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Review Article

Associations between Body Mass Index and Breast Cancer Markers

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ABSTRACT

Body mass index (BMI) and breast cancer biomarkers such as resistin, leptin adiponectin, monocyte chemoattractant protein-1 (MCP-1) and homeostasis model assessment of insulin resistance (HOMA-IR) are highly associated with each other. The report has focused the inter-relationship between BMI and breast cancer biomarkers based on probabilistic modeling. It has been shown that mean BMI is positively associated with leptin (P<0.0001) and MCP-1 (P=0.0002), while it is negatively associated with adiponectin (P=0.0003), HOMA-IR (P<0.0001), and it is higher for healthy women (P=0.0116) than breast cancer women. In addition, variance of BMI is negatively associated with resistin (P=0.1450). On the other hand, mean MCP-1 is positively associated with BMI (P<0.0001). Mean resistin is positively associated with the interaction effect of BMI and leptin (BMI*Leptin) (P=0.0415), while its variance is positively associated with BMI (P=0.0942), and it is negatively associated with BMI*Adiponectin (P=0.1518). Leptin is positively associated with BMI (P<0.0001). Also adiponectin is negatively associated with BMI (P<0.0001), BMI*Leptin (P=0.1729), while it is positively associated with Age*BMI (P=0.0017) and BMI*Resistin (P=0.0615). It can be concluded that BMI and breast cancer biomarkers are strongly associated with each other. Care should be taken on BMI for breast cancer women.

Keywords: Adiponectin; Breast cancer biomarkers; BMI; Leptin; Resistin; Joint mean variance modeling

INTRODUCTION

BMI has been a fundamental psychosocial issue among human beings for millennia. It is a composite measure of height and weight, which is defined as BMI= Weight(kg) / Height(m^2). An individual fatness index is measured by BMI. It is considered as the risk factor for the growth of many diseases such as breast cancer, diabetes, cardiovascular diseases, etc. [1-5]. In general, BMI less than or equal to 25 kg/m^2 is treated as the normal, otherwise it is considered as obesity.

Excess weight has been associated with a variety of cancers such as postmenopausal breast, colon, renal, esophageal, endometrial etc. The International Research Agency on Cancer has predicted that BMI causes 9% of breast cancer, 25% of renal cancer, 11% of colon cancer, 39% of endometrial cancer, and 37% of esophageal cancer [6]. Calle *et al.* [7] pointed that BMI was associated with a greater risk of death from 14 cancers such as esophagus, liver, colon and rectum, gallbladder, kidney, pancreas, non-Hodgkin lymphoma, stomach, multiple myeloma, breast, prostate, cervix, uterus, and ovary, and it was predicted that BMI may account for 20% of all cancer deaths in women and 14% in men [7].

BMI is a well-known risk factor for postmenopausal breast cancer, whereas debatable outcomes have been presented in premenopausal women [8-10]. A large sample meta-analysis reported an inverse association between BMI and the chance of premenopausal breast cancer [11]. Recently, two large prevention data studies have shown that premenopausal women with higher BMI are at increased risk for growing breast cancer [12,13].

The associations between BMI and breast cancer are still contradictable [8,9,11,14-16]. These can be studied based on statistical modeling of BMI on the breast cancer biomarkers such as leptin, resistin, adiponectin and MCP-1, along with other explanatory variables. On the other hand, each breast cancer biomarker should be modeled on BMI along with other explanatory variables. The current report focuses the associations between BMI and breast cancer biomarkers based on modeling of BMI, MCP-1, adiponection, resistin, and leptin. For a data set given in [17, 18], these models have been studied in [19-23]. From these models, the associations between BMI and breast cancer biomarkers are reported in the current article.

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MATERIALS AND METHODS

Materials

The data set is available in the UCI Machine Learning Repository, and its detailed description is given in [17, 18]. For immediate using of the covariates in the report, these are restated as BMI (kg/m^2), Age, HOMA-IR, Insulin (μU/mL), Glucose (mg/dL), Adiponectin (μg/mL), Resistin (ng/mL), MCP-1, Leptin(ng/mL), Types of Patient (TYOP) (1=healthy controls; 2=patients).

Statistical methods

The considered data set given in [17, 18] is a multivariate data set. The interested responses are BMI, resistin, MCP-1, adiponectin, leptin which are all positive continuous heterogeneous and non-normally distributed. These 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 [24-26]. Both the JGLMs under the Log-normal and Gamma distributions are very shortly given in recent articles [22-23], which are not reproduced herein. For more discussions on JGLMs, readers can visit [24, 25].

Statistical and graphical analysis

For ready reference, first we examine BMI model on age, insulin, glucose, and breast cancer biomarkers. The detailed analysis is given by Das et al. [19]. It is mentioned herein that BMI and breast cancer biomarkers such as MCP-1, resistin, leptin and adiponectin can be modeled adopting JGLMs under both the Log-normal & Gamma distributions [24-26]. Log-normal JGLMs fit of BMI is better than the Gamma fit, which is presented in Table 1, and its fitting diagnostic is revealed in Figure 1. Figure 1 displays the absolute residuals plot against the predicted BMI values, which is closely a flat straight line, implying that variance is constant with the running means. Figure 2 represents the normal probability plot of the fitted BMI mean Log-normal model in Table 1. No lack of fit is identified in both the figures. So, Log-normal fitted BMI model is an approximate form of its true model. Fitted BMI mean & dispersion models are as follows (Table 1).

Fitted Log-normal BMI mean ($\hat{Z}$) model (from Table 1) is $\hat{Z}$ = Log(BMI)= 3.0370 – 0.0421 HOMA-IR + 0.0015 Glucose + 0.0123

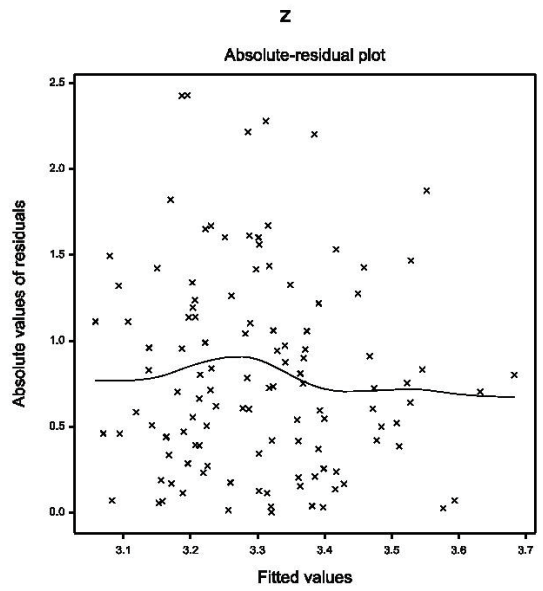

Figure 1: For the joint Log-normal BMI fitted models (Table 1), the (a) absolute residuals plot against the fitted values.

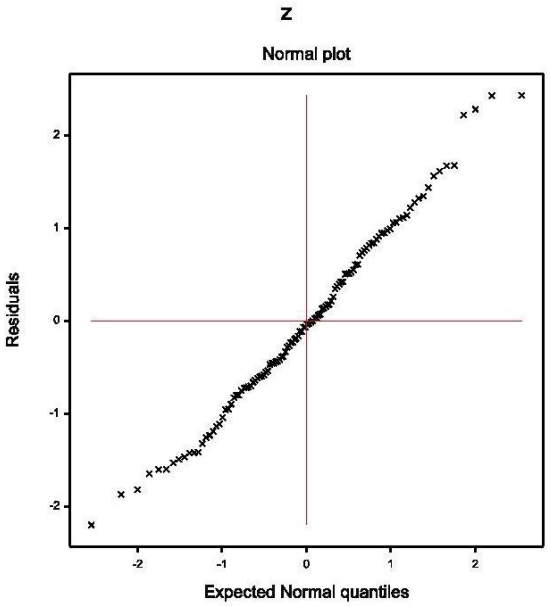

Figure 2: The normal probability plot for the mean BMI model.

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

Model	Covariates	Log-normal				Gamma			
		Estimate	s.e.	t-value	P-Value	Estimate	s.e.	t-value	P-Value
Mean	Constant	3.0370	0.08363	36.3122	<0.0001	3.0460	0.08367	36.4013	<0.0001
	Glucose (x3)	0.0015	0.00084	1.7961	0.0753	0.0016	0.00085	1.8502	0.0670
	Insulin (x4)	0.0123	0.00318	3.8502	0.0002	0.0121	0.00318	3.8281	0.0002
	HOMA-IR (x5)	-0.0421	0.01033	-4.0823	<0.0001	-0.0421	0.01019	-4.1333	<0.0001
	Leptin (x6)	0.0053	0.00063	8.2341	<0.0001	0.0052	0.00065	8.0953	<0.0001
	Adiponectin (x7)	-0.0068	0.00184	-3.7363	0.0003	-0.0068	0.00186	-3.6552	0.0004
	MCP-1 (x9)	0.0001	0.00005	3.8724	0.0002	0.0001	0.00006	3.7272	0.0003
	Patient's typ (Fx10)	-0.0708	0.02758	-2.5681	0.0116	-0.0699	0.02768	-2.5241	0.0130
Dispersion	Constant	-4.445	0.7261	-6.1224	<0.0001	-4.358	0.7167	-6.0821	<0.0001
	Age (x1)	0.015	0.0107	1.3652	0.1751	0.013	0.0108	1.2652	0.2085
	Resistin (x8)	-0.019	0.0132	-1.4683	0.1450	-0.020	0.0134	-1.5082	0.1344
	Insulin (x4)	-0.018	0.0156	-1.1784	0.2413	-0.019	0.0157	-1.2233	0.2239
		AIC= 613.9				AIC=615.062			

Insulin - 0.0068 Adiponectin + 0.0001 MCP-1 + 0.0053 Leptin – 0.0708 TYOP, and the BMI fitted Log-normal variance ($\hat{\sigma}^2$) model is $\hat{\sigma}^2$ = exp. (-4.445 - 0.018 Insulin – 0.019 Resistin + 0.015Age).

Breast cancer biomarker MCP-1 analysis is given by Kim et al. [20], and for ready reference it is reproduced in Table 2. Fitted MCP-1 mean & dispersion models are as follows.

MCP-1Gamma fitted mean ($\hat{\mu}$) model (from Table 2) is $\hat{\mu}$ = exp(5.1791 – 0.0265 Insulin + 0.0455 BMI – 0.0192 Leptin + 0.0220 Resistin + 0.0009 Insulin*Leptin), and MCP-1Gamma fitted dispersion ($\hat{\sigma}^2$) model (from Table 2) is $\hat{\sigma}^2$ = exp(0.7374 – 0.0868 Insulin – 0.0293 Age + 0.0051 Age*Insulin + 0.0053 Glucose – 0.8286 HOMA-IR – 0.0997 Leptin – 0.0405 Resistin + 0.0007 Glucose*Leptin + 0.0010 Leptin*Resistin) (Table 2).

Breast cancer biomarker adiponectin analysis is given by Das and Lee [21], and for ready reference it is reproduced in Table 3. Fitted adiponectin mean & dispersion models are as follows.

Adiponectin Gamma fitted mean ($\hat{\mu}$) model (from Table 3) is $\hat{\mu}$ = exp(6.7778 - 0.1475 BMI - 0.0617 Age + 0.0020 Age*BMI - 0.0662 Resistin + 0.0282 Leptin + 0.0018 BMI*Resistin – 0.0008 BMI*Leptin), and Adiponectin Gamma fitted variance ($\hat{\sigma}^2$) model (from Table 3) is $\hat{\sigma}^2$ = exp(-2.318 + 0.017Age). Breast cancer biomarker resistin analysis is given by Das and Lee [22], and for ready reference it is reproduced in Table 4. Fitted resistin mean & dispersion models are as follows.

Resistin Gamma fitted mean ($\hat{\mu}$) model (from Table 4) is $\hat{\mu}$ = exp(1.6651 – 0.0306 Leptin - 0.0052 Age + 0.0888 Adiponectin + 0.5421 TYOP – 0.1087 HOMA-IR+ 0.0007 MCP-1 + 0.0015 Age*HOMA-IR - 0.0028 BMI + 0.0068 Glucose + 0.0014 BMI*Leptin - 0.0010 Glucose*Adiponectin - 0.0009 Leptin*Adiponectin), and Resistin Gamma fitted variance ($\hat{\sigma}^2$) model (from Table 4) is $\hat{\sigma}^2$ = exp(-4.8464 + 0.7971 TYOP + 0.1090 BMI + 0.0129 Leptin + 0.1885 Adiponectin – 0.0083 BMI*Adiponectin).

Breast cancer biomarker leptin analysis is given by Das and Lee [23], and for ready reference it is reproduced in Table 5. Fitted leptin mean & dispersion models are as follows.

Leptin Gamma fitted mean ($\hat{\mu}$) model (from Table 5) is $\hat{\mu}$ = exp(-0.227 + 0.092 BMI + 0.006 Glucose + 0.010 Insulin + 0.025 Adiponectin + 0.016 Resistin – 0.001 MCP.1 – 0.001

Table 2: Results for mean & dispersion models for MCP-1 from Log-Normal and Gamma fit.

Model	Covariate	Gamma Model				Log-normal Model			
		estimate	s.e.	t-value	P-value	Estimate	s.e.	t-value	P-value
Mean	Constant	5.1791	0..27784	18.641	<0.0001	4.9439	0.28594	17.290	<0.0001
Model	BMI (x2)	0.0455	0.01066	4.265	<0.0001	0.0465	0.01101	4.226	<0.0001
	Insulin (x4)	-0.0265	0.00449	-5.900	<0.0001	-0.0225	0.00494	-4.566	<0.0001
	Leptin (x6)	-0.0192	0.00336	-5.730	<0.0001	-0.0174	0.00345	-5.038	<0.0001
	Insulin *Leptin	0.0009	0.00017	5.458	<0.0001	0.0009	0.00018	4.846	<0.0001
	Resistin (x8)	0.0220	0.00348	6.327	<0.0001	0.0239	0.00345	6.923	<0.0001
Dispersion	Constant	0.7374	1.5228	0.484	0.6293	1.0110	1.5513	0.652	0.5158
Model	Age (x1)	-0.0293	0.0161	-1.826	0.0706	-0.0328	0.0156	-2.097	0.0383
	Insulin (x4)	-0.0868	0.0733	-1.184	0.2390	-0.0613	0.0720	-0.851	0.3966
	Age* Insulin	0.0051	0.0016	3.098	0.0025	0.0054	0.0015	3.488	0.0008
	HOMA-IR (x5)	-0.8286	0.2928	-2.830	0.0055	-0.9607	0.2825	-3.400	0.0009
	Glucose (x3)	0.0053	0.0144	0.371	0.7113	0.0069	0.0143	0.483	0.6300
	Leptin (x6)	-0.0997	0.0421	-2.365	0.0198	-0.1177	0.0416	-2.826	0.0056
	Glucose* Leptin	0.0007	0.0004	1.756	0.0819	0.0008	0.0004	2.091	0.0388
	Resistin (x8)	-0.0405	0.0227	-1.781	0.0777	-0.0524	0.0224	-2.332	0.0215
	Leptin*Resistin	0.0010	0.0004	2.411	0.0176	0.0013	0.0004	3.114	0.0024
		AIC=1572.816				AIC=1575			

Table 3: Results for mean and dispersion models for Adiponectin from Log-Normal and Gamma fit.

Model	Covariate	Log-normal fit				Gamma fit			
		Estimate	S.E.	t-value	P-value	Estimate	S.E.	t-value	P-value
Mean	Constant	6.8667	1.0012	6.858	<0.0001	6.7778	0.9853	6.879	<0.0001
	Age (x1)	-0.0627	0.0178	-3.525	0.0006	-0.0617	0.0174	-3.550	0.0006
	BMI (x2)	-0.1512	0.0367	-4.122	<0.0001	-0.1475	0.0361	-4.087	<0.0001
	AGE*BMI	0.0020	0.0006	3.067	0.0027	0.0020	0.0006	3.214	0.0017
	Leptin (x6)	0.0217	0.0184	1.179	0.2409	0.0282	0.0180	1.566	0.1202
	Resistin (x8)	-0.0701	0.0296	-2.371	0..0195	-0.0662	0.0289	-2.293	0.0237
	BMI*Resistin	0.0020	0.0010	2.003	0.0476	0.0018	0.0010	1.886	0.0615
	BMI*Leptin	-0.0006	0.0006	-0.976	0.3312	-0.0008	0.0006	-1.372	0.1729
Dispersion	Constant	-2.325	0.6674	-3.483	0.0007	-2.318	0.6595	-3.515	0.0006
	Age (x1)	0.019	0.0114	1.690	0.0939	0.017	0.0112	1.553	0.1233
AIC				**673.8**				**673.368**	

Table 4: Results for mean & dispersion models for Resistin from Log-Normal and Gamma fit.

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 (x1)	-0.0052	0.0033	-1.547	0.1249	-0.0063	0.00345	-1.817	0.0721
	Leptin (x6)	-0.0306	0.0226	-1.352	0.1793	-0.0256	0.02334	-1.097	0.2751
	Adiponectin (x8)	0.0888	0.0553	1.607	0.1111	0.0483	0.05623	0.860	0.3917
	MCP-1 (x9)	0.0007	0.0001	4.402	<0.0001	0.0007	0.00015	4.253	<0.0001
	Patient's typ (Fx10)	0.5421	0.1084	4.999	<0.0001	0.4341	0.11120	3.904	0.0001
	HOMA-IR (x5)	-0.1087	0.0593	-1.832	0.0698	-0.1026	0.06124	-1.675	0.0969
	Age*HOMA-IR	0.0015	0.0009	1.631	0.1059	0.0016	0.00096	1.637	0.1046
	BMI (x2)	-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 (x3)	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
Disper-sion	Constant	-4.8464	1.7259	-2.808	0.0059	-4.6565	1.8505	-2.516	0.0134
	Leptin (x6)	0.0129	0.0091	1.427	0.1566	0.0124	0.0088	1.412	0.1609
	Patient's typ (Fx10)	0.7971	0.3097	2.574	0.0114	0.8184	0.3140	2.606	0.0105
	BMI (x2)	0.1090	0.0645	1.689	0.0942	0.1081	0.0690	1.567	0.1201
	Adiponectin (x7)	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			

Table 5: Associations of leptin with BMI, diabetes, age and breast cancer biomarkers.

Response	Associated with	Types of association	P-value
Leptin mean	BMI (x2)	Positive	<0.0001
	Glucose (x3)	Positive	0.0135
	Insulin (x4)	Positive	0.0557
	Adiponectin (x7)	Positive	0.0110
	Resistin (x8)	Positive	0.0073
	MCP-1(x9)	Negative	0.0330
	Adiponectin*Resistin	Negative	0.0966
Leptin variance	Age (x1)	Positive	0.0034
	Resistin (x8)	Positive	0.0028
	Age*Resistin	Negative	0.0009

Adiponectin*Resistin), and Leptin Gamma fitted variance ($\hat{\sigma}^2$) model (from Table 5) is $\hat{\sigma}^2$ = exp(-3.809 + 0.042 Age + 0.153 Resistin – 0.003 Age*Resistin).

RESULTS

In Table 1, it is shown that mean BMI is positively associated with leptin (P<0.0001) and MCP-1 (P=0.0002), while it is negatively associated with adiponectin (P=0.0003), HOMA-IR (P<0.0001), and it is higher for healthy women (P=0.0116) than breast cancer women. In addition, variance of BMI is negatively associated with resistin (P=0.1450). On the other hand, from Table 2, mean MCP-1 is positively associated with BMI (P<0.0001). In Table 3, it is shown that mean adiponectin is negatively associated with BMI (P<0.0001), BMI*Leptin (P=0.1729), while it is positively associated with Age*BMI (P=0.0017) and BMI*Resistin (P=0.0615). From Table 4, it is noted that mean resistin is positively associated with BMI*Leptin (P=0.0415), while its variance is positively associated with BMI (P=0.0942), and it is negatively associated with BMI*Adiponectin (P=0.1518). In Table 5, it is shown that mean leptin is positively associated with BMI (P<0.0001).

DISCUSSION

The summarized analyses of BMI, MCP-1, adiponection, resistin and lepin are given in Tables 1-5. From Table 1, mean BMI is directly associated with leptin (P<0.0001), or MCP-1 (P=0.0002), concluding that it increases as leptin, or MCP-1 rises. In addition, it is inversely associated with adiponectin (P=0.0003), or HOMA-IR (P<0.0001), interpreting that it increases as adiponectin, or HOMA-IR decreases. Mean BMI is inversely associated with patient types (1=healthy women; 2= breast cancer patients) (P=0.0116), indicating that BMI is higher for healthy women than breast cancer women. Variance of BMI is partially inversely associated with resistin (P=0.1450), interpreting that BMI variance rises as resistin level decreases. Note that in epidemiology, partially significant effect is treated as confounder.

From Table 2, it is observed that MCP-1 is directly associated with BMI (P<0.0001), indicating that it increases as BMI increases. This is also observed from the BMI model as stated above. From Table 3, it is noted that mean adiponectin is inversely associated with BMI (P<0.0001), indicating that it decreases as BMI rises. This is also observed from BMI model. Mean adiponectin is directly associated with BMI*Resistin (P=0.0615), concluding that it rises as the interaction effect BMI*Resistin increases. In addition, mean adiponectin is inversely associated with BMI*Leptin (P=0.1729), indicating that it decreases as BMI*Leptin rises. Moreover, mean adiponectin is directly associated with Age*BMI (P=0.0017), concluding that it rises as the interaction effect Age*BMI increases. This implies that overweight women at older ages have higher level of adiponectin. From Table 4, mean resistin is directly associated

with the interaction effect of BMI*Leptin (P=0.0415), concluding that it rises as interaction effect of BMI*Leptin increases. Variance of resistin is directly associated with BMI (P=0.0942), interpreting that it increases as BMI increases. Variance of resistin is inversely associated with BMI*Adiponectin (P=0.1518), indicating that it rises as BMI*Adiponectin decreases. From Table 5, mean leptin is directly associated with BMI (P<0.0001), indicating that it rises as BMI rises. This is also observed in BMI model. All the above summarized associations between BMI and breast cancer biomarkers are displayed in Table 6.

Table 6: Associations between BMI & breast cancer biomarkers.

Model	Response	Associated with	Association types	P-vale
Mean	BMI (x2)	Leptin (x6)	Positive	<0.0001
		Adiponectin (x7)	Negative	0.0003
		MAC-1 (x9)	Positive	0.0002
		HOMA-IR (x5)	Negative	<0.0001
		Patient's type (Fx10)	Negative	0.0116
Dispersion		Resistin (x8)	Negative	0.1450
Mean	MCP-1(x9)	BMI (x2)	Positive	<0.0001
Mean	Resistin (x8)	BMI*Leptin	Positive	0.0415
Dispersion		BMI (x2)	Positive	0.0942
		BMI*Adiponectin	Negative	0.1518
Mean	Leptin (x6)	BMI (x2)	Positive	<0.0001
Mean	Adiponectin (x7)	BMI (x2)	Negative	<0.0001
		Age*BMI	Positive	0.0017
		BMI*Resistin	Positive	0.0615
		BMI*Leptin	Negative	0.1729

The present derived associations between BMI and breast cancer biomarkers are little compared with the previous findings as the earlier research articles have not considered all these BC biomarkers along with BMI. In addition, the earlier articles have not considered probabilistic joint modeling to derive these associations. All these reported results herein are only based on the articles [19-23].

CONCLUSIONS

The report examines the associations between BMI and breast cancer biomarkers such as MCP-1, leptin, adiponection and resistin. These associations are reported herein considering the models of BMI and each breast cancer biomarkers. From these models, it can be concluded that BMI and breast cancer biomarkers are associated in both mean and variance models. BMI increases as leptin, or MCP-1 increases, or adiponection, or resistin, or HOMA-IR decreases. Many interaction effects such as BMI*Leptin and BMI*Adiponectin are associated with resistin, while BMI*Resistin, BMI*Leptin and Age*BMI are associated with adiponectin. The report gives clear associations between BMI and breast cancer biomarkers which are very helpful to the researchers and medical practitioners. Medical practitioners and women should care on BMI along with breast cancer biomarkers.

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

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