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Association of Resistin with BMI, Age, Diabetes and Breast Cancer Biomarkers

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Abstract

Breast cancer is the most often observed worldwide as the second cause of cancer-related death in women. High resistin level is associated with breast cancer, therefore it is considered as a breast cancer biomarker. For a real data set, the article shows that mean resistin is positively associated with monocyte chemoattractant protein-1 (MCP-1) ($p<0.0001$), types of patients ($p<0.0001$), interaction effect of Body Mass Index (BMI) and leptin (BMI*Leptin) ($p=0.0415$), Homeostasis Model Assessment Score (HOMA)*Age ($p=0.1059$), Adiponectin ($p=0.1111$), while it is negatively associated with HOMA ($p=0.0698$), Age ($p=0.1249$), Leptin*Adiponectin ($p=0.0736$), Glucose*Adiponectin ($p=0.1007$). Variance of resistin is positively associated with class of patients ($p=0.0114$) and BMI ($p=0.0942$). Some partially significant effects (around 15% level of significance) are included in the models treated as confounder according to Epidemiology. It is concluded that resistin is higher for younger women with breast cancer, higher levels of MCP-1, adiponectin, and higher interaction effects of BMI*Leptin, Age*HOMA.

Keywords: Adiponectin; BMI; Breast cancer; Leptin; MCP-1; Resistin; Non-constant variance

Introduction

Serum resistin known as adipose tissue-specific secretory factor is a cysteine-rich adipose-derived peptide hormone that in humans is encoded by the *RETN* gene [1]. Its normal range in humans is from 7 to 22 ng mL^{-1}. The effects of leptin and adiponectin in various cancers have been summarized in many recent review and research articles [2-5]. The role of resistin in the cancer development has been discussed in some recent review and research articles [6-10]. Recent article has shown that the interaction effect of resistin and BMI is positively associated with adiponectin, while both the marginal effects BMI and resistin are negatively associated. Role of resistin has been examined in different rodent models of diabetes and obesity. It has been reported that resistin levels have elevated in both diet-induced and genetically obese mice [11]. The cause for the imbalances in the measured resistin levels stays unclear, so there might be limitation to conduct animal models of obesity to test the role of resistin in tumor development [12]. Serum resistin genetics has been drawn considerable research interests [13]. It was reported that resistin gene polymorphism (-420°C>G) was associated with BMI, and the women carrying G-allele had lower BMI compared to women carrying C/C homozygotes [14].

The association of resistin with age, BMI, diabetes and breast cancer biomarkers all together have been little studied in medical literaure. Most of the cases it has been only studied using simple correlation and regression considering resistin with any other. The given data set is a multivariate data, and the association of resistin can only be determined by using probabilistic modeling with BMI, age, diabetes and other breast cancer biomarkers. This has been very little studied in medical literature, using the original properties of the data set. The article aims to focus the real associations of resistin with BMI, glucose, age, insulin and many other breast cancer biomarkers through probabilistic modeling. In addition, the effects of the explanatory factors on resistin have been examined in the report.

Materials and Statistical Methods

Materials

The article examines the association of resistin with BMI, glucose, age, insulin, and other breast cancer biomarkers with a real data set of 116 (52 healthy controls & 64 patients) subjects containing 10 (1 attribute and 9 continuous) study variables, and the data set can be obtained from the UCI Machine Learning Repository. The data collection process, study population and covariates description have been clearly expressed in [15]. It has not been reproduced herein. For ready presenting the study variables in the article, they are reproduced as BMI (kg/m^2), Age (years), Glucose (mg/dL), Insulin (μU/mL), HOMA, Leptin (ng/mL), Adiponectin (μg /mL), Resistin (ng/mL), MCP-1 (pg/dL), Types of subjects (1=healthy controls; 2=patients).

Statistical methods

The associations of resistin with BMI, age diabetes and breast cancer biomarkers are examined in the report with the help of probabilistic modeling. The response resistin is continuous positive and heteroscedastic. It may be modeled by variance stabilization transformation, if the variance is stabilized with the transformation. But it is not stabilized with any suitable transformation. Therefore, it can be modeled with the help of Joint Generalized Linear Models (JGLMs) under Gamma and Log-normal distributions. JGLMs have been described in many books and research articles [16-19]. Therefore, it is not restated herein. Interested readers may go through.

Statistical and graphical analysis

The response resistin is modeled by JGLMs using both the distributions, and it is treated as the dependent variable, and the rest others are treated as the explanatory variables. The final model has been

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chosen based on the lowest Akaike Information Criterion (AIC) value (within each class), which minimizes both the squared error loss and predicted additive errors [20]. In the mean model some insignificant effects such as BMI, Glucose, Leptin and Adiponectin are included due to marginality rule given by Nelder, which indicates that if the joint interaction effect is significant (or partially significant), then their marginal effects should be included in the model. Similarly, in the variance model, BMI and Adiponectin are included. In Epidemiology, partially significant effects are known as confounders. Following, Epidemiology, some partially significant factors (around 15%) are included in the model as confounder. Note that for better fit, some insignificant or partially significant factors should be included in the model. Resistin analysis JGLM results for both the Log-normal and Gamma models are displayed in Table 1. Based on AIC rule, Gamma model (AIC=729.369) shows better fit than Log-normal (AIC=731.2).

Final fitted model presents all valid interpretations. Therefore, it should be selected by examining with model diagnostic tools, namely graphical analysis. Gamma fitted resistin model is the final selected model based on AIC value. It has been examined using residuals & normal probability plots in Figure 1. The absolute residuals are plotted against the resistin Gamma fitted values in (Figure 1a), which is almost flat line with the running means, except the right tail. Right tail is increasing due to a larger value located at the right boundary. (Figure 1b) reveals the normal probability plot for the resistin Gamma fitted mean model, which shows no discrepancy in fitting. Both the plots show that resistin fitted Gamma model is approximately identical to the true unknown model.

Results

The summarized results of resistin analysis for both Log-normal and Gamma fitted models are presented, it is noted that mean resistin is positively associated with Monocyte Chemoattractant Protein-1 (MCP-1) ($p<0.0001$), types of patients ($p<0.0001$), interaction effect of body mass index (BMI) and leptin (BMI*Leptin) (p=0.0415), Homeostasis Model Assessment Score (HOMA)*Age (p=0.1059), Adiponectin (p=0.1111), while it is negatively associated with HOMA (p=0.0698), Age (p=0.1249), Leptin*Adiponectin (p=0.0736), Glucose*Adiponectin (p=0.1007). Variance of resistin is positively associated with types of patients (p=0.0114), BMI (p=0.0942), Leptin (p=0.1566), Adiponectin (p=0.2020). While it is negatively associated with BMI*Adiponectin (p=0.1518).

Gamma fitted Resistin mean ($\hat{\mu}$) model is $\hat{\mu}$ =exp(1.6651 - 0.0052 Age – 0.0306 Leptin + 0.0888 Adiponectin + 0.0007 MCP-1 + 0.5421 Types of patient – 0.1087 HOMA + 0.0015 Age*HOMA - 0.0028 BMI + 0.0014 BMI*Leptin + 0.0068 Glucose- 0.0010 Glucose*Adiponectin - 0.0009 Leptin*Adiponectin), and Gamma fitted Resistin variance ($\hat{\sigma}^2$) model is $\hat{\sigma}^2$=exp(-4.8464 + 0.0129 Leptin + 0.7971 Types of patients + 0.1090 BMI + 0.1885 Adiponectin – 0.0083 BMI*Adiponectin).

The above two equations show the mean & variance relationship of resistin with the remaining covariates. It is found that mean resistin is expressed by Age, Leptin, Adiponectin, MCP-1, Types of patients, HOMA, Age*HOMA, BMI, BMI*Leptin, Glucose, Glucose*Adiponectin, Leptin*Adiponectin, while its variance is explained by Leptin, Types of patients, BMI, Adiponectin, and BMI*Adiponectin. Note that both mean and variance of resistin are modeled simultaneously by iterative method. Using t-statistics, the significance of regression coefficients are tested (Table 1).

Discussion

Final fitted resistin analysis results are given in, and also its mean and variance models are given above. The above two resistin models conclude the following. It is found that mean resistin is negatively (partially significant) associated with age (p=0.1249), implying that

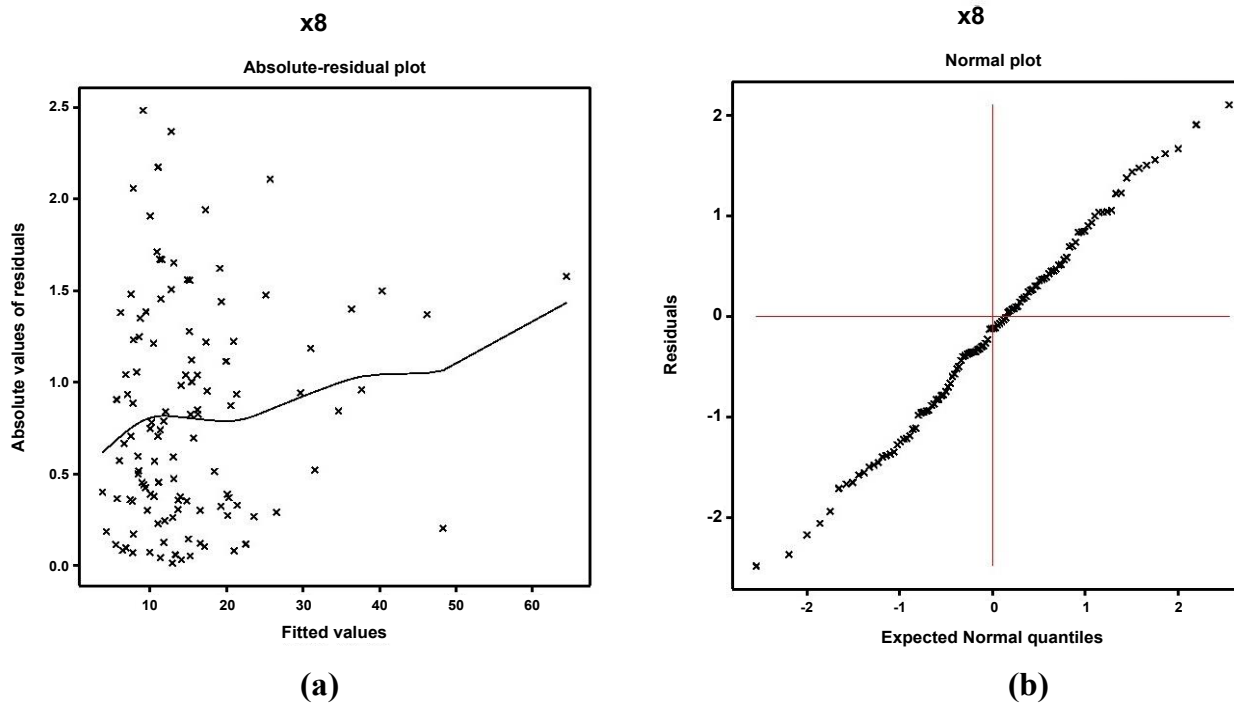

Figure 1: For the resistin Gamma fitted models (Table 1). **(a)** Absolute residuals plot with respect to resistin fitted values; **(b)** The normal probability resistin mean model plot.

Model	Covariates	Gamma fit				Log-normal fit			
		Estimate	S.E	t-value	p-value	Estimate	S.E	t-value	p-value
Mean	Constant	1.6651	0.7909	2.105	0.0377	2.0242	0.81494	2.484	0.0146
	Age	-0.0052	0.0033	-1.547	0.1249	-0.0063	0.00345	-1.817	0.0721
	Leptin	-0.0306	0.0226	-1.352	0.1793	-0.0256	0.02334	-1.097	0.2751
	Adiponectin	0.0888	0.0553	1.607	0.1111	0.0483	0.05623	0.860	0.3917
	MCP-1	0.0007	0.0001	4.402	<0.0001	0.0007	0.00015	4.253	<0.0001
	Class of patients	0.5421	0.1084	4.999	<0.0001	0.4341	0.11120	3.904	0.0001
	HOMA	-0.1087	0.0593	-1.832	0.0698	-0.1026	0.06124	-1.675	0.0969
	Age*HOMA	0.0015	0.0009	1.631	0.1059	0.0016	0.00096	1.637	0.1046
	BMI	-0.0028	0.0175	-0.158	0.8747	-0.0003	0.01808	-0.015	0.9880
	Leptin*BMI	0.0014	0.0007	2.064	0.0415	0.0011	0.00072	1.529	0.1293
	Glucose	0.0068	0.0062	1.084	0.2808	0.0030	0.00650	0.456	0.6493
	Adiponectin*Glucose	-0.0010	0.0006	-1.656	0.1007	-0.0006	0.00061	-1.000	0.3196
	Leptin*Adiponectin	-0.0009	0.0005	-1.807	0.0736	-0.0006	0.00052	-1.180	0.2407
Dispersion	Constant	-4.8464	1.7259	-2.808	0.0059	-4.6565	1.8505	-2.516	0.0134
	Leptin	0.0129	0.0091	1.427	0.1566	0.0124	0.0088	1.412	0.1609
	Class of patients	0.7971	0.3097	2.574	0.0114	0.8184	0.3140	2.606	0.0105
	BMI	0.1090	0.0645	1.689	0.0942	0.1081	0.0690	1.567	0.1201
	Adiponectin	0.1885	0.1468	1.284	0.2020	0.1771	0.1542	1.149	0.2532
	BMI*Adiponectin	-0.0083	0.0058	-1.444	0.1518	-0.0081	0.0060	-1.342	0.1825
	AIC	729.369				731.2			

Abbreviation: MCP-1: Monocyte Chemoattractant Protein-1; HOMA: Homeostasis Model Assessment Score; BMI: Body Mass Index; AIC: Akaike Information Criterion.

Table 1: Results for mean & dispersion models for Resistin from Log-Normal and Gamma fit.

younger women must have higher resistin levels than older. It is also negatively (partially significant) associated with leptin (p=0.1793), indicating that its levels decrease as the leptin levels increase. It is positively (partially significant) associated with adiponectin (p=0.1111), concluding that its levels increase as the adiponectin levels increase. It is positively (significantly) associated with types of subjects (1=healthy controls; 2=patients) (p<0.0001), interpreting that its levels are higher for breast cancer women than healthy. It is negatively (partially significant) associated with HOMA (p=0.0698), indicating that its levels decrease as the HOMA levels increase. It is positively (partially significant) associated with the interaction effect Age*HOMA (p=0.1059), concluding that its levels increase as the joint effect Age*HOMA increases. It is noted herein that both the age and HOMA are negatively partially associated with resistin, while their interaction effect Age*HOMA is positively associated. Mean resistin is positively associated with the BMI*Leptin (p=0.0415), indicating that its levels increase as the joint effect BMI*Leptin increases. Note that BMI is insignificant, whereas leptin is partially negatively associated with resistin. On the other hand mean resistin is negatively (partially significant) associated with both Glucose*Adiponectin (p=0.1007) and Leptin*Adiponectin (p=0.0736), interpreting that its levels increase as their interaction effects decrease. It is noted that glucose is insignificant, but leptin is partially negatively associated, while adiponectin is partially positively associated with resistin.

Variance model of resistin concludes that resistin variance is positively associated with types of subjects (1=healthy controls; 2=patients) (p=0.0114), interpreting that it is higher for breast cancer women than healthy. Resistin variance is partially positively associated with BMI (p=0.0942), indicating that it is higher for women with higher BMI. It is partially negatively associated with BMI*Adiponectin (p=0.1518), implying that it increases as the joint effect of BMI*Adiponectin decreases. Note that BMI is partially positively associated, while adiponectin is insignificant, but their interaction effect is negatively associated with resistin variance. In addition, leptin (p=0.1566) is partially negatively associated with resistin variance.

The present resistin analysis shows that BMI is not directly associated with mean resistin, while it is directly associated with resistin variance. In addition, BMI has effect on mean and variance of resistin through BMI*Leptin and BMI*Adiponectin, respectively. Glucose has no direct effect on resistin, but it has effect on it through Glucose*Adiponectin. Note that resistin has many effects on HOMA, MCP-1, leptin and adiponectin. The report shows that breast cancer biomarkers such as resistin, HOMA, MCP-1, leptin and adiponectin are complexly associated. Many previous articles have shown that BMI is directly associated with resistin and other breast cancer biomarkers [3-10], but the report shows that BMI has no direct effect, but it has many indirect effects on resistin. Best of our knowledge, very little studies have been done to examine the associations of resistin with many factors through probabilistic modeling, so the present results are not compared with the previous outcomes.

Conclusions

The associations of resistin with BMI, age, glucose and other breast cancer biomarkers have been obtained in the report with probabilistic modeling. The final predicted resistin model has been derived based on lowest AIC value, small standard error of the parameter estimates, using model checking plots, and on comparison of both the Log-normal and Gamma models. Thus, the derived resistin model is approximately true model. Hence, the obtained associations of resistin are correct to the best of our knowledge. In the report many interaction effects such as Age*HOMA, BMI*Leptin, Glucose*Adiponectin are obtained in the mean model, whereas BMI*Adiponectin is obtained in the variance model. These are not possible to identify by usual correlation and regression analysis. Again, the resistin has very complex association with the remaining factors, so simple correlation will give incorrect association. Therefore, the research should have greater faith on the present results than those emanating from bi-variate simple correlation, odds ratio, simple and multiple regression models. The report has derived that resistin is positively associated with adiponectin, MCP-1, Age*HOMA, BMI*Leptin, whereas it is negatively associated with age,

leptin, HOMA, Glucose*Adiponectin and Leptin*Adiponectin.

The present associations of resistin are only related with the data set given in. It is expected that the associations will be identical for similar data set, only the models may be little changed with respect to regression coefficients, which has not been verified herein. In addition, the present data set does not include many other diabetes markers such as HbA1c, random plasma glucose and 2 hours post plasma glucose. Subsequent research articles may consider all these diabetes and breast cancer markers, and along with BMI and age.

It is shown that resistin levels are significantly higher for breast cancer women, so it can be treated as a breast cancer biomarker. Most of the outcomes of the report are completely new in the breast cancer literature. Hope that the report will enrich to the medical practitioners as well as the breast cancer women. It is concluded that resistin is higher for younger women with breast cancer, higher levels of MCP-1, adiponectin, and higher interaction effects of BMI*Leptin, Age*HOMA. Younger women should be care on resistin levels along with MCP-1 and BMI.

Conflict of Interest

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

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