

## Special Article - Diabetes Statistics

## Role of Insulin on Breast Cancer Patients

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Insulin resistance is the fundamental cause of many diseases such as obesity, diabetes, breast cancer, cardiovascular diseases. It leads to many abnormalities which are correlated with metabolic syndrome. The report derives the association of insulin with glucose, Body Mass Index (BMI), age & breast cancer biomarkers. It is derived herein that mean insulin is positively associated with BMI ( $P < 0.0001$ ), leptin ( $P = 0.0009$ ), homeostasis model assessment score insulin resistance (HOMA-IR) ( $P < 0.0001$ ), glucose\*resistin ( $P < 0.0001$ ), monocyte chemoattractant protein-1 (MCP-1)\*age ( $P = 0.0909$ ), glucose\*adiponectin ( $P = 0.0424$ ), HOMA-IR\*MCP-1 ( $P < 0.0001$ ), while it is negatively associated with resistin ( $P < 0.0001$ ), MCP-1 ( $P = 0.0264$ ), glucose ( $P = 0.0665$ ), adiponectin ( $P = 0.0783$ ), BMI\*HOMA-IR ( $P < 0.0001$ ), glucose\*HOMA-IR ( $P < 0.0001$ ), leptin\*adiponectin ( $P = 0.0713$ ), age ( $P = 0.1039$ ) (partially). Insulin levels variance is higher for breast cancer patients ( $P = 0.0003$ ) than normal. It is negatively associated with age ( $P = 0.0165$ ), glucose\*MCP-1 ( $P = 0.0003$ ), leptin ( $P = 0.0828$ ), while it is positively associated with HOMA-IR ( $P < 0.0001$ ), MCP-1 ( $P = 0.0014$ ). Insulin plays a very complex associations with age, BMI, glucose and breast cancer markers, which is shown in the report.

**Keywords:** Body mass index; Breast cancer; Glucose; HOMA-IR; Insulin; Resistin; Non-constant variance

**Introduction**

Insulin Resistance (IR) is a primary legislator of glucose homeostasis, and it is determined by environmental and genetic factors. IR leads to impaired glucose tolerance, and it plays a principal pathophysiological role in the advancement of diabetes [1-3]. The insulin growth factor 1 receptor and insulin receptor play the main roles in the etiology of both breast cancer and diabetes mellitus [4-8]. Approximately 10% of breast cancer patients have pre-existing diabetes mellitus, that may affect breast cancer prognosis, progression and treatment options [5-8]. Insulin appears to be an important factor linking between diabetes and breast cancer [9,10]. Insulin resistance is associated with many metabolic syndrome. An increased body fat is mainly associated with many diseases such as hypertension, type 2 diabetes mellitus, and dyslipidaemia [11-13]. IR is highly associated with obesity (or BMI) and HOMA-IR [14,15].

Present medical literature shows that insulin is associated with many diseases, risk factors and disease biomarkers. Most of the earlier findings have been derived based on simple correlation coefficient, Logistic regression, simple and multiple regression analysis which are not appropriate statistical approach always for modeling of a heterogenous multivariate data set. Earlier findings invite many doubts and debates. For a multivariate data set with non-constant response variance, the associations of many covariates with the response can only be examined based on appropriate modeling. There is a very little study regarding the associations of insulin with Breast Cancer (BC) biomarkers along with biological factors using proper probabilistic modeling. The report examines the associations of insulin with BC biomarkers, age, BMI and glucose based on joint mean & dispersion probabilistic modeling. It examines the following hypotheses. What is the relationship of insulin with age, BMI, glucose

& BC biomarkers? What are the associations of insulin with the age, BMI, glucose & BC markers? What are the effects of insulin on BMI, glucose & BC markers? These queries have been searched in the report with a real data set of 116 women along with 10 study characters.

**Material and Methods****Materials**

**Study design and participants:** At the beginning of the study a total 154 Portuguese women were recruited from the Gynaecology Department of the University Hospital Centre of Coimbra (CHUC) between 2009 and 2013, who were newly diagnosed with BC. The recruited women had been divided into four exploratory groups based to their BMI and the presence or absence of BC. These groups are: (1) Control Without Over Weight (CTWOW) with BMI <25kg/m<sup>2</sup>, n = 29; (2) Control With Over Weight (OW) (CTOW) with BMI >25kg/m<sup>2</sup>, n = 48; (3) Breast Cancer WOW (BCWOW) with BMI <25kg/m<sup>2</sup>, n = 30; and (4) Breast Cancer OW (BCOW) with BMI >25kg/m<sup>2</sup>, n = 47. The CTWOW group were selected at the Internal Medicine Department during annual check-up of the aforementioned hospital. Women CTOW group were also selected at this Department, in their first Nutrition consultation. These women were selected in the study if they had never been diagnosed with family history of BC or malignant disease.

Breast cancer patients without & with over weight groups were selected and surgically operated at the Gynaecology Department of CHUC. These patients had been newly diagnosed with BC from a positive mammography and had histologically confirmed breast cancer without no prior cancer treatment. These selected patients were free from any infection or any other acute disease at the study enrolment time. The same physician collected anthropometric data (height, weight) and all the clinical information (personal,

**Table 1:** Insulin analysis results for mean and dispersion models from Log-Normal & Gamma fit.

Model	Variables	Gamma fit				Log-normal fit			
		Estimate	s.e.	t-value	p-value	Estimate	s.e.	t-value	p-value
Mean	Intercept	0.66861	0.22661	2.95111	0.00391	1.35501	0.32831	4.1271	<0.0001
	Age	-0.00282	0.00171	-1.64111	0.10391	-0.00341	0.00231	-1.4701	0.14471
	HOMA-IR	1.32401	0.09211	14.3791	<0.0001	0.88281	0.08921	9.9021	<0.0001
	MCP-1	-0.00041	0.00021	-2.25411	0.02642	-0.00051	0.00021	-2.4641	0.01541
	Age* MCP-1	0.00012	0.00012	1.70711	0.09092	0.00012	0.00011	2.2161	0.0291
	BMI	0.02951	0.00492	5.97211	<0.0001	0.01892	0.00591	3.2001	0.00181
	BMI*HOMA-1R	-0.01572	0.00262	-6.00411	<0.0001	-0.00772	0.00261	-2.9771	0.00371
	RESIS	-0.03291	0.00372	-8.80321	<0.0001	-0.03172	0.00512	-6.1751	<0.0001
	GLUCO	-0.00282	0.00152	-1.85521	0.06651	-0.00591	0.00262	-2.3191	0.02241
	GLUCO*HOMA-1R	-0.00471	0.00021	-23.6892	<0.0001	-0.00371	0.00022	-19.0711	<0.0001
	ADIPO	-0.02711	0.01521	-1.77921	0.07831	-0.06671	0.02492	-2.6791	0.00862
	GLUCO*ADIPO	0.00042	0.00021	2.05421	0.04261	0.00081	0.00032	2.9331	0.00422
	GLUCO*RESIS	0.00032	0.00011	9.20721	<0.0001	0.00031	0.00011	6.4592	<0.0001
	HOMA-1R*MCP-1	0.00012	0.00011	7.27921	<0.0001	0.00011	0.00011	6.6542	<0.0001
	LEPTI	0.00481	0.00141	3.40921	0.00091	0.00792	0.00211	3.8012	0.00022
LEPTI*ADIPO	-0.00021	0.00012	-1.82321	0.07131	-0.00032	0.00021	-1.5202	0.13172	
Disper- sion	Intercept	-3.75501	1.43242	-2.62211	0.01011	-3.45532	2.32181	-1.4882	0.13992
	Age	-0.02151	0.00882	-2.43911	0.01651	-0.03522	0.00981	-3.5742	0.00052
	GLUCO	0.00371	0.01531	0.24411	0.80772	0.02822	0.02471	1.1422	0.25622
	MCP-1	0.00701	0.00211	3.29211	0.00142	0.00272	0.00372	0.7292	0.46772
	GLUCO*MCP-1	-0.00011	0.00011	-3.76011	0.00032	0.00012	0.00012	-1.1312	0.26081
	HOMA-IR	0.41681	0.06001	6.94312	<0.0001	-	-	-	-
	LEPT I	-0.01401	0.00801	-1.75212	0.08281	-0.01041	0.01091	-0.9492	0.34491
	TYOPA	1.16521	0.30821	3.78112	0.00032	1.33111	0.36261	3.6712	0.00041
<b>AIC</b>		318.773				396.0			

family medical history) each of the selected patient during the first consultation. Then, fasting blood samples were procured by venous puncture for biochemical examinations, which was conducted by the same physician, and immediately they were transferred to the same hospital Laboratory of Physiology of the Faculty of Medicine. The study design was approved by the CHUC Ethical Committee, and all recruited participants gave their written aware consent prior to joining the study. Finally, a total of 116 (64 with BC & 52 control participants) was selected in the current study, and the rest 38 women were removed from the study due to having BMI>40kg/m<sup>2</sup>.

The data set can be obtained from UCI Machine Learning Repository, and its detailed statement is given in [16,17]. For current using of the factors & covariates in the article, these are restated as BMI (kg/m<sup>2</sup>), Age, HOMA-IR, Glucose (mg/dL) (GLUCO), Insulin (μU/mL) (INSUL), Adiponectin (μg/mL) (ADIPO), MCP-1, Leptin(ng/mL) (LEPTI), Resistin (ng/mL) (RESIS), Types of Patient (TYOPA) (1=healthy controls; 2=patients). Some related studies are given in [18-20].

**Statistical methods**

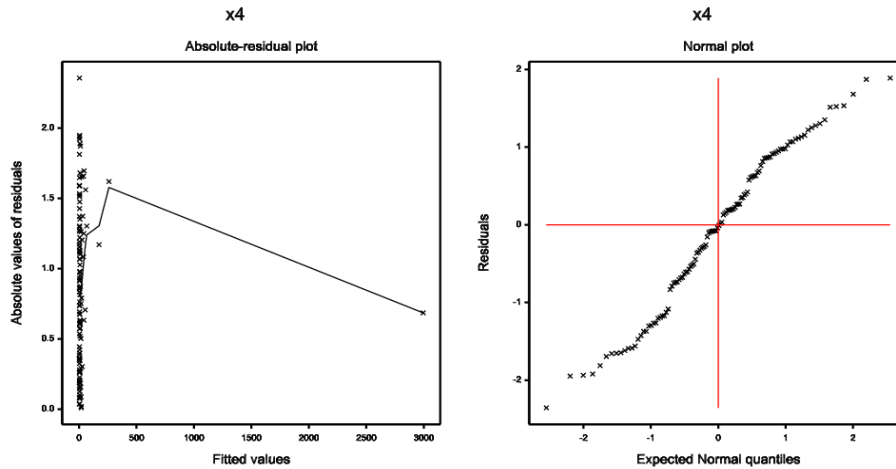
The data given in [16,17] is a multivariate data set. The report aims to derive the relationship of insulin with age, BMI, glucose and

BC biomarkers. The interested response herein is insulin which is non-constant variance, positive continuous non-normally distributed random variable. It can simply be modeled by suitable transformation, if the variance is stabilized with the transformation. But the response insulin is not stabilized by any suitable transformation. Therefore, insulin can be modeled by

Log-normal and Gamma Joint Generalized Linear Models (JGLMs), which are elaborately given in [21-24]. These are not restated herein, and the interested readers may visit [20,23].

**Statistical & graphical analysis**

The random variable insulin is considered as the dependent variable and the rest others are considered as the independent variables. As the interested response insulin is not stabilized by any suitable transformation, so it has been modeled by both Log-normal and Gamma JGLMs. The final models have been accepted depending on the lowest Akaike Information Criterion (AIC) value (within each class), which minimizes both the squared error loss and predicted additive errors [25]. Some insignificant effects or partially significant effects are included in both mean and dispersion models (Table 1) due to marginality rule [26], or for better model fitting [25,27]. The analyses outcomes are presented in Table 1, which shows that Gamma



**Figure 1:** For the joint Gamma fitted insulin level models (Table 1), the (a) absolute residuals plot with respect to the fitted values, and (b) the normal probability plot for the mean model.

fit (AIC= 318.773) is better than Log-normal fit (AIC=396.0). Note that in Log-normal dispersion model HOMA-IR is aliased, which is not included in that model.

Data produced probabilistic model should be tested by model checking tools before accepting as the valid model. The derived Gamma fitted insulin model (Table 1) has been examined by model diagnostic plots in Figure 1. Figure 1(a) presents the absolute insulin Gamma fitted residuals plots against the fitted values, where they all are located at a point randomly, except a smaller absolute residual value located at the right boundary. Therefore, the right tail of Figure 1(a) is decreasing. Figure 1(b) displays the mean insulin Gamma fitted normal probability plot (Table 1), which shows no lack of fit. Thus, Figure 1(a) and Figure 1(b) have proved that Gamma fitted models are approximately true insulin model (Table 1).

### Results

The insulin analysis outputs for both the Gamma & Log-normal fitted models are displayed in Table 1. The following outcomes are related to the Gamma fitted models (Table 1). It is derived herein that mean insulin is positively associated with BMI (P<0.0001), leptin (P=0.0009), homeostasis model assessment score insulin resistance (HOMA-IR) (P<0.0001), glucose\*resistin (P<0.0001), monocyte chemoattractant protein-1 (MCP-1)\*age (P=0.0909), glucose\*adiponectin (P=0.0424), HOMA-IR\*MCP-1 (P<0.0001), while it is negatively associated with resistin (P<0.0001), MCP-1 (P=0.0264), glucose (P=0.0665), adiponectin (P=0.0783), BMI\*HOMA-IR (P<0.0001), glucose\*HOMA-IR (P<0.0001), leptin\*adiponectin (P=0.0713), age (P=0.1039) (partially). Insulin levels variance is higher for breast cancer patients (P=0.0003) than normal. It is negatively associated with age (P=0.0165), glucose\*MCP-1 (P=0.0003), leptin (P=0.0828), while it is positively associated with HOMA-IR (P<0.0001), MCP-1 (P=0.0014).

Insulin Gamma fitted mean ( $\hat{\mu}$ ) model (Table 1) is  $\hat{\mu} = \exp(0.6686+1.3240 \text{ HOMA-IR}-0.0028 \text{ Age}-0.0004 \text{ MCP-1}+0.0001 \mu\text{MCP-1*Age}+0.0295 \text{ BMI}-0.0157 \text{ HOMA-IR*BMI}-0.0329 \text{ RESIS}-0.0028 \text{ GLUCO}-0.0047 \text{ GLUCO*HOMA-IR}-0.0271 \text{ ADIPO}+0.0004 \text{ GLUCO*ADIPO}+0.0003 \text{ GLUCO*RESIS}+0.0001$

$\text{HOMA-IR*MCP-1}+0.0048 \text{ LEPTI}-0.0002 \text{ LEPTI*ADIPO}$ ), and the Insulin Gamma fitted dispersion ( $\hat{\sigma}^2$ ) model (Table 1) is  $\hat{\sigma}^2 = \exp(-3.7550+0.0037 \text{ GLUCO}-0.0215 \text{ Age}+0.007 \text{ MCP-1}-0.0001 \text{ GLUCO*MCP-1}+0.4168 \text{ HOMA-IR}-0.014 \text{ LEPTI}+1.1652 \text{ TYOPA}$ ).

The mean & dispersion relationship of insulin are displayed by the above two equations. It is noted that mean insulin is explained by Age, BMI, HOMA-IR, MCP-1, MCP-1\*Age, HOMA-IR\*BMI, RESIS, GLUCO, GLUCO\*HOMA-IR, ADIPO, GLUCO\*ADIPO, GLUCO\*RESIS, HOMA-IR\*MCP-1, LEPTI, LEPTI\*ADIPO, while its dispersion is explained by Age, MCP-1, GLUCO\*MCP-1, HOMA-IR, LEPTI, TYOPA.

### Discussion

Final insulin level analysis outcomes (Table 1), mean & dispersion models are given above. From mean insulin model, it is observed that insulin level is negatively associated with glucose (P=0.0665) & age (P=0.1039) (partially), concluding that it decreases as glucose level increases, or also at older ages. Therefore, at older ages, glucose level increases as it is negatively associated with insulin. So, type 2 diabetes is frequently observed at older ages. Insulin is positively associated with HOMA-IR (P<0.0001), indicating that it increases as HOMA-IR increases. Equivalently, HOMA-IR can be considered as an alternative measure of insulin. It is negatively associated with MCP-1 (P=0.0264), interpreting that it decreases as MCP-1 increases. Note that MCP-1 is higher for BC patients, which have lower insulin levels, and they may be type 2 diabetes also. Both age and MCP-1 are negatively associated with insulin, while their joint interaction effects Age\*MCP-1(P=0.0909) is positively associated with insulin, indicating that it increases as their joint effect increases. BC patients with older ages have higher MCP-1, but may not have always lower insulin level as the joint interaction effect Age\*MCP-1 increases insulin level. So, older BC patients should not always be type 2 diabetes. Insulin is positively associated with BMI (P<0.0001) and HOMA-IR (P<0.0001), while their interaction effect BMI\*HOMA-IR (P<0.0001) is negatively associated with insulin. Again, it is negatively associated with MCP-1 (P=0.0264), resistin (P<0.0001), glucose (P=0.0665), adiponectin (P=0.0783), and positively associated with HOMA-IR, but the interaction effects HOMA-IR\*MCP-1 (P<0.0001),

glucose\*resistin ( $P<0.0001$ ), glucose\*adiponectin ( $P=0.0424$ ) are positively associated with it, while glucose\*HOMA-IR ( $P<0.0001$ ) is negatively associated with it. On the hand leptin ( $P=0.0009$ ) is positively associated with insulin, while adiponectin is negatively associated with it, but their joint interaction effect leptin\*adiponectin ( $P=0.0713$ ) is negatively associated with it.

Gamma fitted insulin variance model shows that Insulin Levels Variance (ILV) is positively associated with TYOPA ( $P=0.0003$ ), and negatively associated with age ( $P=0.0165$ ), indicating that it is higher for BC women and older patients, than normal and younger. ILV is directly associated with HOMA-IR ( $P<0.0001$ ), MCP-1 ( $P=0.0014$ ), while it is inversely associated with glucose\*MCP-1 ( $P=0.0003$ ) and leptin ( $P=0.0828$ ) (partially). These indicate that ILV increases as HOMA-IR, or MCP-1 increases, or leptin, or glucose\*MCP-1 decreases. Best of our knowledge, all the above associations related to insulin variance have not been reported in the earlier studies.

Interpretations of the present derived insulin analysis results have been presented above. The associations and effects of insulin on breast cancer biomarkers, BMI, age and glucose are described above. The report focuses that insulin level increases if BMI, or HOMA-IR, or leptin, Age\*MCP-1, GLUCO\*ADIPO, GLUCO\*RESIS, HOMA-IR\*MCP-1 increases, or MCP-1, or adiponectin, or resistin, or glucose, or BMI\*HOMA-IR, or GLUCO\*HOMA-IR, or LEPTIN\*ADIPO decreases. The present association types of (insulin & BMI), (insulin & HOMA-IR), (insulin & glucose) and (insulin & leptin) are supported by earlier articles [1,2,6,7,13-15]. Note that mean insulin level is not significantly higher for breast cancer women than normal. It was doubt in earlier findings [6-10]. Herein it is derived that insulin variance is higher for BC women than normal. The explanatory factors for insulin variance have not been focused in any earlier article.

Sirtuin 1 (SIRT1) is a prototype mammalian NAD(+)-dependent protein deacetylase that has emerged as a key metabolic sensor in various metabolic tissues. Association between SIRT1 and insulin resistance has been focused in many reports based on statistical analysis using GraphPad Prism 5.0 software [27-30]. SIRT1 is not included in the considered data set [16,17]. Also the correlation between the prognostic factors of breast cancer and apparent diffusion coefficient in diffusion weighted imaging sequences of malignant lesions have been discussed with Pearson correlation test [31-33]. These studies may be performed based on probabilistic modeling which may give many interesting findings.

## Conclusion

The effects of insulin on glucose, BMI, age and breast cancer biomarkers have been developed in the report based on probabilistic insulin modeling. The mean & dispersion models of insulin have been obtained in the report using both Log-normal & Gamma JGLMs. Final fitted model for insulin has been accepted based on smallest AIC value, comparison of outputs from both the distributions, small standard error of the estimates (Table 1) and graphical analysis. Both the distributions fitted results show almost similar interpretations. So, the interpretations regarding the insulin associations have been derived in the report based on approximately a true model. Moreover, the obtained outputs support many earlier reported associations such

as (insulin & BMI), (insulin & glucose), (insulin & HOMA-IR) and (insulin & leptin). In addition, the report focuses the insulin level is not significantly higher for breast cancer women. It has shown many new factors that have explained the insulin levels mean & dispersion functions which have not been reported in earlier articles. The report presents a very complex associations of insulin with age, BMI, glucose and BC markers, which are really helpful for practitioners as well as researchers. Insulin levels should be examined regularly at older ages and BC women.

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