COMMON MECHANISMS IN THE PATHOGENESIS OF METABOLIC SYNDROME, ATHEROSCLEROSIS AND BREAST CARCINOMA AND THE POSSIBILITIES OF USING OMEGA-3 POLYUNSATURATED ACIDS IN THEIR PREVENTION AND THERAPY

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Abstrakt

Breast cancer is the most common cancer disease among women in economically developed countries. The exact cause of the disease is not fully understood, but a variety of risk factors applies here. The main aim of the presented article is to analyse possibilities of health prevention and therapy perspective of the breast carcinoma. The next aim is to analyse possibilities of using Omega-3 polyunsaturated acids in the prevention and therapy of metabolic syndrome, atherosclerosis in the context of breast carcinoma. Investigation of the phenomena was realised on the base of methods of content analysis, analyses and synthesis, induction and deduction, method of anchored theory in the sense of studying the concept as the main category, as well as causal and operational thinking. It has been investigated that the prevention has an important role in the reduction of incidence of breast carcinoma. Population of Central and Western Europe consume food with increased content of of omega-6 polyunsaturated fatty acids at the expense of omega-3 polyunsaturated fatty acids. Consumption of high-fat diet rich in saturated fatty acids is associated with changes in the proportions of bacterial genera and species of intestinal microbiota. In this way there is development of dysbiosis. It can be concluded that the mutual disproportions between the fatty acids, as well as dysbiosis, are risk factors for prevalence of breast carcinoma, but also cause of the development of chronic diseases as Diabetes mellitus, atherosclerosis, metabolic syndrome , too.

Keywords

Polyunsaturated fatty acids, endotoxemia, microbiome, breast cancer, health prevention.

INTRODUCTION

Breast cancer is the most common cancer in women worldwide, accounting for about 23% of all cancers in women, and age-adjusted incidence rates are increasing in most countries. This increase parallels the rising in lifestyle-related diseases, such as type 2 diabetes and the metabolic syndrome (Agnoli et al., 2015, Chan et al., 2015, Bhandari et al., 2014, Hauner et al., 2014, Liqibel, 2011, Bjorge et al., 2010). Metabolic syndrome is defined as a cluster of independent risk factors of type 2 diabetes mellitus and coronary heart disease, including impaired fasting glucose and impaired glucose tolerance, as well as central obesity, dyslipidemia with typical increasing of triglyceride levels and decreasing of high density lipoprotein levels and arterial hypertension, which contribute to the increased risk of type 2 diabetes mellitus, and severe cardiovascular diseases, in particular ischemic heart disease (Rivas-Urbina et al., 2018, Huang, 2009, Galajda, 2007).

Diabetes mellitus, atherosclerosis, metabolic syndrome and breast cancer are much more prevalent in developed countries, where a sedentary lifestyle and a high intake of refined carbohydrates and

saturated fats are more prevalent, than in developing countries (Uzunlulu et al. 2016, Wang et al., 2015, Vona-Davis, 2007); however, developing countries are increasingly adopting many of the lifestyle characteristics of more affluent societies. The diabetic condition induces change in several hormonal systems, including insulin, insulin-like growth factors, estrogen and other cytokines, and growth factors, that may affect the risk of breast cancer. The interaction of these hormonal factors in the diabetic state is complex and it is most likely involved in cancer promotion, because most of these hormonal factors are known to play an important role in carcinogenesis (Feroni et al., 2015, Cohen et al., 2012, Alokail et al., 2009).

AIMS, RESEARCH QUESTION

The main aim of the presented article is to analyse on the base of the content analysis of resources a broader health prevention and therapy perspective of the breast carcinoma. The next aim is to analyse possibilities of using Omega-3 polyunsaturated acids in the prevention and therapy of metabolic syndrome, atherosclerosis in the context of breast carcinoma.

The research question: “Represent the mutual disproportions between the fatty acids, as well as dysbiosis, risk factors for prevalence of the breast carcinoma?

METHODS

From the point of view of methodology of investigation of the phenomena, methods of content analysis, of analyses and synthesis, induction and deduction were chosen and applied to the method of anchored theory in the sense of studying the concept as the main category, as well as causal and operational thinking.

SOLUTION TO THE PROBLEM AND A PREDICTION REGARDING THE VARIABLES

The pathogenesis of various human diseases, such as obesity, diabetes mellitus, atherosclerosis and cancer is associated with persisting low-grade inflammation. Low level of circulating Gram-negative bacteria endotoxin (lipopolysaccharide - LPS) is one of the key contributions to the development of low-grade inflammation. LPS together with a moderate degree of inflammation induced developing metabolic endotoxemia, which supports the development of several metabolic diseases of a chronic problem, and possible carcinogenic progress of the disease (Gonzalez-Quintela et al., 2013). Through the breaking the physiological composition of the intestinal microflora, it increases the representation of the Gram-negative bacteria comprising in its wall LPS endotoxin. LPS stimulates inflammatory processes in the body, followed by the production of inflammatory cytokines such as TNF-alpha (tumor necrosis factor alpha), IL-6 (IL-6 - interleukin-6), IL-1. Dysbiotic microflora is more than 1 g of active LPS, which is a basic component of the walls of the Gram-negative bacteria (Laugerette et al., 2011). The change in the composition of intestinal microflora has a direct connection to energy balance. In the study of Krajmalnik-Brown et al. (Krajmalnik-Brown et al., 2012) was described the increased participation of the Firmicutes obese people compared with non-obese people, where the predominant strain Bacteroidetes. The major qualitative changes in the composition of intestinal microflora during obesity is a significant drop of Bifidobacterium spp. in combination with the increased participation of Staphylococcus aureus, which contributes to induction and maintenance

of a slight degree of inflammation, which plays in the pathogenesis of obesity important role (Cani et al., 2009). Inflammation mechanism is favoured by the presence of lymphocytes and macrophages in the adipose tissues (Cinkajzlová et al., 2017, Sun et al., 2012). This is supported by the presence of the production of inflammatory cytokines, which may act on the endothelium, hepatocytes, and also for the beta cells of the pancreas (Jung et al., 2014, Cerf, 2013, Imai et al., 2013).

Endothelial cell or hepatocyte through inflammation, leading to dysfunction of cells, in the case of pancreatic beta cells, cell death occurs. The indicators of ongoing inflammation in higher levels of inflammatory cytokines such as IL-6 and TNF-alpha (Cieslak et al., 2015, Ramos-Nino, 2013, Imai et al., 2013, Papa et al., 2012, Laugerette et al., 2011, Andel et al., 2009). Consummation of high-fat diet is associated with infiltration of macrophages with increased expression of inflammatory cytokines in adipose tissue and with the increase in the levels of circulating inflammatory cytokines (TNF-alpha, IL-6, IL-1beta) in the blood plasma. The level of LPS in plasma, as well as in the intestine is increased, presumably due to dysregulation of the composition of the intestinal microbiome. The most notably, Firmicutes to Bacteroidetes ratio is changed, counts of Enterobacteriaceae are increased and counts of Bifidobacteria decreased in the gut content. High-fat diet induces inflammation, including increased expression of inflammatory cytokine inducted by Toll-like receptor 4 (TLR 4), the inducible nitric oxide synthase (iNOS), cycloxygenase-2 (COX-2) (Jung et al., 2014, Cerf, 2013, Imai et al., 2013) and by the activation of nuclear factor kappa B (NFkB) (Skankar et al., 2015, Baker et al., 2011) in the colon. Increased intestinal permeability in the colon due to reduced expression of tight-junction protein was also observed (Calder et al., 2013; Kim et al., 2012).

Persistent low-grade inflammation is associated with the development of insulin resistance which, either directly (hyperinsulinemia), or indirectly (increased synthesis of adipokines - TNF-alpha, IL-6 and leptin) supports proliferation and growth of breast cancer cells (Moreira et al., 2012, Grisouard et al., 2011, Shukla et al., 2009).

Fatty acids profile within the organism is significantly affected by the diet. Therefore, physiological and pathological changes of the organism are interfering. Effect of high-fat diet consummation (as the risk factor for development of breast cancer) was extensively studied (Luo et al., 2017, Vehovský et al., 2015, El-Sayed Haggag et al., 2014, Abbot et al., 2012). However, results of these studies are still controversial (Prentice et al., 2006). Further analysis of epidemiological studies showed interconnection between higher intake of fatty acids and elevated probability of mammary carcinoma development (Kotepui, 2016, Boyd et al., 2003). Other studies showed that higher intake of omega-3 fatty acids act inhibitory towards the development of breast cancer (HuertaYépez et al., 2016, Fabian et al., 2015, Sun et al., 2012, Anne et al., 2009, Rose, Connolly, 1999). Wirfält et al. (Wirfält et al., 2005) explains the different results obtained when examining the relationship fats (fatty acids) - breast cancer, the type of food containing the specific strengths of the various fatty acids.

The gut microbiota plays an important role in human metabolism; previous studies suggest that the imbalance can cause a metabolic endotoxemia that may be linked to weight gain and insulin resistance (Radilla-Vázguez et al., 2016, Boutagy et al., 2016). In humans, energyenriched diets increasing weight gain and insulin resistance associate with absorption of endotoxin from the gastrointestinal track.

This “metabolic endotoxemia” resulting from the increased intestinal permeability/motility may lead to low grade inflammation. Severity of inflammation may depend on a complex interplay between specific proteins, receptors, and lipoproteins that mediate the endotoxin bioactivity and metabolic fate (Hawkesworth et al., 2013, Pussinen et al., 2011). Laugerette et al. (Laugerette et al., 2012) explored how the composition and abundance of fatty acids in the diet could promote endotoxemia and inflammation parameters in the blood.

According to the results, concentration of endotoxin in plasma is unrelated to the amount of consumed fat, but rather correlates with the qualitative abundance of fatty acids in diet. The highest concentration of endotoxemia was observed in the groups supplemented with oils rich in polyunsaturated fatty acids (rapeseed and sunflower oil). Interestingly, significantly higher concentration of IL-6 and LBP (LPS - binding protein) in serum, and higher expression of IL1beta in fat tissue was reported in the group fed diet containing palm oil (rich in saturated fatty acids). Determination of LBP is a more appropriate parameter which reflects the long-term effects of LPS endotoxin rather than LPS alone because of its short half-life in blood plasma and rapid uptake by various receptors and transporters (Laugerette et al., 2012, Erridge et al., 2007). The authors also concluded that the development of inflammatory response is not characteristic for all saturated fatty acids, but is rather fatty acids type-specific. The group, which consumed rapeseed oil had despite a high level of endotoxemia notably low grade inflammation due to high levels of sCD14 (soluble CD14). CD14 is a glycophosphatidylinositollinked protein expressed by myeloid cells and also circulates as a plasma protein lacking the glycophosphatidylinositol anchor. Both membrane and soluble CD14 function to enhance activation of cells by LPS, which we refer to as receptor function (Viriyakosol et al., 2000). Increased levels of sCD14 act as a buffering system against LPS and regulates the inflammatory response of the organism. LBP to sCD14 ratio reflects inflammatory activity and transport of LPS (Laugerette, et al., 2012, Stehle et al., 2012, Fang et al., 2015). A meta-analysis of observational and interventional studies described protective effects of regular intake of omega - 3 polyunsaturated fatty acids (n - 3 PUFA) in chronic inflammatory cardiometabolic disorders (Fergusson et al., 2014; Rangel - Huerta et al., 2012; Xin et al., 2012; Tierney et al., 2011; Wang et al., 2006). Dietary intake of n-3 FA leads to their incorporation into cell membrane lipids. Increased apoptosis in human breast carcinoma cells (BC cells) following exposure to long-chain n-3 PUFA such as eicosapentaenoic and docosahexaenoic acids is generally ascribed to their inhibition of COX-2 which promotes mammary carcinogenesis.

In addition however, long-chain n-3 PUFA are particularly likely to activate peroxisome proliferator-activated receptor (PPAR)-gamma, a key regulator of lipid metabolism but also capable of modulating proliferative activity in a variety of cells including mammary cells (Deckelbaum et al., 2006; Stoll, 2002). Expression of PPAR-gamma in the nucleus is activated by second messengers such as J series prostaglandins and the latter have been shown to cause apoptosis in vivo in explants of human BC cells in immunosuppressed mice. Experimental evidence suggests that when it is incorporated into the cell membrane, n-3 FA enhances lipid peroxidation and that this can lead to increased apoptosis in transformed or malignant mammary epithelial cells (Stoll, 2002, Chajés et al., 1995). Insulin-like growth factor 1 (IGF1)

stimulates mitosis and inhibits apoptosis. Some published results have shown an association between circulating IGF1 and breast-cancer risk, but it has been unclear whether this relationship is consistent or whether it is modified by IGF binding protein 3 (IGFBP3), menopausal status, oestrogen receptor status or other factors (Key et al., 2010).

CONCLUSION

It can be concluded that the mutual disproportions between the fatty acids, as well as dysbiosis, are risk factors for prevalence of breast carcinoma, but also cause of the development of chronic diseases as Diabetes mellitus, atherosclerosis, metabolic syndrome, too.

In nowadays there exist a lot of risk factors that influence daily lifestyle and contribute to the development various diseases including cancer, cardiovascular, metabolic diseases. One of the main causes of these diseases is diet, mainly high-fat diet which is associated with increased expression of inflammatory markers resulting dysregulation of the composition of the intestinal microbiome.

Clinical results mentioned in this review are controversial, therefore are necessary other experimental studies focused on role of n-3 PUFA and specific transcription factors in metabolism of cancer, cardiovascular and metabolic diseases and microbiome.

REFERENCES

Abbott SK, Else PL, Atkins TA, Hulbert AJ. (2012). Fatty acid composition of membrane bilayers: importance of diet polyunsaturated fat balance. Biochim Biophys Acta. 2012 May;1818(5):1309-17.

Agnoli C, Grioni S, Sieri S, Sacerdote C, Ricceri F, Tumino R, Frasca G, Pala V, Mattiello A, Chiodini P, Iacoviello L, De Curtis A, Panico S, Krogh V. (2015). Metabolic syndrome and breast cancer risk: a case-cohort study nested in a multicentre italian cohort. PLoS One. 2015 Jun 1;10(6):e0128891.

Alokail MS, Al-Daghri NM, Al-Attas OS, Hussain T. (2009). Combined effects of obesity and type 2 diabetes contribute to increased breast cancer risk in premenopausal women. Cardiovasc Diabetol. 2009 Jun 23;8:33.

Andel M, Polák J, Kraml P, Dlouhý P, Stich V. (2009). Chronic mild inflammation links obesity, metabolic syndrome, atherosclerosis and diabetes. Vnitr Lek. 2009 Jul-Aug;55(7-8):659-65.

Baker RG1, Hayden MS, Ghosh S. (2011). NF-κB, inflammation, and metabolic disease. NF-κB, inflammation, and metabolic disease. Cell Metab. 2011 Jan 5;13(1):11-22.

Bhandari R, Kelley GA, Hartley TA, Rockett IR. (2014). Metabolic syndrome is associated with increased breast cancer risk: a systematic review with meta-analysis. Int J Breast Cancer. 2014;2014:189384.

Bjørge T, Lukanova A, Jonsson H, Tretli S, Ulmer H, Manjer J, Stocks T, Selmer R, Nagel G, Almquist M, Concin H, Hallmans G, Häggström C, Stattin P, Engeland A. (2010). Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. Cancer Epidemiol Biomarkers Prev. 2010 Jul;19(7):1737-45.

Boutagy NE, McMillan RP, Frisard MI, Hulver MW. (2016). Metabolic endotoxemia with obesity: Is it real and is it relevant? Biochimie. 2016 May;124:11-20.

Boyd NF, Stone J, Vogt KN, Connelly BS, Martin LJ, Minkin S. (2003). Dietary fat and breast cancer risk revisited: a meta-analysis of the published literature. Br J Cancer. 2003 Nov 3;89(9):1672-85.

Calder PC. (2013). Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? Br J Clin Pharmacol. 2013 Mar;75(3):645-62.

Cani PD, Delzenne NM. (2009). Interplay between obesity and associated metabolic disorders: new insights into the gut microbiota. Curr Opin Pharmacol. 2009 Dec;9(6):737-43.

Cerf ME. (2013). Beta cell dysfunction and insulin resistance. Front Endocrinol (Lausanne). 2013 Mar 27;4:37.

Cieślak M, Wojtczak A, Cieślak M. (2015). Role of pro-inflammatory cytokines of pancreatic islets and prospects of elaboration of new methods for the diabetes treatment. Acta Biochim Pol. 2015;62(1):15-21.

Cinkajzlová A, Mráz M, Haluzík M. (2017). Lymphocytes and macrophages in adipose tissue in obesity: markers or makers of subclinical inflammation? Protoplasma. 2017 May;254(3):1219-1232.

Cohen DH, LeRoith D. (2012). Obesity, type 2 diabetes, and cancer: the insulin and IGF connection. Endocr Relat Cancer. 2012 Sep 5;19(5):F27-45.

Deckelbaum RJ, Worgall TS, Seo T. (2006). n-3 Fatty acids and gene expression. Am J Clin Nutr. 2006 Jun;83(6 Suppl):1520S-1525S.

Endogenous Hormones and Breast Cancer Collaborative Group, Key TJ, Appleby PN, Reeves GK, Roddam AW. (2010). Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol. 2010 Jun;11(6):530-42.

Erridge C, Attina T, Spickett CM, Webb DJ. (2007). A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. Am J Clin Nutr. 2007 Nov;86(5):1286-92.

Fabian CJ, Kimler BF, Hursting SD. (2015). Omega-3 fatty acids for breast cancer prevention and survivorship. Breast Cancer Res. 2015 May 4;17:62.

Fang Y, Sun M, Ramani K. (2015). Heat-passing framework for robust interpretation of data in networks. PLoS One. 2015 Feb 10;10(2):e0116121.

Ferguson JF, Mulvey CK, Patel PN, Shah RY, Doveikis J, Zhang W, Tabita-Martinez J, Terembula K, Eiden M, Koulman A, Griffin JL, Mehta NN, Shah R, Propert KJ, Song WL, Reilly MP. (2014). Omega-3 PUFA supplementation and the response to evoked endotoxemia in healthy volunteers. Mol Nutr Food Res. 2014 Mar;58(3):601-13.

Ferroni P, Riondino S, Buonomo O, Palmirotta R, Guadagni F, Roselli M. (2015). Type 2 Diabetes and Breast Cancer: The Interplay between Impaired Glucose Metabolism and Oxidant Stress. Oxid Med Cell Longev. 2015;2015:183928.

Galajda P. (2007). Metabolicky syndrom, kardiovaskularne a metabolicke rizika. In Via practica. 2007, vol. 4 (S4): 5 – 9.

Gonzalez-Quintela A, Alonso M, Campos J, Vizcaino L , Loidi L , Gude F. (2013). Determinants of serum concentrations of lipopolysaccharide-

binding protein (LBP) in the adult population: the role of obesity. PLoS One. 2013;8(1):e54600.

Grisouard J, Dembinski K, Mayer D, Keller U, Müller B, Christ-Crain M. Targeting AMP-activated protein kinase in adipocytes to modulate obesity-related adipokine production associated with insulin resistance and breast cancer cell proliferation. Diabetol Metab Syndr. 2011 Jul 20;3:16.

Haggag Mel-S, Elsanhoty RM, Ramadan MF. (2014). Impact of dietary oils and fats on lipid peroxidation in liver and blood of albino rats. Asian Pac J Trop Biomed. 2014 Jan;4(1):52-8.

Hauner D, Hauner H. (2014). Metabolic syndrome and breast cancer: is there a link? Breast Care (Basel). 2014 Apr;9(4):277-81.

Hawkesworth S, Moore SE, Fulford AJ, Barclay GR, Darboe AA, Mark H, Nyan OA, Prentice AM. (2013). Evidence for metabolic endotoxemia in obese and diabetic Gambian women. Nutr Diabetes. 2013 Aug 26;3:e83.

Huang PL. (2009). A comprehensive definition for metabolic syndrome. Dis Model Mech. 2009 May-Jun;2(5-6):231-7.

Huerta-Yépez S, Tirado-Rodriguez AB, Hankinson O. (2016). Role of diets rich in omega-3 and omega-6 in the development of cancer. Bol Med Hosp Infant Mex. 2016 Nov - Dec;73(6):446-456.

Chajès V, Sattler W, Stranzl A, Kostner GM. (1995). Influence of n-3 fatty acids on the growth of human breast cancer cells in vitro: relationship to peroxides and vitamin-E. Breast Cancer Res Treat. 1995 Jun;34(3):199-212.

Chan DS, Norat T. (2015). Obesity and breast cancer: not only a risk factor of the disease. Curr Treat Options Oncol. 2015 May;16(5):22.

Imai Y, Dobrian AD, Weaver JR, Butcher MJ, Cole BK, Galkina EV, Morris MA, Taylor-Fishwick DA, Nadler JL. (2013). Interaction between cytokines and inflammatory cells in islet dysfunction, insulin resistance and vascular disease. Diabetes Obes Metab. 2013 Sep;15 Suppl 3:117-29.

Jung UJ, Choi MS. (2014). Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci. 2014 Apr 11;15(4):6184-223.

Kim KA, Gu W, Lee IA, Joh EH, Kim DH. (2012). High fat diet-induced gut microbiota inflammation and obesity in mice via the TLR4 signaling pathway. PLoS One. 2012;7(10):e47713.

Kotepui M. (2016). Diet and risk of breast cancer. Contemp Oncol (Pozn). 2016;20(1):13-9.

Krajmalnik-Brown R, Ilhan ZE, Kang DW, DiBaise JK. (2012). Effects of gut microbes on nutrient absorption and energy regulation. Nutr Clin Pract. 2012 Apr;27(2):201-14.

Laugerette F, Furet JP, Debard C, Daira P, Loizon E, Géloën A, Soulage CO, Simonet C, Lefils-Lacourtablaise J, Bernoud-Hubac N, Bodennec J, Peretti N, Vidal H, Michalski MC. (2012). Oil composition of high-fat diet affects metabolic inflammation differently in connection with endotoxin receptors in mice. Am J Physiol Endocrinol Metab. 2012 Feb 1;302(3):E374-86.

Laugerette F, Vors C, Géloën A, Chauvin MA, Soulage C, Lambert-Porcheron S, Peretti N, Alligier M, Burcelin R, Laville M, Vidal H, Michalski MC. (2011). Emulsified lipids increase endotoxemia: possible role in early postprandial low-grade inflammation. J Nutr Biochem. 2011 Jan;22(1):53-9.

Laugerette F, Vors C, Peretti N, Michalski MC. (2011). Complex links between dietary lipids, endogenous endotoxins and metabolic inflammation. Biochimie. 2011 Jan;93(1):39-45.

Ligibel J. (2011). Obesity and breast cancer. Oncology (Williston Park). 2011 Oct;25(11):994-1000.

Luo JB, Feng L, Jiang WD, Liu Y, Wu P, Jiang J, Kuang SY, Tang L, Tang WN, Zhang YA, Zhou XQ. (2017). Physical and Flavor Characteristics, Fatty Acid Profile, Antioxidant Status and Nrf2-Dependent Antioxidant Enzyme Gene Expression Changes in Young Grass Carp (Ctenopharyngodon idella) Fillets Fed Dietary Valine. PLoS One. 2017 Jan 24;12(1):e0169270.

Moreira AP, Texeira TF, Ferreira AB, Peluzio Mdo C, Alfenas Rde C. (2012). Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia. Br J Nutr. 2012 Sep;108(5):801-9.

Papa FR. (2012). Endoplasmic reticulum stress, pancreatic β-cell degeneration, and diabetes. Cold Spring Harb Perspect Med. 2012 Sep 1;2(9):a007666.

Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, Margolis KL, Limacher MC, Manson JE, Parker LM, Paskett E, Phillips L, Robbins J, Rossouw JE, Sarto GE, Shikany JM, Stefanick ML, Thomson CA, Van Horn L, Vitolins MZ, Wactawski-Wende J, Wallace RB, Wassertheil-Smoller S, Whitlock E, Yano K, Adams-Campbell L, Anderson GL, Assaf AR, Beresford SA, Black HR, Brunner RL, Brzyski RG, Ford L, Gass M, Hays J, Heber D, Heiss G, Hendrix SL, Hsia J, Hubbell FA, Jackson RD, Johnson KC, Kotchen JM, LaCroix AZ, Lane DS, Langer RD, Lasser NL, Henderson MM. (2006). Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA. 2006 Feb 8;295(6):629-42.

Pussinen PJ, Havulinna AS, Lehto M, Sundvall J, Salomaa V. (2011). Endotoxemia is associated with an increased risk of incident diabetes. Diabetes Care. 2011 Feb;34(2):392-7.

Radilla-Vázquez RB, Parra-Rojas I, Martínez-Hernández NE, Márquez-Sandoval YF, Illades-Aguiar B, Castro-Alarcón N. (2016). Gut Microbiota and Metabolic Endotoxemia in Young Obese Mexican Subjects. Obes Facts. 2016;9(1):1-11.

Ramos-Nino ME. (2013). The role of chronic inflammation in obesity-associated cancers. ISRN Oncol. 2013 May 30;2013:697521.

Rangel-Huerta OD, Aguilera CM, Mesa MD, Gil A. (2012). Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomakers: a systematic review of randomised clinical trials. Br J Nutr. 2012 Jun;107 Suppl 2:S159-70.

Rivas-Urbina A, Benitez S, Perez A, Sanchez-Quesada JL. (2018). Modified low-density lipoproteins as biomarkers in diabetes and metabolic syndrome. Front Biosci (Landmark Ed). 2018 Jan 1;23:1220-1240.

Rose DP, Connolly JM. (1999). Omega-3 fatty acids as cancer chemopreventive agents. Pharmacol Ther. 1999 Sep;83(3):217-44.

Shankar E, Bhaskaran N, MacLennan GT, Liu G, Daneshgari F, Gupta S. (2015). Inflammatory Signaling Involved in High-Fat Diet Induced Prostate Diseases. J Urol Res. 2015 Jan 1;2(1). pii: 1018.

Shukla A, Grisouard J, Ehemann V, Hermani A, Enzmann H, Mayer D. (2009). Analysis of signaling pathways related to cell proliferation stimulated by insulin analogs in human mammary epithelial cell lines. Endocr Relat Cancer. 2009 Jun;16(2):429-41.

Stehle JR Jr, Leng X, Kitzman DW, Nicklas BJ, Kritchevsky SB, High KP. (2012). Lipopolysaccharide-binding protein, a surrogate marker of microbial translocation, is associated with physical function in healthy older adults. J Gerontol A Biol Sci Med Sci. 2012 Nov;67(11):1212-8.

Stoll BA. (2002). N-3 fatty acids and lipid peroxidation in breast cancer inhibition. Br J Nutr. 2002 Mar;87(3):193-8.

Sun S, Ji Y, Kersten S, Qi L. (2012). Mechanisms of inflammatory responses in obese adipose tissue. Annu Rev Nutr. 2012 Aug 21;32:261-86.

Thiébaut AC, Chajès V, Gerber M, Boutron-Ruault MC, Joulin V, Lenoir G, Berrino F, Riboli E, Bénichou J, Clavel-Chapelon F. (2009). Dietary intakes of omega-6 and omega-3 polyunsaturated fatty acids and the risk of breast cancer. Int J Cancer. 2009 Feb 15;124(4):924-31.

Tierney AC, McMonagle J, Shaw DI, Gulseth HL, Helal O, Saris WH, Paniagua JA, Gołąbek-Leszczyñska I, Defoort C, Williams CM, Karsltröm B, Vessby B, Dembinska-Kiec A, López-Miranda J, Blaak EE, Drevon CA, Gibney MJ, Lovegrove JA, Roche HM. (2011). Effects of dietary fat modification on insulin sensitivity and on other risk factors of the metabolic syndrome--LIPGENE: a European randomized dietary intervention study. Int J Obes (Lond). 2011 Jun;35(6):800-9.

Uzunlulu M, Telci Caklili O, Oguz A. (2016). Association between Metabolic Syndrome and Cancer. Ann Nutr Metab. 2016;68(3):173-9.

Vehovský K, Stupka R, Čítek R, Šprysl M, Okrouhlá M, Brzobohatý L. (2015). Factors affecting the fatty acid composition and fat oxidative stability in pigs. JCEA. 2015. 16(1): 122-129.

Viriyakosol S, Mathison JC, Tobias PS, Kirkland TN. (2000). Structure-function analysis of CD14 as a soluble receptor for lipopolysaccharide. J Biol Chem. 2000 Feb 4;275(5):3144-9.

Vona-Davis L, Howard-McNatt M, Rose DP. (2007). Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. Obes Rev. 2007 Sep;8(5):395-408.

Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J. (2006). n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr. 2006 Jul;84(1):5-17.

Wang M, Cheng N, Zheng S, Wang D, Hu X, Ren X, Pei H, Ma H, Mu H, Bai Y. (2015). Metabolic syndrome and the risk of breast cancer among postmenopausal women in North-

West China. Climacteric. 2015;18(6):852-8.

Wirfält E, Mattisson I, Gullberg B, Olsson H, Berglund G. (2005). Fat from different foods show diverging relations with breast cancer risk in postmenopausal women. Nutr Cancer. 2005;53(2):135-43.

Xin W, Wei W, Li X. (2012). Effects of fish oil supplementation on inflammatory markers in chronic heart failure: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2012 Sep 20;12:77.

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