COMMENTARY

Potential Study Perspectives on Mechanisms and Correlations Between Adiposity and Malignancy

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Abstract

Adiposity is a well-recognized risk factor of type 2 diabetes and cardiovascular disease, and recently there is increasing evidence that excess body weight is an avoidable cause of cancer, including gastrointestinal, endometrial, esophageal adenocarcinoma, colorectal, postmenopausal breast, prostate, and renal malignancies. The mechanisms whereby adiposity is associated with tumor development remains not well understood. There are some most studied hypothesized mechanisms such as, high levels of insulin and free levels of insulin-like growth factors, sex hormones, adipocytokines, and inflammatory cytokines, adiposity-induced hypoxia, and so on. The potential mechanisms and conclusions in adiposity associated with increased risk for developing malignancy, and the underlying cellular and molecular mechanisms will be studied very well in the near future.

Keywords: Perspectives - adiposity - malignancy

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Introduction

The global epidemic of adiposity is now recognized as one of the most important public health problems facing the world today. Epidemiological surveys from many countries show that the mean weight of the population is in-creasing and that the prevalences of clinically-significant overweight and adiposity are rising rapidly in adults and, of particular concern, in children and adolescents. Up to one-third of the adults in some westernized countries are obese and over two-thirds in certain smaller populations such as Pacific Islanders; very few countries remain unaffected by adiposity (WHO/NUT/NCD, 2000). It is predicted that, by 2015, 1.6 billion people will be overweight including 700 million obese. The greatest increases are forecast in the USA (with 75% of adults overweight or obese), South America, Europe, Central Asia and the Pacific Rim. The combined prevalence of overweight and adiposity among children could exceed 40% in the Americas, Middle East and North Africa.adiposity predisposes to type 2 diabetes, cardiovascular disease, some malignancies and numerous other disorders, including osteoarthritis. It is thought to account for almost 60% of the risk for developing type 2 diabetes, over 20% of that for hypertension and coronary-heart disease, and between 10% and 30% for various malignancies. Approximately 5% of all malignancies in Europe can be attributed to excess body weight.The highest attributable proportions were formalignancies of the endometrium (39%), kidney (25%) and gall bladder (24%), while the great-est attributable number of cases was colorectal malignancy (21 500 cases per year). Reducing the prevalence of overweight and adiposity in Europe by half could potentially lead to a reduction of 36 000 in cases of malignancy per year (Bergstromet al., 2001).

As already mentioned, adiposity has been firmly linked with various malignancies. Several studies have demonstrated that overweight and adiposity increase the risk of developing several forms of diseases, including several malignancy. Wolf and Colditz (1998) and James et al. (2004) have estimated the proportion of total risk of developing several major diseases that can be attributed to adiposity. There are some discrepancies between the two reports, probably due to differences in the study populations and sampling periods (Wolf and Colditz used only American data from the 1988 and1994 National Health Interview Survey). Overall, however, adiposity appears to contribute about 60% of the total risk for type 2 diabetes, up to 40% of that for hypertension and endometrial carcinoma, 20~30% of the risk for coronary heart disease, stroke, osteoarthritis and gall-bladder disease, and about 10% for carcinoma of the breast and colon (Figure1).

In the White hall prospective cohort study of 18 403 middle-aged government employees in London followed up for a median of 28 years, obese or over weight men showed excess deaths from carcinoma of the colon, rectum, liver (hepatocellular carcinoma), bladder and lymphoma, following adjustment for covariates including socioeconomic status and physical activity (Batty et al., 2005). In the US prospective study of over 900 000 adults followed for 16 years, Calle et al. found

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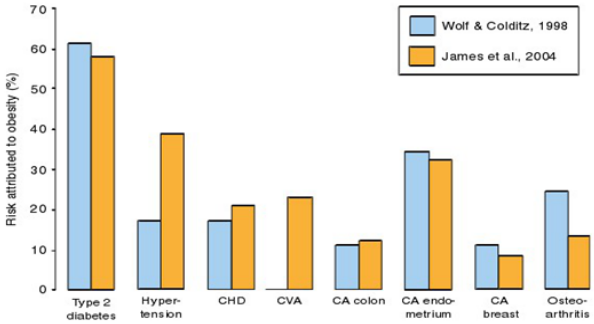

Figure 1. Percentage of Risk Attributed to Adiposity in Developing Certain Diseases in North American and Global Populations, as Estimated by Wolf and Colditz (1998) and James et al. (2004) respectively. Both reports used a BMI risk threshold of 30 kg/m^2

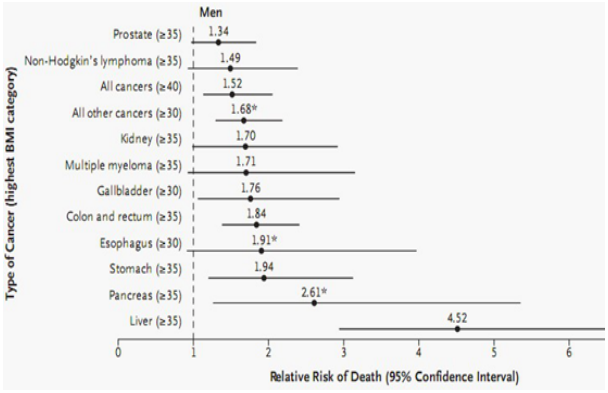

Figure 2. Summary of Mortality from Malignancy According to Body-mass Index for U.S. Men in the Malignancy Prevention Study II, 1982 through 1998. For each relative risk, the comparison was between men in the highest body-mass-index (BMI) category (indicated in parentheses) and men in the reference category (body-mass index, 18.5 to 24.9). Asterisks indicate relative risks for men who never smoked. Results of the linear test for trend were significant ($P \leq 0.05$) for all malignancy sites

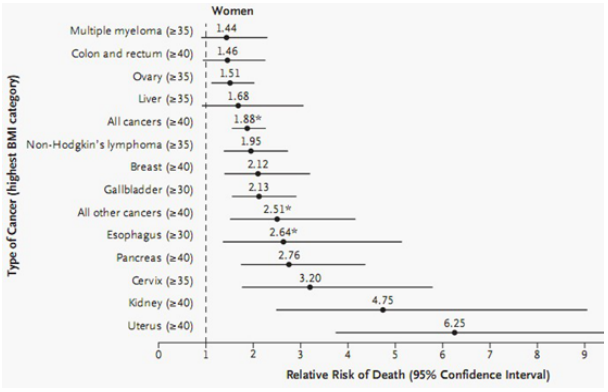

Figure 3. Summary of Mortality from Malignancy according to Body-mass Index for U.S. Women in the Malignancy Prevention Study II, 1982 through 1998. For each relative risk, the comparison was between women in the highest body-mass-index (BMI) category (indicated in parentheses) and women in the reference category (body-mass index, 18.5 to 24.9). Asterisks indicate relative risks for women who never smoked. Results of the linear test for trend were significant ($P \leq 0.05$) for all malignancy sites

that BMI was significantly associated with risk of death from malignancies of the gut (including hepatocellular carcinoma), genitourinary tract, breast and haematological malignancies including non-Hodgkin lymphoma and multiple myeloma (Calle et al., 2003). Over-all, subjects with BMI 40 kg/m^2 had a 50–60%increased risk of malignancies compared with those of normal weight. From these data, adiposity and overweight might account for up to 14% of all malignancy-related deaths in men and 20% in women, which is estimated (Figure 2, 3). In both men and women, increasing BMI is significantly associated with higher death rates from malignancies of the oesophagus, colon and rectum, liver, gall bladder, pancreas and kidney, as well as non-Hodgkin lymphoma and multiple myeloma. The associations between adiposity and particular maignancies may be affected by body fat distribution, and may result from diverse factors including diet and abnormal levels of hormones and inflammatory cytokines.

General Gender-related Malignancies and Adiposity

Gynaecological malignancies

What's more, Calle et al. (2003) noted increased risk of death from prostate and stomach carcinoma in obese men and malignancies of the breast, uterus, cervix and ovary in obese women. In the Nurses'Health Study, it was noted that weight gain after 18 years of age was associated with an increased risk of postmenopausal breast malignancy. It was calculated that 15% of breast malignancy cases in this population could be attributed to weight gain of 2 kg since age 18, and 4.4%to weight gain of 2 kg after the menopause (Eliassen et al., 2006). Breast malignancy risk appears to be increased, but only in postmenopausal women (Van Gaaland Mertens, 1998; IARC, 2002). Weight gain during adult life may be an important risk factor (McTiernan, 2000). Diagnosis may also be delayed because of the reluctance of obese women to consult doctors, and the difficulty of detecting small tumors in obese breasts (Verrijken et al., 2006). Endometrial cancer, which usually occurs in postmenopausal women, is consistently associated with adiposity (Rose, 1996; Bray, 2002). One possible explanation of the increased risk of endometrial and breast malignancy in obese women is the increased production of oestrogens through the conversion of androstenedione to oestrone (which is then reduced to oestradiol in peripheral tissues), under the action of the aromatase enzyme in adipose tissue.

Prostate malignancy

In men, adiposity (and perhaps high fat intake)increases the risk of poorly-differentiated prostate malignancy (Barnard et al., 2002; Verrijken et al., 2006). Some studies have demonstrated an overall increased risk of prostate tumor with increasing BMI or body weight, whereas others have failed to confirm any such association. This discrepancy may be explained by the differing effects of key hormones on the development of specific types of prostate tumor. Androgens are thought to promote the initiation and progression of well-differentiated prostate

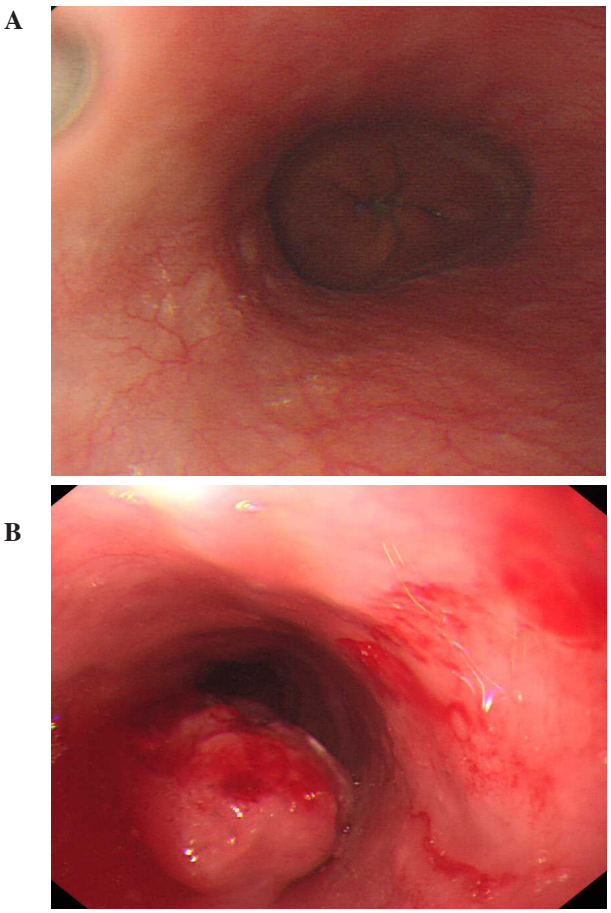

Figure 4. Oesophageal Complications of Adiposity: (A) Barrett's oesophagus, with ascending gastric-type mucosa (appearing darker); (B) Gastrointestinal carcinoma or carcinoma of the oesophagus with Barrett's oesophagus. Notice: Illustrations courtesy of gastroenterology dept. , reproduced by kind permission of the director of the Department of Gastroenterology, Shanghai Tenth People's Hospital, Tongji University School of Medicine , Shanghai 200072, China

tumor, while protecting against poorly-differentiated tumors. By contrast, hyperinsulinaemia has been associated with an increased risk of poorly-differentiated prostate tumor, while leptin may also play a role in these tumors. Recent cohort studies indicate that obese subjects have an increased risk of poorly-differentiated, androgen independent prostate tumors – which would be expected from the low testosterone and raised insulin and leptin levels characteristic of adiposity. Unfortunately, these tumors are more aggressive and less likely to respond to conventional therapy.

Non Gender-related Malignancies and Adiposity

Haematological malignancies

In both sexes, haematological malignancies associated with overweight and adiposity include non-Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukaemia and multiple myeloma. Possible causes include the low-grade chronic inflammation that accompanies adiposity, with increased production of pro-inflammatory cytokines such as interleukin-6, TNF-αand leptin. These cytokines regulate T- and B-cell responses and enhance B-cell proliferation and survival, thus providing an environment that favors the development of these disorders (Skibola, 2007).The reduced physical activity levels and poor diet that are commonly associated with adiposity may also play a role. Physical inactivity and high consumption of dairy and saturated fats is suggested to increase the risk of non-Hodgkin lymphoma, whereas a diet rich in fish, fruit and vegetables is apparently protective (Skibola, 2007). One possible mechanism for the increased risk associated with dairy products relates to the high calcium content of these foods, which may inhibit the formation of 1, 25 dihydroxy vitamin D, the active form of the vitamin. Vitamin D has potentially potent anti-carcinogenic properties, because it inhibits growth and triggers apoptosis inpreneoplastic cells (Skibola, 2007).

Gastrointestinal malignancies

Links between adiposity and malignancy are only partly explained by body weight. It has been estimated that the risk of colorectal malignancy increases by 7% for every 2 kg/m^2 increase in BMI, or by around 4% for every 2 cm increase in waist circumference (Moghaddam, Woodward and Huxley, 2007). In two large prospective cohort studies, adiposity in women (BMI 29 kg/m^2) or central adiposity in men (WHR 0.99) confer redan approximately 1.5-fold increased risk of devel-oping colorectal malignancy relative to subjects with normal weight (Giovannucciet al., 1995; Martinez et al., 1997). Colorectal malignancy has been attributed to dietary factors in around 75% of sporadic cases in Western countries, while high physical activity levels seem to protect against the disease. Proposed mechanisms include metabolic stress and chronic low-grade inflammation, perhaps compounded by adverse dietary factors such as red and processed meat and loss of the protective effects of dietary fibre and n-3 polyunsaturated fatty acids (Johnson and Lund, 2007). adiposity has also been shown to be associated with the presence of adenomatous polyps in the colon, which are believed to be premalignant lesions in the development of colorectal malignancy (Bird et al., 1998). Colonic and rectal malignancies are independently associated with adiposity, especially in men; physical inactivity and a high fat intake may also contribute (Murphy et al., 2000).

In addition, the association with hepatocellular carcinoma appears to be explained by progression of non-alcoholic fatty liver (a common finding in adiposity) to cirrhosis, which in about 7% of cases becomes complicated by the development of this tumor. Simple steatosis is benign, whereas NASH is characterized by hepatocyte injury, inflammation and fibrosis, which can lead to cirrhosis, liver failure and hepatocellular carcinoma (HCC). As the name suggests, most cases have simple steatosis (fatty liver), which in itself is benign but can process in up to40% of cases to non-alcoholic steatohepatitis (NASH) and in 10% to cirrhosis. Hepatocellular carcinoma is a recognized risk. adiposity now explains a significant proportion of new cases of oesophageal adenocarcinoma possibly by causing gastro-oesophageal reflux, a risk factor for the premalignant changes of Barrett's oesophagus. Hiatus hernia and

associated gastro-oesophageal reflux are well-recognized as complications of adiposity (Stene-Larsen et al., 1988), although Lundell et al. (Lundell et al., 1995) did not find significant relationships between the severity of reflux and various measures of adiposity. The associations are attributed to raised intraabdominal pressure due to visceral fat accumulation.Gastro-oesophageal reflux is potentially important, because it predisposes to Barrett'soesophagus, that is, transformation of the normal squamous epithelium of the oesophagus into a gastric-type mucosa. This is a pre-malignant condition and probably accounts for the association of adiposity with carcinoma of the oesophagus (Figure 4).

Potential Correlations and Conclusions

From above all, adiposity and overweight predispose to many malignancies. Prevalence and deaths are increased for malignancies of the oesophagus, colon and rectum, liver, gall-bladder, pancreas and kidney. Postmenopausal obese women are at increased risk of breast, uterine, cervical and ovarian malignancies, while obese men have a higher prevalence of poorly-differentiated prostate malignancy. Aetiological factors may include raised insulin and IGF-1 levels. Haematological malignancies (especially lymphomas) are more common; pro-inflammatory cytokines generated by adipose tissue, and perhaps physical inactivity and overconsumption of dairy products, may also contribute. Overall, working with'cancer or malignancy'would be a challenge for both sides, but could be the basis for an effective partnership that will at last begin to contain the global spread of adiposity and its consequences.

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