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Predictive value of triglyceride/glucose index (TyG) in predicting breast cancer in patients with breast mass

E.G. ALKURT, M.B. ÖZKAN, V.B. TURHAN

Department of General Surgery, University of Hitit Erol Olçok Training and Research Hospital, Corum, Turkey

Abstract. – OBJECTIVE: Since both breast carcinogenesis and the triglyceride glucose index (TyG) are associated with metabolic syndrome, this study aims at focussing on the TyG index in the breast control group to investigate risk factors causing breast cancer. The predictive value of triglyceride glucose score in predicting breast cancer was investigated.

PATIENTS AND METHODS: Patients with a pathological diagnosis of cancer and patients with benign breast lesions who were operated on between May 2018 and December 2021 were included in the study. Patients were divided into two groups: those with Breast Cancer (BC) and those with benign breast lesions. The predictive value of the TyG in predicting breast cancer was investigated. The mean standard deviation (SD) or median values with a 25-75 percent interquartile range (IQR) were used to represent the distribution of continuous data. The Student's *t*-test was used to evaluate parametric values, and the Mann-Whitney U test was used to analyze non-parametric values. The Chi-square test was used to see if categorical variables could be compared. The optimal cut-off points for the TyG value had been determined using receiver operating curve (ROC) analysis. Cut-off points that are optimal for the TyG value were determined using receiver operating curve (ROC) analysis.

RESULTS: The patients in the study had a median age of 51 [IQR (25-75) = 44-62]. Of the 510 patients who had been operated for a breast lesion, 13 were male and 499 were female. While the median glucose value of the patients was 97 [IQR (25-75) = 89-109-9], the median triglyceride value was 155 [IQR (25-75): 86-159]. When glucose and triglyceride values were examined, group I seemed to have significantly lower values ($p<0.001$, $p=0.001$, respectively). The mass size was larger in group 2 ($p<0.001$). In addition, ln TyG was statistically higher in the malignant group ($p<0.001$). Receiver operating characteristic curves were obtained for TyG levels in BC diagnosis. (AUC = 0.606, standard error 0.025, $p<0.001$; 95% CI = 0.556-0.655). The cut-off value for TyG was 8,628. The sensitivity of this value was 57.5% and the specificity was 42.6%.

CONCLUSIONS: In this study, we investigated the predictive effect of the TyG index in distinguishing benign and malignant lesions of the breast and concluded that the TyG index can be used to differentiate BC in patients with BC.

Key Words:
Breast cancer, Benign breast lesions, Triglyceride glucose score.

Introduction

Breast cancer (BC) is the most common cancer in women worldwide, as well as the common cause of cancer death. In 2017, more than 250,000 new cases of BC were discovered in the United States[1]. Nearly 2.3 million new cases of BC were diagnosed in 2020 and 685,000 deaths from BC worldwide[2].

Early menarche, late pregnancy, short breastfeeding periods, hormonal menopause medicines, oral contraceptives, breast density, and a family history of BC both are major risk factors for BC[3,4].

Metabolic syndrome, a group of metabolic disorders, has been linked to a variety of cancers, including BC[5,6]. Insulin resistance (IR), which plays a key role in the development of metabolic syndrome, is now recognized as a key factor in carcinogenesis[7]. IR can be assessed with a variety of techniques, including the hyperinsulinemic-euglycemic clamp and insulin tolerance testing[8,9]. However, simple, low-cost, and easy-to-use approaches have surpassed these intrusive and expensive procedures.

The triglyceride glucose (TyG) index is a novel metabolic syndrome test with high specificity and sensitivity[10]. Furthermore, the TyG index is a new and efficient IR indicator[11].

Because both breast carcinogenesis and the TyG index are associated with metabolic syndrome, we hypothesized that there would be a direct connection between the two. As a result, the

Corresponding Author: Ertuğrul Gazi Alkurt, MD; e-mail: egalkurt@hotmail.com

objective of this study was to investigate risk factors for breast carcinogenesis using the TyG index in the breast control group. The triglyceride glucose score's predictive effectiveness in predicting breast cancer was investigated.

Patients and Methods

Study Population

After the Hitit University Non-Invasive Clinical Research Ethics Committee accepted our investigation with the decision numbered 29.12.2021 dated 2021-88, a retrospective, cross-sectional study was designed. We collected data by examining patient files and computer records. Patients with a pathological diagnosis of cancer and patients with benign breast lesions who had been operated between May 2018 and December 2021 were included in the study. The study was planned in accordance with the Helsinki Declaration.

Patients were divided into two groups: those with BC and those with benign breast lesions. The following are the working group's eligibility requirements: (1) people aged 19 and up who had received a pathologically BC diagnosis between May 2018 and December 2021; (2) untreated BC after diagnosis; (3) patients who could read, understand, and approve; (4) patients whose medical record and paraffin block could be searched; (5) patients whose preoperative TG and glucose values could be reached. Those with missing data were excluded. Data from the relevant hospital were obtained from computer records and patient files.

For the control group, the following requirements were met: (1) women 18 years and older, (2) patients with benign breast lesions with histopathology and immunohistochemical results who had been operated between May 2018 and December 2021; (3) people who showed no signs or symptoms of BC; (4) patients without evidence of chronic disease and (5) patients whose preoperative TG and glucose values could be achieved.

Measurements

A power analysis was calculated using an effect size of 0.8, alpha level adjusted at 0.05, and power adjusted at 0.82, resulting in a total sample size of 139 subjects.

Demographic data of the patients were recorded. Fasting TG [mg/dl] x fasting glucose [mg/dl] was used to calculate the ln TyG index[12] (ln: natural logarithm of a number). The constant "e" is used to calculate natural logarithms (2.71828182845904).

Statistical Analysis

The SPSS 22.0 for Windows data analysis program (IBM Corp., Armonk, NY, USA) was used to conduct the analysis. The study aimed at retrospectively examining two separate clinical entities. The Shapiro-Wilk and Kolmogorov-Smirnoff tests were used to determine the data's normal distribution. The mean standard deviation (SD) or median values with a 25-75 percent interquartile range (IQR) were used to represent the distribution of continuous data. The Student's *t*-test was used to evaluate parametric values, and the Mann-Whitney U test was used to analyze non-parametric values. The Chi-square test was used to see if categorical variables could be compared. The optimal cut-off points for the TyG value had been determined using receiver operating curve (ROC) analysis. Cut-off points that are optimal for the TyG value were determined using receiver operating curve (ROC) analysis. Group differences with a *p*-value lower than 0.05 were deemed statistically significant.

Results

The patients in the study had a median age of 51 [IQR (25-75) = 44-62]. Of the 510 patients who were operated on for a breast lesion, 13 were male and 499 were female. The median hospital stay was 3 days. While the median glucose value of the patients was 97 [IQR (25-75) = 89-109-9], the median triglyceride value was 155 [IQR (25-75) = 86-159] (Table I).

Then, the patients were divided into two groups: benign breast lesions (Group I) and malignant breast lesions (Group II). All malignant breast lesions were reported as invasive ductal carcinoma. When the groups were compared, the patients in Group II were reported to be older than those in Group I ($p<0.001$). In addition, the length of hospital stay was longer in Group II ($p<0.001$). While there were 13 male patients in Group I, there were only 4 male patients in Group II. The number of female patients was statistically higher in both groups ($p=0.033$). When glucose and triglyceride values were examined, Group I showed significantly lower values ($p<0.001$, $p=0.001$, respectively). The mass size was larger in Group 2 ($p<0.001$). In addition, ln TyG was statistically higher in the malignant group ($p<0.001$) (Table I).

Roc analysis was performed for TyG, glucose, and triglyceride value (Figure 1). Re-

Table I. Clinical and laboratory characteristics of patients.

	Total (n=510)	Benign (n=207)	Breast Cancer (n=303)	*p*-value
Age, y, median (IQR 25-75)	51 (44-62)	46 (25-55)	57 (47.5-69)	<0.001*
Sex, n				
Male	13	9	4	0.033†
Female	499	198	301	
Hospital Stay, d, median (IQR 25-75)	3 (2-9)	2 (2-3)	8 (3-13)	<0.001*
Glucose, mg/dl, median (IQR 25-75)	97 (89-109.9)	94 (85-105.4)	99 (91-114)	<0.001*
Triglyceride, mg/dl, median (IQR 25-75)	115 (86-159)	106 (80-144)	124 (90-178.5)	0.001*
Mass Size, cm	2 (1.6-3)	2 (1.5-2)	2.5 (1.8-3.5)	0.001*
ln TyG	8.6 (8.2-9.1)	8.56 (8.16-8.8)	8.7 (8.3-9.1)	<0.001*

IQR: Interquartile range; y: year; d: day; mg/dl: milligram/deciliter.
*Mann-Whitney U test; †Chi-Square test.

ceiver operating characteristic (ROC) curves were obtained for TyG levels in BC diagnosis (AUC=0.606, standard error 0.025, $p<0.001$; 95% CI=0.556-0.655). The cut-off value for TyG was 8,628. The sensitivity of this value was 57.5% and the specificity was 42.6%. Values for glucose and triglycerides are given in Table II.

Discussion

In this study, we investigated the effect of the TyG index on benign and malignant lesions of the breast, and it was concluded that the TyG index can be used to differentiate BC types in patients with BC.

Metabolic syndrome is an important pathogenic condition in the development of many cancers.

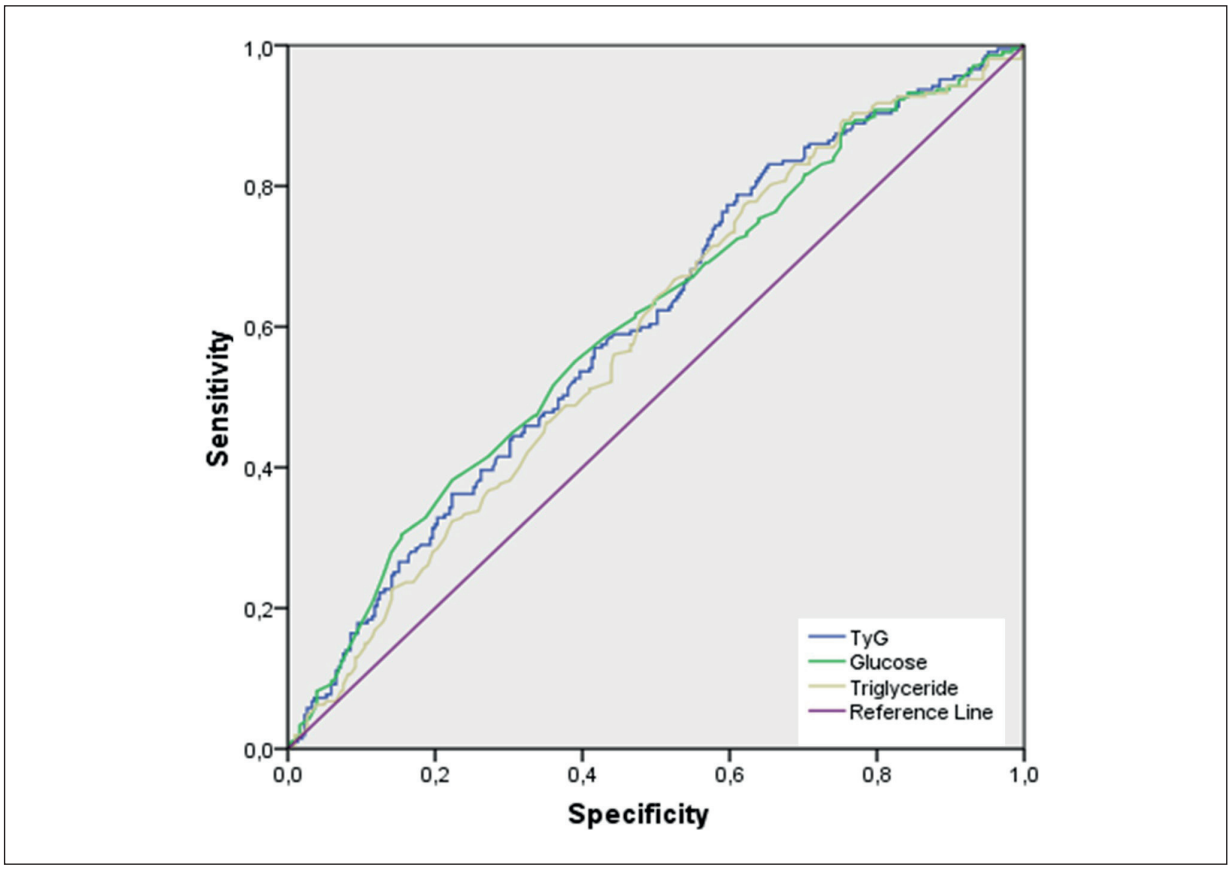

Figure 1. Receiver operating characteristic (ROC) curves obtained for TyG, glucose and triglyceride levels.

Table II. Comparison of the groups with regard to TyG levels, glucose, and triglyceride levels.

	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	*p*-value*
TyG	0.606	0.556-0.655	8.628	57.5	42.6	<0.001
Glucose (mg/dl)	0.604	0.555-0.564	95.5	55.1	39.0	<0.001
Triglyceride (mg/dl)	0.587	0.538-0.637	114.5	56	44.3	<0.001

AUC: Area under the curve; TyG: Triglyceride-glucose index.
*Mann-Whitney U test.

Although IR is an indicator of metabolic syndrome, it also plays a role in carcinogenesis[7]. IR can be measured using a variety of methods such as hyperinsulinemic-euglycemic clamp and insulin tolerance testing[8,9]. Instead of these invasive and expensive procedures, the TyG index is used as a biomarker of IR. The TyG index is derived using fasting triglycerides and plasma glucose and is a simple, inexpensive, and easy-to-use tool[13,14]. Sánchez−Íñigo et al[15] concluded in their study that the TyG index may be useful for the early detection of individuals at high risk of developing cardiovascular events. In addition, based on the data of 116 colorectal cancer (CRS) patients as a result of the historical cohort study on 27,944 individuals, Okamura et al[16] reported the cut-off value of TyG for colorectal cancer as 8.272, sensitivity and specificity as 62%, 66%, respectively. These data suggested that patients with high TyG values should be included in the screening program[16]. In addition, Kim et al[17] conducted the same study for gastric cancers and concluded that the increase in the TyG index was significantly associated with gastric cancer. Similar results were obtained for lung cancer, obesity-related cancers, and prostate cancer[18-20]. In our study, the cut-off value for TyG was 8.628. This value had a sensitivity of 57.5% and a specificity of 42.6%. This shows that a high TyG value may be a precursor for BC screening.

Hyperinsulinemia is caused by IR, and it promotes the PI3K/Akt/mTOR/S6K signaling pathway in cancer[21]. Increased serum TG, which is part of the TyG index, also activates the Akt signaling pathway *via* the G protein-coupled receptor[22]. Akt has been found in a variety of cancers, including BC. Increased IGF-1 levels are also linked to IR[23,24]. IGF-1 regulates cell proliferation, survival, and angiogenesis by activating the IGF-1 receptor[25]. IGF-1 stimulates cell growth by promoting the production of vascular endothelial growth factors. The favorable association between the expression of IGF-1 and IGF-1 receptors in BC has been documented in numerous investigations[26,27]. Hyperglycemia also enhances cellular sensitivity to IGF-I, which results in enhanced cell proliferation and migration[28].

Hyperinsulinemia, IGF-1, c-peptide, and fasting insulin levels have been shown in many studies to be risk factors for BC[29-32]. Kabat et al[32] showed the association of high serum insulin levels with BC but stated that glucose levels alone did not affect BC. Zhu et al[26] demonstrated a positive association between elevated circulating IGF-1 levels and BC. Circulating insulin, C-peptide, IGF-1, and IR were all found to be positively and synergistically associated with BC in Chinese women in a study of BC and benign lesions of the breast[27]. IR is associated with both cancer-specific and all-cause mortality in postmenopausal women, making it a risk factor for BC[33].

In addition, Panigoro et al[34] indicated TyG index to have a significant impact on BC risk. In their study, the TyG index was found to have a non-linear dose-response relationship with BC. In the study conducted with 212 BC patients and 212 control groups, TyG > 8.87 was found to be significant. However, unlike our study, the sensitivity and specificity were not investigated and evaluated as precursors. Using these baseline data, to the best of our knowledge, our study is the only study in the literature examining the relationship between TyG and BC in the group of patients operated on for benign breast lesions and cancer patients. In our study, we found that the TyG index is a significant risk factor in patients with BC.

Limitations

Due to the hospital-based study system, one of our study's shortcomings could have been selection bias. A larger or national survey is also needed to investigate factors connected to histological subtypes of BC, as different risk factors may exist for different histological subtypes of BC.

Finally, lipid and glucose levels fluctuate depending on how long it has been since the last meal. This may also have affected the results. However, although our study is retrospective-based, the number of patients is higher than

the number of patients in similar studies, providing better data for this result. In addition, as far as we know, our study is the only study in the literature examining the relationship between TyG and BC in a group of patients who had been operated for benign breast lesions and cancer patients.

Conclusions

The TyG index consists of triglyceride and glucose levels, and the TyG index is expected to be a useful risk marker for BC. In our study, we determined that a high TyG index is an important risk factor in patients with BC. Fasting TG [mg/dl] x fasting glucose [mg/dl] was used to calculate the TyG index in our study. As a result of this calculation, it should be kept in mind that patients with values > 8.628 may have breast cancer rather than a benign lesion. Larger multi-centered, and prospective studies are needed to confirm this finding.

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Conflict of Interest

The authors declare no conflict of interest.

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References

1) Waks AG, Winer EP. Breast cancer treatment: a review. JAMA 2019; 321: 288-300.
2) Lei S, Zheng R, Zhang S, Wang S, Chen R, Sun K, Zeng H, Zhou J, Wie W. Global patterns of breast cancer incidence and mortality: A population–based cancer registry data analysis from 2000 to 2020. Cancer Commun 2021; 41: 1183-1194.
3) Yilmaz S, Ünal GK, Aslan HS, Değirmencioğlu S, Aykota MR. Ultrasound-guided wire localization biopsy in non-palpable breast lesions: predictive factors for malignancy. Eur Rev Med Pharmacol Sci 2022; 26: 1320-1327.
4) Zhang Y, Zhou Y, Mao F, Yao R, Sun Q. Ki–67 index, progesterone receptor expression, histologic grade and tumor size in predicting breast cancer recurrence risk: A consecutive cohort study. Cancer Commun 2020; 40: 181-193.
5) Battelli MG, Bortolotti M, Polito L, Bolognesi A. Metabolic syndrome and cancer risk: the role of xanthine oxidoreductase. Redox Biol 2019; 21: 101070.
6) Li P, Wang T, Zeng C, Yang M, Li G, Han J, Wu W. Association between metabolic syndrome and prognosis of breast cancer: a meta-analysis of follow-up studies. Diabetol Metabol Syndr 2020; 12: 1-12.
7) Braun S, Bitton-Worms K, LeRoith D. The link between the metabolic syndrome and cancer. Int J Biol Sci 2011; 7: 1003.
8) Bergman RN, Prager R, Volund A, Olefsky JM. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. The J Clin Investig 1987; 79: 790-800.
9) DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol Endocrinol Metab 1979; 237: E214.
10) Angoorani P, Heshmat R, Ejtahed HS, Motlagh ME, Ziaodini H, Taheri M, Aminaee T, Goodarzi A, Qorbani M, Kelishadi R. Validity of triglyceride–glucose index as an indicator for metabolic syndrome in children and adolescents: the CASPIAN-V study. Eat Weight Disord 2018; 23: 877-883.
11) Sánchez-García A, Rodríguez-Gutiérrez R, Mancillas-Adame L, González-Nava V, González-Colmenero AD, Solis RC, Álvarez-Villalobos NA, González-González JG. Diagnostic accuracy of the triglyceride and glucose index for insulin resistance: a systematic review. Int J Endocrinol 2020; 2020: 4678526.
12) Park K, Ahn CW, Lee SB, Kabg S, Nam JS, Lee BK, Kim JH, Park JS. Elevated TyG index predicts progression of coronary artery calcification. Diabetes Care 2019; 42: 1569-1573.
13) Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as a surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord 2008; 6: 299-304.
14) Du T, Yuan G, Zhang M, Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. Cardiovasc Diabetol 2014; 13: 1-10.
15) Sánchez–Íñigo L, Navarro–González D, Fernández–Montero A, Pastrana-Delgado J, Martines JA. The TyG index may predict the development of cardiovascular events. Eur J Clin Invest 2016; 46: 189-197.
16) Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukuri M. Triglyceride–glucose index (TyG index) is a predictor of incident colorectal cancer: a population-based longitudinal study. BMC Endocr Disord 2020; 20: 1-7.
17) Kim YM, Kim JH, Park JS, Baik SJ, Chun J, Youn YH, Park H. Association between the triglyceride-glucose index and gastric carcinogenesis: a health checkup cohort study. Gastric Cancer 2021; 25: 33-41.

18) Yan X, Gao Y, Tong J, Tian M, Dai J, Zhuang Y. Association Between Triglyceride Glucose Index and Non-Small Cell Lung Cancer Risk in Chinese Population. Front Oncol 2021; 11: 300.

19) Fritz J, Bjørge T, Nagel G, Manjer J, Engeland A, Häggström C, Concin H, Teleka S, Tretli S, Gylling B, Lang A, Stattin P, Stocks T, Ulmer H. The triglyceride-glucose index is a measure of insulin resistance and the risk of obesity-related cancers. Int J Epidemiol 2020; 49: 193-204.

20) Horsanali MO, Eren H, Dıl E, Kazaz IO, Uzun H. A novel prognostic risk factor for patients undergoing radical prostatectomy: Triglyceride–glucose index. Int J Clin Pract 2021; 75: 13978.

21) Khan KH, Yap TA, Yan L, Cunnigham D. Targeting the PI3K-AKT-mTOR signaling network in cancer. Chin J Cancer 2013; 32: 253.

22) Sekine Y, Koike H, Nakano T, Nakajima K, Suzuki K. Remnant lipoproteins stimulate proliferation and activate MAPK and Akt signaling pathways via G protein-coupled receptor in PC-3 prostate cancer cells. Clin Chim Acta 2007; 383: 78-84.

23) Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 2001; 131: 3109-3120.

24) Friedrich N, Thuesen B, Jørgensen T, Jull A, Spielhagen C, Wallaschofksi H, Linneberg A. The association between IGF-I and insulin resistance: a general population study in Danish adults. Diabetes Care 2012; 35: 768-773.

25) Aaronson SA. Growth factors and cancer. Sci 1991; 254: 1146-1153.

26) Zhu Y, Wang T, Wu J, Huang O, Zhu L, He J, Li Y, Clen W, Chen X, Shen K. Associations Between Circulating Insulin-Like Growth Factor 1 and Mortality in Women with Invasive Breast Cancer. Front Oncol 2020; 10: 1384.

27) Zhu Y, Wang T, Wu J, Huang O, Zhu L, He J, Li Y, Chen W, Chen X, Shen K. Biomarkers of Insulin and the Insulin-Like Growth Factor Axis in Relation to Breast Cancer Risk in Chinese Women. Onco Targets Ther 2020; 13: 8027.

28) Maile LA, Capps BE, Ling Y, Xi G, Clemmons DR. Hyperglycemia alters the responsiveness of smooth muscle cells to insulin-like growth factor-I. Endocrinol 2007; 148: 2435-2443.

29) Toniolo P, Bruning PF, Akhmedkhanov A, Bonfrer JMG, Koenig KL, Lukanova A, Shore RE, Zeleniuch-Jacquotte A. Serum insulin–like growth factor–I and breast cancer. Int J Cancer 2000; 88: 828-832.

30) Verheus M, Peeters PH, Rinaldi S, Dossus L, Biessy C, Olsen A, Tjønneland A, Overvad K , Jeppesen M, Cavel-Chapelon F, Téhard B, Nagel G, Linseisen J, Boeing H, Lahmann PH, Arvaniti A, Psaltopoulou T, Trichopoulou A, Palli D, Tumino R, Panico S, Sacerdote C, Sieri S, van Gils CH, Bueno-de-Mesquita BH, González CA, Ardanaz E, Larranaga N, Garcia CM, Navarro C, Quirós JR, Key T, Allen N, Bingham S, Khaw KT, Slimani N, Riboli E, Kaak R. Serum C–peptide levels and breast cancer risk: Results from the European prospective investigation into cancer and nutrition (EPIC). Int Cancer 2006; 119: 659-667.

31) Keinan–Boker L, Bueno de Mesquita HB, Kaaks R, van Gils CH, van Noord PAH, Rinaldi S, Riboli E, Seidell JC, Grobbee DE, Peeters PHM. Circulating levels of insulin–like growth factor I, its binding proteins –1, –2, –3, C–peptide and risk of postmenopausal breast cancer. Int J Cancer 2003; 106: 90-95.

32) Kabat GC, Kim M, Caan BJ, Chlebowski RT, Gunter MJ, jo GYF, Rodriguez BL, Shikany JM, Strickler HD, Vitolins MZ, Rohan TE. Repeated measures of serum glucose and insulin in relation to postmenopausal breast cancer. Int J Cancer 2009; 125: 2704-2710.

33) Pan K, Nelson RA, Wactawski-Wende J, Lee DJ, Manson JE, Aragaki AK, Mortimer JE, Phillips LS, Rohan T, Ho GYF, Saquib N, Shadyab AH, Nassir R, Rhee JJ, Hurria A, Chlebowski RT. Insulin resistance and cancer-specific and all-cause mortality in postmenopausal women: the Women's Health Initiative. J Natl Cancer Inst 2020; 112: 170-178.

34) Panigoro SS, Sutandyo N, Witjaksono F, Siregar NC, Ramli R, Hariani R, Pangarsa EA, Prajoko YW, Puruhita N, Hamdani W, Bayu D, Madjid M, Yulidar D, Fransiska JE, Widyawati R, Tripriadi ES, Ade FWW, Yunda DK, Pranata R. The Association Between Triglyceride-Glucose Index as a Marker of Insulin Resistance and the Risk of Breast Cancer. Front Endocrinol (Lausanne) 2021; 12: 745236.