BRCA1 mutation, leptin and estrogen levels in breast cancer patients

I. Rzepka-Górska, B. Tarnowski, A. Chudecka-Glaz, B. Górski[1]

Chair and Department of Gynecological Surgery and Oncology of Adults and Adolescents
[1]Hereditary Cancer Center, Department of Genetics and Pathology
Pomeranian Medical University, Szczecin (Poland)

Summary

Pre- and postmenopausal patients with breast cancer were screened for mutation of the BRCA1 gene and estrogens and leptin levels were measured. In postmenopausal BRCA1 mutation carriers, leptin levels were significantly lower and correlated with the body mass index (BMI). No significant difference in leptin levels was revealed between pre- and postmenopausal patients. Our findings suggest the existence of an alternative mechanism responsible for carcinogenesis in breast cancer patients with a genetic background.

Key words: Leptin, BRCA 1 mutation, Breast cancer.

Introduction

Three mutations in the BRCA1 gene (5382insC, C61G, 4153delA) account for the majority of mutations identified in Polish breast cancer and breast-ovarian cancer families [1 ,2]. The risk of breast cancer in BRCA1 mutation carriers is estimated at 80% [3]. Breast malignancies in patients without genetic predisposition to cancer appear to be associated with hormonal disorders and obesity [4]. However, most breast cancers in obese premenopausal women with high body mass index (BMI) values lacked estrogen receptors [5] as expected of tumors with a genetic background [6]. This discrepancy prompted us to study serum levels of leptin and estrone in breast cancer patients with or without a mutant BRCA1 gene.

Materials and Methods

We enrolled 40 premenopausal and 81 postmenopausal women with breast cancer. Clinical remission was ascertained in all patients at the time of the study with physical examination, cancer marker levels, ultrasonography, and chest radiographs. BRCA1 mutation was disclosed in 18 patients. The BMI was calculated. Leptin and estrone levels were measured in 68 and 46 patients, respectively, using EIA kits from IBL. In the postmenopausal group the estradiol levels were also measured.

The study protocol was approved by the local Bioethics Committee.

As the distribution of the results deviated from normal, statistical analysis was done with the non-parametric Mann-Whitney U-test. Linear correlation was applied to search for associations between the variables studied.

Results

Mean leptin and estrone concentrations and BMI values in pre- and postmenopausal patients with and without the BRCA1 mutation are presented in Tables 1 and 2. Correlations between BMI and estradiol ($R = -0.402819$, $p < 0.01$), BMI and leptin ($R = 0.515828$, $p < 0.001$) were disclosed in all postmenopausal patients. Postmenopausal breast cancer patients with a normal BRCA1 gene revealed correlations for BMI and estradiol ($R = -0.452436$; $p < 0.01$) and BMI and leptin ($R = 0.529818$, $p < 0.005$). In patients with the mutation, BMI correlated with leptin only ($R = 0.617813$, $p < 0.05$).

Discussion

We found higher BMI values ($p < 0.05$) in postmenopausal as compared with premenopausal breast cancer patients (Table 1). Correlations between BMI and leptin ($p < 0.001$) and BMI and estradiol ($p < 0.005$) were revealed in postmenopausal patients. Leptin levels in pre- and postmenopausal patients did not differ significantly (Table 1). Ozet *et al.* [7] failed to find any significant differences in leptin and BMI values between pre- and postmenopausal patients with breast cancer. Coskun *et al.*[8] found no difference in serum leptin levels between controls and breast cancer patients in remission or progression of the tumor. Petridou *et al.* [9] observed significantly lower leptin levels in premenopausal patients with breast cancer as compared with controls. Hereditary breast cancer is diagnosed more often in premenopausal women due to the younger age at onset.

Table 1. — *BMI and leptin in pre- and postmenopausal patients with breast cancer.*

	BMI		p	Leptin		p
	PM n = 40	M n = 81		PM n = 22	M n = 46	
Mean [pg/ml]	25.92	27.83	$p < 0.05$	8902.5	9271.48	NS
Confidence interval [pg/ml]	24.81-27.04	26.68-28.98		7531.34-10273.66	816.57-10426.39	

PM: premenopausal women; M: postmenopausal women; NS: not significant.

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Table 2. — *BMI, leptin and estrone in postmenopausal breast cancer patients depending on the BRCA1 mutation.*

	BMI		p	Estrone		p	Leptin		p
	BRCA1(+) n = 18	BRCA1(–) n = 53	NS	BRCA1(+) n = 14	BRCA1(–) n = 32	NS	BRCA1(+) n = 13	BRCA1(–) n = 33	p < 0.05
Mean [pg/ml]	28.9	27.8		69.5	100.09		7460.1	9985.1	
Confidence interval [pg/ml]	24.7-31.24	26.52-29.25		35.619-103.081	81.306-118.874		4983.9-9936.3	8701-11269.2	

NS: not significant.

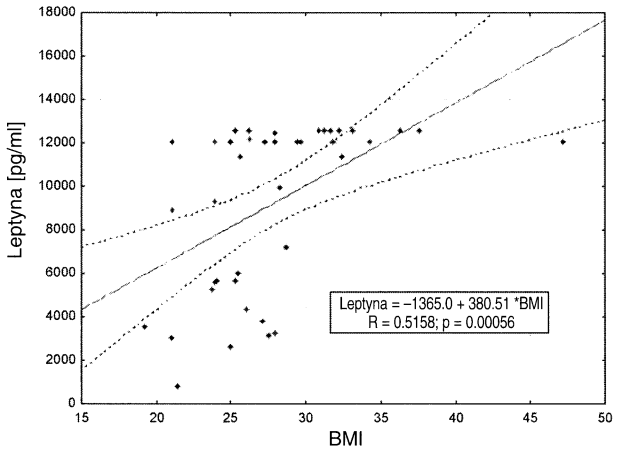

Figure 1 — Correlation between BMI and serum leptin levels in postmenopausal women with breast cancer.

Transformation of androstenedione to estrone, the chief postmenopausal estrogen, involves extragonadal aromatization stimulated by leptin. The risk of breast cancer appears to be higher in women who are obese or demonstrate elevated estradiol levels [7]. Catalano *et al.* [10] reported that leptin stimulates the synthesis of estrogens by activating aromatase in granulosa cells of the ovary and in the adipose tissue stroma. Although estradiol can be generated from estrone, this route is of minor importance as compared with gonadal steroidogenesis. Prophylactic salpingo-oophorectomy aimed at reducing estrogen levels is done to minimize the risk of breast cancer in BRCA1 mutation carriers [11].

Our patients with the BRCA1 mutation demonstrated significantly lower levels of leptin ($p < 0.05$, Table 2). Apparently, estrone synthesized by extragonadal aromatization was of lesser importance for breast tumorigenesis than ovarian estrogens. An indirect proof for this possibility comes from our finding that estrone levels did not differ significantly in postmenopausal patients with and without the BRCA1 mutation (Table 2). Ozet *et al.* [7] found that breast cancer patients positive for estrogen receptors and treated with tamoxifen demonstrate elevated serum leptin during the first six months of therapy. Although the mechanism remains unclear, these authors believe that tamoxifen enhances the expression of leptin mRNA by acting through estrogen receptors. Daling *et al.* [5] reported that some tumors in obese patients are receptor-negative. Therefore, other mechanisms of tumorigenesis not associated with extragonadal aromatization can be envisaged.

The role of insulin and leptin (adipocytokine leptin) is worth consideration. According to Takekoshi *et al.* [12], a non-steroidal route of action for leptin may involve protein kinase C. Lower levels of leptin observed in our patients with the BRCA1 mutation may be indirectly associated with the absence of estrogen receptors [6] and suggest the existence of an alternative mechanism responsible for carcinogenesis in these patients.

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Address reprint requests to:
Prof. I. RZEPKA-GÓRSKA, M.D.
al. Powstańców Wielkopolskich 72
70-111 Szczecin (Poland)