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Serum resistin is inversely related to breast cancer risk in premenopausal women

Georgia P. Georgiou [a], Xeni Provatopoulou [b], Eleni Kalogera [b], Gerasimos Siasos [c, d], Evangelos Menenakos [a], George C. Zografos [a], Antonia Gounaris [b, *]

[a] 1st Department of Propaedeutic Surgery, Hippokratio Hospital, School of Medicine, University of Athens, Athens, Greece
[b] Research Center, Hellenic Anticancer Institute, Athens, Greece
[c] Department of Biological Chemistry, School of Medicine, University of Athens, Athens, Greece
[d] 1st Department of Cardiology, School of Medicine, University of Athens, Athens, Greece

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ABSTRACT

Background: Adipokines have been suggested as potential mediators linking obesity and breast cancer. Resistin is the least-studied adipokine with diverse findings regarding its association with disease development and progression. The present study aimed to determine resistin serum levels in breast cancer in relation to the histological type of disease and to investigate their association with breast cancer risk.

Methods: The study included 216 women, of which 163 were diagnosed with breast cancer (58 with IDC, 52 with DCIS and 53 with LN) and 53 were healthy. Serum levels of resistin, leptin and adiponectin were quantitatively determined in duplicates by ELISA. Differences in resistin levels among patient groups were evaluated with Kruskal–Wallis and Mann–Whitney tests. The association of resistin with breast cancer risk was evaluated by multiple logistic regression analysis.

Results: Resistin levels varied between histological types of breast cancer ($p = 0.044$). Significant differences in serum resistin were observed in IDC patients compared to those with DCIS and to controls ($p < 0.014$ and $p < 0.03$, respectively). Decreased levels of resistin, adiponectin and leptin were observed in premenopausal patients. Resistin was associated with a reduced risk for ductal carcinoma only in premenopausal women (OR: 0.364, 95% CI: 0.154–0.862, $p < 0.022$).

Conclusion: Our findings indicate that resistin levels were inversely related to breast cancer risk in premenopausal women, supporting a protective role of resistin for these patients. Further advances in adipokine research may lead to tangible benefits for overweight/obese women at an increased risk for breast cancer.

Introduction

Worldwide, breast cancer (BC) is the most frequently diagnosed cancer and the second cause of cancer-related death in women [1]. As its prevalence increases with age, BC is more common in older postmenopausal women. During the last decades, BC incidence rates have been rising dramatically primarily due to the prolonged life-span and the increased exposure to well-established risk factors. These include age and reproductive factors such as earlier age at menarche, later age at menopause, older age at first birth, decreased parity, and use of hormone replacement therapy or oral contraceptives [2,3]. Histological characteristics, notably atypical hyperplasia of the mammary gland and carcinoma *in situ* as well as high breast density on mammographic screening have been associated with an increased risk of BC [4]. Among lifestyle habits, alcohol consumption has been moderately related to BC development [2,3]. Obesity is considered an important risk factor of BC, particularly in postmenopausal women [2,5]. Other common risk factors for BC include the presence of germline mutations in BRCA1 or 2 genes and a family history of BC [2,4]. Despite the identification of numerous factors that are associated with BC risk, it is interesting that more than 50% of BC cases appear to arise in the absence of known risk factors [6].

* Corresponding author. Research Center, Hellenic Anticancer Institute, 11 Valtetsiou st, 10680, Athens, Greece. Fax: +30 2103643723.
E-mail address: antgouna@otenet.gr (A. Gounaris).

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Obesity has been recognized as a major public health issue in industrialized countries that is growing rapidly and affects a significant part of the population across all age, gender and ethnic groups. It is well-established that obesity increases the risk for various types of cancer including colon, prostate and breast [7–9]. Many studies have provided strong evidence that obesity is associated with BC primarily in the postmenopausal population, even though the underlying mechanisms remain largely unclear [8–10]. It has actually been reported that excess body weight significantly increases postmenopausal BC risk by 30–50% [11]. Obesity has also been associated with characteristics of a more aggressive BC phenotype such as increased tumor burden, higher histopathological grade and high incidence of lymph node metastasis [12–14]. In addition, there is evidence that overweight/obese patients present poorer outcomes, being at an increased risk for BC progression and BC-related mortality regardless of their menopausal status [5,14,15].

Recently, adipokines have been suggested as potential mediators linking obesity and BC by several experimental and epidemiological studies [6,12,16–24]. The adipose tissue is nowadays considered not only a fat-storing tissue but also an endocrine organ secreting various adipokines. Adipokines are a group of biologically active polypeptides mainly produced by adipose tissue and released in the systemic circulation. They can act on target tissues by autocrine, paracrine or endocrine mechanisms and have been proposed to influence both BC risk and biological behavior [24,25]. However, their role and associated mechanisms mediating the effect of obesity on BC development and progression in pre- and postmenopausal women need to be further elucidated.

Resistin, also known as adipocyte-secreted factor or found in inflammatory zone 3 (FIZZ3), is a novel adipokine involved in the regulation of insulin resistance [26,27]. It is a 12.5 kDa hormone encoded by the RSTN gene and a member of the newly discovered family of cysteine-rich proteins called “resistin-like molecules” (RELMs) [27–29]. Although resistin was originally described as an adipocyte-derived cytokine in rodents, it is mostly expressed by macrophages in humans [30]. Up-regulation of resistin has been observed in obesity while its levels have been associated with inflammatory markers, suggesting its implication in obesity-related pathologic conditions accompanied by chronic inflammation [31]. Thus, resistin has been proposed as a potential link between obesity and atherosclerosis, cardiovascular diseases, rheumatic diseases, non-alcoholic fatty liver disease and various malignancies [31]. Recent studies have demonstrated that circulating resistin levels are significantly elevated in patients with breast, gastric, colorectal and endometrial cancer as well as with esophageal squamous cell carcinoma and lymphoma [32–41].

Until today, an exceptionally limited number of studies have examined the association between resistin expression and BC with diverse findings. Moreover, most reports have investigated resistin in postmenopausal individuals while very few data are currently available on its role in premenopausal BC. The wide range and inconsistency between findings can be partly attributed to inhomogeneity of study design, differences in detection methods and small sample sizes resulting in limited power to detect small differences in resistin levels. Better-controlled studies, accounting for potential confounders using appropriate statistical models, are needed to unequivocally establish whether resistin is associated with BC pathogenesis in the pre- and postmenopausal population.

In the present study, we investigated serum resistin in patients with newly diagnosed BC compared to healthy controls. Resistin levels were analyzed in relation to the histopathological type of the disease, in three distinct groups of patients with invasive ductal carcinoma (IDC), *in situ* ductal carcinoma (DCIS) and lobular neoplasia (LN). Logistic regression analysis was applied to assess the potential association between serum resistin levels and BC risk in pre- and postmenopausal women.

Materials and methods

Patient population

The study included 216 female patients with a mean age of 56.66 ± 11.39 years, who visited the Breast Cancer Unit, at Hippokratio Hospital, in Athens, Greece. From June 2010 to March 2013, women who had undergone mammary biopsy with a diagnosis of BC or surgery for the disease were asked to participate in the study. Healthy controls were 53 women with mean age 56.21 ± 17.72 years who attended the Breast Unit for their annual mammography and clinical breast examination, during which the presence of BC or suspicious findings was excluded. The study was approved by the hospital's ethics committee, and written informed consent was obtained from all individual participants included in the study.

Inclusion criteria consisted of the presence of histological confirmed BC. Participants with body weight over 120 kg, diabetes mellitus type 2 (DMT2), chronic renal failure, other types of cancer, severe autoimmune diseases, severe osteoarthritis, severe chronic respiratory problems, or severe heart failure were excluded from the study. All women completed an extensive interviewer-administered questionnaire regarding their demographic, reproductive and anthropometric characteristics.

Sample analysis

Peripheral blood samples were collected from all participants between 8:00 and 10:00 am, after overnight fasting. Blood samples were collected into sterile tubes, were allowed to clot for 30 min at room temperature, were centrifuged, and then aliquoted and subsequently stored at −80 °C according to standard protocols. Serum levels of the adipokines resistin, leptin and adiponectin were quantitatively determined in duplicates by enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's instructions (BioVendor Laboratorni Medicina a.s., Brno, Cz).

Statistical analysis

Analyses were conducted using SPSS (IBM Statistical Package for Social Sciences v. 21.0, Chicago, IL). Parameter distributions were not normal as indicated by Kolmogorov–Smirnov test, and differences in serum resistin levels among patient groups were evaluated with the non-parametric Kruskal–Wallis and Mann–Whitney tests, as appropriate. Multiple logistic regression analyses were applied to assess the association between resistin levels and the risk of specific histological cancer type versus healthy subjects. The analysis was also performed separately for pre- and peri/postmenopausal women. In all models, we controlled for age and external hormonal use (oral contraceptives among premenopausal women or hormone replacement treatment (HRT) among peri/postmenopausal women), parity and body mass index (BMI). A p-value of less than 0.05 was considered statistically significant.

Results

The study included 216 women, of which 163 were diagnosed with BC and 53 were healthy. Among BC patients, 58 women had IDC, 52 had DCIS and 53 had LN. Demographic, reproductive and anthropometric characteristics of the 216 participants are shown in Table 1. Patient groups presented significant differences in age and WHR. Moreover, they significantly differed in reproductive characteristics including parity and number of births, lactation and