Increased long-term recreational physical activity is associated with older age at natural menopause among heavy smokers: the California Teachers Study

Aina Emaus, M.D.[1,2], **Christina Dieli-Conwright, Ph.D.**[1], **Xinxin Xu, M.S.**[1], **James V. Lacey Jr., Ph.D.**[1], **Sue A. Ingles, Dr.P.H.**[3], **Peggy Reynolds, Ph.D., M.P.H.**[4,5], **Leslie Bernstein, Ph.D.**[1,†], and **Katherine D. Henderson, Ph.D.**[1]

[1]Department of Population Sciences, City of Hope National Medical Center, Duarte, CA, USA

[2]Department of Oncology, Oslo University Hospital, Ulleval, Norway

[3]Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, CA, USA

[4]Cancer Prevention Institute of California, Berkeley, CA, USA

[5]Department of Health Research and Policy, Stanford University School of Medicine, Palo Alto CA

Abstract

Objective—Although physical activity modulates the hypothalamic-ovarian-pituitary axis, the few studies investigating whether physical activity is associated with age at natural menopause have had mixed results. We set out to determine whether physical activity is associated with the timing of natural menopause in a large cohort of California women, overall, and by smoking history.

Methods—We investigated the association between long-term physical activity (hours/week/year) and age at natural menopause among 97,945 women in the California Teachers Study. Multivariable Cox proportional hazards regression methods were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). The impact of cigarette smoking (never smoker, former-light smoker, former-heavy smoker, current-light smoker, current-heavy smoker) as an effect modifier was evaluated.

Results—In a multivariable model adjusting for body mass index at age 18, age at menarche, race/ethnicity, and age at first full-term pregnancy, increased physical activity was statistically significantly associated with older age at natural menopause (p_{trend}=0.005). Higher body mass index at age 18 (p_{trend}=0.0003) and older age at menarche (p_{trend}=0.0003) were also associated with older age at natural menopause. Hispanic ethnicity (vs. non-Hispanic whites, HR 1.17, 95% CI 1.09–1.26), current smokers (vs. never smokers, HR 1.68, 95% CI 1.60–1.75 for current-light smokers; HR 1.38, 95% CI 1.33–1.44 for current-heavy smokers) and older age at first full-term pregnancy (HR $_{29,\ 2+\ full\text{-}term\ pregnancies\ vs.\ <29,\ 2+\ full\text{-}term\ pregnancies}$ 1.10, 95% CI 1.06–1.14) were associated with earlier age at natural menopause. Upon stratification by smoking history, increased physical activity was statistically significantly associated with older natural menopause among heavy smokers only (HR$_{Highest\ vs.\ Lowest\ quartile}$ 0.88, 95% CI 0.81–0.97, p_{trend}=0.02 for

[†]Corresponding Author (Author to whom reprint requests should be sent): Leslie Bernstein, PhD, Professor, Department of Population Sciences, Division of Cancer Etiology, Beckman Research Institute, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010, (626) 256-4673 (Phone), (626) 471-7308 (Fax), Lbernstein@coh.org.

former-heavy smokers; $HR_{\text{Highest vs. Lowest quartile}}$ 0.89, 95% CI 0.80–0.99, p_{trend}=0.04 for current-heavy smokers).

Conclusion—Age at natural menopause is a complex trait; the determinants of age at natural menopause, including physical activity, may differ by smoking status.

Keywords

Physical activity; smoking status; age at natural menopause; reproductive factors; cohort studies

Introduction

Older age at natural menopause has been associated with increased postmenopausal breast cancer risk,[1–7] but lower risks for cardiovascular disease[8] and osteoporosis.[9] Previous studies have established that age at natural menopause is likely determined by a combination of genetic and environmental factors.[10–12] Smoking[13–20] and lower parity[20–24] have been associated with earlier onset of natural menopause, but are estimated to explain less than 10% of the variance in age at natural menopause.[10]

We hypothesized that physical activity would be associated with older age at natural menopause upon consideration of evidence linking physical activity with the hypothalamic-pituitary-ovarian axis.[25–28] Few studies have addressed the possible association between physical activity and age at natural menopause. One European study reported that low physical activity was associated with earlier natural menopause;[29] while two other studies reported no such association.[24, 30] We examined the effect of physical activity on the timing of natural menopause, overall and by smoking history, among California Teachers Study (CTS) participants.

Methods

Study Participants

The CTS is a prospective cohort study of 133,479 female, current or retired public school professionals, all members of the California State Teachers Retirement System, who enrolled in the cohort by completing a mailed questionnaire in 1995–1996 (i.e., baseline). Detailed information on the development and follow-up of the CTS has been reported previously.[31]

Measurement of menopausal status, type of menopause and age at menopause

Menopausal status and type were derived from self-reported baseline data. Respondents reported whether menstrual periods had stopped permanently (No, Yes-within the last 6 months, Yes-more than 6 months ago). If a respondent indicated that her periods had not stopped permanently, or she was currently pregnant, she was classified as premenopausal. If a respondent indicated that her periods had stopped permanently within the last six months and she was not currently pregnant, she was classified as perimenopausal. If a respondent answered that her periods had stopped permanently, she was then asked 'When did you have your last period?' (<35, 35–39, 40–43, 44–46, 47–49, 50–52, 53–55 and 56 years). She was then also asked 'Why did your periods stop?' (natural menopause, surgery, medication or chemotherapy, radiation, other). A series of questions assessed if and when the respondent had undergone any gynecologic surgeries, and whether and when she had used any menopausal hormone therapy (HT). Participants were categorized as postmenopausal if they met any of the following criteria: 1) periods stopped permanently at least 6 months prior to cohort entry, 2) had experienced a bilateral oophorectomy (referred to herein as a surgical menopause), 3) were age 56 years or older at baseline and not already classified as

premenopausal, postmenopausal or perimenopausal, 4) started using HT to treat menopausal symptoms before periods stopped, or 5) had experienced a hysterectomy before age 56 years but were 56 years or older at baseline. Exclusion of participants in 'Group 3' of participants categorized as postmenopausal described above, specifically those who were 56 years or older at baseline and not already classified as premenopausal, postmenopausal or perimenopausal (N=283), did not materially alter the results from those shown and are thus treated as described above for analyses described herein.

Event and censoring ages were all defined in a manner similar to that used in a previous study of factors associated with age at natural menopause in the Hawai'i and Los Angeles Multiethnic Cohort Study.[12] A participant who indicated that she experienced a natural menopause and, at baseline, was older than the maximum age of her selected age-at-menopause category, was assigned the midpoint of her age-at-menopause category (33, 37, 41, 45, 48, 51, 54 or 57 years, respectively) as her event age. Alternatively, if a participant's age at baseline was within the category she selected for her age-at-menopause category, her age at natural menopause was set to the midpoint between the start of the category and baseline age. Analyses in which the event age was set to the youngest age of the appropriate category or to the oldest age of the appropriate category, did not differ markedly from those presented and thus the midpoints were used.

Censoring ages were calculated using coding rules in parallel to those described above for participants with a natural menopause, in which the age at last period category was applied for the following three censored groups: (1) perimenopausal participants (defined as last menstrual period less than 6 months before the baseline questionnaire and not pregnant at that time; N=2,388, 2.4%); (2) participants with a surgical menopause (defined as a bilateral oophorectomy; N=9,577, 9.8%): and (3) participants with a menopause due to other reasons (including medication/chemotherapy/radiation/other reason/experienced a hysterectomy before age 56 years but were 56 years or older at baseline; N=1,789, 1.8%). Age of HT initiation category was applied as the censoring time, again using parallel rules, for participants who were classified as postmenopausal due to start of HT use before periods stopped (N=4,502, 4.6%). Similarly, for premenopausal participants, the censoring age was set to the midpoint between the start of the above age-at-menopause category and baseline age (N=48,082, 49.1%).

Measurement of exposures

On the baseline questionnaire participants were asked to provide information on recreational physical activity for two intensity levels, strenuous and moderate, for six time intervals (during high school, between the ages of 18–24, 25–34, 35–44 and 45–54 years). For this analysis, an estimate of the average annual hours per week of long-term combined strenuous and moderate physical activity was calculated as follows.

For each intensity level and time period, participants reported the average number of hours per week (categories: none, 0.5, 1, 1.5, 2, 3, 4–6, 7–10, and ≥11) and the average number of months per year (categories: 1–3, 4–5, 7–9, and 10–12) that they engaged in physical activity. For each intensity level and time period, we calculated the average hours per week per year by multiplying hours per week (using midpoint of category where appropriate) by months per year (using midpoint of category) and then dividing by 12 months.

In calculating the final physical activity variable, for each intensity level, only the average hours per week of physical activity for each year through the event or censoring age was counted. For participants with an event or censoring age after 54 years only physical activity through age 54 was available (N=3,355, 3.4%); exclusion of this group, due to concerns that the physical activity would not properly represent the physical activity after age 54, did not

materially alter the results from those shown; therefore results shown include these participants.

The average hours per week for all eligible years were then summed to calculate the average annual hours per week of long-term recreational physical activity for each intensity level. Average annual hours per week of long-term strenuous recreational physical activity and average annual hours per week of long-term moderate recreational physical activity were then summed to estimate average annual hours per week of long-term combined strenuous and moderate recreational physical activity (h/wk/y); this total long-term physical activity variable was categorized into quartiles (<1.61, 1.61–3.449, 3.45–6.239, 6.24 h/wk/y).

In addition to physical activity, we considered the following factorsfor which data were collected at baseline: race/ethnicity [non-Hispanic white, non-Hispanic African American, Hispanic, Asian, other (other included Native American, mixed race and other/undeclared race/ethnicity)], smoking history [never smokers (never smokers included 2,277 participants who started smoking at or after the age at menopause), former smokers with known total pack-years (ever smokers who stopped smoking at least one year earlier than the age at menopause), current smokers with known total pack-years (ever smokers who began smoking no later than the age at menopause and who stopped smoking no sooner than the age at menopause) and unknown; former smokers and current smokers were further dichotomized by median total pack-years through the event or censoring age (the median pack-years was 4.4 for former smokers and 18 for current smokers)], body mass index (BMI) at age 18 years [(weight in kg)/(height in m)^2 or kg/m^2; (16.00–19.99, 20.00–24.99, 25.00–29.99, 30.00–54.99 kg/m^2 or unknown; BMI at age 18 values of <16.00 and 55.00 or greater were considered out of the normal range and assigned a missing value) (21)], age at menarche (10, 11–12, 13–14, 15 years of age, or unknown, the 11–12 years of age category was the reference group in all models), and a combined variable for age at first full-term pregnancy and parity (<29 and 2+ full-term pregnancy, <29 and 1 full-term pregnancy, 29 and 2+ full-term pregnancy, 29 and 1 full-term pregnancy, ever pregnant and no full-term pregnancy, never pregnant, or unknown).

Statistical analyses

Participants were excluded, in sequence, from this analysis if at baseline, they were 80 years or older (N=7,059), had a prior cancer diagnosis (breast, endometrial, cervix, ovary, lung, leukemia, Hodgkin's disease, lymphoma, colorectal, thyroid, melanoma; N=12,135), provided insufficient information by which to determine menopausal status or age at natural menopause (N=15,764; includes 11,427 participants with incomplete information on whether and/or when periods had ceased, 4,057 participants who were premenopausal at the time they underwent hysterectomy (without bilateral oophorectomy) before age 56 and were less than age 56 at baseline, 235 participants who began using HT before their periods stopped and for whom type of HT use was unknown, and 45 participants who began using HT before their periods stopped and for whom age at HT initiation was unknown), or had never had a menstrual period (N=2), or had missing information on physical activity (N=574). The final analytic cohort included 97,945 participants.

We used univariable and multivariable Cox proportional hazards regression methods *(22)* to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between physical activity and risk of natural menopause, adjusted for potential confounding factors. Participants effectively entered the study at birth and remained under follow-up until they experienced natural menopause (i.e., the outcome of interest) or were censored at the first of the following events: surgical menopause; menopause due to another reason, such as chemotherapy or radiation, menopause due to HT initiation prior to periods stopping; or completion of the baseline questionnaire (for women who were premenopausal at baseline).

Models were stratified by age (1-year age intervals) at cohort entry to control for potential cohort effects. To determine a final model we fit a series of multivariable failure-time models in which a woman failed at natural menopause. A forward stepwise regression was employed, in which a variable entered the model when the overall p value was less than 0.05. A backward stepwise regression approach was then used to confirm the final model, with variables being retained when the overall p value was less than 0.05. We checked the proportional hazards assumption for physical activity (in different categories) and the risk of natural menopausal by visually examining Kaplan-Meier survival curves and plotting scaled Schoenfeld residuals by time; no evidence for a violation of proportional hazards assumption was observed.

P values for trend in ordinal variables were calculated using long-term combined strenuous and moderate recreational physical activity and BMI at age 18 years as continuous variables, and the midpoints of the categories shown above for age at menarche. Participants with missing/unknown data for a variable were deleted from the appropriate model when assessing the p for trend for that variable, but the unknown group was considered as a separate category in models assessing the HRs by level of categorical variable. HRs less than 1.0 indicate that risk of natural menopause in the exposed group was lower than the risk of natural menopause in the unexposed (referent) group, and therefore can be interpreted as indicating the exposed group was more likely than the referent group to have a natural menopause at a later age.

We stratified the final multivariable model by baseline smoking status (never smokers, former-light smokers, former-heavy smokers, current-light smokers and current-heavy smokers). Heterogeneity of HR estimates in physical activity across smoking categories (never smokers vs. ever smokers, never smokers and ever-light smokers vs. ever-heavy smokers, and never smokers and former smokers vs. all current smokers) or other exposures of interest were evaluated in Cox regression models. Additional analyses in which the cohort entry was defined as the age started high school (15 years) did not differ measurably from the results presented herein. We also assessed any effects of timing or intensity of physical activity or age-specific physical activity on age at natural menopause; we did not find any differences in effects from those presented.

All quoted levels of statistical significance (*p* values) are two-sided. A type-1 error rate of 0.05 was used as the threshold for statistical significance. Analyses were performed using PROC PHREG in SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina). P values were not adjusted for multiple comparisons.

Results

Table 1 presents selected baseline characteristics, overall and by long-term combined strenuous and moderate recreational physical activity, for the 97,945 participants, which are similar to those for the entire CTS cohort.[31] The average age at baseline in the analytic cohort was 50.2 years. Among postmenopausal participants, the median ages (ranges) of natural menopause, surgical menopause and menopause due to another reason were 51 (33–57) years, 45 (33–57) years, and 47 (23–57) years, respectively (data not shown). 86.2% of participants were non-Hispanic white, 69.4% were never smokers, and 89.3% had a BMI at age 18 years of 24.99 or less. 85% of participants had an age at menarche of either 11–12 or 13–14. 41.4% of participants had two or more full-term pregnancies and had their first full-term pregnancy before age 29 years. 7.0%, 13.8% and 8.9% of participants had full-term pregnancy profiles of <29 and 1 full-term pregnancy, 29 and 2+ full-term pregnancies, and 29 and 1 full-term pregnancy, respectively. 21.4% were never pregnant and 6.5% were ever pregnant with no full-term pregnancy.

Among all participants (Table 2), increasing long-term combined strenuous and moderate recreational physical activity was associated with older age at natural menopause (HR$_{\text{highest vs. lowest quartile}}$ 0.95, 95% CI 0.92–0.98; p$_{\text{trend}}$=0.005), as were higher BMI at age 18 years (HR $_{30.00 \text{ vs. } <20.00}$ 0.88, 95% CI 0.81–0.95; p$_{\text{trend}}$=0.0003) and older age at menarche (HR$_{\text{age 15 years or later vs. ages 11–12 years}}$ 0.91, 95% CI 0.87–0.95; p$_{\text{trend}}$=0.0003). Compared to non-Hispanic whites, Hispanics were more likely to have an earlier age at natural menopause (HR$_{\text{Hispanic vs. white}}$ 1.17, 95% CI 1.09–1.26). Compared to never smokers, former-light smoking and former-heavy smoking was associated with older age at natural menopause (HR$_{\text{Former-light vs. never}}$ 0.96, 95% CI 0.92–0.99; HR$_{\text{Former-heavy vs. never}}$ 0.93, 95% CI 0.90–0.96), while current-light or current-heavy smoking was associated with earlier age at natural menopause (HR$_{\text{Current-light vs. never}}$ 1.68, 95% CI 1.60–1.75; HR$_{\text{Current-heavy vs. never}}$ 1.38, 95% CI 1.33–1.44). Participants who had only one full-term pregnancy with age at delivery of 29 years or older had higher risk of earlier natural menopause than participants with first full-term pregnancy at younger ages (<29) and 2 or more full-term pregnancies during lifetime (HR $_{29, 1 \text{ full-term pregnancy vs. } <29, 2+ \text{ full-term pregnancy}}$ 1.18, 95% CI 1.13–1.24).

Stratification of the final multivariable model by baseline smoking status showed that physical activity was associated with age at natural menopause only among ever-heavy smokers (p$_{\text{trend}}$=0.02 for former-heavy smokers, p$_{\text{trend}}$=0.04 for current-heavy smokers; Table 3). Compared to the corresponding lowest quartile of physical activity, the HRs for the association between highest quartile of physical activity and age at natural menopause was 0.88 (95% CI 0.81–0.97) among former-heavy smokers, and 0.89 (95% CI 0.80–0.99) among current-heavy smokers. Stratification by smoking history also revealed differences in the associations between other factors and age at natural menopause: the association between Hispanic race/ethnicity and earlier age at natural menopause was apparent only among never smokers (HR 1.26, 95% CI 1.16–1.37) and former-light smokers (HR 1.25, 95% CI 1.00–1.57), compared to whites. We detected a marginally significant interaction between physical activity (continuous measure) and smoking status (never plus ever-light smoker vs. ever-heavy smoker) (P$_{\text{interaction}}$=0.06, data not shown). None of the other interactions between physical activity and risk of natural menopause was statistically significant (data not shown).

Discussion

As life expectancies increase, women will be living more years in the postmenopausal period, a period of modified risk for many later-life health outcomes, including postmenopausal breast cancer.[1, 2, 6, 7] Age at natural menopause, according to studies primarily performed in the developed world, has been shown to be roughly normally distributed, with an approximate mean of 51 years and an approximate range of 40–58 years.[33–37] Observational epidemiologic studies designed to identify lifestyle and reproductive factors responsible for the variation in ages at natural menopause have been inconsistent, with smoking[13–20] and parity[20–24] being perhaps the most consistently observed to be associated with age at natural menopause. Recent studies have also suggested that genetic factors affect age at natural menopause, although no genetic determinants have been confirmed.[10, 11]

Results presented here suggest that determinants of age at natural menopause may differ by smoking status. Among never smokers, former-light smokers and current-light smokers, physical activity was not associated with age at natural menopause. Conversely, among both groups of heavy smokers, former-heavy and current-heavy, increased long-term physical activity was associated with older age at natural menopause.

We hypothesized that increased physical activity would be associated with older age at natural menopause upon consideration of evidence of a dose response between increasing intensity/duration of physical activity and higher likelihood of irregular or anovulatory menstrual cycles, shortened luteal phases and secondary amenorrhea.[25–28] In light of the fact that a woman has a fixed follicle pool and therefore possibly a fixed number of ovulatory cycles, we hypothesized that increased physical activity might delay menopause by causing menstrual cycles during which follicles are not recruited into the pre-ovulatory candidate pool. This scenario could preserve follicles and/or ovulatory cycles, as might be supported by the oocyte attrition theory of the etiology of natural menopause.[38–40] Some evidence suggests that depletion of the follicle pool may continue regardless of ovulation status [for review see [41]]; even if physical activity prevents ovulation, physical activity may not concurrently delay follicle pool depletion. Our results elucidate a more complex association between physical activity and age at natural menopause, in which physical activity may counteract the effects of smoking on age at natural menopause among smokers, but have little or no effect on age at natural menopause in the absence of smoking.

Smokers were shown to experience menopause earlier than non-smokers as early as 1949,[13] an association which has been confirmed.[14–20] Prior studies demonstrated that smoking is associated with fewer retrieved oocytes,[42] longer time to conception[43] and lower luteal-phase estrogen levels.[44] Although smoking has a clear, deleterious effect on reproductive outcomes the mechanism by which smoking advances age at natural menopause is not understood, but appears to be multifaceted. Mice exposed to benzo(a)pyrene have an increased rate of follicular depletion.[45] Nicotine and cotinine appear to impair meiotic spindle function and down-regulate aromatase activity in granulosa cells.[42, 46, 47] Cigarette smoke extract may induce oxidative stress and apoptosis.[48] Oxidative stress has been shown in turn to trigger and modulate apoptosis[49] and many apoptosis inhibitors appear to have antioxidant properties (for review see [50]). Apoptosis is a likely process by which follicles are removed from the viable pool both during gestation and upon commencement of normal reproductive cycling.[51]

The oxidative stress pathway is a likely avenue by which physical activity and smoking interact to affect age at natural menopause. Prior studies suggest that increased physical activity positively impacts antioxidant defense,[52] and extends the lifespan.[53, 54] Physical activity appears to induce mitochondrial metabolism and reactive oxygen species formation; supplementation with reactive oxygen species-reducing antioxidants appears to inhibit the health-promoting effects of physical activity (for review see [55]). Recent research shows that age-related declines in oxidative capacity can be largely ameliorated by regular endurance exercise.[56]

To our knowledge, no study has addressed possible effect modification by smoking of the association between physical activity and age at natural menopause. Three prior observational studies have investigated the possible association between physical activity and age at natural menopause; one reported results consistent with ours.[29] Two other studies found no association between physical activity and age at natural menopause.[24, 30] The study by Bromberger et al.[24] included few extreme exercisers and the study by Nilsson et al.[30] included only 349 women in the final analysis. Insufficient variation in intensity and/or duration of smoking, or the lack of consideration of smoking status in those analyses may account for mixed results.

The CTS is an excellent resource for examining the relationship between physical activity and timing of natural menopause. The CTS collected extensive exposure information, including physical activity during reproductive years. This, in combination with the cohort size, and large proportion of never smokers, allows a variety of factors to be examined and,

when appropriate, included in statistical models as covariates. Further, although a large proportion of CTS participants are non-Hispanic white, we had sufficient numbers of Hispanics to clarify the association between Hispanic ethnicity and earlier age at natural menopause reported previously;[12] upon stratification by smoking this association was apparent among never smokers and ever-light smokers, not among ever-heavy smokers. Future work in a Hispanic population with a larger proportion of smokers is needed to confirm this finding.

Potential limitations include possible misclassification of menopausal status. The 1995–1996 CTS questionnaire defined menopause as no menstrual period for 6 months, however more recently the standard criterion has become 12 consecutive months of amenorrhea. Another limitation arises from the categorical nature of the variable for age at menopause, which precluded generating hazard ratios per single-year increments in age at natural menopause. Alternative methods for coding ages at outcomes/censoring ages, including setting the event/censoring age first to the lower boundary, and second, to the upper boundary of the age at menopause category, produced results similar to those shown. Although the CTS is a prospective cohort, this analysis used information reported at baseline, which imposed a particular limitation on the current analysis due to the possible introduction of errors in recall. However the categorical nature of the data is expected to minimize errors in recall[57, 58]. Although it might be argued that women with a surgical menopause would be likely to remember the type (natural vs. surgical menopause) and timing of their menopause more accurately than women with non-surgical menopausal transitions, particularly those with longer transitions, any misclassification of exposures might be expected to be non-differential with respect to menopausal status, type and timing. The exclusion of participants 80 years or older at baseline was made to address the concern that recall of key exposures and event/censoring ages would become more inaccurate with increasing age. The small number of Japanese participants precluded assessment of the effect seen in the Multiethnic Cohort Study in which Japanese race/ethnicity, vs. white race/ethnicity, was associated with later age at natural menopause.[12] Finally, it is possible that women who participate in more physical activity during their lives, have generally healthier lifestyles overall. Future analyses are required to further address such concerns.

Conclusions

This work supports consideration of age at natural menopause as a complex trait and highlights the importance of smoking to future studies. In an increasingly non-smoking, developed world, it is probable that the set of factors determining timing of natural menopause will change.

Acknowledgments

References

1. Trichopoulos D, MacMahon B, Cole P. Menopause and breast cancer risk. J Natl Cancer Inst. 1972; 48(3):605–13. [PubMed: 5058966]

2. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. Nature. 1983; 303(5920):767–70. [PubMed: 6866078]

3. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev. 1993; 15(1):36–47. [PubMed: 8405211]

4. Burger HG. The endocrinology of the menopause. Maturitas. 1996; 23(2):129–36. [PubMed: 8735351]

5. Burger HG, Dudley EC, Hopper JL, et al. Prospectively measured levels of serum follicle-stimulating hormone, estradiol, and the dimeric inhibins during the menopausal transition in a population-based cohort of women. J Clin Endocrinol Metab. 1999; 84(11):4025–30. [PubMed: 10566644]

6. Bernstein L. Epidemiology of endocrine-related risk factors for breast cancer. J Mammary Gland Biol Neoplasia. 2002; 7(1):3–15. [PubMed: 12160084]

7. Hankinson SE, Colditz GA, Willett WC. Towards an integrated model for breast cancer etiology: the lifelong interplay of genes, lifestyle, and hormones. Breast Cancer Res. 2004; 6(5):213–8. [PubMed: 15318928]

8. Snowdon DA, Kane RL, Beeson WL, et al. Is early natural menopause a biologic marker of health and aging? Am J Public Health. 1989; 79(6):709–14. [PubMed: 2729468]

9. Kritz-Silverstein D, Barrett-Connor E. Early menopause, number of reproductive years, and bone mineral density in postmenopausal women. Am J Public Health. 1993; 83(7):983–8. [PubMed: 8328621]

10. van Noord PA, Dubas JS, Dorland M, Boersma H, te Velde E. Age at natural menopause in a population-based screening cohort: the role of menarche, fecundity, and lifestyle factors. Fertil Steril. 1997; 68(1):95–102. [PubMed: 9207591]

11. de Bruin JP, Bovenhuis H, van Noord PA, et al. The role of genetic factors in age at natural menopause. Hum Reprod. 2001; 16(9):2014–8. [PubMed: 11527915]

12. Henderson KD, Bernstein L, Henderson B, Kolonel L, Pike MC. Predictors of the timing of natural menopause in the Multiethnic Cohort Study. Am J Epidemiol. 2008; 167(11):1287–94. [PubMed: 18359953]

13. Bernhard P. Certain injurious effects of cigarette smoking on women. Mediziniche Monatsschrift. 1949; 3:58–60.

14. Bailey A, Robinson D, Vessey M. Smoking and age of natural menopause. Lancet. 1977; 2(8040): 722. [PubMed: 71536]

15. Jick H, Porter J, Morrison AS. Relation between smoking and age of natural menopause. Lancet. 1977; i:1354–1355. [PubMed: 69066]

16. Lindquist O, Bengtsson C. Menopausal age in relation to smoking. Acta Med Scand. 1979; 205(1–2):73–7. [PubMed: 760407]

17. Kaufman DW, Slone D, Rosenberg L, Miettinen OS, Shapiro S, Daniell HW. Cigarette smoking and age at natural menopause. Estrogen receptors, breast cancer, and smoking. Am J Public Health. 1980; 70(4):420–2. [PubMed: 7361965]

18. Andersen FS, Transbol I, Christiansen C. Is cigarette smoking a promotor of the menopause? Acta Med Scand. 1982; 212(3):137–9. [PubMed: 7148504]

19. Gold EB, Bromberger J, Crawford S, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol. 2001; 153(9):865–74. [PubMed: 11323317]

20. Celentano E, Galasso R, Berrino F, et al. Correlates of age at natural menopause in the cohorts of EPIC-Italy. Tumori. 2003; 89(6):608–14. [PubMed: 14870825]

21. MacMahon B, Worcester J. Age at menopause. United States--1960–1962. Vital Health Stat 1. 1966; 11(19):1–20.

22. Willett W, Stampfer MJ, Bain C, et al. Cigarette smoking, relative weight, and menopause. Am J Epidemiol. 1983; 117(6):651–8. [PubMed: 6859020]

23. Whelan EA, Sandler DP, McConnaughey DR, Weinberg CR. Menstrual and reproductive characteristics and age at natural menopause. Am J Epidemiol. 1990; 131(4):625–32. [PubMed: 2316494]

24. Bromberger JT, Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prospective study of the determinants of age at menopause. Am J Epidemiol. 1997; 145(2):124–33. [PubMed: 9006309]

25. Warren MP. The effects of exercise on pubertal progression and reproductive function in girls. J Clin Endocrinol Metab. 1980; 51(5):1150–7. [PubMed: 6775000]

26. Frisch RE, Gotz-Welbergen AV, McArthur JW, et al. Delayed menarche and amenorrhea of college athletes in relation to age of onset of training. JAMA. 1981; 246(14):1559–63. [PubMed: 7277629]

27. Bernstein L, Ross RK, Lobo RA, Hanisch R, Krailo MD, Henderson BE. The effects of moderate physical activity on menstrual cycle patterns in adolescence: implications for breast cancer prevention. Br J Cancer. 1987; 55(6):681–5. [PubMed: 3620313]

28. De Cree C. Sex steroid metabolism and menstrual irregularities in the exercising female. A review. Sports Med. 1998; 25(6):369–406. [PubMed: 9680659]

29. Dratva J, Gomez Real F, Schindler C, et al. Is age at menopause increasing across Europe? Results on age at menopause and determinants from two population-based studies. Menopause. 2009; 16(2):385–94. [PubMed: 19034049]

30. Nilsson P, Moller L, Koster A, Hollnagel H. Social and biological predictors of early menopause: a model for premature aging. J Intern Med. 1997; 242(4):299–305. [PubMed: 9366808]

31. Bernstein L, Allen M, Anton-Culver H, et al. High breast cancer incidence rates among California teachers: results from the California Teachers Study (United States). Cancer Causes Control. 2002; 13(7):625–35. [PubMed: 12296510]

32. Krailo MD, Pike MC. Estimation of the distribution of age at natural menopause from prevalence data. Am J Epidemiol. 1983; 117(3):356–61. [PubMed: 6829563]

33. Treloar AE. Menstrual cyclicity and the pre-menopause. Maturitas. 1981; 3(3–4):249–64. [PubMed: 7334935]

34. Spira A. The decline of fecundity with age. Maturitas. 1988; (Suppl 1):15–22. [PubMed: 3237107]

35. Wood JW. Fecundity and natural fertility in humans. Oxf Rev Reprod Biol. 1989; 11:61–109. [PubMed: 2697833]

36. Morabia A, Costanza M. International variability in ages at menarche, first livebirth, and menopause. Am J Epi. 1998; 148(12):1195–1205.

37. The North American Menopause Society. Menopause Core Curriculum Study Guide. The North American Menopause Society; 2002.

38. Faddy MJ. Follicle dynamics during ovarian ageing. Mol Cell Endocrinol. 2000; 163:43–48. [PubMed: 10963872]

39. Faddy MJ, Gosden RG. A model conforming the decline in follicle numbers to the age of menopause in women. Hum Reprod. 1996; 11(7):1484–6. [PubMed: 8671489]

40. Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod. 1992; 7(10):1342–6. [PubMed: 1291557]

41. te Velde ER, Pearson PL. The variability of female reproductive ageing. Hum Reprod Update. 2002; 8(2):141–54. [PubMed: 12099629]

42. Zenzes MT. Smoking and reproduction: gene damage to human gametes and embryos. Hum Reprod Update. 2000; 6(2):122–31. [PubMed: 10782570]

43. Curtis KM, Savitz DA, Arbuckle TE. Effects of cigarette smoking, caffeine consumption, and alcohol intake on fecundability. Am J Epidemiol. 1997; 146(1):32–41. [PubMed: 9215221]

44. MacMahon B, Trichopoulos D, Cole P, Brown J. Cigarette smoking and urinary estrogens. N Engl J Med. 1982; 307(17):1062–5. [PubMed: 7121516]

45. Shiromizu K, Mattison DR. The effect of intraovarian injection of benzo(a)pyrene on primordial oocyte number and ovarian aryl hydrocarbon [benzo(a)pyrene] hydroxylase activity. Toxicol Appl Pharmacol. 1984; 76(1):18–25. [PubMed: 6484988]

46. Barbieri RL, Gochberg J, Ryan KJ. Nicotine, cotinine, and anabasine inhibit aromatase in human trophoblast in vitro. J Clin Invest. 1986; 77(6):1727–33. [PubMed: 3711333]

47. Barbieri RL, McShane PM, Ryan KJ, Barbieri O. Constituents of cigarette smoke inhibit human granulosa cell aromatase. Embryotoxicity of benzo(a)pyrene and some of its synthetic derivatives in Swiss mice. Fertil Steril. 1986; 46(2):232–6. [PubMed: 3732529]

48. Carnevali S, Petruzzelli S, Longoni B, et al. Cigarette smoke extract induces oxidative stress and apoptosis in human lung fibroblasts. American Journal of Physiology - Lung Cellular & Molecular Physiology. 2003; 284(6):L955–63. [PubMed: 12547733]

49. Chandra J, Samali A, Orrenius S. Triggering and modulation of apoptosis by oxidative stress. Free Radic Biol Med. 2000; 29(3–4):323–333. [PubMed: 11035261]

50. Buttke TM, Sandstrom PA. Oxidative stress as a mediator of apoptosis. Immunol Today. 1994; 15(1):7–10. [PubMed: 8136014]

51. Depalo R, Nappi L, Loverro G, et al. Evidence of apoptosis in human primordial and primary follicles. Hum Reprod. 2003; 18(12):2678–2682. [PubMed: 14645191]

52. Covas MI, Elosua R, Fito M, Alcantara M, Coca L, Marrugat J. Relationship between physical activity and oxidative stress biomarkers in women. Med Sci Sports Exerc. 2002; 34(5):814–9. [PubMed: 11984300]

53. Paffenbarger RS, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality and longevity of college alumni. N Engl J Med. 1986; 314:605–613. [PubMed: 3945246]

54. Warburton D, Nicol C, Bredin S. Health benefits of physical activity: the evidence. Can Med Ass J. 2006; 174:801–809. [PubMed: 16534088]

55. Ristow M, Zarse K. How increased oxidative stress promotes longevity and metabolic health: The concept of mitochondrial hormesis (mitohormesis). Exp Gerontol. 45(6):410–8. [PubMed: 20350594]

56. Lanza IR, Short DK, Short KR, et al. Endurance exercise as a countermeasure for aging. Diabetes. 2008; 57(11):2933–42. [PubMed: 18716044]

57. Rodstrom K, Bengtsson C, Lissner L, Bjorkelund C. Reproducibility of self-reported menopause age at the 24-year follow-up of a population study of women in Goteborg, Sweden. Menopause. 2005; 12(3):275–80. [PubMed: 15879916]

58. Bosetti C, Tavani A, Negri E, Trichopoulos D, La Vecchia C. Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. J Clin Epidemiol. 2001; 54(9):902–6. [PubMed: 11520649]

Table 1

Distribution of baseline characteristics by long-term combined strenuous and moderate recreational physical activity among 97,945 participants in the California Teachers Study, established 1995–1996[a]

	N (%)[b]	Long-term Combined Strenuous and Moderate Recreational Physical Activity (hours/week/year)			
		Quartile 1 < 1.61 54.5 (12.8)	Quartile 2 1.61–3.449 50.2 (12.6)	Quartile 3 3.45–6.239 48.3 (12.7)	Quartile 4 6.24 47.6 (13.2)
		%[c]	%[c]	%[c]	%[c]
Mean age in years (SD)	50.2 (13.1)				
Menopausal status					
Premenopausal	48,082 (49.1)	19.0	25.6	27.8	27.6
Perimenopausal	2,388 (2.4)	26.2	27.4	24.5	21.9
Postmenopausal, natural menopause	31,607 (32.3)	32.0	25.2	22.3	20.6
Postmenopausal, surgical menopause	9,577 (9.8)	30.6	24.8	22.2	22.4
Postmenopausal, other reason	1,789 (1.8)	30.4	24.5	22.8	22.4
Postmenopausal, due to HT initiation[d]	4,502 (4.6)	26.0	28.3	25.0	20.7
Age at menopause among postmenopausal participants, by type of menopause					
Age at natural menopause (in years)					
<35	99 (0.3)	32.9	19.7	21.6	25.8
35–39	507 (1.6)	29.5	23.6	22.9	24.0
40–43	1,767 (5.6)	30.4	24.1	22.2	23.3
44–46	3,440 (10.9)	32.0	24.2	23.4	20.4
47–49	6,422 (20.3)	32.1	25.8	22.5	19.6
50–52	10,301 (32.6)	32.3	26.0	21.7	20.0
53–55	6,825 (21.6)	31.9	24.8	22.4	20.9
56+	2,246 (7.1)	32.6	23.1	21.9	22.4
Age at surgical menopause (in years)					
<35	731 (7.6)	26.7	22.3	22.7	28.3
35–39	1,161 (12.1)	29.6	22.7	23.3	24.4
40–43	1,692 (17.7)	29.0	25.1	23.3	22.6
44–46	1,967 (20.5)	30.3	26.3	21.2	22.2
47–49	1,771 (18.5)	31.9	25.5	22.3	20.3
50–52	1,267 (13.2)	32.7	23.1	22.9	21.3

		Long-term Combined Strenuous and Moderate Recreational Physical Activity (hours/week/year)			
		Quartile 1 < 1.61	Quartile 2 1.61–3.449	Quartile 3 3.45–6.239	Quartile 4 6.24
53–55	665 (6.9)	34.2	27.1	19.8	18.9
56+	323 (3.4)	36.9	26.0	17.8	19.3
Age at menopause, other reasons (in years)					
<35	145 (8.1)	31.5	13.9	27.4	27.2
35–39	114 (6.4)	20.7	15.8	30.3	33.2
40–43	142 (7.9)	34.0	22.0	20.6	23.4
44–46	186 (10.4)	29.5	23.5	22.7	24.3
47–49	239 (13.4)	27.4	28.4	24.0	20.2
50–52	268 (15.0)	27.0	29.1	20.3	23.6
53–55	214 (12.0)	36.9	27.2	21.7	14.2
56+	481 (26.9)	33.7	24.9	21.2	20.2
Race/ethnicity					
Non-Hispanic White	84,413 (86.2)	23.5	25.9	25.8	24.8
African American	2,473 (2.5)	34.6	22.3	22.6	20.5
Hispanic	4,565 (4.7)	26.4	24.5	25.0	24.1
Asian	3,774 (3.9)	37.0	24.5	20.8	17.7
Other[e]	2,720 (2.8)	22.3	22.8	23.6	31.3
Smoking status[f]					
Never	67,986 (69.4)	24.5	25.3	25.6	24.7
Former-light smoker	10,122 (10.3)	22.0	26.3	26.9	24.8
Former-heavy smoker	10,110 (10.3)	23.9	27.7	25.6	22.8
Current-light smoker	4,458 (4.6)	25.3	24.6	23.3	26.8
Current-heavy smoker	4,288 (4.4)	30.0	24.7	21.8	23.5
BMI at age 18 years (kg/m^2)					
<20.00	31,528 (33.5)	24.7	25.3	25.1	25.0
20.00–24.99	52,435 (55.8)	23.0	25.6	26.4	25.1
25.00–29.99	7,391 (7.9)	27.5	26.8	24.0	21.7
30.00	2,664 (2.8)	31.4	28.2	21.3	19.1
Age at menarche (in years)					
10	6,827 (7.0)	27.5	24.4	25.0	23.1

		Long-term Combined Strenuous and Moderate Recreational Physical Activity (hours/week/year)			
		Quartile 1 < 1.61	Quartile 2 1.61–3.449	Quartile 3 3.45–6.239	Quartile 4 6.24
11–12	41,667 (42.8)	24.8	26.3	25.6	23.4
13–14	41,154 (42.2)	23.9	25.5	25.6	25.1
15	7,784 (8.0)	22.7	23.6	24.8	28.9
Age at first full-term pregnancy (in years) and parity					
<29, 2+ full-term pregnancies	40,589 (41.4)	27.2	26.8	24.7	21.4
<29, 1 full-term pregnancy	6,876 (7.0)	24.7	25.2	25.3	24.8
29, 2+ full-term pregnancies	13,487 (13.8)	23.6	26.8	26.7	22.9
29, 1 full-term pregnancy	8,702 (8.9)	22.7	25.3	26.4	25.6
Ever pregnant, no full-term pregnancy	6,331 (6.5)	18.3	22.8	27.6	31.3
Never pregnant	20,994 (21.4)	22.1	23.5	25.1	29.3

[a] Participants with unknown values are not shown in table. These include 474 with missing smoking status, 507 ever smokers with unknown total pack-years, 3,927 with missing BMI at age 18 years, 513 with missing age at menarche, 966 with missing or unknown number of full-term pregnancies or age at first full term pregnancy.

[b] Number of participants and crude column percent.

[c] Age-adjusted row percent.

[d] Participants classified as postmenopausal due to initiation of HT to treat menopausal symptoms before periods stopped.

[e] Other race/ethnicity includes Native American participants, and participants of mixed, other or undeclared racial/ethnic status.

[f] Never smokers include 2,277 participants who started smoking at or after the age at menopause. Former or current smokers were dichotomized as light or heavy smokers based on median total pack-years (4.375 for former smokers, 18 for current smokers).

Table 2

Age-stratified multivariable adjusted hazards ratios[a] (HRs) and 95% confidence intervals (CIs) for the associations between physical activity and relative timing of natural menopause among 97,945 participants in the California Teachers Study, established 1995–1996

	Person-Years	No. with Natural Menopause	HR[a,b]	95% CI	p-trend[c]
Long-term combined physical activity (hours/week/year)					
Quartile 1 (< 1.61)	1,137,311	10,590	1.00	Reference	
Quartile 2 (1.61–3.449)	1,090,225	7,769	0.97	0.94–1.00	
Quartile 3 (3.45–6.239)	1,072,019	6,764	0.96	0.93–0.99	
Quartile 4 (6.24)	1,054,036	6,484	0.95	0.92–0.98	0.005
Race/ethnicity					
Non-Hispanic White	3,776,357	28,259	1.00	Reference	
African American	110,685	861	0.97	0.91–1.04	
Hispanic	184,695	747	1.17	1.09–1.26	
Asian	164,311	989	1.00	0.94–1.06	
Other[d]	117,543	751	0.98	0.91–1.06	
Smoking status[e]					
Never	2,965,083	18,852	1.00	Reference	
Former-light smoker	458,157	3,209	0.96	0.92–0.99	
Former-heavy smoker	479,293	4,138	0.93	0.90–0.96	
Current-light smoker	200,089	2,136	1.68	1.60–1.75	
Current-heavy smoker	205,379	2,847	1.38	1.33–1.44	
BMI at age 18 years (kg/m^2)					
<20.00	1,397,576	9,920	1.00	Reference	
20.00–24.99	2,332,413	16,901	0.97	0.95–1.00	
25.00–29.99	324,549	2,161	0.95	0.91–1.00	
30.00	116,707	702	0.88	0.81–0.95	0.0003
Age at menarche (in years)					
10	303,067	2,068	1.01	0.96–1.06	
11–12	1,847,919	13,194	1.00	Reference	
13–14	1,834,750	13,662	0.99	0.97–1.01	
15	345,748	2,594	0.91	0.87–0.95	0.0003

	Person-Years	No. with Natural Menopause	HR[a,b]	95% CI	p-trend[c]
Age at first full-term pregnancy (in years) and parity					
<29, 2+ full-term pregnancies	1,889,929	16,628	1.00	Reference	
<29, 1 full-term pregnancy	300,427	2,068	1.09	1.04–1.14	
29, 2+ full-term pregnancies	606,456	3,885	1.10	1.06–1.14	
29, 1 full-term pregnancy	373,387	2,039	1.18	1.13–1.24	
Ever pregnant, no full-term pregnancy	262,255	1,157	1.21	1.14–1.28	
Never pregnant	880,014	5,594	1.26	1.22–1.30	

[a] Hazard ratios are adjusted for all factors shown in table and stratified by age in years at cohort entry.

[b] A hazard ratio less than 1.00 indicates that among members of each age group, the 'risk' of experiencing a natural menopause was lower in the exposed vs. referent group (e.g. natural menopause occurred later in the exposed vs. referent group.) Conversely, a hazard ratio greater than 1.00 indicates that among member of each age group, the 'risk' of experiencing a natural menopause was higher in the exposed vs. referent group (e.g. natural menopause occurred earlier in the exposed vs. referent group.)

[c] Multivariable p values for trend were calculated using the continuous variables for physical activity, BMI at age 18; and were calculated using the midpoints of the categories shown above for age at menarche. Participants with missing or unknown data for a variable were considered as a separate category in models producing hazard ratios (the results for which are not shown) and deleted from the appropriate model when assessing the p for trend for that variable.

[d] Other race/ethnicity includes Native American participants, and participants of mixed, other or undeclared racial/ethnic status.

[e] Never smokers include 2,277 participants who started smoking at or after the age at menopause. Former or current smokers were dichotomized as light or heavy smokers based on median total pack-years (4.375 for former smokers, 18 for current smokers).

Table 3

Age-stratified multivariable adjusted hazard ratios[a] (HRs) and 95% confidence intervals (CIs) for the association between physical activity and relative timing of natural menopause among 97,945 participants in the California Teachers Study, established 1995–1996, by smoking status[b]

	Never smokers			Former-light smokers			Former-heavy smokers			Current-light smokers			Current-heavy smokers		
	No. with Natural Menopause	HR[a,c]	95% CI	No. with Natural Menopause	HR[a,c]	95% CI	No. with Natural Menopause	HR[a,c]	95% CI	No. with Natural Menopause	HR[a,c]	95% CI	No. with Natural Menopause	HR[a,c]	95% CI
Long-term combined physical activity (hours/week/year)															
Quartile 1 (<1.61)	6,680	1.00	Reference	954	1.00	Reference	1,184	1.00	Reference	658	1.00	Reference	962	1.00	Reference
Quartile 2 (1.61–3.449)	4,565	0.96	0.93–1.00	814	0.98	0.89–1.08	1,099	0.92	0.84–1.00	533	0.98	0.87–1.11	652	0.97	0.88–1.07
Quartile 3 (3.45–6.239)	3,910	0.96	0.92–1.00	763	1.00	0.91–1.11	973	0.99	0.91–1.08	457	0.93	0.82–1.05	583	0.91	0.82–1.01
Quartile 4 (6.24)	3,697	0.98	0.94–1.02	678	0.93	0.84–1.03	882	0.88	0.81–0.97	488	0.96	0.85–1.09	650	0.89	0.80–0.99
P-trend[d]			0.26			0.28			0.02			0.58			0.04
Race/ethnicity															
Non-Hispanic White	16,592	1.00	Reference	2,878	1.00	Reference	3,878	1.00	Reference	1,892	1.00	Reference	2,661	1.00	Reference
African American	505	1.00	0.92–1.10	88	1.00	0.80–1.24	87	0.95	0.77–1.18	99	0.86	0.69–1.07	62	0.79	0.61–1.03
Hispanic	545	1.26	1.16–1.37	81	1.25	1.00–1.57	42	0.81	0.60–1.11	50	0.94	0.70–1.25	17	0.81	0.50–1.32
Asian	750	1.08	1.00–1.16	84	0.82	0.65–1.02	61	0.79	0.62–1.03	42	0.73	0.54–1.00	35	0.86	0.61–1.22
Other[e]	460	0.99	0.90–1.09	78	1.24	0.99–1.56	70	0.92	0.72–1.17	53	0.78	0.59–1.03	72	1.08	0.85–1.37
BMI at age 18 years (kg/m²)															
<20.00	6,161	1.00	Reference	1,024	1.00	Reference	1,200	1.00	Reference	644	1.00	Reference	776	1.00	Reference
20.00–24.99	9,884	0.96	0.93–0.99	1,736	0.99	0.91–1.07	2,322	0.92	0.86–0.99	1,168	1.02	0.92–1.12	1,582	1.00	0.91–1.09
25.00–29.99	1,213	0.94	0.88–1.00	203	0.97	0.83–1.13	317	0.89	0.78–1.00	138	1.04	0.86–1.26	256	1.01	0.87–1.17
30.00	387	0.82	0.74–0.91	84	1.00	0.80–1.26	113	0.78	0.64–0.96	30	0.96	0.65–1.40	80	1.18	0.93–1.50
P-trend[d]			0.0001			0.30			0.01			0.72			0.12
Age at menarche (in years)															
10	1,223	1.02	0.96–1.09	201	0.90	0.78–1.05	289	1.03	0.91–1.17	134	1.15	0.96–1.39	199	0.92	0.79–1.08
11–12	7,865	1.00	Reference	1,336	1.00	Reference	1,737	1.00	Reference	904	1.00	Reference	1,187	1.00	Reference
13–14	8,184	1.01	0.97–1.04	1,402	0.95	0.88–1.03	1,779	0.95	0.89–1.02	899	1.01	0.92–1.11	1,203	0.98	0.91–1.07
15	1,522	0.89	0.84–0.94	263	0.85	0.74–0.97	327	0.89	0.79–1.00	192	1.11	0.95–1.31	251	0.95	0.82–1.09
P-trend[d]			0.005			0.14			0.02			0.91			0.88

Age at first full-term pregnancy (in years) and parity

	Never smokers			Former-light smokers			Former-heavy smokers			Current-light smokers			Current-heavy smokers		
	No. with Natural Menopause	HR[a,c]	95% CI	No. with Natural Menopause	HR[a,c]	95% CI	No. with Natural Menopause	HR[a,c]	95% CI	No. with Natural Menopause	HR[a,c]	95% CI	No. with Natural Menopause	HR[a,c]	95% CI
<29, 2+ full-term pregnancies	10,116	1.00	Reference	1,715	1.00	Reference	2,094	1.00	Reference	1,095	1.00	Reference	1,416	1.00	Reference
<29, 1 full-term pregnancy	1,141	1.08	1.02–1.15	197	1.09	0.94–1.27	263	1.17	1.02–1.33	186	1.09	0.93–1.29	246	1.06	0.92–1.22
29, 2+ full-term pregnancies	2,377	1.08	1.03–1.13	482	1.12	1.01–1.25	482	1.15	1.03–1.27	213	1.10	0.95–1.29	272	1.09	0.96–1.25
29, 1 full-term pregnancy	1,192	1.19	1.12–1.27	220	1.08	0.94–1.25	296	1.15	1.01–1.30	136	1.55	1.28–1.86	166	1.03	0.87–1.21
Ever pregnant, no full-term pregnancy	600	1.26	1.16–1.37	112	1.26	1.03–1.53	209	1.26	1.09–1.46	102	1.01	0.81–1.24	115	1.03	0.85–1.25
Never pregnant	3,272	1.28	1.23–1.33	463	1.36	1.22–1.51	777	1.28	1.18–1.40	380	1.19	1.05–1.34	614	1.08	0.98–1.19

[a] Hazard ratios are adjusted for all factors shown in table and stratified by age in years at cohort entry.

[b] Never smokers include 2,277 participants who started smoking at or after the age at menopause. Former or current smokers were dichotomized as light or heavy smokers based on median total pack-years (4.375 for former smokers, 18 for current smokers).

[c] A hazard ratio less than 1.00 indicates that among members of each age group, the 'risk' of experiencing a natural menopause was lower in the exposed vs. referent group (e.g. natural menopause occurred later in the exposed vs. referent group.) Conversely, a hazard ratio greater than 1.00 indicates that among member of each age group, the 'risk' of experiencing a natural menopause was higher in the exposed vs. referent group (e.g. natural menopause occurred earlier in the exposed vs. referent group.)

[d] Multivariable p values for trend were calculated using the continuous variables for physical activity, BMI at age 18, and were calculated using the midpoints of the categories shown above for age at menarche. Participants with missing or unknown data for a variable were considered as a separate category in models producing hazard ratios (the results for which are not shown) and deleted from the appropriate model when assessing the p for trend for that variable.

[e] Other race/ethnicity includes Native American participants, and participants of mixed, other or undeclared racial/ethnic status.