MINI-REVIEW

Equol, Adiponectin, Insulin Levels and Risk of Breast Cancer

Machiko Minatoya[1]*, Goro Kutomi[2], Sumiyo Asakura[1], Seiko Otokozawa[1], Yukiko Sugiyama[1], Yoshie Nagata[1], Mitsuru Mori[1], Koichi Hirata[2]

Abstract

Breast cancer is one of the most frequently diagnosed cancers and the leading cause of cancer death among women. Soy isoflavones have been widely studied and among all isoflavones equol has been gaining interest with regard to its relationship with breast cancer risk. Obesity has been revealed as one of the breast cancer risk factors, known to be associated with high levels of circulating insulin and decreased levels of adiponectin. Hence there have been many studies investigating relationships between insulin and adiponectin levels and breast cancer risk. Additionally recent findings have suggested that insulin and adiponectin themselves may have influence on breast cancer development, independent of obesity. In the present review, we discuss the relationships between breast cancer risk and equol, insulin and adiponectin levels, which are three important factors in our ongoing hospital-based case-control study. Herein these factors are reviewed not only from the clinical viewpoint but also from possible chemical and biological points of view which may explain clinical observations.

Keywords: Breast cancer - isoflavones - equol - insulin - adiponectin - menopausal status

Asian Pacific J Cancer Prev, **14 (4)**, 2191-2199

Introduction

Breast cancer is one of the most frequently diagnosed cancers and the leading cause of cancer death among women. There has been interest in protective role of soy isoflavones against breast cancer. Soy isoflavones are widely studied and the data have shown their biological activities such as an affinity for estrogen receptor, which may act as antiestrogens by competing for the binding sites of estrogen receptors (Martin et al., 1978). Among all the isoflavones, equol, a metabolite of daidzein, has gaining interest due to its possible effects on cancer risk. *In vitro* studies equol was found to be more biologically active than daidzein, with a higher affinity for the estrogen receptor and a more potent antioxidant activity, and this suggests that it may be advantageous to convert daidzein to equol to enhance its estrogenic potency. Some epidemiological studies suggest that the ability to produce equol is associated with reduced risk of breast cancer while others have reported no or adverse effects (Trock et al., 2006; Wu et al., 2008; Dong et al., 2011). One of the potential reasons for these inconsistences could be inter-individual differences in isoflavone metabolism (Setchell et al., 2002; Heinonen et al., 2003; Setchell and Cole, 2006). Most of these studies did not determine the equol producer status. According to studies approximately only 30-50% of individuals are capable to produce equol (Hutchins et al., 1995; Kelly et al., 1995; Lampe et al., 1998; Arai et al., 2000; Akaza et al., 2002). However, how one becomes an equol producer remains unknown. Recent studies suggest that soy isoflavones may provide a clinical benefit for breast cancer (Lampe, 2010) however, in most part the role of equol in relation to breast cancer remains unclear.

Additionally many studies have established that obesity is one of the common factors in breast cancer especially in postmenopausal women. Obesity is associated with high levels of circulating insulin. Insulin has shown to stimulate cell proliferation in normal breast tissue and in human breast cancer cell lines (Ish-Shalom et al., 1997; Chappell et al., 2001) and enhanced breast tumor growth in animal models (Shafie and Grantham, 1981; Shafie and Hilf, 1981). Some epidemiological studies have measured insulin to evaluate its association with breast cancer development. However, only few studies providing data on fasting levels of insulin and breast cancer found no consistent association.

Furthermore obesity and excessive adipose tissue is known to lead to decreased production of the peptide adiponectin. Adiponectin circulates in the plasma at concentrations correlates inversely with body mass index (BMI) (Vona-Davis and Rose, 2007). Thus it has been proposed that adiponectin may be a biological link between obesity and increased breast cancer risk. It is considered that adiponectin may influence on breast cancer risk through its effects on insulin resistance but some recent studies suggest that adipose tissue-derived

*[1]Department of Public Health, [2]Department of Surgery I, Sapporo Medical University School of Medicine, Japan *For correspondence: m.minatoya@sapmed.ac.jp*

hormones, including adiponectin may also be directly involved in breast cancer development (Miyoshi et al., 2003; Mantzorof et al., 2004; Petridou et al., 2004; Rose et al., 2004; Lorincz et al., 2006; Tworonger et al., 2007) and some studies revealed the antiangiogenic and antitumoral effects of adiponectin (Kumor et al., 2009). However, relatively small numbers of cohort studies have examined breast cancer risk in association with adiponectin levels and remain inconclusive.

As mentioned above obesity is considered to be one of the risk factors of breast cancer, there have been researches focused on other adipokines such as resistin (Kang et al., 2007) which is increased in obesity (Steppan et al., 2001) and leptin (Chen et al., 2006) which increase with BMI (Ruhl and Everhart, 2001) and on insulin resistance (Oh et al., 2011; Al Awadhi et al., 2012), which is linked to obesity as well (Rajala and Scherer, 2003). Additionally several studies have used C-peptide as a maker of insulin secretion instead of using direct measurements of insulin levels (Bruning et al., 1992; Yang et al., 2001) or used glucose levels which consequently increase as insulin resistance increases (Kaaks, 1996; Vona-Davis et al., 2007). Likewise, there have been studies focused not only on insulin levels but also on related factors such as insulin-like growth factor I (IGF-1), insulin-like growth factor binding proteins (IGFBPs), (Jernstrom and Barrett-Connor, 1999; Kaaks et al., 2002; Gunter et al., 2009).

In our ongoing hospital-based case-control study we focus particularly on the following three factors, equol, insulin and adiponectin levels in serum and investigate the relationships between breast cancer risk and these factors. Herein, we reviewed articles which discussed breast cancer risk in relation to equol, adiponectin and insulin, which are considered to be important as risk factors and biomarkers of breast cancer. To better understand the potential involvement of these factors in breast cancer, we examined not only clinical observations but also possible chemistry and biology behind these clinical observations.

Equol

Chemistry and biological property of equol

Equol is a chiral molecule and can exist as two isomers, R- and S-equol. S-(-)-equol is the metabolite of daidzein by intestinal bacteria. Equol is expected to prevent hormone-dependent diseases including breast cancer due to its ability to bind both estrogen receptors (ER) α and β (Kinjo et al., 2004; Muthyala et al., 2004), especially S-(-)-equol is known to have a much stronger affinity for ER β compared to R-(+)-equol (Setchell et al., 2005; Jackson et al., 2011), and moreover due to its superior anti-oxidative potential to all the isoflavones (Arora et al., 1998; Rufer et al., 2006). In addition, equol binds to sex hormone binding globulin and competitively inhibits estradiol and testosterone binding in a dose-dependent manner (Martin et al., 1996). Only little research that focused on equol specifically has conducted whereas mechanisms of soy isoflavone on breast cancer have been well done. *In vitro* studies have demonstrated that equol, both racemic and S-equol inhibited the growth of the breast cancer cell line MDA-MB-231 at higher concentration ($\geq$10 μM) but in contrast, equol at lower concentration ($\leq$10 μM) stimulated the proliferation of ER positive breast cancer cells. The compounds also showed effects in inhibiting the invasion of MDA-MB-231 cancer cells through matrigel (Magee et al., 2006). Another study reported that (±)-equol have proliferative effects on MCF-7 cell growth *in vitro* within the concentration of plasma equol 2.10-3.21 μM. *In vivo* study internal exposures to equol did not stimulate growth of estrogen-dependent human breast tumor (MCF-7) growth, increase the cell proliferation in tumors or induce an estrogen-responsive pS2 expression (Ju et al., 2006). It is difficult to interpret the effect of equol on breast cancer since findings from *in vitro* studies did not necessarily support *in vivo* studies. There is the need for more *in vivo* studies to explain *in vitro* results.

Epidemiological studies of equol on breast cancer

Few epidemiological studies have investigated the association between equol and breast cancer risk. Some results have suggested positive relationship between equol exposure and breast cancer risk. Ingram et al. (1997) conducted a case-control study to assess the association between phytoestrogen intake and the risk of breast cancer. Urine collection and blood samples from 144 pairs of cases and controls were analyzed. Their findings were that increasing excretion of equol was associated with a significant reduction in risk of breast cancer development. The risk for the highest quartile of excretion was one quarter that of the lowest quartile of excretion after the adjustment (odds ratio (OR), 0.27; 95% confidence interval (CI), 0.10-0.69; P=0.009), represented a four-fold reduction in risk. Menopausal status was not mentioned. In their conclusion, there was a substantial reduction in breast cancer risk among women with a high intake (as measured by excretion) of isoflavonoid phytoestrogen, equol. Furthermore, two ethnic based studies have reported. Goodman et al. (2009) examined the association of urinary phytoestrogens with the risk of postmenopausal breast cancer in the multiethnic cohort study. A nested case-control study of 251 cases and 462 controls was conducted in Hawaii. The risk of breast cancer was reduced among White women with the highest compared with the lowest quartile excretion of equol (OR, 0.27; 95%CI, 0.08-0.95), although the trend risk was not significant (P=0.07). No relation of urinary equol to the risk of breast cancer was found among all subjects. Their findings may support the hypothesis that diet rich in isoflavones from soy products reduced the risk of postmenopausal breast cancer, particularly in populations with comparatively high excretion of phytoestrogens. Similarly analyses of a case-control study of breast cancer conducted among Asian-American (Chinese, Filipino and Japanese) women ages of 25 and 74 years in Los Angeles County by Wu et al. (2004) showed 49% of controls had measurable levels of plasma equol compared with 39% of cases, but the difference was not statistically significant. A nested case-control study by Verheus et al. (2007) investigated the association between plasma isoflavone levels and breast cancer risk in a prospective manner in Dutch population. Plasma levels of including equol of 383 cases and 383 controls

were measured. Women with detectable equol levels were shown to have decreased breast cancer risk, compared with women with nondetectable levels (OR, 0.87; 95%CI, 0.63-1.21), and when women with detectable levels above the median were compared with women with nondetectable levels, the protection was somewhat stronger (OR, 0.77; 95%CI, 0.49-1.21). Results were the same in pre- or perimenopausal women and in postmenopausal women. In their conclusion, there was no statistically significant association with reduced breast cancer risk and plasma equol. Zheng et al. (1999) conducted a population-based case-control study in the urban Shanghai area to evaluate urinary excretion of isoflavonoids and risk of breast cancer. 60 case-control pairs who were selected and their urine samples were assayed for isoflavonoids. In their result, mean urinary equol was lower in cases than controls, however, OR and 95%CI for the association of breast cancer with urinary excretion of equol was not analyzed because of the difficulty in making groups of cases and controls due to its extremely low levels in urine samples. In their summary, despite a small sample size, this study showed that urinary excretion of total isoflavonoids was substantially and statistically significantly lower in breast cancer patients than in controls in a population with generally high soy consumption, however, did not show specifically in equol excretion. In contrast, Grace et al. (2004) investigated phytoestrogen concentrations of women aged 45-75 years in serum and urine as biomarkers for dietary phytoestrogen intake and their relation to breast cancer risk in UK. Measurements of 114 spot urines and 97 serum samples from breast cancer cases were compared with those of 219 urines and 187 serum samples from healthy controls. They have found that for urine, 39% of cases were equol producers compared with 31% of controls and for serum, 39% of cases were equol producers compared with 37% of controls. In this study menopausal status was not stated. In their conclusion, exposure to all isoflavones was associated with increased breast cancer risk, significantly so for equol. For a doubling of levels, OR increased by 20-45% (OR, 1.34; 95%CI, 1.06-1.70, P=0.013 for urine equol and OR, 1.46; 95%CI, 1.05-2.02, P=0.024 for serum equol). In the follow up study, Ward et al. (2008) analyzed phytoestrogens in serum and urine samples of breast cancers cases and control individuals in the European Prospective into Cancer-Norfolk (aged 45-75 years). Although their results showed that breast cancer risk was marginally increased with higher levels of total urinary isoflavones; among those with estrogen receptor-positive tumors, the risk of breast cancer was increased with higher levels of urinary equol (OR, 1.07; 95%CI, 1.01-1.12, P=0.013), in their conclusion, no association between serum or urinary equol and breast cancer risk was found. Among seven articles reviewed, only one result showed that equol exposure increased breast cancer risk, while three studies observed no association between equol exposure and breast cancer risk, remaining articles showed reduced breast cancer risk with higher equol measurements but with limitations. These inconsistent findings from epidemiological studies can be explained by the fact that these studies have been conducted in Western populations who generally have the low isoflavone intake and Asian populations who tend to consume high amount of isoflavones. Isoflavone intake in Europe and USA is about 3 mg/d (Messina, 2010) whereas in Japan and Chinese cities is 25-50 mg/d (Ju et al., 2006). Differences from these results suggest that isoflavone metabolism may differ between countries and/or ethnic groups due to differences in intestinal microflora. Furthermore some of these epidemiological studies stated their limitations in relatively small number of samples, which may be a cause of inconsistency in results. Other effect modifiers including ER/PR status, pre/postmenopausal status and equol producing status are also needed to be considered when analyzing epidemiological study results comprehensively.

Insulin

Chemistry and biological property of insulin

The primary translation product of the insulin gene is preproinsulin, a 110-amino-acid-long peptide that is processed in the pancreatic β-cells to yield proinsulin. Risk of breast cancer is increased in association with obesity, which is characterized by increased insulin resistance, with consequent increase in circulating levels of insulin. Insulin is most widely known for its metabolic effects (Scheen, 1996; Whitelaw, 1998), but it has mitogenic effects as stimulating cell mitosis and migration and inhibiting apoptosis in DNA damaged untransformed breast epithelial cells as well (Merlo et al., 1995). Generally the metabolic effects of insulin are mediated by way of the phosphatidylinositol 3-kinase (PI3K) pathway, while the mitogenic effects of insulin are the activation of Ras and the mitogen-activated protein kinase (MAPK) pathway (Rose and Vona-Davis, 2012). The capacity for stimulation of the PI3K pathway by insulin is lost when insulin resistance with hyperlipidemia is present, but MAPK activation is enhanced and insulin-induced prenylation of Ras protein is increased (Gallagher and LeRoith, 2010; Drazin, 2011). Insulin may also increase the risk of breast cancer by alterations in circulating estrogen levels. Chronic hyperlipidemia is associated with increased ovarian estrogen production, reduced hepatic secretion of sex hormone-binding globulin, and increased free estradiol levels (Porestsky et al., 1987; Pugeat et al., 1991, Calle and Kaaks 2004). Insulin is also known to promote cell proliferation in normal breast tissue and in human breast cancer cell lines (Ish-Shalom et al., 1997; Chappell et al., 2001) and enhance breast tumor growth in animal models (Shafie and Grantham, 1981). A number of cell culture experiments have been performed to examine the effect of insulin on breast cancer cell growth. The growth of the ER-(+) MCF-7, T47D and ZR-75-1 human breast cancer cell lines were promoted by insulin addition, and in all cases, insulin stimulated insulin receptor (IR) tyrosine kinase activity and thymidine incorporation (Ogasawara and Sirbasku, 1988; Milazzo et al., 1992). The effects of insulin on ER-(-) human breast cancer cell lines were complicated and the interpretation was limited. Gliozzo et al. (1998) reported that cultured MDA-MB-157 cells showed a strong mitogenic response to exogenous insulin. Malaguarnera et al. (2012) also used the same cell line and

observed similar stimulatory effects on breast cancer cell proliferation. In contrast, two other ER-(-) human breast cancer cell lines, MDA-MB-468 and MDA-MB-231, did not show a significant mitogenic response (Osborne et al., 1978; Sepp-Lorenzino et al., 1994; Belfiore et al., 1996).

Epidemiological studies of insulin on breast cancer

To our knowledge, there are only a few prospective studies have directly assessed the association between insulin levels and breast cancer risk. Del Giudice et al. (1998) conducted a case-control study comparing plasma insulin levels in 99 premenopausal women with breast cancer and 99 controls to proof the hypothesis that insulin may play an important role in development of breast cancer. They found that elevated insulin levels were significantly associated with breast cancer after adjusting age and weight and the risk was higher in the highest insulin quintile compared to the lowest quintile (OR, 2.83; 95%CI, 1.22-6.58). The result was independent of diet and other known risk factors for breast cancer. In their conclusion, circulating insulin levels are elevated in women with premenopausal breast cancer. In contrast to the previous report, the other report from a case-control study of investigating the relationship between breast cancer and fasting insulin (Jernstrom, 1999) revealed that fasting insulin was significantly positively correlated with both current weight and weight gain but the levels of insulin did not differ significantly between women with and without breast cancer. They concluded that the increased risk of breast cancer was not associated with fasting insulin. Kaaks et al. (2002) conducted measurements of plasma concentration of insulin within two prospective cohorts of 513 breast cancer cases and 987 controls. They found that breast cancer risk showed no clear associations with levels of insulin and this result did not support the hypothesis that elevated plasma insulin levels were associated with increased breast cancer risk, which was supporting Jernstorm results. Mink et al. (2002) examined the association of breast cancer incidence with serum levels of insulin in a cohort of 7894 women aged 45-64 years from four US communities. 187 breast cancer cases were ascertained after average 7.1 years of fellow-up period. They found that breast cancer was positively associated with BMI but not with serum insulin level and concluded that circulating insulin levels were not predictable of future breast cancer incidence. Muti et al. (2002) analyzed the hypothesis that serum insulin levels were associated with breast cancer using a nested case-control study in Italy. 133 breast cancer cases and 503 controls were finally analyzed and in their results, insulin showed a weaker association with breast cancer, the adjusted relative risk of the highest quartile vs. the lowest was 1.7 (95%CI, 0.7-4.1, P trend=0.14) in premenopausal women, but not in postmenopausal women. They also found that both pre- and postmenopausal women, insulin was positively related to BMI (r=0.30 for both groups, P<0.005). Gunter et al. (2009) conducted a case-cohort study of incident breast cancer among postmenopausal women. They observed a strong positive association between the risk of breast cancer and fasting insulin levels in postmenopausal women with hazard ratio (HR) for highest vs. lowest quartile of insulin level was 1.46 (95%CI, 1.00-2.13; P trend, 0.02), however, the association with insulin level varied by hormone therapy (HT) use. The association was observed only in women with non HT users with HR for highest vs. lowest quartile of insulin level was 2.40 (95%CI, 1.30-4.41; P trend<0.001) after the adjustments, and this finding was consistent with data from other studies that showed that HT use interacts with the association between obesity and postmenopausal breast cancer (Lahmann et al., 2004; Li et al., 2006; Ahn et al., 2007). In their summary, hyperlipidemia was an independent risk factor for postmenopausal breast cancer and therefore interventions aimed at lowering fasting insulin levels may reduce the risk of breast cancer in postmenopausal women. Kabat et al. (2009) conducted a longitudinal study of postmenopausal breast cancer risk. They reported that mean insulin levels were higher in cases compared to non-cases at baseline and at years 1 and 3 with statistically non-significant difference whereas in year 6 mean insulin was lower in cases compared to non-cases. They also found that baseline insulin levels were positively associated with breast cancer risk with statistically significant linear trends over increasing tertiles. For all participants, the multivariable hazard ratio for the highest tertile of serum insulin compared to the lowest was 2.22 (95%CI, 1.39-3.53). Additionally the association of insulin with breast cancer was strongest among lean women (BMI<25 kg/m^2) and weakest among obese women (BMI ≥ 30 kg/m^2). They confirmed that the association of insulin with breast cancer was significant regardless of hormone use status. Their results suggest that baseline insulin levels were positively associated with risk of postmenopausal breast cancer. Among seven studies reviewed in this paper, three articles stated that there are significant associations between insulin levels and breast cancer, one article observed the same only in premenopausal women, while three articles concluded that there are no significant associations. Given these inconsistent considerations, further investigations of effects of insulin on breast cancer are warranted.

Adiponectin

Chemistry and biological property of adiponectin

Adiponectin is a 224-amino-acid-long polypeptide hormone and known as one of the adipokines. Adiponectin, the gene product of the adipose most abundant gene transcript 1 (apM1) and adiponectin cDNA was first isolated by large scale random sequencing of the human adipose tissue cDNA library. It is a collagen-like protein that is exclusively synthesized in white adipose tissue, is induced during adipocyte differentiation, and circulates at relatively high concentrations in the serum (Maeda et al., 1996). Its effects on the metabolic process such as gluconeogenesis, glucose uptake, lipid-β-oxidation, triglyceride clearance, protection from endothelial dysfunction, insulin sensitivity and weight loss have been revealed (Arita et al., 1999; Matsuzawa et al., 1999; Weyer et al., 2001; Okamoto et al., 2002; Yamauchi et al., 2003). Adiponectin level was found to be inversely correlated to body fat percentage and it tend to be lower

in obesity (Arita, 1999). It is also known that levels of adiponectin are reduced in diabetics compared to non-diabetics. Besides these metabolic effects, adiponectin has been shown to suppress proliferation of macrophages (Yokota et al., 2000, Diez, 2003), to lead endothelial cell apoptosis and reduction of tumor vascularization by inducing caspase enzyme activation (Brakenhielm et al., 2004). Furthermore, it has been reported that MCF-7 breast cancer cells responded to adiponectin by reducing their growth, AMP kinase activation and p42/p44 MAP kinase inactivation receptors (Dieudonne et al., 2006) and others also reported that adiponectin can inhibit proliferation of MCF-7 breast cancer cells (Arditi et al., 2007; Jarde et al., 2008). Korner et al. (2007) have reported that exposure of T47D breast cancer cells to adiponectin significantly inhibited the percentage of viable cells and proliferation and therefore suggesting that adiponectin may act by not only altering the hormonal milieu but also directly inhibiting the proliferation of breast cancer cells *in vitro*. Also it was reported that adiponectin can suppress cell growth in ER-(-) MDA-MB-231 breast cancer cell line (Kang et al., 2005; Wang et al., 2006). Despite these experimental results, the mechanisms underlying the proliferation effects of adiponectin are not fully understood. Studies of the effects of adiponectin on the apoptosis of breast cancer cells *in vitro* lead inconclusive results, some reported that the apoptosis was increased by adiponectin treatment but others did not observe the same results.

Epidemiological studies of adiponectin on breast cancer

While several studies have suggested conflicting and controversial role for adiponectin in breast cancer risk, some research have reported associations between adiponectin levels and breast cancer risk from epidemiological aspect. Miyoshi et al. (2003) conducted a case-control study on 102 breast cancer patients and 100 healthy women to examine the association of the serum adiponectin levels with breast cancer risk. They have found that women in the low tertile of serum adiponectin levels were associated with a significantly ($P<0.05$) increased risk for breast cancer compared with women in high tertile (OR, 3.63; 95%CI, 1.61-8.19). This association was observed both in the premenopausal women (OR, 3.45, 95%CI, 0.89-13.50) and in the postmenopausal women (OR, 3.90; 95%CI, 1.23-12.44). Besides the frequency of large (>2cm) tumors and that of high histological grade (2+3) tumors were significantly higher in breast cancer patients in the low tertile of the serum adiponectin levels than those in the high and intermediate tertiles ($P<0.005$ and $P<0.05$, respectively). In their conclusion, the low serum adiponectin levels are significantly associated with an increased risk for breast cancer and that tumors arising in women with the low serum adiponectin levels are more likely to be biologically aggressive phenotype. Mantzoros et al. (2004) evaluated the association of adiponectin with the occurrence of breast cancer in a case-control study comprising 174 women with breast cancer and 167 controls. They have found an inverse, fairly strong, and statistically significant association of serum adiponectin with breast cancer (OR, 0.84; 95%CI, 0.71-0.99). This was only significant in postmenopausal women (OR, 0.82; 95%CI, 0.67-1.00) but not in premenopausal women. Chen et al. (2006) analyzed the correlations between the serum levels of adiponectin and the clinicopathological parameters in 100 breast cancer patients and 100 controls. They found serum levels were decreased significantly for adiponectin in the breast cancer patients in comparison to controls. ($P=0.003$). Among the clinicopathological parameters, ER, PR, HER2/neu, lymph node metastasis, tumor stage, and tumor grade all showed no effect on the serum levels of adiponectin. BMI was negatively correlated to serum adiponectin. In their conclusion, the results suggest that low serum adiponectin levels are associated with an increased risk for breast cancer. Kang et al. (2007) evaluated the relationship between serum adiponectin and breast cancer risk in 41 breast cancer patients and 43 controls. In their report the mean serum adiponectin levels was lower in the breast cancer group than the control group (6.93±3.2 μg/mL, 7.60±3.5 μg/mL, respectively), but this difference did not reach statistical significance ($P=0.37$). Besides there was no significant difference in serum adiponectin levels between cases and controls in either pre- or post-menopausal women ($P=0.22$, $P=0.89$, respectively). They also have investigated the relationship between serum adiponectin levels and clinicopathological characteristics of tumor. No significant difference was found in the frequency of large sized or highly differentiated tumors, or status of PR. The negativity of ER was significantly increased in the patients with less than the median adiponectin level ($P=0.032$). In their conclusion, the low serum adiponectin levels are likely to be associated with increased breast cancer risk in Korean women. Tworoger et al. (2007) conducted a prospective case-control study within the Nurses' Health Study (NHS) and NHSII to examine the association between plasma adiponectin concentrations and breast cancer risk. To our knowledge this is the largest case-control study of adiponectin levels and breast cancer risk up to the date including 1477 breast cancer cases and 2198 controls. They found that overall no association between plasma adiponectin levels and breast cancer risk, but there was a nearly significant interaction by menopausal status with a relative risk, top vs. bottom quartile of 0.73 (95%CI, 0.55-0.98; P trend=0.08) among postmenopausal women and 1.30 (95%CI, 0.80-2.10; P trend=0.09). Their results suggested that adiponectin may have an inverse association with breast cancer risk among postmenopausal women, particularly in a low-estrogen environment but have little or no association among premenopausal women. Korner et al. (2007) measured total and high-molecular weight (HMW) adiponectin in a hospital based case-control study of 74 breast cancer patients and 76 controls. In their results, women with the highest adiponectin levels had a 65% reduced risk of breast cancer ($P=0.04$). Using HMW instead of total adiponectin showed similar results. In addition to the *in vivo* study, they investigated the effect of adiponectin on proliferation in the T47D breast cancer cell line *in vitro* and found that the exposure of T47D cells to adiponectin significantly inhibited the percentage of viable cells to 86% and proliferation to 66% but had no

effect on apoptosis. They concluded that adiponectin may act as a biomarker of carcinogenesis. Tian et al. (2007) evaluated the association of measures of adiponectin with the development of breast cancer in a case-control study with 244 cases and 244 controls in Taipei. In their results, a fairly robust inverse association of adiponectin with the breast cancer risk was observed only in postmenopausal women (OR, 0.55; 95%CI, 0.23-0.97), but not in premenopausal women. Additionally, the plasma adiponectin levels tended to be inversely associated with ER-positive (OR, 0.53; 95%CI, 0.27-0.98), but not ER-negative breast tumors. In their conclusion, adiponectin may have an independent role in breast cancer carcinogenesis, particularly in the postmenopausal and ER-positive breast cancer risk. Oh et al. (2011) examined associations between breast cancer recurrence and adiponectin in a cohort of 747 patients. An inverse trend across the quartiles was observed for the serum adiponectin concentration in ER/PR-negative patients (P trend=0.027) but not in ER/PR-positive patients. Compared to the highest quartile for adiponectin level, the lowest quartile showed a hazard ratio of 2.82. Their findings suggested that assessing adiponectin concentrations may assist in establishing prognosis in ER/PR-negative cancers and interventions to increase serum adiponectin levels may represent a therapeutic option for reducing recurrence risk and improving prognosis in ER/PR-negative breast cancer. Gulcelik et al. (2012) evaluated the serum adiponectin levels in 87 breast cancer patients assessed the relation with menopausal status, receptor status and stage of disease. They have found that the serum adiponectin levels of breast cancer patients were lower than controls (8583±2095 ng/mL for cases and 13905±3263 ng/mL for control) and this difference was statistically significant (P<0.001). Also they found that the adiponectin levels decreased in relation to stage increases for breast cancer. Additionally there was no significant difference in adiponectin concentrations between pre- and postmenopausal breast cancer patients and adiponectin levels were not statistically different according to receptor status. In their conclusion, the low serum adiponectin level might be associated with breast cancer regardless of the menopausal and receptor status. Al Awadhi et al. (2012) evaluated the associations between circulating adipokines and breast cancer with 144 breast cancer cases and 77 controls. In their result, adiponectin level was significantly higher (P<0.05) in patients compared to controls. Their analysis showed that high levels of adiponectin (OR, 5.1; 95%CI, 2.2-11.5) was associated with breast cancer. In their conclusion, findings from their study confirmed that adipokines were associated with breast cancer. Among ten articles reviewed, three articles observed an inverse association between adiponectin levels and breast cancer risk only in postmenopausal women, one article observed the same result but only in ER/PR-negative breast cancer group. None of the articles showed an opposite observations in association with adiponectin levels and breast cancer risk. These accumulated clinical data support a role of adiponectin concentrations in breast cancer, however, to fully elucidate the mechanisms underlying the effect of adiponectin, larger prospective studies are needed.

Conclusion

In summary, a number of clinical and experimental data to suggest the importance of understanding effects of soy isoflavones, especially equol, insulin and adiponectin respectively on breast cancer. The evidence suggests that being an equol producer has a clinical benefit in some people, on the other hand, suggestions that isoflavones may have adverse effects in women with breast cancer or at increased risk of the disease has arisen mainly from animal studies and is generally not supported by clinical and epidemiological studies. Therefore interpretation of these results needs to be carried out carefully with consideration of equol producing status. Insulin action and endocrine and paracrine activities of the adipokines were established *in vitro* experiment, however, translation of its significance into human breast cancer needs to be conducted together with clinical and epidemiological studies. A role of adiponectin as a risk factor and possible diagnostic marker for breast cancer has been proposed, but again, biochemical mechanisms of how adiponectin influences on inhibiting breast cancer cell proliferation and leading apoptosis of breast cancer cell line are unclear. To elucidate the mechanism, additional studies of the expression and activation of adiponectin *in vitro* along with animal studies *in vivo* and clinical studies are essential. It is also very crucial to consider that the relationship between these factors; equol, insulin and adiponectin and breast cancer risk can differ depending on hormone receptor status and/or menopausal status. Hence further clinical and epidemiological analyses should be conducted including equol producing status, hormone receptor status and menopausal status for better understanding the precise role of these factors in breast cancer.

Acknowledgements

This study is supported by a Grant-in-aid for Scientific Research (Project Number 24659325) from the Ministry of Education, Science, Sports and Culture of Japan.

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