Metabolism and Target Organ Damage
Is liver fibrosis a risk factor for gynaecological cancers?


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<tbody>
<tr>
<td>Manuscript Title:</td>
<td>Commentary</td>
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Abstract

A recent study by Crudele et al. (Sci Rep. 2023;13:17793. doi: 10.1038/s41598-023-44243-y) reported on the association between surrogate indices of liver fibrosis and risk of gynecological cancers among dysmetabolic women. To put this study in context, notions regarding sex dimorphism in nonalcoholic fatty liver disease (NAFLD) are discussed. Additionally, meta-analytic reviews regarding the risk of extrahepatic cancers are reviewed. Next, I discuss on the relationship of metabolic dysfunction-associated fatty liver disease (MAFLD) with extra-hepatic cancers, notably including the breast and cancers of the female reproductive systems in humans. The pathomechanisms potentially accounting for this association include genetics, deregulated sex hormones, chronic subclinical inflammatory state, dysmetabolic milieu, oxidative stress, gut dysbiosis and altered immune surveillance.

Keywords – breast cancer, uterine cancer, NAFLD, MAFLD,
In the 1980s, when the definitions of nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD) were first coined (1,2) the primary concern of hepatologists was that a subsets of NAFLD/NASH individuals were at risk of progressing to cirrhosis. However, advancement of science has shown that the majority of (non-cirrhotic) NAFLD patients die owing to liver-unrelated causes, i.e. cardiovascular and extra-hepatic cancers (3). While the former outcome may be predicted owing to the strong association between NAFLD and the metabolic syndrome (4), the development of extra-hepatic cancer has come as somewhat more unexpected. At any rate, these findings strongly suggest that liver fibrosis is as major determinant of the natural course of NAFLD.

In this context, the discovery of sexual dimorphism in the NAFLD arena (5) has come as one of the most intriguing lessons for molecular biologists and clinical investigators. Indeed, to the detriment of precision medicine approaches, assessment of sex as a biological variable in Physiology and Medicine has historically been neglected, and only in the more recent past has it begun to be remedied (6).

Putting all the above notions together, a seminal meta-analytic review by Mantovani, et al. (7) were first in reporting that NAFLD was associated with a 1.2- to 1.5-fold increased risk of developing gynecological cancers irrespective of potential confounders (i.e age, smoking, obesity, and diabetes). However, the umbrella meta-analysis conducted by Yi et al., based on the analysis of 39 previously published meta-analyses, reported that individuals with NAFLD exhibited an increased risk of a variety of extra-hepatic cancers including breast cancer; the association of NAFLD with the female genital tract, though, was non-significant (8). Of interest, a large meta-analysis of 64 studies totaling 41,027 individuals found that the uterine and breast cancer were among the most common extrahepatic cancers, occurring over eight-fold more commonly than hepatocellular carcinoma in NAFLD; however, these cancer types were not associated with the stage of hepatic fibrosis in this study (9).
While NAFLD remains a diagnosis of exclusion, the nomenclature “metabolic dysfunction-associated fatty liver disease” (MAFLD) emphasizes positive criteria (10). Dysmetabolism may trigger cancer initiation and progression through a variety of pathomechanisms, which are acknowledged potential risk factors for cancer in humans. These comprise hormonal derangement, insulin resistance, chronic hyperglycemia, dysregulation of insulin-like growth factors, cell proliferation and angiogenesis and inhibited apoptosis, chronic systemic low-grade inflammation, increased formation of reactive oxygen species, increasing cell cycle rates, and decreased tumor suppressor function (11). On these grounds, MAFLD is expected to be even more strongly associated with extra-hepatic cancers than NAFLD, although it remains uncertain whether the female genital tract is specifically affected.

Studies address this research question. In the first, Liu et al (12) studied 352,911 individuals from the UK Biobank, 23,345 of whom developed cancers. Of interest, these authors found that, compared to non-MAFLD controls, those with MAFLD had significantly increased odds of corpus uteri (hazard ratio [HR] = 2.36, 95% CI 1.99-2.80), and breast (1.19, 1.11-1.27) cancers (12). In the second, Wei et al (13) investigated the incidence rates of cancer associated with MAFLD in their historical cohort of 47,801 participants managed at a tertiary Chinese hospital, 33.7% of whom had MAFLD. During a median 3.3-year follow-up, MAFLD individuals exhibited higher incidence of cancer than the MAFLD-free controls and, after adjustment for confounding factors, MAFLD was found to be moderately associated with the cancers of the female genital tract: labium, uterus, cervix, and ovary [hazard ratio (HR) 2.24; 95% CI 1.09-4.60].

A recent study conducted by Yaun among 151,391 Chinese participants in the Kailuan cohort reported substantially increased risk of breast cancer in MAFLD associated with excessive alcohol consumption (HR =7.27, 95% CI: 2.33–22.69) and, to a lower extent, in MAFLD with metabolic dysregulation, (HR =1.99, 95% CI: 1.01–3.92); and in MAFLD with overweight and metabolic dysregulation (HR =1.33, 95% CI: 1.02–1.74) (14). Interestingly, these authors also found that liver fibrosis was
associated with increased odds of overall incident cancer and various site-specific cancer incidence and mortality among MAFLD patients (14).

The importance of hepatic fibrosis as a determinant of cancer risk is also pinpointed by the study by Chung et al (15). These authors leveraged the Korean National Health Insurance Service database to categorize the 9,718,182 participants into three groups: (a) single-etiology MAFLD (=29%) (SMAFLD); (b) mixed-etiology MAFLD (M-MAFLD) (e.g., concurrent liver diseases and/or heavy alcohol consumption = 7%); and (c) MAFLD-free controls. During the median 8.3-year follow-up, it was the M-MAFLD with fibrosis group (defined with BARD score $\geq 2$) that suffered the highest odds of all-cancer incidence (aHR = 1.38, 95% CI = 1.36–1.39), followed by the M-MAFLD without fibrosis group (aHR = 1.09, 95% CI = 1.06–1.11) (15). Cancer-related mortality exhibited similar trends (15).

With this intriguing backset highlighting the potential risk of cancer of the female genital tract specifically among those individuals with fibrotic liver disease, Crudele et al (16) utilized the AST/ALT-to-platelet ratio (AARPRI), a surrogate index of hepatic fibrosis, to ascertain whether NAFLD, more than obesity per se, is a risk factor for the development of cancer of the female genital system. To this end, 653 women with metabolic dysfunction were followed-up for 8-years. Data have shown that a set of surrogate indices of liver fibrosis scores (AARPRI, APRI, FIB-4, mFIB4) could significantly differentiate those women who developed cancer from those who did not ($p < 0.001$). Receiver-operating curve (ROC) analysis showed that these non-invasive indices had good sensitivity, and specificity in identifying those cancer-developing women ($p < 0.001$). Moreover, increased AARPRI had the highest odds of development of genital cancer among women [odds ratio (OR)= 6, ($p < 0.001$) (16). The authors conclude that their study supports the notion that it is NAFLD, more than obesity, that is linked with the milieu of gynecological cancers (16). The findings from this study are closely reminiscent of the seminal study by Allen et al (17). These authors, by comparing to 441 age and sex-matched controls 4,722 USA NAFLD patients, found that NAFLD was
associated with an approximately 2-fold increased risk of developing cancers [IRR =1.9 (95% CI, 1.3–2.7)] during a median follow-up of 8 years (range, 1–21). Interestingly, the uterus was among the most often affected organs. Additionally, this study also found that the increased risk of cancer was more strongly associated with NAFLD than with obesity, identified through body mass index (17).

Collectively, the above studies would support the utilization of scores of hepatic fibrosis to triage those individuals at risk of developing cancer (18).

The study by Crudele et al raises two research questions: why is the female genital tract so susceptible to carcinogenesis in the setting of dysmetabolic dysfunction? and what is the specific role of hepatic fibrosis in the development of gynecological cancers?

Probably the best answer to the first question derives from the observation that metabolism is strictly involved during pregnancy and lactation (19). This tight involvement supports the logical expectation that the functional collaboration between the female genital tract and metabolism may turn dysfunctional whenever long-standing metabolic dysfunction occurs. In other words, insulin resistance, chronic excess of nutrient-associated oxidative stress and subclinical, long-lasting inflammatory state could conceivably trigger all the steps involved in initiation, growth, and diffusion of gynecological cancers (11). Supporting this notion, Lin et al. in their retrospective analysis of 725 consecutive patients with endometrial cancer found a strong association between MAFLD and cervical stromal involvement) (OR = 1.974, 95% confidence interval (CI) = 1.065-3.659, p = 0.031), which, in its turn is a predictor of overall survival (20).

Regarding the second research question, more advanced stages of liver fibrosis might merely identify more severe or more prolonged metabolic dysfunction. Additional mechanistic explanations involve risky genetic polymorphisms such as recently reported by Tai (21); and gut dysbiosis and altered composition of bile salts cannot be neglected (18).
Not only NAFLD/MAFLD adult individuals are prone to incident gynecological cancers as discussed above, but also the prevalence of NAFLD ranges up to 81.3%, with higher prevalence in breast, and gynecological cancers (21). These data, which are consistent with mutual and bi-directional associations, prompt additional studies investigating all the innumerable clinical and molecular underpinnings of the association between metabolic dysfunction, hepatic fibrosis, and gynecological cancers.

Graphical abstract
References


Dear Jennifer,


In my commentary both the NAFLD and the MAFLD are utilized, in agreement with the studies that are being commented.

Ideally, my submission would fit in the SI guest edited by Dr Ballestri and entitled: The Latest Research Progress of Nonalcoholic Fatty Liver Disease.

There are some potential Reviewers that I would recommend being charged with the peer review process of my submission. Their names and contact details are listed as follows:

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Looking forward to reading the editorial and, hopefully, Reviewers’ comments at your earliest opportunity.

Kind Regards

Amedeo