Cancer Biology & Therapy 10:12, 1240-1243; December 15, 2010; © 2010 Landes Bioscience

Metabolic syndrome affects breast cancer risk in postmenopausal women

National Cancer Institute of Naples experience

Immacolata Capasso,[1] Emanuela Esposito,[1] Francesca Pentimalli,[2,3] Anna Crispo,[4] Maurizio Montella,[4] Maria Grimaldi,[4] MariaRosaria De Marco,[4] Ernestina Cavalcanti,[5] Massimiliano D'Aiuto,[1] Alfredo Fucito,[1] Giuseppe Frasci,[1] Nicola Maurea,[6] Giuseppe Esposito,[5] Tonino Pedicini,[1] Aldo Vecchione,[1] Giuseppe D'Aiuto[1] and Antonio Giordano[2,3,7]

[1]Department of Senology; [4]Division of Epidemiology; [5]Division of Clinical Pathology; and [6]Division of Cardiology; National Cancer Institute of Naples; G. Pascale; [2]Centro Ricerche Oncologiche Mercongliano; F. Lo Vuolo, Avellino, Italy; [3]Sbarro Health Research Organization; Philadelphia, PA USA; [7]Department of Human Pathology & Oncology; University of Siena; Siena, Italy

Key words: metabolic syndrome, breast cancer, weight gain, insulin resistance, body mass index, insulin-like growth factor 1 (IGF-1), high-density lipoprotein cholesterol (HDL-C), hyperinsulinemia, hyperandrogenic status, postmenopausal

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; MS, metabolic syndrome; NCEP, national cholesterol education program; ATP III, adult treatment panel III; WC, waist circumference; WHR, waist and hip ratio; IGF-1, insulin-like growth factor 1; IGFBP1, insulin-like growth factor binding protein 1; IGFBP2, insulin-like growth factor binding protein 2; IL-1, interleukin 1; IL-6, interleukin 6; PAI-1, plasminogen activator inhibitor type 1; SHBG, sex hormone binding globulin; TNFα, tumor necrosis factor alpha

Postmenopausal women show the highest incidence of breast cancer in the female population and are often affected by metabolic syndrome. Metabolic syndrome (MS)—characterized by central adiposity, insulin resistance, low serum high-density lipoprotein cholesterol (HDL-C), high serum triglyceride and high blood pressure—seems to be strictly correlated to breast carcinogenesis. We enrolled 777 healthy women and women with breast cancer in our nested case-control study to evaluate the association between MS and breast cancer, analyzing anthropometric parameters (weight, height, BMI, waist and hip circumference), blood pressure, serum HDL-C, triglyceride, fasting plasma glucose, insulin, testosterone and uric acid levels and administering a questionnaire about physical activity, food intake, tobacco use, alcohol abuse, personal and familial history of disease. We found an higher prevalence of metabolic syndrome (30%) in postmenopausal breast cancer patients compared to healthy women (19%). None of the individual MS features was strong enough to be considered responsible for breast carcinogenesis alone. However, of the 63 postmenopausal breast cancer cases associated to MS, 30% presented three or more MS features, suggesting that the activation of multiple molecular pathways underlying MS might contribute to tumorigenesis. Our data support the hypothesis that MS may be an indicator of breast cancer risk in postmenopausal women. The unsettlement of the hormonal arrangement in postmenopausal, along with an increase in visceral adiposity, probably favour the hormone-dependent cell proliferation, which drives tumorigenesis. Adjustments in lifestyle with physical activity intensification and healthy diet could represent modifiable factors for the primary prevention of sporadic breast cancer.

Introduction

Breast cancer incidence and metabolic syndrome (MS) prevalence are increasing in parallel in the western industrialized countries, both associated to sedentary life[1-3] and energy-dense diet.[4-7] Physical inactivity and saturated fatty diet contribute to the spread of overweight and obesity.[7-9] Central body fat and insulin resistance in overweight and obese women appear to be crucial in determining MS.[10] MS, according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), can be defined as the presence of at least three of the following clinical criteria: waist circumference >88 cm in women, HDL-C <50 mg/dl, blood pressure ≥130/85 mmHg, fasting plasma glucose ≥110 mg/dl, triglyceride >150 mg/dl.[10] MS affects about 22% of the general population. Postmenopausal women are often affected by MS and show the highest incidence of breast cancer in the female population. Moreover, women presenting hyperandrogenic status with decreased levels of sex hormone binding globulin (SHBG) and high free testosterone serum concentration develop more frequently breast cancers.[11,12] So, weight gain, consequent insulin resistance and hormonal changes in postmenopausal

*Correspondence to: Immacolata Capasso; Email: icapasso@tiscali.it
Submitted: 08/12/10; Accepted: 08/31/10
DOI: 10.4161/cbt.10.12.13473

deeply contribute synergistically to breast carcinogenesis.[13,14] Consistently, visceral fat is rich in aromatase, the converter enzyme of testosterone in estrone that stimulates ductal cell proliferation. Moreover, intra-abdominal fat, which is a source of free fatty acids, adiponectin and antiapoptotic factors such as TNFα, IL-1, IL-6 and PAI-1, is independently associated with all five of the MS criteria.[10,15] Also, high body mass index (BMI) values determine chronic hyperinsulinemia that causes insulin resistance.[4] Chronic hyperinsulinemia reduces the levels of insulin-like growth factor binding proteins, IGFBP1 and IGFBP2, thereby raising IGF-1 bioavailability.[16,17] IGF-1 functions both as a growth as well as gonadotrophic factor and is responsible for the free androgens fraction regulation, by inhibiting the hepatic synthesis of SHBG.[11,12,16] So far, many studies have examined the association of individual MS features with breast cancer risk but only a few examined the role of MS per se in relation to breast cancer onset.[18-21] Therefore, we set out to analyze the association between MS and breast cancer in a cohort of 777 patients; establishing whether such an association exist could have important implications in breast cancer prevention.

Results

A broad range of women, spanning 35–75 years in age and 19–48 kg/m² in BMI, was represented in our population with average patients middle-aged and overweight. Among the 777 women included in the study 210 cases and 289 controls were defined as postmenopausal (mean age 57.5 years, range = 45–75 years) with Odds Ratio of postmenopausal breast cancer of 1.61. (95% CI 1.07 to 1.77). There were no significant differences in MS prevalence between cases and controls in premenopausal, whereas the prevalence of MS in postmenopausal was 30% (63 pts) for cases (95% CI= 0.24 to 0.35) and 19% for controls (57 pts) (95% CI = 0.15 to 0.22) (**Fig. 1**). MS was present in almost one third of postmenopausal women operated for breast cancer (cases). Among the 63 cases of postmenopausal breast cancer associated to MS, 37 patients (18%) presented three criteria of MS (low grade MS) (95% CI = 0.13 to 0.22) and 26 patients (12%) more than three criteria (high grade MS) (95% CI = 0.08 to 0.15). OR confirms this trend for low grade MS 1.31 (95% CI 1.07 to 1.23) and for high grade MS 1.69 (95% CI 0.94 to 3.05) respectively. Both cases and controls were characterized by high BMI percentage (60% of cases compared to 62% of controls), but even in this subgroup the prevalence of MS observed was higher in cases than in controls (36% for cases compared to 22% for controls). Waist circumference >88 cm was measured in 62% of cases (OR 2.66 95% CI 2.06 to 3.49) and 38% of controls. In relation to age, 40% of cases in the age range of 55–65 years fulfilled MS criteria, whereas only 22% of controls in the same age range fulfilled the same criteria ($p < 0.05$). 32% of cases presented HDL-C <50 mg/dl (95% CI = 0.27 to 0.37) with OR of breast cancer 1.29 (95% CI 1.06 to 1.56) compared to 26% of controls (95% CI = 0.30 to 0.22). Hyperinsulinemia was detected in 7% of cases and only in 3.5% of controls ($p < 0.05$) with OR 2.14 (95% CI 1.78 to 2.99). 76% of all women presenting hyperinsulinemia and affected by breast cancer, showed more than three criteria of MS and MS was positively associated to each criteria, whereas only 50% of controls with hyperinsulinemia presented any other MS criteria. The hyperandrogenic status, determined by testosterone dosage on blood serum was weakly higher in cases subgroup (14% versus 10%) and although not statistically significant, it is impressing its strict correlation to the other MS parameters in breast cancer affected women. Among all women with hyperandrogenic status 34% of cases presented more than three MS criteria fulfilled. Further 39% of cases presented high blood pressure (95% CI = 0.33 to 0.44) with OR of 1.54 (95% CI 1.05 to 1.37) compared to 33% of controls (95% CI = 0.28 to 0.37) ($p < 0.05$). Hyperuricemia was noticed in 11% of cases (95% CI = 0.28 to 0.50) and 5% of controls (95% CI = 0.15 to 0.25) ($p < 0.01$) and was associated with OR of 1.72 (95% CI 1.01 to 1.76).

Discussion

The data emerged from our study underline the existing linkage between the biochemical alterations characterizing MS and breast carcinogenesis. Our outcomes showed an higher prevalence of MS (30%) among women with breast cancer in postmenopausal compared to healthy women (19%). Both android fat distribution (WC >88 cm) and insulin resistance correlate to MS in the subgroup of postmenopausal breast cancer affected women, as expected, and are positively and independently associated with more than three of the other criteria of MS.[4,10] We did not find differences in BMI between cases and controls; however, waist circumference, hyperinsulinemia, low serum HDL-C and hyperandrogenic status all seem to affect breast cancer risk.[23,24] Even though none of the MS features seems strong enough to individually influence breast carcinogenesis, the coexistence with others increases breast cancer risk. This finding probably reflects the fact that different molecular pathways need to be activated to induce breast tumorigenesis. Consistent with this, in our subgroup of postmenopausal breast cancer patients the presence of one MS feature was mostly correlated to the others. Moreover, in our study, age did impact on the relation between MS and breast cancer development. In the age range of 55–65 years, 40% of breast cancer cases presented more than three MS features. It is tempting speculate that the switchover from premenopausal to postmenopausal constitutes a window during which the unsettlement of the hormonal arrangement, along with genetic and epigenetic factors, favor the initiation of breast carcinogenesis.[25] In vitro studies have shown that low serum HDL-C stimulates the growth of hormone dependent breast cancer cells.[23,24,26] Low serum HDL-C is independently associated with increased postmenopausal breast cancer risk among obese and overweight women. Furthermore serum HDL-C may be considered a marker of androgen status, because hormones finely tune the levels of serum HDL-C, by regulating the activity of the lipolytic enzyme hepatic lipase.[17,23] Visceral adiposity developed in postmenopausal and detectable through waist and hip circumference measurement, more than BMI, seems to be the great determinant that leads to all other MS features, particularly impaired glucose tolerance and lower HDL-C.[10] Indeed 53% of all breast cancer affected women was found to have WC >88 cm. Therefore, the

outcomes of our study suggest that visceral adiposity, with android fat distribution, hyperinsulinemia and free androgen fraction increasing in postmenopausal women contribute to breast carcinogenesis.[4]

Several evidences indicate an association between MS and breast cancer, primarily owing to insulin resistance and low serum HDL-C.[18] Insulin resistance determines the increase of IGF-1 bioavailability that inhibits the hepatic synthesis of SHBG and stimulates cell proliferation through specific receptors. HDL-C can be considered as an independent predictor of increased levels of several cancer-promoting hormones (insulin, estrogens and androgens), which regulate its levels through the modulation of liver hepatic lipase activity. According to our outcomes the keystone of this metabolic arrangement is weight gain and the consequent visceral adiposity typical of the postmenopausal period.[10] This may have a role in MS development and may contribute to breast carcinogenesis through the activation of different pathways involving increased levels of aromatase and IGF-1, reduction of SHBG, pro-inflammatory and anti-apoptotic cytokines. Our results suggest the possibility of applying primary prevention for breast cancer, through lifestyle changes, to postmenopausal women who show MS features. Such preventive strategy will likely not protect from hereditary breast cancer, which represents around 10% of all breast tumors. Currently, for hereditary breast cancer only strict surveillance screenings, prophylactic surgery or chemoprevention support the physician in breast cancer detection and cure. However, for sporadic cancers, environment adjustments, physical activity intensification[1-3] and healthy food intake[7,8] could reduce body metabolic alterations and breast cancer risk. In conclusion, although further studies are required to more precisely assess the relationship between MS and breast cancer, our study paves the way for the development of new primary prevention strategies for sporadic breast cancer.

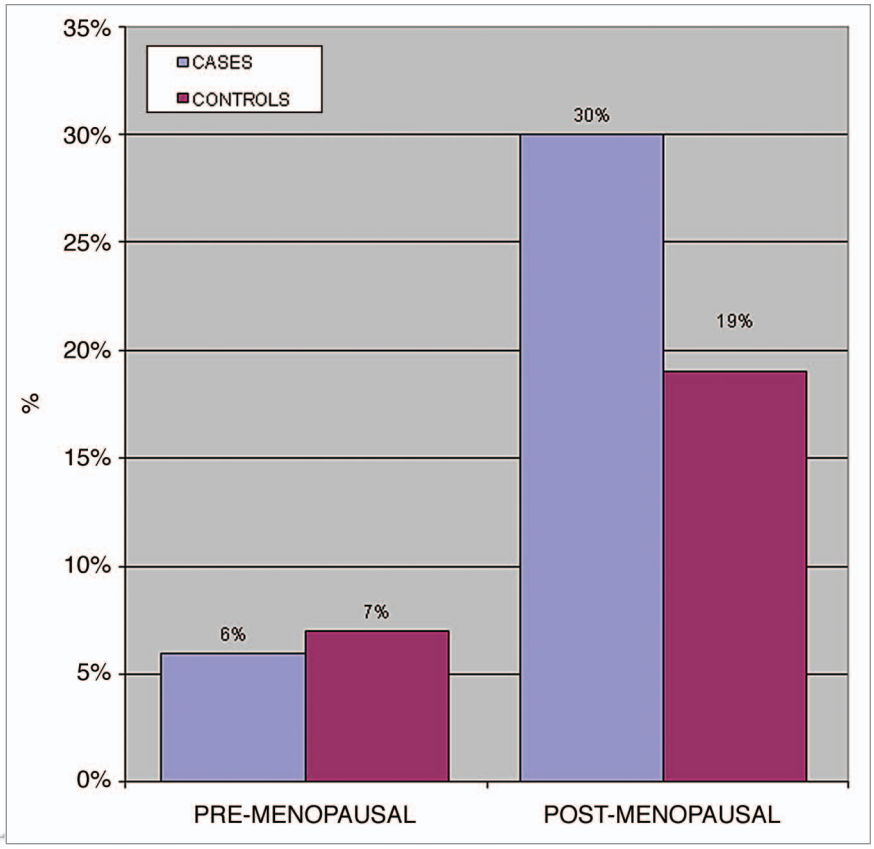

Figure 1. Metabolic syndrome in women with breast cancer. On the y-axis the percentage of patients with metabolic syndrome is reported. Postmenopausal women with breast cancer show a higher prevalence of metabolic syndrome compared to controls.

Patients and Methods

A total of 777 patients have been enrolled in our nested case-control study. 293 of them operated for breast cancer (cases) and 484 healthy women (controls) have been recruited between 2008 and 2009 to take part to our study for evaluating the association between MS and breast cancer. Liver or renal disease, thyroid pathology and coronary artery disease were considered exclusion criteria. After obtaining informed consent, for each woman anthropometric features were measured, including weight in kilograms, height in meters, waist and hip circumference, arterial blood pressure was taken and venous blood was collected.[15] BMI (kg/m²) was calculated from weight and height values according to World Health Organization classification (<25 kg/m² = underweight/normal, ≥25 kg/m² = overweight/obese), waist and hip ratio (WHR) was obtained from waist and hip circumference, measuring the smallest circumference of both to discriminate between android and gynoid fat distribution.[22] From blood samples fasting plasma glucose, HDL-C, triglyceride, uric acid, insulin and testosterone levels were assessed. Fasting plasma glucose, HDL-C and triglyceride were measured according to NCEP ATP III criteria. The normal range for uricemia was 2.6–6.0 mg/dl. Insulin levels were defined in normal range when between 5 and 25 mcU/ml, whereas ≥25 mcU/ml were considered hyperinsulinemia. Testosterone levels were considered in the normal range when 0.20–1.20 ng/ml. Levels >1.20 ng/ml were considered indicative of hyperandrogenic status. Women were asked to answer a questionnaire about chronic diseases, tobacco use, alcohol abuse, food intake, physical activity grade, parity, age of menarche, menopausal status, oral contraceptive use, hormonal therapy use, personal and familial history of cancer. According to the NCEP ATP III,[10] women presenting three disorders were diagnosed with low grade MS,[5] whereas women presenting more than three disorders (four or five) were diagnosed with high grade MS. Chi-squared test and logistic regression analyses (OR and 95% CI) were used to confirm the association between MS and breast cancer and to calculate the risk. Statistical significance was considered at $p < 0.05$.

Acknowledgements

We wish to thank the Sbarro Health Research Organization of Philadelphia for supporting us during our study.

References

1. van Gils CH, Peeters PH, Schoenmakers MC, Nijmeijer RM, Onland-Moret NC, van der Schouw YT, et al. Physical activity and endogenous sex hormone levels in postmenopausal women: a cross-sectional study in the Prospect-EPIC Cohort. Cancer Epidemiol Biomarkers Prev 2009; 18:377-83.
2. Enger SM, Ross RK, Paganini-Hill A, Carpenter CL, Bernstein L. Body size, physical activity and breast cancer hormone receptor status: results from two case-control studies. Cancer Epidemiol Biomarkers Prev 2000; 9:681-7.
3. Friedenreich CM, Courneya KS, Bryant HE. Case-control study of anthropometric measures and breast cancer risk. Int J Cancer 2002; 99:445-52.
4. Kaaks R. Nutrition, hormones and breast cancer: is insulin the missing link? Cancer Causes Control 1996; 7:605-25.
5. Agnoli C, Berrino F, Abagnato CA, Muti P, Panico S, Crosignani P, et al. Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: a nested case-control study. Nutr Metab Cardiovasc Dis 20:41-8.
6. Stoll BA. Western nutrition and the insulin resistance syndrome: a link to breast cancer. Eur J Clin Nutr 1999; 53:83-7.
7. Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, et al. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. Cancer Sci 2005; 96:590-9.
8. Gaard M, Tretli S, Loken EB. Dietary fat and the risk of breast cancer: a prospective study of 25,892 Norwegian women. Int J Cancer 1995; 63:13-7.
9. Lof M, Hilakivi-Clarke L, Sandin SS, de Assis S, Yu W, Weiderpass E. Dietary fat intake and gestational weight gain in relation to estradiol and progesterone plasma levels during pregnancy: a longitudinal study in Swedish women. BMC Womens Health 2009; 9:10.
10. Carr DB, Utzschneider KM, Hull RL, Kodama K, Retzlaff BM, Brunzell JD, et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes 2004; 53:2087-94.
11. Baglietto L, Severi G, English DR, Krishnan K, Hopper JL, McLean C, et al. Circulating steroid hormone levels and risk of breast cancer for postmenopausal women. Cancer Epidemiol Biomarkers Prev 19:492-502.
12. Gillmer MD. Mechanism of action/effects of androgens on lipid metabolism. Int J Fertil 1992; 37:83-92.
13. Bruning PF, Bonfrer JM, van Noord PA, Hart AA, de Jong-Bakker M, Nooijen WJ. Insulin resistance and breast-cancer risk. Int J Cancer 1992; 52:511-6.
14. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998; 351:1393-6.
15. Tian YF, Chu CH, Wu MH, Chang CL, Yang T, Chou YC, et al. Anthropometric measures, plasma adiponectin and breast cancer risk. Endocr Relat Cancer 2007; 14:669-77.
16. Peyrat JP, Bonneterre J, Vennin PH, Jammes H, Beuscart R, Hecquet B, et al. Insulin-like growth factor 1 receptors (IGF1-R) and IGF1 in human breast tumors. J Steroid Biochem Mol Biol 1990; 37:823-7.
17. Kaaks R. [Plasma insulin, IGF-I and breast cancer]. Gynecol Obstet Fertil 2001; 29:185-91.
18. Kabat GC, Kim M, Chlebowski RT, Khandekar J, Ko MG, McTiernan A, et al. A longitudinal study of the metabolic syndrome and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2009; 18:2046-53.
19. Xue F, Michels KB. Diabetes, metabolic syndrome and breast cancer: a review of the current evidence. Am J Clin Nutr 2007; 86:823-35.
20. Healy LA, Ryan AM, Carroll P, Ennis D, Crowley V, Boyle T, et al. Metabolic syndrome, central obesity and insulin resistance are associated with adverse pathological features in postmenopausal breast cancer. Clin Oncol (R Coll Radiol) 2010; 22:281-8.
21. Maiti B, Kundranda MN, Spiro TP, Daw HA. The association of metabolic syndrome with triple-negative breast cancer. Breast Cancer Res Treat 2010; 121:479-83.
22. Adebamowo CA, Ogundiran TO, Adenipekun AA, Oyesegun RA, Campbell OB, Akang EE, et al. Waist-hip ratio and breast cancer risk in urbanized Nigerian women. Breast Cancer Res 2003; 5:18-24.
23. Furberg AS, Veierod MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile and breast cancer risk. J Natl Cancer Inst 2004; 96:1152-60.
24. Moorman PG, Hulka BS, Hiatt RA, Krieger N, Newman B, Vogelman JH, et al. Association between high-density lipoprotein cholesterol and breast cancer varies by menopausal status. Cancer Epidemiol Biomarkers Prev 1998; 7:483-8.
25. Lupien M, Brown M. Cistromics of hormone-dependent cancer. Endocr Relat Cancer 2009; 16:381-9.
26. Rotheneder M, Kostner GM. Effects of low- and high-density lipoproteins on the proliferation of human breast cancer cells in vitro: differences between hormone-dependent and hormone-independent cell lines. Int J Cancer 1989; 43:875-9.