RESEARCH COMMUNICATION

Associations between Adiponectin and Two Different Cancers: Breast and Colon

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Abstract

Objectives: Breast and colon cancer are neoplasms well known to be related to obesity. Adiponectin, a protein that increases in obesity, seems to be involved in the relationship but clinical data are limited. Methods: In this study, we therefore evaluated the serum adiponectin levels in 87 breast and 27 colon cancer patients and assessed the relation with BMI, menopausal status, receptor status and stage of disease. Results: Serum adiponectin levels were lower in cancer cases (8583 ± 2095 ng/ml for breast cancer, 9513 ± 2276 for colon cancer) than in controls (13905 ± 3263). Conclusion: A low serum adiponectin level may be associated with both breast and colon cancer, and that this association is not statistically significant for either receptor or menopausal status in breast cancer groups.

Keywords: Adiponectin - breast cancer - colon cancer - obesity - adipose tissue - adipocytokines

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Introduction

Both breast and colon cancer are common health problems throughout the world, and efforts to understand the underlying causes of these cancer types are increasing. Obesity has been found to be one of the common factors in these cancers. It is also a common health problem in modern times, and it has increased globally in recent decades because of reduced physical activity and eating habits found in developed countries. It is known that obesity has been strongly associated with increased risks, not just for breast and colon cancer, but also for other types of cancer (Wolk et al., 2001; Kelesidis et al., 2006). It seems that weight gain plays an important role in carcinogenesis of tumors. The mechanism of how obesity induces cancer risks and mediators that are responsible for this relation are under investigation, but the results remain

In addition to adipose tissue, obesity also produces some substances known as adipocytokines. Recent evidence suggests that this adipose tissue is derived from cytokines such as adiponectin, leptin and resistin, which are responsible for the linkage between various cancers, such as breast, colorectal, endometrial, and prostate.

Adiponectin, one of the adipocytokines secreted by adipocytes, is a 247-amino-acid-long polypeptide hormone. The gene for adiponectin is located at chromosomal band 3q27 (Chandran et al., 2003). It has some known effects on the metabolic process such as gluconeogenesis, glucose uptake, lipid β-oxidation, triglyceride clearance, protection from endothelial dysfunction, insulin sensitivity and weight loss (Matsuzawa et al., 1999; Ariya et al., 1999; Weyer et al., 2001; Yamauchi et al., 2003; Okamoto et al., 2002). Levels of the hormone are inversely correlated with body fat percentages; therefore, adiponectin was found to be decreased in obesity (Arita et al., 1999). Plasma concentrations reveal a sexual dimorphism, with females having higher levels than males. Levels of adiponectin are reduced in diabetics compared to non-diabetics. Weight reduction significantly increases circulating levels.

Recent studies have indicated a significiant correlation between the reduced plasma adiponectin levels and the induced risk of various cancers, and some studies revealed the antiangiogenic and antitumoral effects of adiponectin (Kumor et al., 2009). Endometrial, breast, prostate, colon, pancreatic cancer, and more recently non-small cell lung cancer and esophageal cancer have been found to be correlated with the serum adiponectin levels, but this association and how it works has not yet been determined. The association between adiponectin levels and breast and colon cancer, which are the best known types of cancer in relation to obesity, has been shown, but it remains inconclusive. To our knowledge the association of adiponectin with both cancer types has not been studied in the same study cohort. In this case-control study we examined the relationship of serum adiponectin levels with breast cancer and colon cancer in age and body mass index-matched controls and evaluated the relation between adiponectin and tumor stage, ER-PR status and menopausal status.

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Table 1. Characteristics of Patient and Control Groups

	Breast Cancer (n:83)	Colon Cancer (n:27)	Control (n:40)	p value
Age (years)	51.4±12.5	52.1±14,7	52.4±10,4	NS
Body mass index (BMI- kg/m ²)	27.7±4.4	26.8±4.8	26.8±5.9	NS
Adiponectin (ng/ml)	8583±2095	9513±2276	13905±3263	0.001/0.023
Premenopausal (n:41)	8443±2028		13703±3120*	0.001*
Postmenopausal (n:42)	8724±2173		14127±3406*	0.024*

NS, Not significant; *mean adiponectin value of women patients in control group only

Materials and Methods

This case control study was conducted in Turkey at Ankara Oncology Training and Research Hospital from January to December of 2008. A total of 150 cases were admitted in the study of which 83 of the cases were histologically proved breast cancer and 27 of them were histologically proved colon cancer. All of the patients were treated surgically at the same hospital. The patients had no history of medications influencing insulin resistance before taking a blood sample. Forty patients who had not been diagnosed with cancer and did not have a family history of diabetes or cancer, but applied to our hospital for another reason were named as the control group. Diabetes mellitus, cachexia, liver impairment, renal dysfunction and cardiovascular disease were defined as exclusion criteria. Clinical information regarding age, gender, weight and height of the patients was recorded. Using the height and weight value of all participants, body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. A BMI value of under 18.5 is considered underweight; 18.5-24.9 is normal; 25-29.9 is deemed overweight; and greater than 30 is considered

Plasma adiponectin, total cholesterol (TC), low density lipoprotein (LDL) and triglyceride (TG) concentrations were measured after overnight fasting for more than 12 hours and at the same time of the day. Serum adinopectin was measured using ELISA (B-Bridge Human Adiponectin ELISA kit). All blood samples of cancer patients were obtained preoperatively. For the breast cancer group, the menopausal status, tumor stage and estrogen and progesterone receptor (ER-PR) status were also recorded.

Data are presented as means ±S.D. An independent t-test was used to compare variables between case and control groups. The level of significance was set at p< 0.05. Statistical calculations were performed using SPSS for Windows V16.0 (SPSS Inc., Chicago, IL, U.S.A.).

Results

There were 94 women (83 with breast cancer and 11 with colon cancer) and 16 men (all of whom had colon cancer) in the study. The control group consisted of 30 females and 10 males. The mean age was 51.4 ± 12.5 for breast cancer (28-78), 52.1 ± 14.7 for colon cancer (33-89) and 52.4 ± 10.4 for control group (26-75). Calculated BMI values were 27.76, 26.83 and 26.82 for breast cancer, colon cancer and the control group respectively (Table 1). No significant difference between the groups was present for any value (p>0.05).

The mean values of biochemical tests for breast cancer, colon cancer and control groups were as follows: cholesterol 191.2 ± 34.2 , 182.6 ± 37.2 and 187.3 ± 35.1 ; triglycerides 117.7 ± 67 , 133.9 ± 67.3 , 124.4 ± 65.3 ; low density lipoprotein (LDL) $166.3 \pm 37.6, 201.7 \pm 178.4,$ 160.4 ± 40.8 , respectively.

In the breast cancer group 41 patients (%49.3) were premenopausal, while 42 patients (%50.6) were postmenopausal. In the breast cancer group, 67 patients were ER-positive (80.7%), 44 were PR-positive (53%), 16 were ER-negative (19.2%), and 39 were PR negative (46.9%). Twenty-two patients had stage I, 35 had stage II and 26 had stage III breast cancer. In the colon cancer group there were 11 patients in stages I-II and 16 patients in stages III-IV.

The serum adiponectin level of patients both in breast and colon cancer groups were lower than the controls $(8583 \pm 2095 \text{ ng/ml} \text{ for breast cancer}, 9513 \pm 2276 \text{ for}$ colon cancer and 13905 ± 3263 for control group), and this difference was statistically significant (P<0.001 for breast cancer and P=0.023 for colon cancer). Serum total cholesterol, LDL cholesterol and triglyceride concentrations did not show any statistical difference between breast cancer, colon cancer and control groups. Also a negative correlation was present between stage and adiponectin (p<0.001) for both. Adiponectin levels decreased in relation to stage increases for both breast and colon cancer.

According to menopausal status in breast cancer groups, there was no significant difference in adiponectin concentrations and BMI between pre- and postmenopausal breast cancer patients, and they were lower than the controls. Additionally, adiponectin levels were not statistically different according to receptor status.

Discussion

Obesity is a well-defined risk factor for both breast and colon cancer. It is known that one's prognosis is worse among obese patients compared to normal weight subjects (Schlienger et al., 2009). Researchers are evaluating the role of adipocytokines in this relationship. First, Hu E et al. found 247 amino acids polypeptide encoded from adipoQ (adiponectin) cDNA in 1996, and revealed that the expression of adipoQ mRNA is decreased in the adipose tissues of both obese mice and humans (Hu et al.,1996). Since then, researchers knowledgeable about the relation between obesity and cancer have tried to combine this relationship with alternating adipose tissue derived from proteins in obesity. Adiponectin, leptin and resistin are the best known adipocytokines and are the possible causes of the linkage between adiposity and cancer risk. Studies

have shown the relation between adipocytokines and various types of cancer (Miyoshi et al., 2003; Mantzoros et al., 2004; Chen et al., 2006; Petridou et al., 2003; Dal Maso et al., 2004; Ishikawa et al., 2005; Goktas et al., 2005; Wei et al., 2005). We also analyzed the serum levels of adiponectin in Turkish breast and colon cancer patients in age and body mass index-matched controls and in our study. Adiponectin levels were lower in both breast cancer and colon cancer groups than the control group and this difference was statistically significant.

In 2003 Miyoshi Y et al. (2003) first described the possible relation between adiponectin and risk for breast cancer. They found that low adiponectin levels were associated with increased risk for breast cancer. A year later Mantzoros et al. determined similar results (2004). As a result of these efforts, adiponectin entered a new era for investigators trying to find out the possible relations between obesity and cancer. Tworoger and his colleguages first conducted a prospective study with 1477 breast cancer cases for this inverse correlation. In contradistinction to the other studies, they did not found an association overall between plasma adiponectin level and breast cancer. However, the association between plasma adiponectin levels in postmenopausal patients and breast cancer was statistically significant (Tworoger et al., 2007). This is the same result that Mantzoros C et al. found, but in our study adiponectin levels were not significantly different between pre- and postmenopausal breast cancer patients but both were lower than the controls. Also Miyoshi Y et al. and Chen et al. (2006), did not observe a significant corelation between serum adiponectin and estrone levels in postmenopausal women. Nonetheless, Kang et al. (2007) found no statistically significant difference in serum adiponectin levels between cases and controls in either premenopausal and postmenopausal breast cancer patients.

In breast cancer it is likely that obesity is often related to estrogen reseptor status (Kang et al., 2007; Grossmann et al., 2008; Karaduman et al., 2007). In 2008, Grossmann ME and colleagues revealed that estrogen receptor positive MCF-7 and T47D cells were inhibited at lower adiponectin concentrations than ER-negative SK-BR-3 cells (Grossmann et al.,2008). Miyoshi et al, Chen DC et al. and Tworoger et al. did not find an association between adiponectin levels and estrogen receptor status in their trials. On the other hand, Tian et al. (2007) showed a statistically significant inverse association between adiponectin levels and breast cancer risks in ER-positive but not ER-negative breast cancer patients. Kang revealed that ER negativity was significantly increased in patients with a decreased adiponectin level. The association between receptor status and adiponectin is controversial. Our study showed that the relation between serum adiponectin levels and hormone reseptor status was not statistically significant.

Like hormone status, the association between disease stage and plasma adiponectin level is also controversial. There are different studies showing different results about this relationship. Miyoshi Y et al. revealed that plasma adiponectin levels were lesser in advanced stages. Similar to this, adiponectin levels were decreased in the increased

stages of both breast and colon cancer in our study.

We certainly don't know the molecular basis of how adipose tissue synthesized cytokine, and adiponectin play a role in tumor carcinogenesis and progression but recent studies evaluating this mechanism have increased. Takahata et al. showed that receptors of adinonectin, AdipoR1 and AdipoR2 were expressed in both normal breast epithelial cells and breast cancer cells (Takahata et al., 2007). Dieudonne et al. reported that MCF-7 breast cancer cells expressed adiponectin receptors and responded to adiponectin by reducing their growth, AMPkinase activation, and p42/p44 MAP kinase inactivation (Dieudonne et al., 2006). Arditi JD et al. concluded that adiponectin can inhibit the proliferation of MCF-7 breast cancer cells (Arditi et al., 2007). Adiponectin also induces caspase enzyme activation and leads to endothelial cell apoptosis and reduction of tumor vascularization (Brakenhielm et al.,2004). All of these results are the consequences of efforts trying to solve that linkage between obesity and cancer.

Colon cancer is an obesity-related disease, and adiponectin is also important in understanding this relation in colon cancer patients. There are few data in literature and all of them were obtained in the last five years. In 2005, Otake S et al. suggested that decreased plasma adiponectin concentration is associated with the development of colon adenoma in Japanese patients (Otake et al.,2005). Later in his prospective case control study, Wei EK et al. suggested that the risk of colorectal cancer is higher in patients with low adiponectin plasma levels (Wei et al.,2005). Conversely Fukumoto J et al. revealed that there is no measurable association between circulating levels of adiponectin and colorectal adenomas (Fukumoto et al.,2008). The mechanisms of these effects are also a mystery. In a mouse model, Fujisawa T et al. (2008) showed that adiponectin depresses colorectal carcinogenesis and leads the way for further investigations. There is also evidence that adiponectin suppresses colon cancer cells by its receptor mediated AMPK activity (Sugiyama et al., 2009; Kim et al., 2010). In our study plasma adiponectin levels are lower in colon cancer patients than the control group, and this association is statistically significant. Also, in the breast cancer group, adiponectin levels decrease when the stage of colon cancer increases.

Our study has limitations because of the limited number of subjects. Additionally, the causal relation cannot be evaluated with case-control study design. However, the correlation between adiponectin and breast and colon cancer is apparent, and further investigation is needed to understand the molecular mechanisms of this relation. More prospective studies with a large number of cases must be conducted to prove the association between adiponectin and colon cancer.

In conclusion, the low serum adiponectin level might be associated both with breast and colon cancer. This association was not found to demonstrate statistically significant variation with the for receptor and menopausal status in the breast cancer group. However, adiponectin levels decreased with increases in the stage of both breast and colon cancer.

References

- Arditi JD, Venihaki M, Karalis KP, et al (2007). Antiproliferative effect of adiponectin on MCF7 breast cancer cells: a potential hormonal link between obesity and cancer. Horm Metab Res, 39, 9-13.
- Arita Y, Kihara S, Ouchi N, et al (1999). Paradoxical decrease of an adipose specific protein, adiponectin in obesity. Biochem Biophys Res Commun, 257, 79-83.
- Brakenhielm E, Veitonmaki N, Cao R, et al (2004). Adiponectininduced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cellapoptosis. Proc Natl Acad Sci USA, 101, 2476-81.
- Chandran M, Phillips SA, Ciaraldi T, et al (2003). Adiponectin: more than just another fat cell hormone? Diab Care, 26, 2442-50.
- Chen DC, Chung YF, The YT, et al (2006). m Serum adiponectin and leptin levels in Taiwanese breast cancer patients. Cancer Lett, 237, 109-14.
- Dal Maso L, Augustin LS, Karalis A, et al (2004). Circulating adiponectin and endometrial cancer risk. J Clin Endocrinol Metab, 89, 1160-3.
- Dieudonne MN, Bussiere M, Dos Santos E, et al (2006). Adiponectin mediates antiproliferative and apoptotic responses in human MCF7 breast cancer cells. Biochem Biophys Res Commun, 345, 271-9.
- Fujisawa T, Endo H, Tomimoto A, et al (2008). Adiponectin suppresses colorectal carcinogenesis under the high-fat diet condition. Gut, 57, 1531-8.
- Fukumoto J, Otake T, Tajima O, et al (2008). Adiponectin and colorectal adenomas: Self Defense Forces Health Study. Cancer Sci, 99,781-6.
- Goktas S, Yilmaz MI, Caglar K, et al (2005). Prostate cancer and adiponectin. Urology, 65, 1168-72.
- Grossmann ME, Nkhata KJ, Mizuno NK, et al (2008). Effects of adiponectin on breast cancer cell growth and signaling. *Br J Cancer*, **29**, 370-9.
- Hu E, Liang P, Spiegelman BM (1996). AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem, **3**, 10697-703.
- Ishikawa M, Kitayama J, Kazama S, et al (2005). Plasma adiponectin and gastric cancer. Clin Cancer Res, 11, 466-7.
- Kang JH, Yu BY, Youn DS (2007). Relationship of serum adiponectin and resistin levels with breast cancer risk. J Korean Med Sci, 22, 117-21.
- Karaduman M, Bilici A, Ozet A, et al (2007). Tissue levels of adiponectin in breast cancer patients. Med Oncol, 24, 361-6.
- Kelesidis I, Kelesidis T, Mantzoros CS (2006). Adiponectin and cancer: a systematic review. Br J Cancer, 94, 1221-5.
- Kim AY, Lee YS, Kim KH, et al (2010). Adiponectin represses colon cancer cell proliferation via adipoR1- and -R2mediated AMPK activation. Mol Endocrinol, 24, 1441-52.
- Kumor A, Daniel P, Pietruczuk M, et al (2009). Serum leptin, adiponectin, and resistin concentration in colorectal adenoma and carcinoma (CC) patients. Int J Colorectal Dis, 24, 275-278.
- Mantzoros C, Petridou E, Dessypris N, et al (2004). Adiponectin and breast cancer risk. J Clin Endocrinol Metab, 89, 1102-7.
- Matsuzawa Y, Funahashi T, Nakamura T (1999). Molecular mechanism of metabolic syndrome X: contribution of adipocytokines adipocyte derived bioactive substances. Ann N Y Acad Sci, 892, 146-54.
- Miyoshi Y, Funahashi T, Kihara S, et al (2003). Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res, 9, 5699-704.
- Okamoto Y, Kihara S, Ouchi N, et al (2002). Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice.

- Circulation, 106, 2767-70.
- Otake S, Takeda H, Suzuki Y, et al (2005). Association of visceral fat accumulation and plasma adiponectin with colorectal adenoma: evidence for participation of insulin resistance. Clin Cancer Res, 11, 3642-6.
- Petridou E, Mantzoros C, Dessypris N, et al (2003). Plasma adiponectin concentrations in relation to endometrial cancer: a case-control study in Greece. J Clin Endocrinol Metab, 88, 993-7.
- Schlienger JL, Luca F, Vinzio S, et al (2009). Obesity and cancer. *Rev Med Interne*, **30**, 776-82.
- Sugiyama M, Takahashi H, Hosono K, et al (2009). Adiponectin inhibits colorectal cancer cell growth through the AMPK/ mTOR pathway. Int J Oncol, 34, 339-44.
- Takahata C, Miyoshi Y, Irahara N, et al (2007). Demonstration of Adiponectin Receptors 1 and 2 mRNA expression in human breast cancer cells. Cancer Lett, 250, 229-36.
- Tian YF, Chu CH, Wu MH, et al (2007). Anthropometric measures, plasma adiponectin, and breast cancer risk. Endocr Relat Cancer, 14, 669-677.
- Tworoger SS, Eliassen AH, Kelesidis T, et al (2007). Plasma adiponectin concentrations and risk of incident breast cancer. J Clin Endocrinol Metab, 92, 1510-6.
- Wei EK, Giovannucci E, Fuchs CS, et al (2005). Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. J Natl Cancer Inst, 97, 1688-94.
- Weyer C, Funahashi T, Tanaka S, et al (2001). Hypoadiponectinemia in obesity and type 2 diabetes: Close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab, 86, 1930-5.
- Wolk A, Gridley G, Svensson M, et al (2001). A prospective study of obesity and cancer risk (Sweden). Cancer Causes Control, 12, 13-21.
- Yamauchi T, Kamon J, Ito Y, et al (2003). Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature, **423**, 762-9.