Oncology
and Radiotherapy ©
Vol.16 Iss.4:34-38 • Research Article

# Inter-relationship between homeostasis model assessment of insulin resistance and breast cancer biomarkers

**Jinseog Kim[1], Mahashweta Das[2], Ishita Saha[3], Prasenjit Sinha[4], Poonam Singh[5], Rabindra Nath Das[6]**

[1] Department of Big Data and Applied Statistics, Dongguk University, Gyeongju, Korea

[2] Department of History, The University of Burdwan, Burdwan, West Bengal, India

[3] Department of Physiology, Calcutta Medical College and Hospital, Kolkata, WB, India

[4] Department of Statistics, Tripura University, Suryamaninagar, Tripura, India

[5] Department of Statistics, University of Delhi, Delhi, India

[6] Department of Statistics, The University of Burdwan, Burdwan, West Bengal, India

SUMMARY

The relationship between Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Breast Cancer (BC) biomarkers such as leptin, Monocyte Chemoattractant Protein-1 (MCP-1), resistin, adiponectin is little known in the medical literature based on probabilistic modeling. The current report focuses on the inter-relationships between HOMA-IR and BC markers. It has been derived from the gamma fitted mean HOMA-IR model that it is higher for healthy women (P<0.0001) than BC patients. It is positively associated with leptin (P=0.0747), while it is negatively associated with the interaction effect of insulin and leptin (insulin*leptin) (P=0.0016). Variance of HOMA-IR is negatively associated with adiponectin (P=0.0471), while it is positively associated with resistin (P=0.0755) and the interaction effect of glucose and adiponectin (glucose*adiponectin) (P=0.0305). From the log-normal HOMA-IR fitted model, it is shown that variance of HOMA-IR is negatively associated with leptin (P=0.0599). From MCP-1 fitted model, it has been shown that variance of MCP-1 is negatively associated with HOMA-IR (P=0.0055), while resistin fitted model has shown that mean resistin is negatively associated HOMA-IR (P=0.0698) and it is positively associated with the interaction effect of age and HOMA-IR (age*HOMA-IR) (P=0.1059). Several relationships between HOMA-IR & BC markers are reported in the current article. It is interpreted that both HOMA-IR & BC markers are closely interlinked.

**Key words:** adiponectin, breast cancer markers, HOMA-IR, leptin, resistin, probabilistic modelling

**Address for correspondence:**

Rabindra Nath Das, Department of Statistics, the University of Burdwan, Burdwan, West Bengal, India. email: rabin.bwn@gmail.com

**Word count:** 3689 **Table:** 01 **Figures:** 02 **References:** 26

**Received:**- 29 April, 2022, Manuscript No. M- OAR-22-62180

**Editor assigned**:- 30 April, 2022, PreQC No. P- OAR-22-62180 (PQ)

**Reviewed:**- 02 May, 2022, QC No. Q- OAR-22-62180 (Q)

**Revised:**- 04 May, 2022, Manuscript No. R- OAR-22-62180 (R)

**Published:**- 20 May,2022, Invoice No. J- OAR-22-62180

## INTRODUCTION

BC disease is the most life-threatening and frequently occurring malignant tumor in women. The evidence which connects diabetes' biomarkers with BC biomarkers is highly controversial. Recently, the inter-relationships between diabetes and BC biomarkers have been derived using advanced statistical modeling by Kim et al. [1]. and Hockaday et al. [2] present several points that undermine faith in HOMA as a balance of insulin resistance. HOMA's input consists of fasting glucose and insulin concentration and thus will reveal conditions present in the basal state, with the liver as the main focus for insulin action as exposed by the suppression of gluconeogenesis. The HOMA-IR has been observed to be associated with the minimal model measures of insulin action and β-cell function, and hyperinsulinemic glucose clamp, primarily in middle-aged people and younger with normal glucose tolerance and smaller groups of middle-aged people with type 2 diabetes [2-4]. Research reveals that HOMA and other shortcut insulin measures of resistance and secretion can give useful information on risk of growing diabetes and related conditions [4-6]. Some research articles show the association between HOMA-IR, BMI, glucose and insulin [7, 8].

The diabetes mellitus type 2 and BC disease could be associated via metabolic mechanisms connected biomarker insulin and its growth factor [3]. Insulin plays as an advancement factor multiplying cell proliferation and cell death. In addition, insulin is a strong mutagenic agent in cells and tissue [9, 10]. Females are at the highest risk for BC disease if insulin level is high [11]. HOMA-IR is a dependable insulin resistance indicator [12], which is connected with reduced BC survival [13]. It is known that both diabetes mellitus type 2 and BC markers are the interaction yields of genetic and environmental risk factors that share several comorbidities [14]. An investigation on diabetes biomarkers such as fasting blood glucose, C-peptide and HOMA in some Jordanian BC disease females was performed by Al-Zeidaneen et al. [15].

A short literature review regarding the associations of HOMA-IR with BC markers is presented above. The best of our knowledge, there are very few articles focusing on the relationship between HOMA-IR and only one or two BC, or diabetes mellitus type 2 biomarkers. Most of the earlier relationships are studied based

on simple, or multiple, or logistic regression analyses, which are controversial. For the present case, there are 10 multivariate variables, and the responses are HOMA-IR and BC markers such as adiponectin, leptin, resistin and MCP-1. There is no such study for understanding the interrelationships between HOMA-IR and BC markers based on suitable statistical modeling. This invites to perform the present study. The objectives of the current study are:

1. Examining the associations of HOMA-IR with BC markers (adiponectin, leptin, resistin and MCP-1) along with the diabetes mellitus type 2 biomarkers (glucose and insulin levels) and age, BMI, types of subject.
2. Conversely, examining the associations of each BC marker with HOMA-IR and the rest explanatory factors.

These above objectives are focused in the article using the sections materials & methods, statistical analysis & results, discussions, and along with conclusions.

# MATERIALS AND METHODS

## Materials

**Study designs and subjects:** The present study is performed using a secondary data set which is available in UCI Machine Learning Repository. The study subjects of the data set were 154 Portuguese females, who were chosen from the University Hospital Center of Coimbra (UHCC) at Gynecology Department between 2009 and 2013, and they were first diagnosed with BC. The approved BC patients had been categorized into 4 groups depending on their BMI and the BC disease status such as absence or presence. These 4 categories are: (1) without overweight (BMI <25 kg/m$^2$) and control (i.e., no BC disease), subjects number (n=29; (2) with overweight (BMI>25 kg/m$^2$) & control, n = 48; (3) BC disease without overweight (BMI<25 kg/ m$^2$), n = 30; and (4) BC disease with overweight (BMI>25 kg/m$^2$), n=47. The first group (without overweight & control) were selected from the Internal Medicine Department of the aforementioned hospital. Also, women for the second group (overweight & control) were selected from the same Department, and the other two groups were selected from the Gynecology Department of UHCC. These subjects were chosen understanding that they had never been identified with BC family history or malignant disease. These selected subjects were free from any infection or acute disease at the study time. The UHCC Ethical Committee approved the study design, and all considered subjects submitted their written consent before joining the study. For the final study, only 116 (52 control and 64 with BC) subjects were selected, and the remaining 38 subjects were not considered in the study due to high BMI (>40 kg/m$^2$).

The data set has been posted in UCI Machine Learning Repository, and its elaborate discussion is given in [16, 17]. The data set contains 10 covariates/ factors which are Age, BMI (kg/m$^2$), HOMA-IR, Insulin (μU/mL), Glucose (mg/dL), Adiponectin (μg/mL), Leptin (ng/mL), Resistin (ng/mL), MCP-1, Subject types (ST) (1=healthy controls; 2= BC patients).

## Statistical methods

The above considered data set is a multivariate form. The aimed responses are HOMA-IR, resistin, leptin, MCP-1 and adiponectin, which are all positive heterogeneous continuous and non-normally distributed. These dependent variables can be properly modeled applying joint generalized linear models (JGLMs) using both the gamma and log-normal distributions, which are described in [18-20]. It is elaborately described in the book by Lee et al. [18]. For ready reference, it is described here in very shortly. Note that JGLMs of MCP-1 have been derived by Kim et al. [21], while adiponectin, resistin and leptin JGLMs have been developed by Das and Lee [22-24]. The present report derives the HOMA-IR joint models using both the distributions.

**JGLMs under log-normal distribution** For the positive HOMA-IR random response variable Yi, along with heteroscedastic variance $\sigma_i^2$ (known as dispersion parameter), if E(Yi)=μi (known as mean parameter) and Var($Y_i$) = $\sigma_i^2\mu_i^2 = \sigma_i^2 V(\mu_i)$ say, where V(·) is the variance function, and generally, the log transformation $(Z_i = \log Y_i)$ is used to stabilize the variance Var($Z_i$) ≈ $\sigma_i^2$, while the variance may not be stabilized always. For this situation, improved JGLMs for mean and dispersion are considered. Under the response log-normal distribution, JGLMs for mean and dispersion (Zi=logYi) are presented by

$$E(Z_i) = \mu_{zi} \text{ and } Var(Z_i) = \sigma_{zi}^2,$$

$$\mu_{zi} = x_i^t\beta \text{ and } \log(\sigma_{zi}^2) = g_i^t\gamma,$$

where $x_i^t$ and $g_i^t$ are respectively, the vectors of independent explanatory variables linked to the mean regression coefficients β and dispersion regression coefficients γ. Maximum likelihood (ML) and restricted ML (REML) methods are respectively used for estimation of mean and dispersion parameters [18, 19].

## JGLMs under gamma distribution

For the above positive HOMA-IR random response variable Yi, with E($Y_i$)=$\mu_i$ and Var($Y_i$) = $\sigma_i^2 V(\mu_i)$, the variance function $V(\cdot)$ has two parts in GLMs, where one part depends on the mean changes, while the other ($\sigma_i^2$) is independent of mean adjustment. Note that $V(\cdot)$ characterizes the GLMs family distribution. For instance, the distribution is gamma if $V(\mu) = \mu^2$, Poisson if $V(\mu) = \mu$, and normal if $V(\mu) = 1$, etc.

The JGLMs for the mean and dispersion are $\eta_i = g(\mu_i) = x_i^t\beta$ and $\varepsilon_i = h(\sigma_i^2) = w_i^t\gamma$,

where $g(\cdot)$ and $h(\cdot)$ are the GLM link functions associated with the mean and dispersion, respectively; and the vectors $x_i^t$, $w_i^t$ are associated respectively, with the mean and dispersion regression coefficients. Maximum likelihood (ML) and the restricted ML (REML) methods are respectively used for estimation of mean and dispersion parameters [18, 19].

# STATISTICAL ANALYSIS & RESULTS

## Statistical analysis

The random variable HOMA-IR is treated as the response variable and the rest others are treated as the independent variables. Note

that the response HOMA-IR variance is not stabilized by any appropriate transformation; therefore, it is modeled herein using both the log-normal and the gamma JGLMs. The final model is selected based on the lowest Akaike Information Criterion (AIC) value (within each class), that minimizes both the squared error loss and predicted additive errors [25]. Some partially significant or insignificant effects are considered in both the models due to marginality rules suggested by Nelder [26], and also for better fitting [25]. It is well-known that partially significant effects are recommended as confounders in Epidemiology. The HOMA-IR JGLMs analysis results are presented. Note that the gamma fit (AIC= -56.774) shows better results than log-normal fit (AIC= -37.27).

It is important to verify the data developed model using model diagnostic tools before accepting it as the valid final model. Note that all valid interpretations are derived from the final accepted model. The derived gamma fitted HOMA-IR model has been examined by model diagnostic residuals plot (in Figure 1. and normal probability plot (in Figure 2. In Figure 1, the HOMA-IR gamma fitted absolute residuals are plotted with respect to the fitted values. It is observed that all the absolute residuals are randomly located at a point, except only two points, which indicates that variance is constant with the running means. One smaller residual is located at the right boundary, so the smooth fitted curve is decreasing. Figure 2 reveals the mean HOMA-IR gamma fitted normal probability plot, which does not show any fit discrepancy. So, Figure 1 and Figure 2 have supported that the gamma fitted HOMA-IR model is approximately true mode (Table 1).

## RESULTS

Summarized JGLMs results for HOMA-IR are displayed in Table 1. Fitted mean HOMA-IR model (Table 1) shows that mean HOMA-IR level is higher for healthy women (P<0.0001) than BC patients. It is positively associated with leptin (P=0.0747), while it is negatively associated with the interaction effect insulin*leptin (P=0.0016). Variance of HOMA-IR is negatively associated with adiponectin (P=0.0471), while it is positively associated with resistin (P=0.0755) and the interaction effect glucose*adiponectin (P=0.0305). From the log-normal HOMA-IR fitted model (Table 1), it is

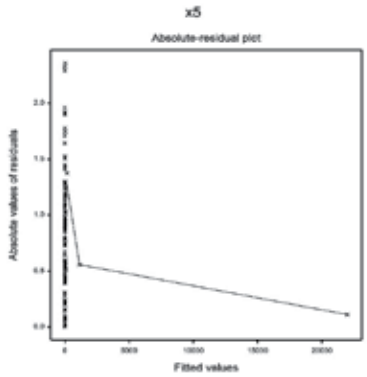


**Fig.1.** For the joint gamma fitted HOMA-IR models (Table 1), the absolute residuals plot with respect to the HOMA-IR fitted values

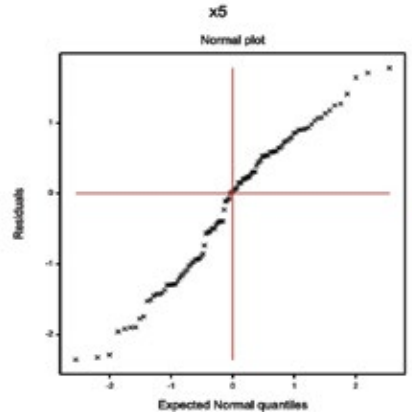


**Fig.2.** For the joint gamma fitted HOMA-IR models (Table 1), the normal probability plot for the HOMA-IR mean model

**Tab.1.** Results for mean and dispersion models for HOMA-IR from Gamma and Log-Normal fit

| Model | Covariate | Gamma fit | | | | Log-normal fit | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Estimate | S.E. | t-value | P-value | estimate | S.E. | t-value | P-value |
| Mean | Constant | -3.1870 | 0.1111 | -28.68 | 0.0232 | -3.0560 | 0.1282 | -23.84 | <0.0001 |
| | BMI(x2) | 0.0214 | 0.0039 | 5.39 | <0.0001 | 0.0156 | 0.0041 | 3.78 | 0.0003 |
| | Insulin(x4) | 0.4245 | 0.0211 | 20.11 | <0.0001 | 0.3940 | 0.0235 | 16.76 | <0.0001 |
| | BMI*Insulin | -0.0041 | 0.0007 | -5.47 | <0.0001 | -0.0030 | 0.0008 | -3.76 | 0.0003 |
| | Glucose(x3) | 0.0187 | 0.0004 | 44.36 | <0.0001 | 0.0188 | 0.0006 | 30.69 | <0.0001 |
| | Glucose*Insulin | -0.0013 | 0.0000 | -31.67 | <0.0001 | -0.0012 | 0.0001 | -22.25 | <0.0001 |
| | Leptin(x6) | 0.0016 | 0.0008 | 1.80 | 0.0747 | 0.0028 | 0.0010 | 2.77 | 0.0066 |
| | Insulin*Leptin | -0.0004 | 0.0001 | -3.23 | 0.0016 | -0.0005 | 0.0002 | -3.31 | 0.0013 |
| | Subject's type | -0.0508 | 0.0126 | -4.02 | <0.0001 | -0.0696 | 0.0131 | -5.33 | <0.0001 |
| Dispersion | Constant | -15.789 | 3.5474 | -4.451 | <0.0001 | -5.3906 | 2.3409 | -2.303 | 0.0232 |
| | Leptin(x6) | -0.005 | 0.0084 | -0.538 | 0.5917 | -0.0176 | 0.0092 | -1.902 | 0.0599 |
| | Glucose(x3) | 0.133 | 0.0397 | 3.345 | 0.0011 | 0.0153 | 0.0228 | 0.671 | 0.5037 |
| | Adiponectin(x7) | -0.457 | 0.2274 | -2.008 | 0.0471 | -0.2384 | 0.1785 | -1.335 | 0.1847 |
| | Glucose* Adiponectin | 0.005 | 0.0025 | 2.192 | 0.0305 | 0.0028 | 0.0019 | 1.444 | 0.1517 |
| | Age(x1) | 0.167 | 0.0640 | 2.605 | 0.0105 | -0.0551 | 0.0159 | -3.463 | 0.0008 |
| | Age*Glucose | -0.003 | 0.0008 | -3.496 | 0.0007 | ..... | ..... | ..... | ..... |
| | Insulin(x4) | 0.244 | 0.1185 | 2.062 | 0.0416 | 0.5235 | 0.0861 | 6.083 | <0.0001 |
| | Age*Insulin | 0.007 | 0.0015 | 4.284 | <0.0001 | 0.0038 | 0.0013 | 3.011 | 0.0032 |
| | Glucose*Insulin | -0.003 | 0.0010 | -3.205 | 0.0018 | -0.0040 | 0.0008 | -5.082 | <0.0001 |
| | Resistin(x8) | 0.028 | 0.0158 | 1.795 | 0.0755 | ..... | ..... | ..... | ..... |
| AIC | | -56.774 | | | | -37.27 | | | |

shown that variance of HOMA-IR is negatively associated with leptin (P=0.0599).

From MCP-1 fitted model [21], it has been shown that variance of MCP-1 is negatively associated with HOMA-IR (P=0.0055), while resistin fitted [22] model has shown that mean resistin is negatively associated HOMA-IR (P=0.0698) and it is positively associated with the interaction effect of age and HOMA-IR (age*HOMA-IR) (P=0.1059).

Gamma fitted HOMA-IR mean ($\hat{\mu}$) model (from Table 1) is

$\hat{\mu}$ = exp(-3.1870 + 0.0214 BMI + 0.4245 Insulin - 0.0041 BMI*Insulin + 0.0187 Glucose - 0.0013Glucose*Insulin + 0.0016 Leptin - 0.0004 Insulin*Leptin - 0.0508 Subject type),

and the gamma fitted HOMA-IR variance ($\hat{\sigma}^2$) model (from Table 1) is

$\hat{\sigma}^2$ = exp(-15.789 - 0.005 Leptin + 0.133 Glucose - 0.457 Adiponectin + 0.005 Glucose*Adiponectin + 0.167 Age - 0.003Age*Glucose + 0.244 Insulin + 0.007 Age*Insulin - 0.003 Glucose*Insulin + 0.028 Resistin).

For the same data set, the models for breast cancer biomarkers such as MCP-1 [21], resistin [22], adiponectin [23] and leptin [24] have already been published.

## DISCUSSION

Inter-relationships between HOMA-IR and BC biomarkers are reported herein from the models of HOMA-IR, and as well as from the models of BC biomarkers such as MCP-1, leptin, resistin, and adiponectin. These BC biomarkers models have been reported in [21-24], while the model of HOMA-IR is reported herein in Table 1.

Fitted HOMA-IR mean model (Table 1) shows that mean HOMA-IR level is negatively associated with subject's type (1=healthy controls; 2=BC patients) (P<0.0001), concluding that mean HOMA-IR level is higher for healthy women (P<0.0001) than BC patients. It is positively associated with leptin (P=0.0747), interpreting that HOMA-IR rises as leptin increases. Mean HOMA-IR level is negatively associated with the interaction effect of insulin*leptin (P=0.0016), implying that it decreases as the interaction effect increases. Note that both insulin (P<0.0001) and leptin (P=0.0747) are positively associated with mean HOMA-IR, so these marginal effects increase the HOMA-IR level, but their joint interaction effect decreases the mean HOMA-IR level.

Further, the mean HOMA-IR is positively associated with BMI (P<0.0001), or glucose (P<0.0001), concluding that it increases as BMI, or glucose level increases. Also the mean HOMA-IR is negatively associated with BMI*insulin (P<0.0001), or glucose*insulin (P<0.0001), implying that it decreases as the interaction effect BMI*insulin, or glucose*insulin increases. Note that all these three marginal effects such as BMI, glucose and insulin are positively associated with the mean HOMA-IR, while their interaction effects BMI*insulin and glucose*insulin are negatively associated with the mean HOMA-IR. Thus, BMI, glucose and insulin level increase the mean HOMA-IR level, but their joint interaction effects BMI*insulin and glucose*insulin decrease the mean HOMA-IR level.

Fitted HOMA-IR variance model (Table 1) presents that variance of HOMA-IR level is negatively associated with adiponectin (P=0.0471), indicating that HOMA-IR level variance decreases as adiponectin level increases. HOMA-IR level variance is positively associated with resistin (P=0.0755), or glucose*adiponectin (P=0.0305), concluding that it increases as resistin, or glucose*adiponectin increases. From the log-normal HOMA-IR fitted variance model, it is shown that variance of HOMA-IR is negatively associated with leptin (P=0.0599), implying that it decreases as the leptin level increases.

Further HOMA-IR level variance is positively associated with age (P=0.0105), or glucose (P=0.0011), or insulin (P=0.0416), age*insulin (P<0.0001), concluding that it increases as any of them increases. Also HOMA-IR level variance is negatively associated with age*glucose (P=0.0007), or glucose*insulin (P=0.0018), implying that it decreases as any of them increases.

From the resistin fitted model [22], it is shown that the mean resistin level is negatively associated with HOMA-IR (P=0.0698), interpreting that it decreases as HOMA-IR level increases. In addition, the mean resistin level is positively associated with the interaction effect age*HOMA-IR (P=0.1059), implying that it increases as age*HOMA-IR increases. From MCP-1 fitted model [21], it is shown that variance of MCP-1 is negatively associated with HOMA-IR (P=0.0055), concluding that MCP-1 variance level decreases as HOMA-IR level increases.

The above results are displayed herein from the models of HOMA-IR, resistin and MCP-1. No relationship between HOMA-IR and adiponectin, or HOMA-IR and leptin has been observed from adiponectin [23] and leptin models [24]. These above associations between HOMA-IR and BC biomarkers are summarized in Table 1. The best of our knowledge, the present report first derives the complex inter-relationships between HOMA-IR and BC biomarkers with many interaction effects. Most of the current outcomes are completely new in medical literature, so the current outcomes are not compared with the earlier results.

## CONCLUSIONS

The inter-relationships between HOM-IR and BC biomarkers are derived in the current report based on probabilistic modeling, where models are accepted based on graphical diagnostic checking, lowest AIC value, comparison of response HOMA-IR distributions, and small standard error of the estimates. The present associations between HOMA-IR and BC biomarkers, though not completely conclusive, are revealing. Medical research should have greater faith in the current probabilistic models as they have been derived based on many statistical criteria satisfaction. In the report, it is concluded that both HOMA-IR and BC biomarkers are closely interlinked. Medical practitioners can predict the BC disease status through the relationships between HOMA-IR and BC biomarkers from this

report. In addition, it may help the BC researchers to develop physiological and biological explanations of these relationships between HOMA-IR and BC biomarkers. Women will be benefited from the report.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

REFERENCES


1. Kim J, Das RN, Lee Y. Inter-relationship between diabetes and breast cancer biomarkers. Oncol Radiother, 2019;13:082-089.
2. Hockaday D, Sayyad M, Yajnik C. Counterpoint:appreciating homeostasis model assessment:more useful earlier than later. Diabetes Care, 2007; 30:2414–2418.
3. Gouveri E, Papanas N, Maltezos E. The female breast and diabetes. Breast, 2011; 20:205–211.
4. Chang AM, Halter JB. Aging and insulin secretion. Am J Physiol Endocrinol Metab, 2003;284:E7–E12.
5. Basu R, Breda E, Oberg AL, Powell CC, Man CD et al. Mechanisms of the age-associated deterioration in glucose tolerance:contribution of alterations in insulin secretion, action, and clearance. Diabetes. 2003; 52:1738–1748.
6. Yoon H, Jeon DJ, Park CE, You HS, Moon AE et al. Relationship between homeostasis model assessment of insulin resistance and beta cell functions and serum 25-hydroxy vitamin D in non-diabetic Korean adults. J Clin. Biochem. Nutri, 2016; 59:139-144.
7. Healy LA, Ryan AM, Rowley S, Boyle T, Connolly ME et al. Obesity increases the risk of postmenopausal breast cancer and is associated with more advanced stage at presentation but no impact on survival. Breast J, 2010;16:95–97.
8. Das RN, Lee Y, Mukherjee S, Oh S. Relationship of body mass index with diabetes & breast cancer biomarkers. J Diabetes Manag., 2019; 9:163-168.
9. Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer:a review of the current evidence. Am J Clin Nutr, 2007; 86:s823–s835.
10. Garcia-Estevez DA, Araujo-Vilar D, Fiestras-Janeiro G, Saavedra A, Cerrato JC et al. Comparison of several insulin sensitivity indices derived from basal plasma insulin and glucose levels with minimal model indices. Horm Metab Res, 2003; 35:13–17
11. Gaudet MM, Patel AV, Teras LR, Sun J, Campbell PT, et al. Obesity-related markers and breast cancer in CPS-II Nutrition Cohort. Int J Mol Epidemiol Genet, 2013; 4:156–166
12. Ligibel JA, Campbell N, Partridge A, Chen WY, Salinardi T et al. Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. J Clin Oncol, 2008; 26:907–912.
13. Duggan C, Irwin ML, Xiao L, Henderson KD, Smith AW et al. Associations of insulin resistance and adiponectin with mortality in women with breast cancer. J Clin Oncol, 2011; 29:32–39.
14. Bjørge T, Lukanova A, Jonsson H, Tretli S, Ulmer H et al. Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. Cancer Epidemiol Biomark Prev, 2010; 19:1737–1745.
15. Al-Zeidaneen SA, Ahmad MN, Al-Ebuos AD. The impact of treatment exposure on diabetes biomarkers among Jordanian breast cancer women:a connection through FBG, C-peptide and HOMA-IR. Curr Gynecol Oncol, 2017; 15:231–238.
16. Patrício M, Pereira J, Crisóstomo J, Matafome P, Gomes M et al. Using Resistin, glucose, age and BMI to predict the presence of breast cancer. BMC Cancer, 2018;18:18-29.
17. Lambe M, Wigertz A, Garmo H, Walldius G, Jungner I et al. Impaired glucose metabolism and diabetes and the risk of breast, endometrial, and ovarian cancer. Cancer Causes Control, 2011;22:1163-1171.
18. Lee Y, Nelder JA, Pawitan Y. Generalized Linear Models with Random Effects (Unified Analysis via H–likelihood) (2nd Ed). Lond:Chapman & Hall 2017.
19. Das RN, Lee Y. Log-normal versus gamma models for analyzing data from quality-improvement experiments. Quality Engineering, 2009; 21:79-87.
20. Qu Y, Tan M, Rybicki L. A unified approach to estimating association measures via a joint generalized linear model for paired binary data. Commun Stat:Theory Methods, 2000; 29:143-156.
21. Kim J, Das RN, Lee Y, Sahoo RK. Association of monocyte chemoattractant protein-1 with age, glucose, BMI, insulin and other breast cancer biomarkers. Oncol Radiother, 2019; 1, 13:005-009.
22. Das RN, Lee Y. Association of resistin with BMI, age diabetes and breastcancer biomarkers. J Oncol Res Treat., 2019; 4:135.
23. Das RN, Lee Y. Association of Serum Adiponectin with Age, BMI and Other Breast Cancer Biomarkers. J Blood Lymph, 2018; 8:233.
24. Das RN, Lee Y. Relationship of leptin with glucose, BMI, age, insulin and breast cancer biomarkers. Arch Gen Intern Med., 2019; 3:01-03.
25. Hastie T, Tibshirani R, Friedman J, The Elements of Statistical Learning, Springer-Verl., Second Edition, 2009.
26. Nelder JA. The statistics of linear models:back to basics. Stat Comput., 1994; 4:221-234.