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Fish Consumption and Colorectal Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence Among the Japanese Population

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Objective: The association between fish consumption and colorectal cancer risk remains inconclusive. The present study systematically reviewed and meta-analyzed epidemiologic data on the association between fish consumption and colorectal cancer risk among Japanese.
Methods: Original data were obtained from MEDLINE searched using PubMed or from searches of the *Ichushi* database, complemented with manual searches. The associations were evaluated based on the strength of evidence, the magnitude of association and biologic plausibility. Meta-analysis was conducted according to the study design.
Results: Five cohort studies and 12 case–control studies were identified. Fish consumption was not significantly associated with colorectal, colon or rectal cancer risks. One cohort study showed a weak positive association with colorectal cancer, and another showed a weak inverse association with colon cancer in men and a moderate and weak inverse association with colon and rectal cancers in women. As regards case–control studies, four studies reported a weak inverse association, whereas one showed a weak positive association with colon cancer. Regarding rectal cancer, four case–control studies showed a weak inverse association, but two reported a weak-to-moderate positive association. The pooled relative risk/odds ratio (95% confidence interval) of colorectal cancer for the highest versus lowest category of fish consumption was 1.03 (0.89–1.18) and 0.84 (0.75–0.94) for cohort and case–control studies, respectively.
Conclusions: There was insufficient evidence to support an association between fish consumption and the risk of colorectal cancer among Japanese.

Key words: systematic review – epidemiology – fish – colorectal cancer – Japanese

INTRODUCTION

Colorectal cancer is a major cause of morbidity and mortality in developed countries (1). In Japan, there has been a remarkable increase in colorectal cancer mortality over the past three decades (1970–2000) (2), and Japan remains among countries with the highest incidence of colorectal cancer worldwide (3). Such an increasing trend has been attributed to the changes in lifestyles, particularly diet characterized by a high consumption of meat and animal fat (4). Fish is widely consumed among island and coastal communities, including Japanese, and thus its role in colorectal cancer risk is a matter of interest.

Fish is a rich source of n-3 fatty acids which are thought to inhibit colon carcinogenesis through several pathways. Fish oil has been shown to decrease DNA adduct levels in colon, increase the apoptosis of colonic cells in rat (5) and exert anti-inflammatory effects (6,7) as well as directly inhibit COX-2 (7), an enzyme involved in the cancer development. Fish also contains vitamin D, which has been inversely associated with colorectal cancer risk (8). Selenium, another nutrient contained in fish, has been shown to exert anticancer effects in *in vitro*, animal and human studies (9,10).

Many epidemiologic studies have investigated the association between fish consumption and the risk of colorectal cancer, and data are inconsistent between cohort and case–control studies. A systematic review and meta-analysis of 18 prospective cohort studies found a marginally significant, inverse association between fish consumption and colorectal cancer (11), with a similar strength of association being reported for colon and rectal cancers. Likewise, an updated review of 19 cohort studies by the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) showed a lower risk of colorectal cancer in cohort studies with increasing fish consumption (7). Based on that review (7), the WCRF/AICR concluded that fish consumption possibly decreases colorectal cancer risk. More recently, a systematic review and meta-analysis including 18 prospective cohort and 19 case–control studies (12) showed a significantly lower risk of colorectal cancer in individuals with a higher consumption of fish. In addition, this review (12) noted a stronger inverse association of fish consumption with rectal cancer than with colon cancer. These pooled findings (7,11,12) suggest that fish consumption may protect against colorectal cancer. However, such accumulating data have been largely derived from studies in Western countries and from those published in English, and less is known in Asian countries, including Japan where fish consumption is among the highest in the world (13).

To assess the strength and consistency of the association between fish consumption and colorectal cancer risk among the Japanese population, we conducted a systematic review and meta-analysis of epidemiologic studies on this issue in Japan. This is one in a series of articles that summarized epidemiologic evidence on the relation of lifestyles with total cancers and major forms of cancer in Japan (14–16).

PATIENTS AND METHODS

Relevant epidemiologic studies were identified by searching MEDLINE for the literature published through November 2012. A search of the *Ichushi* (*Japana Centra Revuo Medicina*) database was also conducted to identify the studies written in Japanese. These methods of literature identification were complemented by manual searches of references from pertinent articles where necessary. We used the term 'fish' combined with 'colorectal cancer', 'colon cancer', 'rectal cancer', 'case–control studies', 'cohort studies', 'Japan' and 'Japanese'. Articles written in either English or Japanese were reviewed. Only studies on Japanese populations living in Japan were included. Individual results were summarized in tables separately according to the study design as cohort or case–control studies.

The studies were evaluated on the basis of the magnitude of association and the strength of evidence. First, relative risks (RRs) or odds ratios (ORs) in each epidemiologic study were grouped by the magnitude of association, considering statistical significance (SS) or no statistical significance (NS), into: strong (symbol ↑↑↑ or ↓↓↓), <0.5 or >2.0 (SS); moderate (symbol ↑↑ or ↓↓), either (i) <0.5 or >2.0 (NS), (ii) >1.5–2.0 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↑ or ↓), either (i) >1.5–2.0 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol −), 0.67–1.5 (NS). Hence, we defined, for each study, the magnitude of association by its strength, i.e. the size of RRs or ORs for the highest consumption group compared with the lowest, and its SS. A two-sided P value <0.05 was considered statistically significant. When multiple publications were derived from analyses of the same or overlapping datasets, we used data from the largest or most recent results only, and selected the incidence as the measure of outcome instead of mortality. After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (17), where evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. We assumed biologic plausibility based on evidence in experimental models, human studies and other pertinent data. Despite the use of this quantitative assessment rule, an arbitrary evaluation is inevitable when considerable variations exist in the magnitude of association between the findings of each study. The final judgment was made based on a consensus of the research group members, and it was therefore not necessarily objective. We further conducted a random-effects meta-analysis (18), and plotted the results within subgroups of cancer site by study type. We selected only the most recent study if there is a possibility of overlapping period of data collection at the same setting, and excluded reports without showing 95% confidence interval (CI); and if 90% CI was reported, we converted it to 95% CI. Meta-analyses were performed using '*metan*' (19) Stata command (version 12.0; StataCorp, College Station, TX, USA). The quantity I^2 was computed to describe the degree of heterogeneity, with values

of 0% indicating no observed heterogeneity and larger values denoting higher heterogeneity (20).

Main Features and Comments

A total of 5 cohort studies (21–25) and 12 case–control studies (26–37) were identified (Supplementary data, Tables S1 and S2). All cohort studies presented results separately for men and women. Among the case–control studies, two studies presented results by sex (31,36), two for men only (28,35) and the remaining eight studies for men and women combined (26,27,29,30,32–34,37). The magnitude of association between fish consumption and colorectal cancer risk is summarized in Tables 1 and 2 for cohort and case–control studies, respectively.

Of five cohort studies, three showed an RR of colon and rectal cancers separately (21,23,24), but not combined; one reported the results for both colon and rectal cancers separately and these sites combined (25), and the remaining study presented data on colorectal cancer only (22). Three studies found no association of fish consumption with colon or rectal cancer mortality (23) and incidence (24,25), or colorectal cancer incidence (25). On the other hand, one study showed that higher fish consumption, including baked or salted fish, was weakly associated with an increased risk of colorectal cancer in either men or women (22). The remaining one reported a weak inverse association of fish consumption with colon cancer but not rectal cancer mortality in men, and a weak and moderate inverse association with rectal and colon cancer mortality in women, respectively.

All case–control studies (26–37) measured ORs for the colon and rectum separately, and only one study additionally (37) reported data on the colon and rectum combined. Of these, four found a weak inverse association of consumption of fresh fish or fish products with colon cancer in both men and women (27,32,37) or in men only (36), while one (28) showed a weak positive association between dried or salted fish consumption and colon cancer in men; the others (26,29–31,33–36) reported no association with colon cancer. Regarding rectal cancer, four exhibited a weak inverse association with fresh fish in both men and women (26,30,32) or in women only (36), whereas two displayed a weak-to-moderate positive association with fish (27), dried or salted fish (28); no association with rectal cancer was observed for the remaining studies in both men and women (29,31,33,34) or in men only (35). The only one study examining the combined colon and rectal cancer only reported no association (37).

Meta-analysis included 12 studies (21–25,27,30,32,33,35–37) after we excluded five reports: two conducted at the same hospital with an overlapping time of survey (29,31) and three without presenting 95% CI (26,28,34). One study showed 90% CI (21), which was then converted to 95% CI. Summary data of cohort studies showed no association between fish consumption and colorectal cancer risk (Fig. 1); the pooled RR or OR of colorectal cancer for the highest level of fish consumption versus the lowest was 1.03 (95% CI 0.89–1.18). In contrast, the combined OR among case–control studies showed a significant reduction in the risk of colorectal cancer (OR, 0.84; 95% CI 0.75–0.94) (Fig. 2). We recorded no significant interstudy heterogeneity among either cohort studies ($I^2 = 0.0\%$, $P = 0.99$) or case–control studies ($I^2 = 0.0\%$, $P = 0.60$).

It is worth discussing several methodological issues on the evidence of the association between fish consumption and

Table 1. Summary of the association between fish consumption and colorectal cancer risk, cohort study

References	Study period	Study population					Magnitude of association[a]		
		Sex	Number of subjects	Age range	Event	Number of incident cases or deaths	Colon	Rectum	Colorectal
Hirayama (21)	1965–82	Men	122 261	40+ years	Death	564	↓	–	NA
		Women	142 857	40+ years	Death	551	↓↓	↓	NA
Khan et al. (22)	1984–2002	Men	1524	40+ years	Death	15	NA	NA	↑
		Women	1634	40+ years	Death	14	NA	NA	↑
Kojima et al. (23)	1988–99	Men	45 181	40–79 years	Death	254	–	–	NA
		Women	62 643	40–79 years	Death	203	–	–	NA
Kobayashi et al. (24)	1990–99	Men	42 525	40–69 years	Incidence	454	–	–	NA
		Women	46 133	40–69 years	Incidence	251	–	–	NA
Sugawara et al. (25)	1995–2003	Men	24 573	40–79 years	Incidence	379	–	–	–
		Women	26 680	40–79 years	Incidence	187	–	–	–

NA, not available.
[a]↑↑↑or ↓↓↓, strong; ↑↑or↓↓, moderate; ↑or↓, weak; –, no association (see the text for a more detailed definition); If the magnitude of association differs between types of fish or between proximal and distal colon, strongest association is reported.

Table 2. Summary of the association between fish consumption and colorectal cancer risk, case–control study

References	Study period	Study subjects				Magnitude of association[a]		
		Sex	Age range	Number of cases	Number of controls	Colon	Rectum	Colorectal
Kondo (26)	1967–73	Men and women	Not specified	205	408	–	↓	NA
Watanabe et al. (27)	1977–83	Men and women	Not specified	203 (M:110, W:93)	203 (M:110, W:93)	↓	↑	NA
Tajima et al. (28)	1981–83	Men	40–79 years	52	111	↑	↑↑	NA
Kato et al. (29)	1986–90	Men and women	Not specified	223	578	–	–	NA
Hoshiyama et al. (30)	1984–90	Men and women	40–69 years	181 (M:98, W:83)	653 (M:343, W:310)	–	↓	NA
Inoue et al. (31)	1988–92	Men	Not specified	257	8,621	–	–	NA
		Women	Not specified	175	23,161	–	–	NA
Kotake et al. (32)	1992–94	Men and women	Not specified	363 (M:214, W:149)	363 (M:214, W:149)	↓	↓	NA
Nishi et al. (33)	1987–90	Men and women	Not specified	330 (M:171, W:159)	660 (M:342, W:318)	–	–	NA
Ping et al. (34)	1986–94	Men and women	40–84 years	100 (M:77, W:23)	265 (NA)	–	–	NA
Murata et al. (35)	1989–97	Men	Not specified	267	395	–	–	NA
Yang et al. (36)	1988–99	Men	40–79 years	976	14,601	↓	–	NA
		Women	40–79 years	639	32,285	–	↓	NA
Kimura et al. (37)	2000–03	Men and women	20–74 years	782	793	↓[b]	–	–

M, men; W, women.
[a]↑↑↑or ↓↓↓, strong; ↑↑or↓↓, moderate;↑or↓, weak; –, no association (see the text for a more detailed definition).
[b]Distal colon.

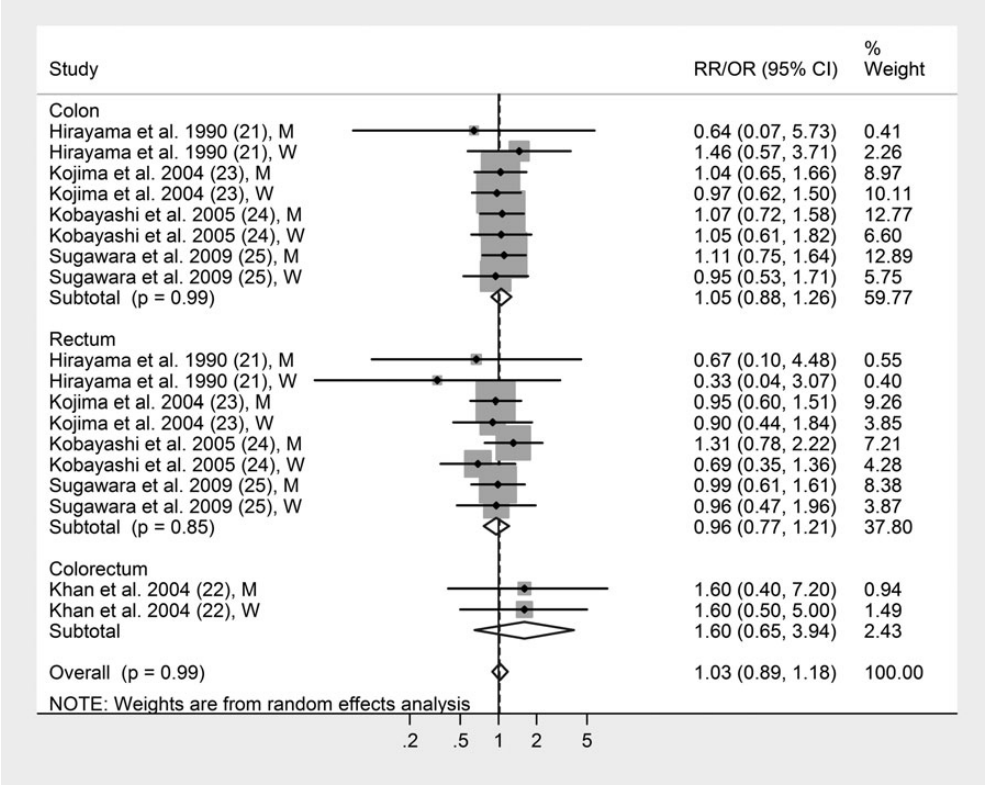

Figure 1. Fish consumption (highest vs. lowest exposure category) and colorectal cancer among Japanese: cohort study. CI, confidence interval; M, men; W, women; OR, odds ratio; RR, relative risk.

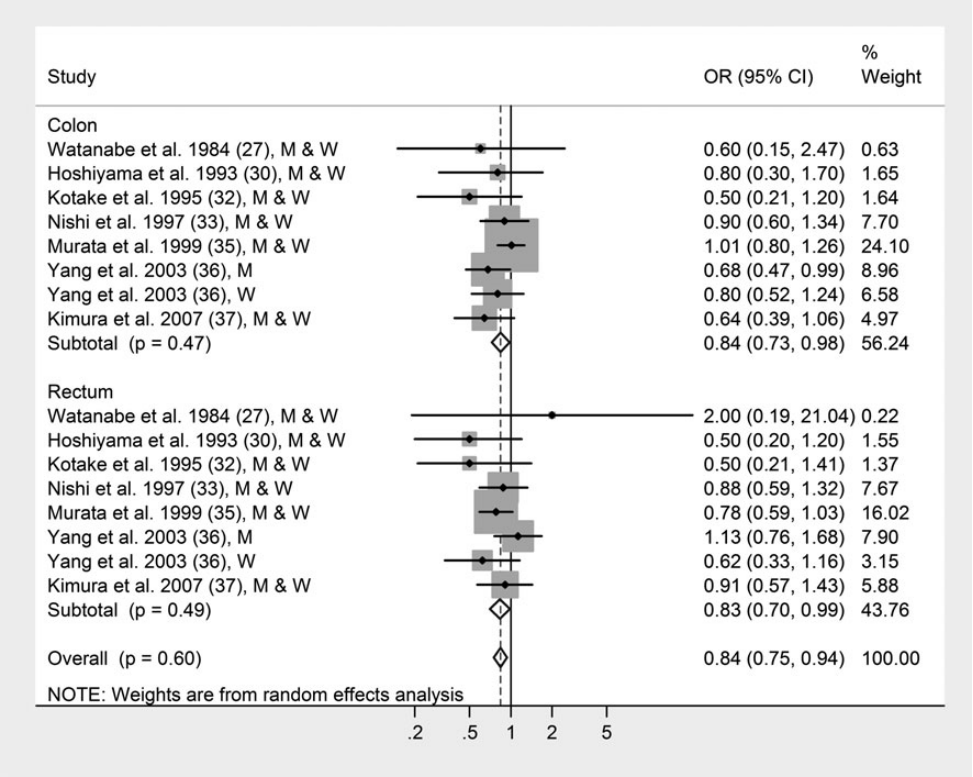

Figure 2. Fish consumption (highest vs. lowest exposure category) and colorectal cancer among Japanese: case–control study.

colorectal cancer in general and in particular for Japanese studies. First, attention should be paid on the interpretation of data from case–control studies. Case–control studies are susceptible to recall bias, leading to differential misclassification of fish consumption among cases and controls. Specifically, an inverse association between fish consumption and colorectal cancer is overestimated if patients with colorectal cancer tend to underreport fish consumption in the past due to the influence of their disease status on recall. Secondly, most case–control studies included in the present review selected controls from among patients or participants who have undergone a health check-up or screening, which might have resulted in various degrees of selection bias among studies. Thirdly, all but one (36) case–control study did not adjust for the intake of meat, including red meat and/or processed meat that have been consistently associated with colorectal cancer risk (7). Fourthly, most case–control studies in the present review did not consider potential confounding effects of smoking (26–35), alcohol drinking (26–34) or physical activity (26–35), a triad of factors associated with colorectal cancer (14–16,38–40). Finally, cohort studies in the present review assessed fish consumption using a food frequency questionnaire with low-to-moderate validity. This would result in non-differential misclassification of fish intake, possibly biasing the estimates toward the null.

It is worth noting that there was a discrepancy between the cohort and case–control studies in the association between fish consumption and colorectal cancer. In meta-analysis, a pooled estimate among cohort studies did not show any association between fish consumption and colorectal cancer, whereas that among case–control studies showed a 16% significant risk reduction. The observed reduction in risk among case–control studies is similar to that found in a previous meta-analysis of 19 case–control studies, including three Japanese reports in the present review (summary OR, 0.83; 95% CI 0.72–0.95) (12). However, given limitations of retrospective studies as discussed above, findings of case–control studies should be interpreted cautiously.

The association between fish consumption and colorectal cancer risk may differ according to race or ethnicity. In the present review, a pooled estimate and particularly results from recent large-scale cohort studies (23–25) showed that fish consumption was not associated with the risk of colon cancer and/or rectal cancer. This observation disagrees with three previous systematic reviews and meta-analyses, which included a majority of western populations, all reporting a marginally significant decrease in the risk of colorectal cancer in cohort studies (7,11,12), with RRs (95% CI) being 0.88 (0.78–1.00), 0.96 (0.92–1.00) and 0.93 (0.86–1.01). The lack of consistency, if any, between them may be partly due to much higher consumption of fish among Japanese than among Westerners (13); the mean consumption of fish (kg/capita/year) in Japan was 71.9, whereas the corresponding data among western populations were 22.4 (USA), 24.5 (UK), 20.0 (Australia), 32.1 (France), 17.0 (Germany) and 24.4 (Canada). If there is a threshold above which fish consumption has no or

little effect on colorectal carcinogenesis, the association between fish consumption and colorectal cancer risk may not be observed in populations who consume high amounts of fish, as in the case for Japanese. In fact, the European Prospective Investigation into Cancer and Nutrition (41) showed no further reduction in the risk of colorectal cancer at a fish consumption level of ≥40 g per day. Alternatively, there might be a difference in the types of fish (lean or fatty fish) consumed or preparation methods (fresh, dried or salted fish) between Japanese and Western studies. For instance, fatty fish is commonly consumed in Japan (36) but may be vulnerable to contamination of polychlorinated biphenyls (42), an organochlorine compound associated with colorectal cancer risk (43). Additionally, nitrosamines present in salted fish have potent carcinogenic effects in laboratory animals (44) and have been associated with an increased risk of colorectal cancer in humans (45). In fact, some studies included in the present work showed a weak-to-moderate positive association between salted fish and colorectal cancer (22,28).

In conclusion, among the Japanese population there was no significant association between fish consumption and colorectal cancer in cohort studies, whereas a weak inverse association was observed for case–control studies.

Evaluation of Evidence on Fish Consumption and Colorectal Cancer in Japanese

From results of the present review and based on the hypothesized biologic plausibility, we conclude that there is insufficient evidence to support an association between fish consumption and colorectal cancer among Japanese.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

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Conflict of interest statement

None declared.

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Appendix

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