



Lack of association between age at menarche and age at menopause: Pró-Saúde Study, Rio de Janeiro, Brazil

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ABSTRACT

Objective: To investigate the association between age at menarche and age at menopause among Brazilian women.

Methods: This study is based on cross-sectional data obtained in 1999 from technical and administrative employees who were recruited for participation at the Pró-Saúde cohort study in Rio de Janeiro, Brazil. The final study population consisted of 1462 women. Participants completed a self-administered multidimensional questionnaire. In addition to the study exposure (age at menarche) and outcome (age at menopause) variables, the following independent variables were selected: parity; schooling; self-classified race; use of oral contraceptives; smoking; and body mass index (BMI). Median ages at natural menopause and the survival curves were estimated by the Kaplan–Meier method. To estimate the association between age at menarche and age at natural menopause, a Cox semi-parametric model was fitted. Women who were still menstruating, who had undergone surgery for the removal of the uterus or ovaries, or who were in perimenopause were censored.

Results: Natural menopause occurred in 205 women. The median and mode for natural menopause were 51.7 and 50 years of age, respectively. In the multivariate analysis, no statistically significant association was observed between age at menarche and age at menopause (HR: 1.01; 95% CI: 0.93–1.11).

Conclusion: In the current study, the hypothesis of an association between age at menarche and age at natural menopause was not confirmed. Specific studies on the determinants of age at menopause should be conducted, due to the importance of menopause in the causality of diseases with high case mortality rate.

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1. Introduction

Ages at menarche and menopause mark two important moments in women's lives, since the interval between the two demarcate their natural reproductive period [1]. Evidence indicates that the early or late occurrence of these events is associated with increased risk of chronic diseases. Early menopause in particular is associated with all-cause mortality [2–4], increased risk of cardiovascular diseases [5], and osteoporosis [6]. Meanwhile, women that experience late menopause show a higher risk of breast cancer [7,8] and endometrial cancer [9].

Mean age at menopause is approximately 50 years [1,10,11] varying among countries. Reynolds and Obermeyer [12], in a literature review, found ranges between 49.3 and 51.4 as compared to 43.5 and 49.4 years for mean age at menopause in developed

and developing countries, respectively. Biological, nutritional, and socio-environmental factors (e.g., working conditions and diseases) may account for these differences, since they influence ovarian function, the termination of which causes natural menopause [10]. Moreover, some authors attribute part of this difference to methodological aspects of the studies like the exclusion of women in perimenopause, following surgical menopause, or in use of hormone replacement therapy [13,14]. In Brazil, according to data from the first population-based study on the determinants of menopause, conducted in Campinas, São Paulo State, mean age at natural menopause was 51.2 years, similar to that found in developed countries [15]. However, a study on smoking and age at menopause carried on in clinics in São Paulo, mean age at menopause was 48.49 years [16].

Age at natural menopause is determined by the exhaustion of ovarian follicles. Natural depletion of follicles begins at birth and continues into perimenopause, when it accelerates. When the decrease in follicles reaches a critical number, menopause occurs [17]. Thus, age at menarche, parity, duration and length of the

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menstrual cycle, and use of oral contraceptives have been cited as possible determinants of age at natural menopause, since they can deplete (or spare) the ovarian follicles, anticipating natural menopause due to either the increase in frequency of ovulation (early menarche and regular menstrual cycles) or interruption in ovulation (pregnancies and use of oral contraceptives) [18–21].

Various factors have been associated with early or late menopause. Smoking for example has been consistently related to its anticipation [16,22–25]. Factors contributing to late menopause include use of oral contraceptives [12], woman's age at first childbirth [26], and irregular menstrual cycles [20,27]. Other characteristics show less consistent results such as schooling [14,28,29], body mass index [30,31], short menstrual cycles [14,32], nulliparity [27], and race/color [13].

Particularly, there is no consensus in the literature concerning the effect of age at menarche on age at menopause. Some studies suggest a direct relationship, meaning that the earlier (or later) the menarche, the earlier (or later) the menopause [14,26,33–35]. Others suggest an inverse association [36–38] or even lack of association [32,39–44].

In Brazil, as occurs in developed countries, mean age at menarche has been declining at a rate of 3 months per decade [45,46]. However, there is also an important variation of the age at menarche, which might be associated to a number of factors such as early nutritional deficiencies [1], socioeconomic conditions [47] general health and lifestyle [44] and genetic parameters [48], among others. That context as well as the scarcity of studies in developing countries makes research to elucidate the relationship between age at menarche and age at menopause mandatory. Accordingly, the aim of the current study was to investigate the association between age at menarche and age at menopause among workers who were included in the Pró-Saúde Study, in Rio de Janeiro, Brazil.

2. Methods

2.1. Study population

This study is based on cross-sectional data obtained from technical and administrative employees working at a university in Rio de Janeiro, who have been accompanied in a cohort study, the Pró-Saúde Study [49]. Baseline took place in two phases (1999 and 2001), and first follow-up occurred in 2006/2007. This article included data from phase 1 (1999), in which all workers were invited to participate. Those on a non-medical leave of absence or temporarily transferred to other institutions at the time of data collection were excluded. From the eligible population of 4428, response rate was 91% ($N=4030$), of whom 2238 were women. In this study, additional eligibility criteria were applied, and women whose age at natural menopause, surgical menopause, or beginning of hormone replacement therapy was not reported (13 women), as well as those that could not provide their age at menarche (30 women) were excluded. The study population also excluded women ≤ 35 years of age (680 women) or those that had entered menopause in this age bracket (53 women), due to high probability of disease related menopause [50]. The final study population thus consisted of 1462 women. Human subjects approval was obtained from the University Ethics Committee (Universidade do Estado do Rio de Janeiro). Written informed consent was obtained from all participants.

2.2. Measurements

Participants answered a self-completed multidimensional questionnaire, applied in their workplace with the help of a previously trained team. Information on age at menarche was obtained with

the question, “How old were you when you had your first menstrual period?” (in complete years). The same applied for age at menopause: “How old were you when you stopped menstruating?”.

A reliability evaluation was performed by way of a test–retest study in a sample of non-tenured employees from the same university ($N=192$). The estimated intraclass correlation coefficients (ICC) for age at menopause and menarche were 0.93 (95% confidence interval [95% CI] 0.90–0.95) and 0.98 (95% CI 0.95–0.99), respectively.

In addition to the main variables of the study (age at menarche and age at menopause), the following independent variables were selected: parity (no children, 1–3 children, 4 or more children); schooling – primary (up to complete primary), secondary (complete secondary), and university (complete university); self-classified race (white, black/brown, indigenous/Asian); use of oral contraceptives (had used, never used); smoking (never smoked, current smoker, former smoker); and body mass index (BMI), based on measured weight and height ($<25.0 \text{ kg/m}^2$; $\geq 25.0 \text{ kg/m}^2$).

Natural menopause was defined, according to the World Health Organization standard, as “the permanent cessation of menstruation, recognized as having occurred after 12 months of amenorrhea, not attributed to hormone use or surgery for the removal of the uterus or ovaries” [10]. Thus, for classification of natural menopause status, the study considered participants that reported spontaneous cessation of menstruation for more than 12 months, except those whose reasons for interruption of menstruation were surgery, use of hormone therapy, or any other cause (pregnancy, radiation, etc). The World Health Organization defines perimenopause as the period immediately prior to and the first year after menopause [10]. For classification of perimenopause, this study considered women that reported having stopped menstruating for less than 6 months or from 6 months to 1 year prior to the data collection.

2.3. Statistical analysis

Since the information on age at natural menopause was only available in complete years, the median was estimated by survival analysis, by interpolation. Median ages at natural menopause and the survival curves were estimated by the Kaplan–Meier method, according to categories of selected variables and differences between strata were evaluated by the log-rank test [51].

To estimate the effect of age at menarche on age at natural menopause, a Cox semi-parametric model was used. Censoring occurred at the age of interview when (i) women were still menstruating ($N=1044$); (ii) were in perimenopause ($N=73$). The third situation, women who had undergone surgery for the removal of the uterus or ovaries ($N=140$) were censored at the informed age of surgery. The target event, natural menopause, occurred in 205 women.

In addition to age at menarche, all variables showing a statistically significant association ($p < 0.20$) with age at menopause in the univariate models were included in the final model. The Schoenfeld and Martingale residues from each variable contained in the final model were evaluated, as were the results for the linear correlation test of the variables with time. The analytical procedures were performed with the R software, version 2.7.2.

3. Results

The time-to-event – natural menopause – presented a median and mode 51.7 and 50 years of age, respectively (Table 1). The median age at menopause occurred a year before for women

Table 1

Median age (in years) at natural menopause according to selected characteristics, Pró-Saúde Study, Rio de Janeiro, Brazil, 1999.

Characteristics	Total N	Natural menopause		Median age at natural menopause (years)	p-Value ^a
		N	%		
Age at menarche					
≤11 years	453	50	11.0	52	0.870
≥12 years	1009	155	15.4	53	
Parity					
No children	270	37	13.7	50	0.003
1–3 children	1018	127	12.5	52	
4 or more children	78	30	38.5	53	
Schooling					
Primary	375	106	28.3	50	0.021
Secondary	455	50	11.0	52	
University	612	43	7.0	52	
Use of oral contraceptives					
Already used	1130	145	12.8	52	0.791
Never used	329	60	18.2	52	
Race/color					
White	713	97	13.6	52	0.675
Black/brown	703	99	14.1	52	
Asian or indigenous	31	7	22.6	53	
Smoking					
Never smoked	718	108	15.0	52	0.027
Current smoker	355	49	13.8	51	
Former smoker	297	33	11.1	53	
BMI (body mass index)					
<25.0 kg/m ²	638	64	10.0	52	0.641
≥25.0 kg/m ²	800	138	17.2	52	
Total	1462	205	14.0	52	ND ^b

^a Log-rank test.^b Not available.

with age at menarche ≤11 years, when compared to those with history of menarche at ≥12 years of age (difference not statistically significant, $p=0.87$). There was an increase in the median age at menopause according to the number of children ($p<0.05$). In addition, in women with less schooling (primary), the median was 2 years less than among those with more schooling (secondary or university) ($p<0.05$). Among current smokers, median age at menopause was 1 year less (51 years of age) than for those who had never smoked (52 years of age), and 2 years less (53 years of age) when compared to former smokers ($p<0.05$). No statistically significant associations were observed between use of oral contraceptives, race/color, or BMI and age at menopause.

In the univariate analysis, the association between age at menarche and age at menopause was marginally (HR = 1.02; 95% CI: 0.94–1.10) (Table 2). A significant association was observed between parity and natural menopause, whereby women who had never given birth showed 89% greater risk of reaching menopause earlier than women with 4 or more children. In the same direction, women with primary schooling had a 55% greater risk of reaching menopause earlier than women with a university education. Comparing smokers and women that had never smoked, the risk of natural menopause occurring earlier was 52% greater among the former.

The Kaplan–Meier curves (Fig. 1) showed similar results. There was no significant difference between median age at menopause according to age at menarche, race/color, or use of oral contraceptives. Meanwhile, median age at menopause did vary according to categories of parity, schooling, and smoking.

In the multivariate analysis, no statistically significant association was observed between age at menarche and age at menopause in the different survival analysis models (Table 3). According to the residues analysis and linear correlation test (model 3), the effects of age at menarche, smoking, and schooling on age at menopause were proportional over time and without a systematic pattern, indicating a good fit for the model.

4. Discussion

In our study population, consisting of technical and administrative public employees in Rio de Janeiro, the hypothesis of association between age at menarche and age at menopause was not corroborated. Similar results have also been reported in different populations, from the United States [19,52], Lebanon [43], Netherlands [32,39] and Mexico [32]. We also investigated other types of relationship between ages at menarche and menopause – linear effect and non-linear association in a separate model for the age group showing the highest probability of occurrence of

Table 2Cox univariate regression of proportional risks for age at natural menopause according to selected variables, Pró-Saúde Study, Rio de Janeiro, Brazil, 1999.^a

Selected characteristics	Hazards ratio	p-Value ^b
Age at menarche (years)	1.02 (0.94–1.10)	0.649
Parity		
4 or more children	1.00	0.006
1–3 children	1.01 (0.67–1.51)	
No children	1.89 (1.15–3.11)	
Schooling		
University	1.00	0.026
Secondary	1.12 (0.745–1.69)	
Primary	1.55 (1.085–2.22)	
Use of oral contraceptives		
Had used	1.00	0.801
Never used	1.04 (0.77–1.41)	
Race/color		
White	1.00	0.690
Black/brown	0.92 (0.70–1.22)	
Asian or indigenous	0.75 (0.35–1.62)	
Smoking		
Never smoked	1.00	0.033
Current smoker	1.53 (1.08–2.15)	
Former smoker	0.91 (0.61–1.34)	
BMI (kg/m ²)	0.94 (0.70–1.27)	0.695

^a Risk of natural menopause occurring earlier.^b Likelihood ratio test.

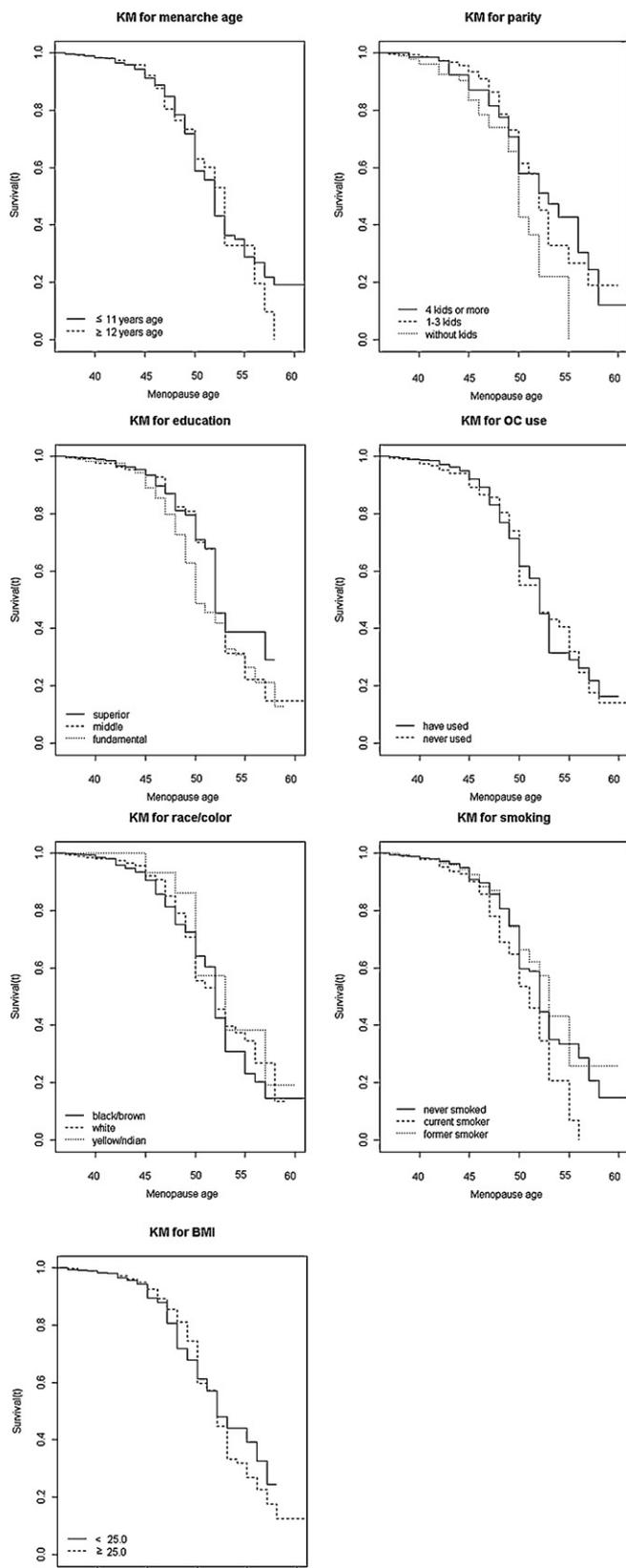


Fig. 1. Survival curves for menopause age, according to selected variables. Pró-Saúde Study, Rio de Janeiro, Brazil, 1999.

the event (around the median age for natural menopause – 45–55 years) (results not shown) – confirming the absence of statistically significant association.

Median age at natural menopause in this population (51.7 years) was close to the values observed in developed countries: England – 52.1 years [53]; France – 52 years [28]; United States – 51 years [54]; Finland – 51 years [47], and Italy – mean of 51.2 years [27]. Although median age at menopause was lower in women with earlier menarche (≤ 11 versus ≥ 12 years), this difference was also not statistically significant.

The biological implications (mechanisms) and clinical implications (consequences) of the three possibilities for associations between age at menopause and age at menarche (lack of association, direct association, or inverse association) are different. Some studies have found a direct association between age at menarche and age at menopause, with early menarche leading to early menopause. This association causes a shift to the left in the entire reproductive period, but without necessarily shortening it. Shifts in mean age at menopause, with or without shortening the fertile period, appear to increase the risk of such diseases as osteoporosis [55].

The inverse association found in other studies – early menarche and late menopause – leads to a lengthening of reproductive life, greater exposure to circulating endogenous hormones, and subsequent increase in the risk of such diseases as endometrial and breast cancer [36].

Since the Pró-Saúde Study does not focus specifically on women's reproductive health, some limitations might have occurred such as the small number of women that reported natural menopause for more than 12 months ($N = 205$), restricting stratified analyses according to different characteristics. In addition, despite the excellent reliability of the information on age at menarche and menopause, memory bias may have occurred due to the retrospective collection of the data. However, there is no reason to believe that any inaccuracies induced by these putative biases were systematic (i.e., reporting of ages that were consistently younger or older than the real ones).

Another limitation relates to the lack of information on duration and regularity of menstrual cycles, which could be important in the association between age at menarche and age at menopause. This is because short menstrual cycles, especially at younger ages, can increase the frequency of ovulation and deplete the ovarian follicles early, leading to early menopause [21]. The results by Weinstein et al. [56], for example, suggest an association ($p = 0.059$) between variable duration of cycles between 35 and 39 years of age and early menopause. In another study, early menarche (≤ 11 years), reporting of short menstrual cycles, and never having been pregnant were associated with early menopause [57]. However, other studies that included information on the duration of menstrual cycles also failed to find an association between ages at menarche and menopause, as did our study [32,43].

The comparison of our findings to those of other studies is not simple, since in most studies age at menarche has been analyzed in an exploratory way along with other variables, as a possible predictor of age at, rather than considering it as the principal exposure [34,39,41,58]. However, in such studies, the results were also inconsistent on the existence of association between age at menarche and age at menopause.

The influence of age at menarche on age at menopause has still not been completely elucidated. Part of the inconsistency in the results can be explained by the data analysis method. The results of studies in which survival analysis was not used [16,32,42,59], and which therefore did not include the contribution of women still at risk of entering natural menopause (censored), present lower mean and median ages than for studies that used survival analysis. This is because in this type of analysis, the time of contribution by

Table 3

Cox multivariate regression of proportional risks for age at natural menopause, Pró-Saúde Study, Rio de Janeiro, Brazil, 1999.

Models	Hazards ratio ^a (HR) (95% CI)	p-Value	Adjusted R ²
Model 1: Age at menarche + parity	1.023 (0.945–1.108)	0.57	0.008
Model 2: Model 1 + schooling	1.009 (0.925–1.101)	0.84	0.012
Model 3: Model 2 + smoking	1.013 (0.926–1.108)	0.78	0.018

^a Risk of natural menopause occurring earlier.

women that are still menstruating, are currently in perimenopause, or whose menopause was surgical, is taken into consideration until censored. However, the inconsistency is not completely explained by the different analytical strategies, since there is no consensus even among studies that used survival analysis. In the literature, we find both early menarche associated with early menopause [14,57] and lack of association [28].

In the current study, the hypothesis of an association between age at menarche and age at natural menopause was not confirmed. Specific studies on the determinants of age at menopause should be conducted, due to the importance of menopause in the causality of diseases with high case mortality [2].

Contributors

Dr. Otero chose the methods, analysed the data and edited the manuscript. Dr. Cruz analysed the data and co-wrote the manuscript. Dr. Faerstein analysed the data and co-wrote the manuscript. Dr. Lopes analysed the data and co-wrote the manuscript. Dr. Chor analysed the data and co-wrote the manuscript.

Competing interest

None.

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