Chapter 6

Obesity and Diabetes Epidemics:
Cancer Repercussions

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Abstract

The prevalence of overweight (body mass index, BMI, between 25 and 30 kg/m^2) and obesity (BMI of 30 kg/m^2 or higher) is increasing rapidly worldwide, especially in developing countries and countries undergoing economic transition to a market economy. One consequence of obesity is an increased risk of developing type II diabetes.

Overall, there is considerable evidence that overweight and obesity are associated with risk for some of the most common cancers. There is convincing evidence of a positive association between overweight/obesity and risk for adenocarcinoma of the oesophagus and the gastric cardia, colorectal cancer, postmenopausal breast cancer, endometrial cancer and kidney cancer (renal-cell). Premenopausal breast cancer seems to be inversely related to obesity. For all other cancer sites the evidence of an association between overweight/obesity and cancer is inadequate, although there are studies suggesting an increased risk of cancers of the liver, gallbladder, pancreas, thyroid gland and in lymphoid and haematopoietic tissue.

Far less is known about the association between diabetes mellitus type I (also called insulin dependent diabetes mellitus or juvenile diabetes), type II diabetes (called non-insulin dependent diabetes mellitus or adult onset diabetes mellitus) and cancer risk. The most common type of diabetes mellitus, type II, seems to be associated with liver and pancreas cancer and probably with colorectal cancer. Some studies suggest an association with endometrial and postmenopausal breast cancer. Studies reporting on the association between type I diabetes mellitus, which is relatively rare in most populations and cancer risk are scanty, but suggest a possible association with endometrial cancer.

Overweight and obesity, as well as type II diabetes mellitus are largely preventable through changes in lifestyle. The fundamental causes of the obesity epidemic—and consequently the diabetes type II epidemic—are societal, resulting from an environment that promotes sedentary lifestyles and over-consumption of energy. The health consequences and economic costs of the overweight, obesity and type II diabetes epidemics are enormous. Avoiding overweight and obesity, as well as preventing type II diabetes mellitus, is an important purpose to prevent cancer and other diseases. Prevention of obesity and type II diabetes should begin early in life and be based on the life-long health eating and physical activity patterns. Substantial public investments in preventing overweight, obesity and type II diabetes mellitus are both appropriate and necessary in order to have a major impact on their adverse health effects including cancer.

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Introduction

The prevalence of overweight and obesity is increasing rapidly worldwide. The increase in prevalence is especially rapid in developing countries undergoing economic transition. As more people are getting overweight and obese the morbidity patterns change. The first changes are usually an increase in hypertension, hyperlipidemia, glucose intolerance and type II diabetes mellitus. Next emerge increasing rates of cardiovascular diseases and long-term complications of diabetes (e.g., renal failure), followed by increasing rates of various types of cancer.[1]

Diabetes is one of the most common endocrine disorders today. It is caused by both environmental and genetic factors. The environmental factors that may lead to development of diabetes includes obesity, physical inactivity, use of drugs and exposure to toxic agents.[2] There are two main types of diabetes. Type I diabetes—or insulin-dependent diabetes mellitus (IDDM)—is mainly diagnosed during childhood or adolescence and is characterized by a diminished ability of the pancreas to produce insulin. Type II diabetes—or non-insulin dependent diabetes mellitus (NIDDM)—constitutes over 90% of all diabetes cases and has mostly been diagnosed after age forty, although recently much younger cases are being reported. In this type of the disease insulin is usually produced, but cannot be properly utilized due to insulin-resistance in target cells. Advanced cases of NIDDM may need treatment with insulin, which makes the use of the terminology IDDM and NIDDM quite confusing. We will therefore use the terms type I and type II diabetes mellitus in the following text. Both type I and type II diabetes mellitus show strong familial aggregation in all populations. Type II diabetes mellitus is clearly, as was mentioned above, the result of an interaction between genetic susceptibility and environmental factors.[3]

Prevalence of Obesity and Measurement of Body Fat

According to the World Health Organization (WHO) approximately 1.6 billion adults worldwide were overweight in 2005 and at least 400 million adults were obese.[4] The numbers will continue to rise and WHO's projections estimate that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese.

Obesity refers to excess storage of body fat. In adult men with weight in the acceptable range, the percentage of body fat is around 15-20%, whereas in women it is around 25-30%. Several methods may be used for measuring percentage body fat (e.g., densitometry and dual energy X-ray absorptiometry (DEXA)), but most of them are impractical for use in larger epidemiological studies. As for measures of relative body composition, the body mass index, BMI, is the most common and accepted measure.

BMI is a simple index of weight-for-height used to classify underweight, overweight and obesity in adults. It is calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). BMI values are age-independent and the same for both sexes. Also, although BMI values may not correspond to the same degree of fatness in different populations (partly

Table 1. Cut-points of body mass index for the classification of weight

BMI	WHO Classification	Description
<18.5 kg/m^2	Underweight	Thin
18.5-24.9 kg/m^2	-	Healthy, normal or acceptable weight
25.0-29.9 kg/m^2	Grade 1 overweight	Overweight
30.0-39.9 kg/m^2	Grade 2 overweight	Obesity
≥40.0 kg/m^2	Grade 3 overweight	Morbid obesity

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because of different body proportions) and ethnic-specific BMI definitions have been suggested, a WHO expert consultation has recently recommended the same cut-off values be used worldwide.[5] The cut-points proposed by WHO are given in Table 1. The five different categories are often termed "thin" (BMI < 18.5), "healthy", "normal" or "acceptable" weight (BMI 18.5-24.9 kg/m^2), "overweight" (BMI 25.0-29.9 kg/m^2), "obesity" (BMI 30.0-39.9 kg/m^2) and "morbid obesity" (≥40.0 kg/m^2).

Worldwide prevalence estimates for obesity (BMI >30 kg/m^2) for 2005 and 2015 are given in Figure 1. The figures are based on data from WHO Global InfoBase 2007.[6] Adult mean BMI levels of 22-23 kg/m^2 are found in Africa and Asia, while levels of 25-27 kg/m^2 are prevalent across North America, Europe and in some Latin American, North African and Pacific Island countries.

The average BMI for adult Europeans is nearly 26.5 kg/m^2.[6] A large proportion of the population is overweight and almost a third of the population, some 130 million people, has a BMI over 30.0 kg/m^2. There is a clear upward trend in body weight, not only among adults but also among children.

Data from the 2003-2004 National Health and Nutrition Examination Survey (NHANES) indicate an increase in the proportion of obese in the US population as well.[7] The age-adjusted prevalence among US adults has more than doubled during the last 25 years and is now well above 30%. About two thirds of the adult population have a BMI of 25 or above. The lowest estimates of obesity on the American continent are found in Brazil and Haiti, some 14 and 8% of the population, respectively.[6]

In South-East Asia the prevalence of obesity is around 5%. Particularly low prevalence of obesity is estimated for India (1.3%), Bangladesh (1.5%) and Sri Lanka (0.1%).

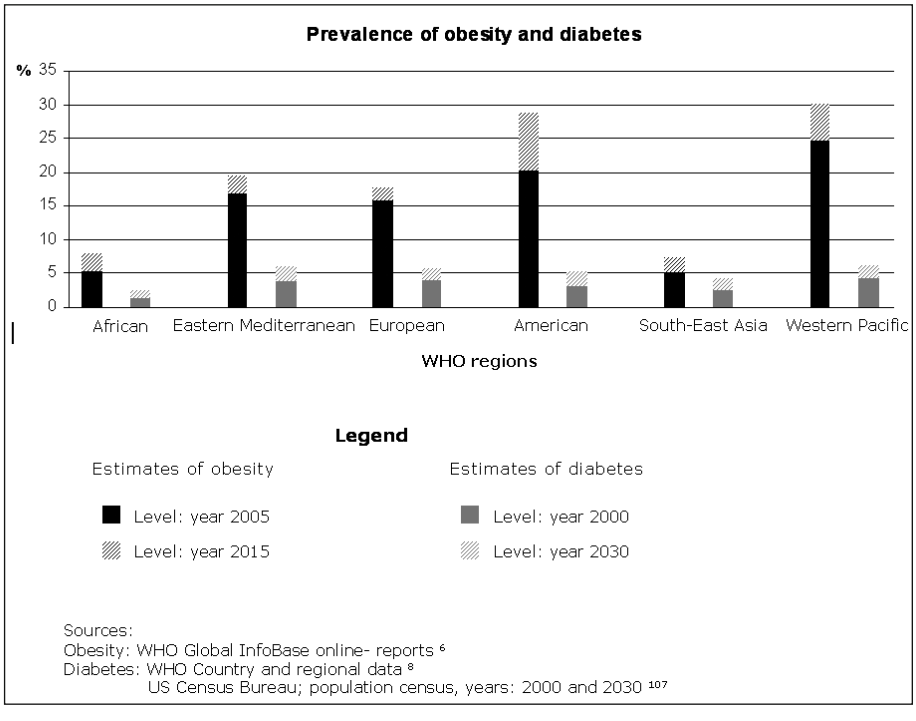

Figure 1. Prevalence of obesity and diabetes worldwide, given as percentages in six different world regions.

The larges variation in obesity within a region is seen in the Western Pacific. The overall prevalence of obesity is estimated to 25%. While very low prevalence is estimated for e.g., Vietnam (0.2%) and Japan (1.6%), remarkably high figures are estimated for Nauru (81%) and Micronesia (70%). In China, the overall prevalence is below 5%, although rates are almost 20% in some cities.

Large variation in obesity prevalence estimates is seen in the Eastern Mediterranean Region as well. Overall, about 17% of the population is estimated to be obese, but the figures range from less than 1% in Afghanistan to more than 40% in Kuwait.

Also, within Africa there is a large variation in obesity prevalence estimates. Very low prevalence (below 0.5%) is estimated for e.g., Zaire, Ethiopia and Eritrea, whereas the obesity prevalence in South Africa is estimated to be 21% and at the Seychelles 28%. In total, the prevalence of obesity in Africa is estimated to 5%. It is expected to rise to about 8% within year 2015.

Prevalence of Diabetes Mellitus

Diabetes mellitus, mostly type II, now affects approximately 6% of the world's adult population with almost 80% of the total residing in developing countries. The number of diabetic patients will reach 300 millions in 2025. More than 97% of those patients will have type II diabetes. Worldwide prevalence estimates for diabetes mellitus in year 2000 and 2030 are given in Figure 1 based on country and regional data from WHO.[8] The region with the highest rates is the Western Pacific where 4.2% of the adult population is affected, followed by European countries with a prevalence of 4%. India leads the global ten in terms of the highest number of people with diabetes with a current figure of 40.9 millions, followed by China with 39.8 millions. Behind them come USA, Russia, Japan, Germany, Pakistan, Brazil, Mexico and Egypt. Developing countries account for seven of the world's top ten.

With the force of globalization and industrialization proceeding at an increasing rate, the prevalence of diabetes is predicted to increase dramatically over the next few decades. The resulting burden of complications and premature mortality will continue to present itself as a major and growing public health problem for most countries.[9]

Association between Obesity and Diabetes Type II

One consequence of obesity is an increased risk of developing type II diabetes. In short, central mechanisms linking increased risk of type II diabetes to obesity include the following: excess body fat and particularly visceral fat release increased amounts of free fatty acids to the blood. Elevation of free fatty acid levels directly affects insulin signaling and causes the liver and skeletal muscles to shift towards greater oxidation of fatty acids for energy production and a relative inhibition of enzymes in the glycolytic cascade. As a result, the capacity of liver and skeletal muscles cells to absorb and metabolize glucose decreases. Also, the tissues capacity to store glucose as glycogen decreases and the cells accumulate more triglycerids instead of glycogen. This state, of reduced responsiveness of muscle, liver and adipose tissue to insulin, is named insulin resistance. To ensure normal glucose and lipid homeostasis the lower response to insulin is compensated by higher than normal secretion of insulin from the beta-cells in the pancreas giving an increased insulin plasma concentration, i.e., hyperinsulinemia. At the extreme, the beta-cells fails to secrete the excess amount of insulin needed and type II diabetes will develop.[10]

Association between Obesity, Diabetes Type II and Risk of Cancer

The global increase in overweight and obesity has a profound impact not only on the prevalence of type II diabetes but also on a wide range of other health aspects such as respiratory and musculoskeletal difficulties, gallbladder disease, cardiovascular diseases and certain types of cancer. The most convincing results regarding an increased BMI and cancer risk are found for oesophageal and gastric cardia adenocarcinomas, colorectal cancer, postmenopausal breast cancer, kidney cancer (renal-cell) and endometrial cancer.[11] Several other types of cancer may also be associated with increased BMI.

Far less is known about type II diabetes' impact on cancer risk. However, it is significant that the greatest risk of cancer in diabetic patients is to the organs in which concentrations of endogenous

insulin reach particularly high levels (i.e., liver and pancreas).[12] Some studies have found decreased cancer risk with long lasting type II diabetes which may reflect the inverse relationship between the duration of this type of diabetes and insulin secretion.[13-15] Meta-analyses have indicated that diabetes type II is associated with a 1.2-fold increased risk of bladder cancer, 1.3-fold increased risk of colorectal cancer, 1.7-fold increased risk of pancreatic cancer and 2.5-fold increased risk of hepatocellular carcinoma.[16]

In the next sections we give a broad presentation on what is currently known about obesity, diabetes type I and II and their impact on cancer repercussions. Type II diabetes accounts for the vast majority of all diagnosed cases of diabetes and most of the literature refers to studies on type II diabetes. However, some studies do not distinguished between type I and type II diabetes mellitus. In the following text we will refer to type I and type II diabetes mellitus whenever type is specified in the literature, otherwise the unspecified term diabetes mellitus will be used.

Current Research on the Associations between Obesity and Diabetes and the Risk of Cancer

Obesity

In 2002 The International Agency for Research on Cancer (IARC) published a thorough review on the association between excess body weight and risk of cancer.[1] The report concluded that there was sufficient evidence for a cancer-preventive effect of avoidance of weight gain for cancer of the colon, breast (postmenopausal), endometrium, kidney (renal-cell) and oesophagus (adenocarcinoma). A joint WHO/FAO expert consultation group reached similar conclusions the following year.[11] It has further been suggested that obesity may increase the risk of cancers of the liver, gallbladder and pancreas.[17] Based on prevalence estimates of obesity and overweight in Europe it has been estimated that 3% of all incident cancers in men in the European Union and 6% of all cancers in women may be attributed to excess body weight.[18] In 2001 this corresponded to 27,000 new cancers among men and 45,000 new cancers among women. In the US, overweight and obesity have been estimated to account for as much as 14% of all deaths from cancer in men and 20% in women.[19]

The mechanisms linking obesity to increased cancer risk may vary according to cancer site. Important aspects include hyperlipidemia, impaired glucose tolerance, insulin resistance and subsequent hyperinsulinemia (see below), altered levels of circulating hormones such as growth hormone and sex hormones and increased level of insulin-like growth factor (IGF-1).[17]

An illustration of the central mechanisms and effects of obesity on diabetes 2 and cancer development is given in Figure 2.

Diabetes

Increasing evidence indicates that individuals with type II diabetes are at elevated risk for several common human malignancies, including cancer of the colon, breast, endometrium, pancreas and liver. Laboratory studies have suggested biologically plausible mechanisms. Insulin, for example, is typically at high levels during the development and early stages of diabetes. Activation of the insulin receptor by its ligand, or cross-activation of the insulin-like growth factor 1 receptor, has been shown to be mitogenic and promote tumorigenesis in various model systems.[20] The risk varies according to tumor site: it is the greatest for primary liver cancer, moderately elevated for pancreatic cancer and relatively low for colorectal, endometrial, breast and renal cancers.[12]

Cancer of the Digestive Organs

Oesophageal Cancer

Oesophageal cancer affects nearly half a million people worldwide each year, making it the 6th most common cancer among men and the 9th most common among women.[21] The mortality is high; some 385,000 people die of the cancer every year. The disease affects about twice as many men as women and the rates are several times higher in the less developed regions of the world

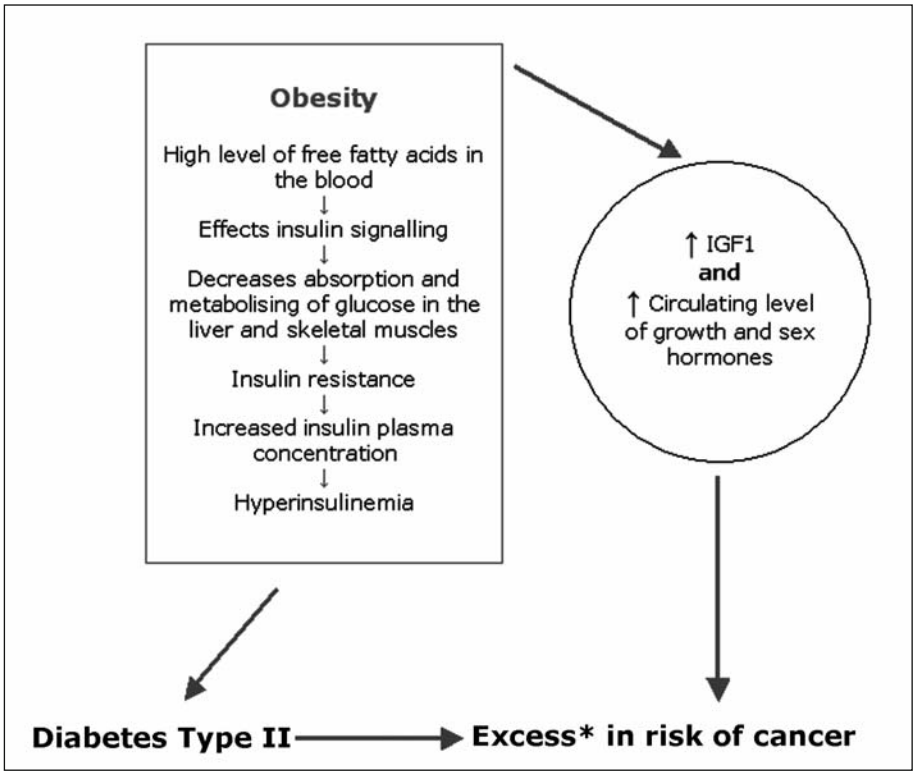

Figure 2. Central mechanisms and effects of obesity on diabetes II and cancer development; *Except for prostate cancer where an inverse association is observed in diabetes patients; ↓ result in; ↑ increased level of IGF1 - insulin-like growth factor.

compared to the more developed parts.[21] The two main histological sub-types of oesophageal cancer are adenocarcinomas and squamous-cell carcinomas.

Obesity

Squamous cell carcinoma of the oesophagus is not found to be related to excess body weight. However, an expert panel stated in 2001 that there is sufficient evidence to conclude that obesity increases the risk of adenocarcinoma of the lower oesophagus.[1] This finding has been confirmed in a recent review.[22] A 2-3 folds increase in risk has been suggested for subjects with a BMI of 25 kg/m^2 or above.[1,22] It has been estimated that more than half of all adenomcarcinomas of the oesophagus in the Unites States of America and more than 40% of the cases in the European Union is attributable to overweight and obesity.[17]

It has been proposed that obesity increases the risk of adenocarcinomas of the oesophagus via increased risk of gastro-oesophageal reflux. However, this pathway is not established.[17]

Diabetes

The relationship between diabetes mellitus and adenocarcinoma of the oesophagus cancer was investigated in a case-control study of US veterans with gastro-oesophageal reflux disease.[23] No association was found. In a Danish study a 30% increase in risk of oesophagus cancer was found in male diabetes patients (95% confidence interval (CI) 1.0-1.6).[24] No increased risk was seen in

women. Except from these studies, reporting contradictory results, little is known about diabetes influence on oesophagus cancer.

Stomach Cancer

Nearly 1 million people are diagnosed with stomach cancer each year.[21] The age-adjusted incidence rate is about twice as high in men as in women (22 and 10 per 100,000, respectively). Generally, there are no overall incidence differences between the more developed parts of the world and the less developed parts. Particularly high age-adjusted incidence rates are seen for men in Korea (69.7 per 100,000) and Japan (62.0 per 100,000). Stomach cancer is the 2nd most common cause of cancer death among men and the 4th most common among women.[21] Cancer of the stomach can be divided in cardia cancer, referring to the upper limit and noncardia cancer. Etiologically cardia cancer seems to be quite similar to cancer of the lower oesophagus.

Obesity

There is scarcity of prospective studies on obesity and stomach cancer. Case-control studies reviewed by an IARC expert panel in 2001 indicate that obesity may double the risk of gastric cardia adenocarcinoma.[1] A recent meta-analysis estimated obese subject to have a 50% (95% CI 20%-80%) increase risk of cardia adenocarcinoma compared to "normal" weight subjects, but the results were heterogeneous between country of origin.[22] No association has been found between obesity and the distal, noncardia type of gastric cancer.[25,26]

Diabetes

Few studies have aimed to investigate a possible association between stomach cancer and diabetes mellitus and the results published show different trends. A reduced risk of stomach cancer overall was observed in diabetes patients in Japan, for both genders,[27] while other studies have found a significant increased risk.[24,28] Results from a cancer incidence study among patients with type I diabetes in Sweden showed a significantly increased risk of stomach cancer overall (standardized incidence rate (SIR) 2.3, 95% CI 1.1-4.1).[29] In a case-control study no evidence of an association was seen between diabetes and cancer of the gastric cardia specifically.[23]

Colorectal Cancer

More than 1 million people worldwide are diagnosed with colorectal cancer every year.[21] Colorectal cancer is the third most common cancer among women and the fourth most common cancer among men. The age-adjusted incidence rate is several times higher in more developed regions of the world (26.6 and 40.0 per 100,000 for women and men, respectively) compared to less developed regions (7.7 and 10.2 per 100,000 for women and men, respectively). More than half a million people worldwide die from colorectal cancer each year.[21]

Obesity

Colorectal cancer is regarded as one of the cancers with greatest prevention potential.[30] Much of the preventive potential ascribes to eating a healthy diet and avoiding physical inactivity. A large number of studies have shown that the risk of colon cancer increases with increasing BMI.[31] Generally, there also seems to be a somewhat increased risk of rectal cancer with increasing BMI, but fewer studies have examined this relationship. An expert panel set down by IARC regarded in 2001 that there is "sufficient evidence" for a colon cancer preventive effect of avoidance of weight gain.[1] More recent studies have confirmed this statement.[32] There is no indication of a threshold effect of obesity; an increased risk of colon cancer has been observed for a wide range of BMI. Overall, cohort studies have shown a 25-100% higher risk of colorectal cancer for overweight and obese subjects compared to leaner ones. For example, in an US study the relative risk (RR) of colorectal cancer for obese men was 1.52 (95% CI 0.9-2.7) compared to "normal" weighted men, whereas obese women had a relative risk of colorectal cancer of 1.26 (95% CI 0.6-2.6) compared to lean peers.[33] In a review paper examining the results from 7 cohort studies and 6 case-control studies the summary relative risk estimate for subjects with a BMI above 28.5 kg/m^2 compared to subjects with BMI below 22.0 kg/m^2 was 1.6 for men and 1.3 for women.[34]

It has been estimated that 35% of the colorectal cancer cases among US men and 28% of the colorectal cancer cases among men in the European Union can be attributed to overweight and obesity.[17] For women the corresponding figures are 21% for US women and 14% for women in the European Union.

In order to elucidate the time in colorectal carcinogenesis when obesity might be most important several studies have examined the association between colorectal adenomas, potential precursors of colorectal cancer and obesity. Overall, there seems to be a stronger association between obesity and large adenomas than for obesity and smaller adenomas. Based on this finding it has been suggested that obesity-related factors may act at a later stage in the development of colorectal cancer, i.e., obesity contributes to promotion and progression towards cancer, rather than initiating. An alternative suggestion is that other factors may lead to small adenomas but not to progression and thereby diluting the association between obesity and smaller adenomas.[1]

The association between obesity and colorectal cancer is found for both sexes but is generally stronger among men than among women.[1] The reason for this gender difference is not known, but the findings imply that the effect of obesity is not simply an indicator of energy imbalance. If the positive association between obesity and colorectal cancer were due to energy imbalance one would expect equal results for men and women. One suggestion is that obesity among postmenopausal women may have an offsetting beneficial effect due to high levels of estrogen that may diminish the detrimental effects of obesity.[1]

Diabetes

An increased incidence of colon cancer in diabetes patients has been observed in a number of studies carried out in different parts of the world. A meta-analysis based on results from 6 case-control studies and 9 cohort studies including both type I and type II diabetes showed an increased risk of colorectal cancer in diabetes mellitus patients.[35] Population-based cohort studies in Denmark, Sweden and the US, including a large numbers of diabetes patients, all reported significantly increased incidence of colorectal cancer.[24,36,37] The Danish study reported 30% increased incidence in male patients and 10% increased incidence in female patients.[24] Results from the Swedish study showed an overall standardized mortality ratio (SMR) of 1.6 in men and 1.5 in women. The increased risks were not related to the duration of diabetes prior to the diagnosis of colon cancer.[36] In diabetic patients in the US study the increased risk of developing colorectal cancer accounted for 30% in men and 16% in women.[37] Colorectal cancer was increased by 39% among type II diabetes patients in a population-based retrospective cohort study (95% CI 1.03-1.82) and the risk was particularly high among men.[38]

Primary Liver Cancer

Some 630,000 persons worldwide are diagnosed with liver cancer every year and about 600,000 die from the disease annually.[21] More than 80% of the liver cancer cases occur in the less developed regions of the world.

Obesity

Only a limited number of papers have reported on risk of liver cancer in relation to BMI. A higher risk of liver cancer and higher liver cancer mortality has been reported for obese than for leaner subjects, but the body of evidence is yet too weak to draw any firm conclusions.[17,39]

Diabetes

A possible association between liver cancer (hepatocellular carcinoma—HCC) and diabetes mellitus has been found in several studies. A meta-analysis showed pooled odds ratios (OR) from 13 cohort studies of 2.5 (95% CI 1.9-3.2) and from 13 case-controls studies of 2.5 (95% CI 1.9-3.2).[40] A 4-fold increase in risk of primary liver cancer was observed in male diabetes type II patients in Sweden.[41] The risk for women was increased more than 3-fold compared to the figures for the general population. Patients with diseases predisposing to liver cancer (hepatitis, hepatic cirrhosis, hemochromatosis and alcoholism) were excluded from the analyses, however the risk

still remained three times higher.[41] Two case-control studies [42,43] and one cohort study[27] also found a significant increased risk of liver cancer in diabetes patients. In an area with high prevalence of hepatitis virus infection, it was found that type II diabetes increased the risk of developing HCC in those who were hepatitis C virus negative or had a high level of total cholesterol.[44]

Gallbladder Cancer

With some exceptions (e.g., in India, Pakistan, Ecuador), gallbladder cancer occurs quite seldom.[45] The etiology of the disease is sparingly known.

Obesity

The number of studies on gallbladder cancer and obesity is restricted, but the findings seem to be rather consistent in that obesity is associated with an increased risk.[17] In a recent meta-analysis of three case-control studies and eight cohort studies the summary relative risk for gallbladder cancer for obese women was 1.88 (95% CI 1.66-2.13) compared to "normal" weight women.[46] In parallel, obese men had a relative risk of 1.66 (95% CI 1.47-1.88). Overweight women had a 28% (95% CI 4%-57%) increased risk of gallbladder cancer compared to leaner women, whereas only a small and nonsignificant increase in risk was found for overweight men (RR 1.05, 95% CI 0.92-1.19).

In a paper from 2001 it was estimated that 24% of the gallbladder cancer cases in the European Union could be attributed to excess body weight.[18] In 2004 corresponding figures of 36% for the US and 27% for the European Union was published.[17] Further, in 2007, based on prevalence data on obesity and overweight in the US population, it was estimated that 12% of the gallbladder cancer cases among men and 30% of the cases among women could be attributed to a BMI of 25 kg/m^2 or above.[46]

It has been suggested that excess weight increases the risk of gallbladder cancer through increased risk of gallstones that subsequently may cause a chronic inflammation.[45]

Diabetes

Diabetes as a risk factor for gallbladder cancer has been investigated in a few studies. A Swedish study reported a 40% significant increased risk of gallbladder cancer in female diabetes patients (95% CI 1.1-1.6) whereas in male patients a 20% increased risk was found (95% CI 0.9-1.7).[41] Risk of gallbladder cancer was not raised in a cancer incidence and mortality study among type I diabetes patients.[47]

Pancreatic Cancer

More than 230,000 people get pancreas cancer every year.[21] The fatality is high and in developed countries pancreatic cancer contributes significantly to cancer mortality with age-adjusted mortality rate of 8.0 and 5.4 per 100,000 for men and women, respectively. In less developed countries the age-adjusted mortality rate is about 2.0-2.6 per 100,000.[21]

Obesity

It has been suggested that obesity is positively related to pancreatic cancer, but the relation is thought to be modest.[48] While earlier studies have not found any association, more recent studies have indicated a relative risk of 1.7 for obese subjects compared to "normal" weight subject.[17] In a meta-analysis including six case-control studies and eight cohort studies the summary relative risk per unit increase in BMI was 1.02 (95% CI 1.01-1.03), corresponding to a relative risk of 1.19 (95% CI 1.10-1.29) for subjects with a BMI of 30 kg/m^2 or above compared to subject with a BMI of 22 kg/m^2.[49] It has been estimated that about one fourth and one fifth of all pancreatic cancer in the US and in the European Union, respectively, is attributed to excess weight.[17]

Diabetes

Type II diabetes is considered to be an important risk factor for pancreatic cancer, while the relation between type I diabetes and pancreatic cancer is unclear.[29] A large number of studies have been published on the association between type II diabetes and pancreatic cancer. However, it is

important to recognize that previous epidemiological studies of the association between diabetes and pancreatic cancer are generally lacking information about the clinical utility of newly identified diabetes as marker for pancreatic cancer. In almost all case-control studies, duration of diabetes is unclear as it has been assessed by self- or proxy report.[50] A meta-analysis of 36 studies on type II diabetes supports a modest causal association.[51] The pooled odds ratio for 17 case-control studies was 1.94 (95% CI 1.53-2.46) and summary estimate for 19 cohort and nested case-control studies was 1.73 (95% CI 1.59-1.88). In 14 of the case-control studies the risk of pancreatic cancer was higher in diabetes patients than in the controls and reached significant level in ten. The combined estimate from all studies was 1.82 (95% CI 1.66-1.99). Results from the cohort studies and the nested case-control studies were remarkably consistent with 15 studies reporting relative risks that were significantly elevated.[51] Similar results were also reported some years ago in another meta-analysis of 11 case-control and 9 cohort studies.[52] The analysis included cases of diabetes diagnosed at least one year prior to the diagnosis or death from pancreatic cancer. The pooled relative risk of pancreatic cancer for the diabetic patients was 2.1 (95% CI 1.6-2.8). The risk was somewhat higher in the cohort studies (RR 2.6, 95% CI 1.6-4.1) than in the case-control studies (OR 1.8, 95% CI 1.1-2.7).[52]

Respiratory Organs

Lung Cancer

Overall, lung cancer is the most frequent type of cancer.[21] Nearly 1.5 million people worldwide get lung cancer every year and about 1.2 millions die of the disease annually. The age-adjusted incidence and mortality rate are about 3 times higher among men than among women (among men 35.5 and 31.2 per 100,000, respectively, among women 12.1 and 10.3 per 100,000, respectively). The age-adjusted incidence and mortality rate are about twice as high in the more developed parts of the world as in the less developed parts.[21]

Obesity

Whether there is an association between BMI and risk of lung cancer is controversial. Several studies have found an inverse association.[1,53] However, as smoking is the primary cause of lung cancer and there is an inverse association between BMI and smoking, an association between BMI and lung cancer may be confounded by smoking habits. Indeed, in nonsmoking populations no association between BMI and lung cancer risk is observed.[17] Also, an increased risk of lung cancer among subjects with a low BMI may be explained by weight loss due to preclinical lung cancer.

Diabetes

Some studies have investigated the hypothesis that the rate of lung cancer is different in diabetic compared with nondiabetic patients but the results are not conclusive. A weak nonsignificant increased risk of lung cancer was seen in female diabetic patients, after adjusting for smoking.[54] Other studies have not found an association between diabetes and risk of lung cancer.[24,27,55,56] However, these studies did not adjust for smoking, the major risk factor for lung cancer and are therefore difficult to interpret. No increased risk of lung cancer in diabetic patients was found in a large UK retrospective study, after adjusting for smoking.[57] In diabetes type I patients a significant increased risk of lung cancer has been observed.[29] A recent study investigated the possible protective effect of diabetes against metastasis in patients with nonsmall cell lung cancer.[58] In fact, they found that stage and diabetes were significant predictors of metastasis.

Skin Melanoma

Nearly 80,000 subjects get malignant melanoma every year.[21] The age-adjusted incidence rate is far higher in the more developed parts of the world than in the less developed parts (8.3 and 0.7 per 100,000, respectively). Particularly, high age-adjusted rates are found in Australia (38.5 per 100,000) and in New Zealand (33.8 per 100,000).[21]

Obesity

Negative, positive and null findings have been reported regarding the association between BMI and malignant melanoma.[1,53,59] It has been suggested that BMI may influence sunbathing habits and hormonal factors, both potentially important for development of malignant melanoma.[1] Overall, no firm conclusion on the association can be drawn.

Diabetes

Little is known about an association between cancer of the skin and diabetes mellitus. Results from one cohort study reported that patients who used insulin therapy to treat type II diabetes had a significantly lower risk of developing nonmelanoma tumor of the skin than patients who used non-insulin anti-diabetics medicines.[60] The protective effect of insulin use became more distinct with increasing age. A study among diabetic patients observed an SIR of 1.0 for melanoma of the skin in both gender and 1.0 and 0.9 for nonmelanoma neoplasms of the skin in men and women, respectively.[24]

Breast Cancer

Breast cancer is by far the most common cancer among women.[21] More than 1.1 million women worldwide are diagnosed with breast cancer every year and more than 400,000 women die from the disease annually. The age-adjusted incidence rate for breast cancer is 67.8 per 100,000 in developed regions of the world and 23.8 per 100,000 in less developed regions.[21]

Obesity

More than 100 epidemiological studies have been conducted to examine the relationship between breast cancer and various measures of obesity. There is convincing evidence that the effect of excess body weight on breast cancer risk varies with menopausal status; the association is negative among premenopausal women and positive among postmenopausal women.

Breast Cancer Risk in Premenopausal Women

The inverse association between BMI and breast cancer risk among premenopausal is modest. Overall, it has been suggested that the risk reduction may be of magnitude 0.6 to 0.7 for women having a BMI of 28 kg/m^2.[1] Two recent prospective studies have shown less impact of excess body weight: in a large study of US nurses obese premenopausal women had a relative risk of breast cancer of 0.81 (95% CI 0.68-0.96) compared to lean women.[61] The risk estimate was more or less the same irrespective of various adjustments for reproductive and lifestyle factors. In a French study overweight premenopausal women had a relative risk of breast cancer of 0.84 (95% CI 0.56-1.27) compared to leaner women.[62]

The mechanism linking BMI to premenopausal breast cancer is not fully known. It has been suggested that excess body weight may be associated with longer or irregular menstrual cycles and polycystic ovary syndrome, increasing the likelihood of anovulation and subsequent decreased levels of estradiol and progesterone. However, this mechanism is still debated.[61]

In contrast to premenopausal breast cancer incidence premenopausal breast cancer mortality does not tend to be higher in lean women than in obese women.[1] That is, obesity worsens the prognosis once breast cancer is established.[63]

Breast Cancer Risk in Postmenopausal Women

After going through the menopause obesity increases both the risk of experiencing breast cancer and the risk of dying from the disease.[1,63] It has been estimated that obese postmenopausal women have a 50% higher risk of breast cancer than lean postmenopausal women.[17,64] When analyzing individual data from eight prospective studies of postmenopausal women performed in developed countries the researchers found a clear significant trend for increasing risk of breast cancer with increasing BMI; compared to women with a BMI of less than 22.5 kg/m^2 the relative risk of breast cancer was 1.10 (95% CI 0.83-1.46) for women with a BMI of 22.5-24.9 kg/m^2, 1.45 (95% CI 1.08-1.95) for women with a BMI of 25.0-27.4 kg/m^2, 1.62 (95% CI 1.17-2.24)

for women with a BMI of 27.5-29.9 kg/m^2 and 1.36 (95% CI 1.00-1.85) for women with a BMI of 30.0 or above (p trend = 0.004).[65] It has been estimated that more than one in five postmenopausal breast cancer cases in the US and one in six cases in the European Union can be attributed to overweight and obesity.[17]

The effect of overweight and obesity on postmenopausal breast cancer risk is often found to be strongest among women who have not taken hormone replacement therapy.[65,66] For instance, in an US prospective study no anthropometrical measures were associated with postmenopausal breast cancer among women who had ever used hormone replacement therapy, whereas among non-users both weight, BMI at baseline, changes in BMI since age 18, and maximum BMI were positively associated to breast cancer risk (relative risk for women who were obese at baseline compared to women who were lean at baseline was 2.52, 95% CI 1.62-3.93).[67] The effect of excess body weight on postmenopausal breast cancer risk may also be modified by age.[67,68]

The biological mechanism behind the association between BMI and postmenopausal breast cancer risk is not clearly understood. One suggestion is that overweight and obese women to a greater extent than leaner women convert androgens to estrogens resulting in higher levels of circulating estrogens which in turn may increase the risk of developing breast cancer.[64]

Diabetes

Diabetes mellitus' relationship with breast cancer remains unclear. However, because insulin is a growth factor, it is hypothesized that the chronic hyperinsulinemia seen in individuals with insulin resistance may have cancer-inducing effects on insulin-sensitive tissues such as the breast. High levels of insulin have been shown to be mitogenic for breast tissue,[69] and insulin receptors are frequently over-expressed in breast cancer cells.[70,71] Associations between breast cancer and serum insulin,[72] as well as its metabolic product, C-peptide,[73] have been documented. Insulin resistance may also promote breast cancer via other mechanisms, such as greater estrogen availability due to decreased levels of sex-hormone-binding globulin,[74] or increased circulating levels of insulin-like growth factor 1.[75]

A recent meta-analysis based on results from 5 case-control studies and 15 cohort studies indicated that diabetes mellitus (largely type II) is associated with increased risk of breast cancer.[76] Analysis of all 20 studies showed that women with diabetes had a statistically significant 20% increased risk of breast cancer compared to women without a diabetes diagnosis (RR 1.20, 95% CI 1.12-1.28). The summary estimates for the case-control studies were RR 1.18 (95% CI 1.05-1.32) and cohort studies RR 1.20 (95% CI 1.11-1.30).[76] Wolf and coworkers combined the results of 4 case-control studies and 6 cohort studies and found that diabetes was associated with a 13% and 25% increased risk of breast cancer in case-control and cohort studies, respectively.[77] Results from a recent case-control study support the hypothesis that diabetes may have a role in the development of breast cancer, influencing risk via both sex hormone and insulin pathways.[78] A history of diabetes was associated with breast cancer risk (OR 1.68, 95% CI 1.15-2.47) after adjusting for reproductive and other confounding factors. The researchers found a stronger diabetes-breast cancer association in women with lower BMI (≤22.7 kg/m^2) than in those with higher BMI (>22.7 kg/m^2).[78]

Female Genital Organs

Endometrial Cancer

Nearly 200,000 new cases of endometrial cancer are registered every year, making it the 7th most common cancer site among women worldwide.[21] The age-adjusted incidence rate is more than 4 times higher in the more developed regions of the world than in the less developed regions (13.6 and 3.0 per 100,000, respectively) and is particularly high in the US (22.5 per 100,000).[21]

Obesity

An expert panel concluded in 2001 that there is convincing evidence that obesity increases the risk of endometrial cancer both among pre and postmenopausal women and that the increase

in risk is of magnitude 2-3 folds.[1] Others have presented an increased risk of 3- to 10-folds for obese women compared to leaner ones.[79] Further, it has been estimated that 39-45% of all endometrial cancer in the European Union (corresponding to at least 14,000 new cases per year) can be attributed to overweight.[17,18] In the US more than half of all endometrial cancer cases may be attributed to overweight and obesity.[17]

The strong association can be exemplified by a recent prospective US study: obese women had a relative risk of breast cancer of 3.03 (95% CI 2.50-3.68) compared to "normal" weight women.[80] Adult weight gain also increased the risk. Similarly as for breast cancer, hormone replacement therapy may modify the relation between body weight and endometrial cancer risk: that is, a stronger association was revealed for never-users than for former and current users.[80]

The association between obesity and increased risk of endometrial cancer is thought to go through changes in the hormonal milieu that in sum result in an increased effect of unopposed estrogen and thereby increase the risk of cancer in hormonally responsive tissues.[79]

Diabetes

The association between diabetes and endometrial cancer and the possible underlying mechanisms has been widely discussed in the literature. Endometrial cancer is a hormone-related malignancy and diabetes mellitus may cause hormonal alterations that promote the development of the disease. A statistically significant 80% excess incidence of endometrial cancer among patients hospitalized with diabetes mellitus was observed in a large Swedish cohort study (SIR 1.8, 95% CI 1.6-2.0).[36] Similar results were reported in another study from Sweden (RR 1.5, 95% CI 1.2-1.8).[55] Obesity has been reported as increasing the risk of both diabetes and endometrial cancer. In the study by Weiderpass and coworkers[36] the risk estimates for endometrial cancer did not change substantially when excluding patients with a discharge diagnosis of obesity from the analysis, pointing on diabetes as the strongest risk factor. Furthermore, it has been suggested that history of obesity and diabetes may increase the mortality after having an endometrial cancer diagnosis.[81] Results from a population-based case-control study in Sweden showed that recent overweight/obesity and diabetes mellitus (type I and II) are associated with increased endometrial cancer risk.[82] Significant increased risk of endometrial cancer has also been seen in type I diabetes patients specifically.[29] Diabetes has further been found to be one of several risk factors related to endometrial cancer in women younger than 50 years of age.[83]

Ovarian Cancer

Some 205,000 women get ovarian cancer every year and about 125,000 die from the disease annually. The age-adjusted incidence and mortality rate is about twice as high in the more developed parts of the world as in the less developed parts (age-adjusted incidence rate 10.2 and 5.0 per 100,000, respectively).[21]

Obesity

The association between BMI and risk of ovarian cancer has been examined in a relatively limited number of studies and the studies have shown conflicting results.[1,79] In a recent review and meta-analysis it is concluded that obesity is a risk factor for ovarian cancer and it is estimated that obese women have a 30% higher risk (95% CI 10%-50%) of epithelial ovarian cancer than women with a BMI within the "normal" range.[84] It is hypothesized that any association between obesity and ovarian cancer risk may be mediated through adipose tissue's influence on the synthesis and bioavailability of endogenous estrogens, androgens and progesterone.[84] As for other hormone-related cancers menopausal status may modify the impact of obesity on ovarian cancer risk.

Diabetes

Few studies have been performed to investigate a possible association between ovarian cancer and diabetes mellitus. A review of cohort studies on the association between history of diabetes mellitus and occurrence of cancer reported that no cohort studies showed any significantly positive or negative association between diabetes and ovarian cancer.[85] Further, two more recent cohort

studies found no association.[28,86] However, one study has found a significant increased risk of ovarian cancer in patients with diabetes type I diagnosed before 30 years old, with greatest risk for those with diabetes diagnosed at ages 10-19 years.[47]

Cervical Cancer

About half a million women worldwide get cervical cancer annually and some 275,000 die of it. More than 400,000 of the new cases and 85% of all deaths occur in the less developed parts of the world.[21]

Obesity

Studies examining risk of cervical cancer in relation to BMI have been inconclusive; both positive association and no associations have been reported.[17,79] It has been suggested that squamous cell carcinoma of the cervix is not associated with BMI, whereas there may be a modest increase of cervical adenocarcinoma with increasing BMI.[79] However, obese women may attend cervical screening more seldom than leaner women and this may confound the findings.[17]

Diabetes

Only a limited number of papers have reported on risk of cervical cancer in relation to diabetes mellitus. Significant increased risk of cervical cancer has been observed in type I diabetes patients specifically.[29] In a population-based cohort study of patients hospitalized with diabetes mellitus the SIR for cervical cancer was 0.9.[24] The incidence rate ratio of cervical cancer was 0.99 in a study among Japanese diabetes patients.[27]

Male Genital Organs

Prostate Cancer

Prostate cancer is the second most common cancer among men; about 680,000 new cases are reported every year. The age-adjusted incidence rate in the more developed parts of the world is 55.6 per 100,000 compared to 9.4 per 100,000 in the less developed parts.[21]

Obesity

The association between BMI and risk of prostate cancer has been examined in a number of studies. In general, body weight does not seem to be strongly associated with prostate cancer. A meta-analysis based on 4 cohort studies and 2 population-based case-control studies gave an 6% increased risk of prostate cancer for overweight men compared to men within the "normal" weight range and a 12% increased risk for obese men.[18] Based on this finding it was further estimated that 4% of the prostate cancer cases in the European Union could be attributed to excess body weight (i.e., about 5000 new cases per year).

It has recently been hypothesized that the nonconclusive findings may, at least in part, be explained by a differential effect of obesity on aggressive and non-aggressive prostate cancer. That is, a negative association between non-aggressive prostate cancer and obesity and a positive association between aggressive prostate cancer and obesity are described.[87] Findings from a recent prospective study support this hypothesis: obese men had a relative risk of non-aggressive prostate cancer of 0.69 (95% CI 0.52-0.93) compared to "normal" weight men, whereas the relative risk of aggressive disease was 1.10 (95% CI 0.83-1.60).[88]

The mechanisms linking obesity to prostate cancer risk are not settled.[89] Androgens have long been thought to increase the risk of prostate, but final confirmation is lacking.[88]

Diabetes

An inverse relationship between diabetes mellitus and prostate cancer has been reported in two large meta-analyses[90,91] and several cohort studies.[92-94] The inverse association is hypothesized to be a result of alterations in sex hormone levels in diabetic patients. In the meta-analysis of Kasper,[91] including 14 studies, diabetic patients showed a statistically significant decrease in the risk of de-

veloping carcinoma of the prostate, RR = 0.84 (95 % CI 0.76-0.93). The results were consistent in both cohort and case-control studies.

Testicular Cancer

Worldwide some 49,000 men are diagnosed with testicular cancer every year. The age-adjusted incidence rate is several folds higher in the more developed parts of the world than in the less developed parts (4.5 and 0.8 per 100,000, respectively) and is particularly high in Norway (10.6 per 100,000) and Denmark (10.3 per 100,000).[21]

Obesity

Some studies have reported on an inverse association between BMI and risk of testicular cancer, whereas others have found no relation.[1] The low number of studies and the inconsistent findings makes it impossible to draw any firm conclusions.

Diabetes

Diabetes as a risk factor for testis cancer is investigated in a limited number of studies. Some results indicate no association between diabetes diagnosis overall and testis cancer[24] or between diabetes type I and testis cancer.[47]

Urinary Organs

Kidney Cancer

Some 180,000 new cases of kidney cancer among men and some 80,000 new cases among women arise worldwide every year.[21] Annual mortality numbers are about 100,000. The age-adjusted incidence and mortality is 5 times higher in the more developed regions of the world than in the less developed parts.

Obesity

A high BMI is an established risk factor for kidney cancer.[95] Whereas no association has been seen between BMI and cancer of renal pelvis, there seems to be a does-response relationship between BMI and risk of renal-cell cancer, the main type of adult kidney neoplasms.[1] The association is seen for both sexes. Overall, obese subjects have a more than 2-fold increase in renal-cell cancer risk compared to subjects with a BMI below 25 kg/m^2. In a meta-analysis based on 7 studies from affluent populations it was estimated that the risk of kidney cancer increased by 6% (95% CI 5%-8%) per unit increase in BMI.[18] Compared to a having a "normal" weight this corresponds to a relative risk of 1.36 for overweight subjects and to a relative risk of 1.84 for obese subjects. Further it is estimated that 25-30% of all kidney cancer in the European Union and more than 40% of all kidney cancer in the US can be attributed to excess body weight.[17,18]

The estimates from the meta-analysis referred to above have been confirmed in a large Norwegian prospective study.[96] More than 6450 renal-cell carcinomas were registered among 2 million subjects for whom height and weight had been measured in a standardized manner. In this study, the relative risk of kidney cancer increased by 5% (95% CI 4%-6%) per unit increase in BMI.

Hypertension is an established risk factor for renal-cell cancer. Obesity increases the risk of hypertension, but the increased risk of renal-cell cancer associated with obesity seems to be mediated through a different mechanism.[17] Hormonal changes like increased levels of peptides, steroid hormones and insulin-like growth factor 1 may be involved.[17,97]

Diabetes

A limited number of studies have focused on diabetes mellitus as a risk factor for kidney cancer. However, one considerably large cohort study reported a significantly increased risk of kidney cancer in both male and female diabetes patients.[98] The SIRs were 1.7 (95% CI 1.4-2.0) and 1.3 (95% CI 1.1-1.6) for women and men, respectively.[98] Diabetes mellitus increased the risk of kidney cancer deaths in the Japanese population.[99] Other studies have not confirmed an association.[43]

Bladder Cancer

Worldwide, more than 350,000 subjects are diagnosed with bladder cancer each year. The age-adjusted incidence rate is about 5 times higher for men than for women (10.1 and 2.5 per 100,000, respectively) and is 3-4 times higher in the more developed parts of the world than in the less developed parts.[21]

Obesity

Data from studies on overweight and obesity and subsequent risk of bladder cancer are inconsistent. Generally, there do not seem to be a strong relation. The findings from a recent study among US adults may serve as a typical example: compared to subjects with a BMI of 18.0-22.9 kg/m^2 subjects with a BMI of 30.0 or above had a incidence rate ratio of 1.16 (95% CI 0.89-1.52).[100]

Diabetes

Diabetes mellitus is suspected as a risk factor for urinary bladder cancer. A meta-analysis based on 16 studies concluded that there is a modestly increased risk in diabetes type II patients.[101] In a case-control study among 252 patients with urinary bladder cancer a significant positive association was seen.[102]

Thyroid Cancer

Thyroid cancer is a rather rare disease. It affects strikingly more women than men, 104,000 and 38,000 new cases emerges per year, respectively.[21]

Obesity

A modest increase in thyroid cancer risk with increasing BMI has been suggested based on findings from case-control studies.[1] In a pooled analysis of 12 case-control studies an odds ratio of 1.2 (95% CI 1.0-1.4) was found for women with the high BMI compared to women with low BMI.[103] No association was seen for men. No association was seen in an US cohort study consisting of both sexes.[104]

Diabetes

A possible association between diabetes and thyroid cancer is unclear. A nonsignificant increased risk for thyroid cancer of 30% in men and 20% in women has been reported.[24] A population-based cohort study showed a 20% increased risk of thyroid cancer in diabetes I patients (95% CI 0.6-2.2).[29]

Lymphoid and Haematopoietic Cancers

Worldwide about 690,000 new cases of nonHodgkin's lymphoma, multiple myeloma and leukemia occur every year.[21] Generally, the age-adjusted incidence rates are higher among men than among women and higher in the more developed parts of the world than in the less developed parts.

Obesity

A modest increase in risk of these cancers with increasing BMI has been seen, with relative risk estimates in the range 1.2-2.0.[17,105] A recent review on nonHodgkin's lymphoma concludes that excess body weight probably has a role in the development of the disease.[105] Further, a meta-analysis including 13 cohort studies and nine case-control studies estimated an average relative risk of nonHodgkin's lymphoma of 1.07 (95% CI 1.01-1.14) for overweight subjects and 1.20 (95% CI 1.07-1.34) for obese subjects compared to subjects with a "normal" weight.[106] It is suggested that a high BMI may affect various histological subtypes differently and that it particularly increases the risk of diffuse large B-cell lymphoma.

Diabetes

A limited number of studies have reported on the association between diabetes mellitus and risk of lymphoid and haematopoietic cancers. A cohort study from Japan reported a significant

increased risk of nonHodgkins lymphoma among men and nonsignificant increase in women.[27] No association was found for nonHodgkins lymphoma and leukaemia in another study.[47] A borderline significant increased risk of all lymphatic and haematopoietic cancer was found in Danish male and female diabetes patients.[24] The same study reported a nonsignificant 10% increased risk of lymphoma and leukemia specifically, in both genders.

Summary of Findings

The findings on obesity, diabetes and risk of cancer presented in this section are summarized in Table 2.

Concluding Remarks and Recommendations for Further Research

Even though there is a substantial body of literature on the association between obesity and cancer for some cancer sites in humans, such as colon, postmenopausal breast cancer, endometrial cancer, kidney cancer (renal-cell) and oesophagus cancer (adenocarcinoma), further studies on

Table 2. Summary of findings relating obesity and diabetes to risk of various cancers

Cancer Site	Obesity	Diabetes Mellitus	
		Type I	Type II
Oesophagus			
- adenocarcinoma	↑*	..	..
- squamous cell carcinoma	-	..	..
Stomach			
- cardia	↑	..	..
- noncardia	..	..	..
Colorectum	↑*	(↑)	(↑)
Liver	..	(↑)	(↑)
Gallbladder	(↑)	..	..
Pancreas	(↑)	(↑)	↑
Lung	..	..	..
Melanoma of the skin	..	..	..
Breast			
- premenopausal	↓	..	..
- postmenopausal	↑*	..	..
Endometrium	↑*	(↑)	(↑)
Ovary	..	..	..
Cervix	..	..	
Prostate	-	(↓)	(↓)
Testis	..	..	..
Kidney (renal-cell)	↑*	..	..
Bladder	..	(↑)	(↑)
Thyroid gland	..	..	..
Lymphoid and haematopoietic tissue	(↑)	..	..

↑: sufficient data to state an increased risk
-: sufficient data to state no impact on risk
(↑): some data to state an increased risk
(↓): some data to state a decreased risk
..: inconclusive or lack of data
*: sufficient evidence for a cancer-preventive effect of avoidance of weight gain as regarded by the IARC expert panel in 2001.[1]

virtually all other cancer sites in humans are needed. Studies on the association between type I diabetes mellitus and cancer are scarce for all cancer sites and further studies are warranted. Type II diabetes mellitus has been more studied than type I diabetes mellitus in regard to cancer risk, but still our comprehension of its impact is very limited. There is some evidence that persons with type II diabetes mellitus are at an increased risk of liver and pancreas cancer and probably also for bladder, colorectal, endometrial and postmenopausal breast cancer. Further studies are needed for confirming these associations, as well as to clarify possible underlying mechanisms of carcinogenicity.

Overweight, obesity and diabetes mellitus type II are now pandemic in many areas of the world and global trends indicate no evidence of decline in their prevalence. A substantial proportion of cancer cases can be attributable to overweight and obesity. As also stated by the IARC expert panel in 2001[1] other specific topics of research to be further developed include:

- Creation of standardized, validated methods to measure body composition and evaluate the need for ethnic, gender and age-specific body mass index and waist cut points.
- Maintenance and enhancement of systems for monitoring trends in body composition in various populations.
- Development of methods to study environmental factors (physical, economic and socio-cultural) that determine behavioral patterns that lead to obesity and diabetes mellitus type II in populations undergoing various stages of economic development.
- Performance of studies on the relationship between different indicators of body composition and fat distribution and cancer risk.
- Performance of clinical intervention such as dietary modification studies in subgroups of age, sex and ethnicity to alter behavior patterns which may influence weight gain and type II diabetes mellitus.
- Establishment of the effectiveness of various community intervention studies to prevent weight gain and type II diabetes mellitus.
- Performance of studies in humans to establish the mechanisms by which weight gain and diabetes mellitus (type I and type II) are/may be related to cancer development.

Overweight, obesity and type II diabetes mellitus cannot be prevented or managed solely at the level of the individual. Governments, the food industry, the media, communities and individuals all need to work together to modify the environment so that it is less conductive to weight gain/obesity and consequently diabetes mellitus type II development. Most current guidelines indicate a desirable BMI range of 18.5 to 25 kg/m^2, based primarily on the relationships of body weight to the risk of cardiovascular diseases, diabetes and total mortality. The benefits of maintaining weight in this range clearly extend to reduced risks of important cancers. Most individuals will experience lower risks of cardiovascular diseases, diabetes and cancer if they maintain their body weight in the lower part of this range.

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