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# Type 2 Diabetes Mellitus and Cancer – a Nutrition-oriented Intervention Study\*

## Introduction

Obesity, hyperinsulinemia and insulin resistance are important factors in the pathogenesis of Type 2 Diabetes mellitus (non-insulin-dependent diabetes mellitus, NIDDM) and in further associated metabolic and cardiovascular disorders like dyslipidemia and hypertension. The common clinical picture is summarized with the term “metabolic syndrome” and has reached pandemic proportions in the Western, industrialized countries. In obesity, it has been convincingly shown in the past years that the number of adipocytes increases and they also increase in size. These adipocytes, as endocrine cells, secrete free fatty acids and proteins, so-called adipokines and adipocytokines, which among other things, contribute to the development of glucose metabolism disorders. In a recent Finnish study epidemiological data was presented [12], which indicate that individual parameters of the metabolic syndrome (e.g. obesity, BMI > 27 kg/m<sup>2</sup>) are associated with an increased risk for prostate carcinoma. A similarly significant study, a 16-year follow up study, was introduced by Coughlin et al [6], in which diabetes mellitus was shown to be an indicator for cancer mortality in a cohort of 467,922 men and 588,321 women in the USA. Their epidemiological conclusion: diabetes mellitus (Type 2) was an independent indicator of cancer mortality, in regard to colon, pancreas and breast carcinoma in women, and also an indicator for liver and bladder carcinoma in men. Such newly revealed relationships

and indications between the most important diseases in the Western world have prompted the American Cancer Society, the American Diabetes Association and the American Heart Association to release common statements, how in a concentrated effort the social and nutritional resources for the preventative protection of the consumer and/or patient should be initiated [4,9].

In a European, prospective investigation that has been published as the “Cancer Norfolk Study,” the authors Khaw et al were able to demonstrate a relationship between elevated HbA1c values, which are often observed in poorly adjusted diabetics, and the risk to develop colorectal carcinoma [11].

Therefore it is not curious that more and more research efforts, both nationally and internationally, are being made to create nutritional strategies that can be so enacted in the long-term in consumers and patients, in order to reduce the risk of developing these diseases or positively influencing their course.

In a controlled, prospective study the authors Deibert, Konig, Schmidt-Trucksass et al [7] introduced clinical data showing that an intervention in obese patients with a formula consisting of soy, yoghurt and honey, in addition to a program of physical activity and life-style coaching, can lead to both a weight reduction without losing muscle mass. and to a significant betterment in the important parameters of the metabolic syndrome. In earlier studies [22] it has been shown that such a nutraceutical formula of soy, skim milk yoghurt and honey

## Summary

Several studies have suggested that the metabolic syndrome may alter the risk of developing a variety of cancers – colon, pancreas, breast, liver, gall bladder – and the associations are biologically plausible. The American key societies – Cancer Society, Diabetes and Heart Associations – have stated that the current approaches to health promotion and prevention of cardiovascular disease, cancer and diabetes do not approach the potential of existing knowledge. A concerted effort to increase application of public health and clinical interventions of known efficacy could substantially reduce the human and economic costs of these diseases. Moreover, cancer survivors received less care for other medical conditions. In addition to a scientifically trend-setting weight reduction study [7], we introduce here data of a dietary intervention study in non-insulin dependent diabetes mellitus (NIDDM), showing that a regular support for 26 weeks of the day-to-day eating habit with a high-soy-protein/milk/yoghurt formulation (Almased®, Bienenbutter, Germany, St. Petersburg, FL, USA) down-regulates hormone (insulin, IL-6) and biochemical (fasting glucose, triglyceride levels) parameters which may contribute to the carcinogenic process.

## Key words

Metabolic Syndrome, Obesity, Adipocyte, Adipokines, Hyperinsulinemia, Insulin Resistance, Cancer, Soy protein-Honey-Skim milk-yoghurt-formula, Intervention Study

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contains bioavailable components like genistein and daidzein; with a regular intake an isoflavoid level in blood can be observed, similar to those measured in for example Japanese women, who have an epidemiological proven reduction in breast cancer risk. It was demonstrated in a nutrition-oriented Phase I study that such a formula is excellently suitable for the nutritional-physiological supplement in chemotherapy protocols [23].

## Study Design and Methods

The study was performed as prospective, open-label field study during the period June, 2003 – February, 2004 by physicians in private practice with the qualification as general practitioner (G.G. and N.S.), and a practice with the diabetes specialty (J.E.-N.); the length of the study, including the recruiting phase, was 32 weeks. 30 men (average age 63,8 y) and 30 (average age 63,3 y) women each were chosen, who fulfilled the study requirements (no insulin-dependent diabetes mellitus type 2, oral medication or diet plan, ambulant therapy possible, informed about the food Almased®/Somisan®, no change in medication nor life style without consent of the physician); of those, 28 men and 23 women were analyzable, because the participants were allowed to cease intake of the soy-honey-skim milk-yoghurt formula at any time and without mentioning the reason. The participants knew that this was not a pharmaceutical study according to AMG. An intervention study with a food product commonly available on the market does not fall under the jurisdiction of an ethics board; blood specimens were utterly necessary for the supervision of the efficacy of the antidiabetic therapy within the framework of the physician therapeutic plan. The patients agreed however to have their data registered with a pseudonym and analyzed for scientific purposes. The length of the study was 26 weeks.

At the time point of recruitment the standard lab workup of blood parameters, fasting blood sugar, HbA1c, insulin, weight were measured, and a glucose tolerance test was performed (visit 0).

Following 8 and 20 weeks (visit 8 and 20) the serum fasting blood sugar and insulin levels were determined.

Following 14 and 26 weeks (visit 14 and 26) the standard lab workup of blood parameters, fasting blood sugar, HbA1c, insulin and weight was again measured, a glucose tolerance test was performed and additionally a self-questionnaire was filled out by the patients who were in the study after 26 weeks, which documented the tolerance of each ingested formula and their subjective well-being.

The participants in the study ingested 50 grams of the soy-honey-skim milk-yoghurt formula daily; they mixed and dissolved the food powder in enough liquid, according to their diet plan. The patients were not to deviate from physician recommendations and documented their diet in a diary.

Glucose, triglyceride and cholesterol values were standardized in an autoanalyzer and measured with enzyme calorimetry and insulin in an RIA-assay. The glucose burden was determined following a 12-hour fast with a drink consisting of 75 grams glucose in 150 ml of water, after one and two hours. According to a Master Protocol all data was recorded in an individual case report form (CRF), from which the data was statistically analysed using ANOVA; all values are represented as average values with standard deviation. According to the study design each participant in the study was his/her own control. The visit zero (0) was the base value (without dietary intervention) of each individual parameter, the change in which was monitored over the course of the study period; a complex food with its unique biotechnological composition

is difficult to test in a blinded fashion, because the taste component, which should be special for food, plays a role for example in the compliance. Because the intervention study was performed with a freely available food and the patient was informed of this, it would have been possible for him to have recognized a placebo based on the taste and appearance.

## Results

Following 14 weeks of ingestion of the soy-honey-skim milk-yoghurt formula, a significant decrease ( $p < 0.05$ ) in the fasting blood sugar of the participants was observed (fasting value should/can be with a diet  $< 120$  mg/dl), which was stabilized on the level of the study collective until week 26 (Figure 1). After 26 weeks, levels were reached, which are on the threshold of the definition of glucose intolerance (126 mg/dl).

As can be seen in Figure 2, the HbA1c value decreased significantly by week 26 ( $p < 0.01$ ), a result that is especially noteworthy in light of the aforementioned correlation between an elevated HbA1c value and the colon carcinoma risk.

Insulin as a growth hormone can serve as a signal for tumor proliferation, because many tumors have insulin and “insulin-like” receptors; experimental results showing this have recently been published from a German group using an endocrine model for hepatocarcinogenesis [8]. In spite of the physiologically short half-life of insulin, a low insulin serum level should be strived for, in order to minimize the risk of growth stimulation of occult tumor cells. As can be seen in Figure 3, the fasting mea-

Due to the food science basis the decision was justified to investigate, (i) whether such a formula (Almased®, Bienenbuttel, Germany, St. Petersburg, FL.) can positively influence the blood parameters in patients with obesity and Type 2 diabetes mellitus who concurrently, as documented in the international literature, also have an increased cancer risk, and (ii), whether tumor patients, who often suffer from Type 2 diabetes mellitus, can be provided with a supplementary, nutritional-preventive enhanced formula for oncology patients (Somisan®, Hamburg, Germany) on the basis of the clinical results of the “mother-formula” (Almased®), in order to simultaneously reduce their risk of illness – diabetes vs. cancer – with an nutritional-physiological contribution.

### Fasting Glucose (mg/dl)

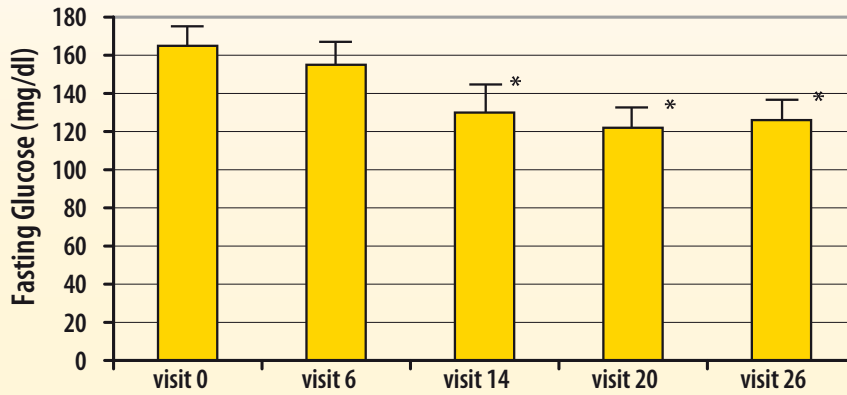


Figure 1: Significant reduction of the fasting glucose value after 26 weeks with the daily intake of 50 grams Almased®. \*  $p < 0.05$

### HbA1c (%)

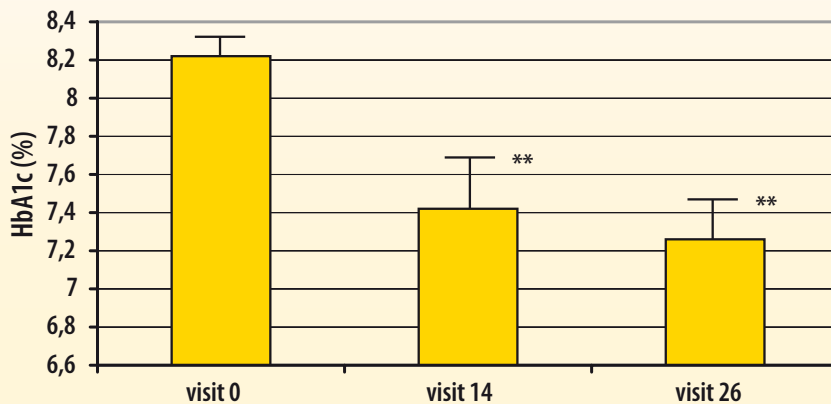


Figure 2: Significant reduction in HbA1c in percent after 26 weeks with the daily intake of 50 grams Almased® without changing the doctoral prescription and/or lifestyle.. \*\*  $p < 0.01$

### Insulin (mU/ml) fasting value 12h

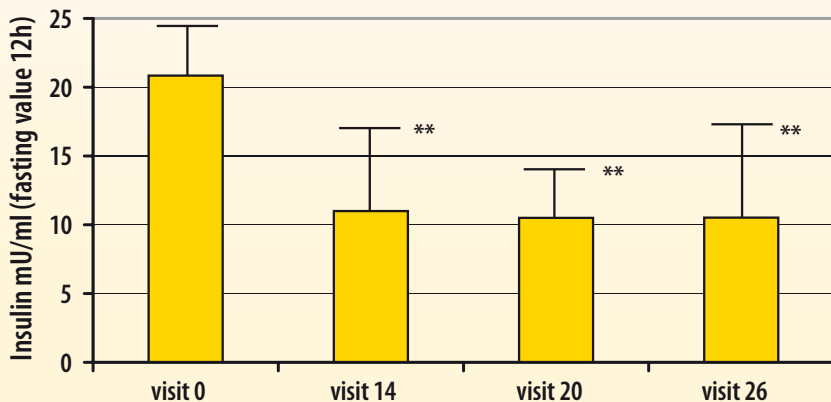


Figure 3: Significant reduction in serum insulin, measured after a 12-hour fasting period, following 14 weeks with a longitudinal stability up to 26 weeks with the daily intake of 50 grams Almased®. \*\*  $p < 0.01$

sured insulin level was significantly ( $p < 0.01$ ) reduced after 14 weeks; this value also stabilized out to study week 26. It is also necessary with every glucose tolerance test to measure the insulin in serum, in order to approximate the extent of the short-term flowing insulin for glucose uptake in the muscles and liver. In the study cohort (open cross-sectional study of the kinetics of the change of the measured parameters: fasting glucose; HbA1c, glucose tolerance test, insulin) an average insulin value of 49.12 mU/ml in the glucose tolerance test was measured following the second measurement (2 hours). This value was reduced in week 14 to 45.09 mU/ml and by week 26 to 36.60 mU/ml, a significant result with  $p < 0.05$ ; parallel to the reduced insulin levels, on average 16% more glucose was taken up in the peripheral glucose stores (liver cells) and glucose-dependent cells of the muscle system, as compared to the starting value measured on visit 0.

The participants in the study showed in the cohort result a weight loss between 2.5 kg as a minimum, and 3.7 kg as a maximum value after 26 weeks; the individual variances were in part substantial. The tendency showed that in comparison to the men, the women lost more weight. All of the other laboratory parameters (e.g. cellular blood parameters, creatine, liver values, electrolytes, iron/iron transport system) showed no significant change, with the exception of the triglycerides, which were also reduced ( $p < 0.05$ ). All participants, who completed the study period, reported a good tolerance for the food, had no problems in integrating 50 grams of the formula in addition to their dietary program in one or two portions over the course of the day, and observed no logistical or compliance disruption in their doctor-prescribed Diabetes Care Program. According to the protocol the patients could drop out of the study without giving a reason; for this reason the drop-outs were not asked for reasons.

## Discussion

R. Nelson [15] recently reported that tumor patients who survived the primary tumor receive less care for other medical conditions that they have or will get. There are assuredly psychological factors involved in that, because the tumor illness itself is such a life-threatening event that other medical conditions, which accompany or follow the completed phase of the successful primary tumor therapy, are judged to be less important. It is however exactly this, that may not be done, because the epidemiological based data in the literature show that the medical conditions obesity, Type 2 diabetes mellitus or chronic infections increase the risk of cancer or recurrence, or worsen the clinical prognosis in regard to malignancy. The data presented here gives the physician a rationale for asking about past tumor illnesses in the case history of diabetes patients, because an antidiabetes therapy – as the epidemiological data show – can have an effect on the course of malignant disease (even completed therapy). Therefore the physician can attempt to establish an individual therapy for these diabetics, whereby he will assuredly put the emphasis of this therapy on (i) nutrition, (ii) exercise, and (iii) medication. On the other hand it is necessary to watch out for possible symptoms of the “metabolic syndrome” in tumor patients, in order that, by an early intervention, types of therapy can be found, which do not negatively influence a malignant disease, and the comorbid manifestation of diabetes mellitus can be prevented.

It will be increasingly necessary to tackle chronic disease preventively through chemoprevention studies and lifestyle modification, if the public health system, according the understanding of the solidarity principle, is to remain affordable on a socially protected basis [16]. The objectives of intervention studies are exercise activity and nutrition. There is no doubt that in the Western industrialized world lack of exercise and improper nutrition are important epigenetic factors for the development of chronic disease [18]. An epidemiological study of

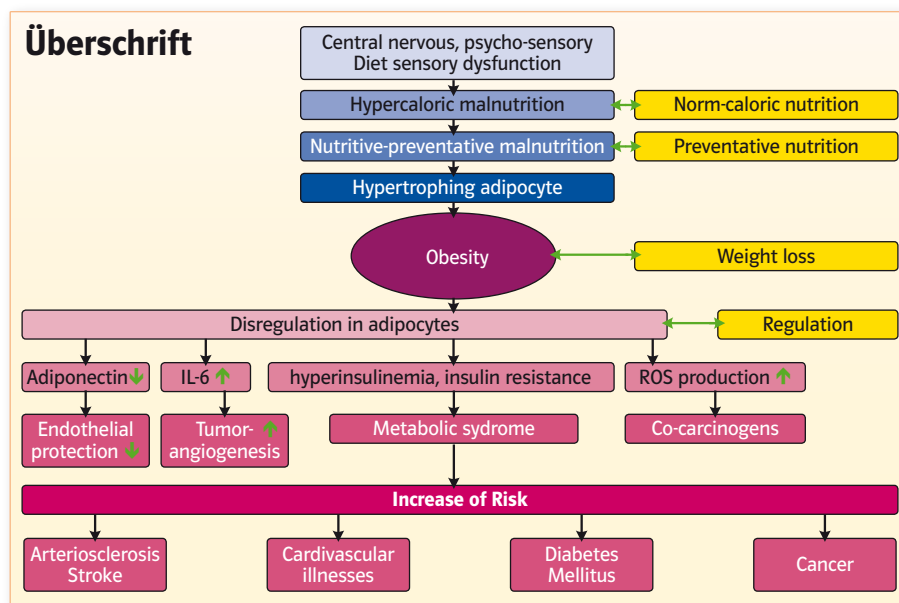


Figure 4: Epigenetics algorithm for the interweaving of the primary diseases in the Western civilized world and the nutritional physiological intervention goals, as shown for a soy-protein/milk/yoghurt formula (Almased®/Somisan®).

the population of Apulia has shown that the incidence of breast cancer in women increases with increased BMI and Type 2 diabetes mellitus [17]. It is exactly in the context of such results that the nutritional-physiological and exercise-oriented intervention study by Deibert et al in 2004 [7] has especial importance. An essential conclusion of that study was that the daily, planned intake of the soy-honey-skim milk yoghurt-formula, together with time-controlled exercise, the achieved weight loss in overweight subjects can be ascribed to a reduction in fat mass and not to a loss of muscle mass, which demonstrates the physiological and pathophysiological significance of one type of cell, namely the mesenchymal stem cell and its transdifferentiation into adipocytes and myocytes. The increased generation of adipocytes (obesity) due to an imbalance in caloric intake and oxidation of the nutrition components in regard to the metabolism, or malnutrition due to an inadequate supply of the important, non-caloric nutritional components, instigates the generation of hypertrophic adipocytes. This pathological cell type secretes increased amounts of adipokines, proteins, which have a negative effect on the metabolism and insulin sen-

sitivity; simultaneously less adiponectin is produced, which has an insulin-sensitizing and endothelium-protective effect. Accompanying this in obesity, as is the case in chronic infection, is an increase in IL-6 secretion, which in turn induces an insulin resistance in organs like the liver, muscles or fat tissue, but also can stimulate tumor growth or angiogenesis; the overexpression of insulin or TNF-alpha stimulates the IL-6 production in an autocrine or paracrine fashion. The hypertrophic adipocyte responds to a chronic hyperglycemic exposure with a increased production of reactive oxygen species (ROS), which induce damage in the blood vessel endothelia and nervous cells [14]; ROS can at least be characterized as a co-carcinogen. Therefore it must be pointed out that study results of weight reduction or regulation of adipokines always must be evaluated, how permanently they ensure the breakdown of fat tissue (adipocytes), in order to not allow a prolonged risk of chronic disease due to the increased secretion of adipocytokines and the production of ROS; these instigate obesity and insulin resistance, increase the risk of breast cancer and are associated with a poor prognosis [20].

It is precisely this question, which role the cell growth hormone insulin plays in carcinogenesis, especially in the case of the increasing pathologically responsive insulin level as a compensation mechanism in a gradually building peripheral insulin resistance, that is of interest to scientists, who are working on the relationship between diabetes mellitus and cancer. YX Yand, S Hennessy and JD Lewis from the University of Pennsylvania School of Medicine have recently published very provocative results [21], that epidemiologically show that the chronic insulin therapy significantly increases the risk of colorectal carcinoma in patients with Type 2 diabetes mellitus. One result from the nutrition-physiological intervention study presented here shows that endogenous insulin can be reduced with the corresponding dietary supplementation with a soy-honey-skim milk-yoghurt formula in Type 2 diabetes mellitus patients; this result is of significant prophylactic importance, in light of the statements from Yang et al [21]. For what period of time the dietary intervention should be performed cannot, of course, be defined from the data presented here; however nutrition plays a significant role in the carcinogenesis and/or prevention of tumor disease respectively, as shown in the initial results of the EPIC-Study. When pre-indicators, such as obesity, hyperinsulinemia, an dyslipidemia, are used as surrogate parameters and lead to treatment by a physician, then progress would be made in preventative medicine on a practical level. A Russian group also reports that a subgroup of tumor patients with endometrial carcinoma with concurrent insulin resistance and/or hyperinsulinemia has a very aggressive course of the tumor disease [3]. A similar result in regard to the malignancy of the endometrial carcinoma in combination with an increased serum level of the “insulin-like growth factor systems” in older women with a higher BMI was reported from an Italian group [1]. An American group has presented similar results, namely a poorer prognosis regarding the entwined risk between endometrial carcinoma and diabetogen-

ic conditions [10]. The Russian working group [3] even recommends that these patients should receive antidiabetic medications (Biguanide, Glitazone) as a support to their cytostatic therapy program, in order to correct their hormonal, metabolic imbalance. According to this rationale one can also consider a nutritional physiological intervention, particularly as shown here, when it leads to a decrease in hyperinsulinemia, or as previously shown [23], to optimize chemotherapy protocols with nutritional components, which evidence-based efficacy (Somisan®, Hamburg, Germany) has shown.

As always on the front lines of science, the “books” are not by any means closed in regard to the relationship between diabetes mellitus and cancer; as the prominent Whitehall study [2] shows, we are, in spite of the 25-year history of data collection, just at the beginning. This study also shows a correlation between the status of a diabetes illness and the incidence of pancreas, liver and lung carcinoma, but demands more and particularly longitudinal laboratory analyses in order to make an adequately assured assertion; a population based case control study in Houston (USA) reports a reduced risk of prostate cancer in diabetes mellitus patients [5]. The role of genetic factors in these processes must still be investigated. The fact remains, as shown in Figure 4, that every citizen and every patient has the option of engaging in nutritional physiological (preventional or curative) support in his/her health or illness.

It has been increasingly recognized in oncology in the recent past that aggressive therapy protocols intrinsically carry the risk that the patient’s constitution declines due to malnutrition, that constitutively stems from the chemotherapy and radiation therapy, and that the risk of mortality increases. In vitro and in vivo research efforts are increasingly being made, in order to understand the correlation between cancer therapies and essential nutrition. An in vitro study from Roomi et al. [19] shows that a particular composition of lysin, prolin, arginin, ascorbate, and epigallocatechin gallate is an excellent candidate for the additional

use in the osteosarcoma therapy, because this mixture inhibits cell invasivity, secretion of MMPs (metalloproteases) and VEGF (angiogenesis factors). The scientific community has recognized early on that the fatal correlation between diabetes and cancer as described here must be resolutely counteracted with nutritional regulation, if the prognosis for cancer patients is to improve. The Spanish working group of Leon-Sanz [13] (Abbot SPAI-97-004 Study Cooperative Group) recently comparatively examined the effect of a high carbohydrate diet (precitene diabet) and a low carbohydrate high mono unsaturated fat diet (Glucerna), both with diabetics and with head and neck carcinoma patients; the read-out parameters were an adequate glucose and lipid control, because many aggressive oncological therapies often pathologically influence these parameters considerably. Thereby it turned out that Glucerna hardly influenced the glucose and lipid levels and therefore should be preferred in the additive, therapeutic nutrition in oncology.

The clearer the clinical and molecular-biological correlations between the illnesses diabetes and cancer become in the future, the more often shall nutrition-oriented recommendations be made from scientists, so that the attending physician can counsel his patients individually to arrange his diet with known nutritional components, which can additively or synergistically support standard therapy regimens. It is to be wished that this disease correlation (cancer and diabetes) would be taken seriously in Germany for the patients’ benefit, and evidenced-based nutrition regimens would be executed as a matter of course as an integral part in a broad treatment concept; thereby a competitive diversity would satisfy the needs of the individual patient.

### **Conflict-of-interest**

KSZ is has a consultant voting member of the scientific advisory board of the Al-mased-Group. KSZ has no stock or profit-sharing in these companies.

## References

- [1] Augustin LS, Dal Maso L, Franceschi, S et al: Association between components of the insulin-like growth factor system and endometrial cancer risk. *Oncology*. 2004; 67:54-59.
- [2] Batty GD, Shipley MJ, Marmot M, et al: Diabetes status and post-load plasma glucose concentration in relation to site-specific cancer mortality: findings from the original Whitehall study. *Cancer Causes Control*. 2004; 15:873-881.
- [3] Berstein LM, Kvatchevskaya JO, Poroshina TE, et al: Insulin resistance, its consequences for the clinical course of the disease, and possibilities of correction in endometrial cancer. *Cancer Res Clin Oncol*. 2004; Aug 18; (Epub ahead of print).
- [4] Clark AM, Raine K, Raphael D: The American Cancer Society, American Diabetes Association and American Heart Association joint statement on preventing cancer, cardiovascular, and diabetes: where are the social determinants? *Diabetes Care*. 2004; 27:3024.
- [5] Coker AL, Sanderson M, Zheng W, et al: Diabetes mellitus and prostate cancer risk among older men: population-based case-control study *Br J Cancer*. 2004; 90:2171-2175.
- [6] Coughlin SS, Calle EE, Teras LR, et al: Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. *Am J Epidemiol*. 2004; 15: 1160-1167.
- [7] Deibert P, König D, Schmidt-Trucksäss A, et al: Weight loss without losing muscle mass in pre-obese and obese subjects induced by a high-soy-protein diet. *Int J Obes Relat Metab Disord*. 2004; 28: 1349-1352.
- [8] Evert M, Sun J, Pichler S, et al: Insulin receptor, insulin receptor substrate-1, Raf-1, and Mek-1 during hormonal hepatocarcinogenesis by intrahepatic pancreatic islet transplantation in diabetic rats. *Cancer Res*. 2004; 64: 8093-8100.
- [9] Eyre H, Kahn R, Roberstson RM, et al: Preventing cancer, cardiovascular diseases, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association and the American Heart Collaborative Writing Committee. *Stroke*. 2004; 35:1999-2010.
- [10] Folsom AR, Anderson KE, Sweeney C, et al: Diabetes as a risk factor for death following endometrial cancer. *Gynecol Oncol*. 2004; 94:740-745.
- [11] Khaw KT, Wareham N, Bingham S et al: Preliminary communication: glycated hemoglobin, diabetes, and incident colorectal cancer in men and women: a prospective analysis from the European prospective investigation into cancer-Norfolk study. *Cancer Epidemiol Biomarkers Prev*. 2004; 13:915-919.
- [12] Laukkanen JA, Laaksonen DE, Niskanen L, et al: Metabolic syndrome and the risk of prostate cancer in Finnish men: a population-based study. *Cancer Epidemiol Biomarkers Prev*. 2004; 13:1646-1650.
- [13] Leon-Sanz W, Garcia-Luna PP, Sanz-Paris A et al: Glycemic and lipid control in hospitalized Type 2 diabetic patients: evaluation of 2 enteral nutrition formulas (low carbohydrate-high mono-unsaturated fat vs high carbohydrate). *J Parenter Enteral Nutr*. 2005; 29:21-29.
- [14] Lin Y, Berg AH, Iyengar P, et al: The hyperglycemia-induced inflammatory response in adipocytes: The role of reactive oxygen species. *J Biol Chem*. 2004; Nov 8 (Epub ahead of print).
- [15] Nelson R: Cancer survivors receive less care for other medical conditions. *Lancet Oncol*. 2004; 5:646.
- [16] Prentice RL: Chronic disease prevention: public health potential and research needs. *Stat Med*. 2004; 23:3409-3420.
- [17] Resta F, Triggiani W, Sabba C, et al: The impact of body mass index and type 2 diabetes on breast cancer: current therapeutic measures of prevention. *Curr Drug Targets Immune Endocr Metabol Disord*. 2004; 4:327-333.
- [18] Roberts CK, Barnard RJ: Effects of exercise and diet on chronic disease. *J Appl Physiol*. 2005; 98:3-30.
- [19] Roomi MW, Ivanov V, Kalinovsky T et al: Antitumour effect of nutrient synergy in human osteosarcoma cells U-20S, MNNG-HOS and Ewings sarcoma SK-ES.1. *Oncol Rep*. 2005; 13:253-257.
- [20] Rose DP, Komninou D, Stephenson GD: Obesity, adipocytokines, and insulin resistance in breast cancer. *Obes Rev*. 2004; 5:153-165.
- [21] Yang YX, Hennessy S, Lewis JD: Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. *Gastroenterology*. 2004; 12:1044-1050.
- [22] Zänker KS, Daftary GV, Gottschalk G, et al: Genistein and Daidzein: Mode of action and bioavailability as chemo-preventative agents in a soy-enriched diet. *Dtsch Z Onkol*. 2001; 33:37-44.
- [23] Zänker KS, Gottschalk G, Adlercreutz H: Phase I trial with an isoflavonoid rich soy/milk/honey supportive nutrition for including into therapy-optimizing-protocols in oncology. *Dtsch Z Onkol*. 2001; 33:136-139.

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