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Original Research Article

## Factors associated with breast cancer occurrence before the age of 40 in Yaoundé

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### ABSTRACT

**Background:** In Cameroon, one third of breast cancers concern women less than 40 of age and young age appeared to be an independent predictor of adverse outcome. This study aimed to determine factors associated with the development of breast cancer before the age of 40 in Yaoundé.

**Methods:** A case-control study was conducted for 7 months, from November 1<sup>st</sup>, 2016 to May 31<sup>st</sup>, 2017 at the General Hospital and the gyneco-obstetric and Paediatric Hospital of Yaoundé. Study compared the socio-demographic, clinical and lifestyle data of 50 women less than 40 of age with breast cancer (cases) with those of 200 women below 40 of age without breast cancer (controls). Descriptive statistics, bivariate and multivariate logistic regressions were performed to assess the socio-demographic, clinical and lifestyle data. Data were computed using the SPSS version 23.0 software. The significance threshold value was set at 0.05.

**Results:** After multivariate analysis, the factors independently associated with the occurrence of breast cancer before the age of 40 were: age  $\geq 30$  (aOR = 2.05); family history of breast cancer (aOR = 8.65); parity  $\geq 1$  (aOR = 2.46); breastfeeding (aOR = 3.39); waist circumference  $\geq 88$  centimeters (cm) (aOR = 4.38); breast density  $\geq 90$  (aOR = 2.89); physical activity  $\leq 3$  hours/week (aOR = 4.78).

**Conclusions:** Breast cancer in women under 40 is associated with family history, reproductive life and women's lifestyles. Breastfeeding more than 12 months, having a balanced diet, supplementary screening tests in women with dense breasts and practicing physical activity; would be effective ways to prevent it in young women.

**Keywords:** Breast cancer, Lifestyle, Risk factor, Young women

### INTRODUCTION

Breast cancer is a major public health issue and the leading cause of death by cancer in women.<sup>1</sup> In 2018, there were an estimated 2.09 million new cases of invasive breast cancer worldwide. The incidence rate of breast cancer increases with age, from 1.5 cases per

100,000 in women 20-24 years of age to a peak of 421.3 cases per 100,000 in women 75-79 years of age.<sup>2</sup>

Approximately 7% of women with breast cancer are diagnosed before the age of 40 years, and this disease accounts for more than 40% of all cancer in women in this age group.<sup>3</sup> In 2017, in the United States, there were

11160 new cases of invasive breast cancer in women under 40 years of age for 990 deaths.<sup>2</sup> Interestingly, breast cancer risk factors, clinical outcomes, and tumor biology are somewhat different in the subgroup of women below 40, suggesting that breast cancer in young women represents a distinct entity.<sup>4</sup> For example, in women over 45, breast cancer is more common in whites than blacks. However, black women under age 35 have more than twice the incidence of invasive breast cancer and three times the breast cancer mortality of young white women.<sup>5</sup> Furthermore; breast cancer at an early age is more likely to be associated with an increased familial risk, especially in women harboring a germline BRCA1 mutation.<sup>6</sup>

In a younger host, breast cancer is characterized by a more aggressive phenotype with a higher percentage of estrogens receptor (ER)-negative ( $p < 0.001$ ), progesterone receptor (PR)-negative ( $p < 0.001$ ), vascular or lymphatic invasion (48.6% v 37.3%,  $p = 0.006$ ) and pathologic grade 3 tumors ( $p < 0.0001$ ) compared with women aged 35-50 years.<sup>7</sup> Although a diagnosis of breast cancer is distressing at any age, this occurrence in young women is fraught with several unique challenges including the impact of chemotherapy, endocrine, and local therapies in both the physiologic health (future fertility, premature menopause, and bone health) and the psychological health of young women as they face a diagnosis of breast cancer.<sup>3</sup>

In Cameroon, breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death in women, accounting for 31.5% of all cancers.<sup>8</sup> The burden of breast cancer remains high in Cameroon due to the lack of preventive action against this. Several studies have shown that more than one-third of women with breast cancer are less than 40 years of age.<sup>8-10</sup> Given the aggressiveness of this cancer in young women, and the fact that it is often diagnosed at advanced stage, we sought to determine the factors associated with in patients less than 40 years of age in order to initiate preventive actions in our setting.

## METHODS

A case-control study was conducted during 7 months, from November 1<sup>st</sup>, 2016 to May 31<sup>st</sup>, 2017, in the gynecology department of the Yaoundé Gyneco-Obstetric and Pediatric Hospital (YGOPH) and the Medical Oncology department of the Yaoundé General Hospital (YGH). We compared women below 40 years of age treated for breast cancer (cases) during this period in both health facilities with controls less than 40 who came for consultation and/or treated in these services for a completely different condition (controls). Each case was compared with four controls. Socio-demographics data (age, level of education, profession, marital status, place of residence, monthly financial income); clinical characteristics (menarchs, contraceptive use, parity, gravidity, age at first pregnancy, age of birth, history of

breastfeeding, breast pathology, breast irradiation, family history of breast cancer or other cancers, anthropometric parameters such as height, weight, body mass index, waist circumference, breast density) and lifestyle habits (consumption of tobacco, beverage, milk, frying, tea, fish, red wine, poultry, fruit, vegetables and soy, number of daily meals, physical activity) were collected using pre-tested survey forms. Additional data were collected from patients' medical records. Research authorizations and ethical approvals have been obtained beforehand from the administration and ethical committees of the YGOPH and YGH respectively. Fifty cases and two hundred controls have been included in this study. Women below 40 years of age treated for breast cancer (cases) during this period in both health facilities were compared with women below 40 who came for consultation and/or treated in these services for a completely different condition (controls).

Patients were recruited consecutively. The minimum sample size was calculated using the Schlesselman formula. Study used the results of Anderson et al. who found that 47.6% of women under 40 with breast cancer had a family history of breast cancer.<sup>11</sup> Each case was opposed with four controls. The minimum size obtained was 43 cases and 172 controls. The recruitment was stopped randomly when we reached 50 cases and 200 controls.

## Statistical analysis

Statistical analysis was done with SPSS version 23.0 (SPSS Inc., Chicago, IL). The differences between the proportions were analyzed using contingency tables by applying the Chi-2 and Fischer tests. The significance threshold was set at 0.05; the association between the variables was assessed by crude odd ratio with its corresponding 95% confidence interval. Logistic regression was performed to eliminate confounders.

## RESULTS

### Socio-demographic features

Table 1 presents the socio-demographic variables after univariate analysis. The risk factors for breast cancer in women under 40 years of age were: age  $\geq 30$  years (OR = 2.55; CI = 1.29-5.01;  $p = 0.006$ ); high school level (OR = 2.2 CI = 1.2 - 4.1;  $p = 0.018$ ) and being a housewife (OR = 2.1; CI = 1.1 - 4.5;  $p = 0.04$ ).

### Clinical characteristics

Table 2 presents the clinical variables after univariate analysis. The risk factors for breast cancer before the age of 40 were: age of menarches  $\geq 14$  years (OR = 5.15; CI = 2.64-10.1;  $p < 0.001$ ); parity  $\geq 1$  (OR = 3.72; CI = 2.39-8.92;  $P < 0.001$ ); gestity  $\geq 4$  (OR = 4.62 ; CI = 2.39-8.92;  $p < 0.001$ ); history of breast feeding (OR = 5.57; CI = 2.57-12.07;  $p < 0.001$ ); family history of breast

cancer (OR = 10.11; CI = 4.8-21.11; p < 0.001); waist circumference  $\geq$  88 cm (OR = 5.38; CI = 2.46-11.76; p < 0.001); breast density  $\geq$  90 (OR = 3.18; CI = 1.59-6.33; p

< 0,001) and hormonal contraception (OR = 2.08; CI = 1.10 - 3.92; p = 0.023).

**Table 1: Socio-demographic features.**

| Variables          | Cases n (%) | Controls n (%) | OR (IC)          | p-value |
|--------------------|-------------|----------------|------------------|---------|
| <b>Age</b>         |             |                |                  |         |
| < 30               | 14 (28.0)   | 99 (49.5)      | 0.39 (0.2-0.77)  | 0.006   |
| $\geq$ 30          | 36 (7.0)    | 101 (50.5)     | 2.55 (1.29-5.01) | 0.006   |
| <b>Study level</b> |             |                |                  |         |
| None               | 2 (4.0)     | 7 (3.5)        | 1.1 (0.2-5.7)    | 0.877   |
| Primary            | 4 (8.0)     | 23 (11.5)      | 0.6 (0.2-2.02)   | 0.564   |
| High school        | 26 (52.0)   | 66 (33.0)      | 2.2 (1.2-4.1)    | 0.018   |
| University         | 18 (36.0)   | 104 (52.0)     | 0.5 (0.3-0.9)    | 0.043   |
| <b>Profession</b>  |             |                |                  |         |
| Student            | 5 (10)      | 65 (32.5)      | 0.2 (0.09-0.6)   | 0.002   |
| Housewife          | 13 (26)     | 28 (14.0)      | 2.1 (1.1-4.5)    | 0.044   |
| Merchant           | 5 (10)      | 29 (14.5)      | 0.7 (0.2-1.8)    | 0.458   |
| Health staff       | 2 (4)       | 14 (7.0)       | 0.5 (0.1-2.5)    | 0.741   |
| Civil servant      | 7 (14)      | 18 (9.0)       | 1.6 (0.6-4.2)    | 0.341   |
| Cultivator         | 1 (2)       | 6 (3.0)        | 0.6 (0.08-5.6)   | 0.764   |
| Other              | 17 (34)     | 40 (20.0)      | 2.05 (1.04-4)    | 0.067   |

OR: Odds Ratio, CI: Confidence Interval.

**Table 2: Clinical characteristics.**

| Variables                              | Cases n (%) | Controls n (%) | OR (CI)           | P-value |
|--|-------------|----------------|-------------------|---------|
| <b>Menarchs</b>                        |             |                |                   |         |
| < 14                                   | 16 (32.0)   | 141 (70)       | 0.19 (0.10-0.38)  | < 0.001 |
| $\geq$ 14                              | 34 (68.0)   | 59 (29.5)      | 5.15 (2.4-10.1)   | < 0.001 |
| <b>Gestity</b>                         |             |                |                   |         |
| 0                                      | 5 (10.0)    | 99 (49.5)      | 0.11 (0.04-0.30)  | < 0.001 |
| 1-3                                    | 19 (38.0)   | 63 (31.5)      | 1.33 (0.70-2.54)  | 0.381   |
| $\geq$ 4                               | 26 (52.0)   | 38 (19.0)      | 4.62 (2.39-8.92)  | < 0.001 |
| <b>Parity</b>                          |             |                |                   |         |
| 0                                      | 12 (24.0)   | 108 (54.0)     | 0.27 (0.13-0.55)  | < 0.001 |
| $\geq$ 1                               | 38 (76.0)   | 92 (46.0)      | 3.72 (1.84-7.53)  | < 0.001 |
| <b>Modern contraceptives use</b>       |             |                |                   |         |
| Yes                                    | 31 (62.0)   | 88 (44.0)      | 2.08 (1.10-3.92)  | 0.023   |
| No                                     | 19 (38.0)   | 112 (56.0)     | 0.48 (0.26-0.91)  | 0.023   |
| <b>Abortion history</b>                |             |                |                   |         |
| Yes                                    | 28 (56.0)   | 41 (20.5)      | 4.94 (2.56-9.51)  | < 0.001 |
| No                                     | 22 (44.0)   | 159 (79.5)     | 0.20 (0.11-0.39)  | < 0.001 |
| <b>Age of first pregnancy</b>          |             |                |                   |         |
| < 20                                   | 12 (26.6)   | 28 (27.7)      | 0.95 (0.43-2.09)  | 1.000   |
| (20-30)                                | 27 (60.0)   | 68 (67.3)      | 0.73 (0.35-1.51)  | 0.391   |
| > 30                                   | 6 (13.3)    | 5 (5.0)        | 2.95 (0.85-10.25) | 0.076   |
| <b>Breastfeeding</b>                   |             |                |                   |         |
| Yes                                    | 38 (76.0)   | 90 (45.0)      | 5.57 (2.57-12.07) | < 0.001 |
| No                                     | 12 (24.0)   | 110 (55.0)     | 0.18 (0.08-0.39)  | < 0.001 |
| <b>History of thoracic irradiation</b> |             |                |                   |         |
| Yes                                    | 5 (10.0)    | 43 (21.5)      | 0.41 (0.5-1.09)   | 0.065   |
| No                                     | 45 (90.0)   | 157 (78.5)     | 2.46 (0.92-6.59)  | 0.065   |
| <b>Family history of breast cancer</b> |             |                |                   |         |

| Variables                  | Cases n (%) | Controls n (%) | OR (CI)           | P-value |
|----------------------------|-------------|----------------|-------------------|---------|
| Yes                        | 25 (50.0)   | 18 (9.0)       | 10.11 (4.8-21.11) | < 0.001 |
| No                         | 25 (50.0)   | 182 (91.0)     | 0.10 (0.05-0.21)  | < 0.001 |
| <b>Waist circumference</b> |             |                |                   |         |
| < 88                       | 34 (68.0)   | 183 (92.0)     | 0.19 (0.09-0.41)  | < 0.001 |
| ≥ 88                       | 16 (32.0)   | 16 (8.0)       | 5.38 (2.46-11.76) | < 0.001 |
| <b>Breast Density</b>      |             |                |                   |         |
| < 90                       | 13 (26.0)   | 102 (52.8)     | 0.32 (0.6-0.63)   | < 0.001 |
| ≥ 90                       | 37 (74.0)   | 94 (47.2)      | 3.18 (1.59-6.33)  | < 0.001 |

OR: Odds Ratio, CI: Confidence Interval.

**Table 3: Patients' lifestyle.**

| Variables  | Cases n (%) | Controls n (%) | OR (IC)            | P-value |
|--|-------------|----------------|--------------------|---------|
| <b>Daily meal frequency</b>                      |             |                |                    |         |
| ≤ 3  | 46 (92.0)   | 197 (99.5)     | 0.12 (0.02-0.66)   | 0.016   |
| > 3  | 4 (8.0)     | 3 (1.5)        | 8.55 (1.52-47.62)  | 0.016   |
| <b>Hours of physical activity per week</b>       |             |                |                    |         |
| ≤ 3  | 47 (94.0)   | 146 (73.4)     | 5.68 (1.70-19.23)  | 0.002   |
| > 3  | 3 (6.0)     | 53 (26.6)      | 0.18 (0.05-0.59)   | 0.002   |
| <b>Consumption of dairy products (days/week)</b> |             |                |                    |         |
| <b>Milk</b>                                      |             |                |                    |         |
| ≥ 3  | 42 (84.0)   | 100 (50)       | 5.25(2.35-11.75)   | 0.001   |
| < 3  | 8 (16.0)    | 100 (50)       | 0.19 (0.09-0.43)   | 0.001   |
| <b>Cheese</b>                                    |             |                |                    |         |
| ≥ 3  | 6 (12.0)    | 20 (10)        | 1.23 (0.48-3.24)   | 0.076   |
| < 3  | 44 (88.0)   | 180 (90)       | 0.81 (0.31-2.15)   | 0.076   |
| <b>Yoghurt</b>                                   |             |                |                    |         |
| ≥ 3  | 25 (50.0)   | 110 (55)       | 0.82 (0.44-1.52)   | 0.059   |
| < 3  | 25 (50.0)   | 90 (45)        | 1.22 (0.66-2.27)   | 0.059   |
| <b>Butter</b>                                    |             |                |                    |         |
| ≥ 3  | 18 (36.0)   | 79(39.5)       | 0.86 (0.45-1.64)   | 0.650   |
| < 3  | 32 (64.0)   | 121(60.5)      | 1.16 (0.61-2,21)   | 0.650   |
| <b>Fries</b>                                     |             |                |                    |         |
| ≥ 3  | 41 (82.0)   | 163 (81.5)     | 1.03 (0.46-2.31)   | 0.935   |
| < 3  | 9 (18.0)    | 37 (18.5)      | 0.97 (0.43-2.16)   | 0,935   |
| <b>Fish</b>                                      |             |                |                    |         |
| ≥ 3  | 49 (98.0)   | 186 (93.0)     | 3.69 (0.47-28.75)  | 0.059   |
| < 3  | 1 (2.0)     | 14 (7.0)       | 0.007 (0.002-0.01) | 0.059   |
| <b>Meat</b>                                      |             |                |                    |         |
| ≥ 3  | 2 (4.0)     | 16 (8.0)       | 3.63 (1.59-8.29)   | 0.001   |
| < 3  | 48 (96.0)   | 184 (92.0)     | 0.27 (0.12-0.63)   | 0.001   |
| <b>Poultry</b>                                   |             |                |                    |         |
| ≥ 3  | 33 (66.0)   | 162 (81.0)     | 0.46 (0.23-0.9)    | 0.022   |
| < 3  | 17 (34.0)   | 38 (19.0)      | 2.20 (1.11-4.35)   | 0.022   |
| <b>Fruits</b>                                    |             |                |                    |         |
| ≥ 3  | 42 (84.0)   | 188 (94.0)     | 0.34 (0.13-0.87)   | 0.036   |
| < 3  | 8 (16.0)    | 12 (6.0)       | 2.98 (1.15-7.76)   | 0.036   |
| <b>Vegetables</b>                                |             |                |                    |         |
| ≥ 3  | 44 (88.0)   | 191 (95.5)     | 0.35 (0.12-1.02)   | 0.087   |
| < 3  | 6 (12.0)    | 9 (4.5)        | 2.89 (0.98-8.55)   | 0.087   |
| <b>Soya</b>                                      |             |                |                    |         |
| ≥ 3  | 4 (8.0)     | 27 (13.5)      | 0.56 (0.19-1.67)   | 0.291   |
| < 3  | 46 (92.0)   | 173 (86.5)     | 1.79 (0.60-5.39)   | 0.291   |

OR: Odds Ratio, CI: Confidence Interval

### Patients' lifestyle

Table 3 presents the patients' lifestyle data. The breast cancer risk factors after univariate analysis were: alcohol consumption (OR = 3.27; CI = 1.24-8.64;  $p = 0.031$ ); a number of meals > 3/day (OR = 8.55; CI = 1.52-47.62;  $p = 0.016$ ); meat consumption > 3 day/week (OR = 3.69; CI = 1.59-8.29;  $p = 0.001$ ) and physical activity  $\leq 3$  hours/week (OR = 5.68; CI = 1.70-19.23;  $p = 0.002$ ).

### Predictive factors of breast cancer after multivariate analysis

After multivariate analysis, the factors independently associated with the occurrence of breast cancer before the age of 40 were: age  $\geq 30$  (aOR = 2.05); family history of breast cancer (aOR = 8.65); parity  $\geq 1$  (aOR = 2.46); breastfeeding (aOR = 3.39); waist circumference  $\geq 88$  cm (aOR = 4.38) breast density  $\geq 90$  (aOR = 2.89); physical activity  $\leq 3$  hours/week (aOR = 4.78) (Table 4).

**Table 4: Predictive factors of breast cancer after multivariate analysis**

| Variables                            | aOR  | (95% CI)   | P-value |
|--------------------------------------|------|------------|---------|
| Age $\geq 30$                        | 2.05 | 1.07-3.49  | 0,024   |
| Parity $\geq 1$                      | 2.46 | 1.01-4.52  | 0.014   |
| Breastfeeding                        | 3.39 | 1.39-7.27  | 0.001   |
| Family history of breast cancer      | 8.65 | 6.8-20.11  | < 0.001 |
| Waist circumference $\geq 88$        | 4.38 | 1.79-9.86  | 0.001   |
| Densité mammaire $\geq 90$           | 2.89 | 1.31-5.11  | 0.001   |
| Physical activity $\leq 3$ h/semaine | 4.78 | 1.54-17.47 | 0.001   |

aOR: adjusted Odds Ratio, CI: Confidence Interval

### DISCUSSION

The age  $\geq 30$  years was a predictive factor of breast cancer in women under 40 in our study. Indeed, the risk of breast cancer in patients under 40 years of age increases with age; in 30-year-old patients, it ranges from 0.45% at 10 years to 4.1% at 30 years. In 40-year-old patients, it ranges from 1.47% at 10 years to 6.84% at 30 years.<sup>12</sup> Kocic et al, and McAree et al, had similar results with a mean age of 35.9 and 34.9 years respectively.<sup>13,14</sup> In both studies, young patients exhibited aggressive tumors features with advanced clinical stage, a higher percentage of ER-negative, PR-negative, vascular or lymphatic invasion and pathologic grade 3 tumors, highlighting the specificity of the tumor in patients below 40 years of age.

Family history of breast cancer was the most important risk factor of developing breast cancer among young women in our study. A positive family history of cancer is a very strong risk factor for women under 35 years of age (RR = 3.22) and suggests the presence of a familial

cancer syndrome including germline mutation BCRA1, BCRA2 and TP5.<sup>3</sup> The risk associated with a positive family history of breast cancer is strongly affected by the number of female first-degree relatives with and without cancer and the age at diagnosis.<sup>15</sup> Indeed, the higher the number of first-degree relatives affected and the earlier the age at diagnosis, the higher the risk of breast cancer in women under 40.

Parity  $\geq 1$  was two-fold associated to the breast cancer risk in women under 40 of age in our study. It is known that increasing parity and age at first full-term pregnancy are established risk factors for breast cancer in the general population, although, parity only provides a protective effect decade after childbirth.<sup>16</sup> This "protective" role of pregnancy is in fact a protective role for cancers occurring after menopause. However, before the age of 40 and immediately after pregnancy, there is a slight increase in the relative risk of 2 to 3 in the first 3 years after birth.<sup>15</sup> Some have hypothesized that the increase in estradiol and progesterone levels associated with pregnancy has an immediate deleterious effect that is replaced, after 10 years, by a protective effect of pregnancy.

Several studies have indicated that breastfeeding offers protection against breast cancer, which is the opposite of our results with a 3 times higher risk in breastfeeding young women.<sup>17</sup> These protective effects of breastfeeding appear to be stronger the longer a woman breastfeeds. The mechanisms explaining the reduction of breast cancer risk associated with breastfeeding involve a reduced susceptibility of the fully differentiated mammary gland to carcinogens and a reduced duration of overall exposure to estrogens and their promoting effect on breast carcinogenesis by anovulation.<sup>18</sup> The short duration of breastfeeding observed in our study population could explain the increased risk of breast cancer in our case as found by Cancer Research UK. They showed that the relative risk of breast cancer decreased by 7.0% for each birth in addition to a decrease of 4.3% for every 12 months of breastfeeding.<sup>19</sup>

Waist circumference (WC)  $\geq 88$  cm was also associated with breast cancer in this study. The role of overweight in the occurrence of breast cancer depends on the menopausal status. Postmenopausal women who are overweight have an increased risk of breast cancer, unlike non-menopausal women.<sup>15</sup> In a study carried out to assess the waist circumference and risk of breast cancer in Korean women, body mass index (BMI) and WC were robustly associated with increased risk for postmenopausal breast cancer ( $p < 0.001$  for both BMI and WC) but not with premenopausal breast cancer. Association between WC and premenopausal breast cancer was only statistically significant when considering BMI although Sellers and col. found that the higher the abdominal fat, the higher the risk of breast cancer in women with a family history of breast cancer, as is the

case for the majority of women below 40 with breast cancer.<sup>20,21</sup>

Young women with dense mammary tissue were three-fold likely to develop breast cancer than their counterparts. Similar results have been found by Duffy et al.<sup>22</sup> The estrogens levels in women with dense breast may not be involved in the occurrence of breast cancer.<sup>23</sup> Carcinogenesis would certainly be related to higher cell volume than in women with less dense breasts. Thus the American College of Radiology recommend supplementary screening tests, which can include a breast ultrasound screening or a breast MRI examination, or both, depending on individual risk factors in patients with dense breast.<sup>24</sup>

Physical activity  $\leq 3$  hours/week five-fold increased the risk of developing BC in young women in this study. Reviewing 73 studies conducted around the world on the association between physical activity and breast cancer risk, Lynch et al found a 25% average risk reduction amongst physically active women as compared to the least active women. It is likely that physical activity is associated with decreased breast cancer risk via multiple interrelated biologic pathways that may involve adiposity, sex hormones, insulin resistance, adipokines, and chronic inflammation.<sup>25</sup> Thus practicing physical activity could be an effective way to prevent breast cancer in young women.

## CONCLUSION

Breast cancer in women under 40 is associated with family history, reproductive life and women's lifestyles. Breastfeeding more than 12 months, having a balanced diet, supplementary screening tests in women with dense breasts and practicing physical activity would be effective ways to prevent it in young women.

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