The "obese liver" and gastrointestinal cancer risk

Amedeo Lonardo[1], Luca Roncucci[2]

[1]Azienda Ospedaliero-Universitaria di Modena, Modena, Italy; [2]University of Modena and Reggio Emilia, Modena, Italy

Correspondence to: Amedeo Lonardo, MD. Operating Unit Metabolic Syndrome, Director, Ospedale Civile di Baggiovara, Via Giardini 1135 Modena 41126, Italy. Email: a.lonardo@libero.it; lonardo.amedeo@aou.mo.it.

Background, definitions and history

From an evolutionary point of view the accumulation of nutrients under the form of fatty substrates offers a protection during periods of famine (1). While the adipose tissue is the physiological reservoir of energetic fatty substrates, the liver is not (2). The normal liver is indeed virtually devoid of any fat content (3). The accumulation of fatty substrates (predominantly triglycerides) in more than 5% of the hepatocytes (often associated with mild inflammatory changes) is named steatosis; steatosis associated with hepatocyte ballooning, inflammatory changes and a variable proportion of hepatic fibrosis defines nonalcoholic steatohepatitis (NASH) (4). Simple steatosis, NASH as well as cirrhosis and hepatocellular carcinoma which may eventually occur in a proportion of patients with steatosis and NASH are collectively alluded to as nonalcoholic fatty liver disease (NAFLD) (4). A variety of extra-hepatic manifestations and complications attests to the systemic nature of NAFLD. These include the metabolic syndrome (type 2 diabetes, visceral obesity, atherogenic dyslipidemia, arterial hypertension, hyperuricemia); cardiovascular disease (atherosclerosis, aortic valve sclerosis, mitral annulus calcification, cardiomyopathy, heart failure, arrhythmias, chronic kidney disease); endocrine derangements (hypothyroidism, PCOS, hypogonadism, deficiency of growth hormone, hyperadrenalism); disorders of the respiratory system (obstructive sleep apnea syndrome, chronic obstructive pulmonary disease); conditions affecting the musculoskeletal system (osteoporosis, osteopenia); the skin (psoriasis); and various types of tumours (colorectal adenoma and carcinoma, carcinoma of pancreas, prostate, and breast) (2).

NAFLD is mutually and bi-directionally connected with the Metabolic Syndrome (4). Interestingly, so strictly are metabolism and immunity linked to each other under the evolutionary and physiological perspective that the excess of energetic substrates may be viewed by the innate immune system similar to an infectious state and this accounts for obesity resulting in a systemic sub-clinical inflammatory state (5,6).

Obesity is commonly defined by two anthropometric indices: body mass index (BMI) and waist circumference. BMI simply relates body weight to squared height (kg/m^2) and does not identify the distribution of body fat nor does it differentiate lean from fat mass. Waist circumference is an index of accumulation of body fat in the visceral compartment and this is relevant given that visceral fat is deemed to be harmful from a metabolic point of view and subcutaneous fat is protective (7). It is waist circumference, not BMI, that is included in the definition of the Metabolic Syndrome based on ethnicity-specific cut-offs which take into account the fact that Asians, compared to other ethnicities, tend to manifest earlier metabolic complications for any given amount of body fat accumulation.

Obesity is a global epidemic accounting for a substantial financial burden worldwide and a phenotypically heterogeneous condition whose health risks span from easy fatigability to cancer, osteoarthritis, cardio-nephro-metabolic diseases (type 2 diabetes, dyslipidemia, NAFLD, arterial hypertension, coronary artery disease arrhythmias,

sudden cardiac death, chronic kidney disease, stroke), asthma, sleep apnea, thrombophlebitis, gallstones, urinary incontinence, depression, male sexual dysfunction, low quality of life, loss of global and healthy years of life.

Obesity & cancer: a dangerous association

Many years ago, in her seminal study, Doctor Calle and Colleagues, by following-up for 16 years 900,000 individuals who were free of cancer at enrollment in 1982 demonstrated that the more severely obese members of their cohort (BMI ≥40) had combined mortality rates owing to all cancer types that were 52% to 62% higher (for men and women, respectively) than those of non-obese controls. The most affected organ sites were the gastrointestinal (GI) tract (esophagus, colon and rectum, liver, gallbladder, pancreas), kidney, and blood (non-Hodgkin's lymphoma and multiple myeloma). Moreover, higher BMI values were also associated with significant trends of increasing risk of mortality owing to cancers of the stomach and prostate (men) and of the genital system (breast, uterus, cervix, and ovary) in women (8). In subsequent years, studies have universally confirmed the finding that obesity is strongly associated with GI cancer and, in particular, colonic and rectal cancer. For example, in their more recent prospective study, Levi and coworkers followed for 40 years adolescents who had stratified them based on BMI at 17 years, and found that the cumulative incidence of colonic and rectal cancer was strictly associated with BMI (9). Along the same line, Renehan *et al.* conducted a systematic review and meta-analysis aimed at assessing the strength of associations between BMI and different sites of cancer as well as to disclose how sex and ethnicity modulate such BMI-cancer associations (10). By analyzing 141 articles, including 282,137 incident cases these authors found that an increase in BMI of 5 kg/m^2 was strongly associated in men,with cancers of esophagus, thyroid, colon, and kidney; in women, with cancers of endometrium, gallbladder, esophagus, and kidney. Increased BMI was more weakly associated positively with rectal cancer in men; postmenopausal breast, pancreatic, and colon cancers in women. Associations were stronger in men than in women for colon and did not generally vary across the various continental regions evaluated (North America, Europe and Australia, and the Asia-Pacific region) (10).

Given that their findings have been universally confirmed by subsequent studies, it may be interesting to discover how Dr. Calle and Colleagues, in their pioneering study,

mechanistically explained the excess of cancer risk observed at various organ sites. The potential biologic mechanisms that were advocated by these Authors included increased levels of endogenous hormones such as sex steroids, insulin, and insulin-like growth factor I, and abdominal obesity contributing to gastroesophageal reflux (8). At that time, probably none had thought that the (obese) liver could be the culprit accounting for the association of obesity with cancer.

NAFLD and GI cancer

A recent line of research has specifically focused on the excess risk of colorectal tumors in asymptomatic individuals with NAFLD undergoing screening colonoscopy (11). Doctor Mantovani and Colleagues, by meta-analyzing 8 cross-sectional and 3 longitudinal observational studies collectively enrolling data of 91,124 asymptomatic adults, approximately one third of whom had NAFLD, and who totaled 14,911 colorectal adenomas and 1,684 colon cancers found that NAFLD diagnosed with either imaging studies or liver biopsy was independently associated with a moderately increased prevalence and incidence of colorectal adenomas and cancer independent of confounding factors such as age, sex, smoking, BMI, diabetes or metabolic syndrome. Prudently, these Authors highlight that the original studies evaluated were based mostly on individuals of Asian descent; that the observational design of the studies which they have meta-analyzed does not allow for proving causality, and also that they cannot rule out the possibility of residual confounding by some unmeasured factors. Based on such limitations, they conclude that additional prospective studies, particularly in European and American individuals, and further research is required to better define the pathobiological mechanisms underlying the association of NAFLD with colonic carcinogenesis (11).

The study by Dr. Allen and Colleagues

Bringing our understanding of such a topic further, Doctors Allen, Hicks, Mara, Larson and Therneau, from the Mayo Clinic Mayo Clinic, Rochester, Minnesota, USA compared all incident cases of NAFLD occurring in adults from 1997 to 2016 in a US population-based cohort to age and sex-matched controls from the same population. In their study population, these Authors evaluated the incidence of cancer (12). A total of 4,722 individuals with NAFLD (age 54, 46% male) and 14,441 age- and sex- matched controls were followed for a median of 8 (range, 1–21) years, during which 2,224
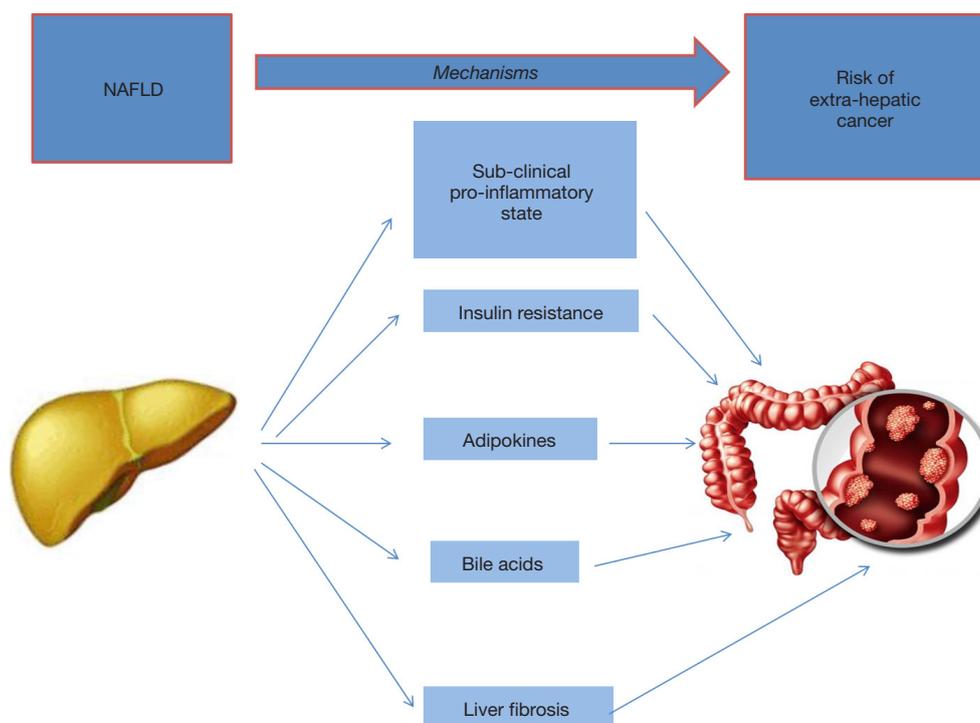
Figure 1 Putative biological mechanisms accounting for the association of NAFLD with extra-hepatic cancer with specific reference to colorectal cancer. NAFLD, nonalcoholic fatty liver disease.

incident cancers occurred. After this longitudinal follow-up, NAFLD turned out to be associated with a nearly 2-fold increased risk of developing cancers [IRR =1.9 (95% CI, 1.3–2.7)]. The most often affected organs were the liver, the GI tract and the uterus. Revolutionizing previous disease paradigms, data of this study have shown that the increased risk of cancer was more strongly associated with NAFLD than with obesity. Indeed, in this study obesity alone was not associated with incident cancer (IRR =1.0; 95% CI, 0.8–1.4) though obesity was evaluated only with BMI (12).

Comments

How can the presence of NAFLD affect the risk of developing extra-hepatic cancers? The answer to this question is now more complex than that given at the times when the paper by Dr Calle was published (i.e., increased levels of endogenous hormones such as sex steroids, insulin, and insulin-like growth factor I, and abdominal obesity) (8). For example the role of the (fatty) liver now cannot be ignored. How would NAFLD increase the risk of cancer? (*Figure 1*). NAFLD is strongly associated with the development of a sub-clinical systemic pro-inflammatory

state and insulin resistance (13) therefore promoting carcinogenesis in several organs and tissues (14,15). In the setting of the dysmetabolic-systemic inflammatory milieu, adipokines may play a role given that they are involved both in steatogenesis lipid accumulation in the liver as well as in colorectal carcinogenesis (16,17).

Adiponectin is an insulin-sensitizing, anti-steatotic and anti-inflammatory adipokine whose concentrations are typically reduced in NAFLD and this has been postulated to link NAFLD with colorectal cancer (11).

Moreover, NAFLD is also associated with a deranged bile acid metabolism (18), in particular their flow on the GI tract is enhanced, producing local inflammation and focal defects on the intestinal mucosa, thus possibly driving the carcinogenic process. This mechanism may be important, in particular, in localizing carcinogenesis in the large bowel (19). Irrespective of the mechanisms involved, the more advanced NAFLD forms are expected to be associated with an increased risk. For example a retrospective study conducted in 6,332 Koreans found that the subjects with NAFLD and advanced fibrosis had a significantly higher risk for colorectal adenoma, advanced adenoma, and multiple adenomas than those with NAFLD without

advanced fibrosis (20).

Research agenda

The finding of NAFLD (rather than obesity) being associated with GI cancer independent of confounders is a major breakthrough. Additional, large, prospective, well conducted studies should better differentiate the risk of colon as opposed to rectal cancer, given that the pathogenesis behind these two cancer sites may be significantly different (21). In addition, the impact of genetics and epigenetics of NAFLD and NASH (22) on the risk of GI cancer should carefully be evaluated given that data suggest some differences, for example, in insulin resistance and cardiovascular risk (23). Finally, waist circumference is a good surrogate marker of abdominal adiposity and is the most clinically accessible measure of adiposopathy and dysfunctional adipose tissue (24). Interestingly, waist circumference is also the strongest predictor of liver fibrosis in patients with NAFLD, irrespective of BMI (25). Therefore, in the future, it will also be important to better stratify patients based on the amount of visceral adipose tissue evaluated with imaging techniques. Finally, should data on the association of colorectal adenoma and carcinoma with the more advanced forms of NAFLD be confirmed, (20) this notion could be exploited to modulate colonoscopic surveillance based on liver status.

In conclusion, the mechanisms underlying the association of NAFLD with colorectal cancer are incompletely understood. While subclinical pro-inflammatory state and insulin resistance are systemic mechanism which can increase the risk of cancer in any organ of the body, adipokines (e.g., adiponectin) and bile acids may localize this risk to the colonic (and rectal) mucosa. Finally, the mechanism(s) mediating the risk in those with fibrosing liver disease remain to be elucidated although, in principle, may be reconducted to one of those named above.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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