Original Contribution

Association of Leukocyte Telomere Length With Breast Cancer Risk: Nested Case-Control Findings From the Shanghai Women’s Health Study

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Telomeres are specialized chromatin structures essential for the maintenance of chromosomal integrity and stability. Telomere shortening has been linked to multiple aging-related diseases, including cancer. Evidence associating telomere length with breast cancer risk—most of which has been from retrospective case-control studies—is conflicting. We conducted a nested case-control study based on the Shanghai Women’s Health Study (1997–2009) in which we evaluated the association of telomere length and breast cancer risk using peripheral blood samples collected before cancer diagnosis (601 cases and 695 controls). We used monochrome multiplex quantitative polymerase chain reaction to measure relative telomere length. Multiple logistic regressions were used to derive adjusted odds ratios with 95% confidence intervals as the measure of association. Telomere length was inversely correlated with age ($r = -0.22$). Women with moderately long telomeres (those in the fourth quintile) had the lowest breast cancer risk. Risk increased in a dose-response manner with decreasing quintile of telomere length; odds ratios were 1.39 (95% CI: 0.95, 2.04), 1.79 (95% CI: 1.17, 2.75), and 2.39 (95% CI: 1.45, 3.92), respectively, for the third, second, and first quintiles compared with the fourth quintile. A slightly elevated risk of breast cancer (odds ratio = 1.35, 95% CI: 0.90, 2.04), although one that was not statistically significant, was found in the top quintile (longest telomeres). Our results support the hypothesis that telomere shortening is associated with increased risk of breast cancer and suggest a possible elevated risk associated with long telomeres.

breast cancer; biomarkers; epidemiology; genetic factors; telomere

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.
components of telomerase complex, which results in short telomeres, leading to bone marrow failure and an elevated risk of cancer (9).

Studies using clinical samples obtained from patients with cancer—including cancers of the breast, lung, and colon/rectum—have shown that, in general, telomere length is shorter in cancer tissues than in adjacent tissues (10). Recently, several epidemiologic studies have evaluated the association of germline telomere length, measured using DNA from peripheral blood cells or buccal cells, with cancer risk and prognosis (11, 12). Regarding breast cancer, results from previous studies have been conflicting. Of the 8 retrospective case-control studies reported to date, 2 showed short telomere length to be associated with increased risk (13, 14), whereas 2 other studies found an elevated risk among women with longer telomeres (15, 16). Four studies showed no significant association (17–20). To our knowledge, only 2 prospective studies have been conducted, and both studies failed to identify any statistically significant associations (14, 21). Reasons for the apparently contradictory results remain unknown. Differences in study designs, sample sizes, analytic approaches, laboratory assay protocols, and background exposures could have contributed to the inconsistent findings. To clarify the association between telomere length and breast cancer risk, we conducted a large case-control study nested within the Shanghai Women’s Health Study using blood samples collected before cancer diagnosis.

MATERIALS AND METHODS

Study population

Subjects of the present study were participants in the Shanghai Women’s Health Study, a population-based cohort study. Detailed methodology for the Shanghai Women’s Health Study has been published elsewhere (22). The study was approved by the relevant institutional review boards for human research. Briefly, from 1997 to 2000, a total of 74,942 Chinese women between the ages of 40 and 70 years who resided in 7 urban communities of Shanghai were recruited into the cohort study, with a response rate of 92.7%. In-person interviews were conducted to collect information regarding demographic characteristics, anthropometrics, usual dietary habits, physical activities, and other lifestyle factors. Of the study participants, 56,831 (75.8%) provided a blood sample at baseline recruitment (Appendix Table 1). Buffy coat samples were stored at −80°C until DNA isolation.

The cohort has been followed using a combination of biennial home visits, record linkage to cancer incidence and mortality data collected by the Shanghai Cancer Registry, and death certificate data collected by the Shanghai Vital Statistics Unit. For cohort members who were diagnosed with cancer, medical charts were reviewed to verify the diagnosis, and detailed information regarding pathologic characteristics of the cancer was obtained.

Included in the current nested case-control study were 601 incident breast cancer cases identified during follow-up of the cohort to December 2009, as well as their matched controls. Incidence-density sampling method was used to select controls from the same risk set as the index case. Cases and controls were individually matched on age (difference ≤730 days), date (difference ≤30 days), and time (morning or afternoon) of sample collection, time interval since last meal (difference ≤2 hours), antibiotic use in the past week (yes vs. no), and menopausal status at time of sample collection. Typically, one control was selected for each case. Because some cases from our substudy could be matched with the controls for cases with other types of cancers, there were second controls for 91 cases and third controls for 3 cases.

Laboratory methods

Genomic DNA was extracted from buffy coats using a QIAamp DNA kit (Qiagen, Valencia, California) following the manufacturer’s protocol. Relative telomere length was measured using a monochrome multiplex quantitative polymerase chain reaction method described recently by Cawthon (23), with minor modifications. Briefly, telomere length assay was carried out in a 15-µL polymerase chain reaction consisting of 1x QuantiFast SYBR Green PCR Master Mix (Qiagen), 700-nM telomere primers telg and teltc, 200-nM albumin primers albugcr1 and albdgcr1, and 5-ng DNA. A multistep thermal cycling procedure was performed on a Bio-Rad (Hercules, California) CFX384 Real-Time System. After amplification, a dissociation curve was performed to confirm the specificity of the reaction. For each standard curve, 2-fold serial dilutions of a reference DNA sample were used to produce a standard curve. Additionally, a calibrator DNA (same as the reference DNA), 2 negative controls, and 2 quality-control DNA samples with a long and short telomere length (Telom TAGGG Telomere Length Assay kit; Roche, Indianapolis, Indiana) were included in each of the 38-well assay plates. Bio-Rad CFX manager version 1.6 software was used to determine the relative telomere length through a 2-step relative quantification. In the first step, the ratio of the telomere repeat copy number to the single-copy gene (albumin) copy number, as a measure of relative telomere length, was determined for each sample based on the standard curve. In the second step, the ratio for each sample was normalized to the calibrator DNA to standardize sample values across all reaction plates. Samples from each matched case-control set were assayed on the same plate. Laboratory personnel were blinded to each subject’s case-control status. Coefficients of variation for the interplate ratio of telomere repeat copy number to the single-copy gene (albumin) copy number were 15.6% and 16.2% for the long and short telomere quality-control samples, respectively. Inter- and intraplate coefficients of variation of calibrator DNA samples were 12.2% and 5.3%, respectively. The mean ratio of long to short telomere quality-control samples in our assays was 2.9, very close to the mean ratio of 2.7 determined by southern blot method (Telom TAGGG Telomere Length Assay kit; Roche), indicating that our protocol to estimate telomere lengths was valid.

Statistical methods

Means and percentages of selected baseline characteristics for cases and controls were calculated and compared.
using \( t \) tests for continuous variables and \( \chi^2 \) tests for categorical variables. Data on relative telomere length were log-transformed so that these data were approximately normally distributed.

We compared the case-control difference of the geometric means of the log-transformed telomere length using a 2-way (case-control status and matched sets) analysis of variance with adjustment for age at blood collection. Because DNA samples for cases and controls in the same matched sets were assayed on the same plates, interplate differences for the matched sets were accounted for automatically.

To evaluate the association between breast cancer risk and telomere length, the ratio for telomere length was categorized into quintiles based on distribution among controls. Odds ratios and 95% confidence intervals were estimated using conditional logistic regression models to account for the matched sets, with additional adjustment for age at blood collection. Further adjustment for other demographic characteristics and known breast cancer risk factors did not materially alter the association between telomere length and breast cancer risk.

Tests for linear trend were estimated using the median value for each telomere length quintile. A restricted cubic spline function was used in the conditional logistic regression model to evaluate the shape of the association (24). The model with 4 knots was used in the analysis because this model had the best fit of data as demonstrated by its having the lowest Akaike information criterion value. Likelihood ratio tests were used to evaluate linear effect, nonlinear effect, and overall effect of telomere length on breast cancer risk. Stratified analyses were performed to evaluate potential interactions. All statistical tests were based on 2-sided probability.

**RESULTS**

Table 1 presents the distributions of selected baseline demographic characteristics and major risk factors for breast cancer cases and matched controls. Cases and controls were comparable in age at blood collection, age at menopause, body mass index (BMI; weight \( \text{kg/m}^2 \)), and participation in leisure-time physical activity. There were significant case-control differences in the distributions of education, age at menarche, age at first live birth, and family history of breast cancer. Very few women in this cohort regularly smoked cigarettes (2.9%), drank alcoholic beverages (2.7%), or took hormone replacement therapy (3.3%).

Telomere length was inversely correlated with age \((r = -0.22; P < 0.0001)\). The geometric means of telomere length were approximately 6.6% (cases) and 4.2% (controls) shorter in women who were 50–59 years of age and 10.9% (cases) and 9.4% (controls) shorter in those who were 60 years of age or older compared with women who were younger than 50 years (data not shown). With the exception of BMI, no apparent association of telomere length was seen for other major breast cancer risk factors listed in Table 1. Both underweight (BMI <18.5) and obesity (BMI \( \geq 30 \)) were associated with reduced telomere length (data not shown).

Overall, no significant difference was observed in geometric means of telomere length between cases and controls (Table 2). Among postmenopausal women, however, telomere length was significantly shorter in cases than in controls \((P = 0.0485)\). No difference was observed among premenopausal women.

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**Table 1.** Comparison of Demographic Characteristics and Known Breast Cancer Risk Factors in Cases and Their Matched Controls, Shanghai Women’s Health Study, 1997–2000

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 601)</th>
<th>Controls (n = 695)</th>
<th>( P ) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristic</td>
<td>% Mean (SD)</td>
<td>% Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Age at blood collection, years</td>
<td>52.7 (8.8)</td>
<td>53.4 (9.0)</td>
<td>0.163</td>
</tr>
<tr>
<td>High school education or above</td>
<td>50.6</td>
<td>38.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family income &gt;30,000 yuan</td>
<td>18.6</td>
<td>17.0</td>
<td>0.4362</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>48.3</td>
<td>50.4</td>
<td>0.449</td>
</tr>
<tr>
<td>Known risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at menopause, years</td>
<td>49.3 (4.6)</td>
<td>48.8 (3.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>Age at menarche, years</td>
<td>14.7 (1.8)</td>
<td>15.0 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at first live birth, years</td>
<td>26.4 (4.1)</td>
<td>25.5 (4.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Number of live births</td>
<td>1.6 (1.1)</td>
<td>1.8 (1.2)</td>
<td>0.971</td>
</tr>
<tr>
<td>Body mass index(^c)</td>
<td>24.4 (3.5)</td>
<td>24.3 (3.5)</td>
<td>0.513</td>
</tr>
<tr>
<td>Ever exercised regularly</td>
<td>34.9</td>
<td>36.7</td>
<td>0.747</td>
</tr>
<tr>
<td>Ever used hormone replacement</td>
<td>3.0</td>
<td>3.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Family history of breast cancer</td>
<td>4.0</td>
<td>1.3</td>
<td>0.163</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.

* \( P \) values were derived from \( t \) tests for continuous variables or \( \chi^2 \) tests for categorical variables.

\(^b\) Among postmenopausal women.

\(^c\) Weight (kg)/height (m)\(^2\).
To estimate odds ratios for the association between breast cancer risk and telomere length, subjects were categorized into 5 groups based on quintile distribution among controls (Table 3). Compared with women in the longest telomere group (top 20%), those in the shortest telomere group (bottom 20%) had a statistically significant increase in the risk of breast cancer (odds ratio (OR) = 1.77, 95% confidence interval (CI): 1.02, 3.06) (Table 3). This association was stronger in postmenopausal women (for quintile 1 vs. quintile 5, OR = 2.32, 95% CI: 0.99, 5.43) than in premenopausal women (for quintile 1 vs. quintile 5, OR = 1.33, 95% CI: 0.63, 2.80), although the interaction test was not statistically significant. Women in the second-longest telomere group (fourth quintile) had the lowest risk

<table>
<thead>
<tr>
<th>Table 2.</th>
<th>Case-Control Differences in Relative Telomere, Shanghai Women’s Health Study, 1997–2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject Category</td>
<td>No. of Subjects</td>
</tr>
<tr>
<td>All women</td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>601</td>
</tr>
<tr>
<td>Controls</td>
<td>695</td>
</tr>
<tr>
<td>Premenopausal women</td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>311</td>
</tr>
<tr>
<td>Controls</td>
<td>345</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>290</td>
</tr>
<tr>
<td>Controls</td>
<td>350</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.  
* Adjusted for age.

<table>
<thead>
<tr>
<th>Table 3.</th>
<th>Adjusted Odds Ratios for the Association Between Telomere Length and Breast Cancer Risk by Menopausal Status, Shanghai Women’s Health Study, 1997–2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintile of Telomere Length by Participant Category</td>
<td>No. of Cases</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>All women</td>
<td></td>
</tr>
<tr>
<td>5 (long)</td>
<td>117</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>119</td>
</tr>
<tr>
<td>2</td>
<td>129</td>
</tr>
<tr>
<td>1 (short)</td>
<td>148</td>
</tr>
<tr>
<td>Premenopausal women</td>
<td></td>
</tr>
<tr>
<td>5 (long)</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>1 (short)</td>
<td>60</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td></td>
</tr>
<tr>
<td>5 (long)</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
</tr>
<tr>
<td>1 (short)</td>
<td>88</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.  
* Adjusted for age at blood collection.  
* Using subjects in the longest telomere group, the fifth quintile was the reference group.  
* Using subjects in the second-longest telomere group, the fourth quintile was the reference group.
of breast cancer, and a reverse J-shaped association was observed using restricted cubic spline function (Figure 1; test for nonlinearity P = 0.0127 in all women combined). When women in the fourth quintile were used as the reference group for risk estimate, odds ratios for multiple groups with a short telomere were statistically significant (Table 3; odds ratios are shown in the right panel). A similar pattern of association was found after excluding cases diagnosed within the first year after blood collection.

Both BMI and physical activity level have been reported to be related to telomere length. Therefore, we investigated potential interactions of telomere lengths with these 2 variables, as well as with years of menstruation (as a measure of cumulative endogenous estrogen exposure), in relation to breast cancer risk (Table 4). A short telomere was associated with elevated breast cancer risk in all groups defined by BMI, physical activity level, and years of menstruation, although not all odds ratios were statistically significant. A 4-fold elevated risk of breast cancer was observed among overweight postmenopausal women (BMI ≥25) who also had a short telomere length (lowest quintile). The test for multiplicative interaction between BMI and telomere length was marginally significant (P = 0.078) (Table 4).

**DISCUSSION**

In the present large case-control study in which we used genomic DNA from peripheral blood cells collected before cancer diagnosis, we observed a reverse J-shaped association between telomere length and breast cancer risk. Compared with the group of women whose telomeres were in the 60th to 79th percentiles of length (fourth quintile), the risk of breast cancer was increased in a dose-response manner with a decreasing quintile of telomeres to a more than 2-fold elevated risk in women with the shortest telomeres (bottom quintile). Women in the top quintile, whose telomere length measured in the top 20%, also had an elevated risk, although the risk estimate was not statistically significant. In general, our study supports the hypothesis that telomere shortening is associated with an elevated risk of breast cancer.

It has been well documented that short telomeres are associated with multiple premature aging syndromes, including ataxia telangiectasia, ataxia-telangiectasia-like disorder, aplastic anemia, Bloom syndrome, Fanconi anemia, Nijmegen breakage syndrome, and dyskeratosis congenita (1, 9). Patients with these syndromes have an elevated risk of cancer. Mouse models also support the notion that telomerase deficiency and short telomere-length increase the risk of a tumor (1). Epidemiologic studies have linked short telomeres in peripheral blood leukocytes to elevated risks of several human cancers, including cancers of the bladder, esophagus, stomach, head and neck, ovary, and kidneys (11, 12, 25). Breast cancer has been investigated in multiple previous studies. However, 8 of 10 previous studies were retrospective case-control studies that used blood samples collected after cancer diagnosis or even cancer treatment to assess telomere length (13–20). Results from these studies have been inconsistent, perhaps because of the influence of cancer diagnosis and treatment on telomeres (26). Indeed, a recent study in which investigators used blood samples collected after cancer diagnosis showed a striking inverse association between telomere length and the risks of cancers of the breast and colon/rectum (14). The association, however, was substantially attenuated when using samples collected before cancer diagnosis (14). Four of the 8 retrospective case-control studies showed no significant association (17–20), and 2 other studies found an elevated risk among women with longer telomeres (15, 16). Only 2 nested case-control studies of breast cancer have examined the association with telomere length (14, 21). Using data and prospectively collected samples from the Nurses' Health Study, De Vivo et al. (21) reported that having a short telomere length was related to a slightly elevated, although not statistically significantly so, risk of breast cancer in postmenopausal women (bottom quartile versus top, OR = 1.25, 95% CI: 0.93, 1.68). Intriguingly, the risk of breast cancer was lowest in the third quartile, similar to what was found in our study. The other published prospective study, which was nested within the European Prospective Investigation Into Cancer and Nutrition-Norfolk cohort, showed that short telomeres were associated with a nonsignificantly elevated breast cancer risk (quintile 4 vs. quintile 1, OR = 1.58, 95% CI: 0.75, 3.31) (14). The sample size for that study, however, was relatively small (199 cases and 420 controls). Although neither of those studies reported statistically significant associations, the direction of association identified in both studies was consistent with the direction found in our study.

The observation of a suggestive elevated risk of breast cancer among women in the longest telomere group is unexpected, although biologically plausible. Long telomeres could be a result of telomerase reactivation, which may
predispose cells to delayed senescence and increase the chance of acquiring genetic abnormalities. It has been shown that a long telomere may be associated with an increased risk of some cancers (12), including lung cancer (27) and non-Hodgkin’s lymphoma (28). Specifically for breast cancer, a previous study also found an elevated risk of cancer related to long telomeres (15). However, blood samples for that study were collected after patients were diagnosed with cancer.

The major strengths of our study include the large sample size and the use of blood samples collected before diagnosis. Very few women smoked cigarettes regularly (2.4%) (22), and thus potential confounding effects due to cigarette smoking should be minimal. Similar to other studies, however, the precision of relative telomere measurement was not optimal, and a relatively large coefficient of variation was observed. However, this measurement error should be random, which tends to attenuate the association between telomeres and breast cancer risk. By analyzing samples from the same case-control set in the same plate and using the monochrome multiplex quantitative polymerase chain reaction method, we should have minimized the impact of interplate variation and detection bias on study results. Extensive data were collected in our study, which allowed us to carefully evaluate the potential influence of confounders on our results. No major confounder, however, was identified in the study. Nevertheless, we cannot completely rule out the possibility of unmeasured or residual confounding effects on our results. The potential for selection bias should be small in this study because of the very high

<table>
<thead>
<tr>
<th>Quartile of Telomere Length</th>
<th>All Women</th>
<th>Postmenopausal Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Second</td>
</tr>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>1.66 1.00, 2.77</td>
<td>1.27 0.82, 1.96</td>
</tr>
<tr>
<td>≥25</td>
<td>2.02 1.19, 3.42</td>
<td>1.24 0.75, 2.03</td>
</tr>
<tr>
<td>P for interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.58 0.92, 2.70</td>
<td>0.89 0.54, 1.47</td>
</tr>
<tr>
<td>No</td>
<td>1.68 1.01, 2.77</td>
<td>1.32 0.86, 2.04</td>
</tr>
<tr>
<td>P for interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of menstruation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;32 years</td>
<td>1.56 0.87, 2.79</td>
<td>0.96 0.57, 1.60</td>
</tr>
<tr>
<td>≥32 years</td>
<td>2.46 1.36, 4.45</td>
<td>1.76 1.04, 2.97</td>
</tr>
<tr>
<td>P for interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>3.01 1.33, 6.81</td>
<td>2.56 1.24, 5.27</td>
</tr>
<tr>
<td>≥25</td>
<td>4.23 1.90, 9.41</td>
<td>2.22 1.02, 4.82</td>
</tr>
<tr>
<td>P for interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
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<tr>
<td>Yes</td>
<td>1.95 0.93, 4.06</td>
<td>1.46 0.71, 2.97</td>
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<tr>
<td>No</td>
<td>2.19 1.02, 4.71</td>
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<td>&lt;32 years</td>
<td>2.35 0.87, 6.39</td>
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<td>3.49 1.37, 8.84</td>
<td>2.67 1.14, 6.30</td>
</tr>
<tr>
<td>P for interaction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

a Adjusted for age at blood collection.
b Weight (kg)/height (m)².
c There were 601 cases and 695 controls.
d There were 290 postmenopausal cases and 350 controls.

response rate (92.7%) at the baseline survey and the very low rate of loss to follow-up (<1%).

In conclusion, our study, a large case-control study using prediagnostic samples, revealed a reverse J-shaped association between telomere length and breast cancer risk. In general, these findings support the hypothesis that telomere shortening is associated with an elevated risk of breast cancer, but they also suggest a possible adverse effect of long telomeres. Additional research is needed to further evaluate the association of telomere length and breast cancer risk.

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REFERENCES


### Appendix Table 1. Comparison of Demographic Characteristics and Known Breast Cancer Risk Factors in Subjects With and Without Blood Samples, Shanghai Women’s Health Study, 1997–2009

<table>
<thead>
<tr>
<th>Variable</th>
<th>Provided a Blood Sample at Baseline</th>
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<tr>
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<td>%</td>
<td>Mean (SD)</td>
<td>%</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Demographic characteristic</td>
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<tr>
<td>Age at blood collection, years</td>
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<td></td>
<td></td>
<td>52.2 (9.1)</td>
<td></td>
</tr>
<tr>
<td>High school education or above</td>
<td>51.7</td>
<td></td>
<td>38.2</td>
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</tr>
<tr>
<td>Family income &gt;30,000 yuan</td>
<td>20.9</td>
<td></td>
<td>16.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>48.9</td>
<td></td>
<td>49.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at menopause, years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>48.8 (4.1)</td>
<td></td>
<td></td>
<td>48.6 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Age at menarche, years</td>
<td>14.9 (1.7)</td>
<td></td>
<td></td>
<td>14.9 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Age at first live birth, years</td>
<td>25.5 (4.2)</td>
<td></td>
<td></td>
<td>25.5 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Number of live births</td>
<td>1.7 (1.2)</td>
<td></td>
<td></td>
<td>1.8 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Body mass index&lt;sup&gt;c&lt;/sup&gt;</td>
<td>23.7 (3.5)</td>
<td></td>
<td></td>
<td>24.1 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Ever exercised regularly</td>
<td>33.2</td>
<td></td>
<td></td>
<td>36.2</td>
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<tr>
<td>Ever used hormone replacement</td>
<td>3.6</td>
<td></td>
<td>3.5</td>
<td></td>
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<tr>
<td>Family history of breast cancer</td>
<td>1.8</td>
<td></td>
<td>1.9</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.

<sup>a</sup> P values were derived from t tests for continuous variables or χ² tests for categorical variables.

<sup>b</sup> Among postmenopausal women.

<sup>c</sup> Weight (kg)/height (m)².