International Journal of Obesity (2002) 26, 961–968
 0307–0565/02 $25.00
www.nature.com/ijo

PAPER

The effects of body mass index on age at menopause

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OBJECTIVE: We examined which of body mass index (BMI, kg/m^2), serum cholesterol (mg/dl), or systolic blood pressure (SBP, mm Hg) affected age at natural menopause.
DESIGN: A population-based follow-up program.
METHODS: We determined the age at natural menopause in 1136 women followed biennially since their first examination in 1958–1959 through the 16th examination in 1988–1989. Four-hundred and ninety-three naturally menopausal women were classified into three groups by BMI, serum cholesterol and SBP measurement levels at age 40 or 41 y: the upper 25%, middle 50%, and lower 25%. We then studied whether there was a difference in age at menopause among the three groups thus classified. The 1136 natural menopausal women were also classified as early ($n=454$; 45–49 y at menopause (48.3 ± 1.2 y)) or late ($n=682$; ≥ 50 y at menopause (52.3 ± 1.6 y)) menopausal and compared for premenopausal trends in BMI, serum cholesterol and SBP in the early and late menopausal women by means of a longitudinal data analysis model.
RESULTS: When women were classified into the three groups based on a BMI that was measured at 40 or 41 y, age at menopause in the upper 25% (50.4 ± 2.8 y) was significantly higher ($P<0.05$) than that in the lower 25% (49.7 ± 2.8 y). The entire premenopausal trend in BMI in late menopausal women shifted upward compared to that in early menopausal women. On the other hand, the premenopausal trend more than 4 y before menopause in serum cholesterol and the entire premenopausal trend in SBP in late menopausal women were identical to those in early menopausal women.
CONCLUSION: Among the variables studied, only BMI is related to age at menopause, and the greater the BMI, the later the age at menopause.
International Journal of Obesity (2002) **26,** 961–968. doi:10.1038/sj.ijo.0802039

Keywords: menopause; body mass index; systolic blood pressure; cholesterol

Introduction

Body weight,[1–6] reproductive factors[7–9] and life style factors[7,10–14] are considered to affect age at natural menopause. Many studies which examine the relationship between body weight and the age at menopause, however, are of a cross-sectional nature.[1,2,5,6] Therefore, caution is necessary when drawing any conclusion concerning cause–effect relationships and a prospective study is needed to elucidate the cause–effect relationships between body weight and age at menopause.

One longitudinal study reports that women who are obese at the age of 18 y experience later menopause than their counterparts,[3] and another 2 y follow-up study of premenopausal women also shows that obese women experience later menopause.[4] However, problems exist in these studies because one measures body weight at an age too distant (approximately 30 y) from menopause and the other too close (approximately 2 y) to menopause. So the causal relationship between body weight and age at menopause has yet to be fully elucidated.

To confirm that body mass index (BMI) but not serum cholesterol and systolic blood pressure (SBP) is related to age at menopause and to clarify that there is a causal relation between BMI and the age at menopause, we addressed the following two questions using the data of women followed longitudinally from the premenopausal period which was not too distant from menopause and not too close to menopause through the postmenopausal period. (1) Of BMI, serum

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Received 1 August 2001; revised 31 January 2002; accepted 13 March 2002

cholesterol and SBP measured at age 40 or 41, is only BMI related to age at menopause? (2) Of the trends in BMI, serum cholesterol and SBP during the premenopausal period (from the age of 39 through the age at menopause), does only BMI in women who experience later menopause shift upward throughout the premenopausal period when compared to that in women who experience earlier menopause?

Subjects and methods

General procedure

Four-thousand one-hundred and ninety women in Nagasaki have received biennial examinations since 1958 as a part of the follow-up program of the Radiation Effects Research Foundation (formerly the Atomic Bomb Casualty Commission). A detailed description of this program has been published elsewhere.[15] The data from 1958–1959 (first examination) through 1988–1989 (16th examination) were analyzed in the present study. At each examination, sitting blood pressure (mm Hg) was measured at the left arm by standard mercury sphygmomanometer after at least 5 min of rest; standing height (in meters) without socks, and body weight (in kilograms) without outer clothing, were measured, and serum cholesterol (mg/dl) was measured in all women. The first Korotkoff phase was used for SBP. BMI (kg/m^2) was calculated as body weight divided by the square of standing height. Serum cholesterol was measured by the following methods during the study period: Liebermann–Burchard reaction method (1958–1972), Zurkowski method (1973–1980), enzymatic analysis method (1981–1987), and automatic analysis by Hitachi-7050 (1988–1989) with quality control monitored by Nagasaki Medical Association.

Calculation of age at menopause

The last menstrual period, defined as the time of menopause when amenorrhea was observed for more than 12 months, excluding pregnancy, was recorded in all women at each examination. The age at menopause was calculated as the difference between the calendar date at menopause and the date of birth. If the date of the last menstrual period could not be remembered exactly, we took the stated age at the last menstrual period and calculated age at menopause as the stated age plus 0.5 y. Information was also collected on whether menopause occurred naturally or surgically.

Subject selection

Of the 4190 women, those excluded: (1) were over 53 y in 1958 (over 50 in 1955); (2) had experienced menopause by 1955; (3) had not experienced menopause as of 1989; or (4) were censored due to death, migration or refusal to participate in examinations. To ensure accuracy of the data on the last menstrual period, we also excluded women examined more than 4 y after the last reported menstrual period (menopause). Of the remaining 1501 women, the 1288 women who had experienced natural menopause were further analyzed.

As shown in the analysis section, we used the serum cholesterol measured at age 40 or 41 for analysis. Because serum cholesterol starts to increase approximately 3–4 y before natural menopause,[16] to avoid the effects of natural menopause on serum cholesterol, the women with natural menopause at age 44 or before were also excluded. The remaining 1136 women who had experienced natural menopause at age 45 y or later were then subjected to the following analyses.

Analysis

(1) Of 1136 women, 493 women were examined at age 40 or 41 y because not all the women started undergoing health examinations at the age of 40 or 41 and not all of them were examined at each examination cycle. Based on their measurement levels of BMI, serum cholesterol and SBP, which were taken at age 40 or 41, they were divided into three groups: the upper 25%, the middle 50%, and the lower 25%. We studied whether there was a difference in age at menopause among the three groups thus classified. If women with a greater BMI experienced menopause at a later age, we should find a significant difference in age at menopause between the three groups classified by BMI. An analysis of covariance (the age at the time of bombing (age ATB) was incorporated to eliminate the cohort effect) was used to compare the age at menopause among three groups classified by BMI, serum cholesterol and SBP measured at age 40 or 41. Analyses were conducted using the Statistical Analysis System program package for personal computers.[17] A *P*-value of less than 0.05 was considered significant.

(2) The 1136 women were also classified as early or late menopausal. Those women ($n=454$) who experienced menopause between 45 and 49 y (mean age is 48.3 ± 1.2 y) were classified as early, and those classified as late menopausal ($n=682$) experienced menopause at 50 y or later (mean age is 52.3 ± 1.6 y). We applied a longitudinal data analysis model to clarify which of the premenopausal trends (BMI, serum cholesterol or SBP) in late menopausal women shifted compared to the trends in early menopausal women. If women with a greater BMI experienced menopause at a later age, the BMI trend in late menopausal women should shift upward compared to that in early menopausal women during the premenopausal period.

At first, in order to find the most suitable analysis model to express the trends in BMI, serum cholesterol and SBP, we simply plotted the means of BMI, serum cholesterol and SBP as functions of the mean age at each examination cycle in early and late menopausal women. BMI, serum cholesterol and SBP as well as age data in order of chronological examination cycles were rearranged with time of menopause as a new datum line and assigned new standardized examination cycles (SEC) as follows. Premenopausal examination

cycles were referred to as 'minus' cycles (the examination cycle just before menopause as SEC-1, two cycles before menopause as SEC-2, and so on) and postmenopausal examination cycles as 'plus' cycles (the examination cycle just after menopause as SEC + 1). BMI, serum cholesterol, SBP and age were averaged at each SEC in early and late menopausal women, respectively. Mean ages of early menopausal women were 39.3 ± 1.5 at SEC −5; 41.3 ± 1.5 at SEC −4; 43.3 ± 1.5 at SEC −3; 45.2 ± 1.5 at SEC −2; 47.1 ± 1.5 at SEC −1; and 49.2 ± 1.5 y at SEC +1. Mean ages of late menopausal women were 39.4 ± 1.8 at SEC −7; 41.4 ± 1.8 at SEC −6; 43.4 ± 1.8 at SEC −5; 45.3 ± 1.9 at SEC −4; 47.3 ± 1.8 at SEC −3; 49.3 ± 1.8 at SEC −2; 51.3 ± 1.8 at SEC −1; and 53.3 ± 1.8 y at SEC +1. To express the trends in BMI, serum cholesterol and SBP from premenopause to just after menopause as a function of age, the mean ± standard errors of BMI, serum cholesterol and SBP were plotted as functions of mean age from 39 through 49 y (from SEC −5 through SEC +1) in early menopausal women and from 39 through 53 y (from SEC −7 through SEC +1) in late menopausal women.

The means of BMI, serum cholesterol, and SBP as functions of mean age are shown in Figure 1. Because the premenopausal trends of BMI and SBP exhibited linear changes both in early and late menopausal women (Figure 1a and c), we used parametric models as shown below. On the other hand, the premenopausal trend in serum cholesterol was not linear, but exhibited a sharp increase approximately 3–4 y before menopause. Thus, in order to analyze the premenopausal trend in serum cholesterol, we added the variables of (*aame*4) and (*aame*4 · *mp*) to the parametric models used for BMI and SBP (See below). To eliminate the cohort effect, age ATB was incorporated in the analysis. In addition, because it has been reported that radiation dose is related to serum cholesterol[18] and hypertensive heart disease,[19] radiation dose — the total kerma (gamma plus neutron) based on the Dosimetry System 86 estimates[20] — was also incorporated in the analysis.

The data were analyzed with a longitudinal data analysis model; this model assumed that there was a correlation between measurements from the same individual, but that there was no correlation between the measurements obtained from different individuals.[21] For each individual, measurement was assumed to change in quadratic shape in age at the time of examination (*age ATE*). A linear random effect of *age ATE* was assumed. This random effect incorporates the correlation structure into the model, which reflects the correlations between measurements of an individual. Analyses were conducted using MLwiN.[22] We used the backward elimination method to select the best model from the full models, using the 10% significance points of chi-square test statistics as the criteria. A *P*-value of less than 0.05 was considered significant.

Parametric models and analyses of premenopausal trends in BMI and SBP. Let y_{ij} be the *i*th measurement of the BMI or SBP of the *j*th subject. The full model is

$$y_{ij} = \text{cons} + a + a^2 + b + a \cdot b + a^2 \cdot b + d + a \cdot d + a^2 \cdot d + mp + a \cdot mp + a^2 \cdot mp + n + a \cdot n + a^2 \cdot n + \varepsilon_{ij}$$

where *cons* = 1; $a = (ageATE - 45)/10$; b = age at the time of bombing ($ageATB/10$); d = kerma dose (Gy); $mp = 1$ if age at menopause ($ageATM$) ≥ 50, $mp = 0$ if $ageATM$ 45–49; and n = not in city or dose unknown subject indicator. Because we were interested in the premenopausal trends, the *ageATE*s used for analysis were younger than the age at menopause. The mean model was a quadratic model in *ageATE* which comprised constant, linear and quadratic effects of *ageATE*, *ageATB*-by-*ageATE* interactions, dose-by-*ageATE* interactions, menopause indicator-by-*ageATE* interactions, and not in city or dose unknown indicator-by-*ageATE* interactions.

The error term is expressed as $\varepsilon_{ij} = v_{oj} + a v_{1j} + e_{ij}$ where

$$v_j = \begin{pmatrix} v_{oj} \\ v_{1j} \end{pmatrix} \sim N(0, \Sigma) \text{ and } e_{ij} \sim N(0, \sigma^2)$$

v_{0j} and v_{1j} are individual variation terms for the *j*th subject, and e_{ij} is a measurement error term for the *i*th measurement of the *j*th subject. Σ is a general unstructured 2×2 covariance matrix, and v_j and e_{ij} are independent.

Parametric model and analysis of premenopausal trend in serum cholesterol. Let y_{ij} be the *i*th measurement of the total cholesterol of the *j*th subject. The full model is

$$y_{ij} = \text{cons} + a + a^2 + b + a \cdot b + a^2 \cdot b + d + a \cdot d + a^2 \cdot d + mp + a \cdot mp + a^2 \cdot mp + aame4 + aame4 \cdot mp + n + a \cdot n + a^2 \cdot n + \varepsilon_{ij}$$

where cons = 1; $a = (ageATE - 45)/10$; $b = ageATB/10$; d = kerma dose (Gy); $mp = 1$ if $ageATM \geq 50$, $mp = 0$ if $ageATM$ 45–49; $aame4 = ((ageATE - ageATM + 4)^{+}/10)^2$; and n = not in city or dose unknown subject indicator. Because we were interested in the premenopausal trend, the *ageATE*s used for analysis were younger than the *ageATM*. The mean model was a quadratic model in *ageATE* which comprised constant, linear and quadratic effects of *ageATE*, *ageATB*-by-*ageATE* interactions, dose-by-*ageATE* interactions, menopause indicator-by-*ageATE* interactions, time since 4 y before menopause to menopause, and its interaction with menopause indicator and not in city or dose unknown indicator-by-*ageATE* interactions.

The error term is expressed as $\varepsilon_{ij} = v_{oj} + a v_{1j} + e_{ij}$ where

$$v_j = \begin{pmatrix} v_{oj} \\ v_{1j} \end{pmatrix} \sim N(0, \Sigma) \text{ and } e_{ij} \sim N(0, \sigma^2)$$

v_{oj} and v_{1j} are individual variation terms for the *j*th subject, and e_{ij} is a measurement error term for the *i*th measurement of the *j*th subject. Σ is a general unstructured 2×2 covariance matrix, and v_j and e_{ij} are independent.

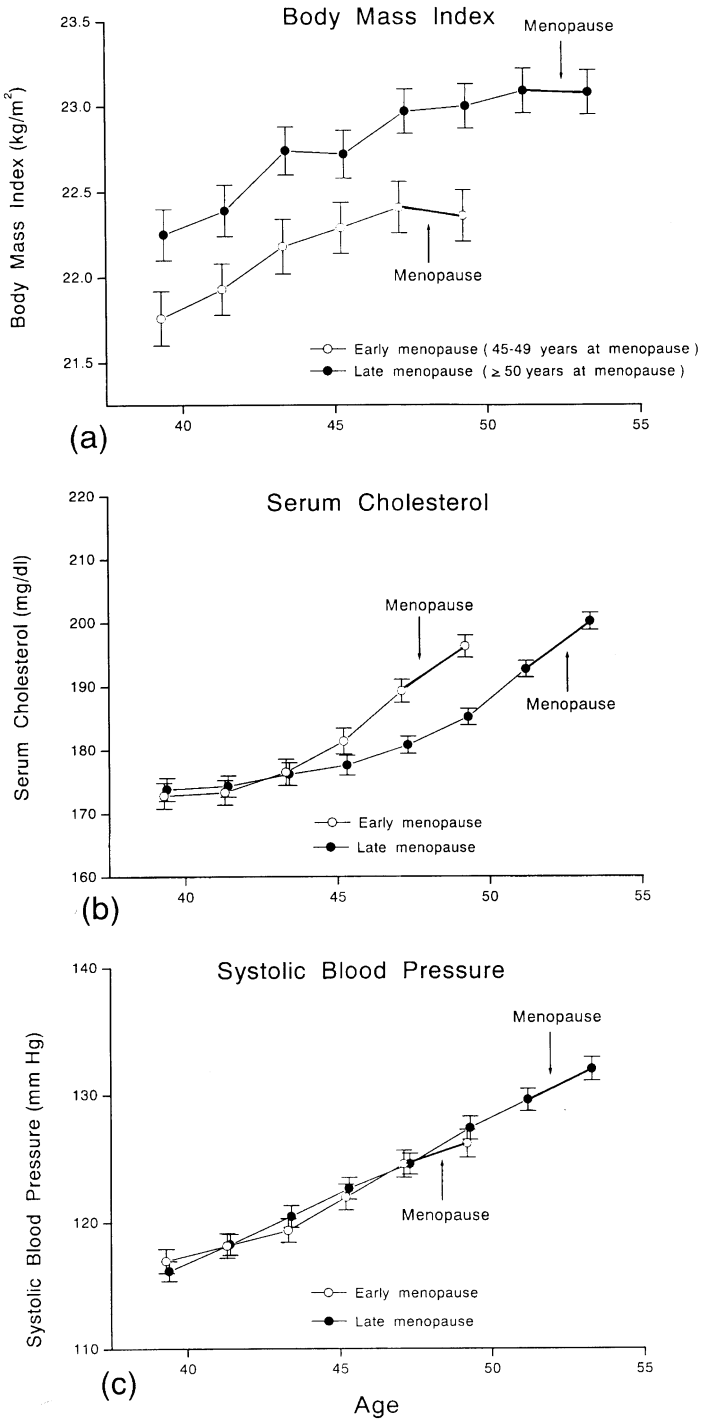

Figure 1 Body mass index, serum cholesterol and systolic blood pressure in early and late menopausal women from 39 to 53 y are presented in (a) upper, (b) middle and (c) lower panels, respectively. (a) The premenopausal trends in body mass index exhibit a linear increase in early and late menopausal women. (b) The premenopausal trends in serum cholesterol in early and late menopausal women increase rapidly approximately 3–4 y before menopause. (c) The premenopausal trends in systolic blood pressure in early and late menopausal women exhibit a linear increase. All data are presented as mean ± s.e.

Note:

$$(ageATE - ageATM + 4)^{+} = \begin{cases} ageATE - ageATM + 4 & if \quad ageATM \geq ageATM - 4 \\ 0 \quad \text{if} & ageATE < ageATM - 4 \end{cases}$$

Results

(1) Age at menopause classified by BMI, serum cholesterol and SBP measured at age 40 or 41 y (Table 1)

Age at menopause in the upper 25% women was significantly higher than that in the lower 25% group when they were classified according to BMI measured at 40 or 41 y. Age at menopause did not differ among the three groups when they were classified according to serum cholesterol and SBP measurements.

(2) Best model for BMI (Table 2 and Figure 2a)

The effect of late menopause on the trend was significantly positive (*mp*; $P=0.0058$), and in late menopausal women, the trend in BMI shifted upward throughout the premenopausal period, compared to the trend for early menopausal women.

Table 1 Effects of body mass index, serum cholesterol and systolic blood pressure measured at age 40 or 41 y on age at menopause

Variables measured at age 40 or 41 y	*Age at menopause*	
Body mass index (kg/m^2)		
Upper 25%: 26.2±2.0 (*n*=125)	50.4 y±2.8	$P<0.05$
Middle 50%: 21.9±1.1 (*n*=248)	50.1 y±2.8	
Lower 25%: 18.8±1.0 (*n*=120)	49.7 y±2.8	
Serum cholesterol (mg/dl)		
Upper 25%: 207.8±18.7 (*n*=130)	50.1 y±2.9	
Middle 50%: 164.9±11.5 (*n*=241)	50.3 y±2.8	
Lower 25%: 131.1±11.1 (*n*=122)	49.7 y±2.9	
Systolic blood pressure (mm Hg)		
Upper 25%: 141.8±15.6 (*n*=123)	50.2 y±2.9	
Middle 50%: 114.8±6.0 (*n*=246)	50.1 y±2.8	
Lower 25%: 98.2±5.0 (*n*=124)	49.9 y±2.9	

Note: values are expressed as mean±s.d.

Table 2 Best model for body mass index; $BMI_{ij} = \text{cons} + a^2 + b + a \cdot b + mp + a^2 \cdot n + \varepsilon_{ij}$

Variable	*Estimate*	*Standard error*	*Test*[a]	P-value[b]
cons	22.909	0.318	—	—
a^2	−0.275	0.077	12.849	0.0003
b	−0.341	0.147	5.405	0.0201
$a \cdot b$	0.477	0.027	312.634	<0.0001
mp	0.496	0.180	7.602	0.0058
$a^2 \cdot n$	−0.347	0.123	8.000	0.0047

[a]Squared Wald test.
[b]Two-sided *P*-value. *BMI*=body mass index; cons=1; *a*=(age at the time of examination − 45)/10; *b*=age at the time of bombing/10; *mp*=1 if age at menopause ≥50, *mp*=0 if age at menopause-45–49; *n*=not in city or dose unknown subject indicator.

(3) Best model for serum cholesterol (Table 3 and Figure 2b)

Among the parameters including the effect of late menopause on the trend—such as *mp*, $a \cdot mp$, $a^2 \cdot mp$ and $aame4 \cdot mp$—only $aame4 \cdot mp$ was selected and had a significantly negative effect on the trend, which indicates that, sometime after 4 y before menopause, the premenopausal trend in serum cholesterol shifted upward in early menopausal women, as compared to the trend for late menopausal women, probably due to the fact that serum cholesterol starts to increase approximately 3–4 y before menopause, but premenopausal trends of serum cholesterol more than 4 y before menopause when the effects of menopause on cholesterol were not observed were identical between early and late menopausal women.

(4) Best model for SBP (Table 4 and Figure 2c)

Parameters including the effect of late menopause on the trend, such as *mp*, $a \cdot mp$, and $a^2 \cdot mp$, were not selected and were not significant, indicating that trends of SBP were identical between early and late menopausal women throughout the premenopausal period.

(5) Effects of radiation on premenopausal trends in BMI, serum cholesterol and SBP

Radiation dose was positively related to the premenopausal trends in serum cholesterol and SBP (Tables 3 and 4), but was not related to the premenopausal trend in BMI (Table 2).

Discussion

Answers to the propositions were that: (1) when women were classified into three groups according to a BMI that was taken at age 40 or 41, age at menopause in the upper 25% was significantly higher than that in the lower 25% group; and (2) throughout the premenopausal period, only the trend in

Table 3 Best model for serum cholesterol; $Serum\ cholesterol_{ij} = \text{cons} + a + b + a^2 \cdot b + d + a \cdot d + aame4 + aame4 \cdot mp + \varepsilon_{ij}$

Variable	*Estimate*	*Standard error*	*Test*[a]	P-value[b]
cons	193.885	2.835	—	—
a	14.162	1.321	114.924	<0.0001
b	−9.637	1.379	48.840	<0.0001
$a^2 \cdot b$	2.066	1.027	4.048	0.0442
d	2.368	1.247	3.609	0.0575
$a \cdot d$	3.029	1.451	4.360	0.0368
aame4	91.775	14.827	38.314	<0.0001
$aame4 \cdot mp$	−42.351	18.402	5.297	0.0214

[a]Squared Wald test.
[b]Two-sided *P*-value. cons=1; *a*=(age at the time of examination (*ageATE*)-45)/10; *b*=age at the time of bombing/10; *d*=kerma dose (Gy); *mp*=1 if age at menopause (*ageATM*)≥50, *mp*=0 if *ageATM* 45–49; *aame4*=$((ageATE - ageATM + 4)^{+}/10)^2$ if *ageATE*≥*ageATM*-4, *aame4*=0 if *ageATE* <*ageATM* − 4.

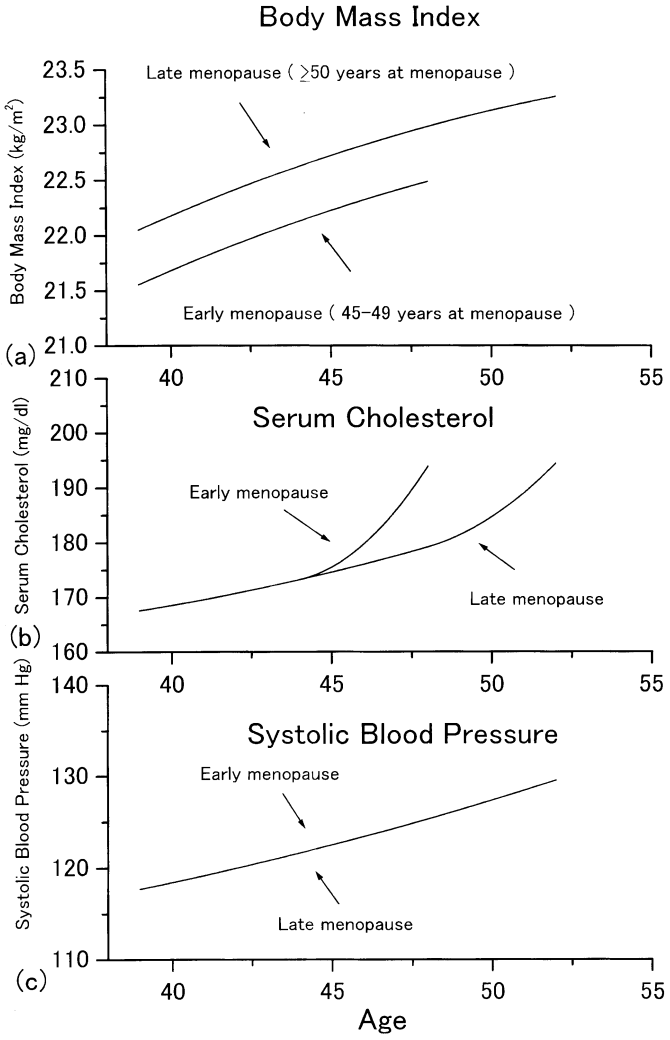

Figure 2 The typical premenopausal trends (age at bombing is 20 y old and radiation dose is 0 Gy) in body mass index, serum cholesterol, and systolic blood pressure in early (age at menopause is 48 y old) and late (age at menopause is 52 y old) menopausal women are illustrated in the (a) upper, (b) middle, and (c) lower panels, respectively. To draw the trend curves, the best models for body mass index, serum cholesterol and systolic blood pressure were used.

Table 4 Best model for systolic Blood Pressure; $SBP_{ij} = \text{cons} + a + b + a \cdot b + a^2 \cdot b + a \cdot d + a^2 \cdot d + \varepsilon_{ij}$

Variable	*Estimate*	*Standard error*	*Test*[a]	P-*value*[b]
cons	116.124	1.779	—	—
a	14.683	1.889	60.429	< 0.0001
b	3.202	0.849	14.217	< 0.0001
$a \cdot b$	−2.872	0.949	9.153	0.0025
$a^2 \cdot b$	0.783	0.412	3.610	0.0574
$a \cdot d$	1.873	0.777	5.800	0.0160
$a^2 \cdot d$	3.591	1.097	10.712	0.0011

[a]Squared Wald test.
[b]Two-sided *P*-value. *SBP* = systolic blood pressure. cons = 1; *a* = (age at the time of examination − 45)/10; *b* = age at the time of bombing/10; *d* = kerma dose (Gy).

BMI in late menopausal women shifted upward compared to that in early menopausal women. These data confirm that BMI, but not serum cholesterol and SBP, is related to age at menopause, ie the greater the BMI, the later the age at menopause.

Although this study suggests that BMI at the age of 39 or older is associated with age at menopause, we did not study the critical age, when BMI might have the greatest effects on age at menopause. There is a report that BMI at the age of 18 is associated with age at menopause,[3] hence the critical age may be younger than 39 y old. The critical age needs to be studied further.

In addition to BMI, reproductive and life style factors have been reported to be associated with age at natural

menopause. Concerning reproductive factors, nulliparous women experience early menopause[7] and increasing parity is associated with later menopause.[8] Early age at menarche has been suggested to be associated with later menopause[9] but the association has not been consistent.[23] Concerning lifestyle factors, smoking[4,11] and malnutrition[12] lead to early menopause. On the other hand, meat consumption,[13] high social economic class[7] and high exercise frequency[14] appear to be associated with later menopause. Although these reproductive and lifestyle factors are considered to be confounding factors of BMI, they were not considered in the present analysis because information on these factors was not collected in the present study. Therefore, analysis of whether BMI before menopause is an independent factor or not is left for future studies.

Estrone is a major endogenous estrogen in postmenopausal women.[24,25] It is formed by peripheral aromatization of plasma androstenedione secreted from ovaries and/or adrenal glands.[26–28] Adipose tissue is one of the loci of this conversion,[29,30] and the transfer constant of conversion of plasma androstenedione to estrone is positively related to body weight.[31] This peripheral mechanism is also active in premenopausal women with normal ovulatory cycles.[26] Although the affinity of estrone for the receptor is one-half to one-third that of estradiol,[26] plasma estrone may supplement the effects of estradiol, which starts to decrease in the mid-thirties.[32,33] Therefore, we think that increased peripheral production of estrone in obese women may contribute patho-physiologically to the delay in age at menopause resulting from obesity.

Serum cholesterol exhibits a sharp increase in association with menopause,[16,34] leading to an increase in ischemic heart disease (IHD) after menopause.[35,36] If the present results are considered in connection with IHD, the following conclusions can be drawn. The greater the BMI, the later the age at menopause, ie obesity delays the age at which serum cholesterol increases rapidly. This suggests that obesity counteracts the promotive effects of menopause on IHD. On the other hand, although obesity is not a direct risk factor for IHD,[37,38] it causes elevated blood pressure[39] and hypercholesterolemia[40] and, therefore, can be deemed an indirect coronary risk factor. In view of the complex interactions between obesity and IHD risk factors, no simple conclusion can be reached about whether obesity has a promotive or suppressive effect on IHD in women. Indeed, it has recently been reported that a U-shaped relation was observed between age at natural menopause and mortality from ischemic heart disease; that is, mortality from ischemic heart disease increased not only in women with an early menopause, but also in women with a very late menopause (aged ≥ 56 y at menopause).[41,42]

In addition to focusing on the well-known association between exposure to atomic bomb radiation and malignant disease,[43] recent studies have also focused on the late effects of ionizing radiation on both cardiovascular disease and coronary risk factors. Mortality from hypertensive disease[19] and the incidence of myocardial infarction[44] increased with radiation dose, and the mean level of cholesterol was significantly higher in irradiated subjects.[18] The result in the present study, that radiation dose is positively related to the premenopausal trends in serum cholesterol and SBP, is consistent with the results of other studies.

Conclusion

When women were classified into three groups based on BMI at age 40 or 41, the age at menopause in those women in the upper 25% was significantly higher than in those in the lower 25%. Throughout the premenopausal period, only the trend in BMI in late menopausal women shifted upward compared to that in early menopausal women. These results confirm that BMI is related to age at menopause and clarify that the greater the BMI, the later the age at menopause.

Acknowledgements

The authors thank Mrs Kaoru Yoshida for preparing the manuscript. This publication is based on research performed at the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan. RERF is a private foundation funded equally by the Japanese Ministry of Health and Welfare and the US Department of Energy through the National Academy of Sciences.

References

1 Lindquist O, Bengtsson C. Serum lipids, arterial blood pressure and body weight in relation to the menopause: Results from a population study of women in Göteborg, Sweden. *Scand J Clin Lab Invest* 1980; **40**: 629–636.
2 Daniell HW. Osteoporosis of the slender smoker. Vertebral compression fractures and loss of metacarpal cortex in relation to postmenopausal cigarette smoking and lack of obesity. *Arch Intern Med* 1976; **136**: 298–304.
3 Sherman B, Wallace R, Bean J, Schlabaugh L. Relationship of body weight to menarcheal and menopausal age: Implications for breast cancer risk. *J Clin Endocrinol Metab* 1981; **52**: 488–493.
4 Willett W, Stampfer MJ, Bain C, Lipnick R, Speizer FE, Rosner B, Cramer D, Hennekens CH. Cigarette smoking, relative weight, and menopause. *Am J Epidemiol* 1983; **117**: 651–658.
5 Leidy LE. Comparison of body size and age at menopause between Mexican-American and white American women. *Ann NY Acad Sci* 1990; **592**: 443–444.
6 Carda SN, Bilge SA, Öztürk TN, Oya G, Ece O, Hamiyet B. The menopausal age, related factors and climacteric symptoms in Turkish women. *Maturitas* 1998; **30**: 37–40.
7 Van Noord PAH, Dubas JS, Dorland M, Boersma H, te Velde ER. Age at natural menopause in a population-based screening cohort; the role of menarche, fecundity and lifestyle factors. *Fertil Steril* 1997; **68**: 95–102.
8 Kaufert PA, Gilbert P, Tate R. Defining menopausal status: the impact of longitudinal data. *Maturitas* 1987; **9**: 217–226.
9 Cramer DW, Xu H, Harlow BL. Does 'incessant' ovulation increases risk for early menopause? *Am J Obstet Gynecol* 1995; **172**: 568–573.
10 Nilsson P, Möller L, Köster A, Hollnagel H. Social and biological predictors of early menopause: a model for premature aging. *J Intern Med* 1997; **242**: 299–305.

11 Cramer DW, Harlow BL, Xu H, Fraer C, Barbieri B. Cross-sectional and case-controlled analyses of the association between smoking and early menopause. *Maturitas* 1995; **22**: 79–87.
12 Khaw KT. Epidemiology of the menopause. *Br Med Bull* 1992; **48**: 249–261.
13 Torgerson DJ, Avenell A, Russell IT, Reid DM. Factors associated with onset of menopause in women aged 45–49. *Maturitas* 1994; **19**: 83–92.
14 Cooper GS, Baird DD, Darden FR. Measures of menopausal status in relation to demographic, reproductive, and behavioral characteristics in a population-based study of women aged 35–49 years. *Am J Epidemiol* 2001; **153**: 1159–1165.
15 Atomic Bomb Casualty Commission. *Research plan for joint ABCC-NIH Adult Health Study in Hiroshima and Nagasaki, Japan*. ABCC Technical Report 11–62; 1962.
16 Akahoshi M, Soda M, Nakashima E, Shimaoka K, Seto S, Yano K. Effects of menopause on trends of serum cholesterol, blood pressure, and body mass index. *Circulation* 1996; **94**: 61–66.
17 SAS/STAT, *User's Guide, Release 6.03 Edition*. SAS Institute Inc.: Cary, NC; 1988.
18 Wong FL, Yamada M, Sasaki H, Kodama K, Hosoda Y. Effects of radiation on the longitudinal trends of total serum cholesterol levels in the atomic bomb survivors. *Radiat Res* 1999; **151**: 736–746.
19 Shimizu Y, Pierce DA, Preston DL, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part II. Noncancer mortality: 1950–1990. *Radiat Res* 1999; **152**: 374–389.
20 Roesch WC (ed.) *U.S.–Japan joint reassessment of atomic bomb radiation dosimetry in Hiroshima and Nagasaki—final report*, Vol. 1. Radiation Effects Research Foundation: Hiroshima; 1987.
21 Goldstein H. Multilevel mixed linear model analysis using interactive generalized least squares. *Biometrika* 1986; **73**: 43–56.
22 Rasbash J, Healy M, Browne W, Cameron B. *MLwiN version 1.02.0002*. Multilevel Models Project, Institute of Education: London; 1998.
23 Whelan EA, Sandler DP, McConnaughey DR, Weinberg CR. Menstrual and reproductive characteristics and age at natural menopause. *Am J Epidemiol* 1990; **131**: 625–632.
24 MacDonald PC, Rombaut RP, Siiteri PK. Plasma precursors of estrogen. I. Extent of conversion of plasma androstenedione to estrone in normal males and non-pregnant normal, castrate and adrenalectomized females. *J Clin Endocrinol Metab* 1967; **27**: 1103–1111.
25 Grodin JM, Siiteri PK, MacDonald PC. Source of estrogen production in postmenopausal women. *J Clin Endcrinol Metab* 1973; **36**: 207–214.
26 Siiteri PK. Post-menopausal estrogen production. *Front Hormone Res* 1975; **3**: 40–44.
27 Judd HL, Judd GE, Lucas WE, Yen SSC. Endocrine function of the postmenopausal ovary: Concentration of androgens and estrogens in ovarian and peripheral vein blood. *J Clin Endocrinol Metab* 1974; **39**: 1020–1024.
28 Vermeulen A. The hormonal activity of the postmenopausal ovary. *J Clin Endocrinol Metab* 1976; **42**: 247–253.
29 Forney JP, Milewich L, Chen GT, Garlock JL, Schwarz BE, Edman CD, MacDonald PC. Aromatization of androstenedione to estrone by human adipose tissue *in vitro*. Correlation with adipose tissue mass, age, and endometrial neoplasia. *J Clin Endocrinol Metab* 1981; **53**: 192–199.
30 Longcope C, Pratt JH, Schneider SH, Fineberg SE. Aromatization of androgens by muscle and adipose tissue in vivo. *J Clin Endocrinol Metab* 1978; **46**: 146–152.
31 MacDonald PC, Edman CD, Hemsell DL, Porter JC, Siiteri PK. Effect of obesity on conversion of plasma androstenedione to estrone in postmenopausal women with and without endometrial cancer. *Am J Obstet Gynecol* 1978; **130**: 448–455.
32 Adamopoulos DA, Loraine JA, Dove GA. Endocrinological studies in women approaching the menopause. *J Obstet Gynaecol Br Commonw* 1971; **78**: 62–79.
33 Sherman BM, West JH, Korenman SG. The menopausal transition: Analysis of LH, FSH, estradiol, and progesterone concentration during menstrual cycles of older women. *J Clin Endocrinol Metab* 1976; **42**: 629–636.
34 Jensen J, Nilas L, Christiansen C. Influence of menopause on serum lipids and lipoproteins. *Maturitas* 1990; **12**: 321–331.
35 Sznajderman M, Oliver MF. Spontaneous premature menopause, ischaemic heart-disease, and serum lipids. *Lancet* 1963; **i**: 962–965.
36 Kannel WB, Hjortland M, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: The Framingham Study. *Ann Intern Med* 1976; **85**: 447–452.
37 Cambien F, Chretien JM, Ducimetiere P, Guize L, Richard JL. Is the relationship between blood pressure and cardiovascular risk dependent on body mass index? *Am J Epidemiol* 1985; **122**: 434–442.
38 Barrett-Connor E, Khaw KT. Is hypertension more benign when associated with obesity? *Circulation* 1985; **72**: 53–60.
39 Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH. Weight and blood pressure: findings in hypertension screening of 1 million Americans. *JAMA* 1978; **240**: 1607–1610.
40 Denke MA, Sempos CT, Grundy SM. Excess body weight. An underrecognized contributor to high blood cholesterol levels in white American men. *Arch Intern Med* 1993; **153**: 1093–1103.
41 Jacobsen BK, Knutsen SF, Fraser GE. Age at natural menopause and total mortality and mortality from ischemic heart disease: the Adventist Health Study. *J Clin Epidemiol* 1999; **52**: 303–307.
42 Jacobsen BK, Heuch I, Kvåle G. On mortality from ischemic heart disease in women with very late menopause. *J Clin Epidemiol* 2000; **53**: 435–436.
43 Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. *Radiat Res* 1996; **146**: 1–27.
44 Wong FL, Yamada M, Sasaki H, Kodama K, Akiba S, Shimaoka K, Hosoda Y. Noncancer disease incidence in the atomic bomb survivors: 1958–1986. *Radiat Res* 1993; **135**: 418–430.