



## Dietary regulation of metastasis

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Published online: 17 November 2018  
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### Abstract

The impact of diet and associated lifestyle choices on the risk of developing cancer is well established. However, whether these parameters also affect cancer recurrence and survival is less well investigated. Virtually nothing is known about the impact of diet on the development of metastases. It is therefore significant that a study in this issue of *Clinical and experimental metastasis* reports that breast cancer-bearing mice fed on a diet rich in long-chain omega-3 fatty acids had a lower incidence of metastasis than control mice, which was associated with modified infiltration of immune cells into the tumors. These findings should form the basis of further pre-clinical evaluation with a view to clinical application.

**Keywords** Metastasis · Diet · Fatty acids · Breast cancer · Microenvironment

It remains challenging to identify precise links between dietary components and tumorigenesis in observational and interventional studies [1]. Nevertheless, poor diet and obesity are widely recognized as risk factors for the development of cancer, and experimental data indicate that dietary and nutritional factors potentially play an important role in cancer prevention. Nutritional regimens typified by the “Mediterranean Diet” are associated with a reduced incidence of several types of cancer. Attempts to identify individual key dietary components responsible for these effects, for example through the use of dietary supplements, have proven disappointing [2].

Efforts to understand the impact of diet on tumor growth, prognosis and recurrence after therapy are less advanced. For breast, prostate and colorectal cancer, losing excess weight and avoiding obesity correlates with lower recurrence rates and better prognosis [2]. While patients with advanced cancer often combine particular dietary regimens or supplements with standard therapies, robust experimental and clinical evidence to support the use of these supplements

remains thin on the ground. Indeed, some supplements can have detrimental effects. For example, delphinidin, a dietary flavonoid that is taken as a dietary supplement due to its reported cancer chemopreventative properties, has been reported to stimulate metastasis formation in experimental animals [3].

Against this background, the study from the Talmadge group [4] published in this issue of *Clinical & Experimental Metastasis* deserves particular attention. The paper reports that in contrast to omega-6 fatty acids, isocaloric and isolipic long-chain omega-3 fatty acid consumption suppressed tumor growth and metastasis formation in the 4T1 model of metastatic breast cancer. Tumors from mice fed on the omega-3 diet had reduced number of neutrophils and macrophages, immune cell types that have been associated with poor prognosis and metastasis. Conversely, increased infiltration of potentially anti-tumor CD3+ lymphocytes was observed. Consistently, survival of the mice on the omega-3 diet was significantly enhanced.

These results are very encouraging, and should stimulate further pre-clinical investigations into the potential anti-metastatic activities of long-chain omega-3 fatty acids. Although little clinical data is available in this regard, long-chain omega-3 fatty acid consumption is associated with lower mortality for many major diseases, including cancer [5]. These and other observations suggest that after further positive pre-clinical studies, clinical trials to investigate the potential metastasis-inhibiting activity of long-chain omega-3 fatty acids may be appropriate. The form in which

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long-chain omega-3 fatty acids are consumed may be decisive, as their consumption is often increased through the use of food supplements such as fish oils. This can be counterproductive in cancer patients receiving cisplatin treatment, because other fatty acids in fish oil can counteract this form of chemotherapy [6]. Nevertheless, the groundbreaking observations reported by Khadge and co-workers [4] give hope that appropriate dietary modification may suppress metastasis formation in cancer patients and thereby improve their survival.

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Editor-in-Chief

## References

1. Mayne ST, Playdon MC, Rock CL (2016) Diet, nutrition, and cancer: past, present and future. *Nat Rev Clin Oncol* 13:504–515
2. Vernieri C, Nichetti F, Raimondi A, Pusceddu S, Platania M, Berrino F, de Braud F (2018) Diet and supplements in cancer prevention and treatment: clinical evidences and future perspectives. *Crit Rev Oncol/Hematol* 123:57–73
3. Thiele W, Rothley M, Teller N, Jung N, Bulat B, Plaumann D, Vanderheiden S, Schmaus A, Cremers N, Goppert B, Dimmler A, Eschbach V, Quagliata L, Thaler S, Marko D, Brase S, Sleeman JP (2013) Delphinidin is a novel inhibitor of lymphangiogenesis, but promotes mammary tumor growth and metastasis formation in syngeneic experimental rats. *Carcinogenesis* 34:2804–2813
4. Khadge S, Thiele GM, Sharp JG, McGuire TR, Klassen LW, Black PN, DiRusso CC, Cook L, Talmadge JE (2018) Long-chain omega-3 polyunsaturated fatty acids decrease mammary tumor growth, multiorgan metastasis and enhance survival. *Clin Exp Metastasis*. <https://doi.org/10.1007/s10585-018-9941-7>
5. Zhang Y, Zhuang P, He W, Chen JN, Wang WQ, Freedman ND, Abnet CC, Wang JB, Jiao JJ (2018) Association of fish and long-chain omega-3 fatty acids intakes with total and cause-specific mortality: prospective analysis of 421309 individuals. *J Intern Med* 284:399–417
6. Daenen LG, Cirkel GA, Houthuijzen JM, Gerrits J, Oosterom I, Roodhart JM, van Tinteren H, Ishihara K, Huitema AD, Verhoeven-Duif NM, Voest EE (2015) Increased plasma levels of chemoresistance-inducing fatty acid 16:4(n-3) after consumption of fish and fish oil. *JAMA Oncol* 1:350–358