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EDITORIAL

Diabetes, insulin and cancer risk

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Abstract

There is a consensus that both type 1 and type 2 diabetes are associated with a spectrum of cancers but the underlying mechanisms are largely unknown. On the other hand, there are ongoing debates about the risk association of insulin use with cancer. We have briefly reviewed recent related research on exploration of risk factors for cancer and pharmacoepidemiological investigations into drug use in diabetes on the risk of cancer, as well as the current understanding of metabolic pathways implicated in intermediary metabolism and cellular growth. Based on the novel findings from the Hong Kong Diabetes Registry and consistent experimental evidence, we argue that use of insulin to control hyperglycemia is unlikely to contribute to increased cancer risk and that dysregulations in the AMP-activated protein kinase pathway due to reduced insulin action and insulin resistance, the insulin-like growth factor-1 (IGF-1)-cholesterol synthesis pathway and renin-angiotensin system, presumably due to reduced insulin secretion and hyperglycemia, may play causal roles in the increased risk of cancer in diabetes. Further exploration into the possible causal relationships between abnormalities of these pathways and the risk of cancer in diabetes is warranted.

Key words: Diabetes; Insulin; Cancer; Hyperglycemia; Cholesterol synthesis pathway; Renin-angiotensin system; adenosine 5′-monophosphate -activated protein kinase pathway

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INTRODUCTION

The prevalence of diabetes has been rapidly increasing in China over the past decades[1], i.e., from 0.9% in 1980, to 3.1% in 1994[2] and further increased to 9.7% in 2008[3]. In addition to cardiovascular disease[4-6] and renal disease[7-8], type 1 and type 2 diabetes are also associated with a spectrum of cancers[9-15], except for prostate cancer with reports showing conflicting results[16-17]. Since the first few reports on increased incidence of cancer in insulin-treated patients, there are ongoing debates regarding the risk association of insulin use with cancer[18-19]. In 2010, the American Diabetes Association and the American Cancer Society reviewed the state of science concerning a number of issues regarding the association between diabetes and cancer, including diabetes treatment and cancer risk, and published a joint consensus report but without conclusions about many of these issues, including insulin usage and cancer risk[20-21]. Further contention about

insulin usage and cancer risk has important implications since millions of people require insulin to control hyperglycemia. To address this issue, we need to consider two fundamental questions. Firstly, does endogenous insulin play a causal role in cancer development? Secondly, does insulin usage play a causal role in cancer development? Many authors suspect that insulin and insulin analogues may promote tumor proliferation[22-25] but the data from the Hong Kong Diabetes Registry and experimental evidence suggests a different story[18,26].

HYPERINSULINEMIA AND CANCER IN NON-DIABETIC SUBJECTS

Circulating insulin levels in non-diabetic or prediabetic subjects are associated with some cancer subtypes[27]. This is often attributed to hyperinsulinemia due to obesity-associated insulin resistance which can promote carcinogenesis through several mechanisms[28]. The adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) pathway is a gatekeeper for energy metabolism intimately related to cell cycles, and is considered a therapeutic target for diabetes, metabolic syndrome[29-31] and cancer[32-33]. Insulin resistance is associated with inhibition of the LKB1-AMPK pathway which promotes energy storage and obesity. In experimental studies, inhibition of the LKB1-AMPK was associated with protein synthesis and cancer development, while its activation by metformin reduced cancer risk. Many tumor cells express insulin and insulin growth factor (IGF-1) receptors which can activate the protein kinase B (Akt) and mitogen-activated protein kinase signaling networks in neoplastic tissues. Although more evidence is needed to confirm these mechanisms, they are supported by the association of cancer risk with circulating levels of insulin and IGF-1 in population-based studies[34-35].

INSULIN USE AND CANCER IN DIABETIC SUBJECTS

However, these mechanisms are not likely to be relevant to people with diabetes, who often have insufficient insulin action and may require insulin to control hyperglycemia. Many of the cohort studies on the association of cancer with insulin use were flawed with biases which can only be addressed by randomized clinical trials. Importantly, insulin use is indicated for hyperglycemia. The latter can independently promote growth of cancer cells which thrive better than normal cells by obtaining energy from glycolysis rather than the tricarboxylic acid cycle in anerobic conditions[36]. In this regard, we reported a 52% (HR: 0.48, 95% CI: 0.32-0.73) reduction of cancer risk among insulin users compared to non users[18], using a validated approach largely free of drug use indication bias, prevent user bias and immortal time bias[37].

HYPERGLYCEMIA AND CANCER

Several large cohort or case-control studies have reported a positive association between hyperglycemia and cancer[38-41]. To date, none of the randomized clinical trials of blood-glucose lowering drugs have included cancer as a predefined clinical endpoint. In a prospective cohort, including new insulin users with carefully matched non-insulin users, we first reported the marked reduction in cancer risk in insulin users and an 18% increase in cancer risk for every 1% increase in glycated hemoglobin (A1c)[18]. These novel findings were corroborated by a meta-analysis of blood glucose lowering trials where intensive glycemic control with 0.3%-0.9% reduction in A1c was associated with 9% (95% CI: 0.79-1.05) reduction in cancer risk[42], although individual trials of intensive glycemic control did not observe a reduction in cancer risk[43]. In a tumor-prone animal model, researchers have reported an increased number and size of liver tumors with reduced apoptosis in insulin-deficient hyperglycemic animals compared to insulin-sufficient mice, which was reversed by insulin therapy[44].

AMPK PATHWAY AND CANCER RISK

The risk association of A1c with cancer has led us to further examine the possible associations of lipids with the risk of cancer, which are tightly linked with glucose metabolism. Using a well characterized prospective cohort, the Hong Kong Diabetes Registry, we first reported the V-shaped risk associations of cancer with various lipid parameters, including low density lipoprotein cholesterol (LDL-C) levels < 2.80 mmol/L and ⩾ 3.80[45], high density lipoprotein cholesterol (HDL-C) levels < 1.0 mmol/L and ⩾ 1.30 mmol/L[46] and triglyceride < 1.70 mmol/L[47].

Here, the risk association of cancer with low HDL-C has been reported in the general population and may be causal[48]. There are consistent reports that show a protective effect of metformin on the risk of cancer[49-50] and cancer mortality[51-52]. In Chinese type 2 diabetic patients, we have further reported the anti-cancer effects of metformin which is enhanced among patients with low HDL-C < 1.0 mmol/L[46]. Since both apolipoprotein (Apo) A-I, the main lipoprotein of HDL-C[53], and metformin can increase insulin sensitivity by activating the AMPK pathway[54], the interactive effects of metformin and HDL-C on cancer risk suggest that an abnormal AMPK pathway may link diabetes and cancer.

INFLAMMATION, THE RENIN ANGIOTENSIN SYSTEM AND THE CHOLESTEROL SYNTHESIS PATHWAY

Although the risk association of low LDL-C and cancer has been reported in the general population, its nature remains elusive[55]. In Chinese type 2 diabetic patients, the presence of albuminuria or low triglyceride (< 1.7 mmol/L) greatly enhanced the low LDL-C-cancer associations but not low LDL-C alone[26,56]. This low LDL-C associated cancer risk was markedly attenuated by use of

statins[47,56]. Intriguingly, high HDL-C (≥ 1.30 mmol/L) also amplified the cancer-promoting effect of co-presence of low LDL-C and albuminuria[26]. Based on these novel findings and literature search, we were able to find evidence to suggest that insulin (or its action) insufficiency and hyperglycemia may increase cancer risk by up-regulating the cholesterol biosynthesis pathway.

The family of sterol regulatory element-binding proteins (SREBPs), including SREBP-1a, 1c and 2[57], are transcription factors which control lipid metabolism through feedback mechanisms. While SREBP-1a and 2 mainly regulate synthesis of enzymes involved in sterol biosynthesis, SREBP-1c regulates synthesis of enzymes involved in free fatty acid and triglyceride[57]. Since insulin selectively activates SREBP-1c[58], we argue that low triglyceride and low LDL-C may reflect insufficient insulin action with impaired activation of the SREBP-1c. The latter may be accompanied by upregulation of the SREBP-1a pathways to increase cholesterol synthesis with increased production of Ras molecules, the latter known to promote oncogenesis. These hypotheses are supported by the anti-cancer effects of statin, an inhibitor of the hydroxymethylglutaryl-CoA reductase, especially in subjects with the subphenotype of low LDL-C+ low triglyceride[47].

Adding to this complexity are the effects of hyperglycemia on oxidative stress, renin-angiotensin system and inflammation, the latter being reflected by albuminuria[59]. In this regard, we have reported cross-talks between cholesterol synthesis and renin angiotensin pathways in promoting carcinogenesis and the additive effects of statins and inhibitors of the renin-angiotensin pathways on cancer risk[60]. While low HDL-C may be pro-atherogenic, high HDL-C can be pro-inflammatory, especially in the presence of systemic inflammation[61]. Thus, the complex synergistic effects among low LDL-C, albuminuria and high HDL-C in increasing cancer risk and the prominent anticancer effects of statins in patients with co-presence of these risk factors strongly suggest that dysregulation of the cholesterol biosynthesis pathway, secondary to hyperglycemia systemic inflammation and activation of the renin angiotensin system, may play a pivotal role linking diabetes and cancer.

CONFOUNDING EFFECTS OF OBESITY IN EXAMINATION OF INSULIN LEVELS AND USAGE FOR CANCER

The associations between obesity and cancer incidence- and mortality in general populations have been repeatedly reported for a member of site-specific cancers[62,63]. In type 2 diabetes, the association between body mass index (BMI) and cancer is not a simple linear one but in a V-shaped manner[64]. Both type 2 diabetic patients with BMI < 24.0 kg/m^2 and ≥ 27.6 kg/m^2 are at increased risk of cancer compared to those who have a BMI at ≥ 24.0 kg/m^2 and < 27.6 kg/m^2[64]. Obesity impairs insulin action and results in insulin resistance and compensatory hyperglycemia[65]; thus potentially confounding the association between insulin levels and cancer, as well as that between insulin usage and cancer. In this regard, one study reported that the association between obesity and cancer is mediated via the AMPK pathway[66], although many authors believe that insulin and the IGF axis may play a role in obesity-related high cancer risk[67]. With the Hong Kong Diabetes Registry, we reported that insulin usage is associated with a reduced risk of cancer[18] and the hazard ratio is unchanged after further adjusting for the non-linear association between BMI and cancer (unpublished data). Obesity and type 2 diabetes share common characteristic changes in lipid profiles: high triglyceride, low HDL-C and increased concentration of small dense LDL-C particles[68,69]. What is interesting among type 2 diabetes is that low HDL-C but not high triglyceride predicts cancer[46-47,64]. Thus, the lipid-cancer risk associations may only partially explain the obesity-cancer association because the V-shaped association between BMI and cancer among type 2 diabetes was observed after adjusting for the non-linear associations of lipids and cancer risk[64]. To this end, the observed insulin usage and reduced cancer risk is independent of BMI-cancer and lipid-cancer associations[18].

CONCLUSION

Based on a series of pharmacoepidemiological analysis and our current understanding of metabolic pathways implicated in intermediary metabolism and cellular growth, it is unlikely that use of insulin to control hyperglycemia will contribute to increased cancer risk. Several lines of evidence further suggest that dysregulation of cholesterol synthesis and the renin-angiotensin system, possibly due to insufficient insulin action and/or hyperglycemia, may play causal roles linking diabetes and cancer, in addition to insulin resistance. While these epidemiological findings require independent replication, experimental studies are needed to define these molecular mechanisms. Meanwhile, there is an urgent need to conduct randomized clinical trials to demonstrate whether normalizing these metabolic abnormalities, including hyperglycemia, dyslipidemia, renin-angiotensin system and inflammation, can attenuate cancer risk in diabetes.

REFERENCES

1 **Chan JC**, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, Hu FB. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; **301**: 2129-2140

2 **Pan XR**, Yang WY, Li GW, Liu J. Prevalence of diabetes and its risk factors in China, 1994. National Diabetes Prevention and Control Cooperative Group. *Diabetes Care* 1997; **20**: 1664-1669

3 **Yang W**, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q, Zhu D, Ge J, Lin L, Chen L, Guo X, Zhao Z, Li Q, Zhou Z, Shan G, He J. Prevalence of diabetes among men and women in China. *N Engl J Med* 2010; **362**: 1090-1101

4 **Yang X**, So WY, Kong AP, Ma RC, Ko GT, Ho CS, Lam CW, Cockram CS, Chan JC, Tong PC. Development and validation of a total coronary heart disease risk score in type 2 dia-

betes mellitus. *Am J Cardiol* 2008; **101**: 596-601
5 **Yang X**, So WY, Kong AP, Ho CS, Lam CW, Stevens RJ, Lyu RR, Yin DD, Cockram CS, Tong PC, Wong V, Chan JC. Development and validation of stroke risk equation for Hong Kong Chinese patients with type 2 diabetes: the Hong Kong Diabetes Registry. *Diabetes Care* 2007; **30**: 65-70
6 **Yang X**, Ma RC, So WY, Kong AP, Ko GT, Ho CS, Lam CW, Cockram CS, Tong PC, Chan JC. Development and validation of a risk score for hospitalization for heart failure in patients with Type 2 diabetes mellitus. *Cardiovasc Diabetol* 2008; **7**: 9
7 **Yang XL**, So WY, Kong AP, Ho CS, Lam CW, Ng MH, Lyu RR, Yin DD, Chow CC, Cockram CS, Tong PC, Chan JC. Modified end-stage renal disease risk score for Chinese type 2 diabetic patients--the Hong Kong Diabetes Registry. *Diabetologia* 2007; **50**: 1348-1350
8 **Yang XL**, So WY, Kong AP, Clarke P, Ho CS, Lam CW, Ng MH, Lyu RR, Yin DD, Chow CC, Cockram CS, Tong PC, Chan JC. End-stage renal disease risk equations for Hong Kong Chinese patients with type 2 diabetes: Hong Kong Diabetes Registry. *Diabetologia* 2006; **49**: 2299-2308
9 **Everhart J**, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. *JAMA* 1995; **273**: 1605-1609
10 **El-Serag HB**, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* 2006; **4**: 369-380
11 **Friberg E**, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* 2007; **50**: 1365-1374
12 **Larsson SC**, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia* 2006; **49**: 2819-2823
13 **Mitri J**, Castillo J, Pittas AG. Diabetes and risk of Non-Hodgkin's lymphoma: a meta-analysis of observational studies. *Diabetes Care* 2008; **31**: 2391-2397
14 **Larsson SC**, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst* 2005; **97**: 1679-1687
15 **Larsson SC**, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer* 2007; **121**: 856-862
16 **Tseng CH**. Diabetes and risk of prostate cancer: a study using the National Health Insurance. *Diabetes Care* 2011; **34**: 616-621
17 **Jee SH**, Park JY, Kim HS, Lee TY, Samet JM. White blood cell count and risk for all-cause, cardiovascular, and cancer mortality in a cohort of Koreans. *Am J Epidemiol* 2005; **162**: 1062-1069
18 **Yang X**, Ko GT, So WY, Ma RC, Yu LW, Kong AP, Zhao H, Chow CC, Tong PC, Chan JC. Associations of hyperglycemia and insulin usage with the risk of cancer in type 2 diabetes: the Hong Kong diabetes registry. *Diabetes* 2010; **59**: 1254-1260
19 **Johnson JA**, Pollak M. Insulin, glucose and the increased risk of cancer in patients with type 2 diabetes. *Diabetologia* 2010; **53**: 2086-2088
20 **Giovannucci E**, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. *Diabetes Care* 2010; **33**: 1674-1685
21 **Giovannucci E**, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. *CA Cancer J Clin* 2010; **60**: 207-221
22 **Pollak M**, Russell-Jones D. Insulin analogues and cancer risk: cause for concern or cause célèbre? *Int J Clin Pract* 2010; **64**: 628-636
23 **Ruiter R**, Visser LE, van Herk-Sukel MP, Coebergh JW, Haak HR, Geelhoed-Duijvestijn PH, Straus SM, Herings RM, Stricker BH. Risk of cancer in patients on insulin glargine and other insulin analogues in comparison with those on human insulin: results from a large population-based follow-up study. *Diabetologia* 2012; **55**: 51-62
24 **Werner H**, Weinstein D, Yehezkel E, Laron Z. Controversies in the use of insulin analogues. *Expert Opin Biol Ther* 2011; **11**: 199-209
25 **Yehezkel E**, Weinstein D, Simon M, Sarfstein R, Laron Z, Werner H. Long-acting insulin analogues elicit atypical signalling events mediated by the insulin receptor and insulin-like growth factor-I receptor. *Diabetologia* 2010; **53**: 2667-2675
26 **Yang X**, So WY, Ma RC, Kong AP, Xu G, Chan JC. Diabetes and cancer: the mechanistic implications of epidemiological analyses from the Hong Kong Diabetes Registry. Diabetes *Metab Res Rev* 2012; Epub ahead of print
27 **Pisani P**. Hyper-insulinaemia and cancer, meta-analyses of epidemiological studies. *Arch Physiol Biochem* 2008; **114**: 63-70
28 **Godsland IF**. Insulin resistance and hyperinsulinaemia in the development and progression of cancer. *Clin Sci (Lond)* 2010; **118**: 315-332
29 **Hegarty BD**, Turner N, Cooney GJ, Kraegen EW. Insulin resistance and fuel homeostasis: the role of AMP-activated protein kinase. *Acta Physiol (Oxf)* 2009; **196**: 129-145
30 **Kraegen EW**, Bruce C, Hegarty BD, Ye JM, Turner N, Cooney G. AMP-activated protein kinase and muscle insulin resistance. *Front Biosci* 2009; **14**: 4658-4672
31 **Ruderman NB**, Saha AK. Metabolic syndrome: adenosine monophosphate-activated protein kinase and malonyl coenzyme A. *Obesity (Silver Spring)* 2006; **14** Suppl 1: 25S-33S
32 **Kuhajda FP**. AMP-activated protein kinase and human cancer: cancer metabolism revisited. *Int J Obes (Lond)* 2008; **32** Suppl 4: S36-S41
33 **Wang W**, Guan KL. AMP-activated protein kinase and cancer. *Acta Physiol (Oxf)* 2009; **196**: 55-63
34 **Pollak M**. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer* 2008; **8**: 915-928
35 **Shackelford DB**, Shaw RJ. The LKB1-AMPK pathway: metabolism and growth control in tumour suppression. *Nat Rev Cancer* 2009; **9**: 563-575
36 **Warburg O**. On the origin of cancer cells. *Science* 1956; **123**: 309-314
37 **Yang XL**, Ma RC, So WY, Kong AP, Xu G, Chan JC. Addressing different biases in analysing drug use on cancer risk in diabetes in non-clinical trial settings-what, why and how? *Diabetes Obes Metab* 2011; Epub ahead of print
38 **Muti P**, Quattrin T, Grant BJ, Krogh V, Micheli A, Schünemann HJ, Ram M, Freudenheim JL, Sieri S, Trevisan M, Berrino F. Fasting glucose is a risk factor for breast cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 1361-1368
39 **Takahashi H**, Mizuta T, Eguchi Y, Kawaguchi Y, Kuwashiro T, Oeda S, Isoda H, Oza N, Iwane S, Izumi K, Anzai K, Ozaki I, Fujimoto K. Post-challenge hyperglycemia is a significant risk factor for the development of hepatocellular carcinoma in patients with chronic hepatitis C. *J Gastroenterol* 2011; **46**: 790-798
40 **Stattin P**, Björ O, Ferrari P, Lukanova A, Lenner P, Lindahl B, Hallmans G, Kaaks R. Prospective study of hyperglycemia and cancer risk. *Diabetes Care* 2007; **30**: 561-567
41 **Saydah SH**, Platz EA, Rifai N, Pollak MN, Brancati FL, Helzlsouer KJ. Association of markers of insulin and glucose control with subsequent colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2003; **12**: 412-418
42 **Johnson JA**, Bowker SL. Intensive glycaemic control and cancer risk in type 2 diabetes: a meta-analysis of major trials. *Diabetologia* 2011; **54**: 25-31
43 **Stefansdottir G**, Zoungas S, Chalmers J, Kengne AP, Knol MJ, Leufkens HG, Patel A, Woodward M, Grobbee DE, De Bruin ML. Intensive glucose control and risk of cancer in patients with type 2 diabetes. *Diabetologia* 2011; **54**: 1608-1614

44 **Yamasaki K**, Hayashi Y, Okamoto S, Osanai M, Lee GH. Insulin-independent promotion of chemically induced hepatocellular tumor development in genetically diabetic mice. *Cancer Sci* 2010; **101**: 65-72

45 **Yang X**, So W, Ko GT, Ma RC, Kong AP, Chow CC, Tong PC, Chan JC. Independent associations between low-density lipoprotein cholesterol and cancer among patients with type 2 diabetes mellitus. *CMAJ* 2008; **179**: 427-437

46 **Yang X**, So WY, Ma RC, Kong AP, Lee HM, Yu LW, Chow CC, Ozaki R, Ko GT, Chan JC. Low HDL cholesterol, metformin use, and cancer risk in type 2 diabetes: the Hong Kong Diabetes Registry. *Diabetes Care* 2011; **34**: 375-380

47 **Yang X**, Ma RC, So WY, Yu LW, Kong AP, Ko GT, Xu G, Ozaki R, Tong PC, Chan JC. Low triglyceride and nonuse of statins is associated with cancer in type 2 diabetes mellitus: the Hong Kong Diabetes Registry. *Cancer* 2011; **117**: 862-871

48 **Jafri H**, Alsheikh-Ali AA, Karas RH. Baseline and on-treatment high-density lipoprotein cholesterol and the risk of cancer in randomized controlled trials of lipid-altering therapy. *J Am Coll Cardiol* 2010; **55**: 2846-2854

49 **Libby G**, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care* 2009; **32**: 1620-1625

50 **Lee MS**, Hsu CC, Wahlqvist ML, Tsai HN, Chang YH, Huang YC. Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. *BMC Cancer* 2011; **11**: 20

51 **Landman GW**, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. *Diabetes Care* 2010; **33**: 322-326

52 **Lee JH**, Kim TI, Jeon SM, Hong SP, Cheon JH, Kim WH. The effects of metformin on the survival of colorectal cancer patients with diabetes mellitus. *Int J Cancer* 2011; Epub ahead of print

53 **Han R**, Lai R, Ding Q, Wang Z, Luo X, Zhang Y, Cui G, He J, Liu W, Chen Y. Apolipoprotein A-I stimulates AMP-activated protein kinase and improves glucose metabolism. *Diabetologia* 2007; **50**: 1960-1968

54 **Ben Sahra I**, Le Marchand-Brustel Y, Tanti JF, Bost F. Metformin in cancer therapy: a new perspective for an old antidiabetic drug? *Mol Cancer Ther* 2010; **9**: 1092-1099

55 **Alsheikh-Ali AA**, Trikalinos TA, Kent DM, Karas RH. Statins, low-density lipoprotein cholesterol, and risk of cancer. *J Am Coll Cardiol* 2008; **52**: 1141-1147

56 **Yang X**, So WY, Ma RC, Ko GT, Kong AP, Zhao H, Luk AO, Lam CW, Ho CS, Tong PC, Chan JC. Low LDL cholesterol, albuminuria, and statins for the risk of cancer in type 2 diabetes: the Hong Kong diabetes registry. *Diabetes Care* 2009; **32**: 1826-1832

57 **Brown MS**, Goldstein JL. The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. *Cell* 1997; **89**: 331-340

58 **Shimomura I**, Bashmakov Y, Ikemoto S, Horton JD, Brown MS, Goldstein JL. Insulin selectively increases SREBP-1c mRNA in the livers of rats with streptozotocin-induced diabetes. *Proc Natl Acad Sci USA* 1999; **96**: 13656-13661

59 **Kalaitzidis R**, Bakris G. Pathogenesis and treatment of microalbuminuria in patients with diabetes: the road ahead. *J Clin Hypertens (Greenwich)* 2009; **11**: 636-643

60 **Yang X**, Zhao H, Sui Y, Ma RC, So WY, Ko GT, Kong AP, Ozaki R, Yeung CY, Xu G, Tong PC, Chan JC. Additive interaction between the renin-angiotensin system and lipid metabolism for cancer in type 2 diabetes. *Diabetes* 2009; **58**: 1518-1525

61 **Nakamura M**, Onoda T, Itai K, Ohsawa M, Satou K, Sakai T, Segawa T, Sasaki J, Tonari Y, Hiramori K, Okayama A. Association between serum C-reactive protein levels and microalbuminuria: a population-based cross-sectional study in northern Iwate, Japan. *Intern Med* 2004; **43**: 919-925

62 **Basen-Engquist K**, Chang M. Obesity and cancer risk: recent review and evidence. *Curr Oncol Rep* 2011; **13**: 71-76

63 **Calle EE**, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003; **348**: 1625-1638

64 **Yang X**, So WY, Ma RC, Ko GT, Kong AP, Wang Q, Cockram CS, Chow CC, Chan JC, Tong PC. Predicting values of lipids and white blood cell count for all-site cancer in type 2 diabetes. *Endocr Relat Cancer* 2008; **15**: 597-607

65 **Benito M**. Tissue specificity on insulin action and resistance: past to recent mechanisms. *Acta Physiol (Oxf)* 2011; **201**: 297-312

66 **Brown KA**, Simpson ER. Obesity and breast cancer: progress to understanding the relationship. *Cancer Res* 2010; **70**: 4-7

67 **Donohoe CL**, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and cancer risk. *Diabetol Metab Syndr* 2011; **3**: 12

68 **Tonstad S**, Després JP. Treatment of lipid disorders in obesity. *Expert Rev Cardiovasc Ther* 2011; **9**: 1069-1080

69 **Mooradian AD**. Dyslipidemia in type 2 diabetes mellitus. *Nat Clin Pract Endocrinol Metab* 2009; **5**: 150-159

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