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Risk Factors for Early Age at Breast Cancer Onset – The "COSA Program" Population-based Study

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Abstract. *Background: Breast cancer is the most frequent cancer in women in western countries. A number of risk factors are now known, but the etiology of the disease is not fully understood. The aim of this study was to determine the effects of reproductive, anthropometric and environmental factors on cancer onset. Patients and Methods: 934 women who developed a non-hereditary breast cancer were recruited from different hospitals in the Auvergne region (France) and completed a questionnaire. Results: The use of oral contraceptives (OC) increased the risk of early cancer development (odds ratio=1.84, 95% confidence interval=1.38-2.44). The age at first OC use appeared to be a major factor since the risk decreased when OC use was after the age of 23 years (odds ratio=0.52, 95% confidence interval=0.34-0.79). A duration of breast-feeding greater than 26 weeks decreased the risk of early cancer development (odds ratio=0.62, 95% confidence interval=0.39-0.97). No overall association was found with anthropometric or lifestyle factors and early age at breast cancer onset. Conclusion: OC use, age at first OC use and lactation were significantly associated with an early age at breast cancer onset. Thus, a number of "risk factors" could be considered as "early onset risk factors".*

Breast cancer is the most prevalent cancer among women in industrialized countries. Approximately 42,000 new cases and 12,000 breast cancer deaths were estimated to occur in the year 2000 in France. Genetic factors, in particular the major susceptibility genes *brca1* and *brca2*, have been shown to account for up to only 10% of breast cancer cases (1), other factors may therefore play a major role in the development of breast cancer. Low penetrance genes which act in concert with environmental factors may account for a large proportion of these carcinomas.

The epidemiology of breast cancer has been widely studied. The major influences on breast cancer risk appear to be certain reproductive factors (lifetime exposure to endogenous hormones), body size and lifestyle factors. An increased breast cancer risk is associated with early age at menarche, later age at menopause, nulliparity and later age at first pregnancy. Breast cancer risk has been positively correlated with body mass index (BMI) and height. Lifestyle factors also play an important role, the effect of smoking has shown controversial results, but the consumption of alcohol is positively associated with breast cancer (2, 3).

These risk factors are largely accepted, even if the association between these factors and breast cancer development remains complex. However few studies have investigated the relationship between these risk factors and early age at breast cancer onset.

The purpose of this descriptive study was to determine whether reproductive factors (use of oral contraceptives, age at menarche and menopause, breast-feeding, number of children and age at first live birth), anthropometric factors (BMI, height, waist and hip measurements) and lifestyle factors (smoking, alcohol and education) play a role in early age at breast cancer onset in a population of 934 women who developed non-hereditary breast cancer.

Patients and Methods

Study population. The COSA (Cancers de l'Ovaire et du Sein en Auvergne) program was a population-based study and consisted of the recruitment of 934 women who had developed breast cancer, identified from different clinics and hospitals in the Auvergne region in France from November 1996 through November 1999. Eligible study subjects were women who had been affected with

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non-hereditary breast cancer. All study subjects received counselling and provided written consent for the study. Participants completed a questionnaire about their medical and reproductive histories in particular and blood samples were collected.

The study group was stratified according to date of birth. The following categories were used: group 1-2 included women who were born in the 1910's and the 1920's; group 3, women who were born in the 1930's; group 4, women who were born in the 1940's and group 5, women who were born after 1950. This classification was created because of the evolution of women's behavior over the twentieth century and the changes in major breast cancer risk factors. For example, the use of oral contraceptives (OC) was about 3% in group 1-2, about 25% in group 3, about 60% in group 4 and more than 80% in the last group. As similar trend was observed for smoking habits and an opposite trend was observed for breast-feeding. The study of risk factors for early age at breast cancer onset must therefore be studied in separate groups according to these lifestyle changes.

Data collection. The questionnaires were administered by the Jean Perrin Centre. They were completed by the subjects at the time of a clinic appointment or later at home when that was not possible. The subjects were asked about their reproductive histories including parity, age at first live birth, duration of nursing, age at menarche, age at menopause and nature of menopause, and exogenous hormone use. "Use" of OC was defined as at least three months of use. Their anthropometric characteristics were also measured. Height, weight, waist and hip measurements were obtained at the clinic or hospital soon after the diagnosis. Additional information such as smoking status ("smoker" was defined as at least one year of smoking), radiation exposure, alcohol consumption, marital status and education were also collected. The breast tumors were classified by anatomopathologists and the Scarff-Bloom-Richardson (SBR) grade was used. The SBR grade of a tumor is based on the degree of glandular formation, mitotic rate and nuclear pleomorphism, each scored from I-III. A well-differentiated tumor is defined as grade I, a moderately differentiated as grade II and a poorly differentiated as grade III.

Data analysis. The software SEM (Jean Perrin Centre, Clermont Ferrand, France) was used for data analyses (4). Univariate analysis was first performed to select the most influential parameters for early age at breast cancer onset. When distribution was gaussian and variances equal, standard tests were used for the study of each group (Chi^2, Student's t-test, ANOVA). If not, the non-parametric Mann-Whitney U-Test and Kruskal-Wallis Test were used. The data are expressed as the difference in years of age at diagnosis ± standard deviation (SD) and compare the age at diagnosis in the four different groups for the risk factors. For the overall population, the difference of age at diagnosis was calculated with 95% confidence interval.

Multivariate models were used to select independent parameters or parameters that had a specific and significant influence on the early onset of the disease. The model used for multiparametric analysis was logistic regression (threshold: $p \leq 0.05$), with the odds ratio (OR) and 95% confidence interval (95% CI). A factor was created for the logistic regression, "young woman in her age bracket" in order to have a dichotomic parameter in the COSA population. If a woman's age at diagnosis was lower than the median of her age bracket, she was considered as a "young woman in her age bracket".

Results

Study subjects. 934 patients with first-time occurrence of breast cancer were included in the COSA program. In the overall population, the mean age at diagnosis was 57.9 (±11.9) years old, the age at menarche was 13 (±1.4), the age at first birth was 23.8 (±4.3) and the age at menopause was 48.9 (±8.4). The mean BMI in this study population was 24.7 (±4.6). A detailed presentation of the baseline characteristics in each birth decade group and in the overall population are reported in Table I.

Univariate analysis of risk. The results of univariate analysis for reproductive factors are reported in Table II with the difference of age at diagnosis and SD for each group. OC use was associated with an early development of breast cancer, a significant decrease in the age at diagnosis was observed in each group. In the overall population, a difference of age at diagnosis of 2.04 years (95% CI=1.88-2.2) was found when women took OC. The age at first OC use seemed to be an early onset factor in groups 4 and 5. Data were not provided for groups 1-2 and 3 because women of these groups did not take OC before the age of 23 years. For all patients, a significant difference of age at diagnosis of 2.62 years (95% CI=2.48-2.76) was detected between women who took OC after the age of 23 and women who took OC before the age of 23 years.

Concerning parity (data not shown), the number of births (0 / one or two children / three or more children) was not associated with early age at onset even though an increased age at diagnosis was noted with nulliparity in group 1-2 (p=0.07). The age at first birth (<20 years / 20-28 years / >28 years) did not modify the age at diagnosis except in group 5, in which it appeared that women who had their first birth before the age of 20 developed cancer later (p=0.08).

The duration of breast-feeding seemed to play a role in the early age at onset. The age at diagnosis was later when the duration of nursing was more than 26 weeks. It can be noted that the difference of age at diagnosis between women who breast-fed more or less than 26 weeks increased with their decade of birth.

An early age at menarche (≤13 years) slightly decreased the age at diagnosis for each group but not significantly. Pooled data showed a significant decrease of age at diagnosis when menarche was before 13 (0.27 years, 95% CI=0.12-0.43). Discordant results were observed for age at natural menopause. A slight early onset was observed when menopause was after 50 years old in groups 1-2 and 3 while in group 4 early onset breast cancer was associated with menopause before 50 years old.

Tables III and IV report the results of univariate analysis of anthropometric factors in premenopausal and

Table I. *Characteristics of each birth decade cohort and in the overall population.*

	Overall population n=934	Group 1-2 n=201 (22%)	Group 3 n=233 (25%)	Group 4 n=277 (30%)	Group 5 n=223 (24%)
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Age at diagnosis	57.9±11.9	74.4±4.5	63.5±3.0	53.2±3.1	42.8±4.8
Age at menarche	13.0±1.4	13.2±1.4	13.2±1.3	13.0±1.6	12.8±1.3
Number of births	1.9±1.3	2.4±1.6	2.4±1.7	2.5±1.4	2.2±1.5
Age at first birth	23.8±4.3	24.0±4.2	24.0±4.0	23.2±4.4	24.1±4.7
Age at menopause	48.9±8.4	49.6±7.3	49.3±10.2	48.5±6.7	43.3±4.2
BMI	24.7±4.6	25.7±4.0	25.8±4.5	24.4±4.8	22.9±4.4

Group 1-2 includes women who were born in the 1910's and the 1920's; Group 3 includes women who were born in the 1930's; Group 4 includes women who were born in the 1940's; Group 5 includes women who were born after 1950. SD: standard deviation.

Table II. *Univariate analysis of the difference of age at diagnosis (Δ) for reproductive factors in each group and in the overall population.*

	Overall population	Group 1-2[a]	Group 3[b]	Group 4[c]	Group 5[d]
Oral contraceptive (OC) use					
Δ (no user; user) ± SD (*p*)	2.04±0.08 (95% CI=1.88-2.20)	3.69±0.76 (0.041)	1.15±0.43 (0.0084)	1.72±0.36 (<0.001)	1.9±0.76 (0.0096)
Age at first oral contraceptive use (years)					
Δ (>23; ≤23) ± SD (*p*)	2.62±0.07 (95% CI=2.48-1.76)	–	–	2.55±0.49 (<0.001)	3.59±0.80 (<0.001)
Breast-feeding					
Δ (>26 weeks; ≤26 weeks) ± SD (*p*)	1.02±0.11 (95% CI=0.80-1.25)	0.58±0.81 (0.55)	0.65±0.50 (0.22)	1.13±0.79 (0.14)	1.73±1.23 (0.17)
Age at menarche (years)					
Δ (>13; ≤13) ± SD (*p*)	0.27±0.08 (95% CI=0.12-0.43)	0.49±0.65 (0.42)	0.33±0.42 (0.51)	0.11±0.40 (0.82)	0.22±0.8 (0.73)
Age at natural menopause (years)					
Δ (≤50; >50) ± SD (*p*)	0.025±0.008 (95% CI=1.13-0.18)	0.95±0.71 (0.17)	0.64±0.49 (0.2)	–2.03±0.48 (<0.001)	–

Women who were born [a]in the 1910's and the 1920's; [b]in the 1930's; [c]in the 1940's; [d]after 1950'. SD: standard deviation; CI: confidence interval.

Table III. *Univariate analysis of the difference of age at diagnosis (Δ) for anthropometric factors in premenopausal women (Groups 4 and 5).*

	Overall population	Group 4[a]	Group 5[b]
Obesity			
Δ (BMI <30; BMI ≥30) ± SD (*p*)	–1.60±0.09 (95% CI=–1.77-–1.43)	–0.93±0.36 (0.28)	–1.94±1.1 (0.11)
Waist measurement			
Δ (>33 inches; ≤33 inches) ± SD (*p*)	1.31±0.05 (95% CI=1.20-1.41)	0.20±0.33 (0.54)	1.85±0.62 (0.059)
Hip measurement			
Δ (>39 inches; ≤39 inches) ± SD (*p*)	0.77±0.06 (95% CI=0.65-0.89)	0.28±0.33 (0.41)	1.01±0.72 (0.4)

Women who were born [a]in the 1940's; [b]after 1950. SD: standard deviation; CI: confidence interval.

postmenopausal women respectively. The relationship between these factors and breast cancer is complex, as various studies have highlighted an association depending on menopausal status (5). For this reason, the univariate analysis separates pre- and postmenopausal women, except for the study of height (which is not correlated with menopause) (Table V) (6). Among premenopausal women, obesity seemed to be associated with a later age at breast cancer onset. No trends were observed among postmenopausal women.

The study of the association between fat deposition (waist and hip measurements) and early age at breast cancer onset revealed the same trends for each group and menopausal status. A waist measurement lower than 33 inches and a hip measurement lower than 39 inches seemed to be factors of

Table IV. *Univariate analysis of the difference of age at diagnosis (Δ) for anthropometric factors in postmenopausal women.*

	Overall population	Group 1-2[a]	Group 3[b]	Group 4[c]	Group 5[d]
Obesity					
Δ (BMI <30; BMI ≥30)±SD (*p*)	0.09±0.17 (95% CI=-0.25-0.42)	–0.26±0.88 (0.77)	0.42±0.51 (0.41)	0.11±0.67 (0.86)	–0.57±0.65 _
Waist measurement					
Δ (>33 inches; ≤33 inches)±SD (*p*)	0.50±0.22 (95% CI=0.07-0.93)	0.39±0.67 (0.56)	0.90±0.4 (0.031)	0.14±0.45 (0.76)	0.03±0.94 (>0.05)
Hip measurement					
Δ (>39 inches; ≥39 inches)±SD (*p*)	0.53±0.25 (95% CI=0.04-1.01)	0.20±0.65 (0.51)	1.07±0.39 (0.012)	0.12±0.45 (0.84)	0.98±1.07 (>0.05)

Women who were born [a]in the 1910's and the 1920's; [b]in the 1930's; [c]in the 1940's; [d]after 1950. SD: standard deviation; CI: confidence interval.

Table V. *Univariate analysis of the difference of age at diagnosis (Δ) for height.*

	Overall population	Group 1-2[a]	Group 3[b]	Group 4[c]	Group 5[d]
Height					
Δ (≤63 inches; >63 inches)±SD (*p*)	0.40±0.07 (95% CI=0.25-0.54)	0.79±0.66 (0.29)	0.33±0.39 (0.34)	0.12±0.38 (0.8)	0.46±0.64 (0.18)

Women who were born [a]in the 1910's and the 1920's; [b]in the 1930's; [c]in the 1940's; [d]after 1950. SD: standard deviation; CI: confidence interval.

Table VI. *Univariate analysis of the difference of age at diagnosis (Δ) for lifestyle factors.*

	Overall population	Group 1-2[a]	Group 3[b]	Group 4[c]	Group 5[d]
Smoking					
Δ (No; Yes)±SD (*p*)	0.37±0.08 (95% CI=0.20-0.53)	1.58±0.84 (0.16)	–1.09±0.54 (0.04)	0.75±0.41 (0.039)	0.33±0.64 (0.62)
Age smoking beginning					
Δ (≥20; <20)±SD (*p*)	1.68±0.47 (95% CI=0.75-2.6)	2.36±1.99 (>0.05)	1.41±0.95 (0.13)	0.24±0.7 (0.54)	2.68±0.82 (0.013)
Alcohol consumption					
Δ (No; Yes)±SD (*p*)	0.34±0.07 (95% CI=0.20-0.48)	0.46±0.69 (0.47)	0.25±0.39 (0.53)	0.29±0.37 (0.43)	0.39±0.65 (0.37)
Education level					
Δ (<; ≥High school)±SD (p)	0.23±0.12 (95% CI=–0.01-0.46)	–0.52±1.45 (0.92)	0.39±0.50 (0.41)	–0.61±0.43 (0.19)	1.76±0.66 (0.014)

Women who were born [a]in the 1910's and the 1920's; [b]in the 1930's; [c]in the 1940's; [d]after 1950. SD: standard deviation; CI: confidence interval.

early age at onset in pre- and postmenopausal women. A significant difference of age at diagnosis was obtained using all the data together.

The study of height (Table V) suggested that taller women developed earlier breast cancer in each group, but not significantly. When data were pooled, a slight but significant difference of age at diagnosis was observed between women smaller than 63 inches *versus* taller women.

The analysis of lifestyle factors is given in Table VI. The effect of smoking on early age at breast cancer onset was not conclusive in this population. A positive difference of age at diagnosis was found between women who did not smoke and women who smoked in groups 1-2, 4, 5, which meant that smoking seemed to decrease the age at diagnosis in these groups contrary to group 3 in which a significant increase in age was reported. For all patients together, a significant effect of smoking on early age at onset was observed (0.37 years, 95% CI=0.20-0.53). Smoking at or before the age of 20 appeared to be a factor for early age at onset in particular in group 5, in which a difference of age at diagnosis of 2.68 years was found ($p<0.05$).

The consumption of alcohol significantly reduced the age of which breast cancer developed when data were taken together. Indeed a difference of 0.34 years in age was reported between women who did not consume alcohol *versus* women who did.

Education appeared to have a significant effect in group 5 with a decrease of 1.76 years of the age at diagnosis when women had a level of education higher than high school. However, the effect of education on this group is complex, women with two years at university presented the earliest age at breast cancer onset. Women in group 5 with a high school level education or with three or four years at university developed breast cancer later, while women with at least five years at university were the last to develop the pathology in this group ($p=0.0072$) (Table VII).

Table VII. *Mean age at diagnosis±SD in each group according to education level.*

	Group 1-2[a]	Group 3[b]	Group 4[c]	Group 5[d]
Education level				
<High school	74.38±4.43	63.61±2.99	53.00±2.97	43.54±4.08
2 years at university	75.70±5.52	63.54±2.84	53.12±3.26	41.20±4.94
3-4 years at university	75.40±6.10	61.68±3.23	53.56±3.07	42.30±6.06
5 years at least at university	69.60±1.30	63.04±3.24	54.47±3.29	43.58±5.66
p value	0.29	0.49	0.31	0.0072

Women who were born [a]in the 1910's and the 1920's; [b]in the 1930's; [c]in the 1940's; [d]after 1950.

Table VIII. *Univariate analysis of the difference of age at diagnosis (Δ) for histological factors.*

	Overall population	Group 1-2[a]	Group 3[b]	Group 4[c]	Group 5[d]
Histological type (invasive ductal carcinoma; invasive lobular carcinoma)					
Δ (Invasive; lobular)±SD (*p*)	0.18±0.11 (95% CI=-0.05-0.4)	2.77±0.91 (0.031)	–0.61±0.65 (0.39)	0.67±0.54 (0.21)	–1.86±0.82 (0.17)
Scarff-Bloom-Richardson (SBR) degrees					
Δ (1,2 degree; 3 degree)±SD (*p*)	1.00±0.13 (95% CI=0.74-1.25)	0.89±0.96 (0.28)	0.18±0.66 (0.79)	0.05±0.48 (0.95)	2.98±1.02 (0.0032)

Women who were born [a]in the 1910's and the 1920's; [b]in the 1930's; [c]in the 1940's; [d]after 1950. SD: standard deviation; CI: confidence interval.

Women in group 1-2 developed cancer with lobular histology earlier, while women in group 5 had significantly earlier SBR grade 3 disease (Table VIII). However, it is important to note that SBR grade was related to the age at first OC use (p=0.0038) (data not shown).

Multivariate analysis of risk. The significant, most influential (p<0.2) and coherent factors in univariate analysis were chosen for the multivariate analysis. The results are reported in Table IX. OC use appeared to be the main factor of early age at breast cancer onset. A major protective factor seemed to be the duration of breast-feeding, with nursing for more than 26 weeks delaying the development of cancer.

Other factors which seemed to play a role in early age at onset in the univariate analysis appeared not to be relevant in the multivariate analysis. The role of education was not brought out in this analysis. Decreased OR were observed with an increase in the level of education. An age at menarche of more than 13 years decreased the risk of an early cancer development but not significantly. The same trends for anthropometric factors were observed, but were still not significant, for example higher waist and hip measurements diminished the risk, while a greater height and a high BMI increased the risk.

The role of the age at first OC use among women who used OC was analysed (Table X). First OC use after the age of 23 years decreased the risk of early breast cancer (OR=0.52, 95% CI=0.34-0.79) and the duration of breast-feeding decreased the risk (OR=0.48, 95% CI=0.23-1.00). The other factors studied were not relevant. These results could be explained by the loss of power of the study because of the small numbers of patients in these categories (392 women). Since the age at first OC use was a main factor of early age at breast cancer onset, age at first OC use was analysed in more detail (Table XI). The relative risks were calculated. This analysis suggested that the later the women took OC, the lower was the relative risk.

Discussion

The aim of this descriptive study was to determine if known risk factors for breast cancer were involved in the early age at onset of this disease in women. Indeed, many papers have searched for risk factors, but few have addressed the relationship between these factors and early age at onset.

Three of the factors in the present study were significantly associated with early age at breast cancer onset. The use of oral contraceptives (OC) increased the risk of early breast cancer, while OC use beginning after the age of 24 years and the duration of breast-feeding of more than 26 weeks decreased the risk. No association was found with other reproductive factors such as parity, age at first birth and age at menarche, or with anthropometric and lifestyle factors.

Oral contraceptive use was by far the most influential factor on breast cancer development. Univariate analysis showed that women who took OC developed breast cancer two years

Table IX. *Multivariate analysis of the whole population between different parameters.*

Parameters	OR[a]	95% CI[b]
OC use[c]	1.84	1.38-2.44
Breast-feeding (>26 weeks)	0.62	0.39-0.97
Education level		
<High school	1	
2 years at university	0.85	0.70-1.03
3-4 years at university	0.72	0.49-1.06
5 years at least at university	0.61	0.35-1.09
Age at menarche (>13 years)	0.89	0.67-1.18
Height (>63 inches)	1.20	0.90-1.61
Hip measurement (>39 inches)	0.92	0.63-1.35
Waist measurement (>33 inches)	0.82	0.63-1.28
BMI		
< 20	1	
20-25	1.06	0.79-1.42
>25	1.12	0.62-2.03
Smoking	0.93	0.68-1.26
Alcohol consumption	0.95	0.73-1.26
SBR grade[d]		
1 2	1.08	0.93-1.26
3	1.28	0.81-2.02

[a]Odds ratio; [b]95% confidence interval; [c]oral contraceptive use for at least 3 months; [d]Scarff-Bloom-Richardson grade.

Table X. *Multivariate analysis for women who used oral contraceptives.*

Parameters	OR[a]	95% CI[b]
Age at first OC use[c] (>23 years)	0.52	0.34-0.79
Breast-feeding (>26 weeks)	0.48	0.23-1.00
Education level		
<High school	1	
2 years at university	0.96	0.76-1.21
3-4 years at university	0.92	0.58-1.47
5 years at least at university	0.89	0.44-1.77
Age at menarche (>13 years)	1.10	0.70-1.79

[a]Odds ratio; [b]95% confidence interval; [c]oral contraceptive use for at least 3 months.

Table XI. *Multivariate analysis for age bracket at first oral contraceptive use.*

	RR[a]	95% CI[b]
Age at first OC use[c]		
<19 years	1	
<24 years	0.82	0.66-1.03
<31 years	0.71	0.56-0.91
≥31 years	0.57	0.42-0.76

[a]Relative risk; [b]95% confidence interval; [c]oral contraceptive use for at least 3 months.

earlier than women who did not, confirmed by the multivariate analysis with an odds ratio of 1.84. The age at first OC use appeared to be a major factor, with more risk being associated with earlier first use. Thus, the OC use and the age at first OC use could be considered as early onset factors.

Other studies of OC and breast cancer risk have shown contradictory results. A combined analysis of data from 51 epidemiological studies on exposure to hormonal contraceptives found that there was an increased risk of breast cancer for women taking OC and in the 10 years after stopping OC (RR=1.07±0.04) (7, 8). This risk was not significant when the OC use was discontinued ten years or more before diagnosis. No association with duration of use, dose or type of hormone was observed, though it appeared that the relative risk for recent users was higher for women who had begun OC before the age of 20 years than for those who began at later ages. The lack of an association between cancer risk and long term OC use could be explained by the lack of information beyond 20 years after the cessation of OC use. On the other hand, a more recent case–control study of 35- to 64-year-old women reported no association between breast cancer and current or former OC use (9).

The relationship between breast-feeding and breast cancer risk has been widely studied. Our results showed that a duration of breast-feeding longer than 26 weeks decreased the risk of developing breast cancer early (OR=0.62, 95% CI=0.39-0.97). Univariate analysis showed an increase of the difference of age at diagnosis with decade of birth, which highlighted the importance of breast-feeding. Indeed the period of breast-feeding is a behavior which decreased strongly with the decade of birth and the effect was all the more important as the behavior decreased. The protective effect of lactation on breast cancer risk is accepted in the literature. Furberg *et al.* (10) have suggested that breast-feeding was associated with a modest reduction in the risk of breast cancer among younger and older women regardless of duration. A review of the epidemiology literature has concluded that the protective effect of long-term breast-feeding was stronger among premenopausal women (11). The Collaborative Group on Hormonal Factors in Breast Cancer analysed 47 epidemiological studies in 30 countries and found that 12 months of breast-feeding diminished the relative risk of breast cancer by 4.3%, in addition to a decrease of 7% for each birth (12). One mechanism explaining the protective effect of breast-feeding was the reduced susceptibility of the fully differentiated mammary gland to carcinogens due to a decrease in proliferative activity of parous epithelium (13).

The other reproductive factors such as age at menarche and parity did not seem to be early onset risk factors, even though they have been shown to be involved in overall breast cancer risk. An early age at menarche increases the risk probably because of the prolonged exposure of breast epithelium to endogenous hormones. Similarly a late age at menopause is considered as a risk factor since it increases the number of ovulatory cycles (13). Concerning parity, a dual effect of pregnancies has been reported. On one hand, parity inhibits the early stages of mammary carcinogenesis (long-term risk reduction) due to the terminal differentiation of breast tissue. On the other hand, there is a short-term risk increase because of the proliferation of breast tissue in response to high gestational hormone levels which render the mammary gland more susceptible to carcinogens. Overall, early pregnancy and high parity are considered to have a protective effect (13-16).

Multivariate analysis showed no overall association between early age at breast cancer onset and anthropometric measurements despite trends observed in the univariate analysis. High BMI and obesity seemed to decrease the age at onset in premenopausal women, and height appeared to be associated with early onset regardless of menopausal status. Many epidemiological studies have investigated the relationship between anthropometric factors and breast cancer risk. All agree that a high BMI is associated with breast cancer risk among postmenopausal women whereas it decreases the risk among premenopausal women. One hypothesis to explain this difference is that an increase of aromatase activity in adipose tissue increases the levels of estrogens (3, 5, 17). Height has also previously been correlated with breast cancer risk (5).

The education level had no significant impact on early age at breast cancer onset, but this was influenced by the date of birth. Only 8% of the women in group 1-2 had an educational level higher than high school, whereas in group 5 it was 44%. Braaten *et al.* (18) reported a straight-line positive relationship between years of education and breast cancer risk. It should be remembered that certain professions have required more years of education in recent decades than in earlier ones. Other studies have focused on the role of socioeconomic status and it appears that women with the highest socioeconomic status are at higher risk of breast cancer than women with the lowest socioeconomic status (19).

The other lifestyle risk factors such as alcohol consumption or smoking were not relevant in the multivariate analysis in this study. The literature reports a positive association between alcohol intake and breast cancer risk (13, 20, 21) but results concerning smoking are not conclusive. Several studies have found no relationship, or a protective effect of smoking on breast cancer (22, 23) whereas others have suggested a slight increase in risk, in particular among premenopausal women and those who started smoking young (24).

It is concluded that OC use, age at first OC use and breast-feeding have an impact on early age at breast cancer onset.

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