The effects of conjugated linoleic acids on breast cancer: A systematic review

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Abstract

Recently prevention strategies for breast cancer are focused on lifestyle modification such as diet. Some dietary factors such as Conjugated linoleic acid (CLA) can lower the risk of breast cancer, metastasis and some factors concerning this malignancy. Many studies have been established in this field, but their results are inconsistent. Therefore, we evaluated this association based on systematic review among published scientific literature. We performed an electronic search using PubMed, Cochrane, Scopus, Google Scholar and Persian database (Iran Medex, magiran) to identify relevant studies. We summarized the findings of 8 papers in this review. Although, three cohort studies were not overall identified a protective effect of CLA dietary intake or CLA content in breast tissue on breast cancer incidence, metastasis and death, one of them showed an inverse association after adjusting for age. Also, among case-control studies a weak inverse association between breast cancer risk and CLA dietary intake and serum levels among post-menopausal women was reported. Besides, a clinical trial showed that some indicator of breast tumor decreased after CLA administration among women with breast adenocarcinoma. Lacking published evidence suggested inconsistent results. So, further well-designed studies are required, particularly in considering the main breast cancer risk factors.

Key Words: Breast cancer, conjugated linoleic acid, systematic review

INTRODUCTION

Globally, Breast cancer is a major health problem in developing and developed countries that affect 1 in 8 women during their life span.[1] Diet modification is the most important preventive and treatment strategy against breast cancer.[2-6] Although dietary fat is associated with increased risk of mammary tumor, some types of fats such as omega-3 and conjugated linoleic acids (CLA) can have protective effects.[7,8]

The relation between this fatty acid intake and breast cancer risk was investigated in a small numbers of studies.[8-15] Therefore, we carried out this systematic review to discuss evidence between incidence,

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metastasis, death and other related factors of breast cancer and CLA dietary intake or CLA serum levels or CLA content in breast fat tissue.

MATERIALS AND METHODS

Search strategy

In order to collect data for this systematic review, we performed a systematic search through the PubMed, Cochrane, Scopus, Google scholar, Iran Medex and Magiran database. The following keywords were used in this searching: "Breast cancer", "breast tumor", "breast neoplasm", "mammary tumor", "breast carcinoma", "conjugated linoleic acids". All studies that covered the association between CLA dietary intake and breast cancer incidence, metastasis or mortality have been collected until November 2013. Also, we manually searched through the references from relevant articles where necessary. We didn't use any filtration in our searches but study selection was limited to articles published in the English or Persian languages.

Inclusion and exclusion criteria

According to our inclusion criteria, we considered human studies with cancer incidence, metastasis, and any cancer marker such as Fatty acid synthase (FASN), Lipoprotein lipase (LPL) and Spot 14, a modifier protein in breast cancer cell's growth as the outcome and CLA as the exposure. We found 394 papers from database search that were screened by the two investigators based on study title and abstract. At the first, we omitted duplicated studies ($n = 255$). Then irrelevant papers (research other CLA outcomes, lack of data and not agree to our objective) were excluded ($n = 55$). After that we removed *in vitro* and animals studies ($n = 75$), nine articles remained that one of them was written in other languages and we didn't access to one full text of them. Not only we classified these seven articles as three cohort, three case-control and one clinical trial, but also we evaluated them based on CLA dietary or serum levels or content in breast fat tissue. Figure 1 shows the flow of studies through the selection process.

Data extraction

From each included study we collected data on these characteristics: The first author's name, published year, country, participant's age, dietary assessment, duration of follow up, duration of intervention, study population, study type, event followed, types of CLA, amount of CLA and adjustment for confounders. Tables 1-4 show the abstracted information of data extraction.

Quality assessment

In order to assess the quality of selected studies, we used a system based on Newcastle-Ottawa Scale. The full score was 10 and the high or median
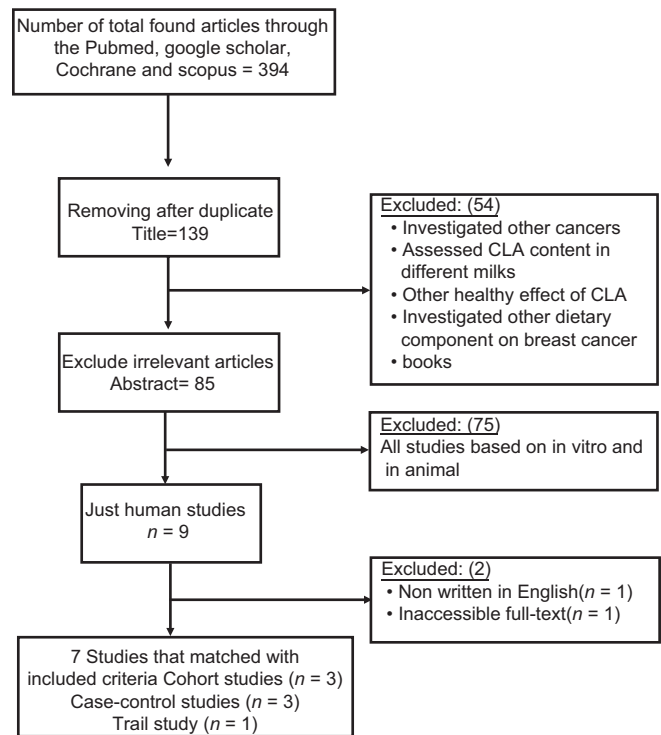

Figure 1: Flow chart of systematic literature search

quality study was defined as a study with ≥ 7 or 4-7 respectively.[16] The quality scores of studies summarized in Tables 5 and 6.

RESULTS

As previous mentioned, in this field, studies categorized in two groups. First group focused on the role of CLA on incidence of breast cancer and second group evaluated the role of CLA in breast cancer after diagnosis and its effects on metastasis. We divided our result to three parts according to types of studies and also in each part, studies belong to one of the two groups.

Cohort studies

3 cohorts were included in this study that 1 of them the CLA content in breast fat tissue on the time of surgery was investigated and patients follow up to metastasis and death incidence that no relation was seen. Others studies tried to find a relationship between CLA dietary intake and risk of breast cancer that didn't find at all.

In a prospective cohort study Swedish cancer-free women have been followed up during 17.4 years and 2952 incident cases of breast cancer were diagnosed.[14] In order to diet assessment, a validated food-frequency questionnaire (FFQ) was used twice, at baseline and ten years later. Also, CLA dietary intake calculated with the use of published data on the CLA concentration of total fat in various foods.[17,18] Overall, no correlation between breast cancer incidence and

Table 1: Characteristics of cohort studies about breast cancer risk and CLA

Author, year	Location	Period and event follow	No. of subject	Dietary assessment	Age	CLA type	CLA intake	CLA content	Statistical adjustment
Chajes, 2009	France	7.5 y, Risk of metastasis	209	NM	24.2-82.9	18:2 9c,11t	NM	44% of total FA in breast	Age at diagnose, height, weight, BMI, menopausal status, AM
Larsson, 2009	Sweden	17.4 y, Breast cancer incidence	61,433	FFQ	43.6-63	18:2 9c,11t	118.4±47 Mg/d	NM	Age, BMI, education, AM, parity, age at first birth, age at menopause, use of OCP, UPH, FHBC, TEI , alcohol, EAC
Voorrips, 2002	Netherland	6.3 y, Breast cancer incidence	62,573	FFQ	55-69	18:2 9c,11t and 9t,11c)	0.2±0.1 g/d	NM	Age, HBC, FHBC, BCOMS, AM, age at menopause, OCP use, parity, AFC, BMI, education, alcohol, smoking, TEI, TEAFI

NM: Not mentioned, AM: Age at menarche, HBC: History of breast cancer, UPH: Use of postmenopausal hormones, FHBC: Family history of breast cancer, TEI: Total energy intake, EAC: Energy-adjusted calcium, BCOMS: Breast cancer in one or more sisters, AFC: Age at first childbirth, TEAFI: Total energy adjusted fat intake, CLA: Conjugated linoleic acid, FA: Fatty acid, BMI: Body mass index

Table 2: Characteristics of clinical trial about breast cancer risk and CLA

Author, year	Location	Event followed	Study population	Intervention	Age	CLA type	CLA dosage	CLAcontent	Statistical adjustment
McGowan, 2013	USA	Variation of gene expression and enzyme	24	12 day (9.5-20.5)	34-80 Mean=55	9c,11t (47%) - 10t,12c (%53)	7,5 gr	0.44% (0.19%-0.85%) of total FA	Age at diagnose, height, weight, BMI, menopausal status, age at menarche

CLA: Conjugated linoleic acid, FA: Fatty acid, BMI: Body mass index

Table 3: Characteristics of case-control studies about breast cancer risk and conjugated linoleic acids

Author, year	Location	Study population	Period	Dietary assessment	Age	CLA type	CLA intake	CLA content	Statistical adjustment
Aro, 2009	Finland	Case pre: 68 post: 127 Control pre: 75 post: 133	3 year	FFQ	25-75	18:2	Case (mg/day) pre: 142±60.6 post: 126±63.9 Control (Mg/day) Pre: 131.9±58.9 Post: 132.8±65.2	Case (In serum) pre: 0.29±0.09 post: 0.30±0.08 Control (In serum) Pre: 0.29±0.08 Post: 0.33±0.08	Age, area, AM, A 1st FTP, OCP, UERT,1st DFHBC, HBBC, education, alcohol intake, smoking, physical activity, waist to hip ratio, BMI
Susan, 2004	New York	Case Pre: 315 Post: 807 Control Pre: 593 Post: 1443	5 year	FFQ	35-79	18:2 (9c, 11t), total CLA	Control Pre: 0.29±0.08 Post: 0.33±0.08 Case Pre: 0.29±0.09 Post: 0.3±0.08	NM	Age, education, HBBC, family history of breast cancer, AMPW

NM: Not mentioned, AM: Age at menarche, A 1st FTP: Age at 1st full-term pregnancy, UERT: Use of estrogen replacement therapy, 1st DFHBC: 1st degree family history of breast cancer, HBBC: History of benign breast disease, AMPW: Age at menopause among postmenopausal women, CLA: Conjugated linoleic acid

Table 4: Characteristics of case-control study about breast cancer risk and conjugated linoleic acids

Author, year	Location	Study population	Period	Dietary assessment	Age	CLA type	CLA intake	CLA content	Statistical adjustment
Chajès, 2002	France	Case=213	4 year	NM	≤37 22: Case and 29: Control 37-49 265: Case and 29: Control	18:2 (9c,11t)	NM	0.44% (0.19-0.75) In breast fat tissue	Age at diagnosis, BMI, menopausal status
		Control=84			>49 156: Case and 30: Control			0.43% (0.14-0.70) In breast fat tissue	

CLA: Conjugated linoleic acid, FA: Fatty acid, BMI: Body mass index

CLA dietary intake was presented. Moreover, in comparison the highest with the lowest quintile of CLA dietary intake, the interaction of CLA and estrogen receptor/progesterone receptor (ER/PR) status on breast cancer incidence weren't significantly approved.

Adjustment for different factors done in this study but the results remained without change.

In the second cohort study,[8] women without cancer follow up in 6.3 years. At the beginning and end of

Table 5: Methodological quality of cohort studies included in the systematic review

First author, year of publication (reference)	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Data analysis that used an energy-adjusted residual or nutrient-density model	Total quality scores
Chajes, 2009	*		*	*	**	*		*	*	8
Larsson, 2009	*		*	*	**	*	*	*	*	9
Voorrips, 2002	*		*	*	**	*		*	*	8

Table 6: Methodological quality of case-control studies included in the systematic review

First author, year of publication	Adequate definition of cases	Representativeness of cases	Selection of control subjects	Definition of control subjects	Control for important factor or additional factor	Exposure assessment	Same method of ascertainment for all subjects	Nonresponse rate	Data analysis that used an energy-adjusted residual or nutrient-density model	Total quality scores
Aro, 2009	*	*	*	*	**	*			*	8
Susan, 2004	*	*	*	*	**	*	*	*	*	10
Chajès, 2002		*	*		*	*	*			5

this study, FFQ for examining dietary intake was used in blinded manner to minimize observer bias. Although 941 cases of breast cancer were found, but no relation was observed with CLA dietary intake. While this effect become manifest when CLA dietary intake was adjusted for age, adjusting for other confounding factors such as energy and fat intake had not same results. Furthermore, when different source of CLA was categorized, it was shown the most dietary intake of CLA (29%) in this population was from butter that it had a significant inverse association with breast cancer incidence.

In the last cohort study, Chajès focused on the CLA content in adipose tissue of invasive breast carcinoma patients with mean age 55 years and the risk of metastasis during 7.5 years. Forty-three percent of patients were premenopausal. High performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GC-MS) used to extract and measure CLA content of adipose tissue. Measurement of CLA was reported as a percentage of total fatty acid. Finally, the analysis showed no considerable association between CLA levels in adipose tissue and risk of metastasis. The same findings were seen about metastasis and death risk related to CLA level in this tissue. To explain the findings, it should be stated that the amount of CLA in breast adipose tissue might be too low to induce the protective effect on tumor.[10]

Generally in three cohort studies the hypothesis that CLA can reduce the risk of death, metastasis or incidence of breast neoplasm wasn't observed.

Case–control studies

Among three case-control studies, one study investigated CLA content in breast tissue and its relation to breast cancer risk that no relation was seen. Another study measured CLA dietary intake and no association was seen but, in the other reaserch both CLA dietary intake and serum levels assessed that an inverse association between both variables with reduction of breast cancer risk among postmenopausal women was absorved.[9]

In a case-control survey, the efficacy of total CLA dietary intake and its isomer (9:11) has been examined in 1166 women with breast cancer as case and 2036 healthy subjects as control. They were matched by age, race and the county of residence. At the baseline dietary assessment was carried out by self-administered FFQ. Although, this study categorized participants to pre and post-menopausal women, no significant difference was detected at all. The extracted data of ER evaluation illustrated a marginally significant decrease breast cancer rate among patients with ER-negative tumor in highest compared to lowest quartile for CLA dietary intake. The important point in this study is its high sample size. However, assessment of some cofounders factors

like physical activity and use of estrogen replacement therapy were ignored in this study.[15]

In the other study, Chajès investigated CLA content in breast adipose tissue and the risk of breast cancer metastasis. The objectives in the case and control groups include 241 women with invasive breast carcinoma and 88 women with benign breast pathologies respectively that weren't matched. There was no change observed in comparison third tertile to first tertile of CLA levels in this tissue with the malignancy metastasis while it was adjusted for BMI and menopausal states. Some limitations should also be indicated such as lack of assessment of physical activity, family history of breast cancer, estrogen replacement therapy and menarche age. Other limitations are, not CLA dietary intake assay and not enough participants in both groups. Furthermore, the control group included women with benign breast disease that were more at risk for breast cancer than healthy women.[10]

Results of another research suggested an inverse association between incidence of breast tumor and CLA serum and dietary intake in postmenopausal women with breast cancer. In this survey dietary intake and serum CLA level in Finnish women aged 25-75 was assessed. Case and control groups comprised premenopausal and postmenopausal women that were individually matched to the breast cancer cases for age and residence.[9]

Clinical trial study

Based on a clinical trial study,[14] 24 women with resectable invasive breast adenocarcinoma were asked to consume seven and half gr of CLA as capsule gel include 50:50 ratio of 9c, 11 t and 10 t, 12 c per day. The mean duration of intervention was 12 days (range 9.5-20.5) before tumor resection. The CLA concentration in plasma was obtained before initiation of intervention and on the day of resection. Also, some enzymes such as FAS, LPL, FAS regulator protein and spot 14 proteins (S14), before and after CLA administration were examined. These two enzymes can provide fatty acids for tumor growth.[19] S14 mediates the induction of lipogenesis by progestin in breast cancer cells and accelerates their growth. High expression of S14 in primary invasive breast cancer is conspicuously recurrence prediction.[20] The measurement showed the higher plasma concentration of 9c, 11t CLA at baseline and after treatment in compared with 10t, 12c CLA. Although, the findings indicated that S14 protein expression decreased after CLA administration that resulted in reduction of proliferation index, no significant change in FAS or LPL expression was observed.

DISCUSSION

This systematic review shows no consistent findings to support the concept that CLA consumption or serum CLA levels or CLA content in breast tissue is associated with a lower risk of breast cancer, metastasis or death. As mentioned previous, among case-control studies, only one of them showed an inverse relation between breast cancer risk and serum level and dietary intake of CLA.[9] Also, among cohort studies, only one survey provided marginally inverse association[8] and only one clinical trial of this research reported a positive effect of CLA on some mediators and enzymes concerning breast cancer. Despite controlling of some cofounders in these studies, results were low reliable due to type of studies and its bias such as sampling and recall bias.

In addition, differences in CLA assessment, dietary intake, serum and tissue, caused difficulty in clear result. These comparisons showed that among two studies CLA content in breast tissue didn't have any relationship with breast cancer incidence, metastasis and death.[10,11] Furthermore, in one of four studies that assessed the risk of breast cancer against dietary CLA intake, an inverse association was seen.[9] Also, one trial was declared that high CLA plasma concentration had favorite effects on tumor indices.[14]

It should be state that in these surveys, average of CLA dietary intake may be lower than CLA amounts which have protective effects.[8,13] According to some studies anticancer effects of CLA were seen in 2.8 g/d of CLA for a 70 Kg person that it was different rather than usual dietary intake in human. So it could be concluded that CLA supplement could supply higher and beneficial effects than dietary CLA.[21]

Also, it is important to considerate that dietary CLA and its effects may be modified by some dietary factors such as fruits, vegetables and other kinds of fats that maybe effective on breast cancer risk and metastasis risk.[22] One considerable confounder factor is that all studies except one of them, omitted the vaccinic acid assessment that can convert to CLA in body.[9]

Although dairy products and meat products are the sources of CLA, the protective impacts between these products with breast carcinoma didn't illustrated.[23,24] Due to some heterocyclic amines and polyaromatic hydrocarbons created in the cooking of red meat, it can alter the favorable effects of CLA. So, dietary patterns which represent a complex integration of food and nutrients, should be concurrently used with food item assessment to explore the association between CLA and the risk of breast cancer, metastasis and death.

Other limitations in these studies include small population, measurement and report bias, loss of CLA measurement in serum, and investigation between CLA in serum and dietary intake and some confounding variables such as body fatness, high-energy intake, physical activity, and family history of breast cancer, estrogen replacement therapy and age at menarche. Also, it's necessary to remind some poor-quality and heterogeneous studies maybe cause misjudge about conclusion.

Further, for their nature, systematic reviews have limitation that definitely our article is not separated from them, like publication, reporting, performance, attrition and detection biases.

Several mechanisms involved in the biological activity of this fatty acid on malignant cells. The inhibitory effects of CLA on breast cancer cells may result from decreased estrogen receptors that it can decrease proliferation of ER-positive cells selectively.[25] ER is over expressed in around 70% of breast cancer cases that is called estrogen receptor positive (ER+). It can stimulate proliferation of mammary cells via increasing in cell division and DNA replication leading to mutation. Also, PR is related to epithelial cell growth. Furthermore, estrogen metabolism produces genotoxic waste like Quinone derivatives that decay DNA base and cause to mutation and malignancy.[26]

It has been shown that CLA may induce apoptosis in ER+ breast epithelial cells via down regulation of anti-apoptosis protein, B-cell lymphoma 2(BCL-2) that result in reduction of breast cancer risk.[27] Also, it seems that this fatty acid influence on these tumors via changing the lipid metabolism in breast fat tissue by reduction of FAS. This enzyme is essential for nourishing the cancer cells.[28] Additionally, some articles revealed the increased activity and expression of FAS caused to disturb the cell cycle controlling so it could not induce apoptosis in S phase.[29] Suppressing of S14 gene expression, a nuclear protein that regulates expression of FAS in mammary epithelial and adipose tissue cells, as well as FAS can be exerted by CLA. Altogether, inhibition of spot 14 proteins and FAS genes expression can lead to prevention of breast cancer cells growth.[30] As well, CLA was proposed as aLXR agonist, inducing genes implicated in cholesterol efflux and increasing the mRNA levels of LXR target genes and HMG-CoA-reductase, as a rate limiting enzyme in the cholesterol biosynthesis process. Therefore, LXR activation by CLA leads to cholesterol cell deprivation by stimulating its efflux resulting to inhibition of cell proliferation and stimulation of apoptosis.[31] Beside mentioned mechanisms, CLA also have effect on caveolae lipid composition and function.

Caveolae are specialized plasma membrane structures that effect on cancer cell functions including cell signaling, growth and apoptosis. This report mentions that CLA can incorporate into caveolae and modulate its function in breast tumor cells.[32]

Another antitumor activity of CLA is related to stearoyl-CoA desaturase (SCD) enzyme. The high protein expression of stearoyl-CoA desaturase-1 (SCD1), which is a synthetic enzyme of MUFA, was shown in the cancerous areas of breast. The cis-9, trans-11 and trans-10, cis-12 CLA isomers regulate human SCD by reducing SCD protein levels. So it can be protective dietary agent against breast cancer.[33]

CONCLUSION

Evidences in this systematic review are inconsistent and suggested CLA consumption might not lead to a significant change in risk of breast cancer. Narrow ranges of CLA dietary intake, measurement and report bias, confounding variables such as body fatness, high-energy intake, other dietary agents, physical activity, and family history of breast cancer, estrogen replacement therapy and age at menarche are probable explanations for these inconsistent results. As well as, main source of CLA, meat and dairy are rich in saturated fatty acids and other components involved in carcinogenic pathway. So, further well designed studies are required, particularly in considering the main breast cancer risk factors.

Conflicts of interest
The authors report no conflicts of interest concerning this study.

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