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Review

Obesity and Liver Cancer in Japan: A Comprehensive Review

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Abstract. *Lifestyle-related factors play a major role in the development of cancer. In recent years, obesity has become widespread in the world and has attracted attention not only as a cause of diabetes mellitus and atherosclerotic diseases but also as a factor in carcinogenesis. In Japan, the number of obesity-related malignancies has been increasing with the westernization of lifestyle. On the other hand, it is estimated that there are more than 10 million nonalcoholic fatty liver disease (NAFLD) patients in Japan. NAFLD is classified into simple fatty liver and nonalcoholic steatohepatitis (NASH), and 10-20% of NASH patients will progress to liver cirrhosis and 2-3% of them will develop hepatocellular carcinoma (HCC) per year. Research interest in metabolism-associated liver cancer has been increasing in recent years. Here in this review, we will comprehensively summarize the current knowledge with regard to the relationship between obesity and HCC in Japan.*

In 2018, 18.1 million people worldwide were diagnosed with cancer, and about 9.6 million people died from it (1), which is a significant increase from 2002 (10.9 million cancer cases and 6.7 million cancer-related deaths), 2008 (12.7 million cancer cases and 7.6 million cancer-related deaths), and 2012 (14.1 million cancer cases and 8.2 million cancer-related deaths) (1-4). On the other hand, the number of cancer-related deaths in Japan was about 380,000 in 2019 (in the order of lung, colon, stomach, pancreas, and liver), and one in three Japanese people died from cancer. This is traditionally thought to be due to the aging of the Japanese population.

Lifestyle-related factors play a major role in the development of cancer (5). In particular, smoking, drinking, overeating, and lack of exercise are the most important risk factors for the development of cancer (5). In recent years, obesity has become widespread in the world and has attracted attention not only as a cause of diabetes mellitus (DM) and atherosclerotic diseases but also as a factor in carcinogenesis (6-10). Currently, there are about 2.2 billion people in the world with a body mass index (BMI) over 25 kg/m^2, which means that about one in three people has a BMI over 25 kg/m^2 (11). It is also estimated that 4 million people die annually from obesity-related diseases, with more people dying from obesity than from malnutrition (12). In developed countries such as Europe and the United States, lifestyle-related cancers such as lung cancer, colon cancer, prostate cancer, and breast cancer are common, while in developing countries, cancers related to viral or bacterial infection, such as gastric cancer, hepatocellular carcinoma (HCC), and cervical cancer, are more common (12). In Japan, the number of obesity-related malignancies such as colorectal cancer, breast cancer, and prostate cancer has been increasing with the westernization of lifestyle, especially diet (13, 14). The recent increase in obesity in Japan suggests that obesity will become one of the major risk factors of cancer in Japan in the future.

While a research group at the University of North Carolina in the United States reported that obese people with a BMI of 30 kg/m^2 or more had a 46% increased risk of COVID-19 incidence, a 113% increased risk of requiring hospitalization, a 74% increased risk of being treated in an intensive care unit, and a 48% increased risk of dying from COVID-19, compared to those who were not obese (15). In addition, liver function in patients with nonalcoholic steatohepatitis (NASH) can deteriorate during the COVID-19 pandemic (16, 17). Thus,

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obesity is also an important social health problem in the COVID-19 pandemic. One of major concerns is that COVID-19 vaccines may have decreased efficacy for persons with obesity compared to those with non-obesity (15).

Nonalcoholic fatty liver disease (NAFLD), which is commonly seen in obese patients, is currently the most frequent liver disease in developed countries, and it is estimated that there are more than 10 million NAFLD patients in Japan (18). NAFLD is classified into simple fatty liver and NASH, and 10-20% of NASH patients will progress to cirrhosis and 2-3% of them will develop HCC per year (18). Our national multicenter study of more than 20,000 cases on the etiology of HCC has shown a clear decrease in hepatitis virus-related HCC (from 85.3% to 64.4% in about 10 years) and a clear increase in non-B non-C HCC including NASH-related HCC (prevalence of NASH-related HCC increased from 1.5% to 7.5% in about 10 years) (19). It is expected that a significant number of cases of burn-out NASH are included in cases of HCC with unknown etiology. There is also a clear trend towards an increase in non-viral causes of cirrhosis, including NASH (20). These epidemiological facts indicate that obesity is also an important factor in HCC. Koike *et al*. named the type of lifestyle-related HCC as metabolism-associated liver cancer (MALC) (21, 22). Research interest in MALC has been increasing in recent years. In this review, we will comprehensively summarize the relationship between obesity and HCC in Japan.

Epidemiology of Obesity and Genetic Background in Japanese People

The Japan Society for the Study of Obesity (JASSO) defines a BMI of 22 kg/m^2 as the appropriate weight (standard weight) that is statistically the least susceptible to disease. For Japanese people, JASSO defines a BMI of 25 kg/m^2 or higher as obesity because it increases the risk of developing complications such as glucose intolerance, dyslipidemia, and hypertension (WHO defines obesity as 30 kg/m^2 or higher). A BMI below 18.5 kg/m^2 is defined as underweight. In the last 20 years, the average BMI of Japanese men has increased from 23 kg/m^2 to 24 kg/m^2, while that of women has remained around 22 kg/m^2. In our analysis of 631 Japanese cases of chronic liver disease (CLD, from 2014 to 2020, median age=65 years, 309 males, 226 liver cirrhosis cases), the mean BMI of 309 men was 24.0 kg/m^2 [107 (34.6%) cases with BMI >25 kg/m^2 and 15 (4.9%) cases with BMI <18.5 kg/m^2], and the mean BMI of 322 women was 23.1 kg/m2 [88 (27.3%) cases with BMI >25 kg/m^2 and 32 (9.9%) cases with BMI <18.5 kg/m^2]. The BMI of female CLD patients tends to be higher than the average Japanese BMI. The distribution of our CLD patients according to BMI is shown in Figure 1.

According to 2013 data, Japan has the lowest rate of obesity with a BMI of 30 kg/m^2 or more among developed countries (<5%), and the United States has the highest rate (about 35%), but in our study of liver disease, the rate of obesity with a BMI of 30 kg/m^2 or more was 7.1% (45/631 cases), and thus CLD patients tend to be rather over-nourished than the average Japanese people. On the other hand, the metabolic syndrome is defined as visceral obesity (visceral and abdominal obesity) with two or more symptoms of hyperglycemia, hypertension, and dyslipidemia (23), and JASSO defined "visceral obesity" as a visceral fat area (VFA) of 100 cm^2 or more, but it should be noted that visceral obesity and BMI are not always correlated. BMI can be affected by not only fat mass but skeletal muscle mass and bone mass.

Obesity genes are associated with energy metabolism (24-26). To date, more than 50 obesity-related genes have been identified, and the relationship between obesity and genetic variations such as the Adrenoceptor Beta 3 (ADRB3), uncoupling protein 1 (UCP1), and the Adrenoceptor Beta 2 (ADRB2) has been clarified (24-26). The *ADRB3* gene is expressed in both brown and white adipose tissues, and is involved in the regulation of energy production in brown adipose tissue and lipolysis in white adipose tissue (27, 28). In 1995, the Trp64Arg polymorphism in the *ADRB3* gene was reported to be involved in visceral obesity, insulin resistance, and early onset of type 2 DM, and a recent meta-analysis confirmed these associations (28). Individuals with the Trp64Arg mutation have a lower basal metabolic rate (BMR) and are therefore more resistant to starvation. The low BMR also means that once obese, weight loss is difficult (29). One in three Japanese people has the Trp64Arg mutation. It is estimated that the Trp64Arg mutation increases the susceptibility to NASH by 2.4-fold, and half of all NASH cases in Japan have the Trp64Arg mutation (30). Like ADRB3, individuals with mutations in UCP1 have a lower BMR due to reduced function of energy-burning brown adipose cells. Approximately one in four Japanese people carry a mutated gene in UCP1 (31). The *ADRB2* gene is mainly expressed in the heart, bronchial smooth muscle, and prostate, but is also present in adipose tissue and involved in lipolysis (32). A Japanese research group reported that about 16% of Japanese people have the Arg16Gly polymorphism of the *ADRB2* gene, and after diet and exercise therapy, the resting metabolic rate of the those carrying this *ADRB2* polymorphism becomes significantly higher than that of non-ADRB2 holders, and thus those that carry the *ADRB2* polymorphism tend to lose weight (33-35).

Obesity as a Risk Factor for HCC

Large-scale clinical epidemiological studies have shown that obesity can be a risk factor for cancer incidence (36, 37). In a 16-year prospective follow-up of 900,000 people in the United States, the risk ratio of HCC-related death among

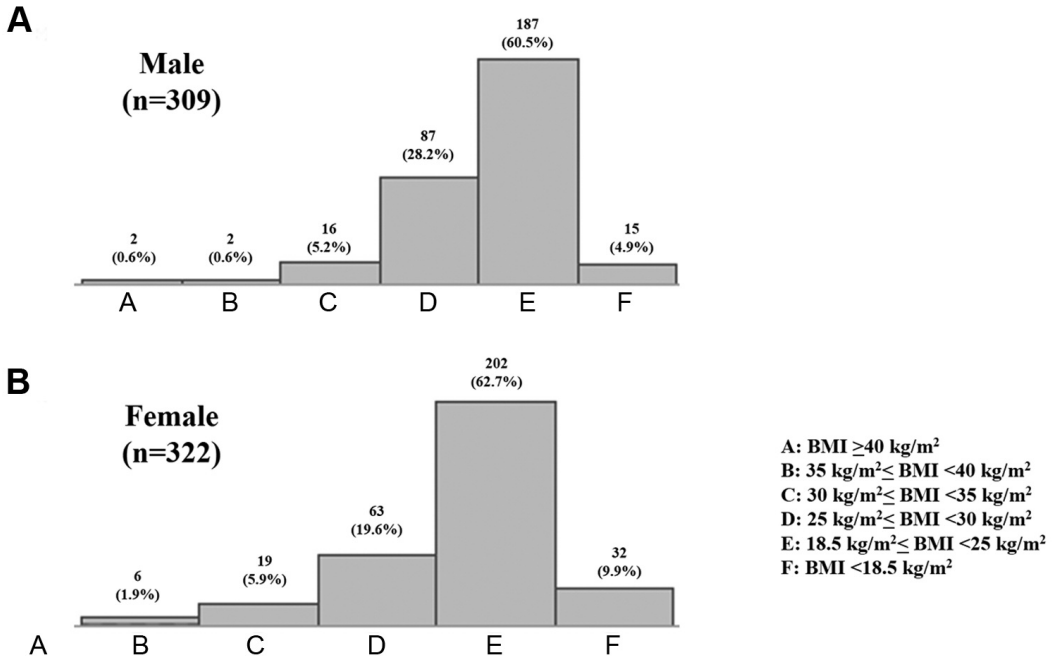

Figure 1. *The distribution of patients with chronic liver disease according to body mass index [BMI, 309 men (A) and 322 women (B)].*

obese people with a BMI ≥35 kg/m^2 was 4.52 for men and 1.68 for women (36). In a Muto and colleague's study of 622 Japanese patients with decompensated LC, risk factors for hepatocarcinogenesis were male, DM, higher BMI, alpha-fetoprotein ≥20 ng/ml, and lower serum albumin levels (38). Increased BMI in cirrhotic patients has also been associated with exacerbation of gastroesophageal varices, which is often complicated with cirrhosis and HCC (39).

Adipose tissue is considered to be the largest endocrine tissue in the human body, and secretes many adipocytokines including adiponectin (40). In particular, the increased secretion of TNF-α, decreased secretion of adiponectin, and increased secretion of leptin are associated with visceral fat accumulation and can cause insulin resistance (40). At the same time, compensatory hyperinsulinemia may occur. The mechanism of carcinogenesis in obesity lies in insulin resistance and its associated hyperinsulinemia. Insulin is known to 1) activate insulin receptor substrate-1 (IRS-1), 2) decrease the synthesis of insulin-like growth factor-1 (IGF-1) binding proteins (IGF-BPs) such as IGF-BP1 and IGF-BP2 in the liver, and 3) increase the amount of active free IGF-1 (41). IGF-1 influences HCC proliferation and progression through anti-apoptosis, increased angiogenesis *via* the production of vascular endothelial growth factor, and enhanced cell proliferative activity (42). Inflammatory cytokines such as TNF-α and IL-6 have been suggested to promote hepatocarcinogenesis (43). IL-6 exerts its effects on cell proliferation and anti-apoptosis through activation of STAT3, whereas TNFα activates c-Jun-NH2-terminal kinase-1 (JNK-1), nuclear factor-kappaB (NFκB), mammalian target of rapamycin (mTOR), extracellular signal-regulated kinase (ERK), *etc*., which have carcinogenic effects (43). In particular, it is well known that alterations in the PI3K/Akt/mTOR pathway are involved in oncogenic processes such as tumor angiogenesis and cancer-associated inflammation (44). Genetic instability caused by oxidative stress-induced DNA damage may lead to carcinogenesis, and iron overload may contribute to oxidative stress-induced DNA. Endoplasmic reticulum stress promotes hepatocarcinogenesis in cooperation with inflammatory cytokines such as TNFα (45).

Autophagy has attracted much attention in basic research as an intracellular mechanism that degrades its own intracellular tissues and provides energy during starvation, and has been shown to be impaired in NASH patients (46). A decline in autophagy in liver sinusoidal endothelial cells can lead to insulin resistance and NASH. Dysfunction in endothelial autophagy promotes liver inflammation and liver fibrosis in the early stages of NASH (46). This autophagy dysfunction is also involved in liver carcinogenesis (47).

NAFLD, NASH and HCC

Many diseases, such as collagen diseases, are known to be caused by environmental factors that induce the disease in addition to the host's susceptibility to the disease. Lifestyle-related diseases, which have been on the rise in recent years, are no exception to this rule. Obesity is the most well-

known factor triggering NAFLD, and most people with a BMI of 30 kg/m^2 or more develop NAFLD (48). The relative risk of developing NASH in highly obese individuals is extremely high, 30 to 50 times higher than in non-obese individuals (BMI <25 kg/m^2) (49). On the other hand, numerous clinical data have been accumulated on NAFLD in non-obese individuals. A recent meta-analysis reported that 40% of patients with NAFLD are lean or non-obese, and progression of liver disease and development of cardiovascular diseases are seen in a significant number of non-obese NAFLD cases in the long-term course (50).

Two factors are involved in the pathogenesis of NAFLD: genetic factors and environmental factors, such as weight gain (51). Patatin-like phospholipase domain containing 3 (*PNPLA3*) gene was reported as a susceptibility gene involved in the development of NAFLD (52, 53). PNPLA3 is localized in lipid droplet membranes and involved in lipid metabolism by promoting trans-amylase and lipase activities, and therefore gene polymorphisms in this region are involved in abnormal lipid metabolism. The PNPLA3 gene can be divided into CC, CG, and GG types, and people with G are more likely to develop NAFLD (GG type >CG type >CC type in the risk of NAFLD) (52, 53). It is known that Japanese people have a high percentage of fatty liver even though they are not as fatty as Westerners. A comparison of the percentage of Japanese and British people with the *PNPLA3* gene GG type showed that 21% of Japanese have the GG type, compared to 5% of British people (51, 54, 55). Because of the high percentage of Japanese with the *PNPLA3* gene GG type, which tends to store fat in the liver, it is thought that Japanese are more likely to develop NASH even if they are not obese. In Japanese NAFLD patients, advanced fibrosis and *PNPLA3* GG genotype were independent risk factors for HCC incidence (54).

Kawaguchi *et al*. identified four disease susceptibility genes (*DYSF, GCKR, PNPLA3*, and *GATAD2A*) in a whole genome association analysis of 902 Japanese NAFLD patients (56). They reported that *GCKR* is associated with simple fatty liver, *GATAD2A* with NASH, *DYSF* with NASH-related HCC, and *PNPLA3* with all of them. By combining these genes, the hazard ratio (HR) for those at the highest risk of developing NAFLD (those with more risk alleles) was 5.0-fold higher than that for those at the lowest risk. They also reported that in patients with more risk alleles, the HR of developing NASH from NAFLD was 4.4 times higher and that of developing NASH-related HCC from NASH was 15.9 times higher (56). Usefulness of the polygenic risk scores (combination of variants in *PNPLA3-TM6SF2-GCKR-MBOAT7*) for the stratification of HCC incidence in NAFLD patients has also been reported (57). Another study reported that a genetic risk score (combined *PNPLA3, TM6SF2*, and *HSD17B13* variants) for fatty liver disease is associated with up to 12 times the risk of cirrhosis and up to 29 times the risk of HCC incidence in the general population (58). While patients with hepatitis C virus (HCV)-related cirrhosis are at risk of developing obesity after sustained virological response (SVR) (59). Liver steatosis can be an adverse predictor after SVR for HCV (60). *PNPLA3* and *HLA-DQB1* polymorphisms can be also linked to HCC incidence after SVR for HCV (61).

DM and HCC

The liver, along with skeletal muscle and adipose tissue, is a major target organ of insulin and an important organ responsible for the homeostasis of glucose metabolism (62). The prevalence of DM in Japan continues to rise. The possible association between DM and major chronic diseases, including cancer, has been emphasized from basic, clinical, and preventive medicine perspectives (63-66). The relationship between DM and HCC can be explained by multiple biological mechanisms, including the suppression of IGF-BP1 production due to excessive insulin secretion and increased oxidative stress due to hyperglycemia (22). In Japan, HCC accounts for more than 90% of primary liver cancers. Diabetic patients have a 2-3 times increased risk of HCC compared to those without diabetes, based on the results of several meta-analyses (67-71). The presence of DM in patients with HCC can be a poor prognostic factor (72). DM is associated with cisplatin sensitivity of HCC cells and invasive ability of HCC cells, and has been reported to interfere with the chemotherapeutic effects for HCC (73). The usefulness of the FIB-4 index (liver fibrosis marker) in liver carcinogenesis in diabetic patients (cut-off value=3.61) has also been reported (74).

It has been reported that insulin and sulfonylurea promote hepatocarcinogenesis, while insulin resistance ameliorators such as metformin inhibit carcinogenesis (75). Metformin is a diabetic drug that improves insulin resistance *via* activation of AMP kinase (AMPK) in hepatocytes (76). Metformin has been shown to have a variety of anti-tumor effects, including direct inhibition of cell proliferation and induction of apoptosis in liver cancer cells (76-78). Therefore, metformin may be useful in the management of diabetic CLD patients, but care should be taken to avoid lactic acidosis. Kawaguchi *et al*. reported that 66.5% of 478 diabetic CLD patients were treated with some kind of antidiabetic drug, and the frequency of prescriptions by drug type was 39.0% for dipeptidyo-peptidase 4 (DPP4) inhibitors, 25.5% for insulin, 25.5% for sulfonylureas, and 17% for metformin (79). Furthermore, favorable effects of dietary habits on liver carcinogenesis have also been reported. A previous meta-analysis also reported that the habit of coffee consumption suppresses HCC development (80). People who drink three or more cups of coffee a day have a 40% lower risk of HCC incidence compared to those who do not (80). It is thought that coffee may prevent HCC incidence by reducing liver inflammation (81).

Obesity, Gut Microbiota and Hepatocarcinogenesis

In the human gastrointestinal tract, there are 500 to 1,000 species of intestinal bacteria, numbering more than 100 trillion, which live in symbiosis with the host by metabolizing substances that the host cannot metabolize and by regulating the host's immune system (82). Changes in the gut microbiota (*i.e.*, dysbiosis), such as an increase in ammonia-producing gram-positive bacteria, have been noted in obese individuals (83). Hyperammonemia and subsequent hypermyostatinemia can induce muscle protein breakdown and can be associated with fat accumulation in the liver (84, 85). Serum myostatin levels have a strong effect on muscle protein breakdown and had a positive correlation with serum ammonia levels in our previous study (84). In obesity, mild inflammatory cell infiltration occurs in white adipose tissue, and chronic inflammation is thought to induce insulin resistance and glucose intolerance. Fatty acids act as ligands for TLR4 to trigger chronic inflammation, and the involvement of endotoxins from gut microbiota in chronic inflammation has attracted attention (86). Lipopolysaccharide (LPS), an endotoxin, is derived from intestinal bacteria, and high-fat-fed mice have altered intestinal microflora and increased LPS levels in their blood (metabolic endotoxemia) (87). LPS can be associated with the progression of hepatic steatosis in the development of NAFLD in rats (88). Administration of antibiotics to high-fat-fed mice reduces the inflammatory response in the intestinal tract, alleviates metabolic endotoxemia, and improves obesity, insulin resistance, and adipose tissue inflammation (87). Conversely, sustained administration of small amounts of LPS to mice causes obesity, insulin resistance, and glucose intolerance similar to those in high-fat-fed mice (89, 90).

The increase in deoxycholic acid, a secondary bile acid associated with changes in the intestinal microbiota, can induce cellular senescence in hepatic stellate cells (irreversible cessation of cell proliferation induced by strong carcinogenic stress such as DNA damage in normal cells) (91). The senescent cells secrete various proteins that promote inflammation and carcinogenesis, such as inflammatory cytokines, chemokines, and extracellular matrix-degrading enzymes, leading to a phenomenon called senescence associated secretory phenotype, which leads to carcinogenesis (91). Unlike apoptosis, senescent cells do not die immediately but survive for a long time.

Sarcopenic Obesity and HCC

The term "primary sarcopenia" refers to a condition in which skeletal muscle mass, strength, or physical function is reduced due to aging, and the term "secondary sarcopenia" refers to a condition in which skeletal muscle mass, strength, or physical function is reduced due to an underlying disease. Cirrhosis, which is often associated with HCC, tends to be associated with secondary sarcopenia (92). Secondary sarcopenia in cirrhosis can be regulated by myostatin in skeletal muscle due to decreased ammonia clearance (84). Sarcopenic obesity, which is a combination of sarcopenia and obesity, is not a mere combination of conditions, but rather a stronger manifestation of metabolic abnormalities and functional disorders (62). It has been shown that obesity and insulin resistance may be a risk factor for sarcopenia, and sarcopenic obesity is a condition in which skeletal muscle is replaced by fat (93). Sarcopenic obesity patients are more likely to suffer from functional decline, falls, fractures, and death than those with sarcopenia alone or obesity alone (94-96). Sarcopenic obesity leads to fat accumulation in muscles and increased insulin resistance (62). It is unclear whether sarcopenia obesity is more strongly associated with liver carcinogenesis than obesity alone.

Sarcopenic obesity is an important condition in HCC. Kobayashi *et al*. classified 465 Japanese HCC patients who underwent hepatectomy into four groups according to sarcopenia and obesity: non-sarcopenic non-obese group, non-sarcopenic obese group, sarcopenic non-obese group, and sarcopenic obesity group, and examined the postoperative and recurrence-free survival rates among the four groups (97). Sarcopenia was defined as a skeletal muscle index (SMI) of <40.31 cm^2/m^2 in male patients on computed tomography (CT) and a SMI of <30.88 cm^2/m^2 in female patients on CT. Obesity was defined as a VFA of ≥ 100 cm^2 in both sexes, and 250 patients (53.8%) had complications of obesity. In the multivariate analysis of prognostic factors, poorly differentiated HCC (HR=1.945, $p=0.011$), TNM stage III or higher (HR=2.267, $p=0.003$), serious complications (HR=1.906, $p=0.016$), and sarcopenic obesity (HR=2.504, $p=0.005$) were independent risk factors for overall survival. Sarcopenic obesity (HR=2.504, $p=0.005$) and TNM stage III or higher (HR=2.972, $p<0.001$) were independent risk factors for postoperative HCC recurrence (98). In living donor liver transplantation for HCC, the presence of preoperative sarcopenic obesity is a contributing factor to HCC recurrence and survival (98). Sarcopenic obesity may be superior to sarcopenia as a predictive factor in HCC patients undergoing hepatic resection, and it should be a priority for researchers and clinicians (99). Sarcopenic obesity assessment should be incorporated for HCC patients. In addition, a worldwide unified consensus for the assessment of sarcopenic obesity should be established. Definition of sarcopenic obesity varies among studies (62). Schematic explanation between obesity, insulin resistance, gut microbiota, sarcopenic obesity, and liver carcinogenesis is shown in Figure 2.

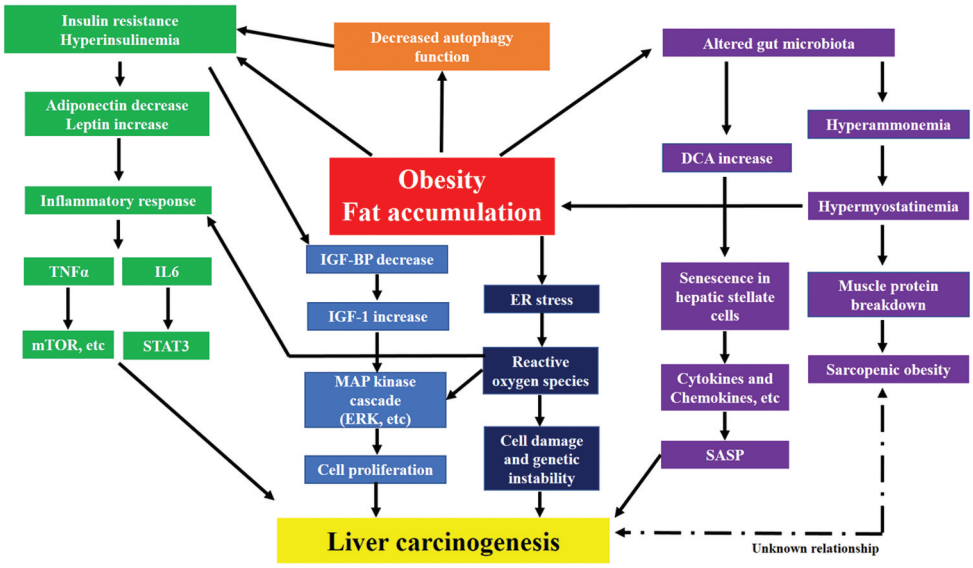

Figure 2. *Schematic description of the interactions between obesity, insulin resistance, gut microbiota, sarcopenic obesity, and liver carcinogenesis. mTOR: Mammalian target of rapamycin; IGF: insulin-like growth factor; IGF-BP: insulin-like growth factor binding protein; SASP: senescence associated secretory phenotype; ERK: extracellular signal-regulated kinase; ER: endoplasmic reticulum; DCA: deoxycholic acid.*

Obesity Control as a Cancer Prevention Mechanism

It is internationally recognized that smoking cessation is the first and most important factor in cancer prevention, but that obesity control comes next. The results of a pooled analysis of seven cohort studies in Japan showed that the risk of cancer was low in men with a BMI of 21.0-26.9 kg/m^2 and in women with a BMI of 21.0-24.9 kg/m^2 (100). In addition, a research group at the National Cancer Center in Japan examined previous studies on Japanese people and identified five factors that are important for the prevention of cancer in Japanese people: smoking cessation, sobriety, diet, physical activity, and maintenance of appropriate weight (101). It was estimated that people who practice these five healthy habits have a 43% lower risk of cancer incidence in men and a 37% lower risk in women compared to those who practice 0 or 1 (101). For both men and women, the higher the amount of physical activity, the lower the risk of developing any type of cancer. In particular, the risk reduction was more clearly seen in the elderly and in those who had more opportunities to play sports or exercise on holidays. According to cancer primary site, the risk of colon, liver, and pancreatic cancer in men, and gastric cancer in women was lowered in those with higher levels of physical activity (102).

Bariatric surgery is a procedure used to treat severe obesity and is effective and safe for highly obese individuals (103). In a recent meta-analysis, bariatric surgery was shown to reduce the overall cancer incidence and obesity-related cancer incidence (104). Bariatric surgery has been reported to significantly reduce the incidence of HCC through the improvement of NASH (105, 106). However, bariatric surgery is not so common in Japan.

Closing Remarks

Recent progress in molecular biology research has gradually elucidated the molecular mechanisms of obesity and hepatocarcinogenesis, and clinical data are gradually being accumulated. In this article, obesity and hepato-carcinogenesis were comprehensively reviewed by introducing representative Japanese data in terms of 1) clinical epidemiology, 2) genetic background, 3) mechanism of carcinogenesis, 4) NAFLD, NASH and hepato-carcinogenesis, 5) DM and hepato-carcinogenesis, 6) intestinal microbiota and hepatocarcino-genesis, 7) sarcopenic obesity in HCC patients, and 8) obesity control as a cancer prevention. As the number of obese patients increases internationally, including in Japan, the relationship between obesity and carcinogenesis has become an important issue that cannot be overlooked, and appropriate intervention for obese patients is required. Further evidence is expected to be accumulated in the future.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Writing the article: H.N.; Editing the article: S.F., A.A., S.N., K.H.; Final approval: all Authors.

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