UNIVERSITI PUTRA MALAYSIA

ASSOCIATION BETWEEN INSULIN RESISTANCE AND CANCER AMONG PATIENTS OF THE DIAGNOSTIC NUCLEAR IMAGING CENTER AT UPM AND HOSPITAL SERDANG

EZINNE OYIDIA KORIE

FPSK(M) 2013 43

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By

EZINNE OYIDIA KORIE

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

December 2013

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DEDICATION

Dedicated to my late brother Kelechi Kalu Okoronkwo Igwe
And
To all who's battled/battling cancer. To the survivors, it is our victory, to those who lost, it is our loss as a society, and to those still fighting, stay strong for cancer is not the end of life, we are all in this together.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science.

ASSOCIATION BETWEEN INSULIN RESISTANCE AND CANCER AMONG PATIENTS OF THE DIAGNOSTIC NUCLEAR IMAGING CENTER AT UPM AND HOSPITAL SERDANG

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December 2013

Chairman: Ahmad Zaid Fattah bin Azman, MBChB, MPH

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Insulin resistance (IR) is a major risk factor for Type 2 diabetes. Type 2 diabetes among other non-communicable diseases are major public health concerns with increased significance and prevalence. Cancer on the other hand was a leading cause of death worldwide in 2008. Studies have attributed the link between carcinogenesis and insulin resistance to hyperinsulinemia. The Hyperinsulinemia Theory proposes that high levels of insulin decreases the production of insulin growth factor 1 (IGF-1) binding proteins and hence increases the levels of free IGF-1. The bioactivity of free IGF-1 has been known to increase tumor turnover rate. The main objective of this study is to determine the association between insulin resistance and cancer among patients at the Diagnostic Nuclear Imaging in University Putra Malaysia and Hospital Serdang, Malaysia. This study hypothesized significant association between insulin resistance and cancer. This case-control study was carried out at the Diagnostic Nuclear Imaging Center at the Medical Faculty in UPM (Universiti Putra Malaysia) and the surgical ward of Hospital Serdang. Based on the sample size calculation, it involved a total sample size of 100 (age and sex matched 45 cases and 55 controls). Consecutive sampling was used for patient recruitment. Insulin resistance was determined by the Homeostasis Model assessment of Insulin resistance (HOMA-IR) which is a validated index of insulin resistance. It correlates strongly and inversely with the basic Insulin Sensitivity Clamp Index; derived from the hyperinsulinemic euglycemic clamp ($r = -0.572$, $P<0.001$) and also a more practical method of measuring insulin resistance in large epidemiological studies. HOMA-IR, metabolic parameters and anthropometric measurements were collected and determined in all subjects. From the results, using logistic regression, insulin resistance was 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). The presence of IR in cancer cases if researched further might have the ability to show insights on the role of insulin resistance on cancer in general and also cancer prevention and treatment.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains.

PERKAITAN ANTARA RINTANGAN INSULIN DAN KANSER DALAM KALANGAN PESAKIT DI PUSAT PENGIMEJAN DIAGNOSTIK NUKLEAR UPM DAN HOSPITAL SERDANG

Oleh

EZINNE OYIDIA KORIE

Disember 2013

Pengerusi: Ahmad Zaid Fattah bin Azman, MBChB, MPH

Fakulti: Perubatan dan Sains Kesihatan

Rintangan insulin (IR) adalah faktor risiko utama untuk diabetis jenis 2. Diabetes jenis 2 adalah dalam kalangan penyakit tidak berjangkit yang menimbulkan kebimbangan awam terhadap kesihatan dengan peningkatan kepentingan dan kelazimannya. Di sisi lain pula, kanser adalah punca utama kematian di seluruh dunia pada tahun 2008. Kajian telah mendapati kaitan antara karsinogenesis dan rintangan insulin yang telah dikaitkan dengan hyperinsulinemia. Teori Hyperinsulinemia mencadangkan bahawa tahap insulin yang tinggi mengurangkan pengeluaran faktor pertumbuhan insulin 1 (IGF-1) yang mengikat protein dan dengan itu meningkatkan tahap IGF-1 bebas. Bioaktiviti IGF-1 bebas dikenali pasti untuk meningkatkan kadar perolehan tumor. Objektif utama kajian ini adalah untuk menentukan hubungan antara rintangan insulin dan kanser dan juga faktor-faktor risiko IR dan kanser di kalangan pesakit di Pusat Pengimejan Diagnostik Nuklear di Universiti Putra Malaysia dan Hospital Serdang, Malaysia. Hipotesis kajian adalah terdapat hubungan yang signifikan antara rintangan insulin dan kanser. Kajian kes kawalan telah dijalankan di Pusat Pengimejan Diagnostik Nuklear di Fakulti Perubatan, UPM (Universiti Putra Malaysia) dan wad pembedahan Hospital Serdang. Berdasarkan pengiraan saiz sampel, ia melibatkan saiz sampel sebanyak 100 (dipadankan umur dan jantina 45 kes dan 55 kawalan). Persampelan berturutan telah digunakan untuk pengambilan pesakit. Rintangan insulin ditentukan oleh Model Penilaian Homeostasis Rintangan Insulin (HOMA-IR) iaitu indeks disahkan tentangan insulin. Ia berkait rapat dan secara songsang dengan Insulin asas Indeks Pengapit Kepekaan yang berasal dari Pengapit Euglycemic Hyperinsulinemic ($r = -0,572$, $P < 0.001$) dan juga kaedah yang lebih praktikal untuk mengukur rintangan insulin dalam kajian epidemiologi yang besar. HOMA-IR, parameter metabolik dan ukuran antropometri telah dikumpulkan dan diputuskan di dalam semua subjek. Daripada keputusan, dengan menggunakan regresi logistik, rintangan insulin bebas yang dikaitkan dengan kanser. Terdapat juga hubungan yang signifikan antara obesiti dan kanser (Diselaraskan OR = 3.33, 95% CI = 1.08, 10.31). (Penyelarasan OR = 12.25 95% CI = 3,20, 46,83.) Kewujudan IR dalam kes-kes kanser mungkin memerlukan kajian

selanjutnnya yang berkeupayaan untuk memberi gambaran peranan rintangan insulin bagi penyakit kanser, pencegahan serta rawatan nya.

ACKNOWLEDGEMENTS

Firstly, for the success of my research and study duration, I owe it all to God who saw me through it all even when it was rocky, I always drew strength from him.

My utmost apprecition to my supervisor, Dr Ahmad Zaid Fattah bin Azman, for his patience and understanding with corrections and explanations throughout my study period. Also my co-supervisors: Prof Abdul Jalil bin Nordin, Dr Norhafizah Mohtarrudin and Dr Faisal Jabar, even in their busy schedules, they still found time to look into my research. That, I very much appreciate.

To the staff and management of the Diagnostic Nuclear Imaging Center in Universiti Putra Malaysia and Hospital Serdang, I wish to express my gratitude for all their help and willingnesss to permit me carry out this research in their institution.

To the staff at the Chemical Pathology Laboratory in Universiti Putra Malaysia; Ms Safarina Mohd Ismuddin and Norazmie Mohd Ramly who helped me with the blood analysis, I could never thank them enough for their efforts.

To my wonderful husband, Chidiebere Francis Korie who was always there for me, encouraging me at all times. His extra efforts went a long way and my cute daughter Kamsi, who was always a good company when I needed some time off.

To my beloved parents, Prof & Mrs S. O Igwe, their continuous calls and encouragement on a daily basis always had me going... What else could a daughter ask for. To my wonderful brothers; Barrister Uzoechi C. Igwe and Barrister Chidiebere I. Igwe, My sister and best friend, Barrister Uzunma Nnenna Udenka and their families for all the unending love and support in all possible ways.

To my best friends at home for all the love and my coursemates in UPM for all the help and encouragement I got from them.

To all the people I met before and in the course of my research; Komathy a/p Kuppusamy at the Imaging center who was always willing to help me with most of my Malay interviews, Diandra Ann and Danielle Lynn David who helped me most of my Malay translations, I appreciate all the help.

I would also love to acknowledge the partial funding of this research by the Research Universiti Grant Scheme (RUGS), of UPM.

Finally, I wish to extend my heartfealt gratitude to all the strangers who were helpful and nice to me in one way or another. One thing is for sure, what goes around, comes around. Good or bad. So for this I very much appreciate and pray that starngers will be nice to you as well.

Ezinne Oyidia Korie

I certify that a Thesis Examination Committee has met on 3rd of December, 2013 to conduct the final examination of Ezinne Oyidia Korie on her thesis entitled "Association Between Insulin Resistance And Cancer Among Patients Of The Diagnostic Nuclear Imaging Centre In UPM And Hospital Serdang" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U. (A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science degree.

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DECLARATION

I declare that the thesis is my original work except for quotations and citations, which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at Universiti Putra Malaysia or other institution.

_____

EZINNE OYIDIA KORIE

Date: 3rd December, 2013

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LIST OF ABBREVIATIONS

AACE	Association of Clinical Endocrinologist
AHA	American Heart Association
ASCO	American Society of Clinical Oncology
ATP III	Adult Treatment Panel III
BBDR	Basel Breast cancer Database
BMI	Body Mass Index
CRC	Colorectal Cancer
CRP	C- Reactive Protein
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DRE	Digital Rectal Examination
ER	Estrogen Receptor
HDL-c	High Density Lipid cholesterol
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
IDF	International Diabetes Federation
IGF-1	Insulin-like Growth Factor 1
IGFBP-3	Insulin-like Growth Factor Binding Protein 3
IP	InterPeritoneal
IPAQ	International Physical Activity Questionnaire
IR	Insulin Resistance
IRS	Insulin Resistance Syndrome
LDL-c	Low density Lipid cholesterol
MetS	Metabolic Syndrome
MONW	Metabolically Obese Normal-Weight individuals
MRI	Magnetic Resonance Imaging
NCR	National Cancer Registry
NCEP	National Cholesterol Education Programme

NIH	National Instiute of Health
NHMS	National Health and Morbidity Survey
NP	Non Poliferative
OR	Odds Ratio
PA	Physical Activity
PET/CT	Positron Emission Tomography-Computed Tomography
PPDN	Pusat Pengimejan Diagnostik Nuklear
PR	Progesterone Receptor
PSA	Prostate Specific Antigen
RASS1	Ras association domain-containing protein 1
SAT	Subcutaneous Adipose Tissue
sICAM-1	soluble Intercellular Cell Adhesion Molecule-1
SD	Standard Deviation
SBP	Systolic Blood Pressure
SHS	Swiss Health Survey
TNM	Tumor, Node, Metastasis
TTDM	Type two Diabetes Milletus
VAT	Visceral Adipose Tissue
VLDL	Very Low Density Lipopeotein
WHO	World Health Organization
WHR	Waist Hip Ratio

CHAPTER 1

INTRODUCTION

1.1 Background

The importance of insulin resistance 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 ie 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. In a mini-review carried out by LeRoith & Roberts Jr, (2003), studies attributed the association between insulin resistance and cancer to this. Fig 1.1 below shows the diagrammatical representation of the mechanism of association between IR and cancer:

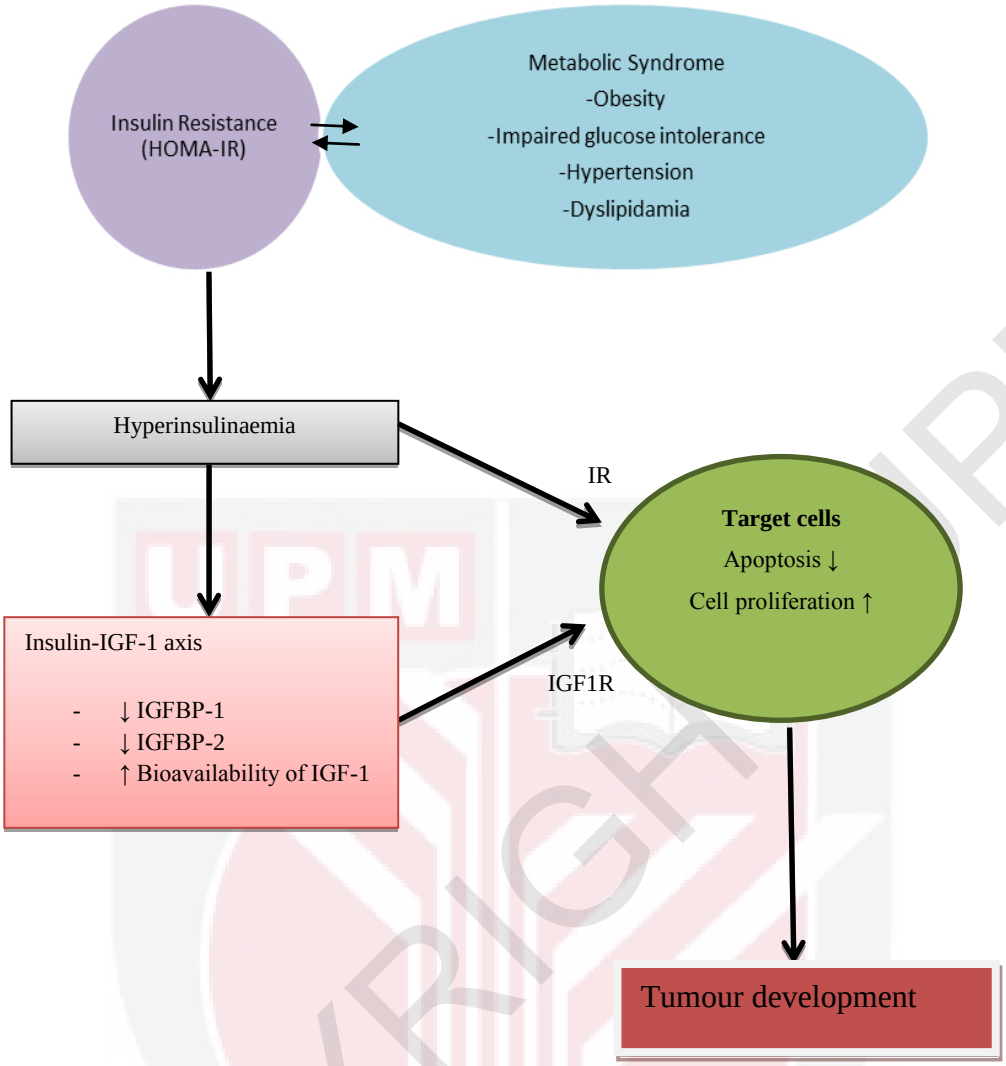


Fig. 1.1: Diagram showing the hyperinsulinemia theory in relation to cancer.

(Diagram adapted from Clayton et. al. 2011 and Calle & Kaaks, 2004).

1.2 Problem Statement

In 2008, cancer 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. (Ariffin and Saleha, 2011).

Even though cancer is a multifactorial disease caused by both 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 individuality of cancer cells is to multiply uncontrollably and therefore reject programmed death.

Insulin resistance which is a major risk factor for cardiovascular diseases and type-2 diabetes is present in an individual long before the actual onset of type-2 Diabetes Milletus (TTDM). Therefore, all type-2 diabetics are insulin resistant but not all

insulin resistant individuals are type 2 diabetics.

Insulin resistance is a stepping stone to type 2 diabetes which is a major public health burden in South-east Asia and Malaysia as can be seen from the statistics.

The International Diabetes Federation (IDF) has predicted that by 2030, the South East Asia Region would have an estimated diabetes prevalence of 10% (120.9 million) (IDF Diabetes Atlas, 2011). The WHO has also estimated that in the year 2030, Malaysia would have a total of 2.48 million people with diabetes.
Malaysia reportedly has a higher prevalence of metabolic syndrome compared to other Asian countries as was seen from a recent nationwide survey (Lau, 2011). It has also been listed as one of the top 10 countries where diabetes has the highest prevalence in the recent global estimate of the prevalence of diabetes for years 2010 and 2030 by the International Diabetes Federation.

Giarach et. al (2006) has attributed the increased prevalence of type 2 diabetes to the ageing population, rising incidence of obesity, sedentary lifestyle among other factors. The First National Health and Morbidity Survey (NHMS,1986) in Malaysia showed diabetes prevalence among adults of age ≥35 years old as 6.3% (NHMS,1986). Ten years later, in NHMS II, the figure had increased by one third to 8.3% among adults of age ≥ 30 years old (NHMS, 1996). The latest Malaysian National Health and Morbidity Survey conducted in 2006, the national prevalence of diabetes was 14.9% among adults ≥ 30 (NHMS, 2006).

This increase has also been present in some of the most common cancers in Malaysia. 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%.

From the statistics above, noticable increase has been observed in the prevalence of of TTDM (which has IR as its major risk factor) as well as incidence of some common cancers.

In this study, insulin resistance was hypothesised as a risk factor for cancer in general in relation to vigorous cell multiplication. As is common knowledge, major risk factors exist for various cancers eg smoking and lung cancer; the major objective of this study was not to contradict these known facts but to show that in the presense of these known risk factors, an individual who is insulin resistant is at an even higher risk of developing cancer than say, a smoker who is not insulin resistance. In other words, in an insulin resistant state, there is reduction in cell death as there is increased levels of IGF-1 in the blood.

The IGF signalling system is a family of ligands (IGF-I and IGF-II), binding proteins and receptors. They play an important role in the growth and development of many tissues and regulate overall growth, mostly prenatal growth. Insulin resistance via the IGF system has been implicated to play a role in carcinogenesis.

Studies now show that individuals with increased levels of circulating IGFs are at

higher risk of developing certain cancers than are individuals with lower levels. According to the meta-analysis done by Renehan *et. al.* (2004), they employed extremely grim and linked analytical methods in studying a group of 26 published data-sets (which included 3609 cases and 7137 controls) that examined the association between circulating concentrations of IGF-I and IGFBP-3 and the prospects of developing prostatic, breast, colon, and lung cancer in adult men and women. After gradation of the analyte levels, they compared the 75th percentile of circulating protein concentration with the 25th percentile and then calculated odds ratios for the development of cancer. Significant associations were observed between the concentration of IGF-I and development of premenopausal breast, prostatic, and colon cancer (odds ratios: 1.64 (95%CI: 1.26,2.08), 1.49 (95% CI: 1.14, 1.95) and 1.18 (95%CI: 0.92, 1.51 respectively). This association was absent between IGF-I values and risk of breast cancer in postmenopausal women or of lung cancer. The level of IGFBP-3 was related with a higher chance of breast cancer developement in premenopausal women (odds ratio 1.51, 95%CI: 1.01, 2.27) and perhaps a protective effect on development of lung cancer. From the above observation, the investigators came to a conclusion that due to the proliferative and anti-apoptotic effects of various IGFs, higher levels of circulating concentrations of IGF-I are a risk factor for development of premenopausal breast, prostatic and colon malignancies.

This study focused on non-diabetic cancer patients of the Diagnostic Nuclear Imaging Center in Universiti Putra Malaysia (*Pusat Pengimejan Diagnostik Nuklear)* and the surgical ward of the Hospital Serdang as cases and non-oncology patients with no recent history of malignancy (last 3years) as controls. All diabetics were excluded.

1.3 Significance of the Study

Even though a number of studies have found association between insulin resistance and selected cancers in various populations but South-east Asians, insulin sensitivity is known to differ among races. 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.) These characteristic was first described as metabolically obese, normal-weight (MONW) individuals by Ruderman *et. al.* (1981). These individuals they say are common in general populations and may account for the increased prevalence of TTDM, cardiovascular disease, and other disorders in individuals having a BMI in the 20-27 kg/m2 range who have added normal weight (2-10 kg of adipose mass) in adult life. Chan *et. al.* (2009) in their review noted that this "metabolically obese" phenotype is common in Asian populations. So far, the biological foundation for the ethnic differences in insulin sensitivity has not been completely clarified. Insulin sensitivity is determined in part by genetic factors, it is possible that this racial/ethnic differences in diabetes risk (IS) are attributable to genetic predisposition as genetic factors alone would not explain the marked increase in prevalence of type 2 diabetes (Shai *et. al.* 2006). In this study, no significant association was found between cancer and family history of diabetes and the study by Shai *et. al.*; adjustment for family history of diabetes did not appear to alter the risk estimates of diabetes milletus for different ethnic groups so they

theorized that the observed ethnic difference in diabetes risk (IS) is likely due to an interaction between diet and lifestyle and increased genetic susceptibility among different ethnicities.

There is a possibility that the insulin-cancer hypothesis may elucidate further on the etiology of common cancers and also offer more insights on the prevention and management. Furthermore, confirming insulin resistance as a major risk factor for cancer may help identify high-risk individuals who may warrant more intensive screening and also aid in the development of therapies that target hyperinsulinemia in early stages of cancer.

1.4 Objectives of the Study

1.4.1 General Objective

To determine the mean difference in HOMA-IR values between cancer(cases) and non-cancer (controls) patients and risk factors of cancer in this study.

1.4.2 Specific Objectives

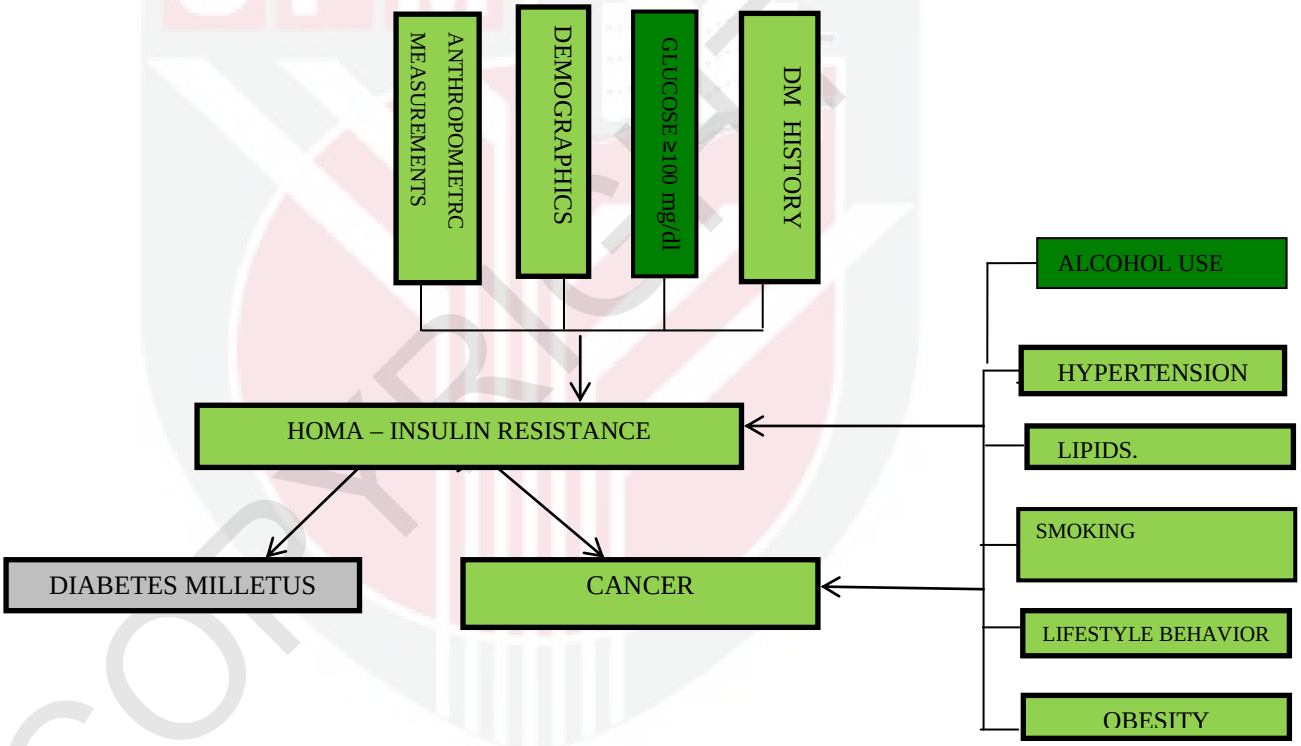
i. To determine the socio-demographic characteristics, prevalence of HOMA-IR, metabolic risk factors (ie obesity, hypertension, lipids level, triglycerides level), and lifestyle behaviors.
ii. To determine the mean difference of HOMA-IR values between cases and controls.
iii. To determine the association between socio-economic factors, metabolic risk factors, lifestyle behaviours, anthropometric measurements and cancer
iv. To determine the predictors of cancer in this study.

1.5 Research Hypothesis

i. There is significant mean difference between the mean HOMA-IR values of cancer patients (cases) and controls.
ii. There is significant association between cancer and HOMA-IR.
iii. There is significant association between demographic factors, socio-economic factors, lifestyle behavior, anthropometric measurements and cancer.

1.6 Conceptual Framework

Some of the major risk factors of insulin resistance have also been found to have significant association with cancer. These risk factors include obesity (Yang et. al. 2009) hypertension (Grossman et. al. 2001), physical inactivity (McTiernan et. al. 2003), lifestyle behaviours (Ornish et. al. 2005) and lipid levels (Hayashi et. al. 2012). The primary objective of this study was to determine the association between insulin resistance and cancer. Family history of diabetes, demographics and anthropometric measurement which also have some sort of effect on the development of insulin resistance was also included in the conceptual framework.



*Variables in green were studied.

Figure 1.6 Risk factors associated with insulin resistance and cancer

REFERENCES

Abbasi, M, Tarafdari, A, Esteghamati, A, Vejdani, K, and Nakhjavani, M. (2010). Insulin resistance and breast carcinogenesis: a cross-sectional study among Iranian women with breast mass. *MetSynRel Dis.*, 8(5), 411-416.

Albanes D, Weinstein S. J, Wright M. E. *et. al.* (2009). Serum Insulin, Glucose, Indices of Insulin Resistance, and Risk of Prostate Cancer. *J Natl Cancer Inst*; 101:1272–1279.

Al-Mahmood A. K, Ismail A. A, Rashid F. A, Bebakar M. (2006). Insulin sensitivity and secretory status of a healthy Malay population. *Mal. J. Med. Scien*., 13(2), 37-44

Ariffin O. Z and Saleha I. T. (2007). NCR Report 2007, Ministry of Health, Malaysia. 2011.

Boffetta, P & Hashibe, M. (2006). Alcohol and cancer. Lancet Oncology, 7(2), 149-56.

Cancer in older adults. (2012). American Society of Clinical Oncology (ASCO): Vigginia.

Anand P, Kunnumakara A. B, Sundaram C. *et. al.* (2008) Cancer is a Preventable Disease that Requires Major Lifestyle Changes: Expert Review. *Phar. Res.* 25(9):2097-2116

Antoniadis A. G, Petridou E. T, Antonopoulos C. N. *et al.* (2011). Insulin resistance in relation to melanoma risk. *Melanoma res. 21*(6), 541-546.

Bachoric P. (2000). Measurement of Low Density- Lipoprotein, In*: Handbook of lipoprotein testing* (eds. Rifai, Warnick and Dominiczak), 2nd edition. Pp.: 245-263. American Association for Clinical Chemistry Inc.

Bao, Y, Nimptsch, K, Wolpin, B, *et. al*. (2011). Dietary insulin load, dietary insulin index, and risk of pancreatic cancer. *Am J Clin Nutri*, 94(3), 862-868.

Bohlke K, Cramer D. W, Trichopoulos D. *et. al.*. (1998). Insulin-like growth factor-I in relation to premenopausal ductal carcinoma in situ of the breast. *Epidemiology,* 9:570–573

Bonadonna RC, Groop L, Kraemer N, *et. al.*. Obesity and insulin resistance in humans: a dose-response study. *Metabolism.* 1990; 39: 452–459.

Burzawa J. K, Schmeler K. M, Soliman P. T *et. al.* (2011). Prospective evaluation of insulin resistance among endometrial cancer patients. *Am J ObGyn*. 204(4): 355.e1-355.e7.

Buschemeyer III W. C and Freedland S. J. (2007). Obesity and Prostate Cancer: Epidemiology and Clinical Implications. J Eur Urol. 52(2):331-343

Bush, K, Kivlahan, D. R, McDonell, M. B, Fihn, S. D. and Bradley, K. A. (1998). The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. *Archives of internal medicine*, *158*(16), 1789.

Byrne C, Colditz G. A, Willett W. C. *et. al.*. (2000). Plasma insulin-like growth factor (IGF) I, IGF-binding protein 3, and mammographic density. *Cancer Research*, 60: 3744–3748

Caceres M, Teran C. G, Rodriguez S and Medina M. (2008.)Prevalence of insulin resistance and its association with metabolic syndrome criteria among Bolivian children and adolescents with obesity. *BMC Pediatr.* 12; 8:31

Cancer Statistics Registrations, England (Series MB1), No. 41, 2010 | 13 June 2012

Capasso I, Esposito E, Montella M *et. al.* (2012). 149 Insulin Resistance, Metabolic Syndrome and Breast Cancer Risk -National Cancer Institute of Naples Experience. *Eur J Cancer.* 48(1) S83

Chan, J. C, Malik, V, Jia, W. *et. al.* (2009). Diabetes in Asia. JAMA: the journal of the American Medical Association, 301(20), 2129-2140.

Chan M. Opening address at the 8th Global Conference on Health Promotion. Helsinki, Finland. June 2013.

Chandalia M, Lin P, Seenivasan T. *et. al.*. (2007) Insulin Resistance and Body Fat Distribution in South Asian Men Compared to Caucasian Men. *PLoS ONE* 2(8): e812.

Chawda, J. G, Jain, S. S, Patel, H. R, Chaduvula, N, and Patel, K. (2011). The relationship between serum lipid levels and the risk of oral cancer. *Indian J Med Paediatr Oncol.*, 32(1), 34.

Cheng H. Y, Taib N. A.M and Mohamed I (2006) Epidemiology of breast cancer in Malaysia: mini-review. *Asian Pacific J Cancer Prev*; 7, 369-374.

Chow W, Gridley G, Fraumeni J. F. Jr, and Järvholm, B. (2000.) Obesity, Hypertension, and the Risk of Kidney Cancer in Men. *N Engl J Med*; 343:1305-1311

Clayton P.E, Banerjee I, Murray P. G and Renehan A. G (2011). Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. *Nat Rev Endocrin* 7: 11-24.

DeFronzo R. A, Tobin J. D, Andres R. (1979) Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237: 214–223.

Del Giudice M. E, Fantus I. G, Ezzat S. *et. al.* (1998.) Insulin and related factors in premenopausal breast cancer risk. *Breast Cancer Res Treat* 47: 111–120.

De Nunzio, C, Freedland, S, Miano, L. *et. al.* (2011). The uncertain relationship between obesity and prostate cancer: an Italian biopsy cohort analysis. *Eur J Surg Oncol: J Eur Soc- Surg Oncol And British Association Of Surgical Oncology*, 37(12), 1025-1029.

Dickson S, Colagiuri S, Faramus E, Petocz P. and Brand-Miller J. C. (2002.) Postprandial Hyperglycemia and Insulin Sensitivity differ among lean young adults of different ethnicities. *J. Nutr.132:2574-2579*

Dominiczak M. and McNamara J. (2000).The system of cardiovascular prevention. In: *Handbook of lipoprotein testing* (eds. Rifai, Warnick and Dominiczak), 2nd edition. Pp.: 103-125. American Association for Clinical Chemistry Inc.

Dupont W. D, Plummer W. D (1990): "*Power and Sample Size Calculations*: A Review and Computer Program", Controlled Clinical Trials; 11:116-28

Eichholzer, M., Schmid, S., Bovey, F. *et. al.* (2012). Impact of overweight and obesity on postmenopausal breast cancer: analysis of 20-year data from Switzerland. *Arch Gynecol Obstet.*, 285(3), 797-803.

Eslam M, Kawaguchi T, Del Campo J. A. *et. al.* (2011.) Use of HOMA-IR in Hepatitis C. *J Viral Hepat.*, 18(10):675-684.

Fair A. M, Dai Q, Shu X. *et. al.* (2007). Energy balance, insulin resistance biomarkers, and breast cancer risk. *Cancer Detect.Prev.* 31(3): 214-219

Fairuz A. R., Maniam T. and Khalid B. A. K (2007). Prevalence of Insulin Resistance in Schizophrenia in HUKM.*Med J Malaysia*; 62 (4):290-293

Ferrannini E. and Mari A. (1998). How to measure insulin sensitivity. *J Hypertens*16: 895–906.

Furberg, A, Veierød, M. B, Wilsgaard, T, Bernstein, L. and Thune, I. (2004). Serum High-Density Lipoprotein Cholesterol, Metabolic Profile, and Breast Cancer Risk. *J Natl Cancer Inst;* 96 (15): 1152-1160.

Gallagher E.J and LeRoith D (2011). Minireview: IGF, Insulin, and Cancer. *Endocrin.*152, 7: 2546-2551.

Garcia J. M, Touza M. G, Hijazi R.A. *et. al.* (2005). Active ghrelin levels and active to total ghrelin ratio in cancer –induced cachexia. *J Clin endocrinol metab.* 90(5):2920-2926.

Garmendia M. L, Pereira A, Alvarado M. E. and Atalah E. (2007). Relation between Insulin Resistance and Breast Cancer among Chilean Women. *Ann.Epidemiol*. 17(6): 403-409.

Garte S (1998). The role of ethnicity in cancer susceptibility gene polymorphisms: the example of CYP1A1. J *Carcinog*. 19(8): 1329–1332.

Giarach A, Manner D, Porta M, (2006). Diabetic microvascular complications: Can patients at risk be identified? A Review. *Int. J Clin Pract*. 60(11): 1471-1483.

Giovannucci E.L (2005 Spring) Obesity, Insulin Resistance and Cancer. *New York Presbyterian Hospital Newsletter*, 5.

Giovannucci, E. L, Ascherio, A., Rimm, E. B. *et. al*. (1995). Physical Activity, Obesity, and Risk for Colon Cancer and Adenoma in Men. *Ann Intern Med.*, 122(5): 327-334

Gonullu G, Kahraman H, Bedir A, Bektas A, Yucel I. (2010). Association between adiponectin, resistin, insulin resistance and colorectal tumours .*Int. J colorectal Dis* 25:205-212.

Goodwin, P, Ennis, M, Bahl, M *et. al.* (2009). High insulin levels in newly diagnosed breast cancer patients reflect underlying insulin resistance and are associated with components of the insulin resistance syndrome. *Bre. Can. Res. Treat.,* 114(3), 517-525.

Grodski S, Brown T, Sidhu S, *et. al*. (2008). Increasing incidence of thyroid cancer is due to increased pathologic detection. *Surgery.* 144(6):1038-43

Grossman, E, Messerli, F. H, Boyko, V, and Goldbourt, U.(2002). Is there an association between hypertension and cancer mortality?.*Am J Med.,* 112(6): 479-486.

Gungor N, Hannon T, Libman I, Bacha F, Arslanian S. (2005). Type 2 diabetes mellitus in youth: the complete picture to date. *PediatrClin North Am*, 52:1579–1609.

Hagstromer, M., Oja, P., and Sjostrom, M. (2006). The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity.*Public health nutrition*, *9*(6), 755-762.

Halpern M T, Ward E. M, Pavluck A. L. *et. al.* (2008). Association of Insurance Status and Ethnicity With Cancer Stage at Diagnosis for 12 Cancer Sites: A Retrospective Analysis. *Obgynsurvey*. 63(6):380-381

Hamburg N. M, McMackin C. J, Huang A. L. *et. al.* (2007). Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. *ArteriosclerThrombVasc Biol*. 27(12):2650-6

Han J. H., Lee Y. T., Kwak K. W. *et. al.* (2010). Relationship between insulin resistance, obesity and serum prostate-specific antigen levels in healthy men. *Asian J Androl*.,12: 400–40

Hankinson S. E, Willett W. C, Colditz G. A *et. al.*. (1998). Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet*, 351: 1393–1396

Harish K, Dharmalingam M, Himanshu M. (2007). Study Protocol: insulin and its role in cancer. *BMC Endo Dis*. 2007, 7:10.

Hashibe M, Brennan P, Chuang S. C *et. al*. (2009). Interaction between Tobacco and Alcohol Use and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev.* 18; 541

Hayashi, N, Matsushima, M, Yamamoto, T. *et. al.* (2012). The impact of hypertriglyceridemia on prostate cancer development in patients aged ≥60 years. *BJU Intl,* 109: 515–519.

International Diabetes Federation. IDF Diabetes Atlas, 5th edn. Brussels, Belgium: International Diabetes Federation, 2011.

Isharwal, S, Misra, A, Wasir, J. S and Nigam, P. (2009). Diet & insulin resistance: a review & Asian Indian perspective. *Indian J Med Res*, 129(5), 485-499.

Jacobs E. J, Rodriguez C, Bain E. B. *et. al.* (2007). Cholesterol-lowering drugs and advanced prostate cancer incidence in a large U.S. cohort. Cancer Epidemiology, Biomarkers & Prevention: *A Publication Of The American Association For Cancer Research, Cosponsored By The American Society Of Preventive Oncology*, 16(11), 2213-2217.

Jayagopal V, Kilpatrick E. S, Jennings P. E, Hepburn D. A, Atkin S. L (2002): Biological variation of homeostasis model assessment-derived insulin resistance in type 2 diabetes.*Diabetes Care.* 25(11):2022-2025

Jee S. H, Ohrr H, Sull J. W. *et. al*. (2005). Fasting serum glucose level and cancer risk in Korean men and women. *J Am Med Ass*. 293(2):194-202.

Johnstone M. T. and Veves A. (Eds.).(2005). *Diabetes and Cardiovascular disease*. Totowa, NJ: Humana Press. Inc

Kaaks, R., Lundin, E., Manjer, J *et. al.* (2002). Prospective study of IGF-I, IGF-binding proteins, and breast cancer risk, in northern and southern Sweden. *Cancer Causes & Control*, *13*(4), 307-316.

Kakuyama T., Kimura S. and Hashiguchi Y.(1994). Fully automated determination of HDL-cholesterol from human serum with Hitachi 911.*Clin Chem*. 40: 1104.

Kamath, S, Chavez, A. O, Gastaldelli, A *et. al.* (2011). Coordinated defects in hepatic long chain fatty acid metabolism and triglyceride accumulation contribute to insulin resistance in non-human primates. PloS one, 6(11), e27617.

Kang, H, Kim, D, Kim, H. *et. al.* (2010). Visceral obesity and insulin resistance as risk factors for colorectal adenoma: a cross-sectional, case-control study. *Am J Gastroenterol.* 105(1), 178-187.

Kirkwood R. B and Sterne J. A. C (2003).*Essential Medical Statistics*, 2nd ed. Vitoria. Blackwell Science LTD.

Kravdal, H, and Syse, A. (2011). Changes over time in the effect of marital status on cancer survival. BMC public health, 11(1), 804.Kirkwood R. B.And Sterne J. A. C (2003).*Essential Medical Statistics*, 2nd ed. Vitoria. Blackwell Science LTD.

Lau C and Muniandy S. (2011). Novel adiponectin-resistin (AR) and insulin resistance (IRAR) indexes are useful integrated diagnostic biomarkers for insulin resistance, type 2 diabetes and metabolic syndrome: a case control study: *CardiovascDiabetol.* 10:8. doi:10.1186/1475-2840-10-8

Lee J. M., Okumura M. J., Davis M. M., Herman W. H, Gurney J. G., (2006). Prevalence and Determinants of Insulin Resistance Among U.S. Adolescents. *Diabetes Care.* 29:2427–2432,

Lebovitz H. (2001). Insulin resistance: definition and consequence. *ExpClinEndocrinol Diabetes.*109(Suppl 2):S135-S148.

Lehr R (1992) Sixteen s-squared over d-squared: a relation for crude sample size estimates. *Stat in Med.* 11: 1099–1102.

Lejeune C, Sassi F, Ellis L *et al.* (2010) Socio-economic disparities in access to treatment and their impact on colorectal cancer survival. *Int J Epidemiol.* 39(3): 710-717

LeRoith D and Roberts Jr C. D. (2003). The insulin-like growth factor system and cancer: Mini-review. *Cancer Letters* 195:127–137

Letchuman G. R, Nazaimoon W. M, Mohamad *et. al.* (2010) Prevalence of Diabetes in the Malaysian National Health Morbidity Survey III 2006. *Med J Malaysia.* 65 (3), 173-179.

Li H, Zhu X, Wang A, Wang A, Zhang Y. (2012). Co-effect of insulin resistance and biomarkers of inflammation and endothelial dysfunction on hypertension. *Hypertens Res.* doi:10.1038/hr.2011.229.[Epub ahead of print]

Lim H. H (1986). Cancer mortality in the Federal capital of Malaysia. *Singapore Med. J.27 (6), 512-518*

Limburg P. J, Stolzenberg-Solomon R. Z, Vierkant R. A *et. al.* (2006). Insulin, Glucose, Insulin Resistance, and Incident Colorectal Cancer in Male Smokers. *Clin Gastro Hep*. 4(12):1514-1521

Lin C. Y, Chen P. C, Kuo H. K. *et. al.* (2010). Effects of obesity, physical activity, and cardiorespiratory fitness on blood pressure, inflammation, and insulin resistance in the National Health and Nutrition Survey 1999-2002.*NutrMetabCardiovasc Dis.* 20(10), 713-9

Loh W., North B., Johnston D. and Godsland I. (2010). Insulin resistance- related biomarker clustering and subclinical inflammation as predictors of cancer mortality during 21.5 years of follow up. *Cancer Causes Control.* 21(5,) 709-718.

Lukanova A, Zeleniuch-Jacquotte A, Lundin E *et. al.* (2004). Prediagnostic levels of C-peptide, IGF-I, IGFBP -1, -2 and -3 and risk of endometrial cancer. *Int J Cancer*. 108: 262–268

McTiernan, A., Kooperberg, C., White, E *et. al.* (2003). Recreational Physical Activity and the Risk of Breast Cancer in Postmenopausal Women.*JAm Med Ass.* 290(10):1331-1336.

Matthews D. R, Hosker J. P, Rudenski A. S. *et. al.* (1985). "Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man." *Diabetologia* 28 (7): 412–9

Mink P.J, Shahar E, Rosamond W.D, Alberg A. J, and Folsom A. R (2002). Serum insulin and glucose levels and breast cancer incidence: the atherosclerosis risk in communities study. *Am J Epidemiol*, 156, 349-68.

Mondul, A, Weinstein, S, Virtamo, J, and Albanes, D. (2011). Serum total and HDL cholesterol and risk of prostate cancer. *Cancer Causes & Control: CCC*, 22(11), 1545-1552.

Mørkrid, K, Jenum, A. K, Sletner, L *et. al.* (2012). Failure to increase insulin secretory capacity during pregnancy-induced insulin resistance is associated with ethnicity and gestational diabetes. *Eur J Endocrin*, 167(4), 579-588.

Muti, P, Quattrin, T, Grant, B. J *et. al.* (2002). Fasting Glucose Is a Risk Factor For Breast Cancer A Prospective Study. *Cancer Epidemiol Biomarkers Prev, 11*(11), 1361-1368.

National Health Morbidity Survey 1986–1987. *Diabetes Mellitus.Volume 4*. Institute for Public Health, Ministry of Health, Malaysia.

Ministry of Health (MOH), Malaysia. (1996). Second National Health and Morbidity Survey, 2006. *NHMS II Report* 2008.

Ministry of Health (MOH), Malaysia. (2008). Third National Health and Morbidity Survey, 2006. *NHMS II Report* 2008.

Nilsen T. I and Vatten L. J. (2001). Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. *Br J Cancer*. 84(3), 417–422

Oh S, Park, C, Lee, E *et. al*. (2011). Adipokines, insulin resistance, metabolic syndrome, and breast cancer recurrence: a cohort study. *Breast Cancer Res.*13(2), R34.

Ornish D, Weidner G, Fair R. W *et. al.* (2005) Intensive Lifestyle Changes May Affect The Progression Of Prostate Cancer. J Urol. 174(3):1065-1070

Otani, T, Iwasaki, M, Ikeda, S *et. al*. (2006). Serum triglycerides and colorectal adenoma in a case-control study among cancer screening examinees (Japan). *Cancer Causes Control.* 17(10), 1245-1252.

Pan S. Y, Johnson K. C, Ugnat A, Shi W. W, Yang M, and the Canadian Cancer Registries Epidemiology Research Group (2004.)Association of Obesity and Cancer Risk in Canada.*Am. J. Epidemiol.*159(3): 259-268

Pathan, A. B, Doijad, R. C., Patil, S. B. *et. al.* (2012). Plasma lipid profile as predictor of cancer: A review. Int. J. Rev. Life. Sci., 2(2), 53-57.

Patel P.S, Shah M. H, Jha F. P. *et. al.* (2004). Alterations in plasma lipid profile patterns in head and neck cancer and oral precancerous conditions. *Indian J Cancer*. 41:25-31.

Peeters, Petra H. M, Noord V, *et. al*. (2000) Hypertension, antihypertensive drugs, and mortality from cancer among women. *J Hypertens.* 16(7): 941-947.

Petridou, E, Sergentanis, T, Antonopoulos, C *et. al.* (2011). Insulin resistance: an independent risk factor for lung cancer?.*Metab.Clin Exp.* 60(8), 1100-1106.

Prospective Studies Collaboration (2009). Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 373: 1083–96

Rampal L, Azhar M. Z, Senan P, *et al*. (2004). Questionnaire booklet, Wellness and quality of life study: tackling lifestyle and health issues using new technologies and novel intervention methods in Malaysia. Faculty of Medicine and Health Sciences. Universiti Putra Malaysia (UPM), Serdang-Malaysia.

Rapp K, Schroeder J, Klenk J *et. al*. (2006). Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. *Diabetologia*. 49(5): 945-952.

Renehan A. G, Zwahlen M, Minder C, *et. al.* (2004). Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* 363:1346-1353.

Roden M., Price T. B, Perseghin G. *et. al.* (1996). Mechanism of free fatty acid-induced insulin resistance in humans: *J Clin Invest.* 97(12): 2859–2865.

Ruderman, N. B, Schneider, S. H, and Berchtold, P. (1981). The" metabolically-obese," normal-weight individual. *Am J Clin Nutri,* 34(8), 1617-1621.

Sato T, Takeda H, Sasaki Y, Kawata S. (2011). Increased homeostasis model assessment-insulin resistance is a risk factor for colorectal adenoma in Japanese males. *Tohoku J Exp Med*. 223(4):297-303.

Sarafidis P. A., Nilsson P.M., (2006). The metabolic syndrome: a glance at its history. *J Hypertens.* 24: 621–626.

Shafique, K., McLoone, P., Qureshi, K. *et. al.* (2012). Cholesterol and the risk of grade-specific prostate cancer incidence: evidence from two large prospective cohort studies with up to 37 years' follow up. *BMC Cancer,* 1225.

Shah F. D, Shukla S. N, Shah P. M, *et. al.* (2008). Significance of Alterations in Plasma Lipid Profile Levels in Breast Cancer. *Integr Cancer Ther.* 7(1): 33-41

Shai, I., Jiang, R., Manson, J. E. *et. al.* (2006). Ethnicity, Obesity, and Risk of Type 2 Diabetes in Women A 20-year follow-up study. *Diabetes Care, 29*(7), 1585-1590.

Shebl, F., Andreotti, G., Meyer, T. *et. al*. (2011). Metabolic syndrome and insulin resistance in relation to biliary tract cancer and stone risks: a population-based study in Shanghai, China. *BJC*, 105(9), 1424-1429. doi:10.1038/bjc.2011.363

Smith G. D, Gunnell D and Holly J.(2000): Cancer and insulin-like growth factor-I. A potential mechanism linking the environment with cancer risk.*BMJ.* 321(7265):847-848.

Solan S, Wallenstein S, Shapiro M, *et. al.* (2013) Cancer Incidence in World Trade Center Rescue and Recovery Workers, 2001-2008. *Environ Health Perspect* (): .doi:10.1289/ehp.1205894.

Stattin P., Bylund A., Rinaldi S *et. al.* (2000). Plasma Insulin-Like Growth Factor-I, Insulin-Like Growth Factor-Binding Proteins, and Prostate Cancer Risk: a Prospective Study. *Journal of the National Cancer Institute;* 92:23

Stefanek, M., McDonald, P. G. and Hess, S. A. (2005), Religion, spirituality and cancer: Current status and methodological challenges. *Psycho-Oncology*, 14: 450–463. doi: 10.1002/pon.861

Stein E. A and Myers G. L., (1995). National Cholesterol Education Program Recommendations for Triglycerides Measurement: Executive Summary. *Clin. Chem.* 41:1421-1426

Steinberger J and Daniels S .R (2003.) Obesity, insulin resistance, diabetes, and cardiovascular risk in children: an American Heart Association scientific statement. *Circulation* 107: 1448–53

Stocks T, Rapp K, Bjørge T, *et. al.*. (2009) Blood Glucose and Risk of Incident and Fatal Cancer in the Metabolic Syndrome and Cancer Project (Me-Can): Analysis of Six Prospective Cohorts. *PLoS Med* . 6(12): e1000201. doi:10.1371/journal.pmed.1000201

Stoll, B. (1998). Association between breast and colorectal cancers. *The Br J Surg*, 85(11), 1468-1472.

Stolzenberg-Solomon R.Z, Chang S.C, Leitzmann M. F *et. al.* (2006). Folate intake, alcohol use, and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Am J Clin Nutr* 83(4) 895-904.

Study Group, European Atherosclerosis Society (1987). Strategies for the prevention of coronary heart disease: A policy statement of the European Atherosclerosis Society. *Eur. Heart J.* 8:77

Tehard B, Friedenreich C. M, Oppert J. M and Clavel-Chapelon (2006). Effect of physical activity on women at increased risk of breast cancer: results from the E3N cohort study. *Cancer Epidemiol Biomarkers Prev.* 15(1):57-64.

The IDF consensus worldwide definition of the metabolic syndrome. (2006). International Diabetes Federation, IDF communication: Belgium.

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2001). NIH Publication No. 01-3670.

Thune, I. and Furberg A. S. (2001) Physical activity and cancer risk: dose-response and cancer, all sites and site-specific. *Med. Sci. Sports Exerc*. 33(6):S530-S550.

Tripkovic I, Tripkovic A, Strnad M, Capkun V, and Zekan L. (2007). Role of Insulin-Like Growth Factor-1 in Colon Cancerogenesis: A Case-Control Study. *Arch Med Res.* 38:519-525.

Tripkovic I, Tripkovic A, Strnad M, Capkun V, and Zekan L.(2004). Insulin Increase in Colon Cancerogenesis: A Case-Control Study. *Arch Med Res.* 35:215-219.

Ulmer, H., Borena, W., Rapp, K *et. al.* (2009). Serum triglyceride concentrations and cancer risk in a large cohort study in Austria. *Br J cancer*, 101(7), 1202-1206.

Vaissière T, Hung R. J, Zaridze D *et. al.* Z(2009). Quantitative Analysis of DNA Methylation Profiles in Lung Cancer Identifies Aberrant DNA Methylation of Specific Genes and Its Association with Gender and Cancer Risk Factors. *Cancer Res.* 69(1):243–52

Wallace T. M, Levy J. C, Matthews D. R (2004). "Use and abuse of HOMA modelling". *Diabetes Care.* 27 (6): 1487–95

Wahlefeld A. W. and Bergmeyer H. U (1974). Eds. *Methods of Enzymatic Analysis.* 2nd English ed. New York, NY: Academic Press Inc.

Wolin K. Y, Carson K, and Colditz G. A (2010). Obesity and cancer. *The Oncologist*. 15(6): 556-565.

World Health Organization. Global Health Risks. Mortality and Burden of Disease Attributable to Selected Major Risks. Geneva: World Health Organization; 2009.

Wu, Q., Wu, Q., and Zhang, A. (2011). Metabolic disturbance and insulin resistance in patients with colorectal cancer.,*Zhonghua Wei Chang WaiKeZaZhi = Chinese J Gastro Surg*.14(4), 261-263.

WHO (2011).Global status report on non – communicable diseases 2010. Geneva: World Health Organization.

Xu W.H, Matthews C.E, Xiang Y.B, *et. al.* (2005) Effect of adiposity and fat distribution on endometrial cancer risk in Shanghai women. *Am J Epidemiol*. 161:939–947

Yang P, Zhou Y, Chen B *et. al*. (2009). Overweight, obesity and gastric cancer risk: Results from a meta-analysis of cohort studies. Eur J Cancer. 45(16):2867-2873

Yoshikawa T, Noguchi Y, Doi C, Makino T and Nomura K (2001). Insulin resistance in patients with cancer: relationships with tumor site, tumor stage, body-weight loss, acute-phase response, and energy expenditure. *Nutri*. 17(7–8):590-593

Zhang Y, Liu Z, Yu X *et. al.* (2010). The association between metabolic abnormality and endometrial cancer: a large case–control study in China. *Gynecol Oncol.* 117:41–46

Zhao, J., Zhu, Y., Wang, P *et. al*. (2012.) Interaction between alcohol drinking and obesity in relation to colorectal cancer risk: a case-control study in Newfoundland and Labrador, Canada. *BMC Public Health.*12:94.