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REVIEW ARTICLE

Metabolic syndrome and breast cancer: an overview

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Summary

Worldwide, breast cancer is the most frequently diagnosed life-threatening cancer in women and the most important cause of cancer-related deaths among women. This disease is on the rise in Turkey.

Metabolic syndrome is a cluster of metabolic disturbances including insulin resistance, dyslipidemia, hypertension, abdominal obesity and high blood sugar. Several studies have examined the association of the individual components of the metabolic syndrome with breast cancer. More recent studies have shown it to be an independent risk factor for breast cancer. It has also been associated with poorer prognosis, increased incidence, a more aggressive tumor phenotype. Basic research studies are now in progress to illuminate the molecular pathways and mechanisms that are behind this correlation. Given the fact that all of the components of metabolic syndrome are modifiable risk factors, preventive measures must be established to improve the outcome of breast cancer patients.

In this review we set the background by taking into account previous studies which have identified the components of metabolic syndrome individually as breast cancer risk factors. Then we present the latest findings which elaborate possible explanations regarding how metabolic syndrome as a single entity may affect breast cancer risk.

Key words: breast cancer, metabolic syndrome, prognosis, predictive

Introduction

Worldwide, breast cancer is the most frequently diagnosed life-threatening cancer in women and the most important cause of cancer-related deaths in European, American, and Latin-American women [1]. Breast cancer incidence has been on the rise in Turkey. Currently, its prevalence is 50/100,000 in the western regions, and 20/100,000 in the eastern regions; this difference is possibly related to social, cultural and economic differences which alter the risk factors [2].

Metabolic syndrome is a cluster of metabolic disturbances including insulin resistance, dyslipidemia, hypertension, abdominal obesity and high blood sugar. Studies conducted in Turkey have shown that not only that metabolic syndrome is very common among both men and women [3], but is also prevalent among medical professionals [4]. Several studies have examined the association of the individual components of the metabolic syndrome with breast cancer. More recent studies have shown it to be an independent risk factor for breast cancer [5]. It has also been associated with poorer prognosis [6], increased incidence [7], a more aggressive tumor phenotype [8].

The mechanisms by which the metabolic syndrome affects breast cancer remain largely unknown. However, hyperinsulinemia and increased levels of insulin like growth factor 1 (IGF-1), increased levels of circulating adipokines, which in turn, affect plasminogen activator inhibitor-1 (PAI-1), pathophysiologic pathways including those involved in inflammation and hormone synthesis and metabolism which also have an impact on blood pressure and the fact that cholesterol is the precursor of carcinogenic steroid hormones, have been put forth as possible explanations.

In this review we set the background by taking into account previous studies which have identified the components of metabolic syndrome individually as breast cancer risk factors. Then we present the latest findings which elaborate the aforementioned possible

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explanations regarding how metabolic syndrome as a single entity may affect breast cancer risk.

Diabetes and breast cancer

Many case control cohort studies have demonstrated the relationship between breast cancer and diabetes. One of them, involving 1.2 million patients in the US (588 321 women) from 1982 to 1988, after adjustment for potential confounding variables, has shown that women with diabetes are more likely to die from breast cancer than women not diagnosed with diabetes (hazard ratio/HR =1.27; 95% confidence interval/CI 1.11-1.45) [9]. Three meta-analyses have looked into this relationship in detail [10-12]. The most recent one, a systematic review, has identified that patients with breast cancer and diabetes had a significantly higher all-cause mortality risk (pooled HR 1.49; 95% CI 1.35-1.65) compared with their nondiabetic counterparts. The finding was shown to be consistent across different populations, generally independent of possible confounding variables, and robust even after accounting for possible publication bias [12]. Also, diabetes has been shown to influence the breast cancer stage, modify treatment regimens, increase risk of being hospitalized for any chemotherapy toxicity and have an adverse effect on disease-free survival [13-16].

Both the pathophysiological and the therapeutic aspects of diabetes have been related with breast cancer. The insulin resistance present in type 2 diabetes is thought to lead to hyperglycemia which promotes cell growth and metabolism, proliferation and differentiation. Additionally, the state of hyperinsulinemia has been shown to increase mitogenicity and the level of androgens, which in turn, displace estrogens from the sex hormone binding globulins, thereby increasing the level of free circulating estrogens which contributes to the development of breast cancer [10].

Insulin may exert its effects directly on epithelial cells by activating AKT and ERK pathways which have important roles in tumorigenesis[17,18]. Furthermore, insulin has been shown to stimulate breast cancer cells synergistically with oestradiol [19]. Insulin receptor (IR) was found to be much more concentrated in breast cancer samples when compared to healthy breast tissue in a study which also discovered that high IR concentration correlated with tumor size, grade, and oestrogen-receptor [20]. Similarly another study has demonstrated that IR expression is a good predictor of disease-free survival [21].

Three studies which we have taken into consideration have demonstrated fasting insulin levels to be directly related to cancer recurrence and death [22-24], however, three have found no consistent association between fasting insulin and breast cancer risk in postmenopausal women [25-27]. The relationship between fasting levels of C peptide and breast cancer has also been intensively looked into. A recently published observational study of 604 women enrolled onto the Health, Eating, Activity, and Lifestyle (HEAL) study who were diagnosed with local or regional breast cancer between 1995 and 1998 has shown that a 1-ng/mL increase in fasting C-peptide levels was associated with a 35% increased risk of death as a result of breast cancer (HR 1.35; 95% CI 1.02-1.87, $p = 0.048$) with a stronger association in certain subgroups, including women with type 2 diabetes, women with a body mass index <25 kg/m^2, women diagnosed with a higher stage of disease, and women whose tumors were estrogen receptor positive [28]. Two other studies have also supported this association [29,30]. The variety in patients and protocols among these studies warrants further research regarding this association. To summarize, we believe that the available data is insufficient to point out an association between blood concentrations of insulin resistance markers and breast-cancer risk.

Insulin may also act through the insulin-like-growth factor (IGF) system which is thought to be a key regulatory pathway in breast cancer [31]. Increased levels of IGF-1 and insulin like growth factor binding protein 3 (IGFBP3) have been shown to be related with increased breast cancer risk [32]. However, the significance of this mechanism is still uncertain.

The treatments available for type 2 diabetes and their relationship with breast cancer have also drawn great interest. Metformin is a biguanide drug that increases skeletal muscle glucose uptake leading to reduction in both hyperglycemia and hyperinsulinemia, is thought to have insulin-independent favorable effects in the treatment and prevention of breast cancer through inhibition of the adenosine monophosphate-activated protein kinase/mammalian target of rapamycin/S6 kinase 1 pathway [33]. Bosco et al. in a multivariate analysis have shown that at-least-one-year metformin users may reduce their incidence of breast cancer [34]. A study published in 2010, which involved a nested case-control analysis among 22,621 female users of oral antidiabetic drugs with type 2 diabetes, has shown that long-term use of metformin is associated with an adjusted odds ratio of 0.44 (95% CI 0.24-0.82) for developing breast cancer compared with no metformin use [35]. Also, retrospective studies have shown higher rates of pathologic response after preoperative chemotherapy in patients with diabetes and breast cancer receiving metformin [36]. Currently, there are clinical trials that are underway evaluating the efficacy of metformin prior to surgery in breast cancer [37].

Breast cancers have been shown to be related with PPAR γ, a nuclear hormone receptor. Decreased expression of PPAR γ has been related with advanced disease, high tumor grade, and more aggressive histology [38]. However, troglitazone, a PPAR γ agonist, has failed to induce any response in a phase II study involving 22 patients [39]. Yet, a recent study has demonstrated that troglitazone acted in synergy with heregulin to induce massive cell death in breast cancer cells by inducing - mainly through caspase - independent necrosis and apoptosis [40]. In our opinion the exploitation of this pathway as a breast cancer treatment pathway deserves further research.

Lastly, in contrast with the treatments mentioned above, long term use of insulin glargine has been associated with increased risk of breast cancer [41]. To sum up, the treatments available for diabetes may have as much as an impact as diabetes itself, therefore, must be looked into via randomized controlled trials.

To summarize, data suggest that type 2 diabetes might be associated with up to 10-20% excess risk for breast cancer [42]. The substantial mortality attributed to diabetes alone, and the comorbidities which have confounding effects that are usually present concomitantly to diabetes such as being overweight, renders any attempt to claim a causal relationship premature. Further understanding of the mechanisms involved in the relationship between type 2 diabetes and breast cancer may lead to the discovery of new therapeutic agents, and help establish more effective preventive measures.

Obesity and breast cancer

Body mass index (BMI) is known to be a risk modifying factor for breast cancer. Epidemiological studies have shown that premenopausal obesity is overall protective for breast cancer [43], whereas postmenopausal obesity causes an increase in the risk for breast cancer [44,45]. Since obesity has a close relationship with increased levels of insulin and insulin like growth factors, it is suggested that this situation could lead to increase in some specific breast cancer subtypes such as triple negative breast cancer. In a study by Maiti et al., women with triple negative breast cancer had a higher prevalence of metabolic syndrome [46]. The same authors demonstrated also that, although increased BMI and hypertension are components of metabolic syndrome, they did not individually show any independent association, implying that there might be some kind of potentiation between elevated blood glucose and dyslipidemia.

Insulin resistance reduces sex hormone-binding globulin levels, causing an increase in free estrogen and androgen levels, hence increasing proliferation of breast epithelial cells. For this reason, it is suggested that premenopausal breast cancer risk may also increase by insulin resistance [47]. A recent analysis showed that, among younger women, obesity had a negative relationship with risk for receptor positive tumors only, suggesting that obesity does not protect from ER^-/PR^-cancers [48]. Also, a recent study showed that oxidized LDL receptors (OLR) may also be a link between cancer and obesity, as well as hyperlipidemia, and is theorized to act as an oncogene by activation of nuclear factor-kB (NF-kB) target genes responsible for proliferation, migration and inhibition of apoptosis and *de novo* lipogenesis genes [49].

Lastly, the effects of adipokines and their receptors in breast cancer have also been demonstrated. It is known that the levels of the adipokine leptin are positively correlated with obesity status, whereas lower adiponectin levels are present with increasing obesity. The adipokines leptin and adiponectin, which are promitogenic, proangiogenic, and proapoptotic, antiinflammatory respectively, are theorized to take place in an interplay which alters the risk of breast cancer [50]. In a recently published study [51], mRNA expression of leptin and its receptor, in adipose tissue and matched tumor samples, respectively, was demonstrated to be associated with obesity status in breast cancer. However, there was no difference in intratumoral leptin adiponectin or its ligand receptors in the same groups.

Hypertension and breast cancer

Elevated blood pressure is one of the leading comorbidities in the world. It also has been proposed to be a risk factor for breast cancer [52], but findings remain controversial [53]. Elevated diastolic blood pressure levels were found to be associated with increased incidence of breast cancer among non pharmacologically treated women. Additionally, it is suggested that elevated blood pressure not only is a risk factor for breast cancer, but also it may affect the survival and recurrence of breast cancer [54]. Researchers found that, after elimination of potential confounders, hypertensive African-American women showed a 1.60-fold higher recurrence risk than non hypertensive ones. However, in that study, anti hypertensive treatment was not eliminated as a potential confounder. On the other hand Largent et al. [55] found that there is a slightly increased risk between hypertension and breast cancer and also with the usage of diuretics. Longer duration of diuretics use is also reported to be related with increased risk of breast cancer. In another study [56], which also showed

a small but significant relationship between breast cancer and hypertension, thiazide and potassium-sparing (plus immediate-release calcium channel blockers) diuretics caused an increase in breast cancer rather than loop diuretics. Some other antihypertension drugs have also been shown to affect the course of breast cancer. In a recent study, beta blocker intake was found to be associated with relapse free survival in triple negative breast cancer patients [57]. The proposed mechanism was explained by the neuroendocrine activation in another article in a mouse model [58]. In that article, mice which were subjected to chronic stress had smaller tumors but more metastases. The administration of the β-antagonist propranolol reversed the macrophage infiltration and hence the metastatic tumor spread.

Not only essential hypertension, but also pregnancy-related hypertension or preeclampsia is also a risk modifier condition in a women's life. Preeclampsia is found to decrease the risk in odds ratio (OR) of breast cancer by 20-30%. The suggested mechanism is that women with preeclampsia have lower levels of estrogen and insulin like growth factor, and higher levels of androgens and human chorionic gonadotropin [59].

As a conclusion, the link between hypertension, usage of related drugs and breast cancer remains controversial. There is not significant evidence to cause a modification in the current treatment guidelines, however, in the future, with better designed trials and studies, the effects of the antihypertensive drugs will be understood more clearly.

Dyslipidemia and breast cancer

Dyslipidemia, as a modifiable risk factor, has been researched extensively with regard to breast cancer. Several mechanisms have been put forth to attempt to explain the mechanisms by which dyslipidemia increases the risk, worsens the prognosis, and affects the treatment of breast cancer. Also, the cholesterol metabolism and the molecular interactions of lipid rafts have been studied.

Research has suggested that low HDL-cholesterol, a well established cardiovascular disease risk factor, may be associated with the incidence of cancer at various sites and organs [60]. This claim has been studied extensively in other case-control and prospective studies, however differences in study population, study design and analysis approaches, have led to mixed results [61-69]. A recently published prospective study, consisting of 15,792 men and women, has demonstrated a modest association of low premenopausal HDL-cholesterol with an increased risk of breast cancer, independent of age, age at menarche, number of live births, race, BMI, and smoking status [70]. HDL has also been shown to exert a protective effect with respect to breast cancer in a certain group of premenopausal women [71].

The molecular mechanisms that relate the lipoprotein levels and breast cancer risk are currently being investigated in multiple aspects.

Epidermal growth factor receptor (EGFR) is overexpressed in about 30% of breast cancers. A recent study has shown that lipid raft localization of EGFR correlates with resistance to growth inhibition via EGFR inhibitors and pharmacological depletion of cholesterol from lipid rafts decreases this resistance in breast cancer cell lines [72].

Cancer cells require a supply of fatty acids (FA) for growth and survival, and interruption of *de novo* FA synthesis in rat models has resulted in anticancer effects. A recently published article has shown that hydrolytic release of FA from triglyceride in circulating lipoprotein particles by the secreted enzyme lipoprotein lipase (LPL), the expression of CD36 and the channel for cellular FA uptake, would be necessary in order to accomplish interruption of *de novo* FA synthesis. Immunohistochemical studies have shown that these are expressed in breast cancer cells [73].

Cholesterol receptor levels have also been associated with metastasis in breast cancer. A recently published study has shown that up-regulated expression of type II very low density lipoprotein receptor correlates with metastasis in breast cancer [74].

To sum up, lipids and lipoproteins, which have been demonstrated to be active molecules with many effects rather than idle means of energy storage, may have as much as an impact in breast cancer, as in cardiovascular disease. Lifestyle interventions, as recommended for cardiovascular disease prevention with respect to dyslipidemia, may be of value to prevent breast cancer mortality.

Conclusion: Metabolic syndrome and breast cancer

Metabolic syndrome is a cluster of metabolic disturbances including insulin resistance, dyslipidemia, hypertension, abdominal obesity, and high blood sugar. As a single entity, metabolic syndrome has been associated with breast cancer in multiple studies [75-78].

In this paper, we thought it would be sensible to give a brief overview about the relationship of breast cancer with each of the components, to underline the complexity of the relationship between breast cancer and metabolic syndrome as a single entity, and give way

to further research which would lead to a more comprehensive understanding.

A more recently published paper has analysed both metabolic syndrome as a single entity and its components as a risk factor of breast cancer for post-menopausal women. The ORs of postmenopausal breast cancer were 1.33 (95% CI 1.09-1.62) for diabetes, 1.19 (95% CI 1.07-1.33) for hypertension, 1.08 (95% CI 0.95-1.22) for hyperlipidemia, 1.26 (95% CI 1.11-1.44) for BMI ≥30 kg/m^2, and 1.22 (95% CI 1.09-1.36) for waist circumference ≥88 cm. The risk of postmenopausal breast cancer was significantly increased in women with metabolic syndrome as a single entity (OR 1.75, 95% CI 1.37-2.22) and the risk was higher in older age (OR 3.04, 95% CI 1.75-5.29, at age ≥70 years) [79].

Metabolic syndrome, as discussed above, causes a myriad of alterations in the body metabolism. Some changes, which are attributable to the sum of all of the effects metabolic syndrome exerts on the body, are searched to better understand the overall mechanism through which the risk of breast cancer is increased. Plasminogen activator inhibitor-1 (PAI-1) is one of the molecules which is hypothesized to be altered by metabolic syndrome. This protein is a physiological inhibitor of urokinase (uPA), a serine protease known to promote cell migration and invasion. However, increased levels of PAI-1 are paradoxically associated with poor prognosis in breast cancer. A recently published study has put forth the hypothesis that, sustained by metabolic syndrome, adipocytokines alter PAI-1 expression to promote angiogenesis, tumor cell migration and procoagulant microparticle formation from endothelial cells, which generate thrombin and further propagates PAI-1 synthesis ultimately forming a vicious circle [80].

To summarize, the relationship between breast cancer and metabolic syndrome with its components, has been well established in multiple studies a myriad of aspects. However, grasping the full clinical picture, with a complete understanding of the molecular mechanisms that are involved continues to prove a challenge. Given the fact that all of the components of metabolic syndrome are modifiable risk factors, it could be suggested that the establishment of preventive measures to lessen the ratio of patients with metabolic syndrome is imperative to improve the outcome of breast cancer patients. Diet, which is one of the most elementary determinants of metabolic status, holds importance in this matter. The general preventive recommendation often includes a reduction of alcohol, red meat and total dietary fat, and increase in vegetable and fruit consumption [81].

We would like to conclude by stating that further research that links each of the components to one another is warranted in order to form a comprehensive understanding of the complex interplay of the multiple aspects of metabolic syndrome in breast cancer.

References

1. Jemal A, Murray T, Ward E et al. Cancer statistics, 2005. CA Cancer J Clin 2005; 55: 10-30.
2. Ozmen V. Breast cancer in the World and Turkey. J Breast Health 2008; 4: 6-12.
3. Gundogan K, Bayram F, Capak M et al. Prevalence of metabolic syndrome in the Mediterranean region of Turkey: evaluation of hypertension, diabetes mellitus, obesity, and dyslipidemia. Metab Syndr Relat Disord 2009; 7: 427-434.
4. Oguz A, Sagun G, Uzunlulu M et al. Frequency of abdominal obesity and metabolic syndrome in healthcare workers and their awareness levels about these entities. Turk Kardiyol Dern Ars 2008; 36: 302-309 (in Turkish with Engl abstr).
5. Kabat GC, Kim M, Rowan T et al. A Longitudinal Study of the Metabolic Syndrome and Risk of Postmenopausal Breast Cancer. Epidemiol Biomarkers Prev 2009; 18: 2046-2053.
6. Pasanisi P, Berrino F, De Petris M et al. Metabolic syndrome as a prognostic factor for breast cancer recurrences. Int J Cancer 2006; 119: 236-238.
7. Agnoli C, Berrino F, Abagnato CA et al. Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: A nested case-control study. Nutr Metab Cardiovasc Dis 2010; 20: 41-48.
8. Healy LA, Ryan AM, Carroll P et al. Metabolic syndrome, central obesity and insulin resistance are associated with adverse pathological features in postmenopausal breast cancer. Clin Oncol (R Coll Radiol) 2010; 22: 281-288.
9. Coughlin SS, Calle EE, Teras LR et al. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 2004; 159: 1160-1167.
10. Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: A review of the current evidence. Am J Clin Nutr 2007; 86: s823-s835.
11. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: A meta-analysis. Int J Cancer 2007; 121: 856-862.
12. Peairs KS, Barone BB, Snyder CF et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. J Clin Oncol 2011; 29: 40-46.
13. Yancik R, Wesley MN, Ries LA et al. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 2001; 285: 885-892.
14. Srokowski P, Fang S, Hortobagyi GN et al. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. J Clin Oncol 2009; 27: 2170-2176.
15. Fleming ST, Pursley HG, Newman B et al. Comorbidity as a predictor of stage of illness for patients with breast cancer. Med Care 2005; 43: 132-141.
16. Du W, Simon MS. Racial disparities in treatment and survival of women with stage I-III breast cancer at a large academic medical center in metropolitan Detroit. Breast Cancer Res Treat 2005; 91: 243-248.
17. Fresno Vara JA, Casado E, de Castro J et al. PI3K/Akt signalling pathway and cancer. Cancer Treat Rev 2004; 30: 193-204.
18. Wolf I, Seger R. The mitogen-activated protein kinase signaling cascade: from bench to bedside. Isr Med Assoc J 2002; 4:

641-647.
19. Lai A, Sarcevic B, Prall OW, Sutherland RL. Insulin/insulin-like growth factor-I and estrogen cooperate to stimulate cyclin E-Cdk2 activation and cell cycle progression in MCF-7 breast cancer cells through differential regulation of cyclin E and p21(WAF1/Cip1). J Biol Chem 2001; 276: 25823-25833.
20. Papa V, Pezzino V, Costantino A et al. Elevated insulin receptor content in human breast cancer. J Clin Invest 1990; 86: 1503-1511.
21. Mathieu MC, Clark GM, Allred DC et al. Insulin receptor expression and clinical outcome in node-negative breast cancer. Proc Assoc Am Physicians 1997; 109: 565-567.
22. Goodwin PJ, Ennis M, Pritchard KI et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol 2002; 20: 42-45.
23. Del Giudice ME, Fantus IG, Ezzat S et al. Insulin and related factors in premenopausal breast cancer risk. Breast Cancer Res Treat 1998; 47: 111-120.
24. Lawlor DA, Smith GD, Ebrahim S. Hyperinsulinaemia and increased risk of breast cancer: Findings from the British Women's Heart and Health Study. Cancer Causes Control 2004; 15: 267-275.
25. Jernstrom H, Barrett-Connor E. Obesity, weight change, fasting insulin, proinsulin, C-peptide, and insulin-like growth factor-1 levels in women with and without breast cancer: The Rancho Bernardo Study. J Womens Health Gend Based Med 1999; 8: 1265-1272.
26. Mink PJ, Shahar E, Rosamond WD et al. Serum insulin and glucose levels and breast cancer incidence: The atherosclerosis risk in communities study. Am J Epidemiol 2002; 156: 349-352.
27. Muti P, Quattrin T, Grant BJ et al. Fasting glucose is a risk factor for breast cancer: A prospective study. Cancer Epidemiol Biomarkers Prev 2002; 11: 1361-1368.
28. Irwin ML, Duggan G, Wang CY et al. Fasting C-peptide levels and death resulting from all causes and breast cancer: the health, eating, activity, and lifestyle study. J Clin Oncol 2011; 29: 47-53.
29. Bruning PF, Bonfrer JM, van Noord PA et al. Insulin resistance and breast-cancer risk. Int J Cancer 1992; 52: 511-521.
30. Yang G, Lu G, Jin F et al. Population-based, case-control study of blood C-peptide level and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2001; 10: 1207-1211.
31. Sachdev D, Yee D. The IGF system and breast cancer. Endocr Relat Cancer 2001; 8: 197-209.
32. Renehan AG, Zwahlen M, Minder C et al. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004; 363: 1346-1353.
33. Vazquez-Martin A, Oliveras-Ferraros C, Del Barco S et al. If mammalian target of metformin indirectly is mammalian target of rapamycin, then the insulin-like growth factor-1 receptor axis will audit the efficacy of metformin in cancer clinical trials. J Clin Oncol 2009; 27: e207-e209.
34. Bosco JL, Antonsen S, Sorensen HT et al. Metformin and incident breast cancer among diabetic women: a population-based case-control study in Denmark. Cancer Epidemiol Biomarkers Prev 2011; 20: 101-111.
35. Bodmer M, Meier C, Krahenbuhl S et al. Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care 2010; 33: 1304-1330.
36. Jiralerspong S, Palla SL, Giordano SH et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol 2009; 27: 3297-3302.
37. Belda-Iniesta C, Pernia O, Simo R. Metformin: a new option in cancer treatment. Clin Transl Oncol 2011; 13: 363-367.
38. Jiang WG, Douglas-Jones A, Mansel RE. Expression of peroxisome proliferator activated receptor-gamma (PPARgamma) and the PPARgamma co-activator, PGC-1 in human breast cancer correlates with clinical outcomes. Int J Cancer 2003; 106: 752-757.
39. Burstein HJ, Demetri GD, Mueller E et al. Use of the peroxisome proliferator-activated receptor (PPAR) gamma ligand troglitazone as treatment for refractory breast cancer: a phase II study. Breast Cancer Res Treat 2003; 79: 391-397.
40. Park BH, Lee SB, Stolz DB et al. Synergistic Interactions between Heregulin and Peroxisome Proliferator-activated Receptor-{gamma} (PPAR{gamma}) Agonist in Breast Cancer Cells. J Biol Chem 2011; 286: 20087-20099.
41. Wilson C. Diabetes: Long-term use of insulin glargine might increase the risk of breast cancer. Nat Rev Endocrinol 2011 Jun 28. doi: 10.1038/nrendo.2011.112.
42. Wolf I, Sadetzki S, Catane R. Diabetes mellitus and breast cancer. Lancet Oncol 2005; 6: 103-111.
43. Ursin G, Longnecker MP, Haile RW et al. A meta-analysis of body mass index and risk of premenopausal breast cancer. Epidemiology 1995; 6: 137-141.
44. Lahmann PH, Hoffmann K, Allen N et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). Int J Cancer 2004; 111: 762-771.
45. Yumuk PF, Dane F, Yumuk VD et al. Impact of body mass index on cancer development. J BUON 2008; 13: 55-59.
46. Maiti B, Kundranda MN, Spiro TP et al. The association of metabolic syndrome with triple-negative breast cancer. Breast Cancer Res Treat 2010; 121: 479-483.
47. Pichard C, Plu-Bureau G, Neves ECM et al. Insulin resistance, obesity and breast cancer risk. Maturitas 2008; 60: 19-30.
48. Yang XR, Chang-Claude J, Goode EL et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst 2011; 103: 250-263.
49. Khaidakov M, Mitra S, Kang BY et al. Oxidized LDL Receptor 1 (OLR1) as a Possible Link between Obesity, Dyslipidemia and Cancer. PLoS One 2011; 6: e20277.
50. Sonmez B, Seker M, Bilici A et al. Is there any correlation among adiponectin levels in serum, tumor tissue and normal tissue of the same patients with breast cancer? J BUON 2011; 16: 227-232.
51. Carroll PA, Healy L, Lysaght J et al. Influence of the metabolic syndrome on leptin and leptin receptor in breast cancer. Mol Carcinog 2011; 50: 643-651.
52. Peeters PH, van Noord PA, Hoes AW et al. Hypertension and breast cancer risk in a 19-year follow-up study (the DOM cohort). Diagnostic investigation into mammarian cancer. J Hypertens 2000; 18: 249-254.
53. Lindgren A, Pukkala E, Tuomilehto J, Nissinen A. Incidence of breast cancer among postmenopausal, hypertensive women. Int J Cancer 2007; 121: 641-644.
54. Braithwaite D, Tammemagi CM, Moore DH et al. Hypertension is an independent predictor of survival disparity between African-American and white breast cancer patients. Int J Cancer 2009; 124: 1213-1219.

55. Largent JA, McEligot AJ, Ziogas A et al. Hypertension, diuretics and breast cancer risk. J Hum Hypertens 2006; 20: 727-732.
56. Li CI, Malone KE, Weiss NS et al. Relation between use of antihypertensive medications and risk of breast carcinoma among women aged 65-79 years. Cancer 2003; 98: 1504-1513.
57. Melhem-Bertrandt A, Chavez-McGregor M, Lei X et al. Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. J Clin Oncol 2011; 29: 2645-2652.
58. Sloan EK, Priceman SJ, Cox BF et al. The sympathetic nervous system induces a metastatic switch in primary breast cancer. Cancer Res 70: 7042-7052.
59. Terry MB, Perrin M, Salafia CM et al. Preeclampsia, Pregnancy-related Hypertension, and Breast Cancer Risk. Am J Epidemiol 2007; 165: 1007-1014.
60. Fiorenza AMBA, Sommariva D. Serum lipoprotein profile in patients with cancer. A comparison with non-cancer subjects. Int J Clin Lab Res 2000; 30: 141-145.
61. Dilman VM, Berstein LM, Ostroumova MN, Tsyrlina YV, Ag G. Peculiarities of hyperlipidaemia in tumour patients. Br J Cancer 1981; 43: 637-643.
62. Kumar K, Sachdanandam P, Arivazhagan R. Studies on the changes in plasma lipids and lipoproteins in patients with benign and malignant breast cancer. Biochemistry Intern 1991; 23: 581-589.
63. Hoyer AP, Engholm G. Serum lipids and breast cancer risk: a cohort study of 5,207 Danish women. Cancer Causes Control 1992; 3: 403-408.
64. Ferraroni M, Gerber M, Decarli A et al. HDL-Cholesterol and Breast Cancer: A Joint Study in Northern Italy and Southern France. Int J Epidemiol 1993; 22: 772-780.
65. Gaard M, Tretli S, Urdaul P. Risk of Breast Cancer in Relation to Blood Lipids: A Prospective Study of 31, 209 Norwegian Women. Cancer Causes Control 1994; 5: 501-509.
66. Kokoglu E, Karaarslan I, Karaarslan HM. Alterations of serum lipids and lipoproteins in breast cancer. Cancer Lett 1994; 82: 175-178.
67. Moorman P, Hulka B, Hiatt R et al. Association between high-density lipoprotein cholesterol and breast cancer varies by menopausal status. Cancer Epidemiol Biomarkers Prev 1998; 7: 483-488.
68. Furberg AS, Veierod MB, Wilsgaard T et al. Serum High-Density Lipoprotein Cholesterol, Metabolic Profile, and Breast Cancer Risk. J Natl Cancer Inst 2004; 96: 1152-1160.
69. Owiredu WK, Donkor S, Addai BW. Serum lipid profile of breast cancer patients. Pak J Biol Sci 2009; 12: 332-338.
70. Kucharska-Newton AM, Rosamond WD et al. HDL-cholesterol and incidence of breast cancer in the ARIC cohort study. Ann Epidemiol 2008; 18: 671-677.
71. Kim Y, Park SK, Han W et al. Serum high-density lipoprotein cholesterol and breast cancer risk by menopausal status, body mass index, and hormonal receptor in Korea. Cancer Epidemiol Biomarkers Prev 2009; 18: 508-515.
72. Irwin ME, Mueller KL, Bohin N et al. Lipid raft localization of EGFR alters the response of cancer cells to the EGFR tyrosine kinase inhibitor gefitinib. J Cell Physiol 2011; 226: 2316-2328.
73. Kuemmerle NB, Rysman E, Lombardo PS et al. Lipoprotein lipase links dietary fat to solid tumor cell proliferation. Mol Cancer Ther 2011; 10: 427-436.
74. He L, Lu Y, Wang P et al. Up-regulated expression of type II very low density lipoprotein receptor correlates with cancer metastasis and has a potential link to β-catenin in different cancers. BMC Cancer 2010; 10: 601.
75. Agnoli C, Berrino F, Abagnato CA et al. Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: a nested case-control study. Nutr Metab Cardiovasc Dis 2010; 20: 41-48.
76. Bjorge T, Lukanova A, Jonsson H et al. Metabolic syndrome and breast cancer in the Me-Can (metabolic syndrome and cancer) project. Cancer Epidemiol Biomarkers Prev 2010; 19: 1737-1745.
77. Kabat GC, Kim M, Chlebowski RT et al. A longitudinal study of the metabolic syndrome and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2009; 18: 2046-2053.
78. Capasso I, Esposito E, Pentimalli F et al. Metabolic syndrome affects breast cancer risk in postmenopausal women: National Cancer Institute of Naples experience. Cancer Biol Ther 2011; 10: 1240-1243.
79. Rosato V, Bosetti C, Talamini R. Metabolic syndrome and the risk of breast cancer in postmenopausal women Ann Oncol 2011 May 5 [Epub ahead of print].
80. Beaulieu LM, Whitley BR, Wiesner TF. Breast cancer and metabolic syndrome linked through the plasminogen activator inhibitor-1 cycle. Bioessays 2007; 29: 1029-1038.
81. Jevtic M, Velicki R, Popovic M. Dietary influence on breast cancer. J BUON 2010; 15: 455-461.