The fatty acid desaturation index of blood lipids, as a biomarker of hepatic stearoyl-CoA desaturase expression, is a predictive factor of breast cancer risk

Véronique Chajès[a,b], Virginie Joulin[c] and Françoise Clavel-Chapelon[b]

[a]Nutrition and Metabolism, International Agency for Research on Cancer, Lyon, [b]UMR 1018, Nutrition, Hormones et Santé des femmes, Centre de Recherche en Epidémiologie et Santé des Populations, Hôpital Paul Brousse and [c]UMR 1009, Hématopoïèse Normale et Pathologique, Institut Gustave Roussy, Villejuif, France

Correspondence to Véronique Chajès, PhD, Nutrition and Metabolism, International Agency for Research on Cancer, Lyon, France
Tel: +33 4 72 73 80 14;
e-mail: chajesv@visitors.iarc.fr

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Purpose of review

This review summarizes epidemiological data linking the fatty acid desaturation index measured in blood lipids, as a biomarker of hepatic stearoyl-CoA desaturase activity, the key enzyme involved in the synthesis of monounsaturated fatty acids from saturated fatty acids, to breast cancer risk. The biological plausibility of this association is discussed.

Recent findings

Epidemiological cohort studies reported an association between a high saturated to monounsaturated fatty acid ratio measured in blood lipids, indicating low stearoyl-CoA desaturase-1 activity, and decreased breast cancer risk. The suppression of stearoyl-CoA desaturase expression reduces cancer cell proliferation and in-vitro invasiveness, and dramatically impairs tumor formation and growth. These effects could not be overcome by supplying exogenous monounsaturated fatty acids.

Summary

Epidemiological findings, in accordance with experimental data, suggested that decreased hepatic stearoyl-CoA desaturase expression/activity may be related to decreased risk of breast cancer.

Keywords

biomarkers, breast cancer, fatty acids, stearoyl-CoA desaturase

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Introduction

The role of fat intake in cancer etiology still remains controversial. Epidemiological studies are limited by the assessment of dietary fat through food-frequency questionnaires, methods shown to be prone to measurement error [1]. Moreover, the conversion of food items into their fatty acid content is complex for numerous reasons, related to the high variation of fatty acid content within the same food according to added fat, cooking methods and industry supply. In this context, dietary measurement error could have masked true associations between dietary fatty acids and cancer risk [2]. In contrast, biomarkers of dietary fatty acids (i.e., serum, plasma, erythrocyte membrane, adipose tissue fatty acid composition) offer objective, qualitative measures of bioavailable amounts of these nutrients irrespective of the source and quality of food, particularly for fatty acids that are not endogenously synthesized, such as essential fatty acids, $n-3$ long-chain polyunsaturated fatty acids (PUFAs) and some *trans* fatty acids [3–6].

In general, saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs) in blood lipid fractions or tissues are somewhat weaker biomarkers than PUFAs or *trans* fatty acids of their respective dietary intakes [5]. Serum, plasma or erythrocyte membrane MUFA and SFA levels reflect endogenous de-novo fatty acid synthesis. One key regulator of SFA and MUFA composition is stearoyl-CoA desaturase (SCD), the endoplasmic reticulum-resident enzyme that catalyzes the introduction of the first double bond in the *cis*-Δ9 position of several saturated fatty acyl-CoAs, principally palmitoyl-CoA and stearoyl-CoA, to form palmitoleyl-CoA and oleyl-CoA [7,8]. Two isoforms of SCD (SCD-1 and SCD-5) have been described for humans, both exhibiting approximately 85% homology with murine SCD-1 [9,10]. The expression of SCD-1 is high in brain, liver, heart, and lung [10], whereas SCD-5 is almost exclusively expressed in fetal brain [9].

In some epidemiological studies on the relationship between biomarkers of dietary fat and cancer risk, the ratio of MUFAs to SFAs, product to substrate ratio also called the desaturation index (or the SFAs to MUFAs ratio, substrate to product ratio called the saturation index) determined in blood lipid fractions, has been used as a reflect of SDC-1 activity [11]. Thus, the use of

biomarkers of fatty acids is a meaningful approach to investigate the relationship between SCD-1 and cancer risk.

The fatty acid desaturation index in blood lipids as a surrogate marker of hepatic stearoyl-CoA desaturase 1 activity/expression

Endogenously synthesized SFAs and MUFAs measured in blood lipid fractions or tissues are weak biomarkers of their respective dietary intakes. For example, results from a cross-sectional study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort showed weak individual correlations between plasma phospholipid oleic acid (18:1 $n-9$) and olive oil or meat intake, the main dietary sources of oleic acid in southern and northern-central Europe, respectively [12], suggesting that dietary contributors of plasma oleic acid concentration may not be strong determinants compared with its endogenous hepatic synthesis from saturated stearic acid [5].

In some human studies, the surrogate marker used for SCD-1 activity is the ratio of the product and precursor for the mammalian microsomal enzyme SCD-1 enzymatic step, either the ratio between 16:1 $n-7$ and 16:0 (desaturation index $n-7$) or the ratio between 18:1 $n-9$ and 18:0 (desaturation index $n-9$) in plasma samples. The validity of the use of the desaturation index measured in blood lipids or tissues as an in-vivo surrogate of SCD-1 activity has been demonstrated in two studies. In a study involving 75 subjects representative of a study population of 294 healthy men, adipose tissue fatty acid desaturation indexes $n-7$ and $n-9$ reflected the expression of the gene encoding SCD-1 in this tissue [13]. A cross-sectional study conducted in a population-based study of 301 healthy men reported some strong correlations between desaturation indexes measured in blood lipid fractions and adipose tissue, and suggested that the desaturation index (particularly 16:1 $n-7$ to 16:0 ratio) in blood-free fatty acids reflect the SCD-1 activity in adipose tissue, whereas the desaturation index obtained from serum triacylglycerols and phospholipids mainly reflect hepatic SCD-1 activity [14]. These data suggest that the fatty acid desaturation index measured in serum or plasma phospholipids can accurately reflect hepatic SCD-1 activity/expression.

The fatty acid desaturation index (or saturation index) and breast cancer risk: data from epidemiological studies

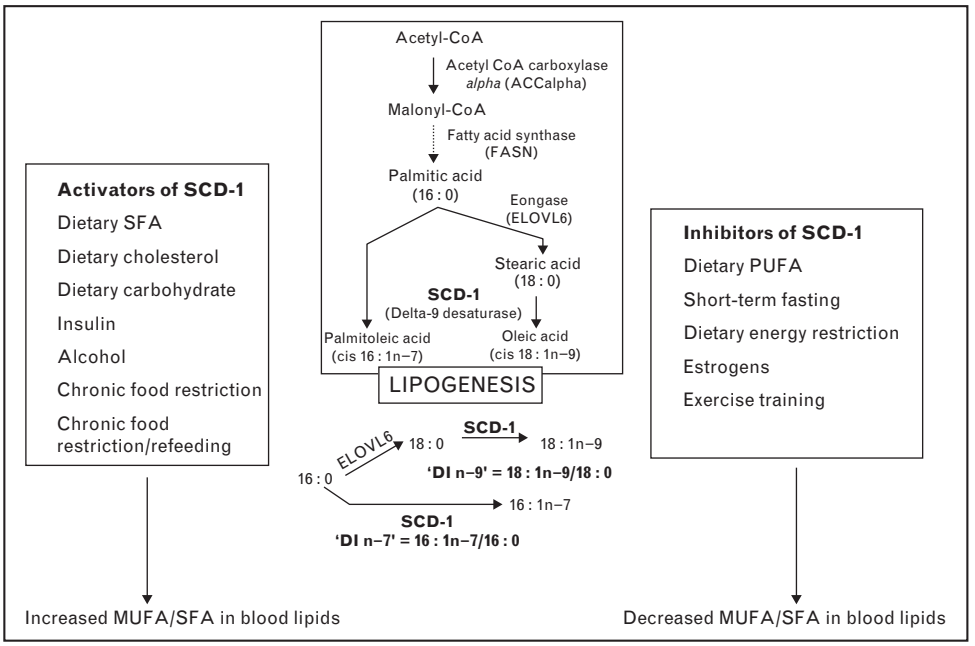
Some epidemiological studies addressed the hypothesis that low SCD-1 activity is associated with decreased breast cancer risk through the use of the fatty acid saturation index (substrate to product ratio) measured in blood lipid fraction or membrane erythrocytes. Thus, the ratios of 16:0 to 16:1 $n-7$ and 18:0 to 18:1 $n-9$ correspond to saturation indices $n-7$ and $n-9$, respectively. In an Italian cohort study, a high saturation index $n-9$ (indicating low SCD-1 activity) measured in erythrocytes was associated with decreased risk of breast cancer in postmenopausal women [15]. Similarly, in a Swedish cohort study, a high saturation index $n-9$ measured prediagnostically in serum phospholipids was associated with decreased risk of breast cancer [16]. In a French cohort study, a high saturation index $n-7$ measured in serum phospholipids was associated with decreased risk of breast cancer [17]. Finally, in a case-control study conducted in China, a high saturation index $n-7$ measured in erythrocyte membrane was associated with decreased risk of breast cancer [18]. These data suggested that low SCD-1 activity estimated through SFAs and MUFAs ratios measured in blood or erythrocyte membrane phospholipids was related to decreased breast cancer risk. The potential pathway underlying the association between prediagnostic plasma SFAs and MUFAs ratio to risk of breast cancer is not known.

Effect of dietary and hormonal factors on the fatty acid desaturation index

Data on how the fatty acid desaturation index is affected by diet, hormones or lifestyle factors are few (summarized in Fig. 1). First of all, short-term fasting has been shown to decrease the expression of the SCD-1 gene in murine liver [19]. Similarly, dietary energy restriction, which reduces spontaneous mammary tumors in rodents irrespective of the type of nutrient restricted, led to decreased expression of SCD-1 in breast tissues in overweight or obese women [20]. Surprisingly, a study reported data indicating that both chronic food restriction and chronic food restriction/refeeding cause an increased expression of SCD-1 in white adipose tissue and liver in rats [21]. These results suggest that short-term fasting and chronic food restriction exert the opposite effect on hepatic SCD-1 expression.

Regarding the effect of dietary fatty acids on SCD-1 expression, a controlled crossover study conducted in 20 subjects showed that a high-dietary intake of SFAs led to increased hepatic SCD-1 activity, principally reflected by the 16:1 $n-7$ to 16:0 ratio in serum cholesterol esters and phospholipids [22]. This is in line with data from an experimental study in mice, where it was suggested that a high-SFA intake was needed to upregulate SCD [23]. Another possibility is that a diet rich in SFAs might counteract the well-known inhibitory effect of a diet rich in PUFAs on the expression of SCD-1 [24]. Thus, the desaturation index $n-7$ in blood lipid fractions could be mainly affected by dietary SFAs, at least in

Figure 1 Regulation of stearoyl-CoA desaturase 1



DI, desaturation index; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; SCD-1, stearoyl-CoA desaturase 1; SFAs, saturated fatty acids.

populations with high-fat diets. As a consequence, a high desaturation index $n-7$ in serum phospholipids or tissues associated with increased breast cancer risk may be, at least in part, the result of a diet rich in SFA. In a study conducted in 162 healthy individuals aimed to compare the effects on insulin sensitivity of a diet rich in SFAs to a diet rich in MUFAs, the proportion of 18:1 $n-9$ was increased whereas the proportion of 16:1 $n-7$ was decreased on the high-MUFA diet [25]. These data could suggest that the desaturation index $n-7$ could be underestimated whereas the desaturation index $n-9$ overestimated on a high-MUFA diet, because a high content of oleic acid in the diet will dilute the signal from newly endogenously synthesized 18:1 $n-9$. In a situation in which the fat intake would be low, the best marker of SCD-1 activity might be the desaturation index $n-9$, because the preferred substrate for SCD is 18:0.

Besides fatty acids, SCD-1 activity is also activated by high-carbohydrate diets, especially those enriched in rapidly absorbed refined carbohydrates such as glucose and fructose [26]. Interestingly, some studies found that chronic ethanol feeding, a known risk factor for breast cancer risk, is associated with increased hepatic expression of SCD-1 in animal models [27–29].

Insulin is a well-documented upregulator of SCD-1 activity [30], suggesting that increased desaturation index associated with increased breast cancer risk might reflect an underlying metabolic profile characterized by chronic hyperinsulinemia. SCD-1 activity might also be affected by estrogens. In high-fat-diet fed mice, 17β-estradiol treatment led to decreased expression of SCD-1 in adipose tissue and liver [31].

Finally, exercise training, a known protective factor for breast cancer risk, has been reported to downregulate hepatic SCD-1 gene expression and protein content in high-fat fed rats [32].

Biological plausibility: relevance of epidemiological data with regard to experimental data

SCD-1 is of particular interest as an increased activity of this lipogenic enzyme has been suggested to play a role in the development of fatty liver [33,34], insulin resistance [35], obesity [7,36] and cancer [15–18]. Increased cellular SCD-1 activity has been suggested to influence fatty acid partitioning by promoting MUFA synthesis but decreasing oxidation [23]. It is known that MUFAs can serve as mediators of signal transduction and cellular differentiation, and unbalanced levels of these mediators have been also implicated in carcinogenesis [37].

The degree of fatty acid unsaturation in membrane phospholipids determines the biophysical properties of the membrane, which, in turn, influences many crucial membrane-associated functions. The fatty acid composition of membrane phospholipids is likely to be affected

by the exogenous fatty acids and by altered activities of lipid-metabolizing enzymes. Despite the overactivation of enzymes that synthesize SFAs (e.g., acetyl-CoA carboxylase-alpha, fatty acid synthase) [38], abundant amounts of MUFAs, mainly oleic acid, are found in cancer cells [39,40]. In-vitro studies have provided new suggestion of a causal relationship between MUFA synthesis and several biological features of the cancer phenotype. The expression of SCD-1 is increased in several human cancers, chemically induced tumors, as well as in oncogene-transformed cells [39,41,42]. Additionally, the suppression of SCD-1 expression reduces cancer cell proliferation and in-vitro invasiveness, and dramatically impairs tumor formation and growth [43–46]. In addition, active SCD-1 may be required for neoplastic cells to survive a lipotoxic stress because SCD-1 knockdown increases basal apoptosis and sensitizes cancer cells to the cytotoxic effects of excess SFAs [45]. SCD-1 has also been identified from a siRNA library as a gene whose suppression impairs human cancer cell survival, further supporting a functional link between SCD-1 and cancer cell growth [46]. Further data showed that the pharmacological inhibition of SCD-1 in cancer cells inactivates acetyl-CoA carboxylase activity via the activation of AMP-activated kinase, leading to decreased cell proliferation [43]. In a model of stable knockdown of SCD-1 gene expression in human lung adenocarcinoma cells, a decreased MUFAs to SFAs ratio was found in tumor cell lipids, as well as decreased cell proliferation and anchorage-independent growth, whereas the rate of apoptosis was increased [44]. Moreover, Akt signaling, commonly deregulated in cancer, was found impaired in SCD-1-ablated tumor cells.

In this latter study [44], one of the most decisive findings was the original demonstration that increased SCD-1 expression/activity is crucial for cell growth, whereas exogenous dietary MUFAs were not. Indeed, the effects of SCD-1 blockade on human lung cancer cell growth and apoptosis in nude mice could not be overcome by supplying abundant MUFAs (i.e., oleic acid) in the diet, suggesting that SCD-1 is a key factor in the regulation of carcinogenesis *in vivo* [44]. The reason for the divergent effects of endogenous and exogenous oleic acid on cell metabolism and cell growth is not known. It has been hypothesized that exogenous and endogenous MUFAs enter separated metabolic compartments and may display different intracellular regulatory roles [47]. Although this hypothesis still needs confirmation, it could be a valuable argument explaining the divergent data regarding the association between exogenous and endogenous MUFAs and breast cancer risk; on the one hand, as described above, a high MUFA-to-SFA ratio measured in blood lipids has been consistently associated with increased risk of breast cancer, on the other hand, a high estimated dietary intake of MUFAs (mainly oleic acid) or olive oil rich in oleic acid has generally shown a negative association with breast cancer risk, at least in Mediterranean countries [48,49].

Conclusion

The association between SFAs and MUFAs ratio measured in blood lipid fractions, as an index of hepatic SCD-1 activity/expression, and breast cancer risk has been reported in numerous epidemiological cohort studies. Additionally, there is evidence that crucial features of tumor formation, both in cultured cancer cells and in tumor xenografts, are determined by the level of SCD-1 expression. Together, this appears to favor endogenously synthesized MUFAs, rather than exogenous MUFAs, as regulators of cancer cell growth. Decreased hepatic SCD-1 expression/activity may be related to decreased risk of breast cancer. Because SCD-1 expression is regulated by dietary and lifestyle factors, new nutritional strategies for cancer prevention could be based on targeting SCD-1 function.

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