RESEARCH ARTICLE

Correlation of age at natural menopause with occupational status and other epidemiologic factors in women from Prefecture of Kavala, Greece

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Abstract
Aim: Aim of this study was to explore possible associations between the timing of natural menopause and occupational status and other determinant epidemiologic factors among women living in the Prefecture of Kavala, a region of North-East Greece.
Methods: The sample of the study comprised of 827 naturally menopausal women, who consented to participate in this questionnaire-based interview study between 2011 and 2016. The study population was recruited from women who were hospitalized or visited the outpatient clinics of the General Hospital of Kavala and women working in the public sector services and private companies in the Prefecture of Kavala.
Results: The mean age of the sample at natural menopause was 49.1 years; 12.2 % had early menopause, and 4.5 % were diagnosed with premature ovarian failure. For the majority of enrolled women (80.5 %) menopause occurred between 45-54 years, and for the rest (2.8 %) after 54 years of age.
In univariate analysis, a statistically significant correlation was found between age at menopause and occupational status, year of birth, mother's age at menopause, age at menarche, and high levels of chronic stress. Multiple regression analysis revealed that occupational status, year of birth and mother's natural menopausal age could predict age at menopause.
Conclusion: Socioeconomic, demographic and familial variables appear to be associated with age at natural menopause in a representative sample of women in the Prefecture of Kavala, Greece. HIPPOKRATIA 2017, 21(1): 32-37.

Keywords: Determinants of age at menopause, occupational status, Greek women

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Introduction

Natural menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause follows 12 consecutive months of amenorrhea, for which there is no other apparent pathological or physiological cause[1].

In industrialized countries, it is generally accepted that the average age at menopause is about 51 years, but this age is lower in developing countries, compared to developed countries[2]. In previous studies, the mean age at natural menopause for Greek women residing in Athens was found to range between 46.6 and 48.6 years[3-5].

Age at menopause has been associated with increased risk for the onset of several chronic diseases[2,6-9]. Thus, it is a notable milestone in the female reproductive life, since it indicates not only the increased risk of morbidity and premature mortality due to the decreased level of sex hormone levels but also a biological marker of overall aging and general health status[10]. The age at natural menopause and the distribution of known and suspected risk factors differ between populations and among women within populations[11]. Many factors have been reported to affect menopausal age[8,12]. These include a number of familial and genetic factors[12], environmental factors[11-13], demographic[12], early life events[12-14], later life events[14], and diseases[15].

The timing of final natural menstrual period could have significant clinical and health implications, because the women are expected to spend more than one-third of their lives in the phase of post menopause. There is an increasing number of studies investigating the factors affecting the menopause age[10], because of the increasing women's life expectancy and their social activities[7], occupational exposure being one of these causes[16-18]. Except for one previous study concerning women residing in Athens, Greece[5], there are no population-based data in Greece on the relationship between age at natural menopause and occupation. This previous study, however, was not detailed regarding the type of occupation. Also, no studies are investigating the age at natural menopause and its determinant factors in provincial Greek women. Therefore, in this work, we aimed to record the age of natural menopause and to explore its relationship with the occupational status of women from the Prefecture of

Kavala in North-East Greece. Our secondary objective was to investigate the extent to which differences in age of onset of natural menopause among women can be explained by determinant epidemiologic risk factors.

Material and Methods

The study was conducted from January 2011 to June 2016. We recruited women from urban, semi-urban, and rural settlements in the Kavala Prefecture in North-East Greece. All procedures complied with the principles of the World Medical Association's Declaration of Helsinki. All ethical and procedural aspects were approved by the Committee of Post-Graduate Studies of the Medical School of Democritus University of Thrace (Protocol No 56-4/10/2010).

Study population

The study population comprised of women from the general population, as well as women hospitalized or visiting various outpatient clinics of the General Hospital of Kavala. Additionally, employees of the General Hospital of Kavala and different companies and organizations of either the private or public sector were enrolled. Sample size calculation for multiple regression analysis depends on the number of predictors and the size of the expected effect. For an expected small effect and for two to six predictors, a sample size of 500 is considered sufficient[19]. In our study, a total of 827 postmenopausal women, who had attained natural menopause, out of 1,300 women approached, agreed to participate in the survey (response rate 63.6 %).

Procedure

Each eligible woman was recruited for a structured interview, either at the hospital or workplace. The duration of every evaluation was from 15 to 25 minutes. Participation in the study was voluntary and the participants could withdraw from the study at any time. All participants were fully informed of the potential risks and benefits of this research. Privacy of the participants was respected during the collection and analysis of data. The main outcome of this structured interview was the assessment of age at natural menopause, which was obtained by asking a woman to recall her age at the last menstrual period and the time passed since then. Also, every woman was asked, whether she was menstruating or not, during the preceding 12 months to minimize the effect of recall error. Menopausal status was defined based on the World Health Organization's definition of menopause: women with 12 or more months of amenorrhea, women whose periods had not stopped because of surgery, medical treatment, pregnancy, breastfeeding, or severe weight loss were defined as naturally postmenopausal[2].

Questionnaire

The questionnaire was constructed based on guidelines of the "Questionnaire design" of the Faculty of Health and Medical Sciences of The University of Western Australia[20], taking into consideration the recommendations of the World Health Organization on collecting data on reproductive life characteristics in women[21]. The validity and reliability of the questionnaire were checked by conducting a pilot study on 15 subjects resulting in a correlation coefficient 88 %. Because different variables were hypothesized as covariates of age at menopause, the questions were designed to collect apart from detailed menopausal history, information regarding the socio-demographic characteristics, reproductive history, familial and lifestyle factors.

Socio-demographic characteristics recorded included the birth year, occupational status, educational level, and marital status. Occupation was recorded into four categories: i) higher and lower level white-collar workers, ii) skilled and unskilled blue-collar and farm workers, iii) other workers: self-employed, hairdressers, hotel-maids, housemaids, merchants, technologists in medical laboratories, saleswomen, babysitters, dressmakers, dishwashers, receptionists, waitresses, cooks, nurses, support staff, and iv) housewives. Educational level was divided into seven levels: i) primary school, ii) junior secondary school, iii) senior secondary school, iv) vocational school, v) university and technological education, vi) Master's level, and vii) Ph.D. level. Marital status was categorized as: married, unmarried, widowed, and divorced or separated.

Familial factors concerned mother's age at natural menopause while reproductive history aspects recorded, included age at menarche, duration of menstrual bleeding, age at first and last birth, use of oral contraceptives, nulliparity, abortion, and breastfeeding. Age of menarche was categorized into five groups: i) younger than 12 years, ii) 12th year, iii) 13th year, iv) 14th year, and v) older than 14 years. Duration of menstrual bleeding was categorized into three groups: i) two-three days, ii) three-five days, and iii) more than five days.

Lifestyle factors recorded, included active smoking, passive smoke exposure, alcohol, and coffee consumption, and exposure to stress. Active smoking was classified into three categories: non-smokers, smokers of less than ten cigarettes per day, and smokers of more than ten cigarettes per day. Passive smoke (second-hand smoke) was classified into two categories: those never exposed to passive smoking and those with a smoking parent when growing up or were exposed later in their home or their working environment. Drinking alcoholic beverages was classified into two categories: never drinking and drinking one or more drinks per day. The frequency of coffee consumption was classified into two categories: never drinking and drinking one or more cups per day. To assess exposure of women to stress, we utilized its categorization according to National Institute of Mental Health[22]: i) routine stress related to the pressure of work, school, family, and other daily responsibilities, ii) stress induced by a sudden negative change, such as divorce, illness or losing a job, iii) traumatic stress experienced following a major accident, war, assault or a natural disaster. First, the

medical history of each participating woman (e.g., medication for stress like sedatives and anxiolytics; psychiatric support) was recorded, and all women were informed about the three types of stress as mentioned earlier. Then, they were asked to choose which of the following replies represented them: i) "I felt little stress in daily life for many years before perimenopause", ii) "I felt moderate to high levels of routine stress in daily life for many years, before perimenopause", iii) "I felt high level of stress for a prolonged period, many years before perimenopause, induced by a sudden negative change, such as financial disaster, vehicle or occupational accident, trauma or illness in myself or a close family member, parental divorce or death of a family member early in life, war experience as a child, a sudden loss of a loved one in later life long before the age of natural menopause".

Statistical analysis

Descriptive statistics were initially calculated. To determine which factors affected the age of natural menopause, t-test, ANOVA, and regression models were used. When statistical significance was derived from the ANOVA model ($p < 0.05$), Tukey multiple comparisons test was used to investigate between which categories statistically significant differences appeared. Multiple linear regression analysis was used to assess association of age at natural menopause (the dependent variable) with selected variables of interest (independent variables).

Statistical analyses were performed using the IBM SPSS Statistics for Windows software, version 21.0 (IBM SPSS, IBM Corp., Armonk, NY, USA). The significance level was set at p-value <0.05.

Results

A total of 827 naturally postmenopausal women were included in this study. The mean age (± standard deviation) of the sample was 60.4 ± 8.4 years. Of those women, 149 (18 %) were housewives, 70 (8.5 %) were retired and 608 (73.5 %) continued to work. The mean age of natural menopause in our sample was 49.1 ± 4.2 years, and the median age was 50 (range 26-58) years. At menopause, 37 women (4.5 %) were younger than 40 years (premature ovarian failure), 101 (12.2 %) were aged between 40-44 years (early menopause), 666 (80.5 %) were aged between 45-54 years, and the rest (23 women; 2.8 %) were older than 54 years (late menopause).

Table 1 shows the factors which affect the age of natural menopause at a statistically significant level ($p < 0.05$) and in indicative level ($p < 0.2$). As shown, occupational status affects age of menopause ($p = 0.001$). More specifically, white-collar workers ($p = 0.046$; Tukey multiple comparisons test) and housewives ($p = 0.001$) have greater menopausal mean age than blue-collar workers. Additionally, younger women (born in more recent years) ($p < 0.001$), those reporting high levels of chronic routine stress ($p = 0.005$), or smoking ($p = 0.006$) demonstrate a trend to younger mean age of menopause. On the other hand, higher age of menarche ($p = 0.026$) or higher mother's age of natural menopause ($p < 0.001$) lead to higher menopause mean age, while higher age at first ($p = 0.185$) or last birth ($p = 0.117$) demonstrate a trend to higher menopause mean age. Table 2 presents the factors which do not affect the age of natural menopause in a univariate model.

Table1: Factors affecting the age of natural menopause of the 827 naturally postmenopausal women included in the study, at a statistically significant and in indicative level.

Factor	p	R^2
Year of birth	<0.001[1]	2 %
Age of menarche	0.026[4]	
Duration of menstruation	0.062[1]	0.04 %
Age of mother's natural menopause	<0.001[1]	14.9 %
High levels of chronic stress	0.005[3]	
Age at first child birth	0.185[2]	0.2 %
Age at last child birth	0.117[2]	0.3 %
Active Smoking	0.006[4]	
Moderate to high levels of routine stress	0.127[3]	
Occupational status	0.001[4]	

[1]: Values without missing for each one of the factors, [2]: Regression, [3]: T-test, [4]: Anova.

Table 2: Factors which do not affect the age of natural menopause of the 827 naturally postmenopausal women included in the study, in the univariate model.

Factor	p
Marital status	0.488
Level of education	0.849
Abortions	0.583
Breastfeeding	0.457
Passive smoker	0.221
Contraceptive use	0.314
Alcohol consumption up to 1 drink/day	0.573
Nulliparity	0.896
Caffeine consumption up to 1 cup /day	0.246

Subsequently, we created a multivariate regression model with the age of natural menopause as the dependent variable and as independent variables all factors presented in Table 1. We used a stepwise regression model with a probability of entry 0.10 and probability of removal 0.20. The used model included the mother's age at menopause of each participating woman. This model interprets only 19 % of the variability of the age of menopause (F-test =16.718, $p < 0.001$, $R^2 = 19$ %, total degrees of freedom =505) and cannot be used to predict the age of menopause, but only to explain how each one of the independent variables affects the age of menopause.

Table 3 displays the association between the age of natural menopause of the mother and the dependent variable (menopause age of the examined woman). More specifically, the increase of the menopausal age of the mother by one year results in an increase of the corresponding age at menopause of her daughter by 0.310 years (about four months) ($p < 0.001$). Also, the year of birth affects the age of menopause. Thus, younger women (born in more recent years) tend to have menopause at a younger age. Specifically, for each decade in age difference, the age of menopause decreased by an average of

Table 3: Coefficients of multivariate regression with mother's menopausal age and association to the dependent variable (menopause age of the examined woman).

Model	B	Std. Error	p
(Constant)	199.216	49.740	<0.001
Mother's natural menopausal age	0.310	0.036	<0.001
Year of birth	-0.085	0.025	0.001
Smoking less than 10 cigarettes[1]	-0.099	0.536	0.853
Smoking more than 10 cigarettes[1]	-0.756	0.408	0.065
White-collar worker[2]	1.354	0.455	0.003
Housewife	1.580	0.550	0.004
Other collar worker[2]	1.535	0.496	0.002

B: the unstandardized regression coefficients, [1]: no smoking is the reference category, [2]: blue collar is the reference category.

approximately 0.085 years (about one month) (p =0.025).

Women who smoked more than ten cigarettes per day had on average 0.756 years (about nine months) earlier age of menopause (indicative level; p =0.065).

White-collar workers (p =0.003), other workers (p =0.004) and housewives (p =0.002) have 1.35 to 1.58 years (from 16 to 19 months) later menopausal age than blue-collar workers.

Discussion

In the present study, we found the mean age of menopause to be 49.1 years and was different compared to previous studies from Athens, Greece, which demonstrated an earlier menopause age[3-5]. In our sample, 4.5 % of women had premature ovarian failure, which is higher than that reported by Akasheh et al[23], but it is lower than that reported by Adamopoulos et al[4]. We found that 12.3 % of the women of our study had early menopause, which is higher than in the study of Akasheh et al[23]. The 2.8 % of our sample with late menopause was higher compared to Adamopoulos et al[4] and lower compared to Cassou et al[15].

The age of women, as calculated by the reported year of birth, was significantly associated with age at natural menopause. Indeed, we found that women born in more recent years tend to have an earlier mean age of menopause, which is in agreement with the results of Hajdini et al[24] but not consistent with others[8,13], who showed that women born in earlier years tend to have an earlier mean age of menopause. Goumalatsos et al[5] on Athens Greek women did not show any particular trend between the year of birth and age at menopause.

Previous studies have shown that a woman's age at menopause is related to her mother's age at menopause[25,26]. Similarities between mother and daughter ages at menopause were also found in our sample. In contrast, Murugan and Vanaja[16] have reported no familial relationship between natural menopause age of the subjects and their mothers**.**

There was no significant relationship between the marital status and the age at menopause in our study, and this is in agreement with some studies[5,6,27], but disagrees with the results of other studies[9,24].

The relationship between occupation and onset of natural menopause has not been fully investigated before. Perhaps, occupational exposure may cause endocrine disruption, possibly affecting the onset of natural menopause[10]. In the present study, a statistically significant correlation between the occupational status and the age at natural menopause was found, similarly to previous studies[16-18,28]. In contrast, other studies have reported no such relationship[5,24,29]. Our results reveal that the mean age at menopause was smaller in blue-collar workers, compared to white-collar workers, other workers, and housewives. These findings were similar to reported results from other studies[18,28].

Our study agrees with previously reported results[24,27], which showed that the level of education of women was not related to age at natural menopause, contradicting earlier reports[6,9,11,13,16,28-30].

Reproductive factors seem to be important in the timing of natural menopause[10]. In the present study, however, age at menopause was not significantly associated with reproductive factors, including age at menarche, duration of menstruation, age of first and last birth, oral contraceptives use, history of breastfeeding, abortion, and nulliparity. More specifically, our results confirm those of Golshiri et al[6] showing that the age of menarche was not significantly associated with the onset of the menopause using multivariate analysis, while other studies showed that age at natural menopause was related to age at menarche[13,29]. No association was observed with age at first or last birth and age at menopause, in agreement with Cassou et al[15]. We found that past use of oral contraceptives was not a predictor of the cessation of the menstrual activity, in agreement with previous publications[16,27], but in disagreement with other studies[11,29]. We failed to find any association between history of breastfeeding and age at menopause, which is in agreement with Batrinos et al[3] but disagrees with Liu et al[30]. We observed a negative association between age at natural menopause and previous abortion, concurring with the results of previous works[6,9]. However, Liu et al found a positive correlation[30]. Consistent with an earlier study from Athens, Greece[3], presented results showed that nulliparity was not reproducibly linked to age at natural menopause, in contrast to other reports[5,15,27].

It has been reported that lifestyle factors can damage the oocytes and decrease the level of sexual hormones, therefore affect the reproductive aging[28]. In the present study, however, age at natural menopause was not significantly associated with lifestyle factors, including active and passive smoke, alcohol and coffee consumption. The polycyclic aromatic hydrocarbons in cigarette smoke are known to be toxic to ovarian follicles and thus

could result in premature loss of ovarian follicles[10] and early natural menopause among smokers[4,12,13,15,25,29]. This conclusion is weakly supported by our study results, as the association found was marginal. Very little is known about the effect of passive smoke exposure on the age at natural menopause[10]. Unlike the findings of Shobeiri et al[25], this study has demonstrated that age at natural menopause was negatively correlated with passive smoking. The frequency of alcohol consumption was not related to the time of menopause. This result is consistent with the finding of Fu et al[8]. On the other hand, other researchers showed that alcohol consumption was associated with age at menopause[11,13]. Our study supports the view of earlier reports, indicating no association between age at natural menopause and coffee consumption[11,16].

High strain jobs may affect the reproductive function, due to their influence on the autonomous nervous system and the neuroendocrine activity[15]. Excessive stress, which increases the levels of stress hormones, can negatively affect the reproductive ability and accelerate menopause[7]. Our results showed that moderate to high levels of routine stress and high level of chronic stress was linked to early age of menopause, but only on univariate analysis. In contrast, Goumalatsos et al[5] found that age at menopause was delayed in women from Athens Greece, who were adolescent during World War II.

This is the first study conducted in a Greek province, which investigates the age at natural menopause and its correlation with the occupational status and other determinant factors. In conclusion, the results of the present study revealed a significant association between occupational status, which determines the socioeconomic status[15,28] and the onset timing of natural menopause. Other equally important parameters, found in our study to affect significantly the age at natural menopause are the year of birth and mother's age at menopause. Our results demonstrate that the age at natural menopause in a representative sample of women in the Prefecture of Kavala, Greece, reflects the interplay of socioeconomic and demographic factors, which have clinical and public health implications regarding the early identification of women at high risk for suffering future morbidity. Thus, is important advising these women about family planning, as they approach midlife. Modification of risk factors, such as occupational exposures, may postpone the onset of menopause more closely to the biologically determined individual time of menopause. These findings should provide direction for further research into the biological processes driving menopause and in particular how genetics and the occupational environment interact. We believe that the results of the current study will contribute towards awareness-raising for further studies and research on this highly significant indicator, which is the age of the natural menopause, and its relation with the employment status, the role of work-related factors, the sudden loss of job, and the unemployment. The ongoing financial crisis in recent years has caused dramatic changes in the socioeconomic status, health behaviors and lifestyle; these changes are likely to have an impact on the health status and probably on the age at menopause. Demographic changes, observed in Greece due to increased life expectancy, combined with economic crisis render necessary future research to focus on this direction.

The main limitation of the current study was the retrospective data collection. The personal interviews helped to diminish this methodological limitation of the study. To minimize reporting errors, participants were encouraged to consult their mother or other family members.

Conflict of interest

Authors declare no conflict of interests.

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