CHEM_ID	CHEMICAL_NAME	IMPORTANCE	SUPER_PATHWAY	SUB_PATHWAY	HMDB	KEGG_ID	ADD_INFO	CRC_SUMMARY	SOURCES
100000463	indolelactate (ILA)	1	Amino Acid		HMDB0000671	C02043	Indole metabolites have been shown to enhance antioxidant activity and inhibit inflammation caused by weakened intestinal barrier and ectopic microflora.	Indole metabolites, including indolelactate (ILA), as well as indole-3-propionic acid (IPA), indole acetic acid (IAA), and indole-3-aldehyde (IAld)may be used as adjuvant regimens for tumor immunotherapy or chemotherapy. ILA is the most widely reported indole metabolite with anticancer activity, as it has been shown to directly inhibit CRC cell proliferation and promote apoptosis in vitro through the AhR of tumor cells. ILA can also promote the production of IL-12 by immune cells to activate cytotoxic T cells by affecting histone modification and chromatin accessibility in dendritic cells. ILA has been shown to alleviate intestinal inflammation and tumorigenicity in mice. Additionally, ILA may enhance function of CD8 T cells by reducing cholesterol levels of tumor tissue.	Jia, 2024 (indole metabolites) Zhang, 2023 (CD8 T cells) Liu, 2023
100001300	alpha-hydroxyisovalerate	3	Amino Acid	Leucine, Isoleucine and Valine Metabolism	HMDB0000407	N/A	α-hydroxyisovalerate has been linked with liver injury, diabetic nephropathy, and MSUD (hindered ability to break down leucine, isoleucine, and valine)	Elevated levels of α-hydroxyisovalerate have been found in pre-diagnostic glioma and glioblastoma cases (unsure how well this can be extrapolated to CRC, since they may affect amino acid metabolism differently). α-hydroxyisovalerate identified as a discriminating metabolite between CRC and adjacent non-cancerous mucosa.	Loding, 2024 (glioma) Brown, 2016 (adjacent mucosa discrimination)
100020860	3-dehydrodeoxycholate	5	Lipid	Secondary Bile Acid Metabolism	HMDB0062742	N/A Derivative of C04482 (deoxycholic acid) map00121 Map04976	N/A	Deoxycholic acid (DCA), from which 3-dehydrodeoxycholate is derived, has been suggested to promote colon cancer growth. Low concentration of DCA significantly increased uPA, uPAR, and cyclin D1 mRNA expression in cancer cells, which are implicated in tumorigenesis and enhancing cell invasiveness. Colon cancers display increased nuclear β-catenin during transition of colorectal adenoma to carcinoma. Small concentrations of DCA may activate β-catenin signaling pathway, but siRNA targeted for β-catenin can suppress this. Sodium deoxycholate, the sodium salt of DCA, has been shown to promote the survival of breast cancer cells by elevating Flk-1 (regulator of VEGF) and reducing levels of pro-apoptotic ceramide. DCA may suppress p53 by stimulating proteasome-mediating p53 degradation through the ERK signaling pathway. Conversely, DCA has been shown to reduced the invasion capacity and stemness of pancreatic adenocarcinoma cells by inhibiting EMT and inducing oxidative stress.	Pai, 2004 (β-catenin and uPAR) Krishnamurthy, 2008 (breast cancer) Qiao, 2001 (p53) Schwarcz, 2023 (pancreatic)
100000437	theophylline (TH)	6	Xenobiotics	Xanthine Metabolism	HMDB0001889	D00371 hsa04020 hsa04022 hsa04024 hsa04080 hsa04270	Not much research links TH directly to CRC.	Theophylline, along with the methylxanthines caffeine and theobromine, may exert antitumor effects through mediating the alternative splicing process (preventing errors). Specifically, TH may increase p53β by suppressing SRSF3. TH may also induce cellular apoptosis, senescence, and decreased colony formation. Contrastingly, it has also been argued that TH alone has no considerable effect on breast cancer cells, but when used in synergy with berberine, a plant alkaloid shown to have anticancer effects on various cancers, apoptotic cell death levels increased.	Chang, 2017 (p53, breast cancer) Hasemi-Niasari, 2018 (synergy with berberine)

100001102	dodecanedioate (C12-DC) (DC12)	7	Lipid	Fatty Acid, Dicarboxylate	HMDB0000623	C02678	DC12 and other dicarboxylic acids may be useful for combatting obesity and treating metabolic disorders (may reduce risk for cancer accordingly). In vitro (with mice), DC12 was catabolized even by adipose tissue and not stored intracellularly.	Not much research has been published on the relation between DC12 and cancer, but carboxylic fatty acids, which includes DC12, have been shown to have therapeutic potential for metabolic diseases, including type 2 diabetes. Considering that a diabetes diagnosis has been shown to increase CRC risk by more than 40%, there may be some significance there.	Goetzman, 2024 (mice obesity) Bharathi, 2020
100008928	2-hydroxybutyrate (2HB)/2-hydroxyisobutyrate (2HIB)	8	Amino Acid	Glutathione Metabolism	HMDB0000729, HMDB00008	C05984 map00640, C21297	2HB generally appears in situations related to deficient energy metabolism and inherited metabolic diseases affecting CNS during early development	Increased serum 2HB levels are often present in lung cancer, CRC, and HCC. However, 2HB levels fell significantly for the patients with prostate cancer in their first three months of hormonal therapy. 2HB concentration in intestinal lumen of CRC patients negatively associated with P. piscolens and C. fastidiosus, indicating that gut microbiota could potentially influence 2HB levels (or vice versa?). Increased 2HB previously identified as major risk factor for insulin resistance and type 2 diabetes (related to "increased lipid oxidation and oxidative stress"); hyperinsulinemia may then promote cell proliferation.	Qin, 2023 Gall, 2010 (insulin resistance) HMBD
100000455	itaconate	9	Energy	TCA Cycle	HMDB0002092	C00490 map00660 map01100	Itaconate is a signaling molecule that affects metabolic and functional cell processes such as glycolysis, TCA cycle 11, 12, amino acid 5, 13, and lipid metabolism.	Itaconate suppresses the synthesis of aspartate and serine/glycine, reducing the proliferation and function of CD8+ T cells, which may promote cancer growth. Targeting endogenous itaconate production may improve antitumor efficacy of T cells in the context of hepatocellular carcinoma (macrophages contribute to T-cell exhaustion in the tumor microenvironment through itaconate-driven changes to gene expression). Itaconate may promote anti-inflammatory cytokine expression in M2-like macrophages, which are associated with worse clinical outcomes in CRC patients. Additionally, itaconate may provide a link between metabolic dysfunction in obese patients and CRC, implying a significant role in early-onset CRC.	Gu, 2023 (HCC) Scheurlen, 2023 (early-onset CRC) Haase, 2024 (tumor immune escape mechanism, don't have access)
100021372	2-hydroxy-4-(methylthio)butanoic acid (HMTBA)	10	Amino Acid	Methionine, Cysteine, SAM and Taurine Metabolism	HMDB0037115	N/A	Not much research has been published on the relation between HMTBA and cancer.	HMTBA may keep gut cells healthy by preventing damage to gut barrier by promoting the production of beneficial antioxidants like taurine and glutathione, even when harmful substances like hydrogen peroxide or TNF were introduced. Since HMTBA improves intestinal homeostasis, it may play a role in preventing CRC.	Martin-Venegas, 2013 (protecting gut barrier)
100002458	3-methylglutaconate (3MGA)	11	Amino Acid	Leucine, Isoleucine and Valine Metabolism	HMDB0000522	N/A	3MGA uria indicates a number of syndromes/mutations characterized by defects in mitochondrial function. In cases where a defect in leucine catabolism exists and the metabolic origin of 3MGA is unknown, it has been proposed that 3MGA may arise from aberrant shunting of isoprenoids to mitochondria or mutation induced effects on ETC-related energy production.	Not much research has been published on the relation between 3MGA and cancer, but 3MGA-urias have been known to cause psychomotor retardation, cardiomyopathy, and neutropenia, which may weaken the immune system and make an individual more prone to cancer.	Su, 2014 Overview of 3MGA-urias

100000774	phenyllactate (PLA)	12	Amino Acid	Phenylalanine Metabolism	HMDB0000779, HMDB0000563	C05607, map00360 map00960 map01064 map01100 map01110	PLA is produced by a variety of lactic acid bacteria but research indicates that it is also produced by gut microbiota.	PLA has great diagnostic efficacy when differentiating between prostate cancer, benign prostatic hyperplasia, and prostatitis. It has also been shown to be a potential early biomarker for colon cancer. Whether PLA has a tumor-promoting or tumor-preventing effect is debated. It has been shown that it may counteract the colon cancer-promoting effects of F. nucleatum, but promote EMT with cervical cancer cells. Additionally, serum PLA levels in liver cancer and oral squamous cell carcinoma patients are elevated. PLA inhibits the growth of F. nucleatum, which is know to reduce immune regulation and promote cell proliferation, in vitro.	Hao, 2024 (prostate cancer) Wu, 2023 (CRC)
100004182	3beta-hydroxy-5-cholenoate (cholenate)	13	Lipid	Secondary Bile Acid Metabolism	HMDB0000308	C17333 map00120	Cholenate belongs to class of organic compounds known as monohydroxy bile acids. Bile acids are known to alter the gut microbiota composition due to antimicrobial properties.	Fecal levels of secondary bile acids, including cholenate, correlate with mucosal and metabolic markers of CRC. Their interdependence with diet and gut microbiota may be a means to modulate CRC risk through diet changes. Not much research on cholenate specifically, but there seems to be a general consensus that bile acids, particularly secondary bile acids may aid in the development of CRC.	Ocvirk, 2018 Nguyen, 2018 Liu, 2022
100006435	N-acetylglucosamine/N-acetylgalactosamine (GlcNAc/GalNAc)	15	Carbohydrate	Aminosugar Metabolism	HMDB0000212, HMDB0000215	C00140 map00520 map01100 map01250 map02010 map02060	Widespread presence of Gal-GalNAc in areas of the colon near cancerous lesions supports field effect theory (interesting to think about if the emphasis placed on differentiating between cancerous and noncancerous tissue should be reconsidered when nearby tissue is at risk too?)	GalNAc-glycans on the surface of cancer cells may aid in adhesion to endothelium, which may promote metastasis in the context of breast cancer. Blocking GalNAc-glycans significantly reduced this effect, but blocking other sugars did not (control). Gal-GalNAc may be a biomarker for early CRC detection, as it appears in rectal mucus and tissue samples of cancerous/precancerous cells in the colon but is absent in normal colon tissue. GalNAc-DSLc4 has been linked to aggressive renal cell carcinoma (RCC) by promoting growth, invasion, and increased ability to adhere to laminin (through interactions with integrins in lipid rafts). Unclear how relevant this is to metabolite, considering GalNAc-DSLc4 is much more complex than Gal-NAc.	Bapu, 2016 (adhesion to endothelium, breast cancer) Yang, 1996 (very old, CRC) Tsuchida, 2018 (GalNAc-DSLc4)
100000809	6-hydroxynicotinate (deprotonated 6-hydroxynicotinic acid, which is a derivative of nicotinic acid)	16	Cofactors and Vitamins	Nicotinate and Nicotinamide Metabolism	HMDB0002658	C01020 map00760 map01100 map01120	Not much research has been done on the link between nicotinic acid and cancer, even less so on 6-hydroxynicotinic acid, EVEN less so on 6-hydroxynicotinate.	Temporarily restricting nicotinic acid (Na) (see relation to 6-hydroxynicotinate under chemical name) intake and production by gut microbiome may increase activity of NAMPT and PARP inhibitors, as well as chemotherapeutics (promoting cancer treatment efficiency). Bit of a stretch here.	Piacente, 2017
100002070	2-hydroxyglutarate (2-HG)	17	Lipid	Fatty Acid, Dicarboxylate	HMDB0059655	C02630 map00650 map00660 map01100	2HG has also been implicated in other diseases such as Alzheimer's and metabolic disorders.	Mutations in IDH1 enzyme may cause it to produce 2-HG, higher levels of which have been linked to a higher risk of brain tumors (specifically gliomas), especially in people who have genetic conditions that affect 2HG metabolism. On the other hand, D-2-HG may also have anti-cancer effects by consuming NADPH and inducing oxidative stress in cancer cells. Additionally, D-2-HG may also make radiation and chemotherapy more effective by hindering DNA repair. Higher D-2-HG levels have also been found in colon cancer cells, especially in metastatic SW620 cells. The same malfunction of IDH1/2 enzymes have been linked to these increased levels.	Dang, 2009 (IDH1, brain cancer) Chou, 2021 (more on gliomas) Atalay, 2022 (CRC)
100001541	2-hydroxy-3-methylvalerate (HMVA)	18	Amino Acid	Leucine, Isoleucine and Valine Metabolism	HMDB0000317	N/A	HMVA primarily used to identify urologic diseases (e.g. phenylketonuria, MSUD), less clear relation to CRC.	HMVA has been used to predict sensitivity of patients to neoadjuvant chemotherapy (NAC) for treatment of muscle-invasive bladder cancer; decreased levels in resistant group.	Zhuang, 2022 (NAC sensitivity) HMDB

100021651	chenodeoxycholic acid sulfate (2) (CDCA-S)	19	Lipid	Primary Bile Acid Metabolism	HMDB0002522	C02528 (chenodeoxycholic acid, from which CDCA sulfate is derived) map00120 map00121 map01100 map04976	Not much research has been published that links CDCA-S directly to CRC.	CDCA may enhance the effectiveness of sorafenib in liver cancer treatment by binding to a region on the EGFR protein and preventing the spread of HepG2 liver cancer cells. Conversely, it has also been shown that CDCA may promote esophageal cancer growth by encouraging production of signaling molecules such as PGE2 and VEGF that help tumor growth and angiogenesis. Unclear to what extent these findings may be extrapolated to CDCA-S.	Zhang, 2022 (liver cancer) Soma, 2006 (esophageal cancer)

Updates on notes:

The two metabolites identified to have opposite directions of association in the leucine, isoleucine, and valine metabolism sub-pathway were 3-methylglutaconate (100002458) and 2-hydroxy-3-methylvalerate (100001541), where 3MG seems to be present in higher concentrations in low risk patients, and vice versa for 2H3MV.

3MG, as an intermediate in leucine degradation, is normally processed via the mevalonate or ketogenesis pathways in the mitochondria. Increased levels typically indicate compromised leucine breakdown/mitochondrial function. This contradicts the higher concentrations found in low-risk patients. Perhaps this could suggest that the difference found may be due to chance, especially since there is no asterisk indicating statistical significance.

Conversely, 2H3MV is not an intermediate in isoleucine degradation, which means that higher levels may imply a shift toward alternative BCAA metabolism. This could indicate mitochondrial dysfunction or oxidative stress (see excerpt below). This may explain the higher concentrations found in high-risk patients.

"We constructed the metabolic pathway based on the molecules showing significant differences between HMP (high metastatic potential) and LMP cell lines […] In addition, we identified a significant increase in the levels of 2-hydroxy-3-methylvalerate (p-value = 1.19 × 10–13; FC = 3.62)[…] All those mentioned metabolites are products of BCAA catabolic pathway; the largest differences observed in the levels of 2-hydroxy-3-methylvalerate [….] indicate accelerated catabolism of isoleucine, leucine and valine, respectively. Elevated levels of those metabolites in growth media suggest their release by the HMP cells."

Indolelactate is produced by a number of bacteria in the gut microbiota.

ILA levels may be increased through diet (e.g. high dietary fiber). "For future research trends, the cooperation and competition between bacteria and indole metabolites need additional attention. Different bacteria could produce different indole metabolites, and it is worth considering how to precisely regulate the ratio of indole metabolites in the tumor microenvironment via diet or synthetic materials."

It is possible that there may a shift in the composition of the gut microbiota in high-risk CRC patients towards species of bacteria that produce higher levels of ILA, potentially to address increased inflammation characteristic among high-risk CRC patients.

[Have high-risk CRC patients been advised to change their diet before these measurements were taken?]

Jia, 2024

Table 1.

The role of microbial indole metabolites in tumor.

Indole metabolites	Commensal	Tumor types targeted	Directly acting cells	Effects	Ref
ILA	*Lactobacillus gallinarum*	Colorectal cancer	Cancer cells	Directly inhibit cancer cell proliferation and promote apoptosis through AhR	15
ILA	*Lactobacillus plantarum*	Colorectal cancer	Dendritic cells/$CD8^+$ T cells	Promote the production of IL-12 in dendritic cells and inhibit the *Saa3* in $CD8^+$ T cells	17
ILA	*Lactobacillus reuteri*	Colorectal cancer	Th17 cells	Reduce Th17 cells by inhibiting the transcriptional activity of RORγt	1
ILA	*Bifidobacterium breve*	Colorectal cancer	Macrophages	Reduce the proportion of $CD86^+$ pro-inflammatory macrophages through the AhR/p-AKT/IL-1b pathway	19