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NAFLD and extrahepatic cancers: have a look at the colon

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A high body-mass index has been demonstrated to be associated with an increased mortality not only from cardiovascular disease but also from certain cancers.[1] An impressive body of evidence further indicates that the risk of colorectal adenoma and cancer is increased in subjects with obesity and related metabolic syndrome.[2] Obesity has indeed a direct and independent relationship with colorectal cancer, although the strength of the association with general obesity seems to be smaller than previously reported.[3] A recent French study suggests that obesity and weight gain are associated with early colorectal carcinogenesis in women especially regarding the distal colon.[4] Several other studies identified an increased risk of developing also other gastrointestinal cancers such as oesophageal adenocarcinoma in the obese population. The association between obesity and other gastrointestinal malignancies, however, has been less robust. Non-alcoholic fatty liver disease (NAFLD) has arisen as one of the most prevalent liver diseases worldwide and usually develops in obese subjects. Pathophysiological insights into this disorder have improved substantially in recent years and, in addition, various clinical associations, such as insulin resistance, diabetes and cardiovascular diseases, have been well recognised.[5, 6] It has been also well established that hepatocellular carcinoma is a commonly observed complication of long-term fatty liver disease.[7] Fewer data were so far available regarding a potential link between NAFLD and extrahepatic cancers.

NAFLD: ASSOCIATED WITH HEPATIC AND EXTRAHEPATIC CANCER?

NAFLD has an increased overall mortality deriving from liver-related and cardiovascular disease, and an almost two-fold risk of diabetes mellitus.[8] It's association with extrahepatic cancers has been less clear so far. Hepatic steatosis is more frequently observed in patients with breast and ovarian cancer, although in this study NAFLD was only diagnosed via ultrasonography.[9] Hwang and colleagues recently presented the first evidence for an association of NAFLD with an increased rate of colorectal adenomatous polyps.[10] In their study, a population of 2917 participants was investigated via colonoscopy, abdominal ultrasonography and liver tests. The prevalence of NAFLD was 41.5% in the adenomatous polyp group versus 30.2% in the control group providing the first evidence that such an association might indeed exist. Wong and colleagues (see page 829) present further evidence that colorectal neoplasms are more prevalent in NASH subjects.[11] In their cross-sectional study, NAFLD patients (n=380) were defined histologically and by proton magnetic resonance spectroscopy. Importantly, NAFLD patients (n=199) had both a significantly higher rate of colorectal adenomas (34.7% vs 21.5%) and advanced neoplasms than healthy controls (18.6% vs 5.5%). In addition, 13/29 (45%) of NAFLD patients with advanced

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neoplasm had right-sided colorectal carcinoma. Furthermore, the presence of inflammation that is, NASH was a clear risk factor for adenoma and carcinoma development. This study performed in a large, well-defined population clearly suggests that NASH patients are indeed a risk population for the development of colorectal carcinoma and therefore screening colonoscopy should be strongly recommended in these patients.

POTENTIAL PLAYERS IN NAFLD-RELATED GASTROINTESTINAL CARCINOGENESIS

Research in recent years has characterized important pathways that might link metabolism, inflammation and cancer development.[12] Mediators derived mainly from the adipose tissue such as adiponectin or leptin could be critically involved in such processes and therefore these so called adipocytokines might reflect attractive candidates linking obesity-related disorders with tumour development both intra- and extrahepatically. Adiponcetin serum levels are significantly decreased in obesity, obesity-related disorders and diabetes mellitus.[13] It has been well established that patients with NAFLD, especially non-alcoholic steatohepatitis (NASH), have significantly lower adiponectin serum levels compared to healthy controls.[14]

An association of obesity and decreased adiponectin serum concentrations with colorectal adenomas and a higher risk of colorectal cancer in men with low adiponectin levels has been shown recently.[15] Another case-control study consisting of 778 cases and 735 controls demonstrated an inverse correlation of total and high molecular weight adiponectin serum levels with colorectal adenoma development.[16] Adiponectin demonstrates anti-carcinogenic effects in vitro as it is able to inhibit the growth of colon cancer cells through stimulating AMP-activated protein kinase activity.[17] In a mouse tumour model, adiponectin substantially inhibited primary tumour growth in a caspase-dependent manner resulting in endothelial-cell apoptosis.[18] Many studies have investigated the effects of leptin, another adipocytokine dysregulated in obesity and NAFLD, on different cancer types in experimental cellular and animal models.[19] Most of the studies indicate that leptin can potentiate the growth of cancer cells (breast, oesophageal, gastric, pancreatic, colorectal, prostate, ovarian and lung carcinoma cell lines), whereas adiponectin seems to decrease cell proliferation. Adiponectin may have an anticarcinogenic effect on the large intestine by interfering with leptin, whereas leptin could conversely exert a carcinogenic effect under conditions of lower adiponectin availability. Although these first studies are mainly descriptive, adipocytokines could be attractive candidates as the missing link between obesity, NAFLD and cancer development.

CONCLUSIONS

What are the clinical implications of this important study demonstrating an association between NAFLD and gastrointestinal carcinogenesis? Recently, it has been shown that in average-risk individuals, 40–49 years of age, men with abdominal obesity or metabolic syndrome might benefit from screening colonoscopy starting at 45 years of age to detect colorectal neoplasms.[20] Data presented in Gut would favour such a strategy of early screening colonoscopy in NASH populations. This, however, also tells us that the knowledge of presence of ‘liver inflammation’ that is, NASH in NAFLD patients might not only be important for the prognosis of liver disease itself but also affect extrahepatic prognosis, that is, cancer development. A better understanding of the key pathways controlling metabolism, inflammation and cancer development is urgently awaited.

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