Letter to the Editor

Fish Oil Exacerbates Colitis in SMAD3 Mice
Lesley M. Butler1 and Mimi C. Yu2

There are seemingly disparate results from epidemiologic studies regarding associations between fish or marine n-3 polyunsaturated fatty acids (PUFA) intake and colorectal cancer risk. A recent report by Woodworth et al. (1) provides clarity for why a potential etiologic factor, such as fish intake, appears protective for colorectal cancer in some populations, but risk enhancing in other populations. For example, we (2) and others (3, 4) have reported positive associations in Chinese populations, whereas a meta-analysis of prospective studies conducted in Western populations reported a statistically nonsignificant inverse association (5; Table 1).

Woodworth et al. demonstrated that a marine PUFA diet increased the risk of colon adenocarcinoma in mice with Helicobacter hepaticus–induced colitis (1). Woodworth et al. concluded that mice with active colitis that were fed high doses of the marine n-3 PUFA, docosahexaenoic acid had impaired immune function and thus were less equipped to mount a successful response to H. hepaticus infection (1). We put forth a novel hypothesis, inspired by these findings, that marine n-3 PUFAs are associated with increased risk of colorectal cancer in humans when in the presence of H. pylori-induced hypergastrinemia.

Hypergastrinemia is a direct result of increased serum gastrin levels caused by gastric H. pylori infection. The prevalence of H. pylori infection varies worldwide, with the highest prevalence in East and Southeast Asian regions and the lowest in Western-developed regions. Hypergastrinemia has proliferative effects on colonic mucosa, and animal data support a role for hypergastrinemia in the progression of colon adenomas (6). There is also prospective epidemiologic data supporting an association between elevated gastrin levels and colorectal cancer risk (7).

As suggested by Woodworth et al., a tolerable upper limit for marine PUFA intake is needed given the adverse effects of fish oil on colorectal cancer susceptibility in the presence of chronic infection. We propose that fish and marine n-3 PUFA intake is associated with increased colorectal cancer risk in chronically infected H. pylori populations with co-occurring hypergastrinemia. In contrast, fish may protect against colorectal cancer by inhibiting the formation of proinflammatory eicosanoids in populations where the prevalence of H. pylori is

Table 1. Selected epidemiologic studies that evaluated associations between fish or marine n-3 PUFA intake and colorectal cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Intake levels</th>
<th>Magnitude of association</th>
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</thead>
<tbody>
<tr>
<td>Butler, 2008 (2)</td>
<td>Singapore chinese</td>
<td>Fourth vs. first quartile marine n-3 PUFA median values (g/1,000 kcal/d): 0.29 vs. 0.09</td>
<td>Overall: HR = 1.22 (95% CI: 1.02–1.45) Advanced disease: HR = 1.33 (95% CI: 1.05–1.70)</td>
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<tr>
<td>Murff, 2009 (3)</td>
<td>Shanghai women</td>
<td>Fourth vs. first quintile fish median values (g/d): 56.12 vs. 14.91</td>
<td>RR = 1.42 (95% CI: 1.01–2.00)</td>
</tr>
<tr>
<td>Chiu, 2003 (4)</td>
<td>Shanghai</td>
<td>Fourth vs. first quartile fish servings per week: ≥9.4 vs. ≤2.6 for men; ≥11.0 vs. ≤2.9 for women</td>
<td>Men: OR = 1.7 (95% CI: 1.2–2.4) Women: OR = 1.2 (95% CI: 0.8–1.7)</td>
</tr>
<tr>
<td>Geelen, 2007 (5)</td>
<td>Meta-analysis: US, Australia, Europe</td>
<td>-</td>
<td>RR = 0.88 (95% CI: 0.78–1.00)</td>
</tr>
</tbody>
</table>

Abbreviations: RR, relative risk; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

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low and hypergastrinemia is rare. We hope that by "connecting the dots" between our earlier findings among a human population and those recently reported by Woodworth et al. using a mouse model, it helps to inform future experimental research into elucidating the potential adverse effect of marine n-3 PUFAs on colorectal carcinogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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