OBESITY AND CANCER RISK

The growing prevalence of obesity not solely in the affluent nations, but also in select populations of third world countries, has been an epidemiological nightmare. As a risk factor, obesity has been linked to type 2 diabetes mellitus, coronary artery disease, hyperlipidemia, fatty liver, degenerative joint diseases, and also numerous types of cancer.

In many countries, cancer rates are increasing in parallel with obesity. Data from the last 25 years have identified obesity as a cause of approximately 14% of cancer deaths in men and 20% in women. Epidemiologic studies in the last four decades have shown both increasing incidences and death from cancers of the colon, breast (in post-menopausal women), endometrium, kidney (renal cell), esophagus (adenocarcinoma), stomach (gastric cardia), pancreas, gallbladder and liver, and possibly others. According to an estimate, 15-20% of all cancer deaths in the United States can be related to overweight and obesity, demonstrating that this health burden may exceed that of cigarette smoking.

The aim of this review is to demonstrate the relationship of obesity as a major risk factor in gastrointestinal cancers. This epidemiological review is not intended to extensively discuss the pathogenesis of obesity in various cancers or to explain the clinical features and management of individual tumors.

Currently, more than two-thirds of adults in the US are overweight or obese; this pandemic of obesity has shown no signs of abating, with prevalence steadily rising over the past two decades. The juxtaposition of growing obesity in developing countries amidst larger populations with malnutrition is due to the introduction of western diet, urbanization, lack of exercise and other negative lifestyle changes.
Body mass index (BMI), as measured by body weight in kilograms divided by height in meter squared, is one method of measuring obesity. Definitions of overweight and obesity are tabulated in Table 1; these measurements however vary from country to country with differences in influencing weight. One must go beyond BMI to properly assess morbidity and mortality risk associated with increased adiposity. Metabolic syndrome (MS) is defined by insulin resistance, hypertension, hyperlipidemia, coronary artery disease, non-alcoholic fatty liver, and waist/hip circumference ratio, another manner of assessing obesity.

In a prospective study of a large cohort, Calle et al found that the heaviest men and women (those with BMI of at least 40) had death rates from all cancers 52% and 62% higher respectively than the rates in men and women of normal weight. The proportion of deaths from cancer attributable to overweight/obesity in US adults of over 50 years of age may be as high as 14% in men and 20% in women.1

The American Medical Association (AMA) has recently stated that it will now call obesity a disease, with the implications of this pronouncement heatedly debated in the scientific and the lay press.

A meta-analysis published in 2002 concluded that obesity was a cause of 11% of colon cancer cases, 9% of postmenopausal breast cancer cases, 39% of endometrial cancer cases, 25% of kidney cancer cases, and 37% of esophageal cancer cases (International Agency for Research on Cancer 2002). The American Cancer Society (ACS) suggested that overweight and obesity were related to mortality from liver cancer, pancreatic cancer, non-Hodgkin’s lymphoma, and myeloma1. Using NCI Surveillance, Epidemiology, and End Results (SEER) data, it was estimated that in 2007 the United States would have about 34,000 new cases of cancer in men (4%) and 50,500 in women (7%) due to obesity.

Although the epidemiological association between obesity and cancer is well known, the pathogenesis is still not clear. Adipose tissue in the body is classified

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Ectopic accumulation of fat in the abdomen is now identified as playing a major role in the consequences of the metabolic syndrome. Ectopic adipose tissue is considered to be a metabolic organ, with far-reaching effects on other tissues. The two terms describing the morphological types of obesity are the apple and the pear type, denoting metabolic (the bad type) and non-metabolic (the not so bad).

Insulin resistance occurring in metabolic obesity is characterized by hyperinsulinemia and type 2 diabetes mellitus. Because of its proliferative and proinflammatory properties, insulin has been implicated in cancer progression. Excess insulin likely promotes tumor formation via many complex pathways. The type-1 insulin-like growth factor receptor (IGF-1R) is a tyrosine kinase receptor with 70% homology to the insulin receptor. Excess insulin binds to IGF-1 receptors in both normal and cancer cells. Receptor bound IGF-1 enhances cell proliferation and survival, by mitogenesis, cell transformation and protection from apoptosis. It also stimulates adipocyte mediated vascular endothelial growth factor. Epidemiological evidence supports the association of hyperinsulinemia with increased risk for cancers of the colon, endometrium, kidney and pancreas. The tumorigenic effects of insulin are probably directly related to changes in endogenous hormone metabolism as well as to insulin receptor stimulation in preneoplasmic target cells.

Leptin, an adipokine, is a 16-kDa protein hormone regulating energy intake, expenditure, and appetite control. It is produced by the white adipose tissue, acts on the hypothalamus in the brain and reduces appetite; deficiency of leptin in experimental animals causes obesity. Leptin is involved with a negative feedback mechanism in body mass index. As a circulating signal however, obese individuals generally exhibit an unusually high circulating concentration of leptin. Leptin induces expression of VEGF (Vascular Endothelial Growth Factor), contributing to cancer progression via its potent pro-angiogenic effect.

Adiponectin, also secreted by adipocytes, is an anti-inflammatory hormone with roles in the metabolism of fatty acids and glucose, the regulation of inflammatory responses, and the modulation of insulin sensitivity. Decreased in patients with the metabolic syndrome, adiponectin has an anti-angiogenic potential.

Other proinflammatory adipokines include prostaglandin E2, TNF-alpha (tumor necrosis factor), interleukin-6, IL-8 (interleukin), IL-10, macrophage inflammatory protein-1, and monocyte chemoattractant protein-1. These factors all produce a cellular environment, conducive to survival and growth of cancer cells.

Factors such as lack of exercise, excessive calorie

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### Table 1. Definitions of Obesity and Overweight

<table>
<thead>
<tr>
<th>BMI</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>Below 18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>Ideal Weight</td>
</tr>
<tr>
<td>25-29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>30-34.9</td>
<td>Obesity Class 1</td>
</tr>
<tr>
<td>35-39.9</td>
<td>Obesity Class 2</td>
</tr>
<tr>
<td>Over 40</td>
<td>Extreme Obesity Class 3</td>
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consumption, fat consumption, lack of fiber in the diet, all well known factors responsible for weight gain, play a complementary role in carcinogenesis. A diet rich in fiber, naturally low in calories, and rich in antioxidants may act in many ways to prevent obesity and cancer.

**Esophageal Cancer**

The epidemiology of esophageal cancer is rapidly changing in the US and many other western nations. In a recent study, the median age of diagnosis was 67 years of age. The age adjusted incidence rate was 4.4 per 100,000 men and women per year. Squamous cell carcinoma is the most frequent histological type world over. The incidence of adenocarcinoma has rapidly increased and currently in the USA, 50% of esophageal cancers are adenocarcinomas. The risk factors for squamous carcinoma include use of tobacco, alcoholism, and infectious agents such as HPV. Other risk factors include ionizing radiation, asbestos, and contamination of food by silica fibers (Iran, China). Rare causes include occupational exposure to products of combustion (chimney sweepers) and diesel pollutants (garage staffers). The role of nitrosamines in the development of esophageal cancer is much debated. Adenocarcinoma of the esophagus differs in its etiological factors. The rise in obesity parallels the increasing prevalence of gastroesophageal reflux disease, which may progress to Barrett’s metaplasia, dysplasia, and cancer. Increase in abdominal girth is associated with an increased incidence of adenocarcinoma, independent of BMI. Adenocarcinoma of the esophagus is more common in Caucasian men.

**Gallbladder Cancer**

In a meta-analysis of studies identified from MEDLINE and EMBASE databases from 1966 to Feb 2007, Larson and Wolk recently noted an association between obesity and gallbladder cancer. Cancer of the gallbladder is rare in Europe and in the United States, except in Native Americans. The highest incidence of gallbladder cancer is noted in Chile, Bolivia, and in Japanese women. Relatively high incidence and mortality rates are reported from certain parts of northern India (cancer belt), Pakistan, Iran, China, Korea, and some eastern European countries. Gallbladder cancer risk is 15% and 66% higher among those who are overweight and obese, respectively, as compared with those of normal weight. The association between obesity and gallbladder cancer risk is greater in women than in men. The etiological factors of gallbladder cancer include genetic disposition and gallstone disease (as in Native Americans and Mexicans), calcification of the gallbladder (porcelain gallbladder), and environmental carcinogens. The topic will be discussed separately in another paper in this series.

**Pancreatic Cancer (PC)**

PC, ranking 10th in incidence of all cancers and 2nd among gastrointestinal cancers, is the leading cause of cancer death in men and women in the USA. PC is the 5th most common cause of cancer mortality in the European Union and is responsible for approximately 70,000 deaths. Risk factors for PC include advanced age, heavy cigarette smoking, excessive alcohol

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consumption, chronic pancreatitis, family history, obesity, and diabetes.16

A high BMI is associated with approximately a doubling of the risk of pancreatic cancer.2,17-19 In a meta-analysis of published data, Gonzalez et al identified a small positive increase in the risk for pancreatic cancer per unit increase in the body mass index.19 A unit increase in body mass index for a male patient of 1.78m (5 ft 10 in), a unit increase in body mass index represented weight gain of about 3 kg (6.6 lbs). For a female patient of 1.64m (5 ft 5 in), a unit increase in body mass index represented weight gain of about 2.5 kg (5.5 lbs). The observed per unit increase in relative risk translated into a 19% higher risk of pancreatic cancer in obese people (BMI > 30 kg/m^2) compared to those of normal body weight (22 kg/m^2). It is the accumulation of metabolic or ectopic fat that is closely related with possible risk for PC. Central obesity as measured by waist-circumference was significantly associated with increased risk of PC in men in a pooled analysis of 30 cohort studies involving 519,643 Asian-Pacific participants and 324 deaths from PC; the RR was 1.08 (95% CI: 1.02-1.14) for every 2-cm increase in waist circumference.20

**Colorectal Cancer (CRC)**

CRC is the third most common cancer worldwide.21 CRC in the US occurs more often in individuals over 50 years of age and the incidence is 35% higher in men than in women. The highest risk is in African-Americans.22 An increase in BMI was associated with a higher risk for CRC with a specific molecular characteristic.

The clinical significance of obesity in terms of oncologic outcomes is highlighted in an excellent review by Rupp et al.23 The article emphasizes that obesity has implications in all aspects of the care of CRC from prevention to surgical treatment to adjuvant and neo-adjuvant treatment. An excellent meta-analysis of prospective studies indicated that the association between obesity and risk of CRC varied by sex and cancer size.24 CRC risk increased with BMI, waist circumference, and waist-hip ratio in both men and women, although the associations were stronger in men. With regard to rectal cancer, the risk increased with increasing BMI in men, whereas no overall association was observed in women.24 In the same year, a similar study was reported from Australia by Moghaddam,20 who analyzed 31 studies with 70000 events and reported that obesity has a direct and independent relationship with CRC, although the magnitude of the association was smaller than previously estimated. Individuals with a BMI >= 30 kg/m^2 have approximately 20% greater risk of developing CRC compared with those with normal weight (BMI < 25kg/m^2). However, for every 2 kg/m^2 increase in BMI, the risk of developing CRC increased by 7%. A 2-cm increase in waist circumference, a measure of central obesity, was associated with a 4% greater risk of CRC.

Deregulation of the proinflammatory cytokines TNF-alpha and IL-6, associated with the development of NAFLD and NASH, is also important in inflammation related carcinogenesis.25, 26

The world risk of obesity is expected to increase from the current number of 300 million to 700 million in 2015. Assuming that obesity increases the risk of CRC by 20%, each year about 10,000 more cases of obesity-related CRC worldwide will occur. The precise pathogenesis of obesity and CRC is not well elucidated but is certainly multifactorial. The role of factors such as insulin and IGF-1, leptin, adipocytokines, and sex hormones, previously discussed, are important. Diabetes mellitus is noted to play an independent added role, as elevated glycohemoglobin levels have been demonstrated to be an independent predictor of early onset of CRC and of right-sided CRC, more advanced in stage at the time of presentation, with reduced 5-year-survival.27 Populations on insulin therapy have been shown to have a threefold higher risk of CRC.28

**Hepatocellular carcinoma (HCC)**

HCC is the fifth most common cancer worldwide and third leading cause of cancer mortality in the US after lung and stomach cancer.29, 30 It is estimated to cause over half a million deaths per year worldwide. Because of the poor prognosis, the incidence and mortality rates are almost equal, with the mortality to incidence ratio being almost 1.31, 32, 33 El-Serag, reporting on HCC, stated that the age adjusted incidence rates of HCC increased two fold between 1985 and 1998.30 The average annual age adjusted rate of HCC as diagnosed by histopathology increased from 1.3 per 100,000 persons during 1978-1980 to 3 per 100,000 during 1996-1998.31,32,33 Etiologically HCC is related to cirrhosis, chronic hepatitis B, hepatitis C, hemochromatosis, primary biliary cirrhosis, alpha 1 anti-trypsin deficiency, and exposure to carcinogens. Many studies from the US and other countries have identified an association between obesity and liver cancer risk.34, 35, 36, 37 An impressive
study from Sweden by Borena et al on metabolic risk factors and primary liver cancer included a prospective analysis of 578,700 adults showing that the risk of liver cancer was twice as high among obese individuals as in non-obese controls. Obesity is recognized to cause non-alcoholic fatty liver disease and the more severe nonalcoholic steatohepatitis (NASH).31, 37

Obesity is associated with chronic low grade systemic inflammation, which contributes to metabolic disorders and progression of simple steatosis to NASH, cirrhosis, and hepatocellular carcinoma. The roles of insulin resistance, cytokines, leptin, and adiponectin have been mentioned earlier.

The impact of the growing epidemic of NASH and its progression to heptacellular carcinoma cannot be assessed at this time. Although the risk for HCC in individuals with NAFLD is likely to be very small, the considerable increase in the prevalence of obesity may contribute to a substantial increase in the number of patients with HCC.

CONCLUSIONS

Obesity is estimated to account for approximately 20% of all cancers. Cancers of esophagus, colon, rectum, gallbladder, pancreas, and liver are currently noted to be associated with obesity, raising concerns about the potential for increased incidence of these along with the growing prevalence of obesity. The pathogenesis of obesity related cancers is probably mediated through proinflammatory cytokines and insulin resistance. There is a potential to reduce the incidence of many of these cancers by addressing nutritional issues related to weight gain very early in childhood. Along with abstinence from cigarette smoking, increasing intake of dietary fiber, and reducing animal fat consumption may go a long way in preventing some of the cancers related to obesity. This review synthesizes the importance of obesity related gastrointestinal cancers. Subsequent papers in this series will discuss the epidemiology of individual cancers in detail.
Reference:


