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Metabolism and Target Organ Damage

Commentary

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Is liver fibrosis a risk factor for gynecological cancers?

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Abstract

A recent study by Crudele *et al.* 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 the relationship of metabolic dysfunction-associated fatty liver disease (MAFLD) with extrahepatic 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, environmental pollution, and altered immune surveillance.

Keywords: Breast cancer, uterine cancer, NAFLD, MAFLD

NAFLD AND GYNECOLOGICAL CANCERS

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 subset 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 from liver-unrelated causes, i.e., cardiovascular and extrahepatic cancers[3]. While the former outcome may be predicted owing to the strong association

between NAFLD and metabolic syndrome[4], the development of extrahepatic cancer has come as somewhat more unexpected. At any rate, these findings strongly suggest that liver fibrosis is a 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, the 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, Mantovani *et al.* were the first to report 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)[7]. 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 extrahepatic cancers including breast cancer[8]. Nevertheless, the association of NAFLD with the female genital tract was non-significant[8]. Of interest, a large meta-analysis of 64 studies totaling 41,027 individuals found that the uterine and breast cancers 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]. Regarding the potential role of variables, such as patient populations and others, in modulating the odds of extrahepatic cancers among those with NAFLD, the study by Mantovani *et al.* found only four studies addressing the association of breast cancer with NAFLD and as many studies evaluated the association of NAFLD with cancer of the female genital tract, which prevents any significant subgroup analysis[7]. Similarly, in the study by Yi *et al.*, the number of included studies in North Americans *vs.* Asians was too small to draw any definite conclusions[8]. Finally, the study by Thomas *et al.* found that the pooled incidence rate for extrahepatic cancer did not vary according to the method of NAFLD diagnosis: liver histology, ICD code, and hepatic imaging; in clinic/hospitals *vs.* population-based studies; in studies from Asia and Europe; in prospective and retrospective studies; and between studies published before or after 2018[9].

MAFLD AND GYNECOLOGICAL CANCERS

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 extrahepatic cancers than NAFLD, although it remains uncertain whether the female genital tract is specifically affected.

Studies have addressed this research question. Liu *et al.* studied 352,911 individuals from the UK Biobank, 23,345 of whom developed cancers[12]. 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]. Wei *et al.* 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[13]. During a median 3.3 -year follow-up, MAFLD individuals exhibited a 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 Yuan *et al.* among 151,391 Chinese participants in the Kailuan cohort reported a 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 ≥ 2) that suffered the highest odds of all-cancer incidence [adjusted HR (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].

THE STUDY BY CRUDELE *ET AL.* [16]

With this intriguing backset highlighting the potential risk of cancer of the female genital tract among those individuals with fibrotic liver disease, Crudele *et al.* utilized the aspartate transaminase/alanine transaminase (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[16]. 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 AARPRI, AST to Platelet Ratio Index (APRI), Fibrosis-4 index (FIB-4), modified FIB-4 (mFIB-4) 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]. However, given the common occurrence of NAFLD/MAFLD in the general population, additional studies are needed to confirm these findings and evaluate the cost/benefit ratio of extensive screening practices aimed at early diagnosis of female genital tract among asymptomatic women with fibrosing NAFLD/MAFLD.

PUTATIVE PATHOMECHANISMS INVOLVED

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? What is the specific role of hepatic fibrosis in the development of gynecological cancers?[16]

Metabolism and reproduction in women

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, oxidative stress associated with chronic excess of nutrients, and subclinical, long-lasting inflammatory state could conceivably trigger all the steps involved in the 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 (Cl) = 1.065-3.659, $P = 0.031$], which, in its turn, is a predictor of overall survival[20].

Liver fibrosis

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, as recently reported by Tai *et al.*[21], and gut dysbiosis and altered composition of bile salts cannot be neglected[18]. A robust body of evidence also suggests that environmental, workplace, and household pollution may be a shared risk factor contributing, on the one hand, to NAFLD/MAFLD and, on the other hand, specifically to gynecological cancers.

Pollution and NAFLD/MAFLD

Environmental pollution may contribute to NAFLD/MAFLD initiation and advancement via different pathogenic routes comprising (1) the endocrine-metabolic pathway, for example, by inducing hypothyroidism, and signaling-disrupting chemical hypotheses; (2) interaction of chemicals with nutrients[22-24].

In humans, with women being more sensitive to these harmful impacts than men, environmental contaminants, such as perfluorinated alkyl substances (PFAS), may contribute to NAFLD development and progression via altered bile acid profiles and perturbed homeostasis of triacylglycerols and ceramides[25]. Moreover, pesticides and other phytopharmaceuticals are pro-oxidant compounds, which may intervene in the pathogenesis of NAFLD via either increased production of reactive oxygen species (ROS), or interaction (therefore acting as endocrine disrupting chemicals), with various nuclear receptors involved in hepatic metabolic pathways[26].

Microplastics can induce profound perturbation in the hepatic immunological micromilieu and induce hepatic fibrosis via the recruitment of Vsig4+ macrophages[27]. A large epidemiological study from the UK biobank, involving approximately half a million individuals, has suggested that air pollution scores were positively associated with the odds of higher liver fibrosis scores and new-onset severe liver disease and that, in agreement, residential greenspaces showed an inverse association with these hepatic outcomes[28]. A clinical study from Italy found that workplace toxicant exposure was strongly associated with metabolic dysfunction-associated steatotic liver disease (MASLD) complications, suggesting that occupational exposure may be a risk factor for the progression of fibrosis in MASLD[29].

Household air pollution may also serve as a gender-specific risk factor for liver health in rural areas, as proven by a large prospective Chinese study disclosing that, compared to men, women with long-term exposure to solid fuel combustion were at a higher risk of NAFLD, liver fibrosis, and hepatic cirrhosis[30].

Pollution and gynecological cancers

The mortality owing to cancer of ovary, uterus, and breast is deemed to be associated with a combination of factors including air quality, vehicle density, presence of chemical and steel industries, and exposure to fertilizers[31].

Eom *et al.* found that the risk of uterine cancers was almost 90% higher in industrial areas than in the control areas[32]. Although incompletely defined, the etiology of uterine cancer is believed to involve hormonal derangements, such as perturbed estrogen homeostasis and insulin resistance, that may result from the action of various air pollutants[32].

DNA mutagenesis of the mammary gland cells is directly induced by aromatic hydrocarbons (the prototype of which is benzo[a]pyrene), which are released by the combustion of coal and petroleum derivatives[33]. A recent study suggests that polypropylene microplastics, deemed to be harmless polymers based on Food and Drug Administration guidelines, instead can enhance the risk of metastatic breast cancer by promoting the secretion of the inflammatory cytokine IL-6 and the progression of cell cycle in breast cancer cells[34].

Finally, some pesticides, which act as endocrine disruptors, affect the hypothalamic-pituitary-ovarian axis and may trigger ovarian cancers in humans[31].

LIMITATIONS AND RESEARCH AGENDA

Investigations addressing the association of NAFLD/MAFLD and gynecological cancers, including the study by Crudele *et al.*, have failed to assess the impact of multiple confounding factors[16]. These include, among others, genetic background and family predisposition to cancer and liver disease, lifestyle habits, exposure to pollutants, stratification of NAFLD/MAFLD, and variability inherent among different patient populations.

Future studies will have to carefully ascertain whether those genetic polymorphisms of genes, such as *PNPLA3*, which are associated with fibrosing liver disease[35], also carry an independent impact on the odds of gynecological cancers.

CONCLUSIONS

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 a higher prevalence in breast and gynecological cancers[36]. 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.

Prospective confirmation, with adequately sized studies, of the notion that fibrosis in NAFLD/MAFLD, evaluated with both the diagnostic standard, i.e., liver histology, and with various non-invasive techniques[37] is associated with a robust risk of gynecological cancers would bear relevant clinical implications. Indeed, the scope of medical assistance for these patients would go far beyond liver-related outcomes, to embrace inter-disciplinary assessment for screening, diagnosis, and management of the various gynecological cancers. Finally, the intricate pathomechanisms associating liver fibrosis with the risk of gynecological cancers remain incompletely understood and in need of further investigation.

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Authors' contributions

The author contributed solely to the article.

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Conflicts of interest

Amedeo Lonardo is the Editor-in-Chief of the journal *Metabolism and Target Organ Damage.*

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Not applicable.

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