The effect of gut metabolites on cancer: Intermittent fasting-mediated changes in ursodeoxycholic acid, deoxycholic acid, and isovaleric acid

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Abstract

Diet has been shown to shape gut microbes which hold implications for human health, including cancer prevention. Preliminary results from a feasibility trial found significant changes in the secondary bile acids, ursodeoxycholic acid (UDCA) and deoxycholic acid (DCA), and a branched-chain fatty acid, isovaleric acid (IVA), after intermittent fasting (IF) (limiting eating to an 8-hour window per day) for 3 months in a subset of patients with stage 0 chronic lymphocytic leukemia/ small lymphocytic lymphoma. It is unknown, however, what role these metabolites may play in the cancer process. The aim of this study was to conduct a preliminary literature review to support the trial's findings and answer, "What effect do IF-mediated changes in the gut microbiota associated with the production of metabolites UDCA, DCA, and IVA have on cancer?" MEDLINE and grey literature (ex. Google Scholar) were searched using a combination of subject headings and keywords such as, "UDCA", "DCA", "IVA", "bile acids" and "cancer." No literature was found directly answering the research question; however, 31 articles were identified as relevant. Pertinent information was extracted using a data extraction form describing the metabolites' origin, potential cancer crosstalk, and associations with IF. **Understanding the impact of IF on the gut microbiome and the resulting metabolites may provide new insights into cancer treatment and/or prevention.** To our knowledge, this is the first study to describe and investigate these metabolites together which, based on preliminary research findings, may be modified by IF and play a potential role in the cancer process.

Background

- Cancer is the leading cause of death in Canada, responsible for 28.2% of all deaths in 2019[1].
- Diet and eating patterns influence cancer incidence and survivorship[2].
- The effectiveness of different dietary pattern depends on individual risk factors
    - E.g. family history, sex, age, gut microbiota profiles and metabolites[3].

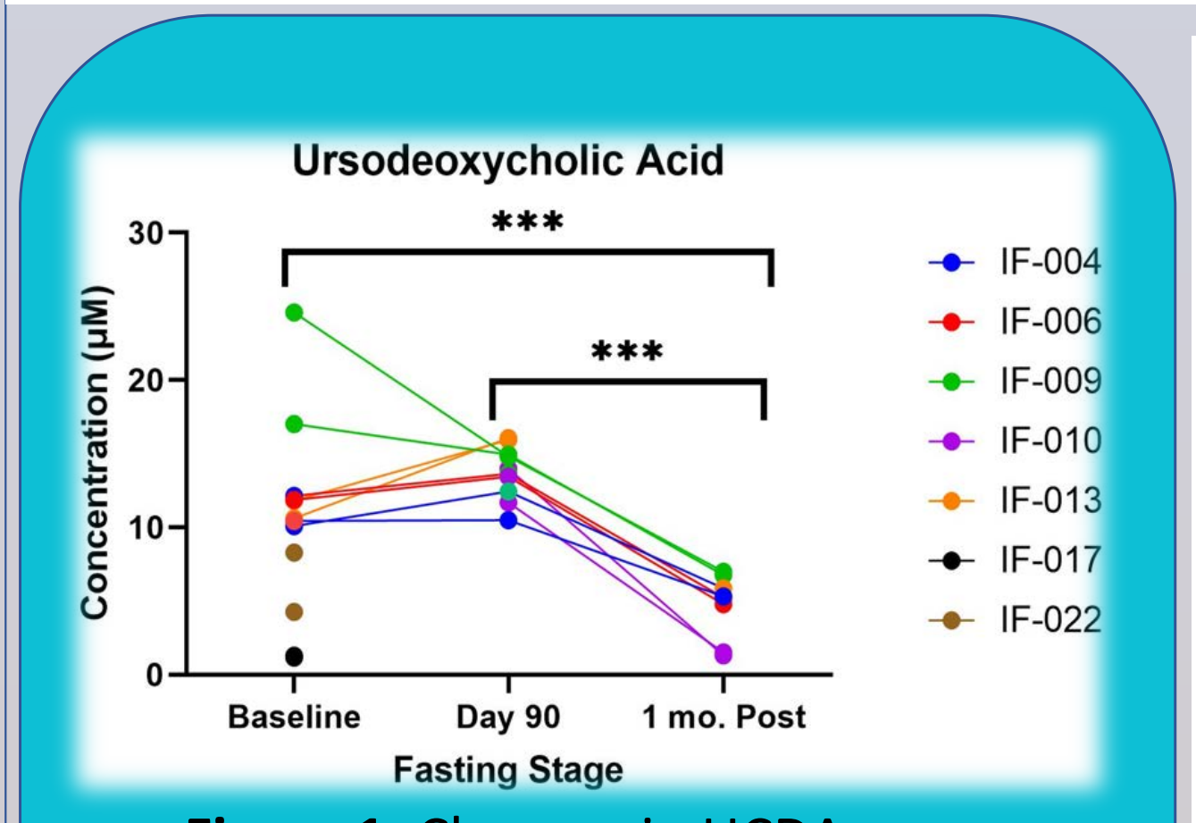

Figure 1. Changes in UCDA

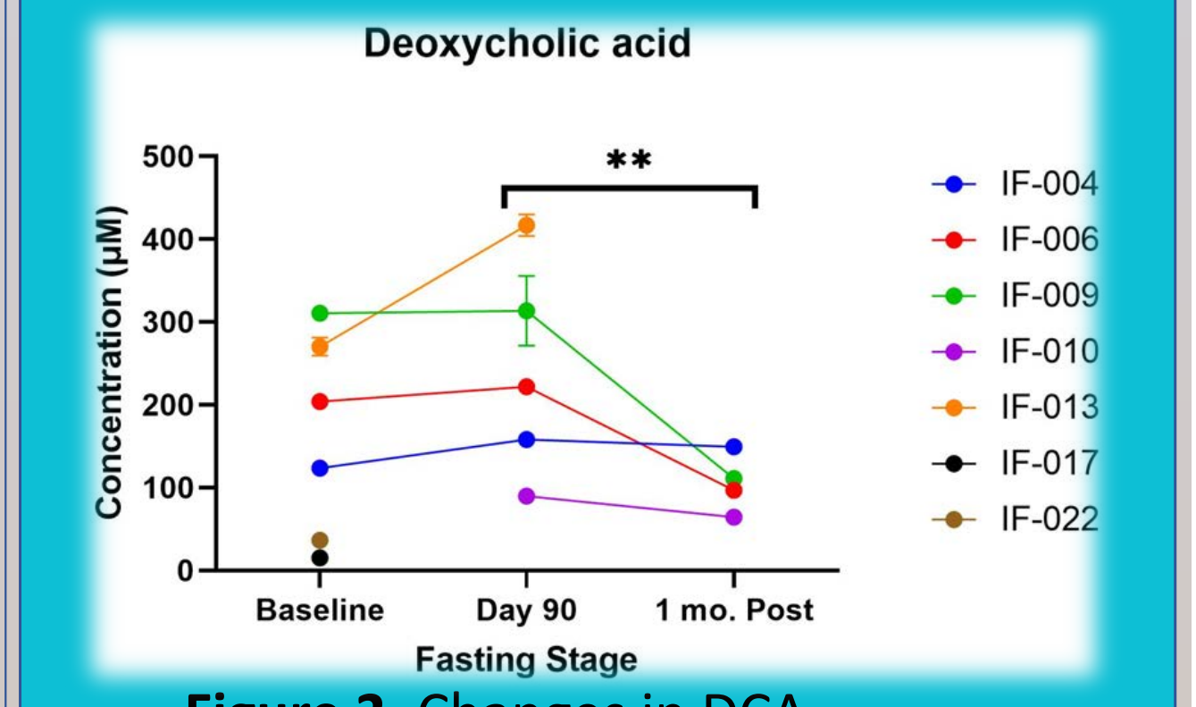

Figure 2. Changes in DCA

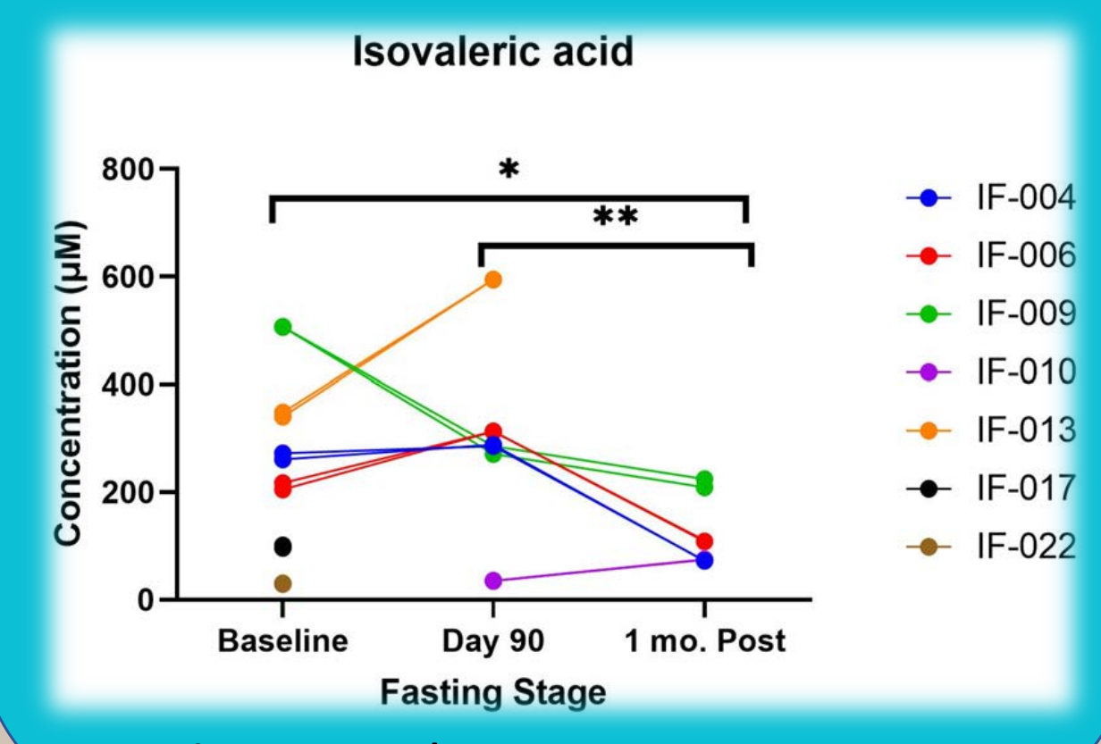

Figure 3. Changes in IVA

A feasibility trial of intermittent fasting was conducted in 15 patients with early stage CLL/SLL at BC Cancer- Victoria (ClinicalTrials.gov registration: NCT04626843) to assess for changes in lymphocyte count (tumor burden), autophagy activation, inflammation, quality of life, and the gut microbiome. Preliminary metabolomic analysis was conducted on samples from seven participants which demonstrated significantly changes in concentrations of UDCA, DCA, and IVA (Figures 1-3). It is unclear, however, what role these metabolites may play in the cancer process.

Research Question:
What effects do IF-mediated changes in the gut microbiota associated with the production of metabolites UDCA, DCA, and IVA have on cancer?

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Methods

A rapid literature review was conducted in MEDLINE and grey literature (ex. Google Scholar) using subject headings and keywords such as, "UDCA," "DCA," "IVA," "bile acids," and "cancer." Articles were included if relevant to the research question, available in English, original research or a literature review. Emphasis was placed on human trials and no limiter was placed on publication dates. A data extraction sheet was created in Excel, informed by the research question, and used to guide the data extraction.

Results

Thirty-one articles were identified that met the inclusion criteria (Table 1). Key findings from the data extraction sheet are shown in Table 2.

- Secondary bile acids (BAs) are products of the gut microbiota (Fig 4):
    - can directly or indirectly regulate microbial composition[4].
    - can act as cancer activators or inhibitors, through various pathways[5,17].
    - Most are promoters of oxidative stress, inflammation and DNA damage[6], including DCA which is cancer inducing[7].
- Short and branch chain fatty acids are produced by bacterial fermentation[10]

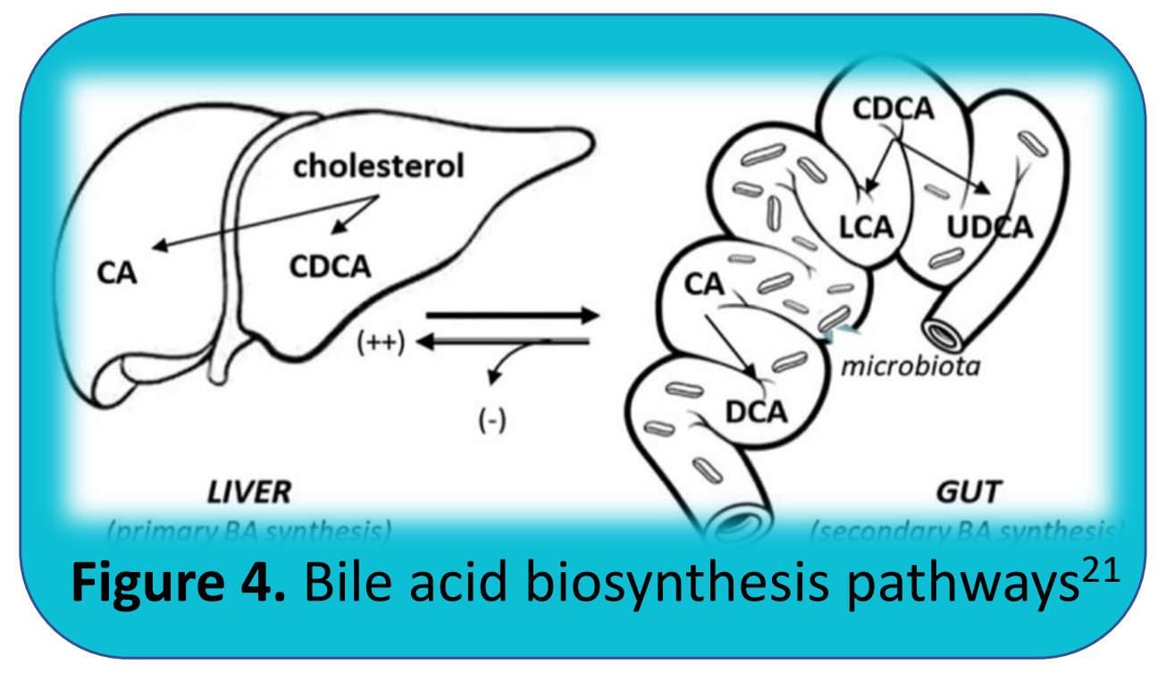

Figure 4. Bile acid biosynthesis pathways[21]

Table 2. Characteristics of ursodeoxycholic acid, deoxycholic acid, and isovaleric acid related to diet and cancer.

	Ursodeoxycholic acid (UDCA)	Deoxycholic acid (DCA)	Isovaleric acid (IVA)
Description & Production	-Hydrophilic, secondary bile acid formed from chenodeoxycholic acid (CDCA) through epimerization by intestinal bacteria[17,18,19,20] -Comprises 3-5% of bile acid pool in humans [18, 21]	-Hydrophobic, secondary bile acid derived from cholic acid through deconjugation and dehydroxylation by intestinal bacteria[7]	-A five-carbon, branched chain fatty acid acquired from the fermentation of leucine by gut bacteria [22]
Associated diet	-Increased with high fat, low fibre diets [23]: ● High fat diet elevated fecal UDCA concentration[24]	-Increased with high fat , low fibre diets[24]: ● Vegans (low fat, high fiber diet) have ~¼ the DCA fecal concentration than omnivores[11] ● Normal diets average 100μm fecal DCA while high fat diets (e.g. Western diet) results in 200-700+μm fecal DCA[25]	-Foods high in protein[19]: ● Most abundant in animal protein (ie. meat, cheese, and fish)[19] -Present in fermented foods[22] -No association between fecal IVA and 14 assessed foods[26]
Cancer effect	Inhibitor [8,9,21,27]	Activator[7,23,28]	Inhibitor[22,29]
Potential mechanism in cancer	-Regulates oxidative to prevent cancer cell proliferation[8,9] -Potent inhibitor of apoptosis[8,21] -Inhibits BA synthesis in liver, alters colonic BA composition, and reduce toxic BAs in blood[27] -Positive impact on glucose homeostasis[21] -Counteract, suppresses cancer proliferation generated by DCA[8,9]	-High DCA concentration forms reactive oxygen and nitrogen species, inducing stress on body cells and increasing risks of mutation[7,23] -Induced cancer stem cells[27] -Stimulates expression of pro-inflammatory IL-8 cytokine[27]	-IVA uses macrophages to regulate inflammatory mediator production[10] -Enhances the production of anti-inflammatory cytokine[10] -May contribute to oncogenesis at high concentrations[11]
Example	-Approved drug for cholesterol gallstone dissolution and primary biliary cholangitis -Off-label use or clinical trials for 16 other conditions[21] -Long term side effects for consumption of UDCA requires further research and data[17]	-Primarily researched as a risk factor for colon cancer7,[16] -Risk factor for esophageal cancer as GERD refluxate contains increased concentrations of bile salts, repeated exposure to DCA triggers inflammation and carcinogenesis[30]	-In n=52 with solid tumors on immune checkpoint inhibitors (PD-1i), high serum IVA concentration was associated with 38% longer progression-free survival, suggesting a link between PD-1i efficacy and the gut microbiota[26]

Discussion

Dietary intake plays a crucial role in metabolism, the gut microbiome and resulting metabolites. For example, Trefflick et al. found a vegan diet with matching energy levels of an omnivore diet, containing one-quarter the fat content and nearly double the grams of fibre, resulted in notably lower levels of total fecal bile acids and secondary bile acids[11]. In particular, DCA, a cancer inducer, was found at a significantly lower fecal concentration in vegan eaters compared to omnivores[11].

Recent studies suggest that the effect of IF and feeding patterns on metabolism can be closely associated with alterations in the gut microbiota[12,13,14], as observed in Stringer's preliminary metabolomic findings (Fig. 1-3). Altering the metabolome can influence the cancer process through a variety of mechanisms, shown in Fig. 5.

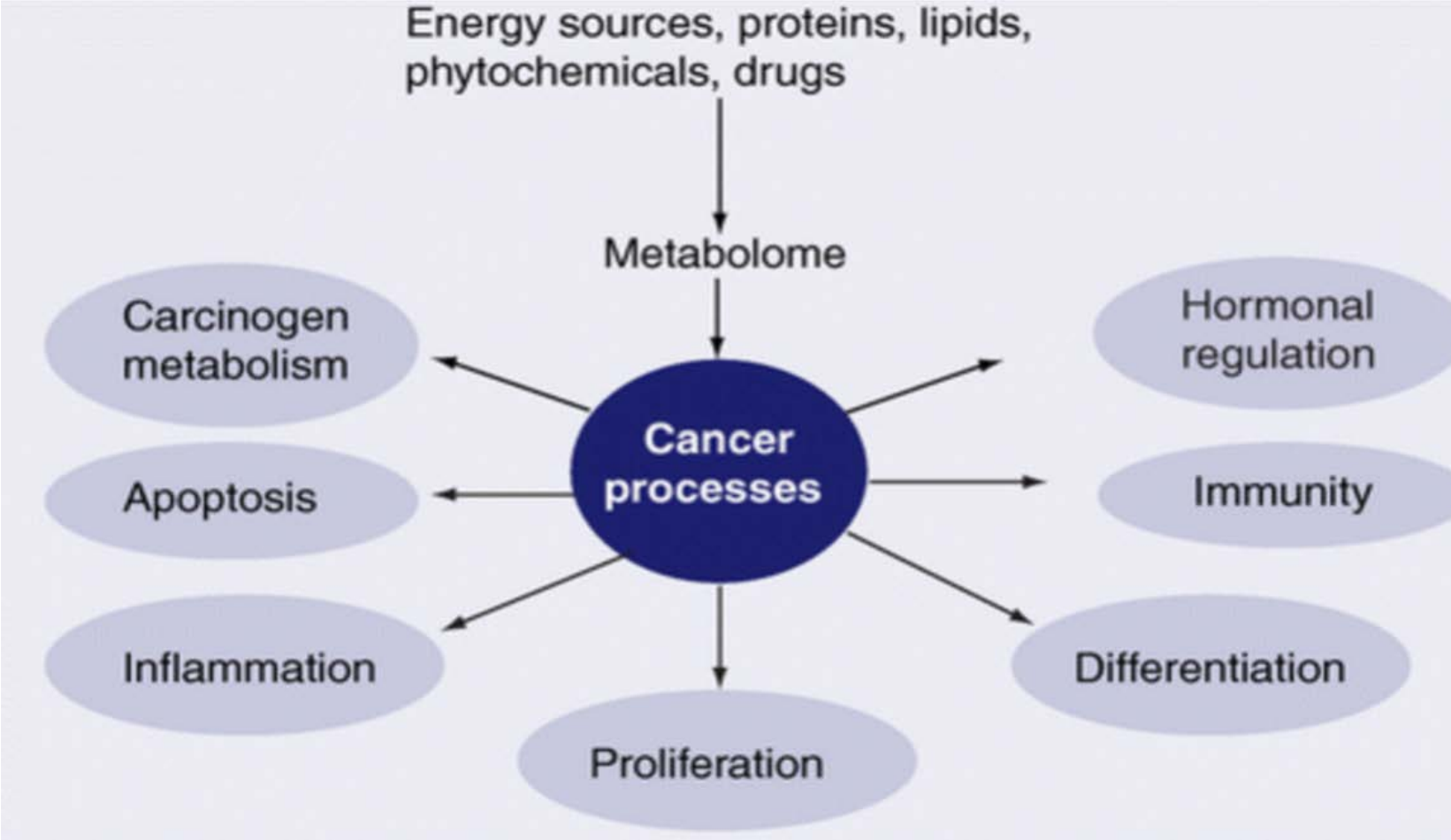

Figure 5. Associations of the metabolome with cancer processes[16].

Our literature review highlights that UDCA, DCA, and IVA undermine many pathways that can influence the development of cancer, including the regulation of oxidative stress[8,9], developing apoptosis resistance[7], and prompting the development of anti-inflammatory cytokines[10]. Additionally, given that UDCA holds the capacity to suppress DCA-induced cell apoptosis[8], there is value to studying the interaction amongst different combinations of metabolites. By understanding the metabolic shifts in cancer, one may identify metabolic changes that underlie cancer processes, such as metastases, and elucidate new biomarkers and/or therapeutic targets for cancer treatment[15,16].

Limitations: This study was based on preliminary results; complete results may differ (anticipated Fall 2023). A formal literature review methodology was not followed, limiting the comprehensiveness of findings.

Conclusions

More research is needed to understand how the timing of eating influences the gut microbiome, associated metabolites and, ultimately, the cancer process.

Full results of the "IF in CLL/SLL Study" are anticipated by the end of 2023 and will be shared on ClinicalTrials.gov. Questions can be directed to Eleah Stringer.

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