 1994; Cramer *et al*., 1995; Nilsson *et al*., 1997; Cooper *et al*., 1999; Harlow and Signorello, 2000) and early natural menopause (Willett *et al*., 1983; Cooper *et al*., 1999; Gold *et al*., 2001) in studies that were primarily of Caucasian women. In this study, smoking was not uniformly associated with POF among ethnic groups. The prevalence of POF was similar for Caucasian and Hispanic women and Hispanic women smoke less than Caucasian women. One explanation for the lack of association of smoking and POF for Hispanic women may be that smoking was assessed at interview rather than prior to POF. Alternately, ethnic differences in nicotine metabolism and pharmacogenetics (Caraballo *et al*., 1998; Perez-Stable *et al*., 1998; Benowitz *et al*., 2002) may account for differences in the association of POF and smoking among ethnic groups.

Health associations

In unadjusted univariate analysis, arthritis, higher mean BMI, diabetes, osteoporosis, disability, poorer self-rated health and female hormone use (excluding oral contraceptives) were associated with POF. After adjustment for socioeconomic status, age at interview and site, only osteoporosis, higher BMI, female hormone use, and disability remained associated with POF, depending on the ethnic group.

In this analysis, a self-reported history of osteoporosis was the most significant health factor associated with POF overall. An association between earlier age at menopause and lower bone density, as well as increased risk for osteoporosis, has been reported (Kritz-Silverstein and Barrett-Connor, 1993; Ohta *et al*., 1996). POF is also associated with increased risk for osteoporosis (Gokmen *et al*., 1995; Hartmann *et al*., 1997). Interestingly, in subset analyses, osteoporosis was associated with POF in Caucasian and Hispanic women but not African American women. The incidence of osteoporosis is lower in African American women and it was suggested that this is due to a higher bone mass with lower initial rates of bone loss in menopause (Luckey *et al*., 1996; Bohannon, 1999). However, it is not clear if this is the basis for a lack of association of osteoporosis with POF in African American women.

Relatively little information is available on the relationship of physical disabilities to POF. Osteoporosis is associated with disability (Kenny and Prestwood, 2000). In multivariate analysis, severe disability was more likely to be associated with POF in Caucasian and not African American women, similar to the association of osteoporosis with POF.

Hormone use (excluding oral contraceptives) was associated with POF. Because of the cross-sectional design, we cannot distinguish hormone use as a risk factor, from use as a therapy, for POF. Hormones may include gonadotrophins and steroids in infertility treatment or hormone replacement for ovarian failure. Ethnic differences in hormone replacement therapy prescription and use may vary from location and medical practice structure (Jahnige and Fiebach, 1997; Brown *et al*., 1999). However, recent hormone use (hormone use in the past 3 months) was not associated with POF. This suggests that the association of female hormone use (excluding oral contraceptives) with POF may not solely represent estrogen replacement therapy, or it may reflect an initial use of hormone replacement therapy followed by its discontinued use.

In multivariate models, higher BMI was associated with POF. Since this analysis considered weight at interview, it does not reflect weight at the time of ovarian failure. Further, because the study was cross-sectional, it is not possible to determine if BMI was the same at the time of POF or if it changed since the onset of POF. In some other studies, higher mean BMI was related to later age at menopause (Leidy, 1996; Kirchengast *et al*., 1998; Frohlich *et al*., 2000), although not in all studies (Gold *et al*., 2001). In another report from SWAN, BMI was associated with ethnicity and physical activity and to a lesser extent, menopausal status and age (Matthews *et al*., 2001). A variety of factors may influence BMI such as ethnicity, race, socioeconomic status and genetics (Wagner and Heyward, 2000). The association of BMI with POF requires longitudinal investigation in order to determine the interpretation and significance of the observation.

POF is associated with autoimmune diseases such as diabetes type 1 (Dorman *et al*., 2001), Addison's disease (Winqvist *et al*., 1995), polyendocrine autoimmunity (Weetman, 1995; Myhre *et al*., 2001), and thyroiditis (Falsetti *et al*., 1999; Luborsky *et al*., 1999). Women with type 1 diabetes experienced menopause ~6–8 years earlier than their non-diabetic sisters or unrelated controls (Dorman *et al*., 2001). However, diabetes type 2 does not appear to be associated with POF (Lopez-Lopez *et al*., 1999). Data on diabetes were collected in this survey, but the type of diabetes was not identified. Diabetes approached significance in univariate but not in multivariate analyses in this study. An association with POF may not have been clearly detected in this study since diabetes type 1 and 2 were not differentiated in data collection.

An association between POF and cancer and cancer-related mortality has been reported (Cramer *et al*., 1983; Cooper and Sandler, 1998). However, women with a history of cancer were excluded in this analysis in order to eliminate chemotherapy or radiation treatment as a basis for ovarian failure (Chiarelli *et al*., 1999).

POF was not associated with a history of cardiovascular disease. In a previous report from SWAN, heart disease was associated with earlier age at natural menopause (Gold *et al*., 2001). However, this apparent difference is consistent with previous studies in which different conclusions were obtained depending on whether POF was identified as a specific study group (Senoz *et al*., 1996) or if POF was not specifically identified in a group of menopausal women (van der Schouw *et al*., 1996). The latter study reported the association between cardiovascular disease, and earlier age at menopause occurred early in the menopause transition but the risk declined with age since menopause (van der Schouw *et al*., 1996). Thus, another possible interpretation of the result in this study is that the risk has already declined in women with POF.

Obviously, in a cross-sectional study design there are limitations in the type of information that can be obtained and in the interpretation of 'associations'. The study group represents a 'window' in time of women aged 40–55 years. Health risks that may be expressed at later ages, such as cardiovascular disease, would not be identified. Also, the cause–effect relationship of POF and health or lifestyle factors cannot be discerned. For example, tobacco use is categorized at the time of interview but information on the use of tobacco before POF occurred was not available in this study.

In summary, POF is not rare. The prevalence of POF varies by ethnicity. Health factors associated with POF, and variations among ethnic groups may differ from those of menopause around age 50 years and would benefit from further study.

Acknowledgements

The Study of Women's Health Across the Nation (SWAN) is funded by the National Institute on Aging, the National Institute of Nursing Research and the Office of Research on Women's Health of the National Institutes of Health. Supplemental funding from the National Institute of Mental Health, the National Institute on Child Health and Human Development, the National Center on Complementary and Alternative Medicine, the Office of Minority Health, and the Office of AIDS Research is also gratefully acknowledged. Clinical centres: University of Michigan, Ann Arbor, MI (U01 NR04061, MaryFran Sowers, PI): Massachusetts General Hospital, Boston, MA (U01 AG12531, Robert Neer, PI); Rush University, Rush–Presbyterian–St. Luke's Medical Center, Chicago, IL (U01 AG12505, Lynda Powell, PI); University of California, Davis/Kaiser (U01 AG12554, Ellen Gold, PI); University of California, Los Angeles (U01 AG12539, Gail Greendale, PI); University of Medicine and Dentistry/New Jersey Medical School, Newark, NJ (U01 AG12535, Gerson Weiss, PI); and the University of Pittsburgh, Pittsburgh, PA (U01 AG12546, Karen Matthews, PI). Laboratory: University of Michigan, Ann Arbor, MI (U01 AG12495, Central Ligand Assay Satellite Services, Daniel McConnell, PI) and Medical Research Laboratories (MRL), Highland Heights, KY (subcontract of U01 AG12553, Evan Stein, Director). Coordinating centre: New England Research Institute, Watertown, MA (U01 AG12553, Sonja McKinlay, PI). Project Officers: Taylor Harden, Carole Hudgings, Marcia Ory, Sheryl Sherman. Steering Committee Chair: Jennifer L.Kelsey. This manuscript was reviewed by the Publications and Presentations Committee of SWAN and has its endorsement.

References

Anasti, J. (1998) Premature ovarian failure: an update. *Fertil. Steril.*, **70**, 1–15.

Anasti, J.N., Kalantaridou, S.N., Kimzey, L.M., Defensor, R.A. and Nelson, L.M. (1998) Bone loss in young women with karyotypically normal spontaneous premature ovarian failure. *Obstet. Gynecol.*, **91**, 12–15.

Benowitz, N.L., Perez-Stable, E.J., Herrera, B. and Jacob, P., III (2002) Slower metabolism and reduced intake of nicotine from cigarette smoking in Chinese-Americans. *J. Natl Cancer Inst.*, **94**, 108–115.

Bohannon, A.D. (1999) Osteoporosis and African American women. *J. Women's Health Gender-Based Med.,* **8**, 609–615.

Bondy, C.A., Nelson, L.M. and Kalantaridou, S.N. (1998) The genetic origins of ovarian failure. *J. Women's Health,* **7**, 1225–1229.

Brown, A.F., Perez-Stable, E.J., Whitaker, E.E., Posner, S.F., Alexander, M., Gathe, J. and Washington, A.E. (1999) Ethnic differences in hormone replacement prescribing patterns. *J. Gen. Intern. Med.*, **14**, 663–669.

Caraballo, R.S., Giovino, G.A., Pechacek, T.F., Mowery, P.D., Richter, P.A., Strauss, W.J., Sharp, D.J., Eriksen, M.P., Pirkle, J.L. and Maurer, K.R. (1998) Racial and ethnic differences in serum cotinine levels of cigarette smokers: Third National Health and Nutrition Examination Survey, 1988–1991. *J. Am. Med. Assoc.*, **280**, 135–139.

Cassou, B., Derriennic, F., Monfort, C., Dell'Accio, P. and Touranchet, A. (1997) Risk factors of early menopause in two generations of gainfully employed French women. *Maturitas*, **26**, 165–174.

Chiarelli, A.M., Marrett, L.D. and Darlington, G. (1999) Early menopause and infertility in females after treatment for childhood cancer diagnosed in 1964–1988 in Ontario, Canada. *Am. J. Epidemiol.*, **150**, 245–254.

Christin-Maitre, S., Vasseur, C., Portnoi, M.F. and Bouchard, P. (1998) Genes and premature ovarian failure. *Mol. Cell. Endocrinol.*, **145**, 75–80.

Cooper, G.S. and Sandler, D.P. (1997) Long-term effects of reproductive-age menstrual cycle patterns on peri- and postmenopausal fracture risk. *Am. J. Epidemiol.*, **145**, 804–809.

Cooper, G.S. and Sandler, D.P. (1998) Age at natural menopause and mortality. *Ann Epidemiol.*, **8**, 229–235.

Cooper, G.S., Hulka, B.S., Baird, D.D., Savitz, D.A., Hughes, C.L., Jr, Weinberg, C.R., Coleman, R.A. and Shields, J.M. (1994) Galactose consumption, metabolism and follicle-stimulating hormone concentrations in women of late reproductive age. *Fertil. Steril.*, **62**, 1168–1175.

Cooper, G.S., Sandler, D.P. and Bohlig, M. (1999) Active and passive smoking and the occurrence of natural menopause. *Epidemiology*, **10**, 771–773.

Coulam, C., Adamson, S. and Annegers, J. (1986) Incidence of premature ovarian failure. *Obstet. Gynecol.*, **67**, 604–606.

Cramer, D.W. (1990) Epidemiologic aspects of early menopause and ovarian cancer. *Ann. NY Acad. Sci*., **592**, 363–375.

Cramer, D. and Xu, H. (1996) Predicting age at menopause. *Maturitas*, **23**, 319–326.

Cramer, D.W., Harlow, B.L., Xu, H., Fraer, C. and Barbieri, R. (1995) Cross-sectional and case-controlled analyses of the association between smoking and early menopause. *Maturitas*, **22**, 79–87.

Cramer, D.W., Hutchison, G.B., Welch, W.R., Scully, R.E. and Ryan, K.J. (1983) Determinants of ovarian cancer risk. I. Reproductive experiences and family history. *J. Natl Cancer Inst.*, **71**, 711–716.

Davison, R.M., Fox, M. and Conway, G.S. (2000) Mapping of the POF1 locus and identification of putative genes for premature ovarian failure. *Mol. Hum. Reprod.*, **6**, 314–318.

de Bruin, J.P., Bovenhuis, H., van Noord, P.A., Pearson, P.L., van Arendonk, J.A., te Velde, E.R., Kuurman, W.W. and Dorland, M. (2001) The role of genetic factors in age at natural menopause. *Hum. Reprod.*, **16**, 2014–2018.

Do, K.A., Treloar, S.A., Pandeya, N., Purdie, D., Green, A.C., Heath, A.C. and Martin, N.G. (1998) Predictive factors of age at menopause in a large Australian twin study. *Hum. Biol.*, **70**, 1073–1091.

Dorman, J., Steenkiste, A., Foley, T., Strotmeyer, E., Burke, J., Kuller, L. and Kwoh, C. (2001) The menopause in type 1 diabetic women: is it premature? *Diabetes*, **50**, 1857–1862.

Faddy, M.J., Gosden, R.G., Gougeon, A., Richardson, S.J. and Nelson, J.F. (1992) Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. *Hum. Reprod.*, **7**, 1342–1346.

Falsetti, L., Scalchi, S., Villani, M.T. and Bugari, G. (1999) Premature ovarian failure. *Gynecol. Endocrinol.*, **13**, 189–195.

Fenichel, P., Sosset, C., Barbarino-Monnier, P., Gobert, B., Hieronimus, S., Bene, M. and Harter, M. (1997) Prevalence, specificity and significance of ovarian antibodies during spontaneous premature ovarian failure. *Hum. Reprod.*, **12**, 2623–2628.

Frohlich, K.L., Kuh, D.J., Hardy, R. and Wadsworth, M.E. (2000) Menstrual patterns during the inception of perimenopause: what are the predictors and what do they predict? *J. Women's Health Gend. Based Med.*, **9**, 35–42.

Gokmen, O., Seckin, N.C., Sener, A.B., Ozaksit, G. and Ekmekci, S. (1995) A

study of premature ovarian failure in Turkish women. *Gynecol. Endocrinol.*, **9**, 283–287.

Gold, E.B., Bromberger, J., Crawford, S., Samuels, S., Greendale, G.A., Harlow, S.D. and Skurnick, J. (2001) Factors associated with age at natural menopause in a multiethnic sample of midlife women. *Am. J. Epidemiol.*, **153**, 865–874.

Harlow, B.L. and Signorello, L.B. (2000) Factors associated with early menopause. *Maturitas*, **35**, 3–9.

Hartmann, B.W., Kirchengast, S., Albrecht, A., Laml, T., Soregi, G. and Huber, J.C. (1997) Androgen serum levels in women with premature ovarian failure compared to fertile and menopausal controls. *Gynecol. Obstet. Invest.*, **44**, 127–131.

Hoek, A., Schoemaker, J. and Drexhage, H.A. (1997) Premature ovarian failure and ovarian autoimmunity. *Endocr. Rev.*, **18**, 107–134.

Jahnige, K. and Fiebach, N. (1997) Postmenopausal estrogen use among African American and white patients at an urban clinic. *J. Women's Health*, **6**, 93–101.

Joakimsen, O., Bonaa, K.H., Stensland-Bugge, E. and Jacobsen, B.K. (2000) Population-based study of age at menopause and ultrasound assessed carotid atherosclerosis: The Tromso Study. *J. Clin. Epidemiol.*, **53**, 525–530.

Kenny, A.M. and Prestwood, K.M. (2000) Osteoporosis. Pathogenesis, diagnosis and treatment in older adults. *Rheum. Dis. Clin. North Am.*, **26**, 569–591.

Kirchengast, S., Grossschmidt, K., Huber, J. and Hauser, G. (1998) Body composition characteristics after menopause. *Coll. Antropol.*, **22**, 393–402.

Kono, S., Sunagawa, Y., Higa, H. and Sunagawa, H. (1990) Age of menopause in Japanese women: trends and recent changes. *Maturitas*, **12**, 43–49.

Kritz-Silverstein, D. and Barrett-Connor, E. (1993) Early menopause, number of reproductive years and bone mineral density in postmenopausal women. *Am J. Public Health,* **83**, 983–988.

Leidy, L. (1996) Timing of menopause in relation to body size and weight change. *Hum. Biol.*, **68**, 967–983.

Lopez-Lopez, R., Huerta, R. and Malacara, J.M. (1999) Age at menopause in women with type 2 diabetes mellitus. *Menopause*, **6**, 174–178.

Luborsky, J.L., Visintin, I., Boyers, S., Asare, T., Caldwell, B. and DeCherney, A. (1990) Ovarian antibodies detected by immobilized antigen immunoassay in patients with premature ovarian failure. *J. Clin. Endocrinol. Metab*., **70**, 69–75.

Luborsky, J.L., Llanes, B., Davies, S., Binor, Z., Radwanska, E. and Pong, R. (1999) Ovarian autoimmunity: greater prevalence of autoantibodies in POF and unexplained infertility than in the general population. *Clin. Immunol.*, **90**, 368–374.

Luckey, M.M., Wallenstein, S., Lapinski, R. and Meier, D.E. (1996) A prospective study of bone loss in African-American and white women—a clinical research center study. *J. Clin. Endocrinol. Metab*., **81**, 2948–2956.

Luoto, R., Kaprio, J. and Uutela, A. (1994) Age at natural menopause and sociodemographic status in Finland. *Am. J. Epidemiol.*, **139**, 64–76.

Matthews, K.A., Abrams, B., Crawford, S., Miles, T., Neer, R., Powell, L.H. and Wesley, D. (2001) Body mass index in mid-life women: relative influence of menopause, hormone use and ethnicity. *Int. J. Obes. Relat. Metab. Disord.*, **25**, 863–873.

McKinlay, S.M. (1996) The normal menopause transition: an overview. *Maturitas*, **23**, 137–145.

McKinlay, S.M., Brambilla, D.J. and Posner, J.G. (1992) The normal menopause transition. *Maturitas*, **14**, 103–115.

Myhre, A.G., Halonen, M., Eskelin, P., Ekwall, O., Hedstrand, H., Rorsman, F., Kampe, O. and Husebye, E.S. (2001) Autoimmune polyendocrine syndrome type 1 (APS I) in Norway. *Clin. Endocrinol. (Oxf.)*, **54**, 211–217.

Nilsson, P., Moller, L., Koster, A. and Hollnagel, H. (1997) Social and biological predictors of early menopause: a model for premature aging. *J. Intern. Med.*, **242**, 299–305.

Ohta, H., Sugimoto, I., Masuda, A., Komukai, S., Suda, Y., Makita, K., Takamatsu, K., Horiguchi, F. and Nozawa, S. (1996) Decreased bone mineral density associated with early menopause progresses for at least ten years: cross-sectional comparisons between early and normal menopausal women. *Bone,* **18**, 227–231.

Perez-Stable, E.J., Herrera, B., Jacob, P., 3rd and Benowitz, N.L. (1998) Nicotine metabolism and intake in black and white smokers. *J. Am. Med. Assoc.*, **280**, 152–156.

Santoro, N. (2001) Research on the mechanisms of premature ovarian failure. *J. Soc. Gynecol Invest.*, **8**, S10–12.

Senoz, S., Direm, B., Gulekli, B. and Gokmen, O. (1996) Estrogen deprivation, rather than age, is responsible for the poor lipid profile and carbohydrate metabolism in women. *Maturitas*, **25**, 107–114.

Torgerson, D.J., Avenell, A., Russell, I.T. and Reid, D.M. (1994) Factors associated with onset of menopause in women aged 45–49. *Maturitas*, **19**, 83–92.

van der Schouw, Y., van der Graaf, Y., Steyerberg, E., Eijkemans, J. and Banga, J. (1996) Age at menopause as a risk factor for cardiovascular mortality. *Lancet*, **347**, 714–718.

van Noord, P.A., Dubas, J.S., Dorland, M., Boersma, H. and te Velde, E. (1997) Age at natural menopause in a population-based screening cohort: the role of menarche, fecundity and lifestyle factors. *Fertil. Steril.*, **68**, 95–102.

Vermeulen, A. (1993) Environment, human reproduction, menopause and andropause. *Environ. Health Perspect.*, **101** (Suppl. 2), 91–100.

Wagner, D.R. and Heyward, V.H. (2000) Measures of body composition in blacks and whites: a comparative review. *Am. J. Clin. Nutr.*, **71**, 1392–1402.

Weetman, A.P. (1995) Autoimmunity to steroid-producing cells and familial polyendocrine autoimmunity. *Baillières Clin. Endocrinol. Metab*., **9**, 157–174.

World Health Organization (1996) Research on Menopause in the 1990s. WHO technical report series 866. World Health Organization, Geneva, Switzerland.

Willett, W., Stampfer, M.J., Bain, C., Lipnick, R., Speizer, F.E., Rosner, B., Cramer, D. and Hennekens, C.H. (1983) Cigarette smoking, relative weight and menopause. *Am. J. Epidemiol.*, **117**, 651–658.

Winqvist, O., Gebre-Medhin, G., Gustafsson, J., Ritzen, E.M., Lundkvist, O., Karlsson, F.A. and Kampe, O. (1995) Identification of the main gonadal autoantigens in patients with adrenal insufficiency and associated ovarian failure. *Clin. Endocrinol. Metab*., **80**, 1717–1723.

Yan, G., Schoenfeld, D., Penney, C., Hurxthal, K., Taylor, A. and Faustman, D. (2000) Identification of premature ovarian failure patients with underlying autoimmunity. *J. Women's Health Gender-Based Med.*, **9**, 275–287.

Submitted on December 20, 2001; resubmitted on July 22, 2002; accepted on September 3, 2002