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

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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.
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 $\chi^2$-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 $\chi^2$-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 I. Menopause status by ethnicity

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Caucasian</th>
<th>Black</th>
<th>Hispanic</th>
<th>Chinese</th>
<th>Japanese</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature menopause (&lt;40 years)</td>
<td>Count</td>
<td>% in ethnic group</td>
<td>95% CI</td>
<td>Count</td>
<td>% in ethnic group</td>
<td>95% CI</td>
</tr>
<tr>
<td>Count</td>
<td>61</td>
<td>1.0</td>
<td>0.7–1.4</td>
<td>177</td>
<td>2.9</td>
<td>2.4–3.5</td>
</tr>
<tr>
<td>% in ethnic group</td>
<td>40</td>
<td>1.4</td>
<td>1.0–2.1</td>
<td>104</td>
<td>3.7</td>
<td>2.9–4.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>21</td>
<td>1.4</td>
<td>0.8–2.5</td>
<td>60</td>
<td>4.1</td>
<td>3.0–5.6</td>
</tr>
<tr>
<td>% in ethnic group</td>
<td>3</td>
<td>0.5</td>
<td>0.1–1.9</td>
<td>13</td>
<td>2.2</td>
<td>1.1–4.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>1</td>
<td>0.14</td>
<td>0.02–1.1</td>
<td>6</td>
<td>0.8</td>
<td>0.3–2.2</td>
</tr>
<tr>
<td>Total count</td>
<td>126</td>
<td>1.1</td>
<td>0.9–1.3</td>
<td>360</td>
<td>3.1</td>
<td>2.7–3.5</td>
</tr>
</tbody>
</table>

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.
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 (± SD) BMI was significantly higher for women with POF (29.3 ± 8.4) compared with non-POF women (26.7 ± 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.
Values were adjusted for site, education, difficulty paying for basics, and age at interview.

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

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

*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 age and 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. Alternatively, 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; Mihre 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.

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