

審査の結果の要旨

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The key research question of my study was: What is the association between fish, n-3 PUFA, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), alpha linolenic acid (ALA), n-6 PUFA, and n-6/n-3 ratio and breast cancer using Japan Public Health Center-based prospective Study data? The main objective of my study was, first to identify basic characteristics of fish, n-3 PUFA, and n-6 PUFA intake with breast cancer risk factors; second to assess breast cancer risk factors by fish, n-3 PUFA, and n-6 PUFA intake quartiles; third to analyze the interaction between fish, n-3 PUFA, and n-6 PUFA and other risk factors; and finally to examine breast cancer risk factors according to ER and PR status.

The key findings of my studies are as follows:

1. A total of 556 breast cancer cases were newly diagnosed among 38,234 women during an average follow-up of 14.1 years. ER PR status information was available for 272 cases and ER PR status information was unavailable for 284 cases. Total fish intake ranged from a mean of 25.9 g/day below the lowest quartile to 126 g/day above the highest quartile. Total n-3 PUFA intake ranged from a mean of 2.1 g/day in the lowest quarter to 4.6 g/day in the highest quarter, while total n-6 PUFA intake ranged from a mean of 6.9 g/day in the lowest quarter to 12.5 g/day in the highest quarter.
2. Breast cancer risk was not associated with the intake of total fish, n-3 PUFA, and n-6 PUFA when analyzed in totality through multivariable Cox proportional hazards regression models with age as the time-scale. Intake of total n-6 was positively

associated with the development of ER+PR+ tumors [multivariable adjusted HR Q4 vs Q1=2.94; p-value=0.02 (95% CI: 1.26-6.89; $p_{\text{trend}}=0.02$)].

3. There were no significant changes in the results after exclusion of former and current smokers [multivariable adjusted HR Q_4 vs $Q_1 = 0.96$ (95% CI: 0.74-1.25; $p_{\text{trend}} = 0.95$ for fish, multivariable adjusted HR Q_4 vs $Q_1 = 0.96$ (95% CI: 0.74-1.25; $p_{\text{trend}} = 0.40$) for total n-3 PUFA, and multivariable adjusted HR Q_4 vs $Q_1 = 0.99$ (95% CI: 0.74-1.33; $p_{\text{trend}} = 0.59$) for n-6 PUFA).
4. The results after stratifying for menopausal status also did not provide any significant association with breast cancer risk [multivariable adjusted HR Q_4 vs $Q_1 = 1.08$ (95% CI: 0.65-1.80; $p_{\text{trend}} = 0.43$) (premenopause) and multivariable adjusted HR Q_4 vs $Q_1 = 0.94$ (95% CI: 0.70-1.27; $p_{\text{trend}} = 0.79$) (postmenopause) for fish, multivariable adjusted HR Q_4 vs $Q_1 = 1.10$ (95% CI: 0.67-1.80; $p_{\text{trend}} = 0.98$) (premenopause) and multivariable adjusted HR Q_4 vs $Q_1 = 0.95$ (95% CI: 0.70-1.29; $p_{\text{trend}} = 0.47$) (postmenopause) for total n-3 PUFA, and multivariable adjusted HR Q_4 vs $Q_1 = 0.71$ (95% CI: 0.43-1.18; $p_{\text{trend}} = 0.11$) and multivariable adjusted HR Q_4 vs $Q_1 = 1.12$ (95% CI: 0.80-1.58; $p_{\text{trend}} = 0.82$) (postmenopause) for n-6 PUFA].

In conclusion, this is the first study in Japan to find that when breast cancer cases are analyzed by ER PR status subtype, intake of total n-6 PUFA was positively associated with ER+PR+ tumors. The overall intake of fish, n-3 PUFA, and n-6 PUFA were not significantly associated with breast cancer risk. However, significant positive associations were found between the intake of total n-6 PUFA and ER+ PR+ tumors. The tumor subtype dependency of this study highlights that studies that have analyzed the association between dietary intake and breast cancer without consideration of different receptor statuses should include tumor

analyses to better understand the relationship between dietary intake and breast cancer. Moreover, further laboratory studies performed in parallel to epidemiologic studies can help in understanding the mechanism of tumor growth in relation to fish, n-3 PUFA, and n-6 PUFA intake. With breast cancer incidence on the rise in Japan, studying the association and understanding the mechanisms to curb the growth through dietary intake is not only beneficial but also necessary.