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Obesity and gastric cancer

Qiang Li[1], Jun Zhang[1], Yongning Zhou[1], Liang Qiao[2]

[1]Division of Gastroenterology and Hepatology, The First Hospital of Lanzhou University, Lanzhou 730000, Gansu Province, China, [2]Storr Liver Unit, Westmead Millennium Institute, The University of Sydney at Westmead Hospital, Westmead, NSW 2145, Australia

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1. ABSTRACT

Obesity is an important public health problem worldwide. It increases the risk of many chronic diseases such as diabetes and cardiovascular diseases. Meanwhile, obesity is a major risk factor for several types of cancer including gastric cancer. Possible mechanisms linking obesity with gastric cancer may include obesity associated gastro-oesophageal reflux, insulin resistance, altered levels of adiponectin, leptin, ghrelin, and an abnormally increased blood level of insulin-like growth factor (IGF). Helicobacter pylori (H. pylori) infection is a well-recognized risk factor for peptic ulcer and gastric cancer. Recent studies have revealed an increased prevalence of H. pylori infection in obese patients, providing another clue for the increased incidence of gastric cancer in obese population. If this connection can be confirmed in animal models and a large cohort of patients, then eradicating H. pylori together with life style modification in obese individuals may help prevent the development of gastric cancer in the increasingly obese population.

2. INTRODUCTION ON OBESITY

Overweight and obesity are abnormal or excessive fat accumulation that may impair health. According to the WHO, overweight refers to a body mass index [BMI, defined as weight (kg)/height (m^2)] being $\geq$25kg/m^2, and obesity refers to a BMI $\geq$30kg/m^2 (1). Normal weight individuals should have a BMI of 18.5–25kg/m^2. Obesity is increasingly prevalent in both developed and developing countries. It is well-established that obesity is closely related to many chronic diseases especially diabetes (2) and cardiovascular diseases (3). Over the last few years, the correlation between obesity and cancer has also attracted widespread attention including gastric cancer (4-9). Very severe obesity (BMI >45kg/m^2) is associated with a markedly shortened life expectancy. In America, adult males with severe obesity have a 13-20 year reduction in life expectancy, while obese adult females have a 5-8 year reduction in their life expectancy (10). Clearly, obesity has become an important public health problem.

3. EPIDEMIOLOGY OF OBESITY

Worldwide, obesity affects more than 1 billion adults, with 300 million being clinically obese in 2008 (11). In the industrialized countries such as America and United Kingdom, the prevalence of obesity has been on the rise. In the USA, about 32.2% of adult men and 35.5% adult women were reported to be obese in 2007-2008 (12), whereas only 15% of the adult population in the USA was obese in 1976-1980 (13). It is predicted that by the year 2050, almost all American people will be overweight or obese (14). Similarly in the United Kingdom, the prevalence of obesity in adults had increased by three to four folds in the past 30 years, and this rising trend is expected to continue so that by the year 2050 about 60% of the nation's population will be obese (15). In the developed Asian countries such as Korea, the overall prevalence of obesity in adults was reported to be 30.6% (32.4% in men and 29.4% in women) in 2001 (16).

This increased prevalence of obesity is not confined to the developed countries. In fact, the proportion of obese people is rapidly increasing in developing countries. For example, in China, the number of obese people in 2002 was four times more than that in 1985. In 2002, of 1.3 billion Chinese, about 184 million (14.7%) were overweight and another 31 million (2.6%) were obese (17).

4. ASSOCIATION BETWEEN OBESITY AND GASTRIC CANCER

Gastric cancer is one of most common cancers worldwide. Globally, gastric cancer ranks fourth in incidence and third in cancer-related mortality (18). In China, gastric cancer ranks the third in men and the fifth in women in cancer-associated death (19), although its incidence has declined during the past decades (20). The precise etiology for gastric cancer still remains uncertain, but it is well-accepted that gastric cancer is probably a synergistic consequence of H. pylori infection, environmental and genetic factors (21, 22).

Many studies have demonstrated that obesity is associated with gastric cancer. In five case-control studies, it was revealed that overweight or obesity is closely associated with gastric cancer. Compared to normal weight subjects, individuals with overweight or obesity have a relative gastric cancer risk of >1 (23-27). If stomach is anatomically divided into proximal (cardia) and distal (non-cardia), a rising trend of cardia gastric cancer and a decreasing trend of non-cardia gastric cancer in USA and China have been observed (28-30). Increased prevalence of obesity is likely correlated with the rising incidence of cardia gastric cancer in the Western countries (23, 31).

5. MECHANISMS LINKING OBESITY WITH GASTRIC CANCER

The exact mechanisms responsible for increased incidence of gastric cancer in obese individuals are unclear. Abnormal gastric motility or gastric reflux, abnormal levels of metabolic endogenous hormones such as insulin, insulin-like growth factors, adiponectin, ghrelin, and leptin, as well as the increased production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNFα) may all play a role individually or synergistically (32, 33) (Figure.1).

5.1 Obesity and reflux

Gastric cancer can be categorized into cardiac and non-cardiac in accordance with the sites of origin. The cardiac cancer is different from the non-cardiac cancer in clinical and pathological features, as well as in prognosis (34). To date, a positive association between overweight and cardiac gastric cancer has been found (OR 1.46, 95% CI 0.98-2.18) (26), but the association between increased BMI and non-cardiac gastric cancer remains debatable (35-37).

Reflux of gastric contents has been widely accepted as a mechanism for the association between obesity and cardiac gastric cancer (38, 39). Obesity may promote gastroesophageal reflux disease through several possible mechanisms: (1) increased intra-abdominal pressure may lead to a displacement and malfunction of the lower esophageal sphincter (40); (2) hiatal hernia is more prevalent among the obese individuals; (3) an increased output of bile and pancreatic enzymes (41). The clue for the association between obesity and cardiac gastric cancer can be further derived from a study showing that obese patients who are H. pylori infected can develop gastroesophageal reflux disease after the eradication of H. pylori (42). Long standing gastroesophageal reflux may lead to Barrett's esophagus which is considered a metaplastic precursor state for cardiac gastric cancer (43).

5.2 Insulin resistance and IGF-1

Insulin resistance (IR) refers to a state of decreased sensitivity of the target organs to insulin. IR causes hyperinsulinemia, reduces IGF binding protein (IGFBP) and increases free insulin-like growth factor-1 (IGF-1) (44, 45). High level of IGF1 is associated with many types of cancers such as those from prostate, colon, and lung (46). IGF1 plays a vital role in mediating the effects of the growth hormone. *In vitro* studies have showed that IGF1 stimulates the proliferation, induces cellular differentiation, and inhibits apoptosis of ovarian cells (47). IGF1 exerts the above effects mainly through binding to IGF1 receptor (IGF1R), which is in turn regulated by IGFBP1-6 (48). Increased expression of IGF1R has been found to be related to tumorigenesis (49) while IGFBPs especially IGFBP3 could inhibit cell growth and stimulate apoptosis (50). The net results of these changes may lead to enhanced DNA synthesis, increased cell proliferation, impaired apoptosis, and subsequently oncogenesis (51).

5.3 Adiponectin

Adiponectin is a hormone mainly produced by adipose tissue. It plays multiple roles in anti-atherosclerosis, anti-inflammation and insulin-sensitivity. Hyperinsulinemia and insulin resistance are associated with decreased level of adiponectin (52), and the latter was

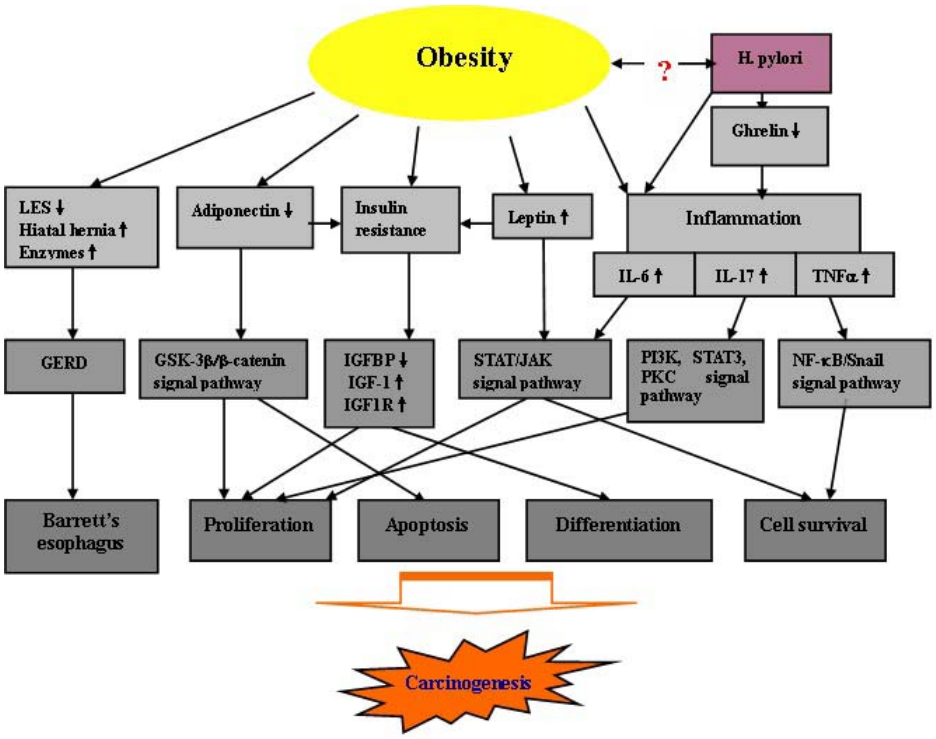

Figure 1. Possible mechanisms linking obesity with gastric cancer. JAK, Janus kinase; GSK-3β, glycogen synthase kinase-3β; NF-κB, nuclear factor-κB; PI3-K, phosphatidylinositol 3-kinase; STAT3, signal transducer and activator of transcription 3; LES, lower esophageal sphincter; GERD, gastroesophageal reflux disease.

found to be associated with an increased risk of cancers such as colorectal cancer (53) and breast cancer (54). *In vitro* and *in vivo* studies have found that adiponectin suppresses the proliferation, induces apoptosis, and arrests the cell cycle progression at G0-G1 phase in breast cancer cells, and these effects are likely mediated by glycogen GSK-3β/β-catenin signaling pathway (55). Significantly low level of adiponectin has been reported in patients with gastric cancer than in normal controls (56). The effect of adiponectin on cancer cells appears to be mediated through membranous adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2) on the tumor cells (57). However, the effect of adiponectin signaling in gastric cancer is still questionable as the expression levels of AdipoR1 and AdipoR2 in gastric cancer were found to be very low (58), and no difference in the plasma adiponectin levels was found between gastric cancer patients and controls (52).

5.4. Leptin

Leptin is a peptide hormone encoded by the ob gene. It is produced and secreted by the white adipose tissues (59). Leptin plays an important role in the regulation of body weight and energy balance by reducing food intake and increasing energy consumption (32, 60). Plasma leptin level is highly correlated with adipose tissue mass and most obese patients have high circulating leptin levels (61). Loss of leptin in mice as a result of mutation in the ob gene, or absence of functional leptin receptor (e.g., in db/db mice) results in obesity and associated metabolic complications such as insulin resistance (62). As the normal physiological function of leptin is mediated by leptin receptors, elevation of plasma leptin level directly leads to a decreased expression of leptin receptors or blunted post-receptor signal pathway in obesity, this status is defined as leptin resistance, which is present in most obese patients (63).

Studies have showed that abnormal leptin signaling might be involved in the development of some cancers. Both leptin and leptin receptor are expressed in normal gastric mucosa (64), and high expression levels of leptin and leptin receptor have been observed in gastric cancer (65). Increased leptin expression in gastric tissues has also been found in patients with H. pylori infection (66). A possible explanation for the link between high leptin level and gastric cancer is that leptin may promote cell proliferation through JAK/STAT signaling pathway (66).

5.5. Obesity-induced inflammation

Obesity is associated with a low-grade systemic inflammation. Increased serum level of C reactive protein (CRP) has been observed in obese people (67) and this is correlated with a high risk of cancer (68). In obesity, increased production of some pro-inflammatory cytokines such as TNFα, IL-6 and monocyte chemoattractant protein 1 (MCP-1) are commonly present, and these cytokines are also considered oncogenic (69). Indeed, TNFα has been reported to promote carcinogenesis through activating NF-κB/Snail signaling pathway (69-71), and IL-6 has been clearly demonstrated to be a strong oncogenic cytokine in

liver cancer (72). Recent study demonstrated that interleukin-17 (IL-17) (73-75) was related to obesity and it could promote tumor growth and metastasis by activating PI3K, STAT3, and protein kinase C(PKC) signaling pathways (76). *In vitro* and *in vivo* studies have showed that the common inflammatory cytokines TNFα, IL-6, IL-17 and MCP-1 could stimulate the growth and inhibit the apoptosis of human gastric cancer cell lines (77-80). H. pylori infection is associated with increased production of inflammatory cytokines including TNFα, IL-6, IL-17 and MCP-1 (80-82).

5.6. Obesity and H. pylori infection

H. pylori infection is closely related to several digestive tract diseases such as chronic gastritis, peptic ulcer, mucosa-associated lymphoid tissue lymphoma (MALT), and more importantly, gastric cancer especially non-cardia gastric cancer (83). In 1994 H. pylori was classified as the class I carcinogen by the WHO. About 50% (over 3 billion) of the world population are infected by H. pylori, and most of the infected individuals reside in the developing countries (84).

Is there any association between the increased prevalence of obesity and the rate of H. pylori infection? In a case-control study involving 414 patients with morbid obesity (BMI $\geq$35kg/m^2 with serious comorbidity or BMI $\geq$40kg/m^2) and 683 control subjects (BMI <25kg/m^2) (85), the overall rate of H. pylori seropositivity was found to be significantly lower in obese patients (43.7%, 181/414) than in controls (60.0%, 410/683) (OR=0.50; 95% CI, 0.39-0.65; p<0.01). Thus, based on this study, it would be less convincing to link H. pylori infection as a risk factor for the development of gastric cancer in patients with morbid obesity (85). However, in a more recent study involving 103 obese and 111 non-obese subjects, higher rate of H. pylori infection was found in obese individuals than in controls and the study population as a whole (57.2%, 27.0%, and 41.5%, respectively) (86), suggesting that obesity may be a risk factor for H. pylori infection. Some previous studies even speculated that H. pylori infection in the early childhood may be a "protective" factor against the development of obesity (87). On the other hand, H. pylori positive individuals tend to have an increased BMI in 18 months following H. pylori eradication (88). Overall, the role of H. pylori in the development of gastric cancer in obese people is controversial. A long term follow-up study and animal models are needed to elucidate the role of H. pylori infection in the development of gastric cancer in the setting of obesity.

5.7. Ghrelin

Ghrelin is a hormone produced by the fundic (oxyntic) glands of the stomach. Physiologically, it regulates the energy balance and participates in the control of appetite through stimulating the secretion of gastric acid and regulating gastrointestinal tract motility (89, 90). Ghrelin plays a role in meal initiation with ghrelin blood levels rising before and falling after eating. Thus, Ghrelin plays an opposite role as leptin, the major satiety hormone. In addition to its physiological functions, ghrelin may inhibit the expression of some pro-inflammatory cytokines such as interleukin 1β (IL-1β), IL-6, and TNFα (91). H. pylori induced chronic inflammation and atrophic gastritis may alter the hormonal milieu of the stomach (92), leading to a decreased production of ghrelin, and if H. pylori is eradicated, the plasma ghrelin level is restored (87). Reduced circulating level of ghrelin may be involved in the enhanced activity of the major inflammatory cytokines such as TNFα and IL-6, which are known oncogenic factors.

6. CONCLUSION

Increased prevalence of obesity worldwide is closely related to the increased incidence of many diseases especially cancers. Gastric cancer is one of the malignancies that may be associated with obesity. Although the mechanisms are not well-established, it is clear that obesity related gastric cancer may be a multifactorial event. More studies such as long term follow up study in a large cohort of patients and animal models should be actively promoted to clarify the causal relations between obesity and gastric cancer and to elucidate the underlying mechanisms. Regardless of the mechanism or risk factors, if a firm connection between obesity and gastric cancer is confirmed, measures that might help prevent obesity or control weight should be of value in preventing the development of gastric cancer in the ever obese population.

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Send correspondence to: Liang Qiao, Storr Liver Unit at Westmead Millennium Institute,Department of Gastroenterology and Hepatology,Western Clinical School at Westmead Hospital, The University of Sydney at Westmead Hospital,Westmead, NSW 2145, Australia, Tel: 9845 9132, Fax: 9845 9103, E-mail: liang.qiao@sydney.edu.au