Yonsei Medical Journal
Vol. 46, No. 4, pp. 449 - 455, 2005

Review Article

# Obesity, Insulin Resistance and Cancer Risk

**Sun Ha Jee,[1,2] Hee Jin Kim,[1,3] and Jakyoung Lee[1]**

*[1]Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Korea;*
*[2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA;*
*[3]Department of Family Medicine, Eulji University School of Medicine, Seoul, Korea.*

Obesity is a known cause of metabolic syndrome which includes Type II diabetes, hypertension, and dyslipidemia. It is well documented that insulin resistance contributes to the mortality and the incidence of metabolic syndromes including central obesity, dyslipidemia, hyperglycemia and hypertension. Both obesity and diabetes are emerging topics for researchers to consider as having a possible causal association with cancer since the two factors have been viewed as risk factors for cancer. The present paper introduced the hypothesis of a possible causal relationship between obesity, insulin resistance and cancer and reviews relevant existing studies in this area. More efforts and studies are needed to clarify the mechanisms and the common risk factors which might be incorporated into interventions to prevent cancer and cardiovascular diseases as top causes of death.

**Key Words:** Obesity, insulin resistance, cancer, mechanism

Over the past 12 years, the prevalence of obesity has increased in Korea from 20.8% in 1992 to 39.2% in 2004 (Fig. 1). Current studies show that obesity and diabetes, a closely related disease, may be risk factors for cancer. It is important to note that both cancer and cardiovascular diseases, the leading causes of death in Korea, are closely associated with obesity. Obesity is a known cause of several metabolic diseases, including Type II diabetes, hypertension, and dyslipidemia.[1] Insulin resistance, which is considered a primary factor in the mechanisms of metabolic syndromes, is also known to raise the risk of cardiovascular disease.[2]

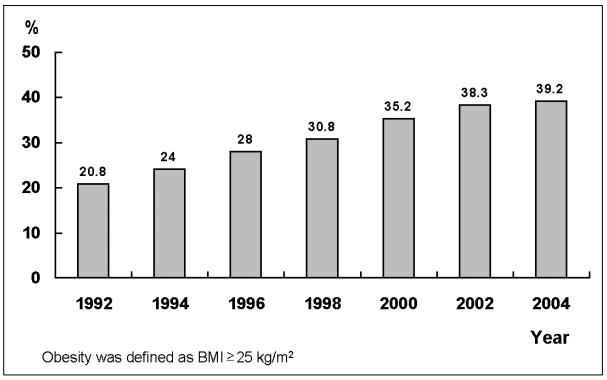


**Fig. 1.** Prevalence of obesity in Korean men.

Currently, both obesity and diabetes are being investigated because these conditions have a possible causal association with cancer, as they have been viewed as risk factors for the disease.[3,4] Common risk factors for chronic diseases such as cardiovascular disease, diabetes, and cancer are: smoking, obesity, and a sedentary lifestyle; however, these risk factors have different mechanisms of action in each of the chronic diseases.[5] Previous studies have hypothesized that risk factors such as obesity, diabetes, insulin resistance, inflammation, and oxidative stress might increase the risk of cancer. However, the association between these risk factors and cancer has not been clearly explained.

The causal relationship between the disease mechanisms and risk factors is not yet fully understood. Understanding the role of insulin resistance in the cause of death in each of these diseases may help to explain the relationship between risk factors, pathogenesis, diseases, and

Received August 3, 2005

*This work was supported by a grant of Ministry of Health and Welfare, Republic of Korea (00-PJ6-PG5-23-0001).*

*Reprint address: requests to Dr. Sun Ha Jee, Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea. Tel: 82-2-2228-1523, Fax: 82-2-365-5118, E-mail: jsunha@yumc.yonsei.ac.kr*

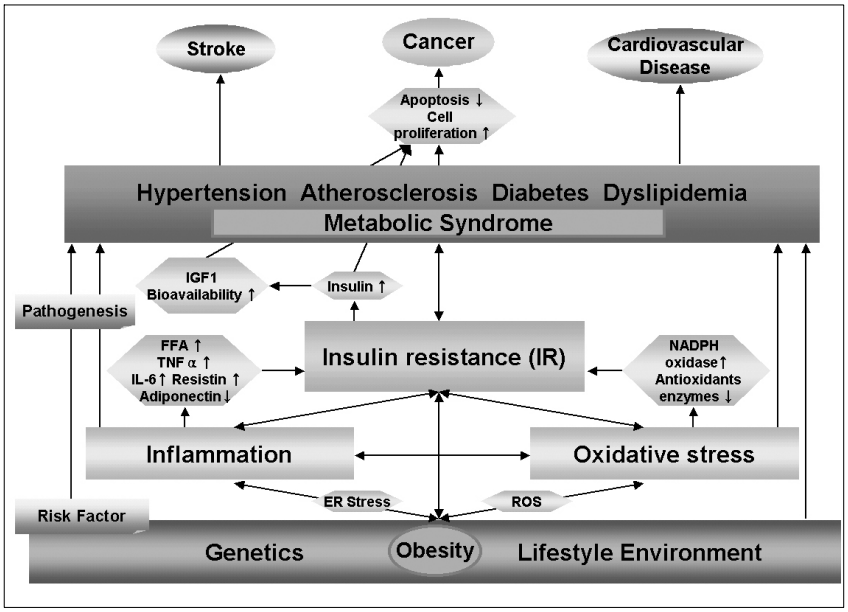


**Fig. 2.** Increased cancer risk through insulin resistance: a multi-dimensional model.

cause of death (Fig. 2). The development of each disease and metabolic syndrome, and the involvement of risk factors in inflammation, insulin resistance, and oxidative stress may interact. Researchers speculate that cancer may share a similar disease and risk factor interaction mechanism with that of cardiovascular disease. Fig. 2 explains the hypothesis of how risk factors affect the disease mechanism and result in a metabolic syndrome and ultimately end in the causes of death. The model focuses not on a possible single mechanism with single risk factor involvement, but instead on the systematic processes of multi-risk factor effects on the development of diseases. Reducing the major causes of death and the incidence of fatal illnesses are the main goals in public health. One of the main prevention strategies is to reduce the prevalence of obesity. This paper introduces the hypothesis that a causal relationship exists between obesity, insulin resistance, and cancer, and also reviews previous relevant studies.

## Mechanisms of developing cancer and insulin resistance

### Inflammatory response and insulin resistance

Insulin is an anti-inflammatory hormone. Macronutrient intake can initiate pro-inflammatory actions. Insulin is also known to be related with pro-inflammatory transcription factors, such as nuclear factor-kappa B (NF-κB), activating protein-1 (AP-1), matrix metalloproteinase-9 (MMP-9), tissue factor (TF), and plasminogen activator inhibitor-1 (PAI-1). If insulin resistance interrupts the regular insulin activities of controlling inflammation and pro-inflammatory transcription factors, then correlated genes may be activated that can enhance the inflammatory process.

Recent studies revealed the role of insulin on anti-inflammation in two perspectives. First, insulin reduced the level of CRP (C reactive protein) and monocyte chemotactic protein-1 (MCP-1) in Type II diabetics who were given the insulin treatment for two weeks. It was observed that insulin also reduced inflammatory markers in patients with severe hyperglycemia. In addition, insulin lowered the concentration level of inflammatory markers in mice injected with an endotoxin that caused inflammation. The inflammatory markers that are controlled by insulin are IL-1β, IL-6, macrophage migration inhibition factor (MIF), and tumor necrosis factor-alpha (TNF-α).[6]

Adipocytes and macrophages share a common role in inflammatory signaling and metabolic responses. Research has shown that TNF-α, IL-6, adiponectin, resistin, and leptin are associated

with various inflammatory and obesity mechanisms. TNF-α and IL-6 were increased among obese subjects. Adiponectin, which is usually decreased in obese people, improves insulin sensitivity and plays a role in anti-inflammatory actions. Resistin, sometimes induced by inflammation, can raise insulin resistance.

A cell has to maintain a balance between metabolism and inflammation; however, in over-nutrition or an obesity state, insulin resistance can occur due to the ineffective process of nutritional metabolism. In metabolic overload states, like glucose metabolism, obesity, and over-nutrition, there are increases in reactive oxygen species (ROS) in the mitochondria, protein production, and also in ER (endoplasmic reticulum) stress. These situations eventually initiate inflammation by activating inflammatory-signaling pathways.

These types of stimuli activate several serine/threonine kinases, and in turn interrupt insulin- signaling pathways. In the inflammatory signal transmission process, the primary process is thought to be a reduced function of the insulin receptors. Inflammatory responses interrupt insulin-signaling pathways and activate insulin resistance.

## Occurrence of oxidative stress and insulin resistance

Oxidative stress interferes with glucose metabolism and insulin secretion in pancreatic beta cells.[7,8] In addition, this stress is known to be a part of the pathogenesis of hypertension and atherosclerosis.[9,10] Recent studies have reported that oxidative stress is higher not only in diabetics, but also in subjects with increased adipose accumulation. The whole-body oxidative stress is known to be related to body mass index (BMI).[11]

According to Furukawa et al.,[12] accumulated adipose tissue increases whole-body oxidative stress in human subjects as well as in mice. In animal experiments, obese mice had increased ROS only in their adipose tissues. The increased ROS is also accompanied by an increase in the appearance of nicotinamide adenine dinuclotide phosphate (NADPH) oxidase and a decrease in anti-oxidative enzymes. In an adipocyte culture experiment, increases in fatty acids resulted in oxidative stress increases, and also a reduction in adiponectin. Fatty acids also raised the levels of PAI-1, IL-6, and MCP-1. In another study with obese mice, an inhibitor for NADPH oxidase reduced the production of ROS in adipose tissue and controlled adipocytokine, as well as diabetes, high cholesterol, and fatty liver. In summary, increased oxidative stress in adipose tissue is an initial step of pathogenesis which can develop into a metabolic syndrome. Thus, this might be one of the targets for the prevention of such metabolic syndromes.

## Cancer and insulin resistance

There are several hypotheses that explain the mechanism of carcinogenesis in obesity through inflammation, oxidative stress, and insulin resistance. It has been suggested that these mechanisms include increased cell proliferation due to hyperinsulinemia, cell growth from growth hormones, and reduced apoptosis.

Insulin resistance is an interrupted state in the biological response to insulin. It is reported that chronic hyperinsulinemia is associated with various types of cancer such as colorectal cancer,[13] pancreatic cancer,[14] endometrial cancer,[15] and breast cancer.[16] The mechanism of the carcinogenesis of insulin is thought to be associated with both insulin receptors and with endogenous hormone metabolism. Specifically, insulin promotes the production and activity of insulin-like growth factor 1 (IGF1), which can promote cell proliferation in an over-nutrition state. In one study, researchers found that insulin and IGF1 promoted cell proliferation and inhibited cell apoptosis.[17] In an experimental animal study, cancer growth was reduced when an IGF1 receptor was removed or when the IGF1 concentration was reduced.[18] Hyperinsulinemia can affect the production of sex hormones such as androgen and estrogen, which may be associated with cancer growth.

Although IGF1 is not relatively increased as BMI increases, researchers assume that free IGF1 can result in cell proliferation.[3] Eighty percent of IGF1 is combined with insulin-like growth factor binding protein (IGFBP3), which is known to interfere with cancer cell growth. Epidemiological experiments and studies report that an increase in IGFBP3 may prevent breast, colorectal, prostate,

and lung cancers. In obese subjects, IGFBP3 levels remained constant or showed a slight increase. While the IGF1 level is occasionally reduced, it is thought that the increase of IGFBP3 in obesity is due to the negative feedback caused by increases in free IGF1.[3,18]

More studies are needed on the factors that may influence cancer, including growth factors, insulin-like growth factor binding proteins, and sex hormones. The role of insulin warrants further research since obesity and metabolic syndromes are on the rise. Comprehensive interventions on lifestyle change are also needed.

## An epidemiological study on cancer risk and metabolic syndromes

It is well documented that insulin resistance contributes to the mortality and incidence of metabolic syndromes including central obesity, dyslipidemia, hyperglycemia, and hypertension.

### Increased cancer risk among diabetics

Diabetes is one of the major health concerns in Western countries. It is estimated that approximately 7% of adults and 15% of the elderly population have diabetes.[19] It has been 100 years since diabetes and cancer were first shown to have a possible association.[20] However, studies associating specific types of cancer with diabetes are inconsistent. For example, some studies indicate that diabetes might increase the risk of endometrial cancer[21] and female colorectal cancer. Other studies suggest that diabetes may not be related with any cancers except for pancreatic cancer and non-Hodgkin's lymphoma.[22,23]

In a prospective study that included 1.3 million Koreans, Jee et al.[24] reported that higher fasting blood sugar levels (140 mg/dL and above) increased the risk of all types of cancer by up to 1.29 times. (Male: HR=1.29; 95% confidence interval [CI], 1.22-1.37, Female: HR=1.23; 1.09-1.39). Specifically, they found that fasting blood sugar levels were highly associated with an increased risk of pancreatic cancer (Male: HR=1.91; 1.52-2.41, Female: HR=2.05; 1.43-2.93). Among men, a higher fasting sugar level was strongly associated with a higher risk of cancer of the esophagus, liver, and colon/rectum, while women had a higher risk of liver and cervical cancer (Fig. 3). The findings on

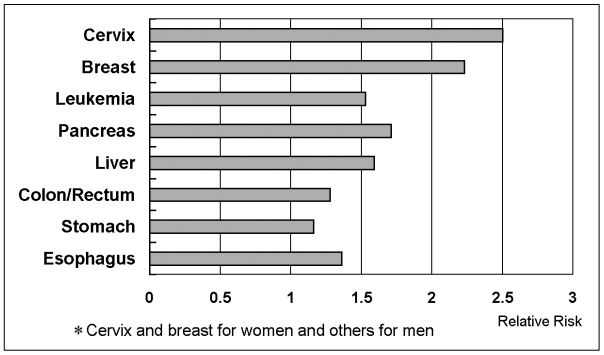


**Fig. 3.** Hazard ratios of diabetes versus non-diabetes on various cancers in Korean men and women. Source: Jee et al. JAMA 2005;293:194-202.

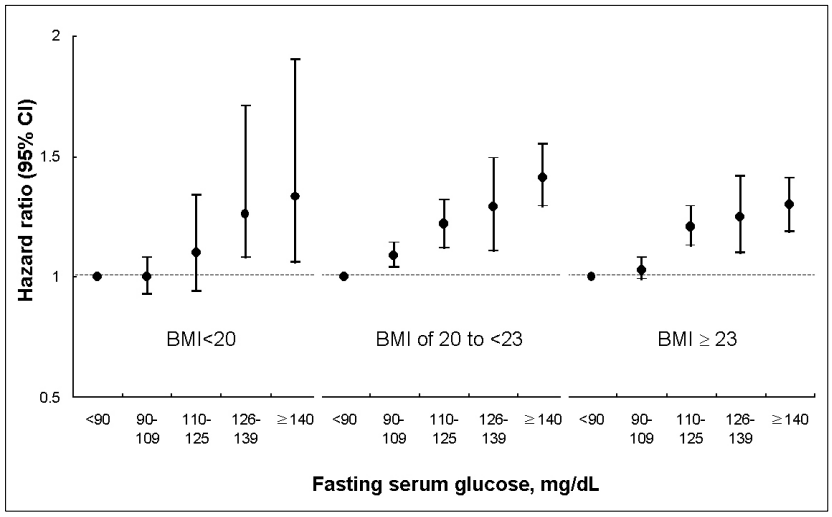


**Fig. 4.** Hazard ratios for all cancer deaths by fasting serum glucose levels in Korean men according to body mass index, 1993-2002. Source: Jee et al. JAMA 2005;293:194-202.

the fasting blood sugar levels and cancer risk were the same for the groups with low and high BMIs (Fig. 4).

In the United States, 65% of the population is overweight and/or obese. Worldwide, obesity is a major public health issue because of its association with diabetes. Findings that associate high fasting blood sugar levels and cancer risk are significant in Korea where there is not a high prevalence of obesity.[25]

Breast cancer, the most common cancer among women, is affected by many risk factors such as age, obesity, hormones, a past history of benign breast tumors, family history, and genetics.[26] Sixteen percent of breast cancer patients over 65 years old are diabetic.[27] The risk factors for Type II diabetes such as age and obesity are also known to be risk factors for breast cancer. Three mechanisms were suggested that connect diabetes and breast cancer: insulin pathway activation, insulin-like growth factor activation, and endogenous sex hormones. Based on the results of cohort research and case-control research, it was concluded that Type II diabetes may contribute to 10 to 20% of breast cancer risk. Gestational diabetes is also thought to increase the risk of breast cancer. Type I diabetes did not show an association with cancer risk. Diabetes and its complications can interfere with cancer treatment and diagnosis, which in turn may negatively affect the treatment results of breast cancer patients.[23]

Colorectal cancer may be also associated with diabetes. Several large-scale prospective studies provided evidence that diabetes is associated with colorectal cancer. Five studies on the association between colorectal cancer and diabetes showed inconsistent results, with different types and ranges of association. The wide range of results between these studies was associated with gender differences. In an 18 year Prospective Nurses' Health Study, Hu et al.[21] reported that there are strong associations between colorectal cancer and diabetes among women. The relative ratio for colorectal cancer was 1.43 (95% CI, 1.10-1.87; $p$= 0.009) and was 2.39 (95% CI, 1.46-3.92; $p$=0.0005) for fatal colorectal cancer. This study revealed that the relative risk of fatal colorectal cancer declined in patients with long-term diabetes. This trend was thought to be due to relatively low insulin levels in the bloodstream caused by a longer period of living in a diabetic state. This supports the hypothesis that hyperinsulinemia in the blood may contribute to the risk of colorectal cancer as a reactive result of insulin resistance.

In a cancer prevention study sponsored by the American Cancer Society, Will et al.[28] compared diabetic patients with non-diabetic patients to determine which group had a higher risk of colorectal cancer over a period of 13 years. The study examined factors such as BMI, family history, physical activity level, race, smoking, diet, alcohol consumption, and aspirin intake. The findings indicated that the risk of colorectal cancer was higher for male diabetic patients (RR=1.30; 1.03-1.65) but not significantly higher for female diabetic patients (RR=1.16; 0.87-1.53). Nilsen et al.[29] followed their subjects for 12 years to determine whether an association existed between colorectal cancer risk factors (i.e. diabetes, blood sugar level, physical activity, or BMI) and the risk of colorectal cancer. After adjusting for age, the risk of colorectal cancer was higher for females (RR=1.55; 1.04-2.31) and was not significantly higher for males with a history of Type II diabetes. In a study by Kono et al.,[30] 821 cases of sigmoid colorectal adenomas were compared with a 4,372-person control group. Family histories were studied and the subjects underwent a 75g oral glucose tolerance test. The subjects were then categorized into a normal group, an impaired glucose tolerance group, a newly-diagnosed non-insulin-dependent diabetes group, and a treatment-in-progress diabetes group. This study found that there was an association between sigmoid colorectal adenomas and non insulin-dependent diabetes. A large-scale case controlled study in Italy compared 1,225 colorectal cancer patients and 4,154 in-patients without cancer.[31] The odds ratio for colorectal cancer was slightly higher among diabetic patients over 40 years old (OR=1.4; 1.1-1.7). A stronger association was found among patients who had been living with diabetes for more than 10 years and also had colorectal cancer that was first diagnosed at the age of 60 and older (OR=1.6; 1.1-2.3). This study also reported that BMI, physical activity, alcohol intake, energy, and fiber intake did not affect the association. These research results support the

hypothesis that diabetes and high insulin levels might be triggering factors for colorectal cancer.[4]

### Increase in cancer among hypertensives

After controlling for age, smoking, physical activity, BMI, alcohol consumption, diabetes, and cholesterol levels in the blood, a cohort study with 450,000 Korean men showed that hypertension was not an independent risk factor for lung cancer, but it did increase the mortality rate among lung cancer patients who were smokers (RR=1.8, 95% CI; 1.0-3.1).[32] In another cohort study involving 570,000 Koreans, hypertension was found to be an independent risk factor for kidney cancer.[33]

### Higher risk for cancer among patients with a high cholesterol level

A total of 7,619 Japanese-Americans were followed for 30 years in a cohort study. The researchers found that a high BMI increased the risk of colon cancer but was not associated with rectal cancer. In addition, triglyceride levels in the blood did not increase the risk of colorectal cancer.[34]

In a study of 103 breast cancer patients compared with 103 members of a control group, the breast cancer patients had higher leptin and triglyceride levels and lower blood high density lipoproteins (HDL).[35]

However, it is still not clear how diseases and their conditions contribute to the risk of cancer, or how the interaction of these collective diseases, along with metabolic syndromes, contribute to cancer. Further studies are needed as follows.

## Suggestions for future studies

According to recent studies on the effects of insulin, most of the results suggested that insulin resistance played a basic role in the development of cancer, although insulin resistance may not be the only factor involved in metabolic syndromes.[36] Hyperinsulinemia, impaired glucose tolerance, Type II diabetes, high triglyceride levels in the blood, and a lowered HDL can be explained in terms of the insulin-resistant effects on the metabolic mechanisms of carbohydrates and fat. In addition, insulin and metabolic syndromes may contribute to the risks associated with coronary heart disease and cerebrovascular disease.[6]

A metabolic syndrome can be described as a complex of risk factors for cancer including obesity, insulin resistance, inflammation, and diseases such as diabetes and atherosclerosis. Additional studies are needed to further investigate the relationship between metabolic syndromes and the mechanism of cancer development. These studies may provide evidence that preventive interventions for metabolic syndromes can reduce the risk of cardiovascular diseases and reduce the risk of cancer. Additional studies are needed to elucidate disease mechanisms and common risk factors in order to develop effective interventions to prevent the current top causes of death: cancer and cardiovascular diseases.

## REFERENCES

1. Garrison RJ, Higgins MW, Kannel WB. Obesity and coronary heart disease. Curr Opin Lipidol 1996;7:199-202.
2. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709-16.
3. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579-91.
4. Komninou D, Ayonote A, Richie JP Jr, Rigas B. Insulin resistance and its contribution to colon carcinogenesis. Exp Biol Med (Maywood) 2003;228:396-405.
5. Renehan AG, Howell A. Preventing cancer, cardiovascular disease, and diabetes. Lancet 2005;365:1449-51.
6. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation 2005;111:1448-54.
7. Maddux BA, See W, Lawrence JC Jr, Goldfine AL, Goldfine ID, Evans JL. Protection against oxidative stress-induced insulin resistance in rat L6 muscle cells by mircomolar concentrations of alpha-lipoic acid. Diabetes 2001;50:404-10.
8. Matsuoka T, Kajimoto Y, Watada H, Kaneto H, Kishimoto M, Umayahara Y, et al. Glycation-dependent, reactive oxygen species-mediated suppression of the insulin gene promoter activity in HIT cells. J Clin Invest 1997;99:144-50.

9. Nakazono K, Watanabe N, Matsuno K, Sasaki J, Sato T, Inoue M. Does superoxide underlie the pathogenesis of hypertension? Proc Natl Acad Sci USA 1991;88: 10045-8.
10. Ohara Y, Peterson TE, Harrison DG. Hypercholesterolemia increases endothelial superoxide anion production. J Clin Invest 1993;91:2546-51.
11. Keaney JF Jr, Larson MG, Vasan RS, Wilson PW, Lipinska I, Corey D, et al. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. Arterioscler Thromb Vasc Biol 2003;23:434-9.
12. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 2004;114:1752-61.
13. Giovannucci E. Insulin and colon cancer. Cancer Causes Control 1995;6:164-79.
14. Weiderpass E, Partanen T, Kaaks R, Vainio H, Porta M, Kauppinen T, et al. Occurrence, trends and environment etiology of pancreatic cancer. Scand J Work Environ Health 1998;24:165-74.
15. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomarkers Prev 2002;11: 1531-43.
16. Kaaks R. Nutrition, hormones, and breast cancer: is insulin the missing link? Cancer Causes Control 1996;7: 605-25.
17. Khandwala HM, McCutcheon IE, Flyvbjerg A, Friend KE. The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev 2000;21: 215-44.
18. Chapman IM, Hartman ML, Pieper KS, Skiles EH, Pezzoli SS, Hintz RL, et al. Recovery of growth hormone release from suppression by exogenous insulin-like growth factor I (IGF-I): evidence for a suppressive action of free rather than bound IGF-I. J Clin Endocrinol Metab 1998;83:2836-42.
19. The DECODE Study Group. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes Care 2003;26:61-9.
20. Weiderpass E, Gridley G, Persson I, Nyren O, Ekbom A, Adami HO. Risk of endometrial and breast cancer in patients with diabetes mellitus. Int J Cancer 1997;71: 360-3.
21. Hu FB, Manson JE, Liu S, Hunter D, Colditz GA, Michels KB, et al. Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. J Natl Cancer Inst 1999;91:542-7.
22. Hjalgrim H, Frisch M, Ekbom A, Kyvik KO, Melbye M, Green A. Cancer and diabetes--a follow-up study of two population-based cohorts of diabetic patients. J Intern Med 1997;241:471-5.
23. Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B. Diabetes mellitus and breast cancer. Lancet Oncol 2005; 6:103-11.
24. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194-202.
25. Cooney KA, Gruber SB. Hyperglycemia, Obesity, and Cancer Risk on the Horizon. JAMA 2005;293:235-6.
26. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. Lancet Oncol 2001;2:133-40.
27. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 2001;285:885-92.
28. Will JC, Galuska DA, Vinicor F, Calle EE. Colorectal cancer: another complication of diabetes mellitus? Am J Epidemiol 1998;147:816-25.
29. Nilsen TI, Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, hyperinsulinemia hypothesis. Br J Cancer 2001:417-22.
30. Kono S, Honjo S, Todoroki I, Nishiwaki M, Hamada H, Nishikawa H, et al. Glucose intolerance and adenomas of the sigmoid colon in Japanese men (Japan). Cancer Causes Control 1998;9:441-6.
31. La Vecchia C, Negri E, Decarli A, Franceschi S. Diabetes mellitus and colorectal cancer risk. Cancer Epidemiol Biomark Prev 1997;6:1007-10.
32. Lee SY, Kim MT, Jee SH, Im JS. Does hypertension increase mortality risk from lung cancer? A prospective cohort study on smoking, hypertension and lung cancer risk among Korean men. J Hypertens 2002;20:617-22.
33. Choi MY, Jee SH, Sull JW, Nam CM. The effect of hypertension on the risk for kidney cancer in Korean men. Kidney Int 2005;67:647-52.
34. Tsushima M, Nomura AM, Lee J, Stemmermann GN. Prospective study of the association of serum triglyceride and glucose with colorectal cancer. Dig Dis Sci 2005;50:499-505.
35. Han C, Zhang HT, Du L, Liu X, Jing J, Zhao X, et al. Serum levels of leptin, insulin, and lipids in relation to breast cancer in China. Endocrine 2005;26:19-24.
36. Dandona P, Aljada A, Mohanty P. The anti-inflammatory and potential anti-atherogenic effect of insulin: a new paradigm. Diabetologia 2002;45:924-30.