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Dietary conjugated linoleic acid and long-chain *n*-3 fatty acids in mammary and prostate cancer protection: a review

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Abstract
The role of dietary fatty acids on cancer is still controversial. To examine the current literature on the protective role of conjugated linoleic acid (CLA) and marine long-chain fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] and the risk of breast and prostate cancer, data from 41 case-control and cohort studies and relevant *in vitro* and animal experiments were included in this 2000–2010 revision. Epidemiological studies on CLA intake or its tissue concentration related to breast and prostate tumorigenesis are not conclusive; EPA and DHA intake have shown important inverse associations just in some studies. Additional research on the analysed association is required.

Keywords: n-*6 and* n-*3 fatty acids, conjugated linoleic acid, eicosapentaenoic acid, docosahexaenoic acid, breast cancer*

Introduction

Conjugated linoleic acid (CLA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are polyunsaturated fatty acids (PUFAs) which have been extensively studied with relation to their anticancer properties. CLA is a heterogeneous group of geometrical and positional isomers of linoleic acid (LA, 18: 2*n*-6) with conjugated double bonds. Dairy products and lean meat from ruminant animals are the major sources of this fatty acid in the human diet (Martins et al. 2007). Long-chain marine *n*-3 PUFAs, EPA (20: 5*n*-3) and DHA (22: 6*n*-3), are found mainly in fatty cold-water fish, seafood and fish oils (Larsson et al. 2004).

Considering their influence on human health, the consumption of fish and seafood usually appears to play a protective role on the risk of several types of cancer (Hu et al. 2008), whereas international nutritional guidelines have lately limited the intake of dairy products such as whole milk, butter and cheese because of their considerable amount of cardiovascular disease (CVD)-related saturated fatty acids and cholesterol. Similarly, available literature has associated a high intake of red and processed meat with an increased risk of various types of cancer (mainly colorectal cancer) causing a negative perception about the role of red meat in health (Alfaia et al. 2010; McAfee et al. 2010). However, the risk associated with red meat consumption may be related to the high-fat intake and/or to the carcinogens generated through certain cooking and processing methods (Navarro et al. 2004; McAfee et al. 2010).

This review examines the current literature referred to the protective role of CLA, EPA and DHA and their dietary sources with a particular focus on the results obtained from epidemiological studies.

Methodology

The purpose of the present study was to review the current literature regarding the CLA and marine

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long-chain fatty acids (EPA and DHA) intake and the consumption of their food sources – meat and dairy products for CLA and fish/seafood products for EPA and DHA – and the risk of breast and prostate cancer. A PubMed search of case-control, cohort and nested case-control studies within cohorts published from 2000 to March 2010 was carried out. Additional published reports were obtained by crossmatching the references of relevant articles.

Thirty-seven studies which satisfied the following conditions were chosen to be included in this review: (1) studies based on a dietary questionnaire, in which odds ratio (OR) or relative risk (RR) concerning CLA, EPA or DHA intakes was calculated; (2) studies based on a dietary questionnaire having calculated OR or RR for meat, diary products, milk, fish or seafood intake and (3) studies based on CLA, EPA or DHA serum or tissue levels used as intake biomarkers, having calculated OR or RR for those fatty acids. Four cohort studies which calculated the hazard ratio (HR) and incidence rate ratio (IRR) were also included (Stripp et al. 2003; Crowe et al. 2008; Witt et al. 2009; Brasky et al. 2010).

Available *in vitro* assays and experimental studies published in the last 10 years were commented, but with no aim of exhaustivity.

Dietary sources of CLA, EPA and DHA

Conjugated linoleic acid

CLA is produced by LA partial ruminal biohydrogenation and/or by its endogenous synthesis in the tissues themselves, particularly in the mammary glands (Dhiman et al. 2005).

Several CLA isomers have been identified according to the position and geometry of their double bonds (Kelley et al. 2007). The two major CLA forms are *cis*-9,*trans*-11-CLA – also called rumenic acid (Kramer et al. 1998) – and *trans*-10,*cis*-12-CLA. Other isomers are *trans*-7,*trans*-9-CLA, *cis*-9,*cis*-11-CLA, *trans*-9,*trans*-11-CLA, *cis*-10,*cis*-12-CLA, *trans*-10,*trans*-12-CLA, *trans*-11,*trans*-13-CLA and *cis*-11,*cis*-13-CLA (Kelley et al. 2007).

Meat and dairy products from ruminant animals are the major dietary sources of *cis*-9,*trans*-11-CLA followed by *trans*-7,*cis*-9-CLA representing 75–90% and 10% of the CLA content, respectively (Palmquist et al. 2005; Kelley et al. 2007). CLA is located in the interstitial non-visible fat of meat being distributed along the muscle fibres and in the subcutaneous depots. This invisible intramuscular fat ranges from 25 to 50 g/kg (2.5–5%) in lean meat. It should be considered that the visible fat is often easily discarded whereas the interstitial fat is always consumed. Thus, the beneficial effects of small amounts of CLA are relatively enhanced in lean meat as compared that those of the fatty meat sub-products because the latter contain a substantial amount of saturated fatty acids and cholesterol (Eynard and Lopez 2003).

Partially hydrogenated oils such as shortenings and margarines containing mainly *trans*-10,*cis*-12-CLA are other CLA sources (Kelley et al. 2007). Supplementary CLA forms are mostly found as an equal mix of *cis*-9,*trans*-11 and *trans*-10,*cis*-12 isomers (Whigham et al. 2007).

A large number of studies have demonstrated that CLA content in milk and meat is affected by several factors such as the animal's breed, age, diet and the food supplements affecting the ruminant diet (Realini et al. 2004; Dhiman et al. 2005; De La Torre et al. 2006; Latimori et al. 2008).

It has been shown that an exclusive pasture diet or a forage diet combined with a low grain supplementation causes a higher meat and dairy food CLA concentration and also influences the fatty acid composition without modifying the physical characteristics of ruminant products (Schmid et al. 2006; Latimori et al. 2008; Daley et al. 2010).

CLA is also a stable compound under storage conditions and normal cooking or processing methods of milk and meat (Dhiman et al. 2005; Schmid et al. 2006; Gagliostro et al. 2007a–c; Sarriés et al. 2009). No changes were observed after storing dairy products at low temperatures or following some processing methods. That is the case of low-fat yogurt, regular-fat yogurt, low-fat and regular-fat ice cream, sour cream or cheeses (MacDonald 2000; Gagliostro et al. 2007a–c). However, it has been suggested that aged cheeses have lower amounts of CLA than those with a shorter ripening period (MacDonald 2000).

EPA and DHA

The content of marine EPA and DHA *n*-3 fatty acids varies greatly according to the fish species, its total fat content, the geographical location and the water temperature. Thus, the *n*-3 fatty acid concentration varies from the Atlantic to the Pacific Ocean. Deep cold-water fishes such as mackerel, tuna and salmon have the highest EPA and DHA content. The fatty acid composition of farming fishes varies according to their diets (Berquin et al. 2008).

Humans are able to convert alpha-linoleic acid from green vegetables and vegetable oils into EPA and DHA. However, the conversion process is very inefficient and depends on a competitive inhibition related to *n*-6 synthesis pathways (Williams and Burdge 2006; Berquin et al. 2008).

A number of strategies to increase *n*-3 PUFA intake in humans have been developed. For instance, feeding animals with fish extracts or algae (oils) implies a DHA increase of about 2-fold in beef, 7-fold in chicken, 6-fold in eggs and 20-fold in salmon (Bourre 2005). Nevertheless, those strategies have been limited due to the adverse effects on sensory qualities and the higher price of the final products (Howe et al. 2002;

Table I. *In vitro* effects of CLA on breast and prostate tumour cells.

Reference	Cell lines	Possible effect	Exposure	Results
Kemp et al. (2003)	Breast (MCF7) and colon (HCT116) cancer cells containing wild-type p53.	Action on cell cycle progression.	CLA in various concentrations or specific isomers for different periods of time.	Inhibited the cell proliferation (*trans*-10, *cis*-12 CLA more effective than *cis*-9,*trans*-11 CLA). Elicited the cell cycle in G1. Induced the accumulation of p53, p27 and p21 tumour suppressors.
Tanmahasamut et al. (2004)	Breast cell line (MCF-7 ER +)	Anti-oestrogenic	Five purified CLA isomers and a mixture of CLA in a concentration range of 25–200 μM/l (mid-normal to supraphysiologic–pharmacologic levels).	The five isomers showed a dose-dependent inhibition of the ER + breast cancer cells growth. The most potent inhibitors were *cis*-9,*cis*-11 and *trans*-10,*cis*-12 (60% inhibition).
De la Torre et al. (2005)	Two breast cancer cell lines (MCF7 and T47D) and prostatic adenocarcinoma (PC3).	Antiproliferative	CLA isomers *cis*-9,*trans*-11, *cis*-9,*cis*-11, *trans*-9, *trans*-11, *trans*-10,*cis*-12, *trans*-7,*cis*-9 and *cis*-11,*trans*-13. Derivatives of *cis*-9,*trans*-11 CLA (*cis*-8,*cis*-11,*trans*-13-20:3) and *trans*-10,*cis*-12 CLA (*cis*-6,*trans*-10, *cis*-12-18:3 and *cis*-8,*trans*-12,*cis*-14-20:3).	*Trans*-9,*trans*-11-18:2 and CLA-conjugated derivatives exhibited the strongest growth-inhibitory effect against cancer cells.
Palombo et al. (2002)	Human prostate carcinoma cells (PC3)	Antiproliferative	Two commercial CLA preparations and their constituent isomers, *cis*-9,*trans*-11; *cis*-9,*cis*-1 and *trans*-10,*cis*-12.	Physiologic levels of two CLA preparations, and the *cis*-11,*trans*-13-conjugated eicosadienoic acid (a *cis*-9,*trans*-11 CLA elongation product), induced dose-dependent inhibitory effects on cancer proliferation.
Ochoa et al. (2004)	Human prostate carcinoma cells (PC3)	Antiproliferative enzyme and oncoprotein gene expression	Individual purified *cis*-9,*trans*-11 CLA and *trans*-10,*cis*-12 CLA and a 50:50 isomer mixture.	Antiproliferative effects of CLA isomers are related to different pathways. *Trans*-10,*cis*-12 works preferentially through apoptosis modulation and cell cycle control, whereas *cis*-9,*trans*-11 CLA isomer affects the AA metabolism.
Song et al. (2006)	Human prostate carcinoma cells (LNCaP)	Apoptosis promotion	50:50 CLA mixture of *cis*-9,*trans*-11 and *trans*-10,*cis*-12 isomers or individual *cis*-9,*trans*-11 or *trans*-10,*cis*-12 CLA isomers at concentrations of 6, 25 and 50 μM.	Only *cis*-9,*trans*-11 CLA isomer significantly increased TNF-α-induced apoptosis (by 59%), which correlated with a reduction in NF-κB transcriptional activity (by 35%), NF-κB binding activity (by 15%), and phosphorylation of IκBα (by 36%).
Ip et al. (2000)	Rat mammary adenocarcinoma cells (NMU)	Apoptosis promotion	Mixture of CLA isomers.	CLA significantly increased the number of apoptotic cells.
Kim et al. (2005)	Breast human tumour cells (MDA-MB-231ER–)	Modulation of 5-lipoxygenase activity	*Cis*-9,*trans*-11 and *trans*-10,*cis*-12 CLA.	*Trans*-10,*cis*-12 CLA reduced 5-HETE production through competition with substrate AA and reduction in FLAP expression.

Notes: CLA, conjugated linoleic acid; AA, arachidonic acid; TNF-α, tumour necrosis factor alpha; NF-κB, nuclear factor kappa B; IκBα, inhibitor of kappa B alpha; 5-HETE, 5-hydroxyeicosatetraenoic acid; FLAP, 5-lipoxygenase-activating protein.

Table II. Experimental CLA, EPA and DHA exposure related to breast and prostate tumours.

Reference	Tumour	Animal model	Dietary treatment	Results
Ip et al. (2001)	Mammary	Rat	Mixture of CLA isomers (*cis*-9,*trans*-11 CLA and *trans*-10,*cis*-12 CLA) or *cis*-9,*trans*-11 CLA rich butter fat.	Suppressed expression of cyclin D1 and cyclin A in the terminal end buds and alveolar clusters.
Yang et al. (2003)	Mammary	Rat	Diet containing 1% CLA (w/w).	Decreased PhIP-induced mutagenesis (38%).
Lock et al. (2004)	Mammary	Rat	VA-enriched diet.	Increased CLA tissue content. Reduced risk of developing premalignant lesions. Decreased proliferative activity of premalignant cells.
Corl et al. (2003)	Mammary	Rat	CLA- and VA-enriched butter.	Increased CLA accumulation in the mammary fat pad. Decreased tumour formation.
Lavillonniere et al. (2003)	Mammary	Rat	Diets containing 1% *cis*-9,*trans*-11 isomer or isomer mixture.	Significant decrease (44–45%) in tumour mass.
Hubbard et al. (2003)	Mammary tumour metastasis	Mouse	Diets containing *cis*-9,*trans*-11 CLA, *trans*-10,*cis*- 12 CLA or a mixture.	Decreased lung tumour volume. Decreased metastatic cell survival in both spontaneous metastasis and implantation.
Banni et al. (1999)	Mammary	Rat	Diets containing 0.5, 1, 1.5 or 2% CLA.	0.5 and 1% dietary CLA decreased TEB density and mammary tumour yield.
Ip et al. (1999)	Mammary	Rat	High CLA butter fat and a mixture of CLA isomers at a level of 0.8%.	CLA reduced the mammary epithelial mass (22%), decreased the TEB population size (30%), suppressed the TEB cell proliferation (30%) and inhibited the mammary tumour yield (53%) during the pubescence mammary gland development.
Cohen et al. (2003)	Prostate	Rat	CLA or CLA in combination with isoflavone-rich soy protein isolate.	No *in vivo* development and growth inhibition of prostate tumour cells.
Robinson et al. (2001)	Mammary	Rat	Long-chain *n*-3 fatty acids.	Decreased tumour growth (31% lower). Beneficial effects on host immune defences (interferon-gamma and tumour necrosis factor-alpha production).
Manna et al. (2007)	Mammary	Rat	Fish oil	Decreased cell proliferation. Reduced DPCs. Increased expression of p53 protein in preneoplastic mammary tissue.
Yuri et al. (2003)	Mammary	Rat	EPA, a 1:1 mixture of EPA plus DHA, or DHA supplementation.	DHA decreased the tumour incidence and multiplicity in MNU-induced mammary carcinogenesis.

Notes: CLA, conjugated linoleic acid; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine (potent mutagen and carcinogen formed at high temperature during meat cooking); TEB, terminal end buds (proliferative compartment within the virgin mouse mammary gland, responsible for the development of the ductal system, and site of significant apoptosis believed to cause canalization of the developing ducts); VA, *trans*-11 18:1, vaccenic acid (fatty acid converted into CLA through endogenous synthesis via 9-desaturase); DPCs, DNA-protein cross links (type of DNA damage used as a biomarker of early carcinogenic exposure or early malignant lesions); MNU, *N*-methyl-*N*-nitrosourea (carcinogen, mutagen and teratogen used to induce cancer in animal models); EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Doughman et al. 2007). In addition, genetic modifications may increase the *n*-3 PUFA content of traditional oils obtained from plants such as canola and soybean. The advent of DHA algal sources provides those fatty acids in a concentrated form through microencapsulation, ensuring stability of this unstable fatty acid (Whelan and Rust 2006).

Trends in meat, dairy and fish consumption

According to the Food and Agriculture Organization of the United Nations (FAO 2010), statistics based on food balance sheet methodology have shown worldwide a relatively stable apparent beef consumption in the last four decades, averaging 9 kg/capita/year, or the equivalent 26 g/capita/day. Argentina has shown the highest intake (153) followed by Australia (117), USA (115), Uruguay (104), Brazil (98) and Canada (91) (values correspond to g/capita/day). Bangladesh, Congo, Ghana, Liberia and the Democratic Republic of Korea showed an apparent consumption lower than 5 g/capita/day.

Global dairy production and availability (total and per capita) have increased since 1980, especially in developing countries (Wang and Li 2008). Average whole milk apparent consumption in 2005 was 130 g/capita/day ranging from less than 10 g/capita/day in Congo, Ghana and Philippines to more than 300 g/capita/day in UK, USA, Romania and Albania. Like milk, the levels of butter, cream and cheese production and consumption showed large between-region and between-country differences (FAO 2010).

Apparent fish and fishery product consumption has shown a continuous increase from 9.9 kg/capita/year in 1960s to 16.4 kg/capita/year in 2005, depending on continent, region, country and per capita income (Laurenti 2007). Thus, Maldives, Iceland, Japan, Portugal, Korea and Norway were the top five consumers in 2005 with a fish and seafood supply quantity varying from 143 to 493 g/capita/day. Other countries such as Bolivia, Ethiopia, Nepal, Pakistan and Sudan showed an apparent consumption lower than 5 g/capita/day (FAO 2010).

The analysis of dietary intake carried out as a part of the European Prospective Investigation into Cancer and Nutrition (EPIC) showed substantial geographic variation in total fish intake, fish sub-groups and the number of fish types consumed. A six- to seven-fold variation in total fish consumption was found both in women and in men between the lowest intake in Germany and the highest one in Spain (Welch et al. 2002).

Breast and prostate cancer incidence

The Second Expert Report of the World Cancer Research Fund and the American Institute for Cancer Research showed in 2007 that age-adjusted rates of breast cancer in women were increasing in most countries, particularly in areas where the incidence had previously been low, such as Japan, China and southern and eastern Europe. The highest incidence rates were in North America, Australia and northern Europe, and the lowest in Africa and Asia. With regard to prostate cancer, the highest age-adjusted incidence rates were in North America, parts of the Caribbean and Oceania, and lowest rates in Melanesia and much of Asia (World Cancer Research Fund 2007).

CLA, EPA, DHA and mammary and prostate cancer

Several *in vitro* assays showed that CLA isomers may be protective in the tumorigenesis process through cell cycle control, anti-oestrogenic, antiproliferative, proapoptotic and antiangiogenic actions. Table I summarizes the studies related to breast and prostate cancer cells exposed to CLA.

The current *in vitro* evidence indicate that long-chain *n*-3 fatty acids inhibit cancer promotion and progression. Several molecular mechanisms have been proposed as follows: the suppression of arachidonic acid-derived eicosanoid biosynthesis (Grimm et al. 2002); the influence on transcription factor activity (Murata et al. 2001; Chambrier et al. 2002; Novak et al. 2003), gene expression (Collett et al. 2001) and signal transduction pathways (Jeyarajah et al. 1999; Duncan et al. 2005) and the alteration of oestrogen metabolism (Yang et al. 2004). Recent data also suggest the potent antiangiogenic effects of EPA and DHA (Spencer et al. 2009).

A number of studies have demonstrated the proapoptotic action of EPA and DHA on human breast cancer cells as well as of DHA on prostate cancer cells (Serini et al. 2009).

Animal studies provide convincing evidence of a negative and positive relationship between *n*-3- and *n*-6-rich PUFA diets, respectively, and breast and prostate tumours. In addition, long-chain *n*-3 PUFA supplementation has shown to reduce the mammary tumour growth in rats (Robinson et al. 2001; Yuri et al. 2003). On the other hand, *n*-6 CLA has also demonstrated many beneficial effects such as significant decrease in mutagenesis, tumour formation and mammary tumour metastasis (Ip et al. 1999, 2001; Banni et al. 1999; Corl et al. 2003; Hubbard et al. 2003; Lavillonniere et al. 2003; Yang et al. 2003). CLA precursor vaccenic acid (VA, *trans*-11 18:1) showed to increase the CLA tissue content through its conversion via Delta9-desaturase (Lock et al. 2004).

Table II presents the latest experimental results on CLA, EPA and DHA exposure related to breast and prostate cancer. No studies involving prostate cancer could be found with relation to EPA and DHA and only one experiment refers to the absence of prostate tumour cell inhibition with relation to CLA (Cohen et al. 2003).

Table III. Case-control studies on the association between either CLA, EPA or DHA intake or their food sources and breast or prostate cancer risk.

Reference	Study	Tumour	Country	Subjects		Exposure	Results*
				Cases (*n*)	Controls (*n*)		
Aro et al. (2000)	Ca/Cl	Breast	Finland	195	208	Dietary CLA	− − − A in postmenopausal women
						Serum CLA	− − − A in postmenopausal women
						Serum VA	− − − A in postmenopausal women
Chajès et al. (2002)	Ca/Cl	Breast	France	241	88	CLA in breast adipose tissue	+ A
Nkondjock et al. (2003)	Ca/Cl	Breast	Canada	414	429	EPA and DHA	NA
Goodstine et al. (2003)	Ca/Cl	Breast	USA	565	554	EPA and DHA	NA
						Long-chain *n*-3/*n*-6 ratio	− A with increasing ratio
Dai et al. (2002)	Ca/Cl	Breast	China	1459	1556	Red meat	+ + A, particularly with deep-fried red meat to well done
						Milk	NA
						Total fish and marine fish	NA
						Freshwater fish	+ + A
Hu et al. (2008)	Ca/Cl	Breast prostate	Canada	5039	19,732	Total meat	+ A with breast cancer, especially for postmenopausal NA with prostate cancer
						Red meat	NA with breast or prostate cancer
						Processed meat	NA with breast cancer + + A with prostate cancer
						Total fish	NA with breast or prostate cancer
Terry et al. (2002)	Ca/Cl	Breast	Sweden	2085	2000	Total, fatty and lean fish	NA
Hirose et al. (2003)	Ca/Cl	Breast	Japan	2385	19,013	Beef	NA
						Milk	− − A, especially among postmenopausal women
						Fish	− − A for cooked/raw fish (*sashimi*) consumption among postmenopausal women
Shannon et al. (2003)	Ca/Cl	Breast	USA	441	370	Red meat	++ + A
						High-fat meat	+ + A
						Low-fat meat	− A
						Dairy products	− A
						High-fat dairy	NA
						Low-fat dairy	− A
						Fish	− − A
Kim et al. (2009)	Ca/Cl	Breast	Korea	358	360	Fatty fish	− − − A
						Lean fish	NA
						EPA and DHA	− − − A in postmenopausal women
Saadatian-Elahi et al. (2002)	Nested Ca/Cl	Breast	USA	197	197	Serum EPA and DHA	NA
Wirfält et al. (2004)	Nested Ca/Cl	Breast	Sweden	237	673	Erythrocyte EPA and DHA	NA
Pala et al. (2001)	Nested Ca/Cl	Breast	Italy	71	141	Erythrocyte EPA and DHA	NA
Kuriki et al. (2007)	Nested Ca/Cl	Breast	Japan	103	309	Dietary and erythrocyte EPA and DHA	− − − A
Shannon et al. (2007)	Ca/Cl	Breast	China	322	1030	Erythrocyte EPA	− − − A
						Erythrocyte DHA	− A

TABLE III – *continued*

Reference	Study	Tumour	Country	Subjects		Exposure	Results*
				Cases (*n*)	Controls (*n*)		
Bagga et al. (2002)	Ca/Cl	Breast	USA	73	74	EPA and DHA in breast adipose tissue	NA
						Long-chain *n*-3/*n*-6 ratio	−A with increasing ratio
Maillard et al. (2002)	Ca/Cl	Breast	France	241	88	DHA in breast adipose tissue	− − −A
						Long-chain *n*-3/*n*-6 ratio	− − −A with increasing ratio
Sonoda et al. (2004)	Ca/Cl	Prostate	Japan	140	140	Total fish	− − −A
						Milk and dairy products	NA
Kristal et al. (2002)	Ca/Cl	Prostate	USA	605	592	EPA and DHA (food + suppl.)	NA
Männistö et al. (2003)	Nested Ca/Cl	Prostate	Finland	198	198	Dietary EPA and DHA	NA
						Serum EPA and DHA	NA
Chavarro et al. (2007)	Nested Ca/Cl	Prostate	USA	476	476	Blood EPA	− −A
						Blood DHA	−A
Fradet et al. (2009)	Ca/Cl	Prostate	USA	466	478	EPA	− − −A
						DHA	− − −A
						Dark fish	− − −A
						Tuna	−A
						Shellfish	− −A
Hedelin et al. (2007)	Ca/Cl	Prostate	Sweden	1499	1130	Fatty fish	− −A
						EPA + DHA	− −A
						EPA + DHA/*n*-6 ratio	− −A with increasing ratio
Shannon et al. (2010)	Ca/Cl	Prostate	USA	127	183	Erythrocyte EPA	NA
						Erythrocyte DHA	NA

Notes: Ca/Cl, case-control; Nested Ca/Cl, nested case-control; CLA, conjugated linoleic acid; VA, vaccenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; *Association level is presented according to the risk classification given by the World Cancer Research Fund and American Institute for Cancer Research 1997: + + + A, strong positive association (OR >2, significant); + + A, moderate positive association (OR 1.5–2, significant; OR >2, not significant); + A, weak positive association (OR <1.5, significant; OR 1.5–2, not significant); − − −A, strong negative association (OR <0.5, significant); − −A, moderate negative association (OR 0.5–0.75, significant; OR <0.5, not significant); −A, weak negative association (OR >0.75, significant; OR 0.5–0.75, not significant); NA, no association.

Table IV. Cohort studies on the association between either CLA, EPA or DHA intake or their food sources and breast or prostate cancer risk.

Reference	Tumour	Country	Follow-up period (years)	Subjects		Exposure	Results*
				Cases (*n*)	Cohort (*n*)		
Voorrips et al. (2002)	Breast	The Netherlands	6.3	941	62,573	Total CLA and VA	+ A
						EPA and DHA	NA
						Milk, butter and other dairy products	NA
						Meat and beef	NA
McCann et al. (2004)	Breast	USA	5	1122	2036	Total CLA	NA in premenopausal or postmenopausal women
						Cis-9,*trans*-11 CLA	− A in premenopausal ER-tumours
Larsson et al. (2009)	Breast	Sweden	17.4	2952	61,433	Total CLA	NA in overall or ER/PR-defined breast cancer
Park et al. (2007)	Prostate	USA	8	4404	82,483	Beef	NA
						Fish and shellfish	NA
						EPA and DHA	NA
Stripp et al. (2003)	Breast	Denmark	3.6	424	23,693	Total fish	+ A in ER + tumours†
						Fatty and lean fish	NA†
Engeset et al. (2006)	Breast	Europe	6.4	4776	310,671	Total, fatty and lean fish	NA
Holmes et al. (2003)	Breast	North America	18	4107	88,647	Total fish	NA in premenopausal or postmenopausal women
Missmer et al. (2002)	Breast	USA and Western Europe	Up to 15	7379	351,041	Total fish, seafood and shellfish	NA
						Dairy products and red meat	NA
Cho et al. (2003)	Breast	North America	8	714	90,655	Total fat	NA
						Long-chain *n*-3 fatty acids	NA
						Total fish	NA
						Red meat	NA
						Dairy products	+ A with high-fat dairy products
Gago-Dominguez et al. (2003)	Breast	China	5.3	314	35,298	Total fish	− A, especially in advanced stages
						Long-chain *n*-3 fatty acids	− − A
Wakai et al. (2005)	Breast	Japan	7.6	129	26,291	Fish fat	− − A
						Long-chain *n*-3 fatty acids	− − A
Thiébaut et al. (2009)	Breast	France	8	1650	56,007	Long-chain *n*-3 fatty acids	NA
Brasky et al. (2010)	Breast	USA	6	880	35,016	Fish oil	− − A‡
Witt et al. (2009)	Breast	Denmark	4.8	463	1083	Total marine FA in adipose tissue	NA‡
						Adipose tissue EPA	NA‡
						Adipose tissue DHA	NA‡
Crowe et al. (2008)	Prostate	Europe	8.7	2727	142,520	Red and processed meat fat	NA‡
						Dairy products fat	NA‡
						Fish and shellfish fat	NA‡
Wallström et al. (2007)	Prostate	Sweden	11	817	10,564	Dietary EPA	NA
						Dietary DHA	+ A

TABLE IV – *continued*

Reference	Tumour	Country	Follow-up period (years)	Subjects		Exposure	Results*
				Cases (*n*)	Cohort (*n*)		
						EPA/DHA supplements	NA
Leitzmann et al. (2004)	Prostate	USA	14	2965	47,866	Dietary EPA	– A
						Dietary DHA	NA

Notes: CLA, conjugated linoleic acid; VA, vaccenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; FA, fatty acids; * Association level is presented according to the risk classification given by the World Cancer Research Fund and American Institute for Cancer Research 1997: + + + A, strong positive association (RR > 2, significant); + + A, moderate positive association (RR 1.5–2, significant; RR > 2, not significant); + A, weak positive association (RR < 1.5, significant; RR 1.5–2, not significant); – – – A, strong negative association (RR < 0.5, significant); – – A, moderate negative association (RR 0.5–0.75, significant; RR < 0.5, not significant); – A, weak negative association (RR > 0.75, significant; RR 0.5–0.75, not significant); NA, no association.; † Results presented as IRR; ‡ Results presented as HR.

A few epidemiological studies have investigated the relationship between CLA intake or tissue concentrations and the tumour incidence. Unfortunately, those studies have yielded far less conclusive results than the animal experiments.

The results of epidemiological studies referred to CLA, EPA and DHA intake and their food sources with relation to the risk of breast and prostate cancer are shown in Tables III and IV.

Discussion

Vegetable fats have been believed to benefit the human health, whereas animal fats were thought to be detrimental, particularly with regard to CVD promotion and cancer development.

The relationship between the dietary fat intake and cancer has been somewhat controversial. However, the analysis of specific food components such as different fatty acids has shown that not all fats of animal origin are disease promoters. For instance, fish and seafood contain long-chain *n*-3 EPA and DHA which appear to be beneficial to the prevention of certain types of cancer such as colon, liver, breast, prostate and lung (Manna et al. 2007). Those fatty acids must be incorporated through the diet or supplements because human endogenous synthesis of these is possible but inefficient (Lucas et al. 2010).

EPA and DHA as well as fish and particularly the fatty fish intake have shown an important inverse relation to breast cancer (Gago-Dominguez et al. 2003; Shannon et al. 2003; Wakai et al. 2005; Kim et al. 2009; Brasky et al. 2010). Coincidently, a significant negative association was found between the EPA and DHA content in whole blood, erythrocyte, serum or breast adipose tissue and the mammary cancer (Maillard et al. 2002; Kuriki et al. 2007; Shannon et al. 2007). However, a large number of studies have found no association (Pala et al. 2001; Bagga et al. 2002; Dai et al. 2002; Missmer et al. 2002; Saadatian-Elahi et al. 2002; Terry et al. 2002; Voorrips et al. 2002; Cho et al. 2003; Goodstine et al. 2003; Holmes et al. 2003; Nkondjock et al. 2003; Stripp et al. 2003; Wirfält et al. 2004; Engeset et al. 2006; Park et al. 2007; Crowe et al. 2008; Hu et al. 2008; Thiébaut et al. 2009; Witt et al. 2009).

Some authors revealed no association between long-chain *n*-3 fatty acids or fish consumption and the prostate cancer risk (Kristal et al. 2002; Männistö et al. 2003; Hu et al. 2008), whereas Sonoda et al. (2004), Fradet et al. (2009) and Hedelin et al. (2007) observed a moderate-to-strong negative association. EPA and DHA content in blood, but not in serum or erythrocyte were inversely related to prostate cancer (Männistö et al. 2003; Chavarro et al. 2007; Shannon et al. 2010).

CLA showed to be a potent anticarcinogenic factor both in *in vitro* and *in vivo* studies (Banni et al. 1999; Ip et al. 1999, 2000, 2001; Palombo et al. 2002; Corl

et al. 2003; Hubbard et al. 2003; Kemp et al. 2003; Lavillonniere et al. 2003; Yang et al. 2003; Ochoa et al. 2004; Tanmahasamut et al. 2004; De la Torre et al. 2005; Kim et al. 2005; Song et al. 2006). Nevertheless, a limited number of epidemiological studies are not conclusive regarding the association between dietary CLA or its food sources and the breast or prostate cancer (Aro et al. 2000; Voorrips et al. 2002; McCann et al. 2004; Park et al. 2007). Thus, Aro et al. (2000) found a decreased breast cancer risk in postmenopausal women in relation to dietary and serum CLA. Prospective cohort studies carried out by Voorrips et al. (2002), Park et al. (2007) and McCann et al. (2004) showed either a weak positive or no association. Several factors may be responsible for those findings. One limitation of the epidemiological versus the experimental studies could be the CLA exposure level. Although a CLA daily consumption of 0.8–3 g has been thought to be protective to cancer, it derives from extrapolating the experimental rat model results to humans (Martins et al. 2007). CLA usual consumption in humans may be under those levels (Ip et al. 1994; McCann et al. 2004; Martins et al. 2007) and the amount of CLA used in animals is attainable just by supplements (Kelley et al. 2007). In addition, the inappropriate dietary assessment instruments frequently used in epidemiological studies and the incomplete dietary CLA databases could contribute to underestimating the CLA consumption (Ritzenthaler et al. 2001; Martins et al. 2007).

Concerning CLA source food intake, low-fat meat, milk and dairy products showed weak to moderate negative relation to breast cancer (Hirose et al. 2003; Shannon et al. 2003). In contrast, no association between the same products and prostate cancer risk has been reported (Sonoda et al. 2004; Hu et al. 2008). High red meat intake has been associated with an elevated risk of breast cancer in some epidemiological studies. It is important to remark that most of them did not consider its cooking methods, which may add mammary carcinogens such as heterocyclic amines and polycyclic aromatic hydrocarbons to meat when cooked at high temperature (Dai et al. 2002; McAfee et al. 2010). In addition, many studies did not discriminate the intake of meat or fish with regard to their fatty content, considering that CLA is contained mainly in low-fat meat and EPA and DHA in fatty marine fish.

The diet complexity and the potential interactions among its different components have recently switched the focus from studies on individual foods or nutrients to those considering the dietary patterns. Although few studies have revealed consistent associations between the dietary patterns and cancer risk, they represent an overall dietary picture that appears as more realistic (Edefonti et al. 2009).

The role of dietary fatty acids on breast and prostate cancer is still controversial. Up to now and according to most human trials, only EPA and DHA seem to have a cancer protective effect. On the other hand, CLA has been less investigated in humans with respect to the other two fatty acids, and the results do not correlate with those obtained from *in vitro* and *in vivo* studies.

In spite of the numerous papers published in the last 10 years, many questions still remain: could a healthy dietary pattern rather than specific food consumption be the key for breast and prostate cancer prevention? Does the fatty acid natural form have the same effect as its synthetic/concentrated presentation and could that be the reason for the differences observed between the experimental and epidemiological results? Which are the specific recommendations regarding CLA, EPA and DHA intake to prevent cancer? Does the genotype have relevant influence on the fatty acid metabolism and on their cancer protective effects? Which is the effect of the lifetime CLA, EPA and DHA intake?

More comprehensive data are required to have a better knowledge of the analysed association. In addition, epidemiologists should find a common and reliable way of estimating the fatty acid intake such as the employment of nutrient biomarkers.

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