International Journal of General Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Metabolic Profile and Negatively Association Between Insulin Resistance and Metastatic Incidence in Indonesian Primary Invasive Breast Cancer: A Cross-Sectional Study

Andhika Rachman[1,2], Zaenal Hakiki Fiantoro[3], Noorwati Sutandyo[4], Dimas Priantono[1], Pradana Zaky Romadhon[5], Reganedgary Jonlean[6]

[1]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia; [2]Siloam MRCCC Semanggi Hospital, Jakarta, Indonesia; [3]Departement of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia; [4]Dharmais National Cancer Referral Hospital, Jakarta, Indonesia; [5]Division of Hematology and Medical Oncology, Department of Internal Medicine, Airlangga University, Surabaya, Indonesia; [6]Tzu Chi Hospital, Jakarta, Indonesia

Correspondence: Andhika Rachman, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Pangeran Diponegoro No. 71, Jakarta, 10430, Indonesia, Tel +62 813 9862 0570, Email andhika_rachman@office.ui.ac.id; andhikarachman@gmail.com

Introduction: Metastatic breast cancer was associated with high morbidity and mortality. Insulin resistance was hypothesized to be related to the incidence of advanced breast cancer. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and Triglyceride/Glucose Index (TyG Index) are two metrics used to measure the degree of insulin resistance. This study aims to assess the relationship between the incidence of metastatic breast cancer and insulin resistance as reflected by both metrics.

Material and Methods: This study is a cross-sectional study involving 150 primary invasive breast cancer patients recruited from two hospitals of different sectors from August 2019 to April 2020. Patients with double cancer and autoimmune disorder were excluded from this study. Data obtained from the patients include age, body mass index (BMI), type 2 diabetes mellitus (T2DM) status and treatment, and low-density lipoprotein (LDL) cholesterol. The electronic medical records (EMR) was consulted to find histopathology examination result, cancer staging, and any missing data. The association between HOMA-IR and TyG with metastatic incidence was analyzed using either the Mann–Whitney test (for non-normally distributed data) or the independent-sample *t*-test (for normally distributed data).

Results: The mean of the TyG index is 8.60, and the median of HOMA-IR is 1.22. We found no significant correlation between both variables and the incidence of metastases.

Conclusion: Insulin resistance was not associated with metastatic breast cancer.

Keywords: HOMA-IR, TyG index, breast cancer, metastases

Introduction

Female breast cancer has surpassed lung cancer as the most found cancer in the world, according to the GLOBOCAN 2020 study, contributing to 11.7% of all cancer cases.[1] It is the leading cause of cancer death in women. In Indonesia, breast cancer has been marked as the leading cancer diagnosis in women and the highest cause of cancer-related mortality in Indonesian women.

Based on data from GLOBOCAN 2020, breast cancer is the most common cancer in Indonesia (16.6%) and is the second highest contributor to all cancer-related mortality in Indonesia (9.6% of all cancer-related deaths).[2] Gondhowiardjo et al[3] found that breast cancer is the second most common cancer according to data from the cancer registry of the Cipto Mangunkusumo Hospital, Indonesia's highest national central referral hospital. However, with the advancement of breast cancer therapeutics, survival rates of metastatic breast cancer have improved.[4]

Breast cancer has been associated with metabolic disturbances, of which insulin resistance is a highly noted aspect of this correlation.[5] The pathophysiological basis of this relationship is still not fully understood. However, hyperinsulinemia has been thought of as the critical actor of this melodrama.[6] Body mass index, an anthropometric indices associated

Received: 25 May 2023
Accepted: 21 July 2023
Published: 1 August 2023

with insulin resistance, was observed to be positively correlated with the risk of breast cancer.[7,8] In addition, Ariaans et al[9] reported that breast cancer treatment might also contribute to the pathogenesis of insulin resistance. On the other hand, insulin resistance may negatively affect the prognosis of breast cancer.[10,11] Thus, proper management of insulin resistance in breast cancer patients is crucial.

Several metrics have been proposed to measure the degree of insulin resistance. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) has been widely used in scientific research to determine the degree of insulin resistance in women with breast cancer. HOMA-IR is the most widely used metric to measure insulin resistance by incorporating fasting plasma glucose and insulin values.[12] An emerging metric is called the triglyceride/glucose index (TyG), which was found to be correlated with the risk and mortality of breast cancer.[13] Existing evidence underlined the superiority of TyG in predicting metabolic syndrome and type 2 diabetes mellitus.[14,15] A study conducted by Nam et al[16] on Korean postmenopausal women reported a positive association between insulin resistance, assessed based on HOMA-IR, and the severity of breast cancer. Panigoro et al[17] observed that the TyG index is related non-linearly to the risk of breast cancer.

This study aims to enrich the existing literature by assessing the burden of insulin resistance in patients with metastatic breast cancer, their interaction, and how both surrogate insulin resistance markers fared in predicting the dynamics of insulin resistance in metastatic breast cancer patients.

Materials and Methods

Study Design, Setting, and Participants

The study is an analytic cross-sectional study conducted in the Hematology-Medical Oncology clinic and outpatient chemotherapy clinic of Cipto Mangunkusumo Hospital, Jakarta, Indonesia, and the medical oncology clinic of Siloam-MRCCC Hospital, Jakarta, Indonesia. Patients were recruited consecutively using the consecutive non-probability sampling approach from August 2019 to March 2020 until the minimum sample amount needed for the study had been fulfilled. The inclusion criteria for the sample are as follows: 1) older than 18 years old, 2) histopathologically diagnosed with primary invasive breast cancer with available hormone receptor data, and 3) has not undergone any chemotherapy regimen within the last three weeks. All patients with current autoimmune or infectious disorders are excluded from this study. In addition, pregnant patients and patients currently consuming anti-retroviral or long-term steroid medications are excluded from the data analysis. After the included patients signed the informed consent form, anthropometrical data were collected using calibrated equipment during their clinic visits. Then, the patient was asked to fast for 8 hours, and their blood was collected at the Clinical Pathology Laboratory of Cipto Mangunkusumo Hospital, Jakarta, Indonesia. The blood was analyzed to obtain each study sample's fasting glucose and plasma insulin levels.

Quantitative Variables, Data Measurement, and Possible Bias

Metastasized breast cancer was defined as histopathologically confirmed stage IV primary invasive breast cancer. We adapted the internal breast cancer diagnostic guideline from Cipto Mangunkusumo Hospital as the diagnostic criteria used in this study. Insulin resistance was defined as the degree of increased insulin production needed to produce a normal biological response.[16,18] It was assessed using the HOMA-IR and TyG index, and the result was categorized based on the cut-off points obtained from the receiver operating characteristic (ROC) curve. Age and body mass index (BMI) were obtained from physical examination during the patient's clinic visit. History of type 2 diabetes mellitus (T2DM) treatment and low-density lipoprotein (LDL) cholesterol levels were also obtained during the examination. Age data were categorized into two groups using 60 years old as the cut-off point. BMI data were categorized per World Health Organization's obesity measurement guideline into obese I (BMI 25–29.9 kg/m^2), obese II (BMI >30 kg/m^2, and non-obese (BMI <25 kg/m^2).[19] History of T2DM and the medications used for the treatment were obtained from the patient during their clinic visit. Low-density lipoprotein cholesterol levels of each patient were obtained using the blood collected from the patients, and the result was categorized into two groups, with 130 mg/dL used as the cut-off point.

The possible bias that may arise from this study includes sampling and publication bias. To minimize sampling bias so that our study populations may capture patients from various backgrounds and the study population characteristic may be more similar to the general Indonesian population, we recruited samples from two large hospitals with differing

patient demographics. Patients recruited from Cipto Mangunkusumo Hospital came from all over Indonesia, mainly treating patients from the lower-to-middle socioeconomic class. On the other hand, Siloam MRCCC hospital is a private flagship hospital of one of Indonesia's largest private hospital groups, thereby representing patients from the middle-to-higher socioeconomic class in Jakarta, the most populous province in Indonesia. To prevent publication bias, we also reported the non-significant result obtained from our analysis in our study.

Study Size and Statistical Analysis

The minimum sample needed for this study was estimated using the sample size equation for categoric predictive multivariate analysis.[20] Based on this equation, at least 160 study subjects are needed. Additional data was collected retrospectively from the included patients' electronic medical records (EMR). The data collected from each patient's EMR were age, histopathology result and interpretation, and cancer staging. If data were not obtained properly during the clinical examinations, the EMR would be checked to obtain any possible missing data. Statistical analysis was done using SPSS software, with the bivariate analysis done between variables. Data will be described in the mean if the distribution is normal, while the median will be used if the distribution is not normal.

Results

A total of 155 study samples were obtained during the recruitment period. After being screened for eligibility, three samples were excluded due to double cancer, and two were excluded because they were diagnosed with an autoimmune disorder. Thus, 150 patients were included in the study (Figure 1).

The mean age was 50 and they were premenopausal. The most common breast cancer molecular subtype among the sample is luminal type B, followed by luminal type A. Most patients were diagnosed with metastatic breast cancer. Among the included sample, 70% received hormonal therapy and 26% were still under active chemotherapy. The mean BMI was 23.9 kg/m^2, with most subjects categorized as non-obese. T2DM was found in 10% of the sample and had LDL cholesterol levels higher than 130 mg/dL. The median value of fasting plasma insulin is 5.6 µIU/mL. Since only the distribution of TyG is normal, we described the TyG using the mean and HOMA-IR using the median. The mean of TyG is 8.60, while the median value of HOMA-IR is 1.22, as can be seen in Table 1.

Bivariate analysis of HOMA-IR and TyG with the incidence of metastases test found no significant correlation between both variables. The difference in both indexes between metastases groupings was not significant (Table 2).

Subgroup analysis was done on postmenopausal subjects. From the analysis, we found no significant correlation between any confounding variables in the postmenopausal subjects, as can be observed in Table 3.

Discussion

This study aimed to elucidate the elusive relationship between metabolic syndrome values and primary invasive breast cancer. From this study, we observed that insulin resistance, as reflected by the HOMA-IR and TyG score, does not correlate with the incidence of metastases in breast cancer, which can be seen in Table 2. However, we noted how BMI,

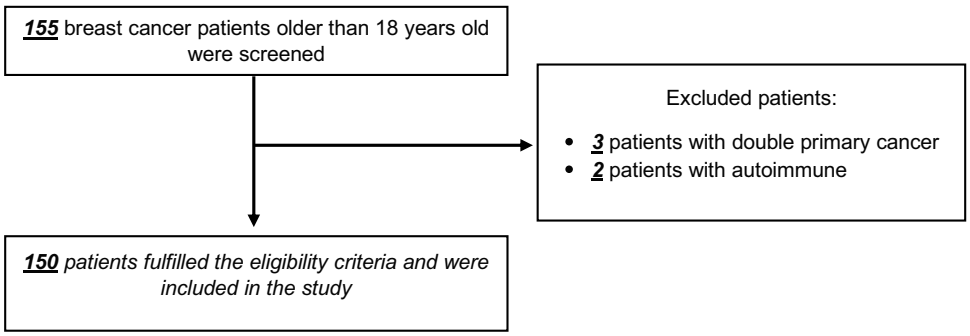

Figure 1 Sample recruitment flow diagram.

Table 1 Study Sample Characteristics

Variable	Description (N=150)
Age, n (%)	
< 60 years old	117 (78)
≥ 60 years old	33 (22)
Molecular subtype, n (%)	
Luminal A	38 (25.4)
Luminal B	93 (62)
Her2 OverExp	9 (6)
Triple negative	10 (6.6)
Hormonal therapy, n (%)	
None	43 (29)
Tamoxifen	62 (41)
Aromatase inhibitor	45 (30)
Last chemotherapy, n (%)	
< 1 month	40 (26.7)
≥ 1 month	110 (73.3)
Metastasis, n (%)	
Not metastasized	79 (52.6)
Metastasized	71 (47.4)
BMI, mean kg/m^2 (SD)	23.9 (3.77)
BMI grouping, n (%)	
Not Obese (< 25 kg/m^2)	101 (67.4)
Obese 1 (25–29.9 kg/m^2)	40 (26.6)
Obese 2 (> 30 kg/m^2)	9 (6)
T2DM, n (%)	
No	134 (89.4)
Yes	16 (10.6)
LDL cholesterol, n (%)	
< 130 mg/dL	94 (62.7)
≥ 130 mg/dL	56 (37.3)
Fasting Blood Glucose, median mg/dL (min-max)	87 (54–339)
Fasting Insulin, median (µIU/mL) (min-max)	5.6 (0.7–29.6)
HOMA-IR, median (min-max)	1.22 (0.11–12.92)
TyG, mean (SD)	8.60 (0.60)

Abbreviations: BMI, body mass index; Her2 OverExp, human epidermal growth factor receptor 2 over expression; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low density lipoprotein; TyG Index, Triglyceride/Glucose Index; T2DM, type 2 diabetes mellitus.

Table 2 Correlation Between HOMA-IR and TyG with Metastasis Incidence

Variable	Metastasized (n= 71)	Not Metastasized (n=79)	P
HOMA-IR, median (Min-max)	1.26 (0.11–12.92)	1.18 (0.34–6.94)	1.00[a]
TyG, mean (SD)	8.70 (0.62)	8.52 (0.57)	0.74[b]

Notes: [a]Analyzed using Mann–Whitney *U*-test. [b]Analyzed using independent sample *t*-test.
Abbreviations: HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; TyG Index, Triglyceride/Glucose Index.

Table 3 Subgroup Analysis in Postmenopausal Subjects

Variable	Metastasized	Not Metastasized	P
T2DM, n (%)			
No	11 (42.3)	15 (57.7)	0.98
Yes	3 (42.8)	4 (57.2)	
BMI grouping, n (%)			
Not Obese (< 25 kg/m2)	10 (41.6)	14 (58.4)	0.19
Obese 1 (25–29.9 kg/m2)	2 (28.6)	5 (71.4)	
Obese 2 (≥ 30 kg/m2)	2 (100)	0 (0)	
HOMA-IR, median (min-max)	1.63 (0.54–12.92)	1.26 (0.64–5.23)	0.43
TyG, mean (SD)	8.70 (0.62)	8.53 (0.58)	0.08

Abbreviations: BMI, body mass index; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; TyG Index, Triglyceride/Glucose Index; T2DM, type 2 diabetes mellitus.

diabetes status, HDL, triglyceride, total cholesterol, and type of hormonal therapy might affect HOMA-IR and TyG index values in primary invasive breast cancer patients.

Nam et al[16] reported the exact opposite finding, stating that increased HOMA-IR value is significantly associated with cancer severity. At the same time, Panigoro et al[17] reported TyG index value was higher in patients with breast cancer. The Women's Health Initiative study mentioned that increased cancer-specific mortality corresponds with increased cancer-specific mortality.[12] Ferguson et al[21] reported that hyperinsulinemia promotes metastasis via insulin receptor (IR) activation. Metabolic syndrome was observed to be associated with primary invasive breast cancer via decreasing levels of adiponectin, a peptide involved in fatty acid oxidation and glucose utilization.[22,23] Furthermore, resistance to chemotherapy in breast cancer patients was related to change in glucose metabolism and administration of diabetes drugs was found to resensitize breast cancer to chemotherapy.[22,24] Kundaktepe et al[25] mentioned that the HOMA-IR value of breast cancer patients is significantly higher compared to the average population, and it was cited that the value was significantly higher in stage IV B breast cancer patients compared to other staging levels. In this study, since the result did not reach statistical significance, we cannot find the area under the curve (AUC) of both scorings' receiver operating curve (ROC).

Theoretically, the hyperglycemic status may affect breast cancer's metastasis and outcome by increasing circulating insulin levels, and hyperinsulinemia was found to increase cancer cell survival.[11,26] This difference may be due to the different socioeconomic and biodemographic characteristics of each study's population, as Tahapary et al[27] found that the value of HOMA-IR and TyG index may vary between populations. As an example of comparison, this study sample population is dominated by samples younger than 60 years old and diagnosed with luminal B subtype, distinctively different from Nam et al[16] which were composed of older samples with luminal A subtype as the majority of diagnosis. A similar example was illustrated by Ferroni et al[28] in which most of the sample was diagnosed with stage II breast cancer, unlike the sample from our study, which mainly comprised patients with stage IV breast cancer.

The blood glucose level status in breast cancer patients was found to be directly impacted by HOMA-IR value, age, and the interaction between both variables.[29] In breast cancer patients, heightened blood glucose levels will impinge on the cancer progressivity and staging via different pathways.[30–32] Regarding aromatase inhibitors, administration of the drug was identified to impact visceral adiposity and glucose metabolism due to its mechanism of action.[33,34] Metabolic disturbance due to obesity impairs insulin sensitivity, and most obese people were ascertained to have at least one afflicted metabolism and insulin sensitivity parameters.[35] The mechanism by which obesity disturbs metabolic status was hypothesized due to adipocyte dysfunction, resulting in decreased adiponectin/leptin ratio.[36,37] Plasminogen activator inhibitor-1 was also noted to be associated with carcinogenesis in obese patients.[38] Since HOMA-IR is calculated by taking into account blood glucose level, diabetes will undoubtedly affect both scorings since diabetes was diagnosed by looking at the blood glucose level.

Nam et al[16] ascertained that age was positively correlated with cancer progressivity. A higher incidence of lymph node metastasis (LMN) in older patients was thought to be contributed by increased coatomer protein complex subunit beta-2 (COPB2) gene expression, which was found to be increased along with age.[39] Diabetes and high blood glucose level were linked to a higher risk of metastasis in breast cancer patients, which was thought to be implicated by the role of angiotensinogen and Akt1 pathway.[30,40] In addition, treatment of diabetes with incretin and metformin decreased the risk of metastases in breast cancer patients with T2DM.[41]

A high level of LDL was recorded to affect breast cancer progression by increasing reactive oxygen species (ROS) formation due to xanthine oxidase activity and promoting cholesterol uptake by the cancer cells via the activation of the LDL receptor.[42–44] Furthermore, total cholesterol and triglyceride levels were also documented to raise the risk of metastasis, possibly mediated by the binding of LDL cholesterol with its receptor.[45,46] Nonetheless, breast cancer patients undergoing chemotherapy were observed to have higher levels of total cholesterol, LDL, and triglyceride, which could explain why we did not report a significant correlation with the incidence of metastases.[47] Chemotherapy was found to affect several metabolic parameters, including fasting blood glucose,[48,49] HbA1c,[48] triglyceride,[50] and LDL.[49] Metastases and advanced staging were also highlighted to be more prevalent in obese breast cancers. This phenomenon was considered due to higher circulating leptin levels in obese patients.[51,52] Nevertheless, Osman et al[53] mentioned that obesity did not significantly affect the incidence of metastasis, in line with the finding in our study. On the other hand, Buch et al[33] reported that adjuvant chemotherapy and hormonal therapy increased the weight of breast cancer patients, implying that obesity happened as a consequence of drug therapies in breast cancer patients instead. The underlying contrivance causing increased body weight in breast cancer patients receiving adjuvant chemotherapy lies in the decreased basal metabolic rate and physical activity levels, thereby increasing adipokine expression and circulating lipid levels and, ultimately, inducing sarcopenic obesity.[48,54]

We also found from subgroup analysis that there was no correlation between any of the confounding variables in the postmenopausal study subjects. Another study noted a significant correlation between cancer progression and obesity in postmenopausal women.[16,55] We used 60 years of age as the cut-off to define menopause per the NCCN guideline. Thus, this may contribute to the different findings of our study when compared with other published studies. The pathogenesis basis of the convergence between menopausal status and obesity in advancing cancer progression lies in heightened neovascularization rate and earlier switching of the tumor to the vascular phenotype.[55] Genetics were also found to play a significant role in the interaction between insulin resistance and breast cancer in postmenopausal women.[56]

The main limitation of this study is its cross-sectional design and the number of patients who met the subject selection criteria during this period was insufficient. As a result, no direct causality may be concluded from the finding obtained from our study. Hence, we suggest conducting a longitudinal study with a larger sample size for future research. Other limitations of this study include the lax exclusion criteria and limited operational definition of menopause used in this study. The study subjects we enrolled in this study were recruited from Indonesia's highest national governmental central referral hospital and one of the largest cancer-focused private hospitals in Jakarta. Thus, we argue that the sample we used in this study represents primary invasive breast cancer patients in Indonesia.

Conclusion

There was no significant correlation between the incidence of metastases in breast cancer patients and insulin resistance parameters.

Ethics Approval and Informed Consent

The Ethics Committee of The Faculty of Medicine, Universitas Indonesia granted ethical approval for this study (ethical approval number: KET-372/UN2.F1/ETIK/PPM.00.02/2023). This study was carried out in accordance with the Helsinki Declaration. All subjects who took part in the study provided written informed consent.

Acknowledgments

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declared no conflicts of interest in this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. IARC. Indonesia; 2020.
3. Gondhowiardjo S, Christina N, Ganapati NPD, et al. Five-year cancer epidemiology at the national referral hospital: hospital-based cancer registry data in Indonesia. *JCO Glob Oncol*. 2021;(7):190–203. doi:10.1200/GO.20.00155
4. Caswell-Jin JL, Plevritis SK, Tian L, et al. Change in survival in metastatic breast cancer with treatment advances: meta-analysis and systematic review. *JNCI Cancer Spectr*. 2018;2(4). doi:10.1093/jncics/pky062
5. Martín-Manzo MV, Lara C, Vargas-de-Leon C, et al. Interaction of breast cancer and insulin resistance on PD1 and TIM3 expression in peripheral blood CD8 T cells. *Pathol Oncol Res*. 2019;25(3):1233–1243. doi:10.1007/s12253-019-00610-7
6. Arcidiacono B, Iiritano S, Nocera A, et al. Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. *Exp Diabetes Res*. 2012;2012:1–12. doi:10.1155/2012/789174
7. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569–578. doi:10.1016/S0140-6736(08)60269-X
8. Rinaldi S, Key TJ, Peeters PHM, et al. Anthropometric measures, endogenous sex steroids and breast cancer risk in postmenopausal women: a study within the EPIC cohort. *Int J Cancer*. 2006;118(11):2832–2839. doi:10.1002/ijc.21730
9. Ariaans G, de Jong S, Gietema JA, Lefrandt JD, de Vries EGE, Jalving M. Cancer-drug induced insulin resistance: innocent bystander or unusual suspect. *Cancer Treat Rev*. 2015;41(4):376–384. doi:10.1016/j.ctrv.2015.02.007
10. Barba M, Sperati F, Stranges S, et al. Fasting glucose and treatment outcome in breast and colorectal cancer patients treated with targeted agents: results from a historic cohort. *Ann Oncol*. 2012;23(7):1838–1845. doi:10.1093/annonc/mdr540
11. Villarreal-Garza C, Shaw-Dulin R, Lara-Medina F, et al. Impact of diabetes and hyperglycemia on survival in advanced breast cancer patients. *Exp Diabetes Res*. 2012;2012:1–8. doi:10.1155/2012/732027
12. Pan K, Nelson RA, Wactawski-Wende J, et al. Insulin resistance and cancer-specific and all-cause mortality in postmenopausal women: the women's health initiative. *JNCI*. 2020;112(2):170–178. doi:10.1093/jnci/djz069
13. Shi H, Zhou L, Yang S, Zhou H. The relationship between triglyceride and glycose (TyG) index and the risk of gynaecologic and breast cancers. *Clin Nutr ESPEN*. 2022;51:345–352. doi:10.1016/j.clnesp.2022.08.004
14. Son DH, Lee HS, Lee YJ, Lee JH, Han JH. Comparison of triglyceride-glucose index and HOMA-IR for predicting prevalence and incidence of metabolic syndrome. *Nutr Metabol Cardiovasc Dis*. 2022;32(3):596–604. doi:10.1016/j.numecd.2021.11.017
15. Park HM, Lee HS, Lee YJ, Lee JH. The triglyceride–glucose index is a more powerful surrogate marker for predicting the prevalence and incidence of type 2 diabetes mellitus than the homeostatic model assessment of insulin resistance. *Diabetes Res Clin Pract*. 2021;180:109042. doi:10.1016/j.diabres.2021.109042
16. Nam S, Park S, Park HS, Kim S, Kim JY, Kim S. Association between insulin resistance and luminal b subtype breast cancer in postmenopausal women. *Medicine*. 2016;95(9):e2825. doi:10.1097/MD.0000000000002825
17. Panigoro SS, Sutandyo N, Witjaksono F, et al. The association between triglyceride-glucose index as a marker of insulin resistance and the risk of breast cancer. *Front Endocrinol*. 2021:12. doi:10.3389/fendo.2021.745236
18. Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. *BMC Endocr Disord*. 2013;13(1):47. doi:10.1186/1472-6823-13-47
19. World Health Organization. *Regional Office for the Western Pacific. The Asia-Pacific Perspective: Redefining Obesity and Its Treatment*. World Health Organization; 2000.
20. Enderlein G, Lemeshow S, Hosmer DW, Klar J, Lwanga St K. Adequacy of sample size in health studies. *Biometr J*. 1991;33(4):504. doi:10.1002/bimj.4710330419
21. Ferguson RD, Novosyadlyy R, Fierz Y, et al. Hyperinsulinemia enhances c-Myc-mediated mammary tumor development and advances metastatic progression to the lung in a mouse model of type 2 diabetes. *Breast Cancer Res*. 2012;14(1):R8. doi:10.1186/bcr3089
22. Amabile MI, Frusone F, De Luca A, et al. Locoregional surgery in metastatic breast cancer: do concomitant metabolic aspects have a role on the management and prognosis in this setting? *J Pers Med*. 2020;10(4):227. doi:10.3390/jpm10040227
23. Ohashi K, Ouchi N, Matsuzawa Y. Anti-inflammatory and anti-atherogenic properties of adiponectin. *Biochimie*. 2012;94(10):2137–2142. doi:10.1016/j.biochi.2012.06.008
24. Samuel S, Varghese E, Kubatka P, Triggle C, Büsselberg D. Metformin: the answer to cancer in a flower? Current knowledge and future prospects of metformin as an anti-cancer agent in breast cancer. *Biomolecules*. 2019;9(12):846. doi:10.3390/biom9120846
25. Kundaktepe BP, Durmus S, Cengiz M, et al. The significance of insulin resistance in nondiabetic breast cancer patients. *J Endocrinol Metab*. 2021;11(2):42–48. doi:10.14740/jem729
26. Chiefari E, Mirabelli M, La Vignera S, et al. Insulin resistance and cancer: in search for a causal link. *Int J Mol Sci*. 2021;22(20):11137. doi:10.3390/ijms222011137
27. Tahapary DL, Pratisthita LB, Fitri NA, et al. Challenges in the diagnosis of insulin resistance: focusing on the role of HOMA-IR and Tryglyceride/glucose index. *Diabetes Metab Syndr*. 2022;16(8):102581. doi:10.1016/j.dsx.2022.102581

28. Ferroni P, Riondino S, Laudisi A, et al. Pretreatment insulin levels as a prognostic factor for breast cancer progression. *Oncologist*. 2016;21(9):1041–1049. doi:10.1634/theoncologist.2015-0462
29. Nath Das R, Karmakar S, Saha I, Sahoo RK, Medda SK, Kottapalli R. The glucose level linkages with breast cancer markers. *Cancer Res Cell Therap*. 2021;5(2):01–04. doi:10.31579/2640-1053/083
30. Sun S, Sun Y, Rong X, Bai L. High glucose promotes breast cancer proliferation and metastasis by impairing angiotensinogen expression. *Biosci Rep*. 2019;39(6). doi:10.1042/BSR20190436
31. Li C, Sun S, Tu Y, et al. High glucose accelerates tumor progression by regulating MEDAG-mediated autophagy levels in breast cancer. *Int J Biol Sci*. 2022;18(11):4289–4300. doi:10.7150/ijbs.70002
32. Raza U, Asif MR, Bin Rehman A, Sheikh A. Hyperlipidemia and hyper glycaemia in breast cancer patients is related to disease stage. *Pak J Med Sci*. 2018;34(1). doi:10.12669/pjms.341.14841
33. Buch K, Gunmalm V, Andersson M, Schwarz P, Brøns C. Effect of chemotherapy and aromatase inhibitors in the adjuvant treatment of breast cancer on glucose and insulin metabolism-a systematic review. *Cancer Med*. 2019;8(1):238–245. doi:10.1002/cam4.1911
34. Cheung YM, Hoermann R, Van K, et al. Effects of aromatase inhibitor therapy on visceral adipose tissue area and cardiometabolic health in postmenopausal women with early and locally advanced breast cancer. *Clin Endocrinol*. 2023;98(2):190–201. doi:10.1111/cen.14839
35. Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. *J Clin Invest*. 2019;129(10):3978–3989. doi:10.1172/JCI129186
36. Castela I, Morais J, Barreiros-Mota I, et al. Decreased adiponectin/leptin ratio relates to insulin resistance in adults with obesity. *Am J Physiol*. 2023;324(2):E115–E119. doi:10.1152/ajpendo.00273.2022
37. Iwase T, Wang X, Shrimanker TV, Kolonin MG, Ueno NT. Body composition and breast cancer risk and treatment: mechanisms and impact. *Breast Cancer Res Treat*. 2021;186(2):273–283. doi:10.1007/s10549-020-06092-5
38. Amin MN, Hussain MDS, Sarwar MDS, et al. How the association between obesity and inflammation may lead to insulin resistance and cancer. *Diabetes Metab Syndr*. 2019;13(2):1213–1224. doi:10.1016/j.dsx.2019.01.041
39. Bhandari A, Zheng C, Sindan N, et al. COPB2 is up-regulated in breast cancer and plays a vital role in the metastasis via N-cadherin and Vimentin. *J Cell Mol Med*. 2019;23(8):5235–5245. doi:10.1111/jcmm.14398
40. Alwhaibi A, Verma A, Adil MS, Somanath PR. The unconventional role of Akt1 in the advanced cancers and in diabetes-promoted carcinogenesis. *Pharmacol Res*. 2019;145:104270. doi:10.1016/j.phrs.2019.104270
41. Jacob L, Kostev K, Rathmann W, Kalder M. Impact of metformin on metastases in patients with breast cancer and type 2 diabetes. *J Diabetes Complications*. 2016;30(6):1056–1059. doi:10.1016/j.jdiacomp.2016.04.003
42. Constantinou C, Mpatsoulis D, Natsos A, et al. The low density lipoprotein receptor modulates the effects of hypogonadism on diet-induced obesity and related metabolic perturbations. *J Lipid Res*. 2014;55(7):1434–1447. doi:10.1194/jlr.M050047
43. Oh SH, Choi SY, Choi HJ, et al. The emerging role of xanthine oxidase inhibition for suppression of breast cancer cell migration and metastasis associated with hypercholesterolemia. *FASEB J*. 2019;33(6):7301–7314. doi:10.1096/fj.201802415RR
44. Cedó L, Reddy ST, Mato E, Blanco-Vaca F, Escolà-Gil JC. HDL and LDL: potential new players in breast cancer development. *J Clin Med*. 2019;8(6):853. doi:10.3390/jcm8060853
45. Liu YL, Qian HX, Qin L, Zhou XJ, Zhang B, Chen X. [Association of serum lipid profile with distant metastasis in breast cancer patients]. *Zhonghua Zhong Liu Za Zhi*. 2012;34(2):129–131. Chinese. doi:10.3760/cma.j.issn.0253-3766.2012.02.010
46. Dias S, Cesário V, Coutinho D, et al. Hypercholesterolemia promotes the intravasation of breast tumor cells through an LDL-LDLR axis. *Res Square*. 2022. doi:10.21203/rs.3.rs-1760715/v1
47. Li X, Li LZ, Tuan WY, et al. Status of lipid and lipoprotein in female breast cancer patients at initial diagnosis and during chemotherapy. *Lipids Health Dis*. 2018;17(1):91. doi:10.1186/s12944-018-0745-1
48. Dieli-Conwright CM, Wong L, Waliany S, Bernstein L, Salehian B, Mortimer JE. An observational study to examine changes in metabolic syndrome components in patients with breast cancer receiving neoadjuvant or adjuvant chemotherapy. *Cancer*. 2016;122(17):2646–2653. doi:10.1002/cncr.30104
49. Guinan EM, Connolly EM, Healy LA, Carroll PA, Kennedy MJ, Hussey J. The development of the metabolic syndrome and insulin resistance after adjuvant treatment for breast cancer. *Cancer Nurs*. 2014;37(5):355–362. doi:10.1097/NCC.0b013e3182a40e6d
50. Hassan MA, Ibrahim I, Saeed MM, Hussien NN. Effect of chemotherapy on lipid profile and insulin resistance among post mastectomy women. *J Pharm Negat Results*. 2023;14. doi:10.47750/pnr.2023.14.02.23
51. Madeddu C, Gramignano G, Floris C, Murenu G, Sollai G, Macciò A. Role of inflammation and oxidative stress in post-menopausal oestrogen-dependent breast cancer. *J Cell Mol Med*. 2014;18(12):2519–2529. doi:10.1111/jcmm.12413
52. Barone I, Giordano C, Bonofiglio D, Andò S, Catalano S. The weight of obesity in breast cancer progression and metastasis: clinical and molecular perspectives. *Semin Cancer Biol*. 2020;60:274–284. doi:10.1016/j.semcancer.2019.09.001
53. Osman MA, Hennessy BT. Obesity correlation with metastases development and response to first-line metastatic chemotherapy in breast cancer. *Clin Med Insights Oncol*. 2015;9:CMO.S32812. doi:10.4137/CMO.S32812
54. Saquib N, Flatt SW, Natarajan L, et al. Weight gain and recovery of pre-cancer weight after breast cancer treatments: evidence from the women's healthy eating and living (WHEL) study. *Breast Cancer Res Treat*. 2007;105(2):177–186. doi:10.1007/s10549-006-9442-2
55. Roy R, Yang J, Shimura T, et al. Escape from breast tumor dormancy: the convergence of obesity and menopause. *Proce Natl Acad Sci*. 2022;119(41). doi:10.1073/pnas.2204758119
56. Jung SY, Mancuso N, Papp J, Sobel E, Zhang ZF, Wei Q. Post genome-wide gene-environment interaction study: the effect of genetically driven insulin resistance on breast cancer risk using Mendelian randomization. *PLoS One*. 2019;14(6):e0218917. doi:10.1371/journal.pone.0218917