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Inter-relationship between diabetes and breast cancer biomarkers

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SUMMARY

The glucose metabolisms and serum lipids are assumed as possible intermediary mechanisms in linking breast cancer (BC) and obesity. The current report examines the associations between diabetes mellitus (DM) markers (glucose and insulin) and BC markers (monocyte chemoattractant protein-1 (MCP-1), resistin, adiponectin, leptin). The glucose model shows that mean glucose levels are higher for breast cancer women ($p=0.0222$) then normal. Mean glucose levels are positively associated with leptin ($p<0.0001$) and homeostasis model assessment score insulin resistance (HOMA-IR) ($p<0.0001$), while they are negatively associated with interaction effects HOMA-IR*leptin ($p<0.0001$) and leptin*adiponectin ($p=0.0883$). On the other hand, variance of glucose levels is positively associated with HOMA-IR ($p<0.0001$) and resistin ($p=0.0218$), while it is negatively associated with leptin ($p<0.0001$), MCP-1 ($p=0.0115$). Insulin model shows that mean insulin levels are positively associated with HOM-IR ($p<0.0001$), leptin ($p=0.0009$), age*MCP-1 ($p=0.0909$), glucose*adiponectin ($p=0.0424$), glucose*resistin ($p<0.0001$), HOMA-IR*MCP-1 ($p<0.0001$), while they are negatively associated with MCP-1 ($p=0.0264$), resistin ($p<0.0001$), adiponectin($p=0.0783$), glucose*HOMA-IR ($p<0.0001$), leptin*adiponectin ($p=0.0713$). The variance of insulin levels is higher for breast cancer women ($p=0.0003$) than normal. Again, it is positively associated with MCP-1 ($p=0.0014$), HOMA-IR ($p<0.0001$), while it is negatively associated with leptin ($p=0.0828$) and glucose*MCP-1 ($p=0.0003$). Many more relationships between BC and DM markers are also reported in the current article. It is concluded that both DM and BC markers have very complex closely interlinked relationships.

Key words: adiponectin, breast cancer markers, diabetes mellitus markers, glucose, insulin, leptin, resistin, non-constant variance

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INTRODUCTION

Cancer and diabetes are common diseases with a terrible impact on human health worldwide. Epidemiologic studies have shown that people with Diabetes Mellitus (DM) are at significantly greater risk for many types of cancer [1-4]. Many research articles have shown that there is a positive link between overweight (obesity, or Body Mass Index (BMI)) and severity of breast cancer (BC) [5-7]. A recent article has shown the relationship between BMI and BC markers [7]. Association between the metabolic syndrome and BC prognosis has been reported [8, 9]. Note that metabolic syndrome is known as a combination of at least three of the following metabolic risks such as elevated serum triglycerides, visceral obesity, reduced high-density lipoprotein cholesterol, raised serum glucose, raised blood pressure [8]. Despite records from in vitro research [10-13], the definite underlying mechanisms of the link between metabolic syndrome, BC progression and obesity have yet to be fully elucidated, and earlier epidemiological research findings remain contradicting [12-16]. For the above association, a mechanism suggests that it is due to increased estrogen levels (sourced from the fat in adipose tissue), which are synthesized from cholesterol [17]. Insulin-like Growth Factors (IGF), glucose metabolisms, leptin, resistin, and lipid have also been postulated as possible intermediate mechanisms which are responsible for correlation between obesity and BC risk [9, 11, 13, 18-20]. A positive correlation between BC risk and triglycerides has been pointed [16]. In addition, the unfavourable hormonal profile (e.g., leptin, or estrogen, elevated insulin) is correlated with low levels of high-density lipoprotein which is assumed to increase BC risk [19, 20].

Most of the previous cancer epidemiological studies are based on Cox model analyses [4], Kaplan Meier analysis [20], Logistic regression, basic statistics such as simple correlation and regression [1, 8, 14, 16], which are not appropriate statistical approach for deriving associations of physiological positive, heterogeneous, non-normal continuous variables. Moreover, the best of our knowledge, very little research articles have considered both the DM and BC markers to find their inter-relationships. Earlier cancer epidemiological research findings regarding the associations between DM and BC markers remain contradicting [12-16]. Therefore, this report aims to give a clear knowledge regarding the inter-relationships between DM markers (glucose and insulin) and BC markers (monocyte chemoattractant protein-1 (MCP-1), resistin, adiponectin,

leptin) based on probabilistic modeling. The current report derives all the findings herein based on the probabilistic models of glucose (derived herein), insulin (derived herein), monocyte chemoattractant protein-1 (MCP-1) [21], resistin [22], adiponectin [23] and leptin [24]. Only the two models of glucose and insulin levels are derived in the report, while the other four models of BC markers such as MCP-1, resistin, leptin, and adiponectin have already been published. The associations between BC and DM markers are reported herein based on the above six models and the published four models of BC markers are not shown herein. Interested readers can go through them [21-24].

MATERIALS AND METHODS

Materials

Participants and study design: Initially total of 154 Portuguese women newly diagnosed with Breast Cancer (BC) were selected from the Gynaecology Department of the University Hospital Centre of Coimbra (CHUC) between 2009 and 2013. The selected women had been classified into four experimental groups based on their Body Mass Index (BMI) and the presence or absence of breast cancer (BC). The four groups are: (1) control with BMI<25 kg/m^2, n=29 (without overweight) (CT); (2) control with BMI>25 kg/m^2, n=48 (with overweight) (CTOW); (3) breast cancer with BMI<25 kg/ m^2, n=30 (without overweight) (BC); and (4) breast cancer with BMI>25 kg/m^2, n=47 (with overweight) (BCOW). The control subjects (without overweight) (CT group) were recruited at the Internal Medicine Department in annual check-up of the aforementioned hospital. Women (with overweight) of the CTOW group were also recruited at this Department, in their first Nutrition consultation. They were all considered in the study if they had never been diagnosed with malignant disease or benign nor have family history of BC.

Patients of BC and BCOW groups were recruited and surgically treated at the Gynaecology Department of CHUC. These women had been newly diagnosed with breast cancer from positive mammography and had histologically confirmed BC without prior cancer treatment. All recruited women were free from any acute or another infectious disease at the time of study enrolment. The same research physician collected all the clinical information (family medical history and personal) as well as anthropometric data (weight and height) each of the selected women during the first consultation.

Selected women were thought postmenopausal at blood collection time if they were reported a bilateral oophorectomy or at least 12 months after menopause. During the first consultation, fasting blood samples were collected by a venous puncture for biochemical analysis, which was performed by the same nurse, and immediately they were delivered to the Laboratory of Physiology of the Faculty of Medicine. The study was approved by the CHUC Ethical Committee, and all women under the study gave their written informed consent prior to entering the study. Finally, a total of 116 (out of which 64 women with BC and 52 control healthy women) were considered in the present study, and the remaining 38 participants were excluded from the study due to having BMI above 40 kg/m^2.

The data set is available in the UCI Machine Learning Repository, and its detailed description is given in [25, 26]. For immediate using of the covariates in the report, these are restated as Body mass index (BMI) (kg/m^2), Age, Homeostasis Model Assessment Score Insulin Resistance (HOMA-IR), Insulin (μU/mL) (INSU), Glucose (mg/dL) (GLUC), Adiponectin (μg/mL) (ADIP), Resistin (ng/mL) (RESI), Monocyte Chemoattractant Protein-1 (MCP-1), Leptin(ng/mL) (LEPT), Types of Patient (TYOP) (1=healthy controls; 2=patients).

Statistical methods

The considered data set given in [25, 26] is a multivariate data set. The interesting responses are glucose, insulin, MCP-1, resistin, adiponectin, leptin which are all positive continuous heterogeneous and non-normally distributed, which are required to be modeled herein. These can be appropriately modeled using Joint Generalized Linear Models (JGLMs) adopting both the Log-normal and Gamma distributions, which are clearly given in [21, 27-29]. Both the JGLMs under the Log-normal and Gamma distributions are very shortly given in a recent article [21], which are not reproduced herein. For more discussions on JGLMs, readers can visit [27, 29]. Models for MCP-1 [21], resistin [22], adiponectin [23] and leptin [24] have already been reported. This report derives the models for glucose and insulin using JGLMs under both the distributions.

Statistical and graphical analysis

The random variable glucose (separately for insulin) is considered as the dependent variable and the remaining others are considered as the independent variables. As the interested response glucose (separately for insulin) is not stabilized by any sui transformation, so it has been jointly 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 [30]. Some insignificant or partially significant effects are included in both the models due to the marginality rule given by Nelder [31] and also for better fitting [30]. Note that partially significant effects are recognized as a confounder in Epidemiology. The analyses outcomes for glucose and insulin levels are presented in 1 and 2, respectively. For both the responses (glucose and insulin levels), Gamma fit (for glucose AIC=771.873) (for insulin AIC=318.773) gives better than Log-normal fit (for glucose AIC=772.5) (for insulin AIC=396.0).

Data produced probabilistic model should be verified by model diagnostic tools before considering it as the valid final model, which interprets all valid conclusions. The derived Gamma fitted models for glucose and insulin (in Tables 1 and 2) have been verified by model diagnostic plots in Figures 1 and 2, respectively. In Figure 1a, the glucose Gamma fitted (Table 1) absolute residuals are plotted against the fitted values, where all the absolute residuals are randomly located at a point, except only two points. Figure 1a is exactly a flat straight line except the right tail, which is increasing as a larger residual is located at the right boundary. This shows that variance is constant with the running means. Figure 1b presents the mean glucose Gamma fitted normal probability plot (Table 1), which does not reveal any fit discrepancy. Thus, Figure 1a and 1b have confirmed that Gamma fitted glucose models are approximately true mode (Table 1). In Figure 2a, the insulin Gamma fitted (Table 2)

absolute residuals are plotted against the fitted values, where all residuals are located at a point randomly, except a lower absolute residual located at the right boundary. So, the right tail of Figure 2a is decreasing. Figure 2b presents the mean insulin Gamma fitted normal probability plot (Table 2), which reveals no lack of fit. Similarly, Figure 2a and 2b have confirmed that Gamma fitted insulin models are approximately true mode (Table 2).

RESULTS

Summarized JGLMs results for glucose and insulin analyses are displayed in Tables 1 and 2, respectively. The fitted glucose model (Table 1) shows that mean glucose levels are higher for

Tab. 1. Results for mean and dispersion models for glucose from Gamma and log-normal fit

Model	Variables	Gamma fit				Log-normal fit			
		Estimate	s.e.	t-value	p-value	Estimate	s.e.	t-value	p-value
Mean	Constant	4.3933	0.0202	218.02	<0.0001	4.3907	0.0199	220.87	<0.0001
	INSU	-0.128	0.0057	-22.58	<0.0001	-0.1282	0.0055	-23.16	<0.0001
	HOMA-IR	0.6248	0.0284	22.03	<0.0001	0.6265	0.028	22.38	<0.0001
	TYOP	0.0216	0.0093	2.32	0.0222	0.0197	0.0091	2.17	0.0322
	LEPT	0.0035	0.0006	6.21	<0.0001	0.0035	0.0005	6.61	<0.0001
	HOMA-IR *LEPT	-0.0017	0.0002	-7.12	<0.0001	-0.0017	0.0002	-7.3	<0.0001
	ADIP	0.0009	0.0012	0.78	0.4371	0.0009	0.0011	0.76	0.4489
	LEPT*ADIP	-0.0001	0.0001	-1.72	0.0883	-0.0001	0.0001	-1.7	0.092
Dispersion	Constant	-8.844	1.0191	-8.678	<0.0001	-8.938	1.0467	-8.539	<0.0001
	Age	0.053	0.016	3.313	0.0013	0.055	0.0163	3.384	0.001
	HOMA-IR	2.005	0.3925	5.108	<0.0001	2.201	0.4058	5.424	<0.0001
	Age* HOMA-IR	-0.007	0.0034	-2.186	0.031	-0.008	0.0035	-2.222	0.0284
	INSU	-0.162	0.0647	-2.51	0.0136	-0.204	0.0657	-3.112	0.0024
	LEPT	-0.039	0.0092	-4.29	<0.0001	-0.042	0.0093	-4.493	<0.0001
	REST	0.129	0.0553	2.327	0.0218	0.136	0.0563	2.413	0.0175
	Age* REST	-0.002	0.0009	-2.082	0.0397	-0.002	0.0009	-2.22	0.0285
	INSU* HOMA-IR	-0.011	0.0028	-3.793	0.0002	-0.01	0.003	-3.491	0.0007
	MCP-1	-0.001	0.0005	-2.571	0.0115	-0.001	0.0005	-2.394	0.0184
AIC		771.873				772.5			

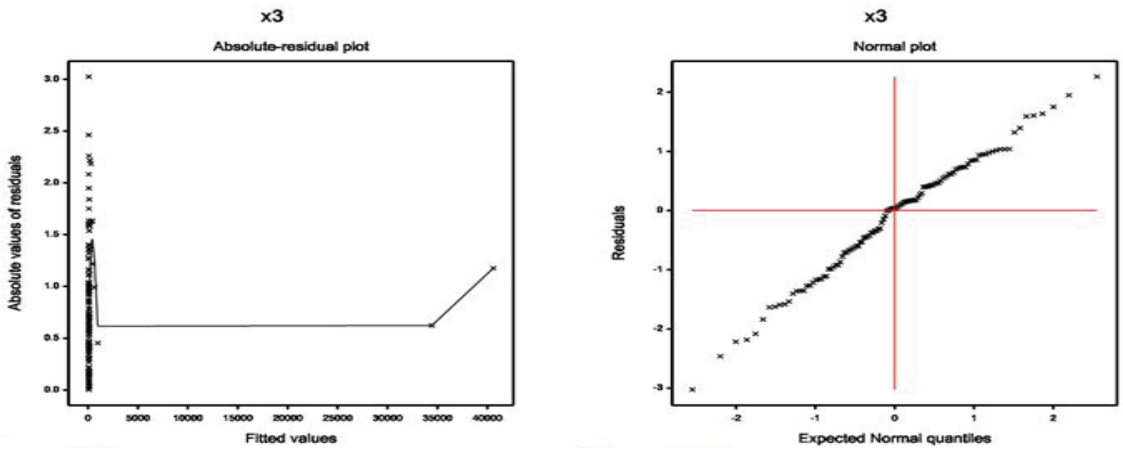

Fig. 1. For the joint Gamma fitted models of glucose level (1), the (a): absolute residuals plot with respect to the fitted values, and; (b): the normal probability plot for the mean model

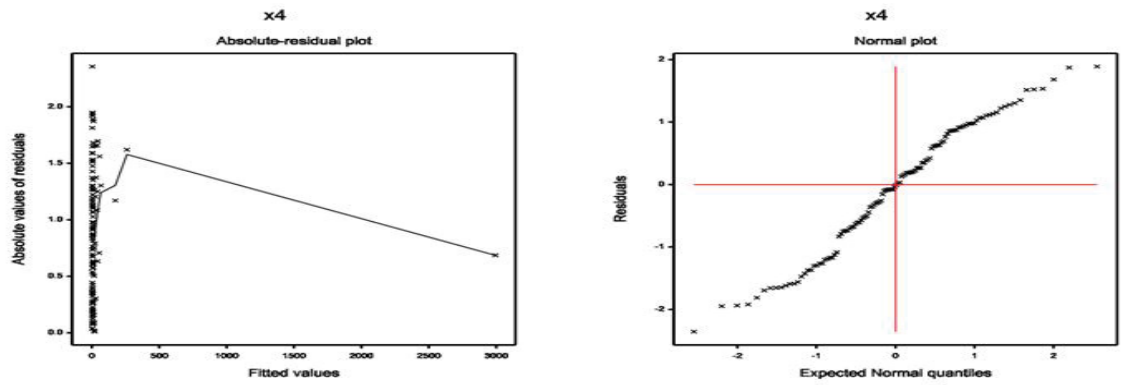

Fig. 2. For the joint Gamma fitted models of insulin level (2), the (a): absolute residuals plot with respect to the fitted values, and; (b): the normal probability plot for the mean model

Tab. 2. Results for mean and dispersion models for insulin from gamma and log-normal fit

Model	Variables	Gamma fit				Log-normal fit			
		Estimate	s.e.	t-value	p-value	Estimate	s.e.	t-value	p-value
Mean	Constant	0.6686	0.2266	2.951	0.0039	1.355	0.3283	4.127	<0.0001
	Age	-0.0028	0.0017	-1.641	0.1039	-0.0034	0.0023	-1.47	0.1447
	HOMA-IR	1.324	0.0921	14.379	<0.0001	0.8828	0.0892	9.902	<0.0001
	MCP-1	-0.0004	0.0002	-2.254	0.0264	-0.0005	0.0002	-2.464	0.0154
	Age* MCP-1	0.0001	0.0001	1.707	0.0909	0.0001	0.0001	2.216	0.029
	BMI	0.0295	0.0049	5.972	<0.0001	0.0189	0.0059	3.2	0.0018
	BMI*HOMA-1R	-0.0157	0.0026	-6.004	<0.0001	-0.0077	0.0026	-2.977	0.0037
	REST	-0.0329	0.0037	-8.803	<0.0001	-0.0317	0.0051	-6.175	<0.0001
	GLUC	-0.0028	0.0015	-1.855	0.0665	-0.0059	0.0026	-2.319	0.0224
	GLUC*HOMA-1R	-0.0047	0.0002	-23.689	<0.0001	-0.0037	0.0002	-19.071	<0.0001
	ADIP	-0.0271	0.0152	-1.779	0.0783	-0.0667	0.0249	-2.679	0.0086
	GLUC*ADIP	0.0004	0.0002	2.054	0.0426	0.0008	0.0003	2.933	0.0042
	GLUC*REST	0.0003	0.0001	9.207	<0.0001	0.0003	0.0001	6.459	<0.0001
	HOMA-1R*MCP-1	0.0001	0.0001	7.279	<0.0001	0.0001	0.0001	6.654	<0.0001
	LEPT	0.0048	0.0014	3.409	0.0009	0.0079	0.0021	3.801	0.0002
	LEPT*ADIP	-0.0002	0.0001	-1.823	0.0713	-0.0003	0.0002	-1.52	0.1317
Dispersion	Constant	-3.755	1.4324	-2.622	0.0101	-3.4553	2.3218	-1.488	0.1399
	Age	-0.0215	0.0088	-2.439	0.0165	-0.0352	0.0098	-3.574	0.0005
	GLUC	0.0037	0.0153	0.244	0.8077	0.0282	0.0247	1.142	0.2562
	MCP-1	0.007	0.0021	3.292	0.0014	0.0027	0.0037	0.729	0.4677
	GLUC*MCP-1	-0.0001	0.0001	-3.76	0.0003	0.0001	0.0001	-1.131	0.2608
	HOMA-IR	0.4168	0.06	6.943	<0.0001	-	-	-	-
	LEPT	-0.014	0.008	-1.752	0.0828	-0.0104	0.0109	-0.949	0.3449
	TYOP	1.1652	0.3082	3.781	0.0003	1.3311	0.3626	3.671	0.0004
AIC		318.773				396			

breast cancer women (p=0.0222) than normal. Glucose levels are positively associated with leptin (p<0.0001) and HOMA-IR (p<0.0001), while they are negatively associated with interaction effects HOMA-IR*leptin (p<0.0001) and leptin*adiponectin (p=0.0883). On the other hand, variance of glucose levels is positively associated with HOMA-IR (p<0.0001) and resistin (p=0.0218), while it is negatively associated with leptin (p<0.0001), MCP-1 (p=0.0115), age*HOMA-IR (p=0.0310), age*resistin (p=0.0397), HOMA-IR*insulin (p=0.0002).

Insulin model shows that mean insulin levels are positively associated with HOM-IR (p<0.0001), leptin (p=0.0009), age*MCP-1 (p=0.0909), glucose*adiponectin (P=0.0424), glucose*resistin (p<0.0001), HOMA-IR*MCP-1 (p<0.0001), while they are negatively associated with MCP-1 (p=0.0264), resistin (p<0.0001), adiponectin (p=0.0783), glucose*HOMA-IR (p<0.0001), BMI*HOMA-IR (p<0.0001), leptin*adiponectin (p=0.0713). The variance of insulin levels is higher for breast cancer women (p=0.0003) than normal. It is positively associated with MCP-1 (p=0.0014), HOMA-IR (p<0.0001), while it is negatively associated with leptin (p=0.0828) and glucose*MCP-1 (p=0.0003).

On the other hand, the MCP-1 model shows that mean MCP-1 is negatively associated with insulin (p<0.0001), while it is positively associated with insulin*leptin (p<0.0001). The variance of MCP-1 is positively associated with age*insulin (p=0.0025) and glucose*leptin (p=0.0819) [21]. The resistin model shows that mean resistin is negatively associated with glucose*adiponectin (p=0.1007) [22]. The leptin model shows that mean leptin is positive associated with glucose (p=0.0135) and insulin (p=0.0557) [24].

Gamma fitted glucose mean ($\hat{\mu}$) model (from 1) is $\hat{\mu}$ =exp(4.3933–0.1280 INSU+0.6284 HOMA-IR+0.0216 TYOP+0.0035 LEPT–0.0017 HOMA-IR*LEPT+0.0009 ADIP–0.0001 LEPT*ADIP), and the Gamma fitted glucose variance ($\hat{\sigma}^2$) model (from 1) is $\hat{\sigma}^2$ =exp(-8,844 + 0.053 Age+2.005 HOMA-I–0.007 Age*HOMA-IR–0.162 INSU–0.039 LEPT+0.129 REST–0.002 Age*REST–0.011 INSU*HOMA-IR–0.001 MCP-1).

Gamma fitted insulin mean ($\hat{\mu}$) model (from 2) is $\hat{\mu}$ =exp(0.6686–0.0028 Age+1.3240 HOMA-IR–0.0004 MCP-1+0.0001 Age*MCP-1 +0.0295 BMI–0.0157 BMI*HOMA-IR- 0.0329 REST-0.0028 GLUC–0.0047 GLUC*HOMA-IR–0.0271 ADIP+0.0004 GLUC*ADIP + 0.0003 GLUC*REST +0.0001 HOMA-IR*MCP-1+0.0048 LEPT-0.0002 LEPT*ADIP), and the Gamma fitted insulin variance ($\hat{\sigma}^2$) model (from 2) is $\hat{\sigma}^2$ =exp(–3.7550–0.0215 Age+0.0037 GLUC+0.007 MCP-1–0.0001 GLUC*MCP-1 +0.4168 HOMA-IR–0.014 LEPT+1.1652 TYOP).

For this data set, the models for BC markers such as MCP-1 [21], resistin [22], adiponectin [23] and leptin [24], and model for BMI [7] have already been published.

DISCUSSION

Inter-relationships between DM and BC markers are reported herein from the models of DM markers such as glucose and insulin, as well as from the models of BC markers such as MCP-1, resistin, leptin, and adiponectin. Models of these BC markers are reported in [21-24], while models of DM markers are reported herein 1 and 2.

Fitted glucose model (1) shows that the Mean Glucose Level

(MGLUCL) is positively associated with Types of Patients (TYOP) (p=0.0222) (1=healthy controls; 2=patients), concluding that it is higher for breast cancer women than normal. It proves that DM women have a greater risk of BC. MGLUCL is positively associated with leptin (p<0.0001), indicating that it rises as leptin increases. It is positively associated with HOMA-IR(p<0.0001), implying that glucose level rises as HOMA-IR rises. These show that DM women have higher levels of leptin and HOMA-IR, and they have greater risk of BC. MGLUCL is negatively associated with interaction effect HOMA-IR*leptin (p<0.0001), interpreting that glucose level rises as HOMA-IR*leptin decreases. It concludes that DM (or equivalently BC risk) women have higher levels of HOMA-IR and leptin but their interaction effect (HOMA-IR*leptin) is at low level. Also, MGLUC is negatively associated with the interaction effect leptin*adiponectin (p=0.0883), implying that glucose level rises as leptin*adiponectin decreases. It concludes that DM women have higher level of leptin and lower interaction effect ofleptin*adiponectin, while adiponectin has no association with glucose, which is also supported by [23]. The variance of glucose level (VGLUCL) is positively associated with HOMA-IR (p<0.0001) and resistin (p=0.0218), concluding that it rises as HOMA-IR, or resistin increases. It implies that glucose variance level is higher for women with higher HOMA-IR, or resistin level, and these women have higher BC risk. VGLUCL is negatively associated with leptin (p<0.0001), MCP-1 (p=0.0115), age*HOMA-IR (p=0.0310), age*resistin (p=0.0397), HOMA-IR*insulin (p=0.0002), implying that it rises as leptin, or MCP-1, or age*HOMA-IR, or age*resistin, or HOMA-IR*insulin decreases.

From 2, fitted mean insulin level (MINSUL) is positively associated with HOM-IR (p<0.0001), leptin (p=0.0009), age*MCP-1 (p=0.0909), glucose*adiponectin (p=0.0424), glucose*resistin (p<0.0001), HOMA-IR*MCP-1 (p<0.0001) implying that it increases as HOMA-IR, or leptin, or age*MCP-1, or glucose*adiponectin, or glucose*resistin, or HOMA-IR*MCP-1increases. Note that MINSUL is negatively associated with age (p=0.1039) and MCP-1 (p=0.0264), while their interaction effect age*MCP-1 is positively associated with it. Similarly, MINSUL is negatively associated with glucose (p=0.0665), adiponectin (p=0.0783), and resistin (p<0.0001), while their two-factor interaction effects glucose*adiponectin (p=0.0424) and glucose*resistin (p<0.0001) are positively associated with it. On the other hand, MINSUL is positively associated with HOM-IR (p<0.0001), and it is negatively associated with MCP-1 (p=0.0264), but their interaction effect HOMA-IR*MCP-1 (p<0.0001) is positively associated with it. Also, MINSUL is positively associated with HOM-IR (p<0.0001), leptin (p=0.0009), and it is negatively associated with glucose (p=0.0665), adiponectin (p=0.0783), but the interaction effects glucose*HOMA-IR (p<0.0001) and leptin*adiponectin (p=0.0713) are negatively associated with it. The variance of insulin level (VINSUL) is positively associated with TYOP (p=0.0003), concluding that it is higher for breast cancer women than normal. VINSUL is positively associated with MCP-1 (p=0.0014), HOMA-IR (p<0.0001), while it is negatively associated with leptin (p=0.0828) and glucose*MCP-1 (p=0.0003). So, it increases if MCP-1, or HOMA-IR level increases, or leptin level, or glucose*MCP-1 effect decreases. Note that VINSUL is positively associated with MCP-1 (p=0.0014) and it is insignificant of glucose (0.8077), while their interaction effect glucose*MCP-1 (p=0.0003) is negatively associated with it.

On the other hand, MCP-1 model shows that mean MCP-1 is negatively associated with insulin (p<0.0001), while it is positively associated with insulin*leptin (p<0.0001). Also variance of MCP-1 is positively associated age*insulin (p=0.0008) and glucose*leptin (p=0.0388) [21]. Resistin model shows that mean resistin is negatively associated with glucose*adiponectin (p=0.1007), and it is positively associated with glucose (p=0.2808) [22]. The leptin model shows that mean leptin is positively associated with glucose (p=0.0135) and insulin (p=0.0557) [24]. The adiponectin model shows that it is insignificant of both insulin (p=0.3627) and glucose (p=0.7054) [23].

The above results are discussed herein from the six models of DM and BC markers of the same data set. Best of our knowledge there are very little models for DM and BC markers together in the existing medical literature. So, it is not possible to discuss herein more inter-relationships between DM and BC markers from the other more research articles. Best of our knowledge, the current report first focuses on the complex interlinked relationships between DM and BC markers with many interaction effects. Most of the present outcomes are completely new in medical literature, so the present results are little compared with the earlier published outcomes.

CONCLUSION

The inter-relationships between DM and BC markers are presented in the report based on probabilistic modeling, where models are selected based on the lowest AIC value, small standard error of the estimates, comparison of distributions of the response variable, and graphical diagnostic checking. The present associations between DM and BC markers, though not completely conclusive, are revealing. Research should have higher faith in these models as they have been accepted based on examining many statistical criteria. It is concluded herein that both DM and BC markers have very complex closely interlinked relationships. Medical practitioners can predict the DM and BC markers relationships from this report. In addition, it may remove many contradicting ideas regarding the relationships between DM and BC markers. Women with diabetes should care about breast cancer risk.

CONFLICT OF INTEREST

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

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