Linoleic acid: A modulator of inflammatory pathways in breast cancer

Jorige Archana*

Professor and Head, Department of Pharmacology

RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad, India

Email: archanacology@gmail.com

Abstract

Linoleic acid (LA) is an essential polyunsaturated fatty acid that plays a critical role in various physiological functions. It is an omega-6 fatty acid that has several health advantages, especially for cellular, cardiovascular, and skin health. However, a balanced approach to intake is necessary due to its impact on inflammation and cancer risk. Dietary LA binds to fatty acid binding protein 5 (FABP5) of malignant cells in triple negative breast cancer (TNBC), an extremely aggressive cancer that has few treatment options. This binding activates a mammalian target of rapamycin (mTOR) growth pathway in cancer cells, triggering a signalling cascade that promotes cell proliferation in triple-negative breast cancer. To promote a better omega-6 to omega-3 ratio, it is advised to balance LA intake with omega-3 fatty acids. For optimum health, whole, less processed foods should be prioritised.

Keywords: Linoleic acid, inflammation, breast cancer

1. Introduction

The influence of our diet and food consumption on health outcomes is now substantiated by ample evidence. Over the past decades, dietary guidelines have advocated for reduced consumption of saturated fats and trans fats, and their replacement with polyunsaturated fats. Polyunsaturated fatty acids (PUFAs) are of two types. Omega-3 fatty acids and omega-6 fatty acids. Linoleic acid (LA) is an omega-6 Fatty acid that humans must obtain from their diet, alongside alpha-linolenic acid (ALA), an omega-3 fatty acid. While bacteria, protozoa, and plants can readily synthesize LA, mammals lack this de novo capability (1). LA is rich in dietary sources like meat, eggs, nuts, seeds, and vegetable oils. Linoleic acid is abundant in soybean, corn, and sunflower oils. Both the increasing availability of vegetable oils and the suggestive evidence of their capacity to lower blood cholesterol levels spiked their intake by 20-fold. The consumption of linoleic acid grew significantly as a result of this dietary modification (2). Although necessary for many physiological processes, a new study indicates that consuming too much LA may affect the onset and progression of cancer.

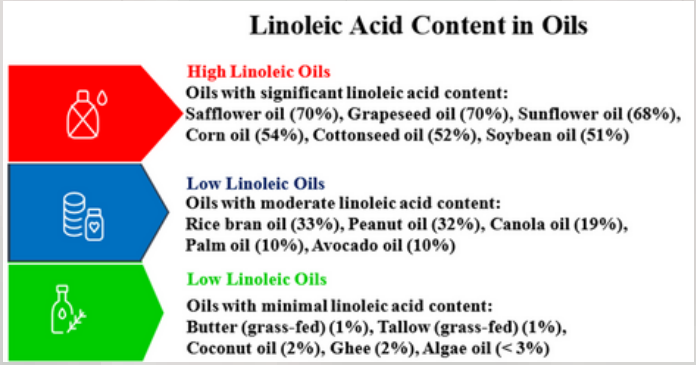

Figure 1. Approximate linoleic acid content in cooking oils

2. Beneficial effects of linoleic acid

Linoleic acid plays several important roles in human health (Table 1)

Table 1. Physiological role of linoleic acid

Benefit	Description	Ref
Skin health	Maintains skin barrier, improves hydration, and helps treat dry skin and eczema.	(3)
Cholesterol regulation	Lowers LDL (bad) cholesterol, reducing risk of cardiovascular disease.	(3)
Cell function	Essential component of cell membranes, supports structural integrity.	(3)
Growth & development	Critical for proper growth, especially in infants and children.	(3)
Immunomodulatory effect	Supports immune function and helps manage inflammation (in balanced amounts).	(4)
Reproductive healtH	Supports hormonal balance and reproductive system function.	(5)
Wound healing	Enhances tissue repair and speeds up the healing process.	(6)

3. Linoleic acid inflammation and cancer

The overall role of LA in cancer is complex and appears to be cancer-type specific. The association between LA intake and cancer risk has produced inconsistent findings. A meta-analysis encompassing multiple prospective cohort studies reported no significant association between dietary or serum LA levels and breast cancer risk. Similarly, studies on colorectal and prostate cancers have not consistently demonstrated a clear link between LA consumption and cancer incidence (7). But according to a review of animal studies, linoleic acid can affect the growth and advancement of tumours, although it may not have a significant impact on the initiation of tumours for many cancer types (8).

High-fat diets (HFDs) rich in LA promote carcinogenesis and accelerate the growth of tumours in cases of breast cancer models. Serna et al. reported “LA induces Akt2 activation, invasion, an increase in NFκB–DNA binding activity, miR34a upregulation and miR9 downregulation in MDA-MB-231 cells” (9). Human research has also discovered a sequence of signalling events that are triggered by the up-regulation of prostaglandin E2 and cyclooxygenase activity brought on by linoleic acid. These studies have characterised important proteins and signalling events that contribute to the acceleration of cell proliferation in breast cancer. Inflammation has a pivotal role in cancer initiation and progression. Especially, chronic inflammation can create a microenvironment that facilitates cell proliferation and metastasis. Newevidence indicates that the metabolism of LA to oxylipins might have detrimental impacts on tumor development and metastasis (10). Oxylipins are generated through various pathways, including the cyclooxygenase pathway, lipoxygenase (LOX) pathway, and cytochrome P450 metabolic pathway. Different classes of oxylipins have opposing effects. The oxylipins derived from omega-6 fatty acids are proinflammatory and proangiogenic, while oxylipins derived from omega-3 fatty acids are anti-inflammatory.

Although they might have significant biological consequences, oxylipins formed from LA have not received as much research attention as eicosanoids derived from AA. Serum oxylipin levels were recently assessed in participants undergoing screening for ovarian, colorectal, lung, and prostate malignancies. A positive correlation between ovarian cancer and five oxylipins was found. These findings highlight the serious negative consequences of increasing LA oxidation or ingestion (11).

Fatty acid–binding protein 5 (FABP5) is a lipid chaperone that is highly expressed in TNBC cells and is associated with poor prognosis. LA binds to FABP5 forming a complex that directly interacts and activates mTORC1 the eventually leads to tumour growth (12).

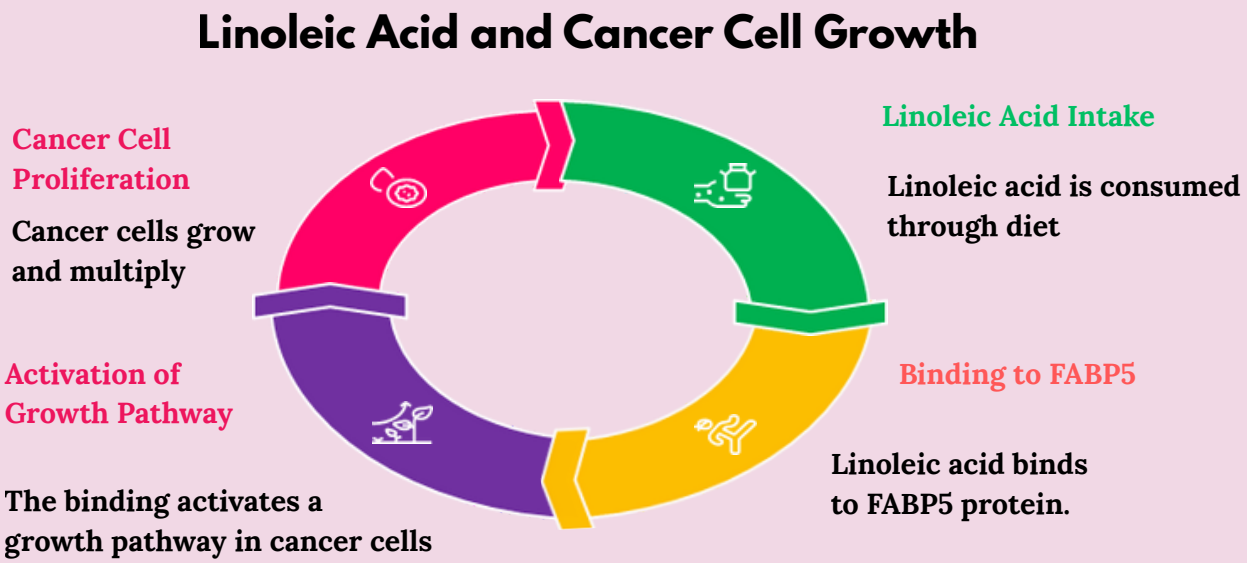

Figure 2. Linoleic acid and cancer cell growth cycle

4. Dietary considerations and recommendations

Given the complex role of LA in cancer biology, dietary recommendations should focus on balance and moderation. While LA is crucial for health, imprudent intake, particularly from processed foods rich in omega-6 PUFAs, may contribute to an inflammatory environment conducive to cancer progression. Incorporating a balanced intake of omega-3 fatty acids, that possess an anti-inflammatory nature, may help to reduce the potential adverse effects of high LA consumption. Maintaining optimal omega-6 PUFAs/ omega-3 PUFAs is essential for mitigating many diseases, including cancer.

5. Future directions

The significance of linoleic acid in cancer and its possible effects on dietary recommendations need to be better understood. Specific Subtypes of Cancer Research to be carried out to assess how LA affects the genesis and development of tumours. Because genetic, epigenetic, and microbial variables may affect LA metabolism, individual differences in metabolic responses to linoleic acid should be investigated. Long-term cohort studies can assist differentiate between causation and correlation and further clarify the association between linoleic acid intake and cancer incidence over time. The molecular and cellular processes via which linoleic acid may either cause or prevent various subtypes of cancer should be the main focus. Research comparing plant-based, Mediterranean, and ketogenic diets with or without LA may shed light on the compound's potential link to cancer.

6. Conclusion

The relationship between linoleic acid and cancer is multifaceted, with evidence suggesting both protective and detrimental effects depending on various factors, including cancer subtype, dietary context, and individual metabolic responses. While small amounts of LA from vegetable oils are generally safe, excessive intake, especially from frequent use or high consumption of processed food may lead to higher levels than the body requires. Further research is necessary to illuminate the mechanisms underlying these associations and to develop personalized dietary guidelines aimed at TNBC prevention and management. In the interim, adopting a balanced diet plentiful of whole foods and low in processed fats remains a prudent approach to health maintenance.

References

1. Malcicka M, Visser B, Ellers J. An evolutionary perspective on linoleic acid synthesis in animals. Evolutionary biology. 2018 Mar;45:15-26.
2. Field CJ, Schley PD. Evidence for potential mechanisms for the effect of conjugated linoleic acid on tumor metabolism and immune function: lessons from n− 3 fatty acids. The American journal of clinical nutrition. 2004 Jun 1;79(6):1190S-8S.
3. Djuricic I, Calder PC. Beneficial outcomes of omega-6 and omega-3 polyunsaturated fatty acids on human health: An update for 2021. Nutrients. 2021 Jul 15;13(7):2421.
4. Gropper SS, Smith JL. Advanced nutrition and human metabolism. Cengage Learning; 2013.
5. Szczuko M, Kikut J, Komorniak N, Bilicki J, Celewicz Z, Ziętek M. The role of arachidonic and linoleic acid derivatives in pathological pregnancies and the human reproduction process. International journal of molecular sciences. 2020 Dec 17;21(24):9628.
6. Lin TK, Zhong L, Santiago JL. Anti-inflammatory and skin barrier repair effects of topical application of some plant oils. International journal of molecular sciences. 2018 Jan;19(1):70.
7. Zock PL, Katan MB. Linoleic acid intake and cancer risk: a review and meta-analysis. Am J Clin Nutr. 1998 Jul;68(1):142-53. doi: 10.1093/ajcn/68.1.142. PMID: 9665108.
8. Welsch CW. Relationship between dietary fat and experimental mammary tumorigenesis: a review and critique. Cancer research. 1992 Apr 1;52(7_Supplement):2040s-8s.
9. Serna-Marquez N, Diaz-Aragon R, Reyes-Uribe E, Cortes-Reynosa P, Salazar EP. Linoleic acid induces migration and invasion through FFAR4-and PI3K-/Akt-dependent pathway in MDA-MB-231 breast cancer cells. Medical oncology. 2017 Jun;34:1-2.
10. Leahy C, Osborne N, Shirota L, Rote P, Lee YK, Song BJ, Yin L, Zhang Y, Garcia V, Hardwick JP. The fatty acid omega hydroxylase genes (CYP4 family) in the progression of metabolic dysfunction-associated steatotic liver disease (MASLD): an RNA sequence database analysis and review. Biochemical pharmacology. 2024 May 1:116241.
11. Mouradian M, Kikawa KD, Johnson ED, Beck KL, Pardini RS. Key roles for GRB2-associated-binding protein 1, phosphatidylinositol-3-kinase, cyclooxygenase 2, prostaglandin E2 and transforming growth factor alpha in linoleic acid-induced upregulation of lung and breast cancer cell growth. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2014 Apr 1;90(4):105-15.
12. Koundouros N, Nagiec MJ, Bullen N, Noch EK, Burgos-Barragan G, Li Z, He L, Cho S, Parang B, Leone D, Andreopoulou E. Direct sensing of dietary ω-6 linoleic acid through FABP5-mTORC1 signaling. Science. 2025 Mar 14;387(6739):eadm9805.