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REVIEW ARTICLE

Bovine milk fat and cancer risk: A double-edged sword?

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Abstract

Among the many macro- and micronutrients contained in cow's milk, one of the most important is the lipid fraction. While the nutritional and physiological benefits of milk consumption after the first years of life are the subject of some debate, there also appear to be conflicting views on the health aspects of the milk lipids, including their involvement in cancer.

Positive *in vitro* and/or *in vivo* data on growth-inhibiting or cytotoxic effects are available for lipid components of milk such as sphingomyelins and their degradation products or various hydroxy fatty acids. Isomers of linoleic acid and branched-chain fatty acids have also been shown to have anticarcinogenic potential in animal models by inducing apoptosis.

On the other hand, there is evidence of an association between increased cancer mortality and the consumption of high-fat milk, which contradicts the tumor-protecting effects observed *in vitro* and *in vivo*. Consumption of high-fat dairy products appears to be associated with an increased risk of developing types of cancer compared to low-fat dairy or other topical soy-based alternatives.

There are ambiguous results for an anticarcinogenic effect of various lipid constituents of cow's milk as well as for an association between general milk fat consumption and the occurrence especially of breast, colorectal, and prostate tumors.

Whether the effects observed in epidemiological studies can be attributed to milk lipids or whether the promising preclinical data on their anti-cancer efficacy can be transferred to humans remains unclear at present, therefore this review summarizes the latest findings.
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Keywords: Cow milk; Milk fat; Lipids; Cancer; Study outcomes.

Abbreviations: 13-MTD, 13-methyltetradecanoic acid; ACF, aberrant crypt foci; ALA, α-linolenic acid; APC, adenomatous polyposis coli; BAK, Bcl-2 homologous antagonist killer; BCFA, branched-chain fatty acid; BMMF, bovine meat and milk factor; BPA, bisphenol A; BRCA, breast cancer susceptibility gene; C1P, ceramide-1-phosphate; cDNA, circular DNA; CI, confidence interval; CLA, conjugated linoleic acid; CVD, cardiovascular disease; DAG, diacylglycerol; DHA, docosahexaenoic acid; DMH, 1,2-dimethylhydrazine; DPA, docosapentaenoic acid; EGFR, epidermal growth factor receptor; EPA, eicosapentaenoic acid; ER, endoplasmic reticulum; ERE, estrogen response element; ERα, estrogen receptor α; FA, fatty acid; FABP, fatty acid binding protein; FAME, fatty acid methyl ester; FFA, free fatty acid; FTO, fat mass and obesity-associated; GD_3, ganglioside D_3; HDL, high-density lipoprotein; HFA, hydroxy fatty acid; HPA, hydroxypalmitic acid; HR, hazard ratio; HSA, hydroxystearic acid; IC50, inhibitory concentration 50; ID50, inhibitory dose 50; IL, interleukin; LA, linoleic acid; LCFA, long-chain fatty acid; MAG, monoacyl glycerol; MCFA, medium-chain fatty acid; MFG, milk fat globule; MFGM, milk fat globule membrane; Min, multiple intestinal neoplasia; mol%, mole percent; mTORC1, mammalian target of rapamycin complex 1; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; MUFA, monounsaturated fatty acid; nCDase, neutral ceramidase; NMU, N-nitroso-N-methylurea; OCFA, odd-chain fatty acid; OPA, oxopalmitic acid; OR, odds ratio; OSA, oxostearic acid; PFAS, poly- and perfluoroalkyl substances; PGE_2, prostaglandin E_2; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; ROS, reactive oxygen species; RR, relative risk; S1P, sphingosin-1-phosphate; S1PR, sphingosin-1-phosphate receptor; SCFA, short-chain fatty acid; SFA, saturated fatty acid; SHFA, saturated hydroxy fatty acid; SMase, sphingomyelinase; SMCFA, short- and medium-chain fatty acid; SPL, sphingosin-1-phosphate lyase; SPPase, sphingosin-1-phosphate phosphatase; STAT, signal transducer and activator of transcription; TAG, triacylglycerol; TLR, Toll-like receptor; TVA, trans vaccenic acid; wt%, weight percent.

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1. Introduction

Milk, as the newborn's first encounter with external energy and developmental components, is of great importance for physical and mental development. Due to its complex composition, milk has been a constant topic of research for decades. Milk has to provide functions in growth and ensuring or improving the survival chances of infant individuals. Research is therefore focused on revealing the secret bioactivities of major components like protein or lipid constituents. This review will address the specific role of cow's milk fats in tumor development and carcinogenesis. As illustrated in Fig. 1, bovine whole milk is composed mainly of about 87 weight percent (wt%) water, 4–5 wt% lactose, 3 wt% protein, 0.8 wt% minerals like calcium, potassium, magnesium, phosphorous, or zinc, 0.1 wt% vitamins (mainly vitamin A, C, D, E, B_1, B_2, B_3, B_6, B_{12}, folate) and 3–4 wt% fat [1,2].

Low-fat, reduced fat, and skim milk contain only about 1.6 and 0.2 wt% fat, respectively [3]. Human milk contains remarkably less protein, calcium, and phosphorous with comparable fat content compared to cow's milk [4]. The fat fraction is almost quantitatively packed in globules, originating from the endoplasmic reticulum (ER) of the mammary secretory cells. The triacylglycerols (TAGs) are specifically found at focal points on the ER membrane or between its bilayer [5,6]. There the lipid droplets form and grow to be finally released into the cytosol, coated with a primary monolayer membrane of proteins and polar lipids from the half of the ER membrane with a diameter ranging from<1 μm to 10 μm which are emulsified in the aqueous phase [7]. These milk fat globules (MFGs) with a mean diameter of 4 μm consist of a TAG-rich lipid core, which is subsequently coated by a bilayer from the apical membrane of the lactating cells, called in combination with the ER monolayer the milk fat globule membrane (MFGM) [8–11]. The MFGM consists primarily of polar lipids and membrane-bound proteins, enzymes (mostly hydrolases, oxidoreductases, and transferases), and glycoproteins and acts as an emulsifier preventing agglomeration by electrostatic and steric repulsion and enzymatic degradation of surrounded fat [12,13]. As shown in Fig. 1, milk fat globules make up about 95% by weight of the total fat content of cow's milk and consist of more than 98% TAGs [8].

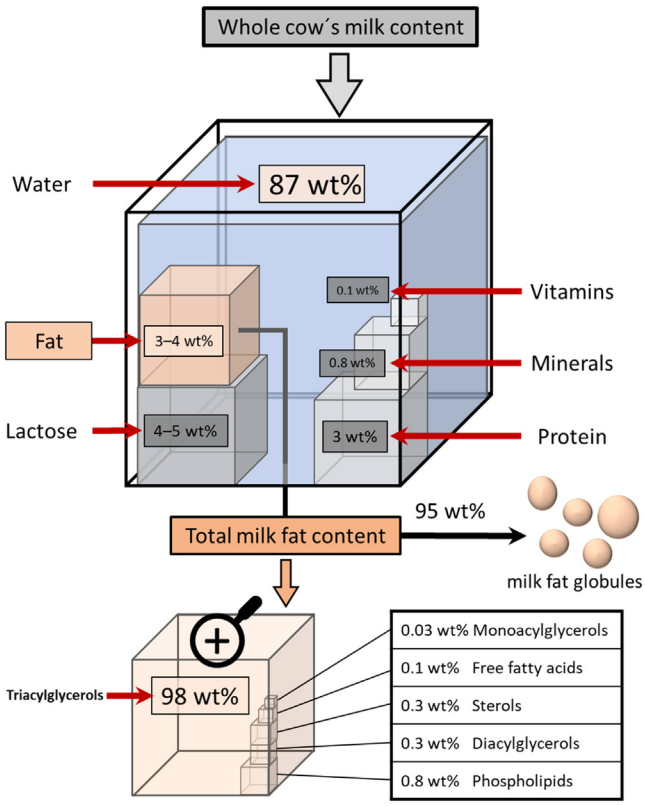


Fig. 1. Approximate composition of whole cow's milk, and particularly the fat content. For better comparability, the respective milk components are shown in cubic form according to their percentage by weight. The total fat content of cow's milk is likewise displayed in enlarged size, with the main components also shown in cubic form in content in percent by weight (mainly triacylglycerols [about 98 wt%]). Approximately 95 wt% of the milk lipids are packed in milk fat globules within their membrane or as triacylglycerols in their lumen and less are present in free form in milk.

1.1. Composition of milk lipids

The composition of bovine milk fat includes mainly TAGs (>98 wt%), followed by diacylglycerols (DAGs; 0.3 wt%), monoacylglycerols (0.03 wt%), free fatty acids (FFAs, 0.1 wt%), phospholipids (0.8 wt%), and sterols (0.3 wt%), followed by trace amounts of carotenoids, fat-soluble vitamins, and flavor compounds [14] (Fig. 1).

Interestingly, about 65% of the phospholipids are part of the MFGM with the rest in the aqueous phase [15]. More than 400 different fatty acids (FAs), from which only about 15 have a share of more than one percent, hereby form the diverse composition of the milk lipids [14,15]. In general, FAs in milk, as shown in Fig. 2, are classified according to their chain length into short-chain (SCFA;<6:0), medium-chain (MCFA; 6:0–12:0), and long-chain (LCFA; >14:0) FAs, with dairy science classifications considering caproic acid (6:0) often to be a SCFA, although it is generally referred to as the shortest MCFA. Alternatively, FAs whose hydrocarbon chains contain between 1 and 12 carbon atoms are also grouped together as short- and medium-chain fatty acids (SMCFAs). About two thirds of the milk FAs are saturated, the rest mainly mono- and polyunsaturated. Of these most common, in bovine milk are mainly found the saturated FAs (SFAs) myristic (14:0, 11.1 wt% or 11.1 mol%), stearic (18:0, 12.2 wt% or 9.8 mol%), and palmitic acid (16:0, 27.9 wt% or 24.9 mol%). The saturated SCFA butyric acid (4:0) only accounts for a share of 3.9 wt% due to its small size, but has a much larger mole fraction of 10.1 mol% [16]. The most abundant monounsaturated FA (MUFA) is oleic acid (18:1, 17.2 wt% or 13.9 mol%) in its cis-configuration, the most common transisomer of an 18:1 FA (vaccenic acid) accounts for 3.9 wt% or 3.2 mol%. The polyunsaturated FAs linoleic acid (LA; 18:2), the isomers of conjugated LA (CLA) and the triunsaturated FA α-linolenic acid (ALA; 18:3) have a portion of some more than 1 wt% each (Fig. 2) [15].

1.2. MFGM lipids

The specific lipid composition of the MFGM mainly includes polar phospho- and sphingolipids, cholesterol (90% of the total sterols [17]) and other minor components. As shown in Fig. 3A, glycerophospholipids consist of a glycerol back with two esterified FAs and a phosphate on the third hydroxyl group linked to different organic substituents like choline, ethanolamine, serine, or inositol .

The share of glycerophospholipids in the total mass of the separated MFGM is about 15–33%. The main representatives are phosphatidyl choline, phosphatidyl ethanolamine, and phosphatidyl inositol with 36%, 30%, and 11% proportion of the total phospholipids [18]. Sphingolipids possess sphingosine, a monounsaturated 18-carbon amino alcohol with two hydroxyl groups and an amino

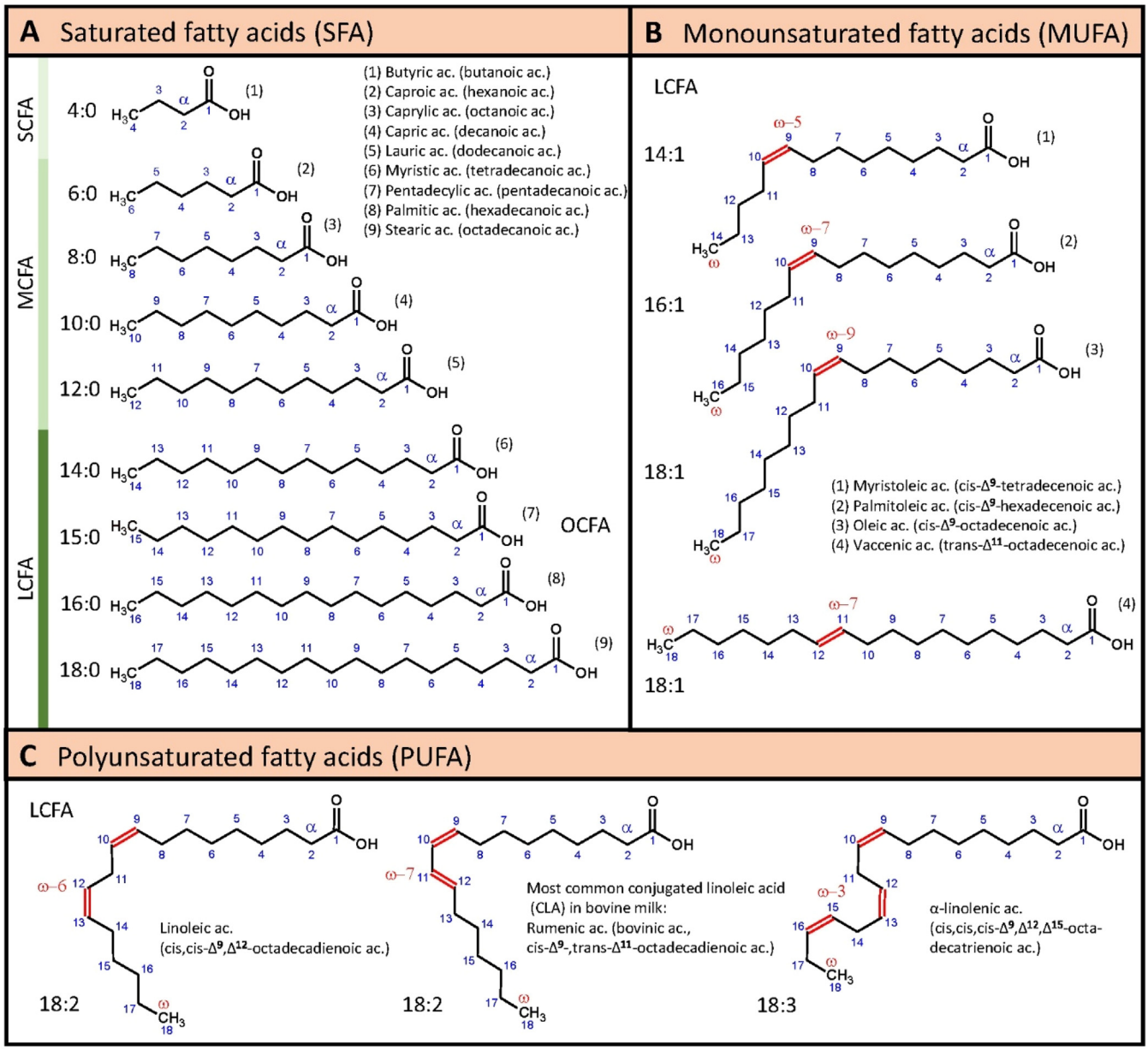


Fig. 2. Major FAs present in cow's milk fat with a weight proportion of over 1% within the fat fraction sorted by saturation status: saturated, monounsaturated, and polyunsaturated. (A) The most common SFAs include SCFAs, MCFAs, and LCFAs, which have an even chain length, with the exception of pentadecyclic acid (15:0), which is an OCFA. (B) The MUFAs are LCFAs, mainly in cis-configuration. The main trans-18:1 FA is vaccenic acid (30–60% of total trans-18:1, [15]). (C) The di-unsaturated FAs LA and rumenic acid, the principal isomer of the CLA (80–90%, [15]), together with the tri-unsaturated FA ALA are the most common PUFAs in bovine milk. The names of the main representatives are given in the delta nomenclature (blue), in addition the numbering corresponding to the omega nomenclature is shown in the structural formulas of the MUFAs and PUFAs (red). Abbreviations: ac., acid; ALA, α-linolenic acid; CLA, conjugated linoleic acid; FA, fatty acid; LA, linoleic acid; LCFA, long-chain fatty acid; MCFA, medium-chain fatty acid; MUFA, monounsaturated fatty acid; OCFA, odd-chain fatty acid; PUFA, polyunsaturated fatty acid; SCFA, short-chain fatty acid; SFA, saturated fatty acid. The chemical structures were drawn using ChemSketch.

group linked with a FA, as base. Depending on the different substitutes of the 1–hydroxyl group, there are three main subclasses of sphingolipids, which can be seen in Fig. 3B: (1) ceramides (substitute: hydrogen), (2) sphingomyelins (substitute: phosphocholine, phosphoethanolamine), and (3) sphingoglycolipids (substitute: saccharide). Sphingomyelins account for about 25% of total MFGM phospholipids [18], the other sphingolipids occur in smaller proportions. Probably during the experimental separation of the MFGM from the fat globule cores neutral lipids like TAGs and to a minor extent DAGs appear as components of the MFGM as well. MFGM mass accounts for about 2–6% of total fat globules mass [19].

Finally, it should be considered that the physical structure and thus the composition and functional properties of the milk fat globules are severely impaired after industrial milk processing such as pasteurization, homogenization, or churning. In this context fat globule size is reduced and the composition of the MFGM is altered through loss of phospholipids and adsorption of caseins and whey proteins [20,21].

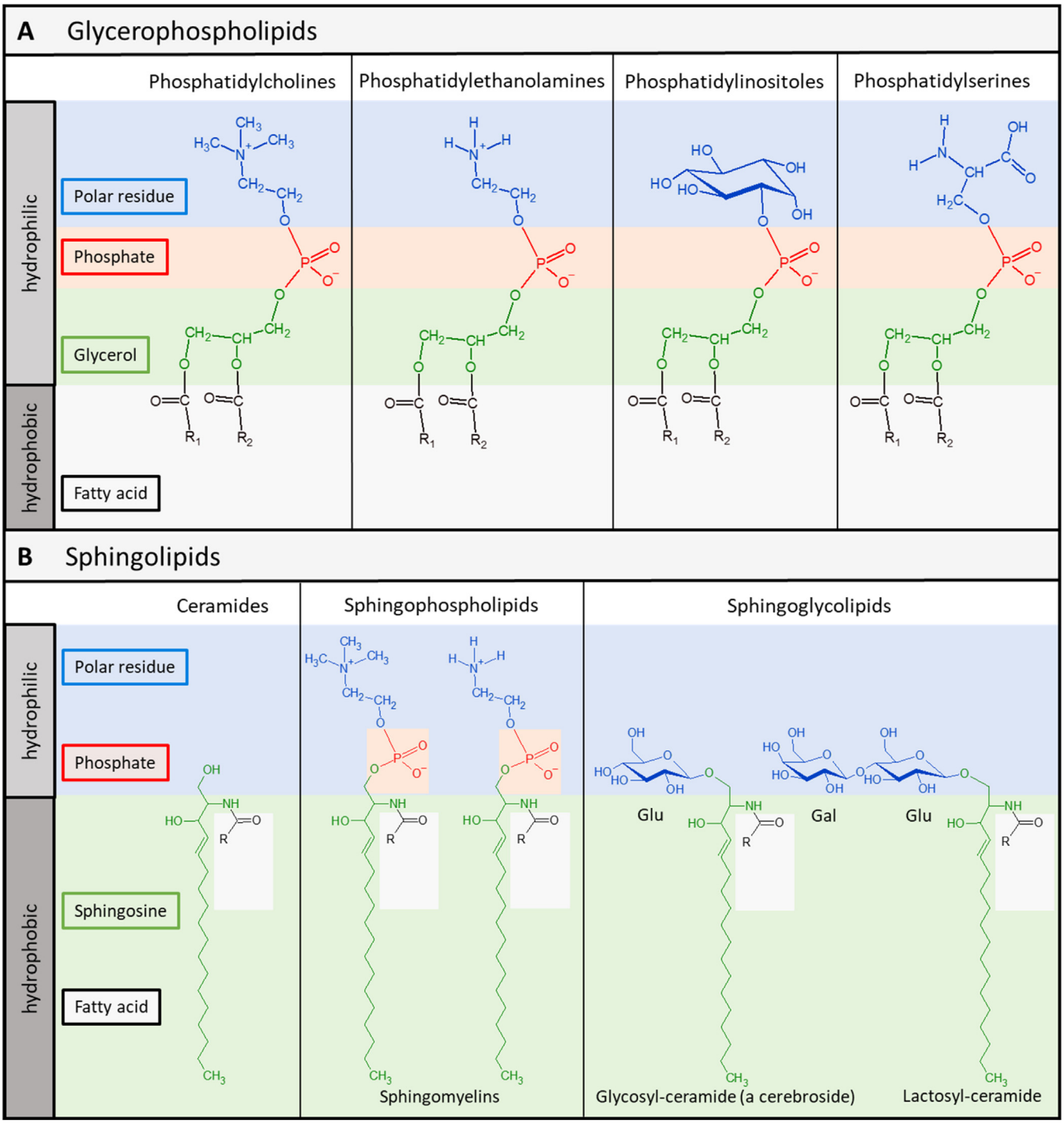


Fig. 3. Main membrane lipids of the MFGs of bovine milk. (A) Glycerophospholipids consist of a hydrophobic FA tail and a hydrophilic head consisting of the glycerol backbone and a polar group linked by a phosphate. (B) Sphingolipids consist of a hydrophobic sphingosine tail esterified with a FA and a polar head group (except ceramides). The polar groups of sphingophospholipids (sphingomyelins) are linked by a phosphate to the sphingosine tail. In sphingoglycolipids, on the other hand, no polar phosphate group is present. Abbreviations: FA, fatty acid; Gal, galactose; Glu, glucose; MFG, milk fat globule. The chemical structures were drawn using ChemSketch.

1.3. Anti-cancer effects of MFGM components

MFGM has a protein to lipid weight ratio of about 1:1 [22] and some of the main proteins are already known for their antitumoral effects like fatty acid binding protein (FABP), which inhibits the growth of breast cancer cell lines *in vitro* [23,24], or breast cancer susceptibility gene (BRCA) 1 and BRCA2 as oncosuppressor proteins [25,26]. Experiments with native MFGM isolate from raw milk (100 μg protein MFGM/mL) revealed anticarcinogenic effects on colorectal carcinoma cell line HT-29 by reduction of cell proliferation and activation of caspase-3 [27]. These effects can be attributed to some phospholipid components besides proteins. Sphingomyelin can suppress colon carcinogenesis by reducing the number of aberrant crypt foci (ACF) and colonic adenocarcinomas in a mouse model (CF1 mice, supplemented with 0.05 wt% sphingomyelin to the diet), sphingosine and ceramide induce

apoptosis in human adenocarcinoma cell line HT-29, and feeding sphingolipids to multiple intestinal neoplasia (Min) mice reduces the number of intestinal tumors [28,29]. Hereby the present 4,5-trans double bond seems to be necessary for the inhibitory effects of ceramide but not for sphingoid bases shown in comparative studies using HT-29 and HCT-116 human colon cancer cells [30].

Further experiments with the sphingolipids glucosylceramide, lactosylceramide, and ganglioside D_3 (GD_3) fed at 30 mg/kg body weight to 1,2-dimethylhydrazine (DMH)-treated female CF1 mice over 4 weeks showed likewise a significant reduction of ACF by>40% [31]. It needs to be mentioned that sphingolipids are not absorbed intact by the intestinal tract but are subject to sequential cleavage by sphingomyelinase (SMase) and/or glycosidase, respectively [32,33], to obtain ceramide, which can be further hydrolyzed by ceramidase to sphingosine [34]. These major breakdown products are most likely to reduce cell growth, influence cell differentiation, or induce apoptosis. So, the digestive products of dietary sphingolipids could probably circumvent defects in the adenomatous polyposis coli (APC)/β-catenin regulatory system, which are often associated with colon tumors like experiments with C57B1/6J$^{Min/+}$ mice expressing a truncated APC protein after being fed with supplemented ceramide, sphingomyelin, glucosyl-, lactosylceramide, and GD_3 suggest [35]. However, it should also be mentioned at this point that in intestinal cells formed sphingosin-1-phosphate (S1P) by sphingosine kinase 1 (Sphk1), which acts as a ligand for the endothelial differentiation genes family of G protein-coupled receptors, also called S1P receptors (S1PRs), stimulates cell proliferation and angiogenesis while suppressing apoptosis [36,37]. To maintain a dynamic intracellular equilibrium between S1P and sphingosine with preferable low intracellular S1P levels, S1P is degraded back to sphingosine by S1P phosphatases (SPPases) or type 2 phosphatidate phosphohydrolases, alternatively, it can be split by S1P lyase (SPL) to ethanolamine phosphate and the remaining long-chain aldehyde (hexadecenal, palmitaldehyde) [38,39]. In colon cancer tissue SPL and SPPases were found to be downregulated in comparison with healthy colon tissue shifting the balance in the direction of S1P which may lead to tumor progression by driving polyp enlargement and stimulating tumor angiogenesis [40]. Further, in a F344 rat's model with azoxymethane -induced colon carcinomas, Sphk1 overexpression could be observed [41]. A similar situation applies in the case of ceramide, which can be phosphorylated by ceramide kinase in the Golgi to form ceramide1-phosphate (C1P) [42]. C1P was shown to be mitogenic and antiapoptotic thereby favoring tumorigenesis and tumor spreading [43,44].

Intestine alkaline SMase activity was found to be decreased by 75% in human colon cancer tissues, acidic and neutral SMase activity by 30% and 50%, respectively [45], but no change in ceramidase activity. In further studies molecular and pharmacological inhibition of neutral ceramidase (nCDase) was followed by decreased colon cancer cell survival, increased apoptosis, and autophagy without seriously affecting noncancerous cells [46].

Regarding the potentially positive effects of MFGM components in milk, there is still controversy as to the extent to which these are altered by milk processing. The diameter of MFGM droplets in bovine milk is usually 4–5 μm. However, their size and composition can differ depending on various factors, such as cow breed, homogenization, processing, and storage temperature. This can result in a size and surface composition that differs drastically from that of native milk fat globules. For example, homogenization can reduce the size of MFGM droplets to 0.5–1 μm [47]. It is not yet known whether and how these structural and compositional changes can alter bioavailability and possible beneficial effects. However, there is some evidence that smaller globules have a higher bioavailability, which could enhance potential health benefits [48].

1.4. MCFA

MCFAs with their aliphatic chain length of 6 to 12 carbon atoms play a special part as natural compounds with anticancerogenic properties. They are, *e.g.*, recognized for their ability to sensitize various cancer cells *in vitro* to ferroptosis, a form of iron-dependent cell death caused by the production of reactive oxygen species (ROS) via the Fenton reaction. This type of programmed cell death occurs through the formation of peroxides resulting from the excessive oxidation of polyunsaturated lipids in cellular membranes. A recent study conducted by Han et al. [49] revealed that lauric (C12), caprylic (C8), or capric acid (C10) can enhance the ferroptosis induced by RSL3 (an inducer of ferroptosis) or LA in U937 cells (human leukemia), A549 cells (human lung cancer), LLC cells (Lewis lung cancer), and RINm5F cells (rat insuloma) by upregulating FA transporter CD36 or acyl-CoA synthetase long-chain family member 4 (ACSL4), an enzyme related in lipid peroxidation. In an *in vitro* study by Narayanan et al. [50], the treatment of human breast and skin cancer cells with capric, caprylic, and caproic acids for 48 h was found to decrease cell viability by 70–90% . Furthermore, lauric acid demonstrated antitumor efficacy against the colorectal cancer cell lines CT26 and HT-29 *in vitro* through ROS accumulation and induction of apoptosis, and *in vivo* additionally through enhanced tumor immune infiltration [51]. In a recent study by Roopashree et al. [52], treatment of human breast cancer cells with the MCFAs caprylic and lauric acid inhibited proliferation of tumor cells by increasing ROS levels and inducing G0/G1 and S phase cell cycle arrest. Additionally, MCFA treatment was found to increase the expression of the proapoptotic proteins Bcl-2 homologous antagonist killer (BAK) and caspase 3, while reducing the expression of phosphorylated epidermal growth factor receptor (EGFR), Akt and mammalian target of rapamycin (mTOR). Caproic (hexanoic) acid was further investigated in a BALB/c mouse colorectal cancer model (inoculation of mouse CRC line CT26) experiment with an oral dosage of 2,760 mg hexanoate/kg/day. Observed suppression of carcinoma growth was mediated by mainly decreased Treg-mediated inhibition of $CD8^+$ *T* cells, and furthermore hexanoate was able to enhance the effectiveness of immune checkpoint inhibition therapy using programmed death-1 (PD-1) antibodies [53]. Results of a prospective study (Southern Community Cohort study) in 2024 concerning the incidence of CRC and MCFA dietary intake revealed a reduced risk of CRC among White participants (hazard ratio (HR)=0.52; 95% confidence interval (CI), 0.30, 0.91; P-trend=0.05), but not in Black individuals (HR=0.92; 95% CI, 0.68, 1.24; P-trend=0.80) when lauric acid intake was higher, but no associations were found for caproic, caprylic, or capric acid [54].

1.5. Hydroxy and oxo fatty acids

Hydroxylated polyunsaturated fatty acid (PUFA) metabolites derived from the milk omega-3 fatty acids docosahexaenoic (DHA), eicosapentaenoic acid (EPA), or *n* - 3 docosapentaenoic acid (DPA) belong as so-called resolvins together with lipoxins, protectins, and maresins, which are derived from arachidonic acid and DHA or *n* - 3 DPA, to a class of signal mediators with protective properties, also known as specialized proresolving mediators [55].

Overall, hydroxy FAs (HFAs) account for less than 1% of the total FAs and are as 2-HFAs common constituents of sphingolipids like sphingomyelin, glucosylceramide and lactosylceramide [56], and as 3-HFAs as intermediates of FA synthesis via the malonyl-CoA pathway [57]. Fig. 4 illustrates certain saturated HFAs (SHFAs), which are less characterized as signaling molecules, but seem to

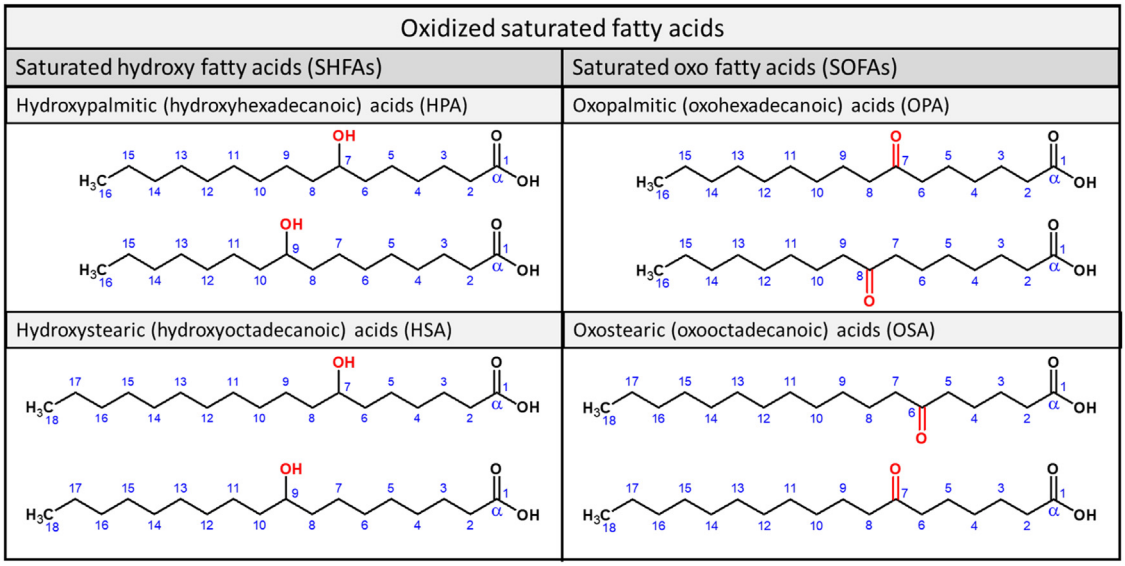


Fig. 4. SFAs with a hydroxy or oxo group. Shown are the palmitic and stearic isomers of the corresponding hydroxy (HPAs and HSAs) and oxo (OPAs and OSAs) FAs with the strongest growth-inhibitory effects in *in vitro* experiments with cancer cells [60]. Abbreviations: FA, fatty acid; HPA, hydroxypalmitic acid; HSA, hydroxystearic acid; OPA, oxopalmitic acid; OSA, oxostearic acid; SFA, saturated fatty acid. The chemical structures were drawn using ChemSketch.

exert anticancerogenic properties. A study investigating different isomers of hydroxystearic (HSA) and hydroxypalmitic acids (HPA) showed growth-inhibitory effects against different human cancer cell lines, including A549 (epithelial lung carcinoma), Caco2 (colorectal adenocarcinoma), and SF268 (astrocytoma) [58]. Interestingly, the SHFAs tested showed no growth-inhibiting potential on U87-MG (brain glioblastoma), so the effect is cell line specific. Especially, hydroxyl groups at positions 7 or to a lesser extent 9 of the stearic or palmitic chains were most potent at concentrations over 25 μM after 72 h treatment in the performed 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay compared to hydroxyl groups at positions 2, 10, or 12 [58]. Calculated half-maximal inhibitory concentration (IC_{50}) values for the three cell lines were in the range of 27–55 μM in the case of both (*R*)- and (*S*)-enantiomers of the 7–hydroxy compounds. Investigation of the mode of the cell cycle arrest showed reduced phosphorylation of histone H3, but no increase in activated caspase 3. Further signal transducer and activator of transcription (STAT) 3 and phospho-STAT expression was downregulated both at mRNA and protein levels [58].

Another class of SFAs, shown in Fig. 4, are saturated oxo or keto FAs (SOFAs). In particular, the representatives of oxopalmitic acid (OPA) and oxostearic acid (OSA) should be mentioned here, some of which have a cell growth-inhibiting effect. Of the various OPA and OSA isomers, 10OPA and 7OPA as well as 10OSA, 9OSA, 8OSA, and 7OSA are mainly found in cow's milk in concentrations of 43.6–96.9 μg/mL [59]. In direct comparison, the OSAs were able to reduce the cell growth of A549 cancer cells more effectively than the OPAs, in particular OSAs with the oxo function in positions 5, 6, 7, and 8, respectively, with IC_{50} values between 26 and 49 μM [60]. In further experiments the OSAs showed concentration-dependent cell growth inhibition in other cell lines as well (Caco2, SF268), starting at a concentration of 50 μM. In this study, the most potent OPAs were 7OPA and 8OPA. Furthermore, a recent study has shown that hydroxy stearic acids were able to reduce the cell viability of pancreatic cancer cells while simultaneously reducing STAT3 signaling and the expression of various proteins involved in the respiratory chain in these tumor cells [61]. Interestingly, HPAs and HSAs are also found in significant quantities in human breast milk, with 16 HPA and 7HSA being the predominant isomers among others [62].

1.6. Anti-cancer effect of CLA

The multiple isomers (a total of 28 options) of the diunsaturated C18 FA LA (18:2 cis-9,12), a $\omega-6$ PUFA with two double bonds with cis-orientation, are collectively referred to as CLA, as shown in Fig. 5.

Precursor FA molecules are C18-FAs from the diet, *e.g.*, LA and ALA, which are hydrogenated by rumen bacteria and in certain cases additionally desaturated by Δ^9-desaturase like transvaccenic acid (TVA, C18:1 t11) [63,64]. The double bonds of CLAs are always separated by a single bond, but can be distributed over the aliphatic tail (from position 6–14 with 4 different isomeric configurations each) with cis-9, trans-11 CLA being the major isomer (about 56.7–79.7 wt% of CLA isomers of 0.56–0.95 wt% total FA methyl ester (FAME) [7]) depending on cows feeding in ruminant fat and therefore also called rumenic acid or bovinic acid. CLA double bond at positions trans7, cis-9 or trans-10 and cis-12 are also common with positions 8 and 10, 11 and 13, or 12 and 14 only in trace amounts. The fat content of cow's milk contains about 2–53 mg/g CLA, making it the richest source of CLA in the diet [63]. Since long, anticancerogenic effects of CLA were reported, *e.g.*, in a two-stage mouse epidermal carcinogenesis experimental system [65], with reduced papilloma development and lowered tumor incidence after CLA-treatment published in 1,987. Since then, many animal studies to investigate the effects of CLA in the context of mammary cancer were conducted. Hereby CLA-enriched diet often inhibited tumor initiation or its progression in rodents. For example, female rats with 7,12-dimethylbenz(a)anthracene-induced mammary tumors showed reduced numbers of adenocarcinomas, tumor weight, and decreased tumor incidence after being fed with diets enriched with a mixture of CLA isomers (0.5–1.5w%) [66]. Interestingly, only the c9,t11 isomer appeared to accumulate in liver and mammary tumor lipids, which may contribute to antitumor protection, as shown in another study in which withdrawal of CLA-rich diet was associated with the appearance of new tumors after the disappearance of CLA in primarily neutral lipids [67]. In an

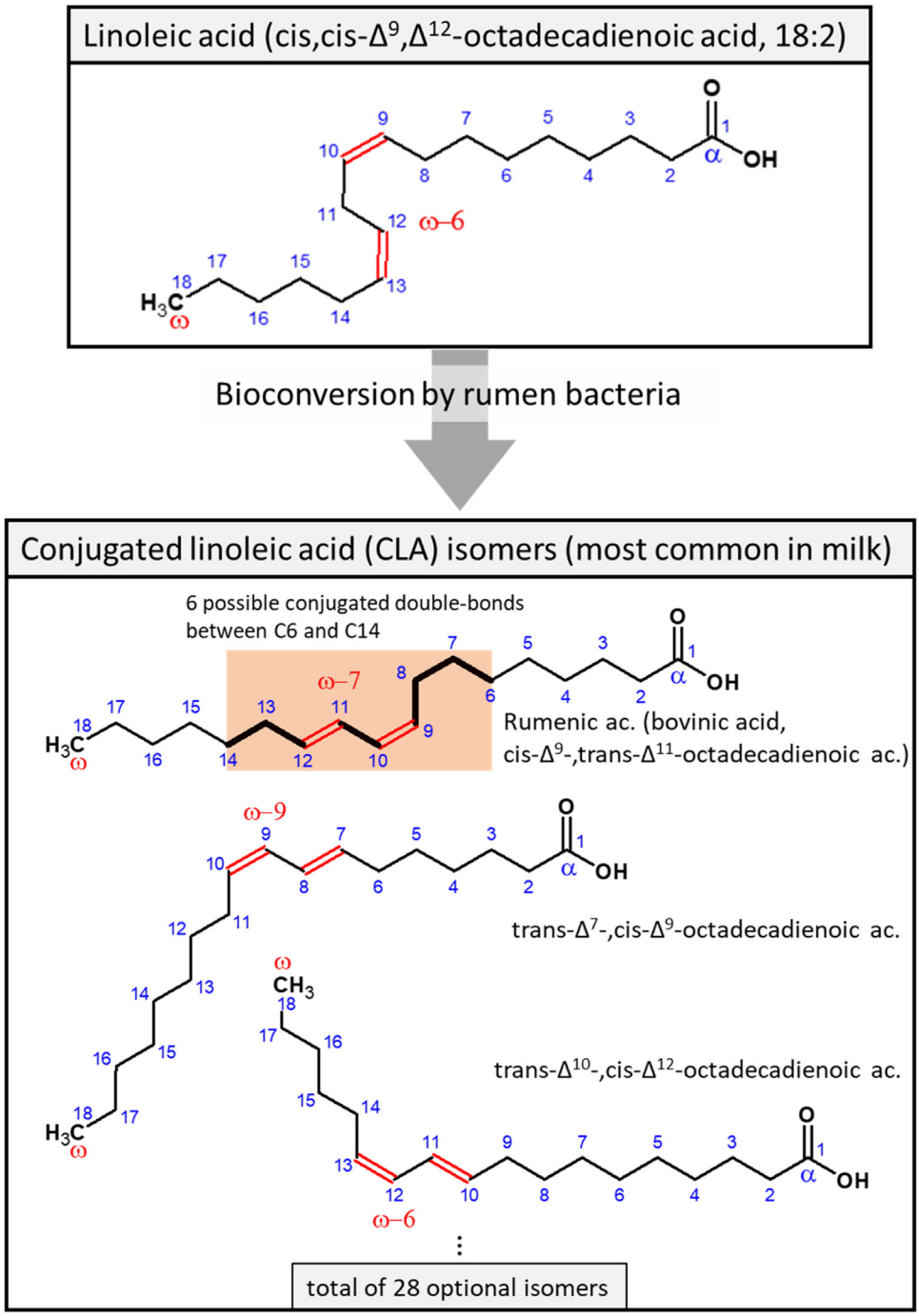


Fig. 5. Main CLA isomers in cow milk. Shown are the three most common CLAs in milk out of a total of 28 possible isomers. The area (C6 to C14) of the 6 possible conjugated double bonds, which can be cis- or trans-orientated, is marked in color. The possible precursors FAs LA or the tri-unsaturated ALA (not shown) can be isomerized, hydrogenated, or desaturated by rumen bacteria to form various CLAs. Most common is the cis-9, trans-11 isomer, followed by trans-7, cis-9 and trans-10, cis-12. The names of the main representatives are given in the delta nomenclature (blue), in addition the numbering corresponding to the omega nomenclature is shown in the structural formulas (red). Abbreviations: ac., acid; ALA, α-linolenic acid; CLA, conjugated linoleic acid; FA, fatty acid; LA, linoleic acid. The chemical structures were drawn using ChemSketch.

N-nitroso-N-methylurea (NMU)-inducible rat tumor model, c9,t11 CLA and an isomeric CLA mixture increased apoptosis rates while decreasing of Bcl-2 expression in premalignant lesions without affecting BAK or Bax proteins [68].

In numerous cell culture studies with different human breast cancer cell lines (*e.g.*, MCF-7, MDA-MB-231, T47D, SKBr3) treatment with CLA in different isomeric mixtures (especially consisting of c9,t11 and t10,c12 CLA), mostly in comparison to LA as control, often showed reduced growth rates, cell viability, and concentration-dependent cytotoxicity [69–76]. The effective concentration range of treatment was about 10–200 μM of CLA variants, which corresponds to physiological human serum conditions with measured CLA concentrations of 10–70 μM with up to 350 μM in individuals taking CLA long-term supplementation [77]. In comparison, daily consumption of 90 g of sheep's cheese for 3 weeks resulted in plasma concentrations for c9,t11 CLA of 28 μM in humans, which

could be increased to 39 μM by consuming the same amount of CLA-enriched cheese [78].

An influence on further tumor entities was moreover investigated by conducting studies with colon, hepatoma, prostate, or melanoma cell lines. Proliferation-inhibitory effects on the colon cancer cell lines Caco2, HT-29, and DLD-1 were shown to be most pronounced with t9,t11-CLA in comparison with other CLA isomers at a concentration of 200 μM [79]. Similar results were obtained with ductal carcinoma (T47D), melanoma (M4Be), lung (A549), or prostate cancer (PC3) cells [80]. Differential efficacy of CLA isomers was also observed, with t10,c12-CLA being most potent against colorectal cancer proliferation (HT-29, MIP-101) and moderately effective on PC-3 prostate cancer cells compared to its c9,t11 and c9,c11 counterparts, even at a concentration of 50 μM [81].

Mechanistic modes of action include for example cell cycle arrest [70,82] and induction of apoptosis with increased cleavage of effector caspases, reduced Bcl-2 protein levels with simultaneously higher Bax and BAK levels, enhanced p53 expression and cytochrome c release from the mitochondria [73,74,83]. In this context, signaling via peroxisome proliferator-activated receptors (PPARs), whose expression of various isoforms was also affected by CLA, also plays a role in apoptotic cell death and cell cycle regulation [71,84]. Involvement in oxidative stress management was also seen in some studies, *e.g.*, by enhancing lipid peroxidation status, followed by induction of increased superoxid dismutase, catalase, and glutathione peroxidase activity [85–87]. Further, CLA was shown to play a role in the eicosanoid metabolism, which has an impact on cancer cell division and growth, by the reduction of cyclooxygenase-2 protein expression via repression of the transcription activity of its promotor [88,89], which was followed by lowered prostaglandin E_2 (PGE_2) synthesis [76,90]. Another possible mechanism of CLA action could be demonstrated by lowered mRNA and protein levels of estrogen receptor α (ERα) with reduced receptor phosphorylation and nuclear binding to the estrogen response element (ERE) [91,92]. In general, the uptake of CLA isomers also results in different fatty acid compositions in different tissues, as some isomers are incorporated into lipids to a greater extent than others. For example, a higher incorporation rate of the c9,t11 isomer, especially in cholesterol esters and triglycerides, was detected in mouse liver lipids compared to the t10,c12 isomer, which was incorporated mainly in phospholipids [93].

In order to assess the potential impact of CLA on cancer growth, several human studies have been also conducted. After the evaluation of participants of the Swedish Mammography Cohort, a group of more than 60,000 women who were interviewed mainly about nutrition between 1987 and 1990, it was suggested that a high intake of high-fat dairy foods and CLA probably reduces the risk of colorectal cancer [94]. In a Finnish study by Aro et al. [95] postmenopausal women with breast cancer showed significantly lower levels of dietary and serum CLA, myristic acid, and TVA in comparison with the controls and a CLA-rich diet was proposed to be protective against breast cancer. On the other hand, the presumed anticancer potential of CLA could not be validated based on cancer cases in the Netherlands Cohort Study on Diet and Cancer [96].

1.7. Branched-chain fatty acids

As minor constituents of milk lipids branched-chain FAs (BCFAs), which are constituents of bacterial membranes and are processed by ruminal digestion processes, are mostly present as SFAs with a chain length of 14–18 carbon atoms [97,98]. These have methyl branches predominantly at the methyl ends forming a propan-2-yl group (iso) or butan-2-yl group (anteiso), as depicted in Fig. 6.

The anteiso-forms of 15:0 and 17:0 account for more than 50 wt% of the total BCFA content of commercial milk, although they only make up just over 1 wt% of the total FA content with a total BCFA content of milk fat FAs of about up to 2 wt% [98,99]. anticancer properties were examined, *e.g.*, for the 48-h treatment with 13-methyltetradecanoic acid (13-MTD), inducing apoptotic cell death in human cancer cell lines K-562, MCF7, DU 145, NCI-SNU-1, SNU-423, NCI-H1688, BxPC3, and HCT-116 with a half-maximum inhibitory dose (ID50) ranging from 10 to 25 μg/mL (corresponding to 41.25 to 103.14 μM) [100]. In addition, in an *in vivo* experimental approach, administration of 13-MTD to BALB/c mice with orthotopically implanted tumors of the prostate carcinoma cell line DU 145 and the hepatocarcinoma cell line LCI-D35 in the respective mouse organs showed growth inhibition of the respective tumor implants [100]. The content of 13-MTD identified in bovine milk depends on the proportion of concentrated forage fed to the cows [101].

1.8. Downsides of milk lipids

Having stated numerous protective effects of milk lipids on cancer, the picture seems less certain when taking the totality of the evidence into account. Various studies in humans found neutral or even risk-increasing associations (*e.g.*, [102–105]), which somewhat questions milk fat to be innocuous and solely beneficial in the context of cancer. As a cautionary note, since SFAs are most abundant in cow's milk fat, the following includes studies that partially fail to differentiate between SFA from cow's milk *versus* other sources to allow for a more exhaustive database (*e.g.*, [106–109]). Similarly, some studies examined the general intake of dairy products without considering their fat content separately (*e.g.*, [110–112]).

A recent systematic review and meta-analysis of prospective cohort studies implied a positive association between high-fat milk intake and the risk of dying from cancer [113]. This relationship vanished for low-fat milk intake [113]. Following more than 200 000 individuals up to 32 years, researchers found a positive linear association between total milk intake and the risk of cancer mortality, whereby an increase in cancer mortality was observed in a dose-dependent manner with increasing milk intake [114]. For each additional half-serving per day of whole milk consumption, cancer mortality risk increased by 11%, whereas no significant increase in risk of dying from cancer was observed for the consumption of skimmed or low-fat milk, cheese, and yoghurt [114]. A large study conducted across over three decades looked at the association between long-term intake of butter *versus* plant-based oil and cancer mortality: Whereas every 10 g/d increment in butter consumption was linked to a 12% increase in cancer mortality (HR=1.12; 95% CI, [1.04, 1.20]), the equivalent of plant-based oil was associated with a 11% reduction in cancer mortality (HR=0.89; 95% CI, [0.85, 0.94]) [102]. Substitution analysis revealed an estimation that for every 10 g/d of butter intake being replaced by the same amount of plant-based oil the risk of dying from cancer was lowered by 17% (HR=0.83; 95% CI, [0.76, 0.90]) [102]. In a similar vein, a systematic analysis of prospective cohort studies tracking over a million participants' dietary fat intake revealed that diets high in source unspecific SFA were linked to an increased cancer mortality (highest *versus* lowest intake: relative risk (RR)=1.09; 95% CI, [1.00, 1.18]), whereas those high in PUFAs were associated with lower cancer mortality (highest *versus* lowest intake: RR=0.92; 95% CI, [0.89, 0.95]) [106]. This is non-trivial due to almost 70% SFA, but very low quantities of PUFAs contained in cow's milk fat as mentioned earlier [14,15]. According to a separate systematic review and meta-analysis on the relationship between source unspecific SFA and cancer, higher relative to lower dietary SFA intake was related to an increased cancer risk

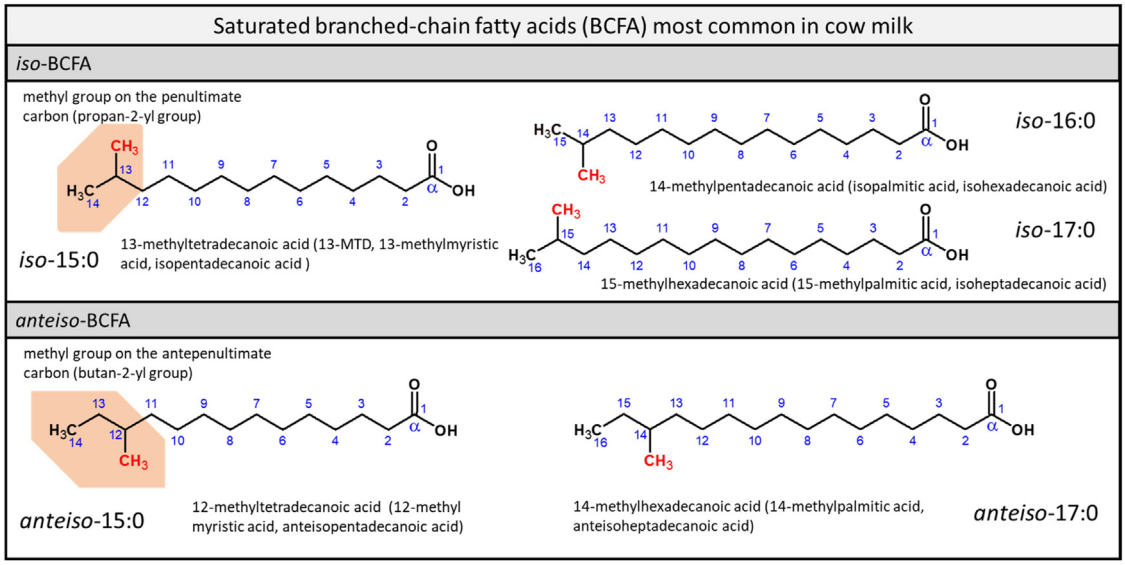


Fig. 6. Saturated BCFAs, which are most common in cow milk. Iso- and anteiso-conformation of the FAs are exemplarily emphasized and the methyl groups are shown in red. The anteiso-15:0 and anteiso-17:0, as well as the iso-16:0 and iso-17:0 have comparable concentrations in cow milk, whereby the concentrations of anteiso-17:0 and anteiso-15:0 are about twice as high. Of the FAs shown, iso-15:0 has the lowest concentration in comparison [98]. Abbreviations: BCFA, branched-chain fatty acid; FA, fatty acid. The chemical structures were drawn using ChemSketch.

(odds ratio (OR)=1.305; 95% CI, [1.172, 1.453]) [115]. More specifically, palmitic acid (16:0), which accounts for approximately 30% of the FAs in milk by weight [14,15], correlated positively with cancer risk (OR=1.267; 95% CI, [1.131, 1.420]) [115]. Higher intakes of stearic acid (18:0), accounting for about 12% of the FAs in milk by weight [14,15], was also associated with a heightened cancer risk (OR=1.177; 95% CI, [1.073, 1.292]) [115]. Further, consuming high amounts of myristic acid (14:0), which accounts for approximately 11% of the FAs in milk by weight [14,15], was linked to an elevated cancer risk (OR=1.191; 95% CI, [1.050, 1.351]) [115]. However, higher intakes of other subtypes of SMFAs such as butyric acid (4:0) and caproic acid (6:0) making up 4.4% and 2.4% by weight [14,15], respectively, indicated no statistically significant relationship with cancer risk.

1.9. Milk lipids and various cancer types

Differentiating between cancer types, higher levels of source unspecific dietary SFA have been found to amplify the risk of breast cancer, prostate cancer, and colorectal cancer, whereas no significant linkage has been found regarding lung cancer, pancreatic cancer, ovarian cancer, and stomach cancer [115]. Yet, research on potential relations between the intake of SFA, including those specifically derived from cowś milk, and other cancer types is still lacking [115]. Contrary to that, another meta-analysis provided evidence for a positive association between total fat, including general SFA intake, and ovarian cancer risk [107]. This is in line with a meta-analysis consisting of case-control and cohort studies, in which whole milk consumption was linked to a heightened risk of ovarian cancer (RR=1.07; 95% CI, [1.03, 1.11]), whereas the intake of low-fat milk reduced the risk (RR=0.95; 95% CI, [0.91, 0.99]) [116].

A large multicentric cohort showed a positive relation between hepatocellular carcinoma risk and the consumption of fat from dairy sources, in a dose-dependent manner, with the highest risk occurring in the group that consumed 381.7 g or more of dairy products daily, whereas fat from nondairy sources was inversely associated [117]. Increased risk of cancer of the oral cavity and pharynx coincided with a heightened intake of butter in an Italian case-control study [118]. Corroborating later findings, an ecological analysis indicated a positive correlation between animal fat consumption and various cancer types [119]. Examining 40 different countries, the consumption of milk, butter, and cheese was associated with a greater incidence of breast-, ovary-, and corpus uteri cancers as well as greater mortality rates of these cancers [110]. In a biobank cohort study of older Chinese citizens (aged>50 years) with a follow up approximately one decade later, higher milk consumption was linked to a 33% increase of total cancer mortality and a threefold increase in esophagus cancer when consuming more than three portions per week relative to no consumption [111]. In addition, a large-scale cohort study conducted in the United States revealed a positive association between liver cancer risk and the consumption of high-fat dairy, high-fat milk, total milk, and dairy, while the consumption of low-fat dairy, low-fat milk, yoghurt, and cheese did not significantly affect liver cancer risk [120]. Milk intake was positively related to the risk of hepatocellular carcinoma, which is the most common pathological type of liver cancer.

Most cancer type specific research has looked at breast and prostate cancer. In a prospective study, Norwegian women who drunk 0.75 L or more of whole milk per day had an almost threefold RR of developing breast cancer compared to those consuming 0.15 L or less [121]. However, for the consumption of low-fat milk or skim milk the risk of developing breast cancer remained unaffected [121]. A meta-analysis concluded that relative breast cancer risk is positively correlated with the intake of milk and cheese [112]. A more recent meta-analysis found that women with a high-fat dairy intake tended to have an increased breast cancer occurrence risk, whereas low-fat dairy intake had the potency to lower that risk [122]. In a cross-sectional study among premenopausal and postmenopausal women a high-fat dairy food intake was positively related to mammographic breast density, which is a marker of breast cancer [103]. Yet, these results were antagonistic in that the intake of low-fat dairy products was inversely associated with breast density [103]. Similarly, in a case-control study consuming dairy products with a high-fat content were related to an increased risk of breast cancer whereas low-fat dairy products seemed to be protective [104]. Women in the United States diagnosed with early-stage primary breast cancer consuming large amounts of high-fat

dairy had an increased risk of breast cancer mortality, whereas low-fat dairy consumption was unrelated to the outcome [123]. Tentative analyses showed that associations between general SFA intake (including nondairy sources) and breast cancer outcome were weaker, which, according to the authors, could possibly argue for a risk uniquely imposed by lipids in dairy products [123]. A recent mendelian randomization study looking at six different cancer types (*i.e.*, breast, ovarian, endometrial, colorectal, prostate, and bladder cancer) found a causal association between the proportion of milk fat intake and breast cancer risk only [105].

Yet, a summary analysis of prospective studies yielded no significant association between animal fat intake (including sources from dairy) and breast cancer [108]. Moreover, a further mendelian randomization study found no statistically significant relationship between SFA intake (source unspecific) and breast cancer [109]. In a cohort study among North American women, higher consumption of dairy milk was associated with an increased HR of breast cancer 1.50 (95% CI, [1.22, 1.84]), whilst substituting dairy milk with soy milk considerably reduced HR to 0.68 (95% CI, [0.55, 0.85]) [124]. Since the results were similar between high-fat and low-fat milk, milk fat may not explain the marked risk increase in breast cancer [124]. This points to rather inconclusive evidence with respect to milk fat intake and the link to breast cancer.

Examining men diagnosed with prostate cancer, the risk of lethal prostate cancer was elevated by an increase in whole milk intake (highest *vs.* lowest intake HR=2.15; 95% CI, [1.28, 3.60]), whereas the risk decreased by increasing the intake of low-fat dairy (highest *versus* lowest intake HR=0.62; 95% CI, [0.40, 0.95]) [125]. Tracking a cohort of North American physicians over a period of 28 years, high *versus* low whole milk intake was associated with an elevated risk for fatal prostate cancer [126]. Yet, the skim or low-fat analogue showed merely a positive relationship with the risk of low-grade, early stage, prostate cancer and cases detected by screening [126]. According to a meta-analysis of population-based cohort studies, whole milk intake elevated prostate cancer mortality in a dose-proportional manner [127]. A prospective cohort study of Japanese men showed an elevated risk of prostate cancer with an increased intake of dairy products – specifically myristic and palmitic acid were related in a dose-dependent manner [128]. Palmitate, which is abundant in cow's milk] [15], has been shown to interact with oncogenic factors (Src kinase) in promoting prostate tumorigenesis [129]. In contrast, according to a meta-analysis of prospective cohort studies high *versus* low intakes of whole milk was associated with a lower RR of prostate cancer, whereas high *versus* low intakes of low-fat milk was related to an increased RR [130]. Unlike other data, these results suggest that other components of milk than its fat content may be the culprit [130]. As systematically reviewed by Sargsyan and Dubasi [131], it remains unclear whether the majority of findings hinting at a positive link between milk intake and prostate cancer risk are explained by the fat content in milk, nonfat constituents, or both.

1.10. Beyond observational exploration

Epidemiological data fail to elucidate the underlying causal mechanisms. In observational studies, biases may occur due to confounding factors that were not sufficiently controlled for. For example, high-fat diet induced obesity could be responsible for suppressing antitumor immunity [132], emphasizing that studies need to adjust not only for body mass index and physical activity (*e.g.*, [106]), but also for total caloric intake. The overconsumption of calories, which happens easily by the intake of milk fat due to its high energy density, can lead to excess body fat (*e.g.*, [133]), which itself constitutes a heightened risk factor for cancer incidence as reviewed by Anderson et al. [134]. Excess body weight is associated with increased activity in inflammatory pathways [135], which is causally related to cancer development (reviewed in [136]). More specifically, some evidence suggests that SFA can activate Toll-like receptor 4 (TLR4) or TLR2-mediated proinflammatory signaling pathways ([137,138]; reviewed in [139–141]), which have been linked to tumorigenesis (reviewed in [142]). Exploring acute effects within a randomized controlled trial (RCT) revealed that consuming a single meal containing SFA impaired the arterial endothelial function and the anti-inflammatory activity of high-density lipoproteins (HDL) (whereas PUFA improved these properties) [143], which has potential deleterious effects with respect to cancer in the long run [144]. Red blood cell phospholipid SFA, which reflect dietary intake of a few months, have been found to be positively linked to proinflammatory markers, whereby palmitic acid was predicting interleukin-6 (IL-6), and stearic acid was linked to C-reactive protein [145], mirroring mechanisms possibly related to cancer risk (reviewed in [146]). SFA create ROS that mutate the p53 tumor suppressor protein, which in turn is known to be critical in prostate cancer progression (reviewed in [147]). Moreover, miRNAs of milk damage p53-dependent gene regulatory pathways which also promotes prostate cancer risk [148]. Thus, different compounds in milk and several mechanisms may be at play – working in direct or secondary pathways.

1.11. Substitution studies

Summarizing 15 RCTs, in which interventions were conducted to reduce SFA intake for at least 2 years by replacing them with PUFA, MUFA, carbohydrates, or protein, showed little or no effect on cancer diagnosis and cancer deaths – yet the authors highlighted that the evidence is of insufficient completeness and quality [149]. Adding to the controversy, a recent summary of multiple systematic reviews suggests that only very low to low certainty evidence exists that the reduction or replacement of SFA intake is linked to a very small reduction in risk for cancer incidence and cancer mortality [150]. However, a very recent systematic review and meta-analysis of RCTs replacing cow's milk with soymilk in the diet provided the indication of improving humans' lipid profile, blood pressure, and inflammatory markers [151], which is beneficial for disease prevention with no exemption for cancer ([152]; reviewed in [146,153]).

1.12. Early life exposure

Most prospective studies focused on adults in midlife instead of early life exposure which seems critical for cancer risk later in life (reviewed in [154,155]). A cohort study in the UK found that colorectal cancer risk in adulthood almost tripled when comparing high and low total dairy or milk intake during childhood [156], but this investigation lacks in analyzing milk fat separately. In a Norwegian study, childhood milk consumption was associated with lower breast cancer risk in young (but not older) women, yet the milk fat consumed during childhood did show neither beneficial nor harmful effects on adult breast cancer [157]. Data collected in a meta-analysis, albeit limited, suggested that milk intake during childhood and adolescence and cancer risk later in life are orthogonal – even if stratified according to the milk's fat content (reviewed in [158]).

2. Metastases

Metastasis formation is the most predictive causal factor leading to death in individuals suffering from cancer [159,160] – being responsible for ~90% of cancer deaths (reviewed in [161]).

Meta-analytical findings indicated that not total dietary fat intake per se, but in particular SFA intake (source unspecific) negatively affects breast cancer survival (highest *versus* lowest intake: HR=1.51; 95% CI, [1.01, 2.09]) [162]. According to a prospective study, high-fat milk intake in patients diagnosed with localized prostate cancer was associated with a 600% increase in dying from cancer, whereas low-fat milk intake did not increase the risk [163]. In a dietary intervention study on women with resected early-stage breast cancer, researchers found lowering general fat intake (SFA intake by about 40%) led to a 24% reduction in risk to relapse after a five-year follow-up compared to the control group [164]. Similarly, in a dietary intervention study designed to reduce general fat intake, women who were diagnosed with breast cancer during that intervention period showed an increased overall survival rate compared to the control group [165]. Furthermore, in a 2-year study, skin cancer patients in the reduced general fat-intake intervention group had ten times lower cancer occurrence in the last 8-month period compared to the control group [166].

The FA receptor CD36 has been identified as having a high potency to initiate metastases, which is amplified by an overall high-fat diet or the dietary FA palmitic acid [167]. In fact, when treating cells with palmitic acid, CD36 expression can be unregulated by up to a 50-fold increase within 12 h [168]. Making up a considerable proportion of fat found in dairy products (reviewed in [169]) palmitic acid acts as a signaling molecule in the formation and progression of diseases like cancer [170]. CD36 serves as a biomarker for glioblastoma progression CD36 and is predictive for patients' survival rate [171]: individuals with tumors of low CD36 expression lived significantly longer relative to those with tumors of high CD36 expression [171]. Similarly, breast cancer survival rate dropped for patients with increasing levels of CD36 expression suggesting that high expressions of CD36 boosts proliferation and migration of breast cancer cells [172]. Inhibiting FA receptor CD36 inhibits the migration and invasion of breast cancer cells [173]. Similar results between CD36 and FA uptake and cancer cell proliferation have been found with regards to ovarian cancer and metastases [174] as well as prostate cancer [175].

Almost half of the patients diagnosed with cancer undertake dietary changes as a response to their diagnosis in the hope of improving their cancer outcome, amongst which the elimination of food groups like milk is popular (reviewed in [176–179]). Whether dietary regimens cutting down on (or introducing) certain lipids would be effective in preventing cancer development and progression needs to be further examined (reviewed in [180,181]). The effectiveness is likely to be conditionally dependent on the type of substitution food or overall change of food pattern (reviewed in [182]).

2.1. Fat in regularly consumed cow's milk

The complexity of milk needs to be stated and as such cannot be viewed exclusively from a reductionist perspective. The discrepancy between looking at milk lipids in isolation and looking at whole dairy foods that contain far more bioactive compounds could partially explain contradicting effects on health as discussed by Thorning et al. [183]. Even the exact composition of FAs in milk is not universal, which could potentially translate into varying effects of its consumption on cancer risks. For instance, horned compared to dehorned cow's milk consists of increased cis-vaccenic acid as well as stearidonic acid and reduced MCFAs [184].

Further, the structure of lipids and its interaction with the food matrix may affect the lipid metabolism and bioavailability of FAs [185]. The digestion and absorption of milk lipids and its effects on human health also depend on how cow's milk is further processed into dairy products [186–189]. For instance, MFGM components have been promoted as potential anticancerous nutraceutical [23,24,190], but as mentioned earlier the treatment of milk causes chemical alterations in MFGM (*e.g.*, [191,192]), which possibly alters its impact on human health [193] although nutritional effects specifically on cancer have not been empirically tested.

Many studies fail to sufficiently differentiate between unfermented pasteurized milk and fermented milk consumption, but some results show considerable differences: Unfermented milk intake has been shown to increase cancer mortality risk, but fermented milk intake was inversely related to cancer outcome [194]. Whereas nonfermented milk activates mTOR complex 1 (mTORC1) signaling cascades, which imposes a risk regarding many cancer types [195], lactic acid bacteria found in fermented milk impedes mTORC1 activation [194]. Nonetheless, the role of milk fat in that context is unclear.

Moreover, exploring potential associations between cow's milk fat intake and cancer pathogenesis is aggravated due to the requirement of teasing apart unique effects of milk fat in isolation and effects attributable to other constituents and contaminants found in regularly consumed milk. Milk intake as predictor for hormone related cancers [110,196] could also plausibly be explained by nonlipid content such as estrogens and growth factors inherent to cow's milk (reviewed in [197–199]). Biological and chemical contaminants in milk include mycotoxins such as aflatoxins, which have been found to be carcinogenic (reviewed in [200]), but also pesticides linked to cancer (reviewed in [201,202]) as well as residues of metals, antibiotics, pathogens [203], bisphenol A (BPA; [204–206]), which have the potency to contribute to cancer development [207], and even low concentrations of poly- and perfluoroalkyl substances (PFAS; [208]) being potentially associated with cancer [209] as well as micro and nanoplastics [210] also related to cancer [211–213].

Moreover, the majority of studies overlooked to differentiate between conventional and organic milk consumption, of which the latter contains considerably less cancer-promoting contaminants [214]. Organic milk production relative to the conventional analogy may reveal more beneficial effects due to a lipid profile that includes higher levels of omega-3 and CLA [215]. Yet, possibly distinct effects between organic and conventional milk consumption on cancer risks have not been studied. Similarly, fortifications of milk with vitamins and minerals such as vitamin D (reviewed in [216]) further complicate accurate investigations.

2.2. Individual variability

Substantial variability exists in how individuals respond to the same food [217]. Effects vary based on genetics, the microbiome, and other lifestyle factors such as physical activity and sleep [217]. Following identical meal consumption, dietary fat lowered the overall glucose response in some participants, while in other individuals the glucose response remained insensitive to the fat contained in meals [217]. Possibly, short- and long-term responses to the consumption of milk fat that are associated favorably or deleteriously to cancer may vary according to individual factors such as genetics and lifestyle. Despite being still in its infancy, research has already started to examine gene-exposure interactions on cancer-related outcomes (see review by [182]).

In keeping with that theme, cow's milk is known to play a significant role in epigenetic regulation of the recipient's genes (reviewed in [218]). Consuming cow's milk has been shown to epigenetically activate and upregulate fat mass and obesity-associated (FTO) expression in humans, which is related to various diseases including cancer (reviewed in [219]). Higher cancer susceptibility is especially present in individuals with FTO gene polymorphisms (reviewed in [220]; breast cancer specific meta-analysis by [221]).

Reducing the intake of SFA and cow's milk is advisable to people who are at risk to develop obesity due to their FTO gene polymorphism [222] (reviewed in [223]). Further, a minority of people with a certain Apolipoprotein E polymorphism have twice the response to SFA intake on their serum lipids [224]. Similarly, PPARα-L162V polymorphism has been observed to interact with SFA intake [225]. An association between PPARγ gene polymorphisms and on the one hand protective effects of milk consumption and on the other hand marginally risk increasing effects of SFA consumption on colorectal cancer has been evidenced in a Japanese study [226]. As the direction, magnitude, and boundary conditions of these effects are often not clear, further studies are required to uncover polymorphisms of (PPAR and other) genes in interaction with environmental exposures, such as milk fat, and their effects on cancer (reviewed in [227,228]). Dietary fat in particular may play a significant role in affecting genetic predispositions to diseases (reviewed in [229]), and thus personalized nutrition advice may be a promising step forwards to derive optimal benefits for the individual in preventing cancer occurrence and progression [230]).

2.3. Milk consumption and infection

Another aspect linking milk consumption with oncogenesis is infection. Based on epidemiological data associating the consumption of milk and red meat, Nobelist Harald zur Hausen postulated the existence of an infectious agent, which he named bovine meat factor, in these types of food [231,232]. Subsequent work led to the isolation of circular DNA (cDNA) molecules capable of replication in cow meat, milk, and dairy products [233,234] and the brain tissues of multiple sclerosis patients [235]. These molecules, now termed bovine meat and milk factors (BMMFs), showed sequence similarity with cDNA named SPHINX isolated from animals affected by transmissible encephalopathy [236]. BMMFs were observed by laser microdissection in the lamina propria of the colon obtained from colon cancer patients [237].

The proposed mechanism of action of BMMFs involves macrophage-mediated inflammation in the lamina propria of the colon, potentially leading to random mutations that could evolve over approximately three decades into cancer [238]. After the initial trigger of the inflammation process, BMMFs are not necessary to persist in the affected cells. However, no clear evidence exists for a hit-and-run process underlying the BMMF-related oncogenesis.

Although BMMFs represent an intriguing new line of research, it should be kept in mind that, while a correlation between the consumption of red meat and colon cancer is established [239,240], there is still – as discussed in the current review – no consensus regarding the association between the intake of milk or dairy products and increased risk of oncogenesis, namely colon or breast cancers [241]. In addition, BMMFs have been isolated not only from cow (Bos taurus) derivatives but from several other sources, including buffalos, swine, sheep, goats, chickens, seafood, fruit, and vegetables [242–245]. Such a wide distribution of BMMF sources weakens the association between these cDNAs and cancer.

Moreover, the biochemistry of these cDNAs is still not completely elucidated. It is unclear whether BMMFs are single- or double-stranded, and it has been suggested that they could be viruses, plasmids, or bacteriophages (the latter two associated with Acinetobacter spp.) [241].

3. Limitations

The current review spans *in vitro*-, animal-, cross-sectional-, case-control-, cohort-, mendelian randomization, and RCT studies as well as meta-analyses thereof, which are summarized in Table 1 . The heterogeneity of study designs aggravates the comparability and aggregation of data, and shortcomings of each design may contribute to reasons for why studies essentially contradict each other. Although most epidemiological studies have been adjusted for some potential confounding variables, there is still a possibility that residual confounding factors may be present (*e.g.*, the lack to control for total energy intake). Nuances may get lost in large scale studies due to too much "lumping" [246], such as the exact details of the product in which milk lipids are contained as well as assessing all clinically relevant variables about human participants. On the contrary, excessive "splitting" narrows the scope of application and thus reduces the generalizability while at the same time it provides valuable accuracy [247]. For example, prior examinations often neglected that types and subtypes of cancer can be fundamentally different (reviewed in [248,249]) and thus may be distinctively associated with dietary patterns [250]––an area, which would benefit from more "splitting". However, whether effects of specific cow's milk FAs on specific human cancer cell lines under well-controlled laboratory conditions will be replicated *in vivo* is uncertain. Thus, the "lumping" *versus* "splitting" tradeoff runs like a thread through the current review, reflects an evidentiary challenge, and underscores the complexity of the phenomenon under investigation. Moreover, assessing dietary intake or adherence to dietary interventions can produce considerable measurement errors due to recall- or desirability bias ([251]; reviewed in [252,253]). For instance, this could explain the null-results of the association between SFA intake and breast cancer risk in pooled analyses of cohort studies using food frequency questionnaires compared to a positive link between SFA intake and breast cancer assessed by the food diary [254]. Additionally, scientific efforts to study dietary behavior, such as those described here, face the problem of a lack of uniform taxonomy [255]. Moreover, investigations, especially those of interventional nature, fall short in establishing potential nonlinear relationships. U-shaped curve relationships in the context of micronutrient supplementation and cancer prevention have been discussed in the past by Mayne et al. [256] and cannot be ruled out regarding associations between milk fat and cancer.

4. Concluding remarks

In sum, anticancer potential has been ascribed to fats derived from cow's milk. Milk lipid components in particular, such as CLA, sphingomyelins or various HFAs, show a promising anticancerogenic effect *in vitro* and in some cases also *in vivo*. Yet, overarching epidemiological findings are inconsistent and partially imply neutral to adverse effects with respect to cancer related risks, with some studies linking increased milk consumption to a higher incidence of cancer. This may be partly explained by the methodological heterogeneity across studies, limitations to isolate effects uniquely attributable to milk lipids, and factors due to individual variation. Future research could focus on identifying further potentially protective and harmful milk lipid components and, in this context, expand on existing *in vitro* data through *in vivo* studies. Furthermore, the bioavailability and plasma levels of potentially interesting compounds need to be investigated in order to confirm their physiological relevance. In addition, further large-scale epidemiological studies are needed to hopefully provide a clearer picture of the association between milk consumption and both morbidity as well as mortality. To combat cancerous milieu most effectively by means of nutritional tools, individually tailored advice may be a promising path forward as methodological possibilities proceed, and further evidence accrues.

Table 1
Diverse studies on the link between cow's milk or its components and cancer.

Year	Cell lines/animals/patients	Substance	Type of study	Results	References
Outcome: possible protective indication of cowś milk for various types of tumors (risk reduction)					
1987	Epidermal carcinogenesis mouse model	CLA	*In vivo*	Reduced papilloma development and lowered tumor incidence	[65]
1991	Mammary tumor rat model	Mixture of CLA isomers	*In vivo*	Reduced tumor weight, and decreased tumor incidence	[66]
1995, 2001	Bovine breast cancer cell lines	FABP	*In vitro*	Growth inhibition of breast cancer cells	[23,24]
2000	Leukemia, breast cancer, colorectal cancer, pancreatic cancer, prostate cancer, gastric cancer, hepatic cancer, and lung cancer cell lines	13-MTD	*In vitro*	Induction of apoptotic cell death in human cancer cell lines	[100]
2000	Mouse model	Sphingolipids (glucosylceramide, lactosylceramide, and ganglioside D3)	*In vivo*	Reduction of ACF	[31]
2000	Mammary tumor rat model	CLA and an isomeric CLA mixture	*In vivo*	Increased apoptosis rates in premalignant lesions	[68]
2000	Prostate cancer and hepatic cancer mouse models	13-MTD	*In vivo*	Growth inhibition of tumor implants	[100]
2000	Women with breast cancer	CLA	Prospective cohort study	Lower levels of dietary and serum CLA in women with breast cancer	[95]
2000, 2003, 2004, 2005, 2006, 2008, 2009, 2009	Breast cancer, colorectal cancer, hepatic cancer, prostate cancer, glioblastoma, and bladder cancer cell lines	CLA in different isomeric mixtures	*In vitro*	Reduced growth rates, cell viability and concentration-dependent cytotoxicity in these cell lines	[69–76]
2003	Colorectal cancer cell lines	Sphingosine and ceramide	*In vitro*	Apoptosis in colorectal cancer cells	[29]
2003	Colorectal adenocarcinoma mouse model	Sphingomyelin	*In vivo*	Suppression of colon carcinogenesis by reducing the number of ACF and colonic adenocarcinomas in a mouse model	[29]
2003	Intestinal tumor mouse model	Sphingolipids	*In vivo*	Reduced number of intestinal tumors	[29]
2005	Women aged 40–76 y	CLA	Prospective cohort study	Reduced risk of colorectal cancer	[94]
2006	Colorectal cancer cell lines	CLA	*In vitro*	Proliferation inhibitory effects on the colon cancer cells	[79]
2013	Colorectal cancer cell lines	Native MFGM isolate from raw milk	*In vitro*	Anticarcinogenic effects on colorectal carcinoma cells, reduction of cell proliferation, and activation of caspase-3	[27]
2015	Meta-analysis of prospective cohort studies	Whole milk	Meta-analysis	lower RR of prostate cancer	[130]
2020	Lung cancer, colorectal cancer, and astrocytoma cell lines	Isomers of hydroxystearic and hydroxypalmitic acids	*In vitro*	Growth-inhibitory effects against different human cancer cells	[58]

(*continued on next page*)

Table 1 (*continued*)

Year	Cell lines/animals/patients	Substance	Type of study	Results	References
Outcome: possible harmful indication of cowś milk for various types of tumors (risk increment)					
1993	Meta-analysis of prospective cohort studies	Milk and cheese	Meta-analysis	Positive correlation with breast cancer risk	[112]
1995	Norwegian women aged 20–54 y	Whole milk	Prospective cohort study	Increased RR of developing breast cancer	[121]
2002	Women from Uruguay	High-fat dairy products	Case-control study	Increased risk of breast cancer	[104]
2005	Men and women	Milk, butter, and cheese	Prospective cohort study	Increased incidence of breast-, ovary-, and corpus uteri cancers, increased mortality rates of these cancers	[110]
2007	Men and women from England and Scotland	Dairy products or milk intake during childhood	Prospective cohort study	Increased colorectal cancer risk in adulthood	[156]
2008	Japanese men aged 45–74	Dairy products, myristic acid, palmitic acid	Prospective cohort study	Elevated risk of prostate cancer	[128]
2012	Men diagnosed with localized prostate cancer	Whole milk	Prospective cohort study	Increased risk of lethal prostate cancer	[125]
2013	Women diagnosed with early-stage invasive breast cancer from the USA	High-fat dairy products	Prospective cohort study	Increased risk of breast cancer mortality	[123]
2013	Men aged 40–84	Whole milk	Prospective cohort Study	Elevated risk for fatal prostate cancer	[126]
2014	Men and women aged 20–85 y	Dairy fat	Prospective cohort study	Increased hepatocellular carcinoma risk	[117]
2016	Meta-analysis of prospective cohort studies	Whole milk	Meta-analysis of population-based cohort studies	Elevated prostate cancer mortality	[127]
2017	Men with newly diagnosed prostate cancer	High-fat milk	Prospective cohort study	Increased cancer mortality	[163]

(*continued on next page*)

Table 1 (*continued*)

Year	Cell lines/animals/patients	Substance	Type of study	Results	References
2019	Men and women without CVD or cancer at baseline	Total milk	Prospective cohort study	Positive association between total milk intake and the risk of dying from cancer	[114]
2019	Prostate cancer cell lines and prostate cancer mouse model	Palmitate	*In vitro* and i*n vivo*	Promoted prostate tumorigenesis	[129]
2020	Meta-analysis of case-control studies and cohort studies	Whole milk	Meta-analysis	Increased risk of ovarian cancer	[116]
2020	Men and women aged≥50 without CVD at baseline	Whole milk	Biobank cohort study	Increased cancer mortality, increased incidence of esophagus cancer	[111]
2020	Women from North America free of cancer at baseline	Whole milk	Prospective cohort study	Increased HR of breast cancer	[124]
2021	Meta-analysis of prospective cohort studies	SFA	Systematic analysis of prospective cohort studies	Increased cancer mortality	[106]
2021	Meta-analysis of observational studies	High-fat dairy products	Meta-analysis	Increased breast cancer occurrence risk	[122]
2022	Meta-analysis of prospective cohort studies	High-fat milk	Systematic review and meta-analysis	Positive association between high-fat milk intake and the risk of dying from cancer	[113]
2024	Meta-analysis of case-control studies and cohort studies	Palmitic acid, stearic acid, and myristic acid	Systematic review and meta-analysis	Increased cancer risk	[115]
2024	Retrieved from different Biobank databases	Percentage of fat in milk consumption	Mendelian randomization study	Increased breast cancer risk	
2025	Women and men free of cancer, CVD, diabetes, or neurodegenerative disease at baseline	Butter	Prospective cohort study	Increased cancer mortality	[102]

Abbreviations: 13-MTD, 13-methyltertadecanoic acid; ACF, aberrant crypt foci; CLA, conjugated linoleic acid; CVD, cardiovascular disease; FABP, fatty acid binding protein; HR, hazard ratio; MFGM, milk fat globule membrane; RR, relative risk; SFA, saturated fatty acid.

Statement of significance

This narrative review focuses on milk fats and the biological advantages and disadvantages of different lipids in relation to tumor diseases. Our article discusses both the growth-inhibiting and thus protective effects as well as the negative aspects of milk consumption on tumor development and progression. This provides a critical and detailed summary of the relevant issue of the role of milk fats in oncology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Laura Elaine Strittmatter: Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Alban Piotrowsky:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Luigi Marongiu:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Sascha Venturelli:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Christian Leischner:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Investigation, Conceptualization.

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