2015

Association between HOMA-IR and cancer

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Abstract

Background: Type 2 diabetes which has insulin resistance as a major risk factor among other non-communicable diseases is a major public health concern with increased significance and prevalence worldwide. Cancer on the other hand was a leading cause of death worldwide in 2008 based on data from the WHO and also 3rd leading cause of death in Malaysia ministry of health hospitals. Studies have found links between carcinogenesis and insulin resistance which has been attributed to hyperinsulinemia. However, studies on the South-east Asian/ Malaysia population are largely absent. Insulin sensitivity is known to differ across different ethnicities with South-east Asians and Asian Indians least insulin sensitive. The aim of this study was to determine the association between cancer and Insulin resistance (IR) regardless of the aforementioned trait. Design: Case-control study. Method: Fasting insulin and glucose concentrations (which were used to derive the Homeostasis model assessment insulin resistant HOMA-IR) were determined in 100 respondent of which 45 were cancer patients and 55 in the control group. Data on demographics, anthropometrics, lifestyle and physical activity level and metabolic parameters were also determined in all respondents. Independent sample t-test was used to check for association between cancer and HOMA-IR and logistic regression was used to control for other co-factors. Results: From the results, there was significant difference between the mean HOMA-IR of the cancer group (3.00 ±1.52) compared to that of the controls (2.07 ±0.69) with a p-value of 0.001. Insulin Resistance was also independently associated with cancer (adjusted OR= 12.25. 95%CI = 3.20- 46.83) There was also significant association between obesity and cancer (adjusted OR = 3.33, 95% CI = 1.08 – 10.31). Conclusion: Even though there were some justifiable discrepancies, significant association was seen between cancer and HOMA-IR in this Malaysian population. These results are in line with previous studies which check for association in select cancers.

Keywords

between, homa-ir, association, cancer

Publication Details

Igwe, E., Azman, A. Z. F., Nordin, A. J. & Mohtarrudin, N. (2015). Association between HOMA-IR and cancer. International Journal of Public Health and Clinical Sciences, 2 (2), 21-34.

IJPHCS
Open Access: e-Journal

International Journal of Public Health and Clinical Sciences
e-ISSN : 2289-7577. Vol.2:No. 2
March/April 2015

ASSOCIATION BETWEEN HOMA-IR AND CANCER IN A MEDICAL CENTRE IN SELANGOR, MALAYSIA

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ABSTRACT

Background: Type 2 diabetes which has insulin resistance as a major risk factor among other non-communicable diseases is a major public health concern with increased significance and prevalence worldwide. Cancer on the other hand was a leading cause of death worldwide in 2008 based on data from the WHO and also 3rd leading cause of death in Malaysia ministry of health hospitals. Studies have found links between carcinogenesis and insulin resistance which has been attributed to hyperinsulinemia. However, studies on the South-east Asian/ Malaysia population are largely absent. Insulin sensitivity is known to differ across different ethnicities with South-east Asians and Asian Indians least insulin sensitive. The aim of this study was to determine the association between cancer and Insulin resistance (IR) regardless of the aforementioned trait.

Design: Case-control study.

Method: Fasting insulin and glucose concentrations (which were used to derive the Homeostasis model assessment insulin resistant HOMA-IR) were determined in 100 respondent of which 45 were cancer patients and 55 in the control group. Data on demographics, anthropometrics, lifestyle and physical activity level and metabolic parameters were also determined in all respondents. Independent sample t-test was used to check for association between cancer and HOMA-IR and logistic regression was used to control for other co-factors.

Results: From the results, there was significant difference between the mean HOMA-IR of the cancer group (3.00 ±1.52) compared to that of the controls (2.07 ±0.69) with a p-value of 0.001. Insulin Resistance was also independently associated with cancer (adjusted OR= 12.25. 95%CI = 3.20- 46.83) There was also significant association between obesity and cancer (adjusted OR = 3.33, 95% CI = 1.08 – 10.31).

Conclusion: Even though there were some justifiable discrepancies, significant association was seen between cancer and HOMA-IR in this Malaysian population. These results are in line with previous studies which check for association in select cancers.

Keywords: Cancer, Insulin Resistance, HOMA-IR, Non-diabetic, Malaysia, Epidemiology.

International Journal of Public Health and Clinical Sciences
e-ISSN : 2289-7577. Vol.2:No. 2
March/April 2015

1.0 Introduction

The worldwide public health burden of cancer has become tremendous. In 2008, it was the most common cause of death worldwide (WHO, 2011) and the 3rd most common cause of death in Malaysia Ministry of Health hospitals in 2007. In Malaysia, there has been a noticable increase in cancer incidence. In the 2006 report of the National cancer registry, the incidence of the 3 most common cancers were; Breast (16.5%), colorectal (13.2%) and lung (9.4%), a year later in 2007, an increase was noticeable in some of these values. The 2007 report of the NCR had Breast cancer incidence at 18.0%, Colorectal at 12.3% and Trachea, Bronchus, Lung at 10.2% (Ariffin & Saleha, 2007).

Even though cancer is a multifactorial disease caused by external factors (tobacco, chemicals, radiation, and infectious organisms) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism), one of the persistent characteristic of cancer cells is its ability to multiply uncontrollably and reject programmed death (Levin et. al., 2004, Darbre, 2011, Narayanan et. al., 2010, Rook & Dalgleish, 2011, Roberts et. al., 2012, Baglietto et. al., 2010, Grivennikov et. al., 2010, Dang, 2012)

The exact role of insulin resistance (IR) in the development as well as progression of cancer has yet to be well established. In humans, insulin functions to balance carbohydrate, protein and lipid metabolism. In the digestion of carbohydrate, insulin regulates glucose stable equilibrium and promotes glucose usage. A defect in this process causes pancreatic β cells to increase insulin production which leads to a state of chronic hyperinsulinemia which is insulin resistance (Gungor et. al., 2005).

Insulin resistance is known to inhibit the production of insulin-like growth factor-1 binding proteins thereby increasing the level of circulating free IGF-1 in the blood (Harish et. al., 2007). The action of insulin as a mitogen on both normal and malignant tissue via the IGF1 system is considered the most plausible mechanism linking insulin resistance to cancer. A number of studies have attributed the association between insulin resistance and cancer to this (LeRoith & Roberts Jr, 2003, Abbasi et. al., 2010, Albanes et. al., 2009, Goodwin et. al., 2009, Garmendia et. al. 2007). However, most of these findings are taken from the western population. To the best of our knowledge, there are only a few published reports on this association in the Asian population (Sato et. al., 2011, Shebl et. al., 2011, Zhang et. al., 2010) and none in the South-east Asian/Malaysian population.

Although the prevalence of IR in Malaysia is unknown, the progressive increase in Type 2 Diabetes Milletus (TTDM) suggests that similar trend maybe occurring insidiously (NHMS II, 2008). Asians especially South-east Asians and Asian Indians have been shown to be much more prone to insulin resistance (leading up to Type 2 diabetes) compared to Caucasians even with relatively little weight gain and much lower BMI (Dickson et. al., 2002). Thus, it is pertinent to also determine the presence of this association in South-east Asians (Malaysians) as it could elucidate further on the aetiology of common cancers and also offer more insights on the prevention and management.

The aim of this case-control study is to assess the association between IR and cancer in this Malaysian population and to determine whether this association is affected other known co-factors (obesity, lipoproteins, and physical inactivity, hypertension and lifestyle behaviours) of insulin resistance.

International Journal of Public Health and Clinical Sciences
e-ISSN : 2289-7577. Vol.2:No. 2
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2.0 Materials and Methods

2.1 Study Location and Study Subjects

This case- control study was conducted in the in a government medical institution in the state of Selangor. Both centres are located next to each other and receive patients from the central region of Malaysia, the Klang Valley. As of 2012, the Klang valley is home roughly to about 7.5million people.

Cases were newly diagnosed cancer patients who came in for imaging scan and histologically confirmed cancer patients in the surgical ward of the institution. Non-cancer patients with no recent history of malignancy were included as controls. Both cases and controls were diabetes free. The respondents were age (±5 years) and sex-matched and they were consecutively recruited.

Using mean and standard from a previous similar study (Garcia et. al. 2005), a sample size of 80 was calculated using the formula for case-control studies by Lehr (1992) for analysis by independent t-test to find a minimum difference between the mean HOMA-IR of the cancer and control group. However, the final recruitment of subjects was 45 cases and 55 controls (100). Alpha was set at 0.05

2.2 Ethical Considerartions

This study was approved by the Medical Research Ethics Committee, Faculty of Medical and Health Sciences, University Putra Malaysia and the Ministry of Health Medical Research Ethics Committee.

All patients were informed that joining in the study was voluntary, anonymous and confidential. An information sheet was provided to respondents concerning the purpose of the study, how information would be processed, stored and used. Contact information was also provided for any questions that could arise about the study.

2.3 Data Collection

2.3.1 Questionnaire and physical measurement

A self – developed questionnaire was used to gather information on the demographics and socioeconomic status, smoking status, alcohol consumption, and family history diabetes of the responders.

The short International Physical Activity Questionnaire (IPAQ) was used to collect information on activity levels.
Obesity defined by BMI of equal 30kg/m^2 and over was calculated using weight and height values determined using the SECA electronic weighting and measuring station.

Blood pressure was measured using a Mec 1000 portable multi parameter patient monitor. Hypertension was defined as a systolic blood pressure of >140mmHg and/or >90mmHg. Waist and hip circumference was measured using a simple measuring tape. A total of 5ml of

fasting blood samples was collected from each subject and put in heparin tubes for analysis on fasting insulin levels and sodium fluoride tubes for analysis on fasting glucose, triglycerides, cholesterol, LDL-cholesterol, HDL- cholesterol levels.

After the blood collection, the samples were taken to the pathology laboratory of the Faculty of medicine and health sciences, University Putra Malaysia. There, the blood samples were centrifuged for 10minutes at the speed of 35000rpm. Following centrifugation, a pipette was used to collect the blood serum and put in and put in Eppendorf tubes for preservation. The samples were preserved in the low temperature freezer which is maintained at a temperature of -70°c. The blood remnant was put in specific waste bins in the laboratory for autoclave and disposal.

Insulin and glucose levels were treated as continuous variables. Glucose levels over 100 mg/dL were considered elevated. IR was measured by the Homeostasis Model Assessment Index (HOMA) and defined as 2.79 or more as values above the 75th percentile (Eslam et. al., 2011).

2.3.2 Biochemical analysis

All laboratory assays was carried out using Cobas® c systems supplied by Roche Diagnostics, Indianapolis, IN.
Fasting glucose was determined using enzymatic reference method with hexokinase.
Mercodia Insulin Elisa immunoassay was used to determine insulin levels and the Rate method and a single point calibration and enzymatic colorimetric method were used to determine the HDL-cholesterol and triglyceride respectively.

2.3.3 Data analysis

- **Descriptive Statistics**

Normal distribution of the continuous variables was accessed using the Kolmogorov-Smirnov test, normal Q-Q plots and histogram which showed that data was normally distributed. The dependent variable was confirmed cancer cases (from histology or imaging.) In the analysis, cases were coded as 1 and controls as 0. While the independent variables were;

HOMA-IR as the main exposure variable of interest and; Obesity, Hypertension, Lipids level, Cholesterol levels, Lifestyle (smoking habit and alcohol intake) and Physical inactivity as the co factors.

- **Bivariate Analysis**

For the continuous variables which included; HOMA-IR, SBP, DBP, Lipids and cholesterol levels, BMI, waist-hip ratio, glucose and insulin levels, comparison was made between CANCER and NON-CANCER groups using independent sample t-test.

The categorical variables which included; HOMA-IR treated as a categorical variable with values higher than 2.79 described as insulin resistant, gender, ethnicity, marital status, education level, smoking and alcohol use, physical activity, history of diabetes, obesity which was defined as BMI equal or greater than 30, hypertension and monthly family income; association was determined using Chi-square.

Some of the variables were recoded into different variables. Among them were;

- Glucose and insulin was used to calculate HOMA-IR
- Waist and hip circumference was recoded to waist-hip ratio
- Height and weight which was recoded to BMI
- BMI was recoded to obese status

2.3.4 Multivariable Analysis

Logistic regression was used to control for other covariates. The crude and adjusted odds ratio of select variables and their corresponding 95% confidence interval (CI) were determined using binary logistic.

The forward LR method was used for the multivariate logistic regression. The underlying principle of the forward LR is basically to find out how all the independent variables collectively affect the dependent variable. This method initially runs the first model with only the constant ($ß_0$) thereafter it searches for predictor which has highest simple correlation with outcome variable and if this significantly improves model, it is retained it goes on to search for predictor which has second highest semi-partial correlation with the dependent variable and if this significantly improves model, it is also retained and it goes on like this. Since the independent variables varied in importance in regards to cancer association with HOMA-IR the most important, the forward LR method was the best option.

All statistical analysis was performed using IBM SPSS version 21.

3.0 Result

The demographics, socio-economic, lifestyle, anthropometric and lifestyle variables are shown in table 1 below.

No significant difference was noticed in the demographic and socio-economic characteristics between the cases and controls. There were more smokers in the control (20%) than the cases (2.2%; p value 0.02). This significant observation was not put in consideration as the smokers were in the control group. The majority of the ethnicity was Malay so alcohol intake was at minimal in this study.

Significant difference was observed in HOMA-IR which was used to define insulin resistance, the metabolic risk factors including Hypertension, triglycerides, Obesity.

In this study, the 45 cancer cases were made up of 16 colorectal cancers (35.56%), 6 breast cancers (13.33%), 5 neuroendocrine tumours (11.11%), 4 paragangliomas (8.89%), 4 stomach cancer (8.89%), 2 lung cancers (4.44%), 2 thyroid cancers (4.44%) and one each of pancreas, Hodgkin lymphoma, cerebral tumour, follicular lymphoma, melanoma and testicular cancer.

In the bivariate analysis, significance mean difference was observed in the HOMA-IR values of the cases vs the controls. Mean HOMA-IR was 3.00 ± 1.52 in cases and 2.07 ± 0.69 in controls; p value 0.001. When HOMA-IR was treated as a categorical variable with values

≥2.79 defined as insulin resistant (Kamath et. al., 2011), 46.7% of the cases and 7.3% of the controls were insulin resistant; p value <0.001.

In the logistic regression model (table 2), 4 variables were significant predictors of cancer. Presence of IR which was defined as a HOMA-IR value ≥ 2.79 was a major predictor in this study (adjusted OR = 12.25. 95% CI 3.20 – 46.83. p < 0.001). Also predictors were hypertension (adjusted OR = 5.03. 95% CI 1.76 – 14.42. p =0.003), obesity (adjusted OR = 3.33. 95% CI 1.08 – 10.31. p =0.037) and triglycerides (adjusted OR = 2.69. 95% CI 1.05 – 6.89. p =0.039). Below are the tabulated results.

Table 1: Characteristics of all respondents; cancer cases and controls

Variables	Case (n=45)		Control (n=55)		
	n	%	n	%	P
DEMOGRAPHICS					
Gender					
Males	27	60	37	67.3	0.451
Females	18	40	18	32.7	
Age(year, Mean & SD)	52.51	11.45	52.09	10.66	0.849
Ethnicity					0.012
Malay	30	66.7	50	90.9	
Chinese	12	26.7	3	5.5	
Indian	3	6.7	2	3.6	
Marital Status					0.033
Single	4	8.9	16	29.1	
Married	39	86.7	36	65.5	
Others(Divorced/Widowed)	2	4.4	3	5.4	
Religion					0.019
Islam	30	66.7	50	90.9	
Buddha	10	22.2	2	3.6	
Others	5	11.1	3	5.4	
Monthly Fam.Income (RM)					0.406
<2000	15	33.3	15	27.3	
2000-2999	3	6.7	2	3.6	
3000-3999	6	13.3	13	23.6	
4000-4999	9	20.0	6	10.9	
≥5000	12	26.7	19	34.5	
Level of Education					0.392
Primary	7	15.6	3	5.5	
Secondary	17	37.8	20	36.4	
Diploma	8	17.8	10	18.2	
Uni. Degree+	13	28.9	22	40.0	

International Journal of Public Health and Clinical Sciences
e-ISSN : 2289-7577. Vol.2:No. 2
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Fam. History of DM					0.822
Present	19	42.2	22	40	
Absent	22	57.8	33	60	
Alcohol Intake					0.957
Drinker	1	2.2	1	1.8	
Quit	3	6.7	3	5.5	
Non-Drinker	41	91.1	51	92.7	
Smoking Status					0.007
Smoker	1	2.2	11	20.0	
Quit	3	6.7	8	14.5	
Non-Smoker	41	91.1	36	65.5	
Physical Activity					<0.001
Low	30	66.7	19	34.5	
Moderate	15	33.3	15	27.3	
High	0	0	21	38.2	
ANTHROPOMETRICS					
BMI					
Mean(kg/m2) (mean & SD)	29.96	7.4	26.40	5.34	0.009
Obesity (BMI ≥ 30)	20.00	44.4	11.00	20.00	0.009
WHR					
Mean(inches) (mean & SD)	0.89	0.12	0.84	0.06	0.014
Obesity (WHR ≥ 0.90)	23	51.1	10	18.2	<0.001
METABOLIC VAR.					
SBP (mean & SD) mmHg	138	15.9	127	21.3	0.005
Hypertension (SBP ≥135)	33	73.3	17	30.9	<0.001
Cholesterol (mean & SD) mM	4.14	1.19	3.90	1.38	0.33
Triglycerides (mean & SD) mM	1.27	0.64	0.88	0.49	0.001
HDL-Cholesterol(mean & SD) mM	0.76	0.33	0.74	0.31	0.66
LDL-Cholesterol(mean & SD) mM	2.34	0.99	2.11	0.81	0.21
Glucose (mean & SD) mg/dl	105.39	44.69	78.49	19.67	<0.001
Glucose ≥ 100	20	44.40	5	9.1	<0.001
Insulin (mean & SD) pmol	11.33	1.98	10.62	2.59	0.12
HOMA-IR (mean & SD)	3.00	1.52	2.07	0.69	<0.001
HOMA ≥ 2.79	21	46.7	4	7.3	<0.001

International Journal of Public Health and Clinical Sciences
e-ISSN : 2289-7577. Vol.2:No. 2
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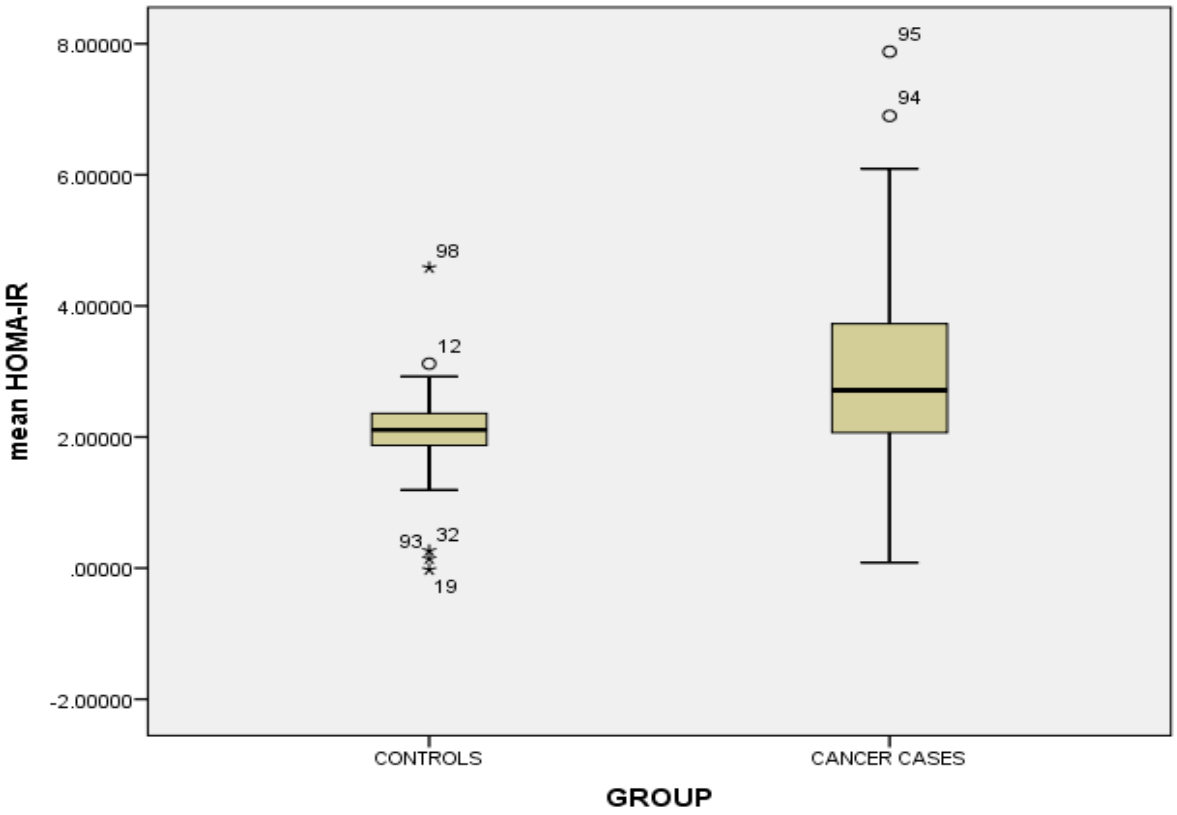

Figure 1: Mean HOMA-IR of cancer cases and controls

Multivariate Logistic Regression, Final Model Showing Adjusted Odds Ratio

Table 3: Adjusted ORs for IR, Hypertension, Obesity and Triglycerides

	B	S.E	p value	Adjusted OR	95% C.I	
					Lower	Upper
HOMA-IR	2.505	0.684	<0.001	12.247	3.203	46.832
Hypertension	1.616	0.537	0.003	5.032	1.756	14.423
Obesity	1.203	0.576	0.037	3.331	1.076	10.307
Triglyceride levels	0.989	0.480	0.039	2.690	1.050	6.888

4.0 Discussion

The major objective of this study which was to determine the association between HOMA-IR and cancer was significant. Even though South-East Asians have been known to be insulin resistant in the absence of IR risk factors, HOMA-IR was still increased in cancer patients compared to the control subjects. This is in line with previous studies (Capasso et. al., 2012, Oh et. al., 2011, Kang et. al., 2009, Loh et. al., 2010) carried out in various populations with reduced risk to be insulin resistant in the absence of the risk factors.

In this study, the effect of insulin resistance was rather strong and remained significant after adjusting for cofounders. In the logistic regression model, which showed adjusted odds ratios [ORs] and 95% confidence intervals [CIs] for HOMA-IR, there was an increased risk for cancer with higher HOMA-IR values (OR = 11.15, 95% CI: 3.45-36.1, P<0.001, model 1). Adjustment for hypertension slightly increased the strength of the association between HOMA-IR and cancer (OR = 12.27, 95% CI: 3.39-44.48, P<0.001, model2). When triglycerides was put into consideration, the magnitude of this association was slightly reduced but remained statistically significant (OR = 9.63, 95% CI: 2.66-34.91, P=0.001, model 3). In the fully adjusted model (table 4.9), which included HOMA-IR, hypertension, triglycerides and obesity, the strength of association between HOMA-IR and cancer was increased from the value in the 3rd model (OR = 12.25, 95% CI: 3.2-46.83, P<0.001, model 4). No significant interactions between HOMA-IR and obesity, hypertension or triglycerides were observed.

When triglyceride was included in the model, the association between HOMA-IR and cancer remained significant but there was infinitesimal reduction in the strength. This is a minor observation but the fact that insulin resistance and triglycerides are closely related could be a possible explanation. Kamath *et. al.*(2011) in their study inferred that liver triglyceride content was proportional to hepatic and peripheral IR.

Cancer has also been commonly associated with metabolic risk factors obesity and lifestyle behaviours. Research has been carried out over the years on the association between hypertension and cancer. Results from these studies have been controversial also. In a review (Grossman et. al., 2002), renal cell cancer was found to be mostly associated with hypertension but no definite association was found between hypertension and other cancer sites. Contrary to the above conclusion, a different study (Peeters et. al., 2000) supported the hypothesis that a positive link exist between select cancer (gastrointestinal, lung, lymphatic, haematopoietic, uterus, cervix and ovary among others) and hypertension.

In this study, of the four components of lipid profile (cholesterol, triglycerides, LDL and HDL) only triglyceride levels were found to have significant association with cancer. Lipids are known for the role they play in cell conformity. Previous studies have found association between lipid profile and cancer. Patel et. al (2004) attributed the reduced levels of plasma cholesterol and other lipid components in patients with head and neck cancer to the use by neoplastic cells for the biogenesis of new membrane. Shah et. al. (2008) also came to a similar conclusion in their study between breast cancer and lipid profile. They found significant differences between levels of the different components of lipid profile between breast cancer cases and controls.

Glucose and insulin were recoded into HOMA-IR in this study. Individually, glucose was significantly associated with cancer but not insulin. Studies carried out on cancer and fasting blood glucose association have been in agreement. Rapp et. al. (2006) found positive association between elevated blood glucose and several cancers. The results from Stocks et. al. (2009) also backed up the earlier results. They also determined the strength of this association. They found that abnormal glucose metabolism independent of BMI was related to an increased risk of cancer in general and several specific sites. This association was found also to be stronger in females than males.

Even though insulin was not significantly associated with cancer in this study, some studies have found this association present while others have not. Clayton et. al. (2011) found no overall increase in cancer risk with insulin treatment. Meanwhile in the mini review carried out by Gallagher and LeRoith (2011), they came to a conclusion that insulin seems to have an independent influence on the development as well as progression of tumor growth.

Lifestyle behaviors including physical activity levels are known as major risk factors for Non-Communicable Diseases in general. In this study, even though smoking habits and alcohol consumption were found to be significantly associated with cancer, the results are not useable in that the frequency for smokers and alcohol users was 1 in both categories. Nonetheless, smoking, alcohol consumption and sedentary lifestyles are known to have some influence on the development of cancers. Hashibe et. al. (2009) agreed that combined effect involving tobacco use and alcohol intake is greater than an interaction on head and neck cancer risk. Results from Stolzenberg-Solomon et. al. (2006) also follow suit that use of alcohol have some influence on the development of breast cancer. Obesity defined by BMI and WHR were also significantly associated with cancer in this study. This is in line with previous studies which have also found this association. Considering physical inactivity in relation to obesity, individuals who are physically inactive are prone to be overweight to obese. Studies carried out decades ago have also found this association between physical activity and cancer. Recent studies have come up with conclusions that breast and colon cancer patients who are physically active are at greater advantage at recovery that patients who are either obese or physically inactive (Wolin et. al., 2010).

These results are in line with previous studies even though a study by Dickson et. al. (2002) found South-East Asians to be insulin resistant in the absence of risk factors, something he attributed to genetic and diet factors. These results were able to prove in part that even at increased risk of being insulin resistant than other races, HOMA-IR is still a risk factor for cancer in Malaysians according to this study.

5.0 Conclusion and recommendation

In conclusion, this case-control study identified some metabolic and lifestyle behaviours which can be modified. However some of the commonly reported risk factors such as HDL, LDL and cholesterol were not found to be significantly associated with cancer in this study. This could have been attributed to some of this study's limitation as reduced sample size and concentration of subject recruitment or it could also mean that no association exist between these variables in a Malaysian

Some of the strengths of this study include:

- HOMA-IR; a validated measure of insulin resistance was used in this study.
- To our knowledge, this is the first study on this association carried out in the South-east Asian region.
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Some of the limitations of this study include;

- Conclusion was based on cancer patients from 2 selected institutions and cannot be generalised for all cancer patients or the Malaysian population in general.
- There exists a possible selection bias among controls as secondary source was used ie individuals attending health screening procedures. It cannot be proved that their exposure prevalence sufficiently shows in the person-time that gave rise to the cases.
- Even though the IGF pathway is the plausible mechanism by which HOMA-IR is associated to cancer, there was no measurement of IGFs or other insulin resistance associated hormones and metabolites or their receptors due to cost and some complex laboratory work involved.

Acknowledgement

This study was funded by research grant (04-01-11-1160RU) from Research University Grant Scheme (RUGS) of University Putra Malaysia. We also would like to thank our collaborator, Associate Professor Dr. Mohd Faisal Jabar for his expert help and kind assistance in recruiting subjects of this study

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