CANCER GENOMICS & PROTEOMICS *17*: 301-307 (2020)
doi:10.21873/cgp.20190

The Role of Circulating Adiponectin and SNP276G>T at *ADIPOQ* Gene in *BRCA*-mutant Women

ANTONELLA DANIELE[1], ANGELO VIRGILIO PARADISO[1], ROSA DIVELLA[1], MARIA DIGENNARO[2], MARGHERITA PATRUNO[2], STEFANIA TOMMASI[3], BRUNELLA PILATO[3], ANTONIO TUFARO[1], MICHELE BARONE[4], CARLA MINOIA[5], DONATELLA COLANGELO[6], EUFEMIA SAVINO[6], PORZIA CASAMASSIMA[6], ELEONORA BRUNO[7], ANDREINA OLIVERIO[7] and PATRIZIA PASANISI[7]

[1]*Experimental Oncology and Biobank Management Unit - IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy;*
[2]*Experimental Oncology - Center for Study of Heredo-Familial Tumors - IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy;*
[3]*Molecular Diagnostics and Pharmacogenetics Unit - IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy;*
[4]*Gastroenterology Section, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy;*
[5]*Onco-Hematology Unit - IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy;*
[6]*Clinical Pathology Laboratory - IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy;*
[7]*Epidemiology and Prevention Unit - Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy*

Abstract. *Background: Environmental factors may influence the lifetime risk of cancer (penetrance) in women with a BRCA mutation. Materials and Methods: In 89 BRCA-mutant women, affected or unaffected by breast/ovarian cancer, we explored serum levels of adipokines and their relation with the polymorphism SNP276G>T as modulators of BRCA penetrance. Results: Affected women had significantly lower adiponectin than healthy women. Affected women with rs1501299 TT had significantly lower adiponectin and higher leptin than GT and GG genotypes. GT genotype was significantly associated with the disease status [odds ratio (OR)=3.24, 95% confidence interval (95% CI)=1.03-10.17]. Women in the lower tertile of serum adiponectin had a RR of BRCA-associated cancer of 2.80, 95% CI=1.1-7.1 (p for trend=0.03) compared with women in the higher tertile. Conclusion: In the SNP rs1501299 the T allele was significantly associated with lower serum levels of adiponectin in affected women, suggesting that the T allele might be related to cancer.*

Women who inherit a germ-line *BRCA1* or *BRCA2* mutation face a high lifetime cumulative risk (penetrance) of developing breast cancer (BC), in the order of 55% compared to 12% in the general population, and ovarian cancer (OC) in the order of 16-59% (1-4). Given the incomplete penetrance, it has been suggested that several factors, genetic (polymorphisms) and/or "environmental", may influence *BRCA* penetrance.

The cancer risk is higher if genotype carriers are obese or have a high energy intake and life-long weight gain (5-8). Obesity may affect *BRCA* penetrance through a number of mechanisms including insulin resistance, induction of a metabolic syndrome, chronic low-grade inflammation and insulin-like growth factor I (IGF-I) regulation. Metabolic syndrome and diabetes are also associated with hereditary BC (6, 9). A case-control analysis of 308 high genetic-risk women showed that high serum levels of IGF-I were associated with significantly greater penetrance (10).

Body weight is regulated by leptin and adiponectin, two adipokines that have pathological signaling cascades in relation to the pathogenesis of various diseases, including cancer (11-20). Leptin is an adipokine produced in white adipose tissue that controls appetite and energy balance, increases with BMI (16) and is linked epidemiologically with obesity-related cancers, including sporadic BC risk (13, 21). Adiponectin, an adipose-derived protein of 244 amino acids, is an endogenous insulin sensitizer that also regulates the secretion of estrogens, TNF-α and IGF-I (11, 14). It has an inverse relationship with adiposity, so its levels are low in obese and diabetic subjects, with a stronger negative correlation with visceral adiposity (16). Adiponectin is inversely related to the risk of obesity-related cancers, including sporadic BC, even after controlling for BMI or other anthropometric markers (18).

Correspondence to: Antonella Daniele, IRCCS Istituto Tumori "Giovanni Paolo II", Viale Orazio Flacco 65, 70124 Bari, Italy. Tel/Fax: +39 805555259, e-mail: anto.dani27@gmail.com

Key Words: BRCA mutation, adipokines, ADIPOQ polymorphism, BRCA-associated cancer.

Serum adiponectin levels have a strong genetic component. Single nucleotide polymorphisms (SNPs) associated with serum adiponectin have emerged from recent genome-wide association studies (22, 23). One of the most commonly studied SNPs at the ADIPOQ locus is a G to T substitution in intron 2 (+276G>T, rs1501299), which has been frequently reported in association with obesity and cancer, including sporadic BC (24, 25). In detail, the genotype rs1501299 GG was associated with low levels of circulating adiponectin, obesity, and sporadic BC, with an odds ratio (OR) of 1.8, 95% confidence interval (95%CI)=1.14-2.85 (25).

The relation between *BRCA*-associated cancer and adipokines is still not clear and the impact of the rs1501299 in *BRCA*-mutant women is not known. A study on a small series of patients suggested that adiponectin is associated with BMI also in *BRCA*-mutant subjects (26). Furthermore, indirect evidence for a relationship comes from studies analysing the role of physical activity in *BRCA1/2* mutation carriers. Physical activity reduces body weight, IGF-I, and insulin resistance and also affects the BC risk in *BRCA*-mutant women (8, 27, 28). Recently, the Women In Steady Exercise Research (WISER) Sister trial on healthy pre-menopausal women at high risk of BC showed that exercise raised adiponectin and lowered leptin, controlling for a change in body fat, suggesting the importance of adipokines in *BRCA* penetrance (29).

In a sample of *BRCA*-mutant women in a dietary intervention trial to reduce serum levels of IGF-I and other markers of insulin resistance (30, 31), we explored the role of the baseline serum levels of adiponectin and leptin and their relation with the SNP276G>T as possible modulators of *BRCA* penetrance.

Materials and Methods

Study design and patients. The multicenter dietary intervention trial on BRCA-mutant women has been described elsewhere (30, 31). Briefly, that study investigated whether an active dietary intervention based on the 'Mediterranean diet' with moderate protein restriction - mainly milk and animal protein, down to 10-12% of total calorie intake - and recommendations for physical activity significantly reduced IGF-I and other markers of insulin resistance. Eligible study subjects were women, aged 18-70, with or without a previous diagnosis of BC/OC, without metastases, who underwent genetic counselling and fulfilled high-risk selection criteria for genetic testing based on personal and/or family history, and were found to be carriers of deleterious *BRCA* mutations.

Among volunteers, all the 89 women recruited at the IRCCS Istituto Tumori "Giovanni Paolo II" of Bari, from September 2017 to July 2019, agreed to be studied for their adipokine pattern and SNP 276G>T and were included in the present analysis. The study was approved by the local Ethics Committee and patients gave their signed informed consent. At baseline, women attended a clinical visit to obtain anthropometric and body composition measurements and gave 20 ml of blood to measure leptin, adiponectin and evaluate rs1501299. Clinical data related to the primary BC/OC were obtained from the Institutional electronic database.

Anthropometric and plicometric measurements. Height and body weight were measured without shoes and heavy clothes using diagnostic devices (Millennium 3 DAVI & CIA, Barcelona, Spain). At the same time, waist and hip circumference (cm) were recorded (professional meter BMI, GIMA, Gessate, Italy) according to standard techniques. The World Health Organization (WHO) definitions of obesity [body mass index (BMI)>30 kg/m^2] and overweight (BMI=25-29.9 kg/m^2) were used. The percentages of fat mass (FM) and free fat mass (FFM) were established using a FAT-1 plicometer (GIMA) which measures the thickness of skin folds in various districts and assesses the subject's nutritional status and the sectorial distribution of its adipose tissue. The Durnin-Womerslay measurement of seven folds (bicipital, tricipital, axillary, subscapular, abdominal, over-iliac and median thigh) was done (32, 33). The ideal weight of each patient was calculated using the Lorenz formula which includes the following calculation: for men: (height in cm -100) – (height in cm -150)/4. For women: (height in cm -100) – (height in cm -150)/2. Blood pressure was measured using an electronic sphygmomanometer.

Laboratory methods. Women gave 20 ml of blood. The samples were aliquoted and stored at –80˚C. Adiponectin and leptin were measured with enzyme–linked immunosorbent assays (ELISA) as described in our previous article (34). Samples were run in duplicate; the sensitivity of the ELISA for adiponectin ranged from 0.079-0.891 ng/ml and for leptin <7.8 pg/ml.

Polymorphism genotyping. Genomic DNA was extracted from whole EDTA-blood using the Qiagen kit (QIAmp DNA Micro-Kit, Hilden, Germany). Polymerase Chain Reaction (PCR) was performed to establish, the presence of the rs1501299 (276G>T) polymorphism using the following primers: forward outer: 5'-CTGAGATGGACGGAGTCTT3-3' and reverse outer 5'-CCAAATCACTTCAGGTTGCTT 3' (Applied Biosystems, Monza, Italy); the final PCR mixture (20 μl) contained DNA (2 μl), 10xPCR buffer (1.5 μl), 2 mM $MgCl_2$ (1.5 μl), 10 mM dNTP (0.3 μl), 0.25 μl of each primer 1 U Taq DNA Polymerase (BIORAD, Milan, Italy) and water. For amplification we used a thermocycler PCR engine (BIORAD). The amplification products were visualized by electrophoretic separation of DNA in a 2% agarose gel in a buffer consisting of tris-base, acetic acid and EDTA brought to final volume with distilled water and supplemented with ethidium bromide. Each participant was classified as one of three genotypes: GG, GT, TT.

Statistical analysis. The parameters under study, tested for normality by a graphic method, were normally distributed. BMI was defined as body weight/height squared (BMI kg/m^2). At baseline, the means of continuous variables in women with a diagnosis of *BRCA*-associated cancer were compared with the healthy women, using the Student's *t*-test. The frequencies of rs1501299 genotypes in the two groups (affected and healthy women) were compared using a χ^2 test. Genotypes were first compared separately using a logistic regression model and controlling for age. We used ANOVA to check for interactions between the three independent variables (GG, GT, TT genotypes) on the dependent variable (adipokines and the other factors).

Crude ORs of cancer with their 95% CI were calculated for the allele contrast, homozygote contrast, dominant genetic model and recessive genetic model. Because genetic mutation is a non-modifiable innate factor and we can follow-up a disease onset from birth according to genetic or environmental factors, we analyzed

Table I. *Baseline characteristics of the study population (89 women).*

Variables*	Women (N=89)
Age (yrs)	48.0±11.3
Menarche (yrs)	12.4±1.4
Age at first live birth (yrs)	27.9±5.0
BRCA mutation (%)	
BRCA1	64.0
BRCA2	30.4
BRCA1/2	5.6
Education (%)	
Primary	28.1
Secondary	37.8
Higher	37.3
Pregnancy (Yes) (%)	69.0
Number of children (%)	
≤2	74.5
>2	25.5
Menopause (%)	61.8
Natural menopause (%)	22.5
Oral contraceptive use (%)	51.9
Smoking in the past (%)	28.1
Genotype (%)	
GG	40.5
GT	33.7
TT	25.8
Tumor site (%)	
Breast	75.5
Ovary	22.6
Breast & Ovary	1.9
Infiltrating duct breast cancer (%)	94.3
ER-negative (%)	42.4
Axillary node metastasis (%)	29.0

*Mean+standard deviation (SD) for continuous variables.

differences in risk according to adipokines using a retrospective analysis based on Cox's regression. The follow-up started at birth and ended at the age of diagnosis of the first cancer. Healthy women were censored at their age at examinations. A p-value <0.05 was considered significant. All statistical tests were two-sided. Analyses were performed using graphic PRISM Version 5.00 software and STATA 14 statistical package.

Results

Baseline characteristics of the study population are reported in Table I. Among the 89 *BRCA*-mutant women (aged 48.0±11.3 years) in the present analyses, the BRCA1 mutation was the most represented (64%); 61.8% of women were under the menopause with only 22.5% under natural menopause. The distribution of the rs1501299 genotypes was GG 40.5%, GT 33.7% and TT 25.8%. In all, 53 women had a previous diagnosis of BC/OC and 36 were unaffected; among the former, 40 (75.5%) had a diagnosis of BC, 12 of OC (22.6%) and 1 (1.9%) had both. Among BC women, the infiltrating duct was the predominant histological type and 42.4% had ER negative tumors.

Table II. *Anthropometric parameters, adipokines and genotypes in affected and healthy BRCA-mutant women.*

	Affected (53)	Healthy (36)	p-Value*
Waist circumferences (cm)	78.9±10.9	74.7±11.2	0.08
Weight (g)	65.2±12.3	63.6±12.5	0.54
BMI (kg/m^2)	24.8±4.0	24.0±4.8	0.44
Fat mass (%)	37.5±5.2	33.9±5.7	**<0.01**
Free fat mass (%)	62.4±5.2	65.8±5.6	**<0.01**
Abdominal plica (mm)	24.0±7.3	21.4±7.7	0.10
Tricipital plica (mm)	25.8±6.7	23.9±7.4	0.22
Subscapular plica (mm)	22.2±8.2	19.5±7.0	0.11
Adiponectin (ng/ml)	8676.6±4524.1	12198.6±6777.5	**<0.01**
Leptin (pg/ml)	17.1±13.3	14.5±9.7	0.32
Genotype (%)			
GG	32.1	52.8	
GT	41.5	22.2	
TT	26.4	25.0	0.10

*t-test p for continuous variables and χ^2 test for frequencies. Bold values show significance.

Table II reports the distribution of anthropometric parameters, the adipokines and the rs1501299 genotypes in the affected and healthy *BRCA*-mutant women. Women with cancer had substantially worse anthropometric and body composition measurements than healthy women, with a significantly higher percentage of FM, a significantly lower percentage of FFM, and significantly lower levels of adiponectin. The distribution of genotypes according to the previous disease status showed GG 32.1%, GT 41.5% TT 26.4% in cancer patients and GG 52.8%, GT 22.2% and TT 25.0% in the healthy ones (p of χ^2 test=0.10) (Table II). Controlling for age, we found significant interactions with the disease status only for adiponectin (p<0.01).

Table III reports the distribution of the tertiles of adipokines and FM in the affected and healthy women, stratified by rs1501299 genotypes. Affected women with TT had significantly lower levels of adiponectin and significantly higher levels of leptin than GT and GG. Healthy women with TT had significantly higher levels of leptin and a higher percentage of FM than GT and GG. Controlling for age, only adiponectin and leptin remained significantly associated with TT in the women with cancer. We did not detect any other significant differences in anthropometric and body composition parameters (data not shown).

The association of polymorphism rs1501299 with the disease status was analyzed by a logistic regression, initially considering four genetic models (allele, homozygote, dominant, recessive). The association of rs1501299 with cancer was not significant in any of the four models.

Table III. *Tertiles of adipokines and FM in the affected and healthy women, stratified by polymorphism rs1501299 genotypes.*

	Affected (%)					Healthy (%)				
	GG	GT	TT	*p*-Value*	*p*-Value**	GG	GT	TT	*p*-Value	*p*-Value*
Adiponectin (ng/ml)										
900-7100	29.4	22.7	71.4			15.8	50	44.4		
7001-12200	35.3	59.1	14.3			36.8	0	11.2		
12201-25400	35.3	18.2	14.3	**0.02**	**0.02**	47.4	50	44.4	0.13	0.24
Leptin (pg/ml)										
3.5-10.2	47.1	13.6	28.6			52.6	25.0	33.3		
10.5-16.2	35.3	45.5	14.3			26.3	75.0	11.1		
17.2-85.1	17.6	40.9	57.1	**0.05**	**0.04**	21.1	0	55.6	**0.01**	0.14
Fat mass (%)										
21.4-33.8	23.5	22.7	28.6			52.6	62.5	33.3		
34.7-39.9	47.1	31.8	28.6			47.4	25.0	11.1		
40.0-45.8	29.1	45.5	42.8	0.79	0.47	0	12.5	55.6	**0.01**	0.11

*p for χ^2 test. **p for ANOVA, controlling for age. Bold values show significance.

Therefore, given the absence of a reference model, we evaluated the association of each genotype with the risk of disease. The GT genotype was the only one significantly associated with the disease status, with an adjusted OR=3.24, 95%CI=1.03-10.17.

We used a Cox's regression model to assess the relation between the adipokines and *BRCA*-associated cancer risk, including as covariates rs1501299, age (tertiles) and FM (tertiles) (Table IV). Compared to women in the higher tertile of serum adiponectin, women in the lower tertile had a RR of *BRCA*-associated cancer of 2.80, 95%CI=1.1-7.1 (p for trend=0.03). The same model did not suggest any significant risk association with the GT genotype (RR=1.58, 95%CI=0.8-3.1). Tertiles of serum leptin were not significantly associated with the risk of *BRCA*-associated cancer.

Table IV. *RR for BRCA-associated cancer by serum levels of adipokines.*

SNP rs1501299	RR*	*p* for trend
Adiponectin (ng/ml)		
12201-25400	1.00	
7001-12200	2.55 (1.2-5.6)	
900-7100	2.80 (1.1-7.1)	**0.03**
Leptin (pg/ml)		
3.5-10.2	1.00	
10.5-16.2	0.90 (0.4-1.9)	
17.2-85.1	1.69 (0.5-2.5)	0.84

*Adjusted for age (tertiles), genotypes and FM (tertiles). Bold value shows significance.

Discussion

This analysis of *BRCA*-mutant women suggests that lower serum levels of adiponectin are significantly associated with the risk of *BRCA*-associated cancer. When we studied the association between the rs1501299 and serum levels of adipokines, the T allele emerged as significantly associated with lower serum levels of adiponectin in women with a previous diagnosis of cancer compared to healthy ones, suggesting that the T allele might be associated with cancer occurrence. Evaluating the association of each polymorphism genotype with the risk of disease, GT was significantly associated with the OR of cancer in *BRCA*-mutant women.

A recent meta-analysis confirmed an inverse relation between adiponectin and cancer risk while high leptin was associated with a significantly higher risk (18). Among cancers, BC, colorectal cancer and endometrial cancer were inversely related with adiponectin. Our data are the first to suggest that circulating adiponectin affects the risk of cancer also in *BRCA*-mutant women, without, however, finding a clear relationship with leptin (about 20% higher risk comparing the higher and the lower tertiles, but without any significant results).

Adiponectin exerts several physiological effects involving different cell pathways and producing various biological results such as modulation of inflammatory responses, of lipid and glucose metabolism, function of vascular endothelial cell adhesion molecules, and characteristics of extracellular matrix components, but until now there was little information on adipokines and cellular *BRCA*-mediated pathways. *BRCA* proteins are known to play protective roles against the carcinogenic effects of estradiol (35). Therefore, since inflammatory adiponectin influences the sex hormone

mechanism of tumorigenesis *via* stimulation of estrogen production by aromatase, this effect might be important in *BRCA*-mutant women (36). Furthermore, *BRCA*-proteins are involved in DNA-repair mechanisms (37). Therefore, the secretion of pro-inflammatory cytokines mediated by adiponectin additively provokes mitochondrial and DNA damage thus affecting cancer risk in *BRCA*-mutant women (36). The present data support the idea that bio-molecular pathways associated with *BRCA* genes (*i.e.* DNA repair, estrogen response) and fat hormone metabolism might be directly related.

Data on the impact of the SNP rs1501299 on adiponectin levels are controversial and results tend to differ on the basis of the population under study and/or the disease status. In a healthy Italian population, Menzaghi *et al*. showed that the G allele (276G>T) was associated with higher body weight, waist circumference, insulin resistance and lower levels of adiponectin (38). Conversely, in an Italian population of patients with cardiovascular diseases the presence of the T allele was significantly associated with lower levels of circulating adiponectin. The same study, comparing cases and controls for their rs1501299 genotypes, suggested that TT+GT significantly increased the risk of cardiovascular disease (39). A meta-analysis on cancer patients has shown that the T allele is associated with significant cancer protection (25). Then, in a Japanese population, Kaklamani *et al*. showed that the G allele was significantly associated with an increased risk of BC, and explained this with the lower levels of circulating adiponectin in GG subjects (24). All these controversial results about genotypes suggest that these variants are markers of one or more haplotypes containing a causal polymorphism affecting plasma adiponectin levels.

The role of rs1501299 in *BRCA*-mutant women is substantially unknown. In our population of *BRCA*-mutant women the rs1501299 TT was associated with significantly higher FM than the GG only in healthy women, independently from circulating adiponectin. Conversely, in the affected women, the rs1501299 TT was associated with significantly lower levels of adiponectin than the GG, independently from the percentage of FM. The low level of adiponectin has usually been interpreted as the consequence of increased adiposity and/or obesity. Our findings are important because they suggest that the hypo-adiponectinemia is primarily due to the rs1501299 TT genotype in *BRCA*-mutation carriers, and lower levels of adiponectin - which have a stronger genetic effect on the etiology of cancer in these women - precede the onset of obesity.

There are several limitations to this study. First of all, the serum levels of adipokines might be affected by cancer treatment and/or dietary habits in the years before trial entry. Hormonal treatments after cancer, for example, might worsen women's body composition and metabolism, thus generating a temporal bias and causing overestimation of the association between adiponectin and disease. However, adiponectin levels have a strong genetic component and its association with rs1501299 is not affected by the retrospective design.

Another limitation is the small number of women in the study. However, we are now extending adiponectin measurements and SNP276G>T evaluation to the whole population of the trial in order to confirm these results in a larger series.

BRCA-mutant women often inquire about less invasive, non-surgical options to reduce their lifetime risk of cancer, including dietary and physical activity recommendations, and physicians need to be able to give them evidence-based answers regarding their lifestyle choices, especially for those who opt not to undergo surgery or chemoprevention. In addition to the genetic component, dietary factors may influence adiponectin levels. Diets low in glycemic load and rich in whole-grain and dietary fiber have been associated with adiponectin levels (40, 41). Other studies showed that diets high in unsaturated fat and low in carbohydrates might raise adiponectin levels (42, 43).

Since our results showed lower adiponectin levels in *BRCA*-mutant women with SNP 276G>T, lifestyle intervention (diet and physical activity) to increase adiponectin levels might be strongly recommended in the presence of the T allele. Therefore, we now intend to repeat adiponectin evaluation at the end of the dietary intervention in order to test whether diet might be a useful primary prevention option in *BRCA*-mutant women, especially those with SNP 276G>T.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Antonella Daniele: First and corresponding author of the paper, design study, nutritional evalutation of patients, practical performance, data analysis, preparation of manuscript; Angelo Virgilio Paradiso, Maria Digennaro and Margherita Patruno: patients recruitment and oncological evaluation; Rosa Divella and Antonio Tufaro: biological bank; Stefania Tommasi and Brunella Pilato: genetic analyses; Michele Barone: writing and editing; Carla Minoia: writing and editing; Donatella Colangelo, Eufemia Savino and Porzia Casamassima: biochemical blood profile; Eleonora. Bruno and Andreina Oliverio: data analyses; Patrizia Pasanisi: principal investigator of the study, author of the paper and contribution to data analyses;

Acknowledgements

The Authors wish to give special thanks to the nursing staff of the Analysis Laboratory, Mrs Mariella Di Nuzzi, Mrs Cecilia Berlen, Mrs Lucia Losacco and Mr Gennaro Sica, for their personal and

valuable contributions in the collection room. The Authors also thank Maria Grazia Guerrini for the editorial support and dr. J.D. Baggott for English editing. Finally, Authors would like to acknowledge with much appreciation all the volunteers who participate into the study.

Funding

The study was funded by the Italian Cancer Research Association (AIRC) grant n. IG-2015-17151 and by the Italian Ministry of Health grant n. GR-2010-2310116.

References

1 Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjakoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG and Easton DF: Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet *72*: 1117-1130, 2003. PMID: 12677558. DOI: 10.1086/375033

2 Berrino J, Berrino F, Francisci S, Peissel B, Azzollini J, Pensotti V, Radice P, Pasanisi P and Manoukian S: Estimate of the penetrance of BRCA mutation and the COS software for the assessment of BRCA mutation probability. Fam Cancer *14*: 117-128, 2015. PMID: 5373702. DOI: 10.1007/s10689-014-9766-8

3 Chen S and Parmigiani G: Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol *25*: 1329-1333, 2007. PMID: 17416853. DOI: 10.1200/JCO.2006.09.1066

4 Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, Evans DG, Izatt L, Eeles RA, Adlard J, Davidson R, Eccles D, Cole T, Cook J, Brewer C, Tischkowitz M, Douglas F, Hodgson S, Walker L, Porteous ME, Morrison PJ, Side LE, Kennedy MJ, Houghton C, Donaldson A, Rogers MT, Dorkins H, Miedzybrodzka Z, Gregory H, Eason J, Barwell J, McCann E, Murray A, Antoniou AC and Easton DF: Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst *105*: 812-822, 2013. PMID: 23628597. DOI: 10.1093/jnci/djt095

5 Bissonauth V, Shatenstein B, Fafard E, Maugard C, Robidoux A, Narod S and Ghadirian P: Weight history, smoking, physical activity and breast cancer risk among french-canadian women non-carriers of more frequent BRCA1/2 mutations. J Cancer Epidemiol *2009*: 748367, 2009. PMID: 2859024. DOI:10.1155/2009/748367

6 Dumais V, Lumingu J, Bedard M, Paquet L, Verma S and Fontaine-Bisson B: Prevalence of insulin resistance, metabolic syndrome, and type 2 diabetes in canadian women at high risk for breast cancer. Breast J *23*: 482-483, 2017. PMID: 28121048. DOI: 0.1111/tbj.12772

7 Nkondjock A and Ghadirian P: Epidemiology of breast cancer among BRCA mutation carriers: An overview. Cancer Lett *205*: 1-8, 2004. PMID: 15040392. DOI: 10.1016/j.canlet.2003.10.005

8 Pettapiece-Phillips R, Narod SA and Kotsopoulos J: The role of body size and physical activity on the risk of breast cancer in BRCA mutation carriers. Cancer Causes Control *26*: 333-344, 2015. PMID: 25579073. DOI: 10.1007/s10552-014-0521-0

9 Bordeleau L, Lipscombe L, Lubinski J, Ghadirian P, Foulkes WD, Neuhausen S, Ainsworth P, Pollak M, Sun P and Narod SA: Diabetes and breast cancer among women with BRCA1 and BRCA2 mutations. Cancer *117*: 1812-1818, 2011. PMID: 21509758. DOI: 10.1002/cncr.25595

10 Pasanisi P, Bruno E, Venturelli E, Manoukian S, Barile M, Peissel B, De Giacomi C, Bonanni B, Berrino J and Berrino F: Serum levels of IGF-I and BRCA penetrance: A case control study in breast cancer families. Fam Cancer *10*: 521-528, 2011. PMID: 21455766. DOI: 10.1007/s10689-011-9437-y

11 Tilg H and Moschen AR: Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol *6*: 772-783, 2006. PMID: 16998510. DOI: 10.1038/nri1937

12 Achari AE and Jain SK: Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. Int J Mol Sci *18(6)*: pii:E1321, 2017. PMID: 28635626. DOI: 10.3390/ijms1806132

13 Gu L, Wang CD, Cao C, Cai LR, Li DH and Zheng YZ: Association of serum leptin with breast cancer: A meta-analysis. Medicine (Baltimore) *98(5)*: e14094, 2019. PMID: 30702563. DOI: 10.1097/MD.0000000000014094

14 Maeda N, Funahashi T, Matsuzawa Y and Shimomura I: Adiponectin, a unique adipocyte-derived factor beyond hormones. Atherosclerosis *292*: 1-9, 2020. PMID: 31731079. DOI: 10.1016/j.atherosclerosis.2019.10.021

15 Ouchi N, Parker JL, Lugus JJ and Walsh K: Adipokines in inflammation and metabolic disease. Nat Rev Immunol *11*: 85-97, 2011. PMID: 21252989. DOI: 10.1038/nri2921

16 Staiger H, Tschritter O, Machann J, Thamer C, Fritsche A, Maerker E, Schick F, Haring HU and Stumvoll M: Relationship of serum adiponectin and leptin concentrations with body fat distribution in humans. Obes Res *11*: 368-372, 2003. PMID: 12634431. DOI: 10.1038/oby.2003.48

17 Yadav A, Kataria MA, Saini V and Yadav A: Role of leptin and adiponectin in insulin resistance. Clin Chim Acta *417*: 80-84, 2013. PMID: 23266767. DOI: 10.1016/j.cca.2012.12.007

18 Yoon YS, Kwon AR, Lee YK and Oh SW: Circulating adipokines and risk of obesity related cancers: A systematic review and meta-analysis. Obes Res Clin Pract *13*: 329-339, 2019. PMID: 31003933. DOI: 10.1016/j.orcp.2019.03.006

19 Divella R, Daniele A, DE LR, Mazzocca A, Ruggieri E, Savino E, Casamassima P, Simone M, Sabba C and Paradiso A: Synergism of adipocytokine profile and ADIPOQ/TNF-alpha polymorphisms in NAFLD-associated MetS predict colorectal liver metastases outgrowth. Cancer Genomics Proteomics *16(6)*: 519-530, 2019. PMID: 31659105. DOI: 10.21873/cgp.20154

20 Wazir U, Al SW, Jiang WG and Mokbel K: Evidence of an autocrine role for leptin and leptin receptor in human breast cancer. Cancer Genomics Proteomics *9(6)*: 383-387, 2012. PMID: 23162077.

21 Gui Y, Pan Q, Chen X, Xu S, Luo X and Chen L: The association between obesity related adipokines and risk of breast cancer: a meta-analysis. Oncotarget *8*: 75389-75399, 2017. PMID: 29088874. DOI: 10.18632/oncotarget.17853

22 Croteau-Chonka DC, Wu Y, Li Y, Fogarty MP, Lange LA, Kuzawa CW, McDade TW, Borja JB, Luo J, AbdelBaky O, Combs TP, Adair LS, Lange EM and Mohlke KL: Population-specific coding variant underlies genome-wide association with adiponectin level. Hum Mol Genet *21*: 463-471, 2012. PMID: 22010046. DOI:10.1093/hmg/ddr480

23 Jee SH, Sull JW, Lee JE, Shin C, Park J, Kimm H, Cho EY, Shin ES, Yun JE, Park JW, Kim SY, Lee SJ, Jee EJ, Baik I, Kao L, Yoon SK, Jang Y, Beaty TH: Adiponectin concentrations: A genome-wide association study. Am J Hum Genet *87*: 545-552, 2010. PMID: 20887962. DOI: 10.1016/j.ajhg.2010.09.004

24 Kaklamani VG, Sadim M, Hsi A, Offit K, Oddoux C, Ostrer H, Ahsan H, Pasche B and Mantzoros C: Variants of the adiponectin and adiponectin receptor 1 genes and breast cancer risk. Cancer Res *68*: 3178-3184, 2008. PMID: 18827209. DOI: 10.1001/jama.300.13.1523

25 Yang Y, Zhang F, Ding R, Skrip L, Wang Y, Lei H and Hu D: ADIPOQ gene polymorphisms and cancer risk: A meta-analysis. Cytokine *61*: 565-571, 2013. PMID: 23200411. DOI: 10.1016/j.cyto.2012.10.030

26 Sambiasi D, De Summa S, Digennaro M, Pilato B, Paradiso A and Tommasi S: Adipokines in hereditary breast cancer patients and healthy relatives. Oncotarget *8*: 101255-101261, 2017. PMID: 29254161. DOI: 10.18632/oncotarget.21018

27 Kohler LN, Garcia DO, Harris RB, Oren E, Roe DJ and Jacobs ET: Adherence to diet and physical activity cancer prevention guidelines and cancer outcomes: A systematic review. Cancer Epidemiol Biomarkers Prev *25*: 1018-1028, 2016. PMID: 27340121. DOI: 10.1158/1055-9965

28 Lammert J, Lubinski J, Gronwald J, Huzarski T, Armel S, Eisen A, Meschino WS, Lynch HT, Snyder C, Eng C, Olopade OI, Ginsburg O, Foulkes WD, Elser C, Cohen SA, Kiechle M, Narod SA and Kotsopoulos J: Physical activity during adolescence and young adulthood and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat *169*: 561-571, 2018. PMID: 29404807. DOI: 10.1007/s10549-018-4694-1

29 Sturgeon K, Digiovanni L, Good J, Salvatore D, Fenderson D, Domchek S, Stopfer J, Galantino ML, Bryan C, Hwang WT and Schmitz K: Exercise-induced dose-response alterations in adiponectin and leptin levels are dependent on body fat changes in women at risk for breast cancer. Cancer Epidemiol Biomarkers Prev *25*: 1195-1200, 2016. PMID: 27197293. DOI: 10.1158/1055-9965

30 Bruno E, Manoukian S, Venturelli E, Oliverio A, Rovera F, Iula G, Morelli D, Peissel B, Azzolini J, Roveda E and Pasanisi P: Adherence to mediterranean diet and metabolic syndrome in BRCA mutation carriers. Integr Cancer Ther *17*: 153-160, 2018. PMID: 28741383. DOI: 10.1177/1534735417721015

31 Pasanisi P, Bruno E, Venturelli E, Morelli D, Oliverio A, Baldassari I, Rovera F, Iula G, Taborelli M, Peissel B, Azzolini J and Manoukian S: A dietary intervention to lower serum levels of IGF-I in BRCA mutation carriers. Cancers (Basel) *10(9)*: pii: E309, 2018. PMID: 30181513. DOI: 10.3390/cancers10090309

32 Costa NA, Marinho AD and Cancado LR: Nutritional requirements of the critically ill patient. Rev Bras Ter Intensiva *24*: 270-277, 2012. PMID: 23917829.

33 Durnin JV and Womersley J: Body fat assessed from total body density and its estimation from skinfold thickness: Measurements on 481 men and women aged from 16 to 72 years. Br J Nutr *32*: 77-97, 1974. PMID: 4843734. DOI: 10.1079/bjn19740060

34 Daniele A, Divella R, Abbate I, Casamassima A, Garrisi VM, Savino E, Casamassima P, Ruggieri E and De Luca R: Assessment of nutritional and inflammatory status to determine the prevalence of malnutrition in patients undergoing surgery for colorectal carcinoma. Anticancer Res *37*: 1281-1287, 2017. PMID: 28314293. DOI: 10.21873/anticanres.11445

35 Pfeffer CM, Ho BN and Singh ATK: The evolution, functions and applications of the breast cancer genes BRCA1 and BRCA2. Cancer Genomics Proteomics *14(5)*: 293-298, 2017. PMID: 28870997. DOI: 10.21873/cgp.20040

36 Avgerinos KI, Spyrou N, Mantzoros CS and Dalamaga M: Obesity and cancer risk: Emerging biological mechanisms and perspectives. Metabolism *92*: 121-135, 2019. PMID: 30445141. DOI: 10.1016/j.metabol.2018.11.001

37 Venkitaraman AR: How do mutations affecting the breast cancer genes BRCA1 and BRCA2 cause cancer susceptibility? DNA Repair (Amst) *81*: 102668, 2019. PMID: 31337537. DOI: 10.1016/j.dnarep.2019.102668

38 Menzaghi C, Ercolino T, Di Paola R, Berg AH, Warram JH, Scherer PE, Trischitta V and Doria A: A haplotype at the adiponectin locus is associated with obesity and other features of the insulin resistance syndrome. Diabetes *51*: 2306-2312, 2002. PMID: 12086965. DOI: 10.2337/diabetes.51.7.2306

39 Filippi E, Sentinelli F, Romeo S, Arca M, Berni A, Tiberti C, Verrienti A, Fanelli M, Fallarino M, Sorropago G and Baroni MG: The adiponectin gene SNP+276G>T associates with early-onset coronary artery disease and with lower levels of adiponectin in younger coronary artery disease patients (age <or=50 years). J Mol Med (Berl) *83*: 711-719, 2005. PMID: 15877215. DOI: 10.1007/s00109-005-0667-z

40 Qi L, Rimm E, Liu S, Rifai N and Hu FB: Dietary glycemic index, glycemic load, cereal fiber, and plasma adiponectin concentration in diabetic men. Diabetes Care *28*: 1022-1028, 2005. PMID: 15855561. DOI: 10.2337/diacare.28.5.1022

41 Yannakoulia M, Yiannakouris N, Melistas L, Kontogianni MD, Malagaris I and Mantzoros CS: A dietary pattern characterized by high consumption of whole-grain cereals and low-fat dairy products and low consumption of refined cereals is positively associated with plasma adiponectin levels in healthy women. Metabolism *57*: 824-830, 2008. PMID: 18502266. DOI: 10.1016/j.metabol.2008.01.027

42 Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F and Giugliano D: Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA *292*: 1440-1446, 2004. PMID: 15383514. DOI: 10.1001/jama.292.12.1440

43 Pischon T, Girman CJ, Rifai N, Hotamisligil GS and Rimm EB: Association between dietary factors and plasma adiponectin concentrations in men. Am J Clin Nutr *81*: 780-786, 2005. PMID: 15817852. DOI: 10.1093/ajcn/81.4.780

Received February 3, 2020
Revised February 13, 2020
Accepted February 27, 2020