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Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: a nested case-control study

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Abstract

Background and aims—The increase in breast cancer incidence over recent decades has been accompanied by an increase in the frequency of metabolic syndrome. Several studies suggest that breast cancer risk is associated with the components of metabolic syndrome (high serum glucose and triglycerides, low HDL-cholesterol, high blood pressure, and abdominal obesity), but no prospective study has investigated risk in relation to the presence of explicitly defined metabolic syndrome. We investigated associations between metabolic syndrome, its components, and breast cancer risk in a nested case-control study on postmenopausal women of the ORDET cohort.

Methods and results—After a median follow-up of 13.5 years, 163 women developed breast cancer; metabolic syndrome was present in 29.8%. Four matched controls per case were selected by incidence density sampling, and rate ratios were estimated by conditional logistic regression. Metabolic syndrome (i.e. presence of three or more metabolic syndrome components) was significantly associated with breast cancer risk (rate ratio 1.58 [95% confidence interval 1.07–2.33]), with a significant risk increase for increasing number of components (P for trend 0.004). Among individual metabolic syndrome components, only low serum HDL-cholesterol and high triglycerides were significantly associated with increased risk.

Conclusions—This prospective study indicates that metabolic syndrome is an important risk factor for breast cancer in postmenopausal women. Although serum HDL-cholesterol and triglycerides had the strongest association with breast cancer, all components may contribute to increased risk by multiple interacting mechanisms. Prevention or reversal of metabolic syndrome by life-style changes may be effective in preventing breast cancer in postmenopausal women.

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Keywords

metabolic syndrome; postmenopausal; breast cancer; nested case-control study; ORDET cohort

INTRODUCTION

The incidence of breast cancer, the most common cancer of women in developed countries, has increased steadily since statistics became available (1). Breast cancer is linked to reproductive and hormone-related factors, such as age at menarche, parity, age at menopause (2), endogenous sex hormone levels (3,4), and also to exogenous estrogens and progestagens (5).

The increase in breast cancer incidence has occurred in parallel with a steady increase in the frequency of type 2 diabetes and metabolic syndrome (6). Metabolic syndrome or insulin resistance syndrome, first described by Reaven in 1988 (7) as syndrome X, is characterized by abdominal obesity, dyslipidemia (high triglycerides and low HDL-cholesterol levels), high fasting blood glucose and high blood pressure levels. Various studies have suggested a direct association between components of metabolic syndrome and breast cancer risk. Thus low HDL-cholesterol (8), high blood glucose (9), high triglycerides (10), postmenopausal overweight (11), abdominal obesity (12), hypertension (13), and high levels of insulin (14), C-peptide (15), and insulin-like growth factor I (IGF-I) (16), have all been associated with increased breast cancer risk. Metabolic and hormonal factors related to metabolic syndrome have also been implicated in breast cancer prognosis (17,18); our own recent study found that presence of metabolic syndrome was associated with a significantly worse prognosis for breast cancer (19).

The mechanisms by which metabolic syndrome may influence the natural history of cancer are poorly understood, but probably include the effect of insulin on the bioavailability of sex hormones and growth factors (20–22) and the effect of overweight and insulin resistance on the bioavailability of inflammatory cytokines (23).

It is important to establish whether metabolic syndrome is a precursor of breast cancer since the syndrome can be reversed or prevented by lifestyle changes (diet and physical activity) (24,25) and the possibility arises that the risk of breast cancer can be reduced by such changes. However, to our knowledge, no prospective study has investigated the relationship of explicitly defined metabolic syndrome to subsequent occurrence of breast cancer. The purpose of the present prospective nested case-control study was to investigate the association of metabolic syndrome and its components with postmenopausal breast cancer risk. We initially investigated postmenopausal women and intend to investigate premenopausal women as the analytic data become available.

MATERIALS AND METHODS

Study subjects

Between June 1987 and June 1992, 10 786 healthy women, aged 35–69 years, resident in Varese Province, northern Italy, were enrolled in ORDET, a prospective study of hormones, diet and breast cancer risk (26). The women were volunteers from the general population. Women with a history of cancer, bilateral ovariectomy, chronic or acute liver disease or had received hormone therapy in the 3 months before recruitment were excluded. After exclusion of these women and those who, immediately after baseline, were lost to follow-up (time=0), 10 633 participants remained. We confined the present study to the 3966 participants who were postmenopausal at recruitment, defined as those who reported no menstruation over the

preceding 12 months. Signed informed consent was obtained from all participants. The Ethical Review Board of the Italian National Cancer Institute of Milan approved the study.

Data collection and anthropometric measurements

Trained nurses collected data on menstrual and reproductive histories, education, occupational history, socioeconomic status, family history of breast cancer and other potential risk factors for breast cancer according to standardized procedures, adherence to which was periodically checked. Anthropometric measurements were made with women in light clothes and without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2); waist-to-hip ratio (WHR) was calculated dividing waist circumference (measured at the narrowest point between the iliac crest and the lower rib, as observed from the front) by hip circumference (measured at the pubic symphysis). Blood pressure was measured three times with the subject in the sitting position, using a standard mercury sphygmomanometer. We considered the mean of the second and third measurements. The first and fifth phases of the Korotkoff sounds were also recorded. Observers had been trained and standardized (27,28) in the measurement of the blood pressure.

Specimen collection

Antecubital venous blood (40 mL) was drawn between 7:30 am and 9:30 am after overnight fasting. The time at venipuncture was recorded. Blood samples were protected from the light and temperature changes and processed by standardized procedures by trained personnel to obtain serum, plasma, red blood cell membranes and buffy coats. A 12-hour urine sample was also obtained. Aliquots were stored in freezers at about −80°C.

Breast cancer cases and selection of control women

The 3966 women were followed-up to December 31, 2003 (median follow-up=13.5 years), through local cancer registry (Lombardy Cancer Registry, Varese Province) characterized by high completeness and quality. The registry identified 181 new breast cancer cases among these women over the follow-up period. Seven had in situ breast cancer and 174 had invasive breast cancer. For each case (including in situ cases), four matched controls were chosen from cohort women with the same menopausal status at recruitment. Matching characteristics were age (±3 years) at recruitment, date of recruitment (±180 days), and laboratory batch (see below). An incidence density sampling protocol was used for control selection. Five invasive breast cancer cases, their matched controls and other two controls were excluded because no serum was available, leaving a total of 176 breast cancer cases (7 in situ, 169 invasive) and 702 controls for the study.

Analysis of serum samples

In the spring of 2007, case and control serum samples were analyzed together in batches by technicians blind to disease status. Each batch contained samples from a maximum of 16 and a minimum of three cases and their matched controls, together with lyophilized quality control serum samples (Lyphochek, Bio-Rad, Milan, Italy). Triglycerides, HDL-cholesterol and glucose were assayed using an automated immune-analyzer (AU400, Olympus Italia, Segrate, Italy); enzymatic colorimetric tests were used to determine triglycerides and HDL-cholesterol; an enzymatic UV test was used to determine glucose. Quality control samples at three concentrations for glucose and triglycerides and two concentrations for HDL-cholesterol were included and evaluated in quadruplicate for each batch. Quality control was performed at three concentrations for triglycerides and glucose and two concentrations for HDL-cholesterol. In each batch, quality control samples were evaluated in quadruplicate. Within-batch quality control coefficients of variation (CVs) were 1.2% (high concentration) and 1.0% (low concentration) for triglycerides, 1.1% for both concentrations for glucose, and 1.5% and 1.6%

respectively for HDL-cholesterol. Average between-batch CVs were 2.1% (high) and 2.3% (low) for triglycerides, 2.8% and 3.7% for glucose, and 3.4% for both concentrations for HDL-cholesterol.

Definition of metabolic syndrome

Metabolic syndrome has been defined in various ways (29,30), nevertheless all definitions require the presence of at least three among abdominal obesity, high blood triglycerides, low HDL-cholesterol, high blood glucose, and high blood pressure. Definitions differ as regards cutoffs. We measured triglycerides, HDL-cholesterol and glucose in serum samples stored for up to 15 years, so that long-term storage effects are likely (31). Glucose levels in particular are likely to have declined as glycolytic activity may continue in frozen samples (32). In order to take account of analyte concentration decay, we choose the cut-off values for metabolic syndrome (including anthropomorphic measurements) as the highest or lowest (HDL-cholesterol) tertiles of the distributions in controls. The following thresholds were used: waist circumference >86 cm; triglycerides >126 mg/dL; HDL-cholesterol ≤55 mg/dL; fasting glucose >88 mg/dL (or previously diagnosed type 2 diabetes); and mean blood pressure (diastolic pressure + 1/3(systolic pressure – diastolic pressure)) ≥106.5 mmHg (or treatment for previously diagnosed hypertension).

We also performed analyses applying the National Cholesterol Education Program (NCEP) (29) criteria for metabolic syndrome. These criteria require the presence of three or more of the following: waist circumference >88 cm; triglycerides ≥150 mg/dL; HDL-cholesterol <50 mg/dL; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg; and fasting glucose ≥110 mg/dL.

Statistical analysis

Multivariate conditional logistic regression was used to estimate rate ratios (RRs) and 95% confidence intervals (CIs) for associations between metabolic syndrome, metabolic syndrome components and breast cancer risk. We categorized subjects into tertiles of each variable used to define metabolic syndrome and dicotomized them into values above and below those indicating metabolic syndrome. We also categorized subjects according to the number of metabolic syndrome components present. However, because of the small number with five components, this category was merged with the category of four components. Additional analyses compared women with and without metabolic syndrome (according to our definition), and women categorized as: no metabolic syndrome components, 1–2 components, and 3–5 components. To assess the significance of linear trends we employed the Wald test on the beta of the categorical variable.

We present a crude model (adjusted only for matching variables) and an adjusted model including the potential confounders: age, age at menarche, years from menopause, number of full-term pregnancies, age at first birth, oral contraceptives (sometime/never), hormone therapy (sometime/never), years of education, history of breast cancer in first degree relatives (yes/no), breastfeeding (yes/no), smoking (pack-years) and alcohol consumption (abstainer/up to 1 drink per day/more than 1 drink per day). The model was not adjusted for BMI because in the present study it was not associated with breast cancer risk.

We excluded 13 cases, their matched controls and a few other controls from the adjusted models because confounding variable information was missing; the analyses were performed on 163 cases and 629 controls. All statistical tests were two-sided, differences were considered significant at the 5% level. All analyses were performed using the STATA version 10.0 statistical package.

RESULTS

Baseline characteristics of the cohort divided into those without and with metabolic syndrome (three or more components) are shown in Table 1. Compared to women without metabolic syndrome (n=556), those diagnosed with metabolic syndrome (n=236) were slightly older, used less oral contraceptives, and had a higher frequency of breastfeeding. Women with metabolic syndrome also had lower frequency of breast cancer family history, drunk less, smoked less and were less educated. The incidence of breast cancer in the study was 0.05 per 100 000 person years.

Table 2 shows the distribution of metabolic syndrome components among the study women. Two hundred sixty-nine (36.6%) women had high mean blood pressure, and an additional 80 women on antihypertensive drugs, were also classified as hypertensive. Two hundred forty (30.3%) women had high fasting blood glucose or reported diabetes (23 women) at baseline, 246 (31.1%) had abdominal obesity, 275 (34.7%) had high fasting triglycerides and 304 (38.4%) had low HDL-cholesterol. One hundred seventy women presented no signs or symptoms of metabolic syndrome (not shown in Table), 204 presented one metabolic syndrome component, 182 two components, 135 three components, 64 four components and 37 all the five components. High blood pressure was the most common component, especially among women with two or three components. Of the 236 study subjects with metabolic syndrome (three or more components), 185 had low HDL-cholesterol, 180 had high triglycerides, 177 had high blood pressure, 169 had abdominal obesity, and 135 had high fasting blood glucose.

Table 3 shows the association between metabolic syndrome variables (dichotomized according to their threshold values) and breast cancer risk. In the adjusted analyses breast cancer risk was directly and significantly associated with high fasting triglycerides (RR 1.59 [95% CI 1.10–2.29]), and low HDL-cholesterol (RR 1.60 [95% CI 1.10–2.33]). Abdominal obesity, high fasting blood glucose and high blood pressure were not significantly associated with breast cancer risk.

Table 4 shows the association between diagnosis of metabolic syndrome and risk of developing breast cancer. When adjusted for confounding variables, metabolic syndrome was a significant predictor of risk (RR 1.58 [95% CI 1.07–2.33]).

Table 4 also shows the effect on risk of increasing number of metabolic syndrome components. Exposure variables were first categorized into five categories with zero components as reference. For the adjusted analysis all categories were associated with a significantly increased risk compared to reference, with a significant linear trend (P 0.004). Exposure variables were next agglomerated into three categories: 0 components (reference), 1–2 components and 3–5 components. In the crude analysis both categories were associated with a significantly increased breast cancer risk compared to reference (RR 1.66 [95%CI 1.01–2.72] and RR 1.99 [95% CI 1.17–3.37] for 1–2 components and 3–5 components, respectively, vs. reference). These associations became stronger in the adjusted model (RR 1.92 [95% CI 1.13–3.24] and RR 2.60 [95% CI 1.47–4.61] for 1–2 components and 3–5 components, respectively, vs. reference). The test for linear trend was significant in both the unadjusted and adjusted analyses (P 0.014 and 0.001, respectively).

When we analyzed the association of breast cancer risk with presence vs. absence of metabolic syndrome according to the NCEP definition, we found that there was no significant association when three or more components vs. less than 3 were considered (RR 1.29 [95% CI 0.80–2.05]). However, the presence of four or more components with NCEP cutoffs was associated with a significantly higher risk of breast cancer that no components (RR 2.21 [95% CI 1.00–4.90]).

DISCUSSION

In this prospective study of postmenopausal women, presence of metabolic syndrome was directly and significantly associated with breast cancer risk. The risks became higher when three or more metabolic syndrome components were present compared to no components. Among individual components, high fasting triglycerides and low serum HDL-cholesterol were significantly associated with increased breast cancer risk in one or more models.

Although several studies have examined the relationship between individual components of metabolic syndrome and breast cancer (8–10,12,13), only a few have investigated breast cancer risk in relation to metabolic syndrome considered as a single entity; and to our knowledge, this is the first study to prospectively assess this relationship. A case-control study, conducted in Georgia (Caucasus) (33), found that metabolic syndrome and its components significantly influenced the formation of hyperplasia in mammary gland, endomyometrium, and uterine cervix. A direct, but non-significant, association between metabolic syndrome and breast cancer risk was found in a screening program in Taiwan (34). Another study (19) found that the risk of breast cancer recurrence was significantly greater in breast cancer patients with metabolic syndrome.

There are several possible mechanisms by which metabolic syndrome may promote the development of postmenopausal breast cancer. Metabolic syndrome is an insulin resistance syndrome, and several studies have implicated insulin in breast cancer development (22). C-peptide serum levels – indicator of pancreatic insulin production – is associated with increased breast cancer risk in postmenopausal women (15), and in breast cancer patients, high serum insulin is associated with poorer prognosis (17). Insulin has a gonadotropic effect (35). It stimulates the ovarian stroma to produce androgens, whose aromatization in peripheral tissues is the main source of estrogens after menopause (26,36). Insulin also upregulates aromatase activity (37). Most estrogens are produced in abdominal, breast, thigh and buttock adipose (38). Abdominal adipose, in particular, is an important source of both androgens and estrogens (39). Obese postmenopausal women produce high levels of estrogens, which are widely considered to mediate the association of obesity with breast cancer (40). In the present study, however, obesity was not associated with breast cancer risk, suggesting that metabolic syndrome has an effect that is independent of obesity. Insulin also lowers liver production of sex hormone-binding globulin (SHBG), thereby increasing sex hormone bioavailability (41) and metabolic syndrome is associated with increased circulating levels of both total (19) and free (21) testosterone. Total and free testosterone in turn are associated with increased breast cancer risk (3,42).

A further mechanism by which insulin may increase breast cancer risk is through its effect on the bioavailability of insulin-like growth factor I (IGF-I). Insulin decreases hepatic production of two IGF-binding proteins, IGFBP1 and IGFBP2 (43,44), thereby increasing IGF-I bioavailability, and stimulates the synthesis of GH-receptor (45,46) thus allowing GH to promote IGF-I synthesis. Both insulin (47) and IGF-I co-operate with estrogens to stimulate the proliferation of breast epithelium cells (16). Several prospective studies have examined the relationship of breast cancer with prediagnostic serum levels of IGF-I, with inconsistent results (16). The first studies found a positive association only in premenopausal women (9,48,49); more recent studies on larger cohorts, however, did not confirm an association before menopause, but highlighted a significant positive association after menopause (50,51).

Metabolic syndrome is also associated with increasing levels of inflammatory cytokines (52) and leptin (53), which can promote cell proliferation through various mechanisms (54,55), and is inversely associated with adiponectin (56), which downregulates tumor cell proliferation and upregulates apoptosis (55).

The present study has several strengths. First, the relation between metabolic syndrome and breast cancer was assessed prospectively, therefore reverse causation is unlikely; the prospective design also minimized selection bias arising from inappropriate selection of controls. Furthermore, this study is characterized by high standardization of baseline data collection, and specimen collection, storage and analysis. Analytical variation was minimized by collecting blood samples from cases and their matched controls under identical conditions and assaying them in the same batch.

A limitation of our study is that triglycerides, HDL-cholesterol and glucose were measured on samples collected between 1987 and 1992, stored at −80°C, and assayed up to 15 years later. For glucose, serum sample concentrations are subject to unpredictable decay over time because glycolysis can occur even at low temperatures (32). Triglycerides and HDL-cholesterol levels can also decay during long-term storage but less than glucose (31). If the rank of subjects does not change (i.e. decay half life is independent of initial concentration) then decay does not bias risk evaluation, although it does render problematic both the definition of metabolic syndrome and results extrapolation to the general population. To take the former problem into account, we defined metabolic syndrome according to the tertile distribution of variables in study subjects. Using this definition, metabolic syndrome was present in 29.8% of our population – a prevalence similar to that recently estimated in representative samples of postmenopausal Italian women using the standard definition of metabolic syndrome (www.cuore.iss.it). Had we used the NCEP definition the prevalence would have been only 17.0%.

Another study limitation is that we measured a single (baseline) serum sample, and hence cannot provide indications of intra-individual variation in analyte levels over time. However other studies have found that for most analytes (except triglycerides) variation is contained (57,58). As with many epidemiological studies, “contributing causes of death” bias could inflate the association between metabolic syndrome and breast cancer. This because metabolic syndrome is a risk factor for other diseases, and subjects who die of these diseases and had metabolic syndrome would no longer be in the risk set from which controls were selected, thereby generating healthier controls. To assess the magnitude of this bias we estimated the association between overall mortality and abdominal obesity, an important component of metabolic syndrome. The number of deaths was small in our cohort so few deaths could be attributed to abdominal obesity (proxy of metabolic syndrome), thus the bias from this source is likely small.

To conclude, the findings of this prospective study suggest that metabolic syndrome is an important risk factor for breast cancer in postmenopausal women. Among the components of metabolic syndrome, serum HDL-cholesterol and serum triglycerides had the strongest association with breast cancer risk, but all components may contribute to the increased risk by multiple mechanisms. Given the high prevalence of metabolic syndrome, it is likely to make a major contribution to breast cancer incidence in postmenopausal women, and because it is preventable through life-style changes (20,25), constitutes an important target for public health initiatives aimed at preventing breast cancer.

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Table 1

Baseline characteristics of study participants (236 with metabolic syndrome and 556 without metabolic syndrome). Figures are means ± standard deviations or numbers (percentages).

	Without metabolic syndrome (n=556)	With metabolic syndrome (n=236)
Age (years)	57.3 ± 5.8	58.8 ± 5.5
Age at menarche (years)	13.3 ± 1.5	13.1 ± 1.6
Number of pregnancies	2.0 ± 1.2	2.2 ± 1.3
Age at first pregnancy (years)	23.9 ± 9.1	23.6 ± 7.8
Age at menopause (years)	48.6 ± 4.9	48.3 ± 5.3
Previous oral contraceptive use	72 (12.9%)	24 (10.2%)
Previous hormone therapy use	117 (21.0%)	50 (21.2%)
Breastfeeding	411 (73.9%)	185 (78.4%)
Family history of breast cancer	51 (9.2%)	16 (6.8%)
Alcohol consumption:		
• None	217 (39.0%)	103 (43.6%)
• ≤1 drink/day	207 (37.2%)	77 (32.6%)
• >1 drink/day	132 (23.7%)	56 (23.7%)
Smoking status:		
• Never smoked	403 (72.5%)	178 (75.4%)
• Former smoker	60 (10.8%)	28 (11.9%)
• Current smoker	92 (16.5%)	28 (11.9%)
Pack-years	3.3 ± 8.2	2.5 ± 6.7
Education:		
• 5 years	340 (61.2%)	182 (77.1%)
• 8 years	122 (21.9%)	35 (14.8%)
• 10–13 years	80 (14.4%)	15 (6.4%)
• 15 or more years	14 (2.5%)	4 (1.7%)
Body mass index (Kg/m^2)	25.0 ± 3.6	29.5 ± 4.0

	Without metabolic syndrome (n=556)	With metabolic syndrome (n=236)
Waist-to-hip ratio	0.79 ± 0.05	0.85 ± 0.07

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Table 2

Classification of study subjects on the basis of number and type of metabolic syndrome components (tertiles definition*)

	1 component	2 components	3 components	4 components	5 components	Total
Abdominal obesity	21	56	78	54	37	**246** (31.1%)
High fasting triglycerides	31	64	87	56	37	**275** (34.7%)
Low HDL- cholesterol	37	82	93	55	37	**304** (38.4%)
Elevated fasting glucose	43	62	57	41	37	**240** (30.3%)
High blood pressure	72	100	90	50	37	**349** (44.1%)
Total	**204**	**182**	**135**	**64**	**37**	**792**

*Abdominal obesity: waist circumference>86 cm; High fasting triglycerides: triglycerides>126 mg/dl; Low HDL-cholesterol: HDL ≤55 mg/dl; Elevated fasting glucose: glucose>88 mg/dl or self-reported diabetes; High blood pressure: Mean blood pressure ≥106.5 mmHg or antihypertensive drug assumption

Table 3

Rate ratios (RR) for developing breast cancer in relation to presence of metabolic syndrome components

	No. controls	No. cases	Crude RR	Adjusted RR*
Abdominal obesity (waist circumference>86 cm)				
No	436	110	1	1
Yes	193	53	1.11 (0.76–1.61)	1.23 (0.83–1.81)
High fasting triglycerides (triglycerides>126 mg/dl)				
No	423	94	1	1
Yes	206	69	**1.49 (1.05–2.11)**	**1.59 (1.10–2.29)**
Low HDL-cholesterol (HDL ≤55 mg/dl)				
No	398	90	1	1
Yes	231	73	1.41 (0.99–2.02)	**1.60 (1.10–2.33)**
Elevated fasting glucose (glucose>88 mg/dl or self-reported diabetes)				
No	444	108	1	1
Yes	185	55	1.23 (0.85–1.80)	1.29 (0.87–1.93)
High blood pressure (mean blood pressure ≥106.5 mmHg or antihypertensive drug assumption)				
No	355	88	1	1
Yes	274	75	1.13 (0.80–1.61)	1.30 (0.89–1.89)

*Adjusted for age, age at menarche, years from menopause, number of full-term pregnancies, age at first birth, oral contraceptive use (sometime/never), hormone therapy use in the past (sometime/never), years of education, family history of breast cancer (yes/no), breastfeeding (yes/no), smoking (pack-years) and alcohol consumption (abstainer/less than or 1 drink per day/more than 1 drink per day)

Table 4

Rate ratios (RR) for developing breast cancer in relation to diagnosis of metabolic syndrome and number of its components

	No. controls	No. cases	Crude RR	Adjusted RR*
Metabolic syndrome				
Yes vs. No (tertiles definition)	179	57	1.37 (0.95–1.98)	**1.58 (1.07–2.33)**
Number of components				
0 components	146	24	1	1
1 component	161	43	1.65 (0.95–2.85)	**1.92 (1.08–3.44)**
2 components	143	39	1.67 (0.96–2.91)	**1.91 (1.07–3.41)**
3 components	101	34	**2.10 (1.17–3.76)**	**2.69 (1.43–5.05)**
4–5 components	78	23	1.83 (0.97–3.48)	**2.48 (1.25–4.91)**
P for trend			**0.030**	**0.004**
Number of components (agglomerated)				
0 components	146	24	1	1
1–2 components	304	82	**1.66 (1.01–2.72)**	**1.92 (1.13–3.24)**
3–5 components	179	57	**1.99 (1.17–3.37)**	**2.60 (1.47–4.61)**
P for trend			**0.014**	**0.001**

*Adjusted for age, age at menarche, years from menopause, number of full-term pregnancies, age at first birth, oral contraceptive use (sometime/never), hormone therapy use in the past (sometime/never), years of education, family history of breast cancer (yes/no), breastfeeding (yes/no), smoking (pack-years) and alcohol consumption (abstainer/less than or 1 drink per day/more than 1 drink per day)