ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Obesity and Breast Cancer: Circulating Adipokines and Their Potential Diagnostic as Risk Biomarkers

Hind Shakir Ahmed*

Department of Chemistry, College of Education for Pure Science (Ibn Al-Haitham), University of Baghdad, Iraq

Article History:

Received on: 11 Mar 2020
Revised on: 12 Apr 2020
Accepted on: 13 Apr 2020

Keywords:

Breast Cancer,
Insulin-Like Growth Factor-1,
Leptin,
Adiponectin,
Resistin

ABSTRACT

Obesity and cancer are two major epidemics of this century. Obesity is related to a higher risk of many types of cancer. Studies have accessed circulating adipokines, as key-mediators in obesity and breast cancer. The study is aimed to examine the circulating levels of insulin-like growth factor-1, leptin, adiponectin, and resistin in premenopausal Iraqi women with breast cancer. The current study was performed during the period from June 2019 to December 2019 at Oncology unit/ Medical City Hospital-Baghdad. A total of 90 premenopausal women with BC/ stage II and III after 2^{nd} dose of chemotherapy were contributed in this study as patients group. Their ages ranged from (35-50) years in addition to 90 premenopausal healthy women were designated as a control group. There was a substantial rise ($p < 0.05$) in fasting serum glucose, total serum cholesterol, triacylglycerol, low-density lipoprotein cholesterol, CA15-3, insulin-like growth factor-1, leptin, leptin/adiponectin ratio, and resistin. While there was a substantial decrease ($p= 0.01$) in serum adiponectin in patients as paralleled to healthy. There was a considerable rise ($p \leq 0.05$) in serum insulin-like growth factor-1, leptin, and resistin, while there was a reduced in serum adiponectin in obese patients as paralleled to overweight, but it was not significant. Additionally, circulating levels of insulin-like growth factor-1, leptin, and resistin were significantly increased ($p= 0.001$) in patients who had tumour size > 5 cm paralleled to those with tumour size 2-5 cm. Higher levels of serum leptin, resistin, and leptin to adiponectin ratio are related to improved breast cancer risk in Iraqi women. The clinical and pathological features of the tumour recommended that these adipokines might affect the development of breast cancer. Thus adipokines, in complicated and interrelated mechanisms, maybe drive breast cancer instigation and progression.

*Corresponding Author

Name: Hind Shakir Ahmed
Phone:
Email: hindshakir82@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i3.2408

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INTRODUCTION

Breast cancer (BC) is the most significant common cancer identified among women in developed countries. It is the second foremost cause of cancer death among women after lung cancer (Allemani *et al.*, 2015). The category of breast carcinoma depends on clinicopathological features and the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Though great progressions in cancer diagnosis and treatment lately, BC remains, a primary

reason for death for a woman (Maclean *et al.*, 2015; Lohman *et al.*, 1988).

It has consistently revealed that the risk for numerous cancer types comprising that of the liver, pancreas, colorectal, and breast is higher in insulin-resistant patients (Cowey and Hardy, 2006). Insulin improves the bioactivity of insulin-like growth factor-1 (IGF-1) (Rose *et al.*, 2004). Also, the bioactivity and bioavailability of IGF-1 are affected by six binding proteins (IGF-binding proteins (IGFBPs) that also exert independent biological actions (Pollak, 2008). The IGFBP-1 has stimulatory and inhibitory influences on IGF-1 bioactivity, with the phosphorylated form of IGFBP-1 inhibiting IGF-1 system, whereas the unphosphorylated form has a stimulatory impact. Adipocyte secretion of IGF-1 has been established to directly stimulate BC cell proliferation *in vitro* (Lubik *et al.*, 2013).

Obesity, as a chief health problem, is connected with increased BC occurrence and consequent mortality. The particular mechanism linking obesity and BC risk remains uncertain. Still, it has been proposed that adipose tissue can produce a group of cytokines counting leptin and adiponectin, which may trigger such relationship and play as prospective biomarkers and treatment targets for the management of this destructive disease (Dossus *et al.*, 2017).

Leptin is a 16 KDa neuroendocrine hormone that acts as a multifunctional protein with 167 amino acids, formed primarily by white adipose tissue. There is negligible leptin production in normal circumstances which increases in particular pathological processes such as inflammation and malignant alterations (Polyzos and Mantzoros, 2015).

Adiponectin is a 247 amino acid. It is a protein hormone that modulates several metabolic processes, comprising glucose regulation and fatty acid oxidation. Adiponectin is secreted from adipose tissue. It has found that adiponectin inversely interrelated with body mass index (BMI) in patients (Ahlstrom *et al.*, 2017).

Resistin is a 12.5 kDa protein secreted by adipocytes, macrophages, and bone marrow cells has been initially concerned in the pathogenesis of obesity-mediated IR, also has been studied expansively for its role in inflammation and obesity-related cancers (Gong *et al.*, 2016). Resistin has been proposed to be an inflammatory marker in humans because macrophages are well-known inflammatory modulators. It was found that resistin favours the transformation of macrophage into foam cells by de restricting cell receptors, a phenomenon that leads to lipid accumulations and alteration in endothelial effective, which may represent the significant problematic event associated with atherosclerosis (Jamaluddin *et al.*, 2012). Therefore, the target of this work is to estimate the circulating levels of IGF-1, leptin, adiponectin, and resistin among premenopausal Iraqi women with BC.

PATIENTS AND METHODS

The current work was performed during the period from June 2019 to December 2019 at Oncology unit/ Medical City Hospital- Baghdad. A total of 90 premenopausal women with BC/ stage II and III after 2^{nd} dose of chemotherapy were included in this study as patients group. Their ages ranged from (35-50) years in addition to 90 premenopausal healthy women were selected according to the normal mammographic outcomes and no history of cancer as a control group.

Additionally, women with BC were categorized according to BMI into two groups: obese (n= 48) and overweight (n= 42). Also, they were categorized according to: the tumors size 2-5 cm (n= 55) or > 5 cm (n= 35).

The study was permitted by an institutional ethics committee of the Iraqi Ministry of Health and Medical City Hospital/ Baghdad, and the procedures followed were in accordance with the applied guidelines. Clinical and pathological information. Weight and height for every subject were also recorded, date and type of treatment, tumour grade, as well as immuno-histochemical evaluation of ER and PR status, obtained from medical records.

Clinicopathologic Characteristics of Tumor

The status of ER and PR were examined by immunohistochemical staining (DAKO, USA).

Measurements

Blood pressures were recorded according to the guidelines adopted by the WHO. The BMI and waist circumference (WC) were determined for patients and controls (Dubois *et al.*, 2013).

Blood glucose and serum lipid profile encompassing: [total cholesterol (TC), triacylglycerol (TAG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)] were determined using Hitachi auto-analyzer. Serum IGF-1 concentration was determined by IRMA-Immunotech kit, France. While, serum CA15-3 concentration was determined using Monobind equipment, USA (Martinetti *et al.*, 2014).

Serum leptin, adiponectin, and resistin were determined using the microplate-ELISA bioassay system as formerly stated (Torre *et al.*, 2015) by (Bio-Rad Laboratories, Inc., Berkeley, CA, USA).

Table 1: Clinicopathological characteristics of patients

Variable	Cases(n= 90)
Histological stage:	
II	36 (40%)
III	54 (60%)
Tumor size:	
> 5 cm	35 (38.89%)
2-5 cm	55 (61.11%)
Lymph node metastasis:	
Positive	50 (55.56%)
Negative	40 (44.44%)
Hormonal receptors:	
ER+	47 (52.22%)
PR+	43 (47.78%)
Family history of BC:	
Positive	52 (57.78%)
Negative	38 (42.22%)
Duration of the Disease (Years)	5.20±3.35

Table 2: Clinical and biochemical characteristics of cases and healthy

Variables	Patients (n=90)	Healthy (n=90)	p-value
Age (Years)	42.20±8.0	38.70±3.24	0.50
WC (cm)	97.0 ± 9.05	72.0±1.05	0.001
BMI (Kg/m2)	36.0±4.50	21.50±1.62	0.001
SBP (mmHg)	138.20±3.50	123.50±1.30	0.001
DBP (mmHg)	87.65±1.50	80.33±0.40	0.05
FSG (mg/dl)	105.20±0.80	85.62±0.45	0.001
TC (mg/dl)	230.50±12.62	115.32±10.15	0.001
TAG (mg/dl)	180.0±10.42	110.60±15.60	0.001
HDL-C (mg/dl)	33.61±2.15	62.35±5.48	0.001
LDL-C (mg/dl)	160.39±8.39	30.85±1.45	0.001
CA15-3 (U/ml)	41.20±6.30	12.50±5.80	0.001
IGF-1 (ng/ml)	210.45±8.20	185.0±2.30	0.001
Leptin (ng/ml)	22.38±2.78	6.20±1.15	0.001
Adiponectin (μg/ml)	6.42±1.02	15.95±2.60	0.01
L/A ratio	3.55±2.32	0.39±0.40	0.05
Resistin (ng/ml)	18.32±2.40	3.50±0.50	0.001

Values are expressed as mean ± SD; $p \leq 0.05$= significant;$p \leq 0.01$= highlysignificant; WC= waist circumferences, BMI= body mass index;SBP= systolic bloodpressure; DBP= diastolic blood pressure; FSG= fasting serum glucose; TC=total cholesterol; TAG=triacylglycerol; HDL-C= high density lipoprotein cholesterol;LDL-C= low density lipoproteincholesterol; IGF-1= insulin like growthfactor-1; L/A= leptin/ adiponectin ratio.

Table 3: Hormonal profile among obese and overweight patients

Variables	Obese (n= 48)	Overweight (n= 42)	p-value
IGF-1 (ng/ml)	240.20±8.45	180.50±6.30	0.001
Leptin (ng/ml)	26.50±4.26	18.25±1.30	0.01
Adiponectin (μg/ml)	5.0±1.42	7.0±1.85	0.06
L/A ratio	5.30±3.0	2.60±0.70	0.06
Resistin (ng/ml)	18.40±3.50	10.30±2.50	0.05

$p \leq 0.05$= significant;$p \leq 0.01$= highly significant; IGF-1= insulin like growth factor-1; L/A= leptin/adiponectin ratio.

Table 4: SerumIGF-1 and adipokines levels according to tumor size in patients group

Variables	Tumor size > 5 cm2-5 cm (n= 35)	(n= 55)	p-value
IGF-1 (ng/ml)	255.0±4.20	165.20±7.35	0.001
Leptin (ng/ml)	28.62±3.42	16.40±2.50	0.001
Adiponectin (μg/ml)	4.75±2.30	7.25±1.50	0.07
L/A ratio	6.02±1.48	2.26±1.66	0.06
Resistin (ng/ml)	15.32±4.50	3.50±1.50	0.001

$p \leq 0.05$= significant, $p \leq 0.01$= highly significant;IGF-1= insulin like growth factor-1; L/A= leptin/adiponectin ratio.

Table 5: Correlation coefficients between serum IGF-1 and adipokines in patients

IGF-1 (ng/ml)	Correlation coefficient (r)	p-value
Leptin (ng/ml)	0.98	0.01
Adiponectin (μg/ml)	-0.72	0.01
L/A ratio	0.26	0.05
Resistin (ng/ml)	0.87	0.01

IGF-1= insulin like growth factor-1; L/A= leptin/adiponectin ratio

Statistical Analysis

All data are shown as means ± SD for all parameters. The t-test was used to equate experimental groups. Also, p-value ≤ 0.05 was deliberated statistically substantial

RESULTS

Clinicopathological characteristics in BC patients included: histological stage, tumor size, lymph node metastasis, hormonal receptor positive, and duration of the disease were illustrated in Table 1.

There was no substantial variance in age between the two groups. While, there was a considerable increase ($p \leq 0.05$) in WC, BMI, SBP, and DBP in BC group as compared to the healthy group, Table 2.

Also, there was a significant increase ($p \leq 0.05$) in FSG, serum TC, TAG, LDL-C, CA15-3, IGF-1, leptin, leptin/adiponectin (L/A) ratio, and resistin. While there was a substantial decrease in serum adiponectin (p= 0.01) in patients as paralleled to healthy, as shown in Table 2.

There was a substantial rise ($p \leq 0.05$) in serum IGF-1, leptin, and resistin in obese patients as paralleled to overweight. While there was a reduced in serum adiponectin in obese patients as paralleled to overweight, but it was not significant. Moreover, there was an elevation in L/A ratio in obese patients, but it was not substantial Table 3.

Additionally, circulating levels of serum IGF-1, leptin, and resistin were significantly increased (p= 0.001) among patients who had tumour size > 5 cm paralleled to those with tumour size 2-5 cm. Also, the ratio of L/A was elevated in cases with tumour size > 5 cm. Though, there was a reduction in serum adiponectin in those patients as compared to patients with tumour size 2-5 cm, Table 4.

Furthermore, correlation coefficients (r) between serum IGF-1 and adipokines in BC patients are

shown in Table 5. There were significant positive correlations between serum IGF-1 and serum leptin, L/A ratio, and resistin in BC patients. At the same time, there was a substantial negative association with serum adiponectin in BC patients.

DISCUSSION

Breast cancer is the most commonly identified cancer in Arab women (Ewertz *et al.*, 2012). It has been examined an association between diverse cancer subtypes and anthropometric measures of obesity (Ma *et al.*, 2013). It has been documented that obesity-associated BC is more frequently ER+ than is the overall case (Chang *et al.*, 2016).

Nevertheless, relations between BMI and premenopausal BC were less reliable. A diffident common of revisions reported that premenopausal obesity is inversely associated with BC risk and proposed a defensive influence (Azoulay *et al.*, 2016).

Results in the current study revealed that BMI is related to progressive stage and grade of breast carcinoma among female patients. These outcomes further funding existing evidence of a greater effect of obesity. Thus, high central obesity may reveal low fitness and low-grade inflammation, which are both related to an elevated risk of cancer (Garg *et al.*, 2014). Epidemiological and clinical evidence proposed that obesity is linked with a higher risk of BC and resistance to BC treatment. It has been suggested that this positive relationship may be confounded by BMI of 25 kg/m^2 at least (Dubois *et al.*, 2013).

Ewertz and colleagues, 2012 determined that the risk of increasing metastasis in early-stage of obese patients increased by 42-46% after ten years, paralleled to overweight patients, and the risk of death due to BC after 30 years was considerably increased by 38% in obese patients. A Women's Health Initiative trial revealed that BMI related to a higher risk of ER+ and PR+ among BC patients (Neuhouser *et al.*, 2015).

As one constituent of metabolic syndrome, hypertension was described to connect with improved BC risk in a meta-analysis, with the pooled risk estimates that was comparable to the present result. Nevertheless, this relationship is composite, and it is still uncertain whether it is causal, as both hypertension and cancer are exaggerated by parallel risk influences such as obesity, smoking, alcohol consumption and physical inactivity (Koene *et al.*, 2016).

Numerous mechanisms have been suggested for an association between hypertension and BC risk. First, both factors may share corporate pathophysiological pathway intermediated by adipose tissue, which could cause chronic inflammation and improved the risk of both BC and hypertension. Additional potential clarification that is hypertension may rise BC risk by obstructing and consequently modifying apoptosis, thus disturbing the regulation of cell turnover.Finally, another study revealed women who used antihypertensive medications exhibited an improved chance of BC paralleled to those without antihypertensive drugs. This may be due to the use of calcium channel blockers was related to an over two-fold improved of BC risk (Largent *et al.*, 2006).

Additionally, the previous study has shown that high glucose can provide the optimal growth environment for tumours (Elgendy *et al.*, 2019).

Sun *et al.* (2019) data proposed that high glucose-stimulated cell proliferation, capability, and anchorage-independent growth, which indicated that high glucose donated to the metastatic behaviour of BC as well. Obesity has influences on a number of hormones and growth factors possibly connected to BC. A significant collection of obesity-associated metabolic concerns comprise different concentrations of circulating adipocytokines and progress of insulin resistance (IR) comprising hyperinsulinemia and impaired glucose metabolism (Dumais *et al.*, 2017).

As LDL and HDL mostly transport cholesterol, these lipids have linked them with BC. It has found that LDL-C level greater than 117 mg/dl is a prognostic influence of tumour stage, also, related with poorer prognosis due to a greater histological grade, higher proliferative rate, and more progressive clinical stage. Furthermore, patients who have LDL-C greater than 144 mg/dl were also prone to have lymph node metastasis (dos Santos *et al.*, 2014). Further significantly, other studies propose that genetically higher LDL-C was related to a greater of BC risk (Nowak and Ärnlöv, 2018).

In the present study, it was observed that a significant increase in serum CA15-3 in the comparison between the control group and all patients group. This result is in harmony with that reported by Khan *et al.* (2016), who found that an increase in serum CA 15-3 concentrations in BC patients paralleled to the control group. These results are in covenant with the current study.

The IGF-1 is an effective growth factor with a role in cancer pathogenesis, which has been associated in epidemiological revisions to cancer. Moreover, it can rise normal cell cycling, leading to improved risk of mutation and malignant transfor-

mation. One probable mechanism clarifying the relationship between obesity and cancer other than estrogen is IR. Insulin improves the activity of IGF-1, and high circulating of IGF-1 levels are interrelated with the risk of BC progress. Thus, higher levels of IGF-1 have been associated with cancer death Shanmugalingam *et al.* (2016).

Cumulative revisions have specified that adipokines, complicated in the mediation of inflammatory diseases and obesity (Deshmukh *et al.*, 2017; Akter *et al.*, 2019), which are in agreement with the present study.

Adipokines, predominantly leptin, may have a chief role in BC biology. Obesity is related to high levels of leptin. Obesity is accompanied by leptin resistance. It has been firmly that BC related to obesity and hyperleptinemia, also with immunological investigation conflicts. This complex network proposes crosstalk among leptin, immune response and development of BC in obese women (Reilly *et al.*, 2005).

Furthermore, adiponectin is convoluted in the reduction of tumour size in animals and declined serum adiponectin concentrations are related to the progression of BC among women. Metabolic dysregulations linked with obesity such as hyperleptinemia and hypoadiponectomia are probable to stimulate cancer cell growth via particular mechanisms. When mammary cells are involved in the process of carcinogenesis, they produce adipokines mostly leptin capable of acting on surrounding cancer cells in an autocrine and paracrine manner (Shacter and Weitzman, 2002).

It has been hypothesized that the L/A ratio could be more convenient as a biomarker because both hormones involved in this formula are aggressive in their final result on tumourigenesis (Santillán-Benítez *et al.*, 2013). Therefore, this variable could designate that metabolic regulation has protective elements against the higher leptin levels.

The current study revealed an elevation in this ratio. So, it could be possible to decrease this ratio by modifying the patient's diet and lifestyle, which would alter the vulnerability to cancer through the inhibition of the leptin pathway. Regarding the CA15-3 level, it appears that obese patients are more susceptible to elevated levels of this marker irrespective of the cancer diagnosis.

Numerous adipokines have been implied in cancer progress, primarily through IR and inflammation. An elevated level of most of these adipokines such as leptin and resistin has shown a pro-carcinogenic role. The present study showed that BC patients had considerable levels of serum resistin than the healthy group.

High levels of resistin have been reported in some forms of malignancies, including (Fasshauer and Blüher, 2015). Additionally, the levels of resistin with breast tumour size, stage and lymph node metastasis. It has been conducted that increased concentrations of resistin were connected with increases in BC risk (Liu *et al.*, 2017).

Serum resistin is consistently correlated with cancer development, including BC. It has also been recommended that the expression of resistin in cancer cells is related to more malignant clinical and pathological processes (Cormanique *et al.*, 2015).

The outcomes of this study indicated that BC patients showed significantly higher mean value of serum resistin than the control group.

Because the earlier revisions documented that resistin is expressed from adipose tissue and also from monocytes and macrophages, and associated with specific inflammatory markers directly, the role of resistin as a further marker of inflammation has traditional growing concern (Yang *et al.*, 2016). Inflammation may be characterized by biomarkers of primary pathologic modifications in breast cells and be related to risk for the BC progress. Consequently, an association between serum resistin concentrations and BC risk might be partially clarified by inflammation (Assiri and Kamel, 2016).

CONCLUSION

Serum IGF-1, adiponectin, and L/A ratio may have a relationship with invasiveness and metastasis of BC. Both high serum leptin and resistin concentrations are probably to be related to improved BC risk among Iraqi women. Clinical and pathological features of the tumour recommended that these adipokines might affect the development of BC. Thus, adipokines in complex and interrelated mechanisms may be drive BC initiation and progression.

Funding support

None

Conflict of interest

The author declares that there is no conflict of interest.

REFERENCES

Ahlstrom, P., Rai, E., Chakma, S., Cho, H. H., Rengasamy, P., Sweeney, G. 2017. Adiponectin improves insulin sensitivity via activation of

autophagic flux. *Journal of Molecular Endocrinology*, 59(4):339–350.

Akter, S., Faruque, M., Nahar, K. 2019. Association of serum IGF1 and adiponectin in prognosis of breast cancer metastasis. *Annals of Oncology*, 30(3):47–64.

Allemani, C., Weir, H. K., Carreira, H., Harewood, R., Spika, D., Wang, X.-S., Bannon, F., Ahn, J. V., Johnson, C. J., Bonaventure, A., Marcos-Gragera, R., Stiller, C., e Silva, G. A., Chen, W.-Q., Ogunbiyi, O. J., Rachet, B., Soeberg, M. J., You, H., Matsuda, T., Bielska-Lasota, M., Storm, H., Tucker, T. C., Coleman, M. P. 2015. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). *The Lancet*, 385(9972):977–1010.

Assiri, A. M., Kamel, H. F. 2016. Evaluation of diagnostic and predictive value of serum adipokines: Leptin, resistin and visfatin in postmenopausal breast cancer. *Obesity Research & Clinical Practice*, 10(4):442–453.

Azoulay, L., Soldera, S., Yin, H., Bouganim, N. 2016. Use of Calcium Channel Blockers and Risk of Breast Cancer. *Epidemiology*, 27(4):594–601.

Chang, C. H., Chiang, C. H., Yen, C. J., Wu, L. C., Lin, J. W., Lai, M. S. 2016. Antihypertensive agents and the risk of breast cancer in women aged 55 years and older. *Journal of Hypertension*, 34(3):558–566.

Cormanique, T., Costa, F., Justina, E., Broto, G., Moraes, J., Fagundes, T., Gomes, E., Takakura, E., Lopes, N., Loli, T., Goto, V., Victorino, V., Panis, C. 2015. *Role of leptin in the pathogenesis of breast cancer. Semina : Ciências Biológicas e Da Saúde*, 36:97–116.

Cowey, S., Hardy, R. W. 2006. The metabolic syndrome: A high-risk state for cancer? *The American Journal of Pathology*, 169(5):1505–1522.

Deshmukh, S. K., Srivastava, S. K., Zubair, H., Bhardwaj, A., Tyagi, N., Al-Ghadhban, A., Singh, A. P., Dyess, D. L., Carter, J. E., Singh, S. 2017. Resistin potentiates chemoresistance and stemness of breast cancer cells: Implications for racially disparate therapeutic outcomes. *Cancer Letters*, 396:21–29.

dos Santos, C. R., Fonseca, I., Dias, S., de Almeida, J. C. M. 2014. Plasma level of LDL-cholesterol at diagnosis is a predictor factor of breast tumor progression. *BMC Cancer*, 14(1):132–132.

Dossus, L., Rinaldi, S., Biessy, C., Hernandez, M., Lajous, M., Monge, A., Ortiz-Panozo, E., Yunes, E., Lopez-Ridaura, R., Torres-Mejía, G., Romieu, I. 2017. Circulating leptin and adiponectin, and breast density in premenopausal Mexican women: the Mexican Teachers' Cohort. *Cancer Causes & Control*, 28(9):939–946.

Dubois, V., Delort, L., Billard, H., Vasson, M.-P., Caldefie-Chezet, F. 2013. Breast Cancer and Obesity: In Vitro Interferences between Adipokines and Proangiogenic Features and/or Antitumor Therapies? *PLoS ONE*, 8(3):e58541–e58541.

Dumais, V., Lumingu, J., Bedard, M., Paquet, L., Verma, S., Fontaine-Bisson, B. 2017. Prevalence of Insulin Resistance, Metabolic Syndrome, and Type 2 Diabetes in Canadian Women at High Risk for Breast Cancer. *The Breast Journal*, 23(4):482–483.

Elgendy, M., Cirò, M., Hosseini, A., Weiszmann, J., Mazzarella, L., Ferrari, E., Cazzoli, R., Curigliano, G., DeCensi, A., Bonanni, B., Budillon, A., Pelicci, P. G., Janssens, V., Ogris, M., Baccarini, M., Lanfrancone, L., Weckwerth, W., Foiani, M., Minucci, S. 2019. Combination of Hypoglycemia and Metformin Impairs Tumor Metabolic Plasticity and Growth by Modulating the PP2A-GSK3β-MCL-1 Axis. *Cancer Cell*, 35(5):798–815.e5.

Ewertz, M., Gray, K. P., Regan, M. M., Ejlertsen, B., Price, K. N., Thürlimann, B., Bonnefoi, H., Forbes, J. F., Paridaens, R. J., Rabaglio, M., Gelber, R. D., Colleoni, M., Láng, I., Smith, I. E., Coates, A. S., Goldhirsch, A., Mouridsen, H. T. 2012. Obesity and Risk of Recurrence or Death After Adjuvant Endocrine Therapy With Letrozole or Tamoxifen in the Breast International Group 1-98 Trial. *Journal of Clinical Oncology*, 30(32):3967–3975.

Fasshauer, M., Blüher, M. 2015. Adipokines in health and disease. *Trends in Pharmacological Sciences*, 36(7):461–470.

Garg, S. K., Maurer, H., Reed, K., Selagamsetty, R. 2014. Diabetes and cancer: two diseases with obesity as a common risk factor. *Diabetes, Obesity and Metabolism*, 16(2):97–110.

Gong, W. J., Zheng, W., Xiao, L., Tan, L. M., Song, J., Li, X. P., Xiao, D., Cui, J. J., Li, X., Zhou, H. H., Yin, J. Y., Liu, Z. Q. 2016. Circulating resistin levels and obesity-related cancer risk: A meta-analysis. *Oncotarget*, (36):57694–704.

Jamaluddin, M. S., Weakley, S. M., Yao, Q., Chen, C. 2012. Resistin: functional roles and therapeutic considerations for cardiovascular disease. *British Journal of Pharmacology*, 165(3):622–632.

Khan, M., Trivedi, H., Atara, A. 2016. Analysis of tumour marker CA 15-3 in breast cancer following surgery. *International Surgery Journal*, 3(3):1491–1494.

Koene, R. J., Prizment, A. E., Blaes, A., Konety, S. H. 2016. Shared Risk Factors in Cardiovascular Dis-

ease and Cancer. *Circulation*, 133(11):1104–1114.

Largent, J. A., McEligot, A. J., Ziogas, A., Reid, C., Hess, J., Leighton, N., Peel, D., Anton-Culver, H. 2006. Hypertension, diuretics and breast cancer risk. *Journal of Human Hypertension*, 20(10):727–732.

Liu, Z., Shi, A., Song, D., Han, B., Zhang, Z., Ma, L., Liu, D., Fan, Z. 2017. Resistin confers resistance to doxorubicin-induced apoptosis in human breast cancer cells through autophagy induction. *American Journal of Cancer Research*, 7(3):574–583.

Lohman, T., Roche, A., Martorell, R. 1988. Anthropometric standardization reference manual. Champaign, Ill. Human Kinetics. ISBN: 9780873221214.

Lubik, A. A., Gunter, J. H., Hollier, B. G., Ettinger, S., Fazli, L., Stylianou, N., Hendy, S. C., Adomat, H. H., Gleave, M. E., Pollak, M., Herington, A., Nelson, C. C. 2013. IGF2 increases de novo steroidogenesis in prostate cancer cells. *Endocrine-Related Cancer*, 20(2):173–186.

Ma, Y., Yang, Y., Wang, F., Zhang, P., Shi, C., Zou, Y., Qin, H. 2013. Obesity and Risk of Colorectal Cancer: A Systematic Review of Prospective Studies. *PLoS ONE*, 8(1):e53916–e53916.

Maclean, R., Jeffreys, M., Ives, A., Jones, T., Verne, J., Ben-Shlomo, Y. 2015. Primary care characteristics and stage of cancer at diagnosis using data from the national cancer registration service, quality outcomes framework and general practice information. *BMC Cancer*, 15(1).

Martinetti, A., Miceli, R., Sottotetti, E., Bartolomeo, M. D., de Braud, F., Gevorgyan, A., Dotti, K., Bajetta, E., Campiglio, M., Bianchi, F., Bregni, G., Pietrantonio, F. 2014. Circulating Biomarkers in Advanced Colorectal Cancer Patients Randomly Assigned to Three Bevacizumab-Based Regimens. *Cancers*, 6(3):1753–1768.

Neuhouser, M. L., Aragaki, A. K., Prentice, R. L., Manson, J. E., Chlebowski, R., Carty, C. L., Ochs-Balcom, H. M., Thomson, C. A., Caan, B. J., Tinker, L. F., Urrutia, R. P., Knudtson, J., Anderson, G. L. 2015. Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk. *JAMA Oncology*, 1(5):611–611.

Nowak, C., Ärnlöv, J. 2018. A Mendelian randomization study of the effects of blood lipids on breast cancer risk. *Nature Communications*, 9(1):3957–3957.

Pollak, M. 2008. Insulin and insulin-like growth factor signalling in neoplasia. *Nature Reviews Cancer*, 8(12):915–928.

Polyzos, S. A., Mantzoros, C. S. 2015. Leptin in Health and Disease: Facts and Expectations at its Twentieth Anniversary. *Metabolism*, 64(1):5–12.

Reilly, M. P., Lehrke, M., Wolfe, M. L., Rohatgi, A., Lazar, M. A., Rader, D. J. 2005. Resistin Is an Inflammatory Marker of Atherosclerosis in Humans. *Circulation*, 111(7):932–939.

Rose, D. P., Komninou, D., Stephenson, G. D. 2004. Obesity, adipocytokines, and insulin resistance in breast cancer. *Obesity Reviews*, 5(3):153–165.

Santillán-Benítez, J. G., Mendieta-Zerón, H., Gómez-Oliván, L. M., Torres-Juárez, J. J., González-Bañales, J. M., Hernández-Peña, L. V., Ordóñez-Quiroz, A. 2013. The Tetrad BMI, Leptin, Leptin/Adiponectin (L/A) Ratio and CA 15-3 are Reliable Biomarkers of Breast Cancer. *Journal of Clinical Laboratory Analysis*, 27(1):12–20.

Shacter, E., Weitzman, S. A. 2002. Chronic inflammation and cancer. *Oncology (Huntingt)*, 16(2):217–243.

Shanmugalingam, T., Bosco, C., Ridley, A. J., Hemelrijck, M. V. 2016. Is there a role for IGF -1 in the development of second primary cancers?

Sun, S., Sun, Y., Rong, X., Bai, L. 2019. High glucose promotes breast cancer proliferation and metastasis by impairing angiotensinogen expression. *Bioscience Reports*, 39(6):1–9.

Torre, Bray, Siegel, Ferlay, Lortet-Tieulent, Jemal 2015. Global cancer statistics. *CA: A Cancer Journal for Clinicians*, 65(2):87–108.

Yang, G., Fan, W., Luo, B., Xu, Z., Wang, P., Tang, S., Xu, P., Yu, M. 2016. Circulating Resistin Levels and Risk of Colorectal Cancer: A Meta-Analysis. *BioMed Research International*, 2016:1–11.