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Associations between Body Mass Index and Breast Cancer Markers

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ABSTRACT

Body mass index (BMI) and breast cancer biomarkers (BCBs) 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 BCBs based on probabilistic modeling. It has been shown that mean BMI is directly associated with leptin (P<0.0001) and MCP-1 (P=0.0002), while it is inversely 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 inversely associated with resistin (P=0.1450). On the other hand, mean MCP-1 is directly associated with BMI (P<0.0001). Mean resistin is directly associated with the interaction effect of BMI and leptin (BMI*Leptin) (P=0.0415), while its variance is directly associated with BMI (P=0.0942), and it is inversely associated with BMI*Adiponectin (P=0.1518). Leptin is directly associated with BMI (P<0.0001). Also adiponectin is inversely associated with BMI (P=0.0001), BMI*Leptin (P=0.0415), while its variance is directly associated with BMI (P=0.0942), and it is inversely associated with BMI*Adiponectin (P=0.1518). Leptin is directly associated with BMI (P=0.0001). Also adiponectin is inversely associated with BMI (P=0.0001), BMI*Leptin (P=0.1729), while it is directly associated with Age*BMI (P=0.0017) and BMI*Resistin (P=0.0615). It can be concluded that BMI and BCBs are strongly associated with each other. Care should be taken on BMI for breast cancer women.

1. 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(m²). 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/m² 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 relationships between BMI and BCBs are still contradictable [8,9,11,14-16]. These can be studied based on statistical modeling of BMI on the BCBs such as leptin, resistin, adiponectin and MCP-1 and other explanatory variables. Again, each BCB should be modeled on BMI and other explanatory variables. The current report focuses the associations between BMI and BCBs based on modeling of BMI, MCP-1, adiponectin, resistin, and leptin. For a data set given in [17,18], these models have been studied in [19-23]. From these models, the relationships between BMI and BCBs are reported in the current article.

2. Materials and Methods

2.1 Materials

The data set can be found 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).

2.2 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].

2.3 Statistical and Graphical Analysis

For ready reference, first we examine BMI model on age, insulin, glucose, and BCBs. The detailed analysis is given by Das et al. [19]. It is mentioned herein that BMI and BCBs 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(a) 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 1(b) 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 (Table 1) is an approximate form of its true model. Fitted BMI mean & dispersion models are as follows:

Fitted Log-normal BMI mean (\(\hat{Z}\)) model (from Table 1) is

\[
\hat{Z} = \log(\text{BMI}) = 3.0370 - 0.0421 \text{HOMA-IR} + 0.0015 \text{Glucose} + 0.0123 \text{Insulin} - 0.0068 \text{Adiponectin} + 0.0001 \text{MCP-1} + 0.0053 \text{Leptin} - 0.0708 \text{TYOP},
\]

and the BMI fitted Log-normal variance (\(\hat{\sigma}^2\)) model is

\[
\hat{\sigma}^2 = \exp(-4.445 - 0.018 \text{Insulin} - 0.019 \text{Resistin} + 0.015 \text{Age}).
\]
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-1 Gamma fitted mean ($\hat{\mu}$) model (from Table 2) is

$$\hat{\mu} = \exp(5.1791 - 0.0265 \text{Insulin} + 0.0455 \text{BMI} - 0.0192 \text{Leptin} + 0.0009 \text{Insulin} \times \text{Leptin})$$

and MCP-1 Gamma fitted dispersion ($\hat{\sigma^2}$) model (from Table 2) is

$$\hat{\sigma^2} = \exp(0.7374 - 0.0868 \text{Insulin} - 0.0293 \text{Age} + 0.0553 \text{Glucose} - 0.0997 \text{Leptin} - 0.0405 \text{Resistin} + 0.0007 \text{Glucose} \times \text{Leptin} + 0.0010 \text{Leptin} \times \text{Resistin})$$

### 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  | 0.000843 | 1.7961 | 0.0753 | 0.0016 | 0.00085 | 1.8502 | 0.0670 |
|          | Insulin (x4)   | 0.0123  | 0.00338 | 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 | 0.001843 | -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  | -1.1764 | 0.2413 | -0.019 | 0.0157 | -1.2233 | 0.2239 |

AIC= 613.9 AIC=615.062

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

$$\hat{\mu} = \exp(6.7778 - 0.1475 \text{BMI} - 0.0617 \text{Age} + 0.0020 \text{Age} \times \text{BMI} - 0.0662 \text{Resistin} + 0.0282 \text{Leptin} + 0.0018 \text{BMI} \times \text{Resistin} - 0.0008 \text{BMI} \times \text{Leptin})$$

and Adiponectin Gamma fitted variance ($\hat{\sigma^2}$) model (from Table 3) is

$$\hat{\sigma^2} = \exp(-2.318 + 0.017 \text{Age})$$
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  |

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 (µ̂) model (from Table 4) is
\[ \hat{\mu} = \exp(1.6651 - 0.0306 \text{Leptin} - 0.0052 \text{Age} + 0.0888 \text{Adiponectin} + 0.5421 \text{TYOP} + 0.1087 \text{HOMA-IR} + 0.0007 \text{MCP-1} + 0.0015 \text{Age} \times \text{HOMA-IR} - 0.0028 \text{BMI}) + 0.0068 \text{Glucose} + 0.0014 \text{BMI} \times \text{Leptin} - 0.0010 \text{Glucose} \times \text{Adiponectin} - 0.0009 \text{Leptin} \times \text{Adiponectin}) \]

and Resistin Gamma fitted variance (σ̂²) model (from Table 4) is
\[ \hat{\sigma}^2 = \exp(-4.8464 + 0.7971 \text{TYOP} + 0.1090 \text{BMI} + 0.0129 \text{Leptin} + 0.1885 \text{Adiponectin} - 0.0083 \text{BMI} \times \text{Adiponectin}) \]

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     | 2.165   | 0.0377  | 2.0242    | 0.81494    | 2.484   | 0.0146  |
|       | Age (x1)   | -0.0052   | 0.0033     | -1.547  | 0.1249  | -0.0663   | 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  |
| Dispersion | 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    | 0.00888    | 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
3. Results

In Table 1, it is shown that mean BMI is directly associated with leptin (P<0.0001) and MCP-1 (P=0.0002), while it is inversely 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 inversely associated with resistin (P=0.1450). On the other hand, from Table 2, mean MCP-1 is directly associated with BMI (P<0.0001). In Table 3, it is shown that mean adiponectin is inversely associated with BMI (P<0.0001), BMI*Leptin (P=0.1729), while it is directly associated with Age*BMI (P=0.0017) and BMI*Resistin (P=0.0615). From Table 4, it is noted that mean resistin is directly associated with BMI*Leptin (P=0.0415), while its variance is directly associated with BMI (P=0.0942), and it is inversely associated with BMI*Adiponectin (P=0.1518). In Table 5, it is shown that mean leptin is directly associated with BMI (P<0.0001).

4. Discussion

The summarized analyses of BMI, MCP-1, adiponectin, 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 (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. It is noted that partially significant effect is treated as confounder in epidemiology.

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 of 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 in-
creases 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 BCBs are displayed in Table 6.

**Table 6. Associations between BMI & breast cancer biomarkers**

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

The present derived associations between BMI and BCBs are little compared with the previous findings as the earlier research articles have not considered all these BCBs 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].

**5. Conclusions**

The report examines the associations between BMI and BCBs such as MCP-1, leptin, adiponectin and resistin. These associations are reported herein considering the models of BMI and each BCB. From these models, it can be concluded that BMI and BCBs are associated in both mean and variance models. BMI increases as leptin, or MCP-1 increases, or adiponectin, 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 adiponecctin. The report gives clear associations between BMI and BCBs 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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