Cancer-related fatigue (CRF) is one of the most frequently reported and disabling symptoms in cancer survivors. With its negative impact on the activities of daily living, work, social activities, and mood, CRF causes severe impairment of quality of life. A previous study showed that omega-6 polyunsaturated fatty acid (PUFA) supplementation unexpectedly reduced CRF compared with omega-3 PUFA supplementation and that omega-6 PUFA supplementation reduced pro-inflammatory serum markers in fatigued American breast cancer survivors. Meanwhile, a recent meta-analysis of individual patient data revealed significant benefits of exercise interventions on CRF. Recently, we completed our randomized controlled trial among early-stage Japanese breast cancer survivors, in which we examined the effect of baseline blood PUFA characteristics on change in CRF during the 12-week trial by exercise group and confirmed that increased Cancer Fatigue Scale (CFS) was associated with both docosahexaenoic acid (DHA) \((p = 0.06)\) and omega-3 index \((p = 0.08)\) at baseline in all participants \((n = 46,\) omega-6/omega-3 ratio \(= 6.79, SD = 1.90)\). On the contrary, DHA at baseline was positively correlated with change in CRF \((r = 0.40, p = 0.06)\) in the control group \((n = 24,\) omega-6/omega-3 ratio \(= 7.0)\). Moreover, eicosapentaenoic acid (EPA) at baseline was positively correlated with leg strength \((r = 0.39, p = 0.10)\) in the exercise group. In conclusion, blood PUFA balance might be associated with the effect of exercise on CRF. In addition, higher EPA in individuals who conducted exercise likely has a beneficial effect on muscle strength. Further investigation is needed to clarify the interaction between PUFAs and exercise for alleviating CRF.

Keywords: omega-3 fatty acids, ω-3, cancer-related fatigue, exercise, cancer survivorship
TABLE 1 | Correlations between blood polyunsaturated fatty acid compositions and change in cancer-related fatigue over 12 weeks.

| Omega-6 PUFAs                      | All (n = 46) | Exercise (n = 23) | Control (n = 23) |
|------------------------------------|--------------|------------------|------------------|
| Linoleic acid                      | 0.06         | -0.28            | 0.28             |
| Arachidonic acid                   | 0.23         | 0.04             | 0.04             |
| Total n-6 PUFAs                    | 0.01         | -0.36            | 0.26             |
| Omega-3 PUFAs                      |              |                  |                  |
| Eicosapentaenoic acid              | 0.18         | 0.33             | 0.18             |
| Docosapentaenoic acid              | 0.19         | 0.20             | 0.24             |
| Docosahexaenoic acid               | 0.28         | 0.20             | 0.27             |
| Total n-3 PUFAs                    | 0.23         | 0.29             | 0.27             |
| Omega-3 index                      | 0.26         | 0.28             | 0.37             |
| Omega-6/omega-3 ratio              | -0.28        | -0.36            | -0.28            |

Cancer-related fatigue was assessed using the Cancer Fatigue Scale.
The exercise group underwent home-based smartphone-supported high-intensity interval training using bodyweight three times a week for 12 weeks. The control group received treatment as usual.

Correlations between blood polyunsaturated fatty acid compositions and change in cancer-related fatigue over 12 weeks. All correlations were significant (p < 0.05).

Omega-3 PUFAs, Polyunsaturated fatty acids.

Reduced CRF compared with omega-3 PUFA supplementation and that omega-6 PUFA supplementation reduced pro-inflammatory serum markers in fatigued American breast cancer survivors. Meanwhile, an earlier large-scale cross-sectional study found that a higher intake of omega-6 PUFAs relative to omega-3 PUFAs was associated with 1.8 times greater C-reactive protein and 2.6 times greater odds of CRF in 633 American breast cancer survivors (Alfano et al., 2012). Strikingly, the findings of these two studies are diametrically opposed, though we must keep in mind the differences in their designs. A weakness of the trial performed by Peppone et al. was that the above result was significant for only a single-item screening question but not for standard CRF measures. Furthermore, caution is needed in extrapolating the results of Americans, who consume a large amount of omega-6 PUFAs and a small amount of omega-3 PUFAs, to the population with high fish consumption.

A recent meta-analysis of individual patient data revealed significant benefits of exercise interventions on CRF (van Vulpen et al., 2020). Ochi revealed the effect of omega-3 PUFAs on improving muscle endurance, inflammatory reaction, and delayed onset muscle soreness (Ochi and Tsuchiya, 2018). We are working on clinical research to improve physical fitness and reduce CRF in breast cancer survivors through exercise, and we are also interested in analyzing whether PUFA balance in the body affects the efficacy of exercise on CRF and muscle strength.

Recently, we, in our randomized controlled trial among early-stage Japanese breast cancer survivors (Ochi et al., 2021), examined the effect of baseline blood PUFA characteristics on change in CRF assessed by the Cancer Fatigue Scale (CFS), which was designed to reflect the nature of fatigue experienced by cancer patients (Okuyama et al., 2000), during the 12 week trial by the exercise group (Table 1). Elevated CRF, defined as an increase in CFS between baseline and 12 weeks, was associated with both docosahexaenoic acid (DHA; Spearman’s rank correlation $r = 0.28, p = 0.06$) and omega-3 index ($r = 0.26, p = 0.08$) at baseline in all participants ($n = 46$, omega-6/omega-3 ratio = 6.79, SD = 1.90). On the contrary, DHA at baseline was positively correlated with change in CRF ($r = 0.40, p = 0.06$) in the control group ($n = 24$, omega-6/omega-3 ratio = 7.0). Moreover, eicosapentaenoic acid (EPA) at baseline was positively correlated with leg strength ($r = 0.39, p = 0.10$) in the exercise group. In our phase II trial, the associations between PUFAs and CRF were not significant, but these trends were consistent with the findings of the trial performed by Peppone et al. We speculate that blood PUFA balance might be associated with the effect of exercise on CRF, and this effect might be clearer in cancer survivors. In addition, higher EPA in individuals who conducted exercise likely has a beneficial effect on muscle strength.

Considering the trial performed by Peppone et al. together with ours, omega-6 PUFAs might be beneficial for reducing CRF, while omega-3 PUFAs might have no benefit regardless of fish-eating habits. As no gold-standard treatment for CRF has been established, further investigation is needed to clarify the interaction between PUFAs and exercise for alleviating CRF. Self-management such as dietary modification and exercise must be both effective and easy to be an acceptable solution in cancer survivorship care.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of the National Cancer
The patients/participants provided their written informed consent to participate in this study.

**AUTHOR CONTRIBUTIONS**

YM and EO conceived and designed the study. YM, KT, and EO drafted the main text and table. All authors reviewed the manuscript, contributed to the acquisition, analysis, and interpretation of data, and approved the completed version of the manuscript.

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**REFERENCES**

Alfano, C. M., Imayama, I., Neuhouser, M. L., Kiecolt-Glaser, J. K., Smith, A. W., Meeske, K., et al. (2012). Fatigue, inflammation, and ω-3 and ω-6 fatty acid intake among breast cancer survivors. *J. Clin. Oncol.* 30, 1280–1287. doi: 10.1200/JCO.2011.36.4109

Bower, J. E., Ganz, P. A., Desmond, K. A., Rowland, J. H., Meyerowitz, B. E., and Belin, T. R. (2000). Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J. Clin. Oncol.* 18, 743–753. doi: 10.1200/JCO.2000.18.4.743

Ochi, E., and Tsuchiya, Y. (2018). Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) in muscle damage and function. *Nutrients* 10:552. doi: 10.3390/nu10050552

Ochi, E., Tsuji, K., Narisawa, T., Shimizu, Y., Kuchiba, A., Suto, A., et al. (2021). Cardiorespiratory fitness in breast cancer survivors: a randomised controlled trial of home-based smartphone supported high intensity interval training. *BMJ Support. Palliat. Care* 1–5. doi: 10.1136/bmjspcare-2021-003141

Okuyama, T., Akechi, T., Kugaya, A., Okamura, H., Shima, Y., Maruguchi, M., et al. (2000). Development and validation of the cancer fatigue scale: a brief, three-dimensional, self-rating scale for assessment of fatigue in cancer patients. *J. Pain Symptom Manage.* 19, 5–14. doi: 10.1016/S0885-3924(99)00138-4

Peppone, L. J., Inglis, J. E., Mustian, K. M., Heckler, C. E., Padula, G. D. A., Mohile, S. G., et al. (2019). Multicenter randomized controlled trial of omega-3 fatty acids versus omega-6 fatty acids for the control of cancer-related fatigue among breast cancer survivors. *JNCI Cancer Spect.* 3:pkz005. doi: 10.1093/jncics/pkz005

Su, K. P. (2009). Biological mechanism of antidepressant effect of omega-3 fatty acids: how does fish oil act as a ’mind-body interface'? *Neurosignals* 17, 144–152. doi: 10.1159/000198167

van Vulpen, J. K., Sweegers, M. G., Peeters, P. H. M., Courneya, K. S., Newton, R. U., Aaronson, N. K., et al. (2020). Moderators of exercise effects on cancer-related fatigue: a meta-analysis of individual patient data. *Med. Sci. Sports Exerc.* 52, 303–314. doi: 10.1249/MSS.0000000000002154

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