Editorial

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Adipose tissue-associated cancer risk: Is it the fat around the liver, or the fat inside the liver?

Giulio Marchesini[1,*], Maria Letizia Petroni[1], Helena Cortez-Pinto[2]

[1]*Department of Medical and Surgical Sciences, "Alma Mater" University, Bologna, Italy;* [2]*Department of Gastroenterology, CHLN, Clínica Universitária de Gastrenterologia, Faculdade de Medicina, Universidade de Lisboa, Portugal*

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The association between obesity and cancer risk has been extensively characterized. In a prospective study of more than 900,000 adults free of cancer at enrollment and observed during a 16-year follow-up, Calle *et al.* were able to calculate the risk of mortality for cancer at different sites in relation to body mass index (BMI), as well as the proportion of all deaths from cancer attributable to overweight and obesity.[1] In both men and women, a high BMI increased the risk of cancer, and for several cancers the risk appeared to increase in a BMI-dependent manner. The authors concluded that overweight and obesity in the adult US population could account for 14% of all cancer deaths in men and 20% of those in women. Notably, cancer at liver site was recorded as one of the sites at higher risk, particularly in men. These data were confirmed by analysis of cancer incidence rates in 221 databases, including nearly 300,000 cases of cancer at different sites, with obesity accounting for a variable population attributable fraction of all cancers.[2]

But "not all fat is alike";[3] we now know that a) visceral fat carries a much higher risk of cardiovascular and metabolic complications compared with total body fat, mediated by inflammatory adipokines, and b) BMI is an inaccurate measure of central obesity, as different ethnicities experience central obesity at a lower BMI than Caucasians.

More limited data are available on the risk of cancer based on anthropometric parameters of visceral adiposity. Zhang *et al.*,[4] in a prospective cohort of the Nurses Health study, showed that the risks of overall mortality, cardiovascular disease-related mortality and cancer-related mortality were all increased in relation to both BMI and waist circumference, but the risks associated with quintiles of waist circumference remained statistically significant after adjustment for BMI (1.00, 1.18, 1.20, 1.34, and 1.63; 95% CI 1.32–2.01; p for trend <0.001). In a systematic review of the association of anthropometric markers of visceral adiposity with malignancy,[5] abdominal adiposity was identified as a stronger predictor than whole body adiposity for cancer at gastro-esophageal and colorectal sites, with differences between gender. Abdominal adiposity was also a stronger predictor of liver cancer, as well as breast and endometrial cancers in post-menopausal women.

In the presence of visceral obesity, fatty liver is nearly the rule – the products of the visceral fat are drained by the portal vein into the liver – contributing to alterations in lipid and glucose homeostasis and to diabetes development, fulfilling the criteria that link non-alcoholic fatty liver disease (NAFLD) to the metabolic syndrome. Therefore, it is no surprise that fatty liver is also associated with the risk of extrahepatic malignancy. In an adult Korean population with steatosis diagnosed by ultrasonography, the risk of colorectal cancer in males and breast cancer in females was approximately doubled, with some relation with advanced NAFLD progression.[6]

In the present issue of *Journal of Hepatology*, Allen *et al.*[7] move one step further and propose that liver fat is primarily involved in the association between obesity and incident hepatic and extrahepatic cancer. Inside the medical record linkage system of the Olmsted County, they identified all individuals with NAFLD on the basis of Mayo Clinic-specific and internationally-validated ICD codes, observed in the period 1997–2016. This cohort was compared with those living in the same area who did not have a NAFLD diagnosis, individually matched by age and sex; both cohorts were followed until death, last visit, or June 2018 for incident cancer diagnosis. Cancers of interest were grouped as gastrointestinal, hormone-sensitive and lung cancers (total, 656 in NAFLD and 1,568 in controls). After adjustment for possible confounders (follow-up of less than 1 year, immortal time bias) and covariates, NAFLD diagnosis conferred a 90% higher risk of overall malignancy (incidence rate ratio [IRR] 1.9, 95% CI 1.3–2.7), with the expected highest excess for liver cancers (IRR 2.8; 95% CI, 1.6–5.1), followed by uterine cancers and gastrointestinal cancers, with gender-specific differences. In the whole setting, obesity was only associated with a trend towards significant malignancy risk (IRR 1.2; 95% CI 0.9–1.6), whereas the risk associated with NAFLD was highly significant (IRR 2.0; 95% CI 1.5–2.9), with no independent effect of obesity. Of note, the risk associated with NAFLD was also present when compared with obese controls, whereas obesity alone, in the absence of NAFLD, did not increase the risk in comparison to non-obese controls (IRR 1.0; 95% CI 0.4–1.4).

How can we explain these intriguing results? The authors themselves are very careful in defining the results as evidence that NAFLD is directly responsible for cancer risk, and indicate

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* Corresponding author. Address: "Alma Mater" University Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital 9, Via Massarenti, I-40138 Bologna, Italy; Tel.: +39 051 2144889, fax: +39 051 6364502.
E-mail address: giulio.marchesini@unibo.it (G. Marchesini).

that liver fat may be a possible *mediator* on the causal pathway linking fat accumulation to cancer. The metabolic effects of visceral and hepatic fat are well established, and include high insulin levels, insulin resistance and a different response in terms of lipolysis and lipogenesis compared with total body fat (Fig. 1). Visceral fat is directly involved in the development of cardiovascular risk and extensively associated with the metabolic syndrome, whereas liver fat represents a good example of fatty acid spillover out of the adipose tissue, originally described by Unger as lipotoxicity and implicated in the pathogenesis of diabetes.[8] Some differences have been described between liver fat and visceral adipose tissue in studies carried out by tracer techniques,[9] and the presence of diabetes might be a confounder. Whereas high insulin levels are likely to exert a proliferative action via MAP-kinase stimulation in the presence of both liver and visceral fat, the role of insulin-like growth factor 1 (IGF-1) deserves attention. IGF-1 is produced in the liver and specific changes in individuals with established liver disease are possible. The adipose tissue microenvironment undergoes important changes during fat accumulation, and these changes might promote cancer initiation and progression in target organs.[10] It was hypothesized that the major tumor-promoting mechanism associated with obesity, could be the indolent inflammation that takes place at particular organ sites, including the liver, pancreas, and gastrointestinal tract,[11] where pro-inflammatory M1 macrophages become more abundant, producing multiple pro-inflammatory cytokines.[12]

Diabetes might be an additional factor associated with cancer development; the presence of fatty liver has been reported to increase the risk of incident type 2 diabetes, after adjustment for obesity,[13] and in the same Korean population the resolution of NAFLD in a 5-year follow-up prevented the development of type 2 diabetes.[14] The possibility that the association of diabetes with cancer (namely, colorectal cancer) might be mediated by IGF-1 has long been postulated; a very recent study explored the effects of genetic variants in the IGF pathway on the risk of colorectal cancer in individuals with diabetes and concluded that unfavorable alleles might be involved.[15]

Modulation of IGF might open a totally new area of pharmacologic intervention for cancer prevention. The IGF pathway is effectively modulated by dietary restriction;[16] weight gain in adulthood is associated with a remarkable increase in the risk of incident adiposity-associated cancers,[17] whereas intentional weight loss results in decreased cancer incidence, particularly in female obesity-related cancers fuelled by liver fat.[18] Finally, bariatric (metabolic) surgery effectively reduces liver fat and promotes regression of non-alcoholic steatohepatitis;[19] accordingly, the large Swedish Obese Subjects study confirmed a reduction of incident cancers in the intervention arm, again in the female obesity-related cancers.[20] Similarly, in a group of overweight post-menopausal women, loss of fat at different body locations was associated with changes in variable biomarkers, related to the risk of breast cancer.[21]

In conclusion, the study is definitely provocative and, as usual, it raises many more questions than it answers. Not all data may be explained on the basis of evidence from the literature – as an example, the association of liver fat with cancer incidence appears to be independent of coexisting diabetes – but it opens a clinically relevant area of research. The authors extensively discuss the limits of their investigation and the possible pitfalls – the effect of liver fat on cancer risk might even be underestimated considering that controls might have undiagnosed NAFLD. These results definitely need extensive external validation. The most plausible explanation for Allen *et al.*'s findings is that the presence of NAFLD works as a reliable marker of predominantly visceral obesity, that associates with indolent inflammation and related pro-carcinogenic hormones, thus increasing the risk of cancer. If confirmed by studies evaluating

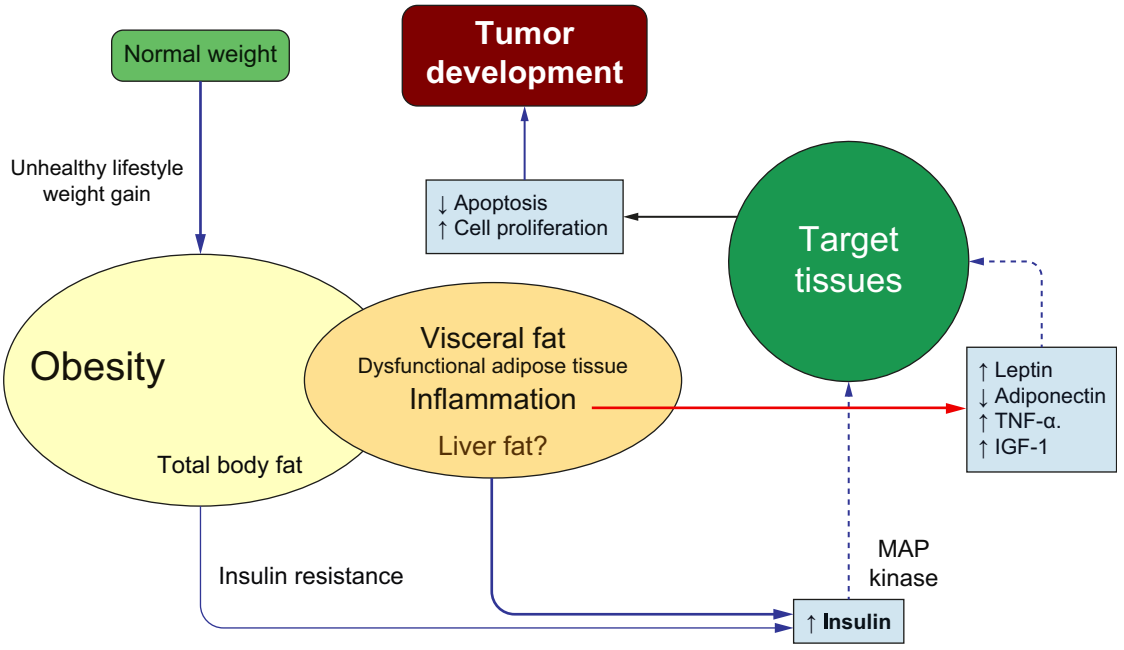

Fig. 1. Proposed mechanism(s) linking fat accumulation to extrahepatic cancer development. The role of insulin resistance/hyperinsulinemia on cancer development may be mediated by MAP-kinase activity, whereas inflammation is expected to act *via* cytokine/adipokine secretion. The specific role of liver fat in tumor development remains uncertain and will require additional data, as discussed in the text.

the predominance of visceral or sub-cutaneous fat, these results will have consequences for the identification of patients at the highest risk of obesity-promoted malignancy.

Conflict of interest

The authors declare no conflicts of interest in relation to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.09.020.

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