HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Environ Res. 2017 April ; 154: 86–92. doi:10.1016/j.envres.2016.12.029.

Consumption of Lake Ontario Sport Fish and the Incidence of Colorectal Cancer in the New York State Angler Cohort Study (NYSACS)

Catherine L. Callahan[a,*,1], **John E. Vena**[b], **Joseph Green**[c], **Mya Swanson**[a], **Lina Mu**[a], and **Matthew R. Bonner**[a,*]

[a]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY 14214

[b]Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC 29425

[c]Pacific Disaster Center, Kihei, HI 96753

Abstract

Fish consumption is hypothesized to reduce the risk of colorectal cancer. Nonetheless, consuming sport fish from the Great Lakes increases exposure to certain persistent organic pollutants, namely polychlorinated biphenyls (PCBs) and organochlorine insecticides, which may increase the risk of cancer. Evidence that exposure to persistent organic pollutants is associated with colorectal cancer is sparse. We examined colorectal cancer incidence in the New York State Angler Cohort Study (NYSACS), a prospective cohort of 17,110 anglers and spouses aged 18 to 40 years at enrollment. In 1991, participants completed a mailed self-administered questionnaire that ascertained the number of years that fish from Lake Ontario were consumed, as well as potential confounders. Forty-one histologically confirmed first primary incident colorectal cancers diagnosed as of December 31, 2008 were identified via the New York State Cancer Registry. Vital status was ascertained by linkage with the Social Security Administration Death File. Rate ratios (RR) and 95% confidence intervals (CI) were calculated with Poisson regression, adjusting for age, pack-years of smoking, and sex. Compared with never consumers, colorectal cancer incidence was statistically non-significantly lower among consumers of Lake Ontario sport fish (RR = 0.66; 95% CI: 0.35; 1.24). Incidence of colon cancer was lower among Lake Ontario fish consumers (RR = 0.45, 95%CI: 0.20; 1.00). We did not observe any evidence of effect measure modification by sex

[*]Author to whom correspondence should be addressed: 9609 Medical Center Drive, Rockville, MD 20850, Phone: (240) 276-5040, Catherine.callahan@nih.gov.

[1]Author present address: Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20892

Ethics statement:

All procedures were approved by the University at Buffalo's Institutional Review Board.

Disclaimer: This article was prepared while Catherine Callahan was employed at the University at Buffalo. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

or age. Although consumption of Lake Ontario sport fish may have an inverse association with colorectal cancer risk, inferences are complicated by a small number of cases and a lack of information regarding potential confounders including other dietary factors. However, our results do not provide support for the hypothesis that consumption of contaminated sport fish increases the risk of colorectal cancer.

Keywords

Persistent organic pollutants; colorectal cancer; fish; colon cancer; organochlorines

1. Introduction

Fish consumption is a major source of exposure to persistent organic pollutants (POPs) a class of heterogeneous synthetic chemicals that resist degradation and bio-accumulate in the food chain and in adipose tissue (Porta et al., 2008). POPs include organochlorine insecticides (OCs) that were heavily used in agriculture and pest control from the 1940s until the 1960s (Purdue et al., 2007) and polychlorinated biphenyls (PCBs), a class of 209 organic synthetic chemicals previously used in a variety of commercial applications (Warner et al., 2012). Lake Ontario fish are known to have high levels of POPs (Turyk et al., 2012). Mechanisms by which POPs may lead to carcinogenesis include increased oxidative stress, genotoxic effects, immune suppression, inflammatory response, and endocrine disruption (Lauby-Secretan et al., 2013). Because POPs are excreted in feces (Moser and McLachlan, 2001; Schlummer et al., 1998) and feces reside in the colon for 1–2 days (Howsam et al., 2004) the colonic epithelium may be a target for carcinogenic insults by POPs. Furthermore, p, p'-Dichlorodiphenyldichloroethylene (DDE) a metabolite of the OC insecticide dichlorodiphenyltrichloroethane (DDT) has been demonstrated to induce proliferation of colorectal adenocarcinoma cells through oxidative stress-mediated pathways (Song et al., 2014a).

PCBs have been classified as carcinogenic to humans by the International Agency for Research on Cancer (Lauby-Secretan et al., 2013), but the epidemiologic evidence regarding PCBs and CRC is sparse. Several hospital-based case-control studies have reported an association between increased risk of CRC and exposure to POPs (Howsam et al., 2004; Lo et al., 2010; Soliman et al., 1997).For instance, in a study of 132 CRC cases and 76 hospital controls that measured serum levels of PCBs after cases were diagnosed those in the highest tertile of mono-*ortho* PCBs were at a 2.94-fold higher odds of being a CRC case than those in the first tertile [95% confidence interval (CI): 1.39; 6.20] (Howsam et al., 2004). Cohort studies of occupational exposure to POPs and risk of developing CRC have been less consistent. A prospective study of pesticide applicators found that self-reported occupational exposure to any of the seven OCs assessed (aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, or toxaphene) was associated with a decreased risk of colon cancer [rate ratio (RR) = 0.6, 95% CI: 0.5; 0.9] although PCBs and other OCs were not assessed and no exposure-response gradient was observed (Purdue et al., 2007). Excess mortality from rectal cancer was observed in an occupational cohort of OC manufacturers (Ditraglia et al., 1981); after an additional 11 years of follow-up the excess mortality was no longer present (Brown, 1992).

CRC mortality was not elevated in a pooled analysis of three cohorts comprised of 24,865 capacitator manufacturer workers [Standardized Mortality Ratio (SMR) any intestinal cancer except rectum = 1.11, 95% CI: 0.97; 1.27, SMR rectal cancer = 1.21, 95% CI: 0.90; 1.59]. However, among long-term female workers only intestinal cancer mortality was elevated (SMR = 1.23, 95% CI: 1.00; 1.49)(Ruder et al., 2014). Mortality from intestinal cancer was also non-statistically significantly elevated in another study of female capacitor workers (SMR = 1.59, 95% CI: 0.68; 3.13) (Mallin et al., 2004). Other occupational studies of farmers (Hoar et al., 1985) and OC manufacturers (MacLennan et al., 2003) have not reported an excess of CRC incidence or CRC-related mortality. Prior studies have had small sample sizes and limited information on the amount and sources of POP exposure. Furthermore, given the relatively high 5-year survival rate of CRC (65.1%)(2016), studies of cancer mortality do not fully capture the association between POP exposure and CRC incidence.

Fish are also source of long-chain omega-3 polyunsaturated fatty acids (n-3 PUFA), which have been suggested to reduce risk of CRC through several mechanisms, including enhancing apoptosis and reducing inflammation(Yang et al., 2014; Yang et al., 2013). A 20 gram increase in daily fish consumption was associated with a slight reduction in risk of CRC in a recent meta-analysis (pooled RR= 0.93, 95% CI: 0.87; 0.99)(Yu et al., 2014). Higher concentrations of n-3 PUFA in serum, plasma, erythrocytes, or adipose tissue have also been associated with decreased risk of CRC (reviewed by(Yang et al., 2014)).

Given that sport fish represents a complex mixture of both potentially beneficial and harmful compounds, considerable uncertainty remains about the association between sport fish consumption and cancer risks. In order to assess whether consumption of sport fish contaminated with POPs impacts risk of CRC, we examined the incidence of CRC in a large prospective cohort study of New York State anglers and their spouses. We hypothesized that consumption of Lake Ontario sport fish would be positively associated with risk of CRC.

2. Materials and Methods

2.1 Study design

The New York State Angler Cohort Study (NYSACS) is a prospective study of 10,518 male anglers, 913 female anglers, and 6,651 spouses/partners of anglers who responded to a mailed survey in 1991 that has been described previously (Buck et al., 1997).. Participants were required to be between 18 and 40 years of age and a resident of one of the 16 counties surrounding Lake Ontario. Potential participants were identified via fishing licenses maintained by the New York State Department of Environmental Conservation. The mailed survey that asked participants if they consumed at least one serving of Lake Ontario and Lake Erie sport fish consumption from 1955–1991. If a participant reported eating sport fish from Lake Ontario or Lake Erie at least once during any of those years, they were classified as a consumer of sport fish from the respective lake. Duration of sport fish consumption was estimated by summing the number of years a consumer reported eating sport fish from the lake of interest. Participants also reported their fish consumption in 1991 in more detail, including the species, amount, and preparation methods of fish consumed from each Great Lake. Socio-demographic characteristics, health and reproductive history, and cigarette

smoking were also assessed in the baseline questionnaire. Return of the questionnaire supplied informed consent. This study and the analyses reported on herein were approved by the University at Buffalo Institutional Review Board.

Participants were censored at the time of any cancer diagnosis, death, movement out of New York State, or at the end of the study (December 31st 2008). Nine percent (1,482) of NYSACS participants were lost to follow-up because they moved out of NYS prior to December 31st, 2008. Incident, first primary, histologically confirmed colorectal cancers were identified via linkage with the New York State Cancer Registry (NYSCR). The sensitivity of the NYSCR for identifying incident cases of breast cancer was 77%(Kato et al., 1999). Fifty CRC cases were identified as of December 31st, 2008. Six NYSACS participants who were reported to be diagnosed with CRC *in situ* and one participant without histologic confirmation of CRC were included as non-cases; two cases were excluded because they were missing information on covariates. This analysis includes 25 cases of colon cancer and 16 cases of rectal cancer. Prevalent cancers (n=196) diagnosed prior to January 1, 1991 were excluded from the analysis.

2.2 Statistical analyses

Baseline characteristics were compared using chi-square, Fisher's exact test, Student's t-test, or a non-parametric equivalent as appropriate. Poisson regression was used to estimate rate ratios (RR) and 95% confidence intervals. Potential covariates considered for adjustment were, age, race, sex, years of education, and pack years of smoking. Participants who were missing information on cigarette smoking (n=713), Lake Ontario sport fish consumption (n=4), age (n=287), or had contributed less than a year to the study (n=89) were excluded from the analyses reported herein. In total these analyses include 41 cases of CRC and 15,766 noncases. Covariates were included in the final model if adjusting for them resulted in a change in the point estimate of 10% or greater; age was forced into all models. The final model included age, sex, and pack-years smoking. Duration of Great Lakes' fish consumption was parametrized by tertiles of the years reported by CRC cases. We also parameterized these categories as a continuous variable to test the statistical significance of the slope. Analyses were also stratified by sex and age to assess potential effect measure modification; p for interactions were calculated by including a product term in the model. All statistical tests were two-sided and analyses were performed using SAS Enterprise Guide (Version 4.3. Copyright © 2006–2010 SAS Institute Inc., Cary, NC, USA).

2.2.1 Sensitivity analysis—Obesity is a strong risk factor for CRC (Boyle et al., 2014; Gribovskaja-Rupp et al., 2011; Le Marchand et al., 1997; Schwartz and Yehuda-Shnaidman, 2014; Simon et al., 2011) that was not assessed at baseline. In order to assess the potential of residual confounding by obesity we performed a sensitivity analysis. We assumed that the prevalence of obesity among non-consumers in 1991 was similar to that of National Health and Nutrition Examination Survey (NHANES) participants between 20 and 39 years old from 1988 to 1994, which was 14.9% for men and 20.6% for women (Flegal et al., 2002). Using the sex distribution of non-consumers, we estimated the prevalence of obesity among non-consumers to be 17.6%. We then used an array approach (Schneeweiss, 2006) to estimate the potential impact residual confounding by obesity may have on our observed

results. We used a range of values from 10% to 90% for the prevalence of obesity among consumers and a range of 1.10 to 1.90 for the rate ratio between obesity and CRC to generate adjusted rate ratios for Lake Ontario sport fish consumption. A recent meta-analysis reported that the pooled relative risk for CRC when comparing obese to normal BMI was 1.33 (95% CI: 1.25; 1.42) (Ma et al., 2013).

3. Results

Descriptive characteristics by Lake Ontario sport fish consumer status are displayed in Table 1. Compared with non-consumers, consumers were more likely to be male, older age, a race other than Caucasian, and report smoking cigarettes.

A total of 41 incident cases of CRC occurred during follow-up, most developed in the cecum, sigmoid colon, or rectum. Rate ratios for developing CRC and Lake Ontario sport fish consumption are displayed in Table 2. Participants that reported ever consuming Lake Ontario sport fish had a statistically non-significant lower incidence of CRC (RR=0.66, 95% CI: 0.35; 1.24); we did not observe a monotonic exposure-response gradient for duration of consumption. When we restricted the analysis to colon cancers only, an inverse association was also observed (RR = 0.45, 95% CI: 0.20; 1.00). Furthermore, when restricted to colon cancer only, the inverse association was stronger among those who consumed Lake Ontario sport fish for eight years or more (RR = 0.24, 95% CI: 0.07; 0.87) and the linear trend was statistically significant (p for trend = 0.02). We did not observe an association between rectal cancer and Lake Ontario sport-fish consumption. The associations between Lake Ontario sport fish consumption and risk of CRC were similar by sex or age strata (data not shown).

We conducted a sensitivity analysis in order to determine whether residual confounding by obesity was an alternative explanation for our observed results, the results of which are presented in Table 3. We used an array of values for the prevalence of obesity among Lake Ontario fish consumers and the RR between obesity and risk of CRC to calculate what the obesity-adjusted RR would be under a series of possible scenarios. If the prevalence of obesity were 10% among consumers and 17.7% among non-consumers and the RR between obesity and CRC was 1.9, the obesity-adjusted RR would be 0.70. If the prevalence of obesity were higher among consumers than non-consumers the observed inverse association would be strengthened.

Rate ratios for Lake Erie sport fish consumption and CRC are presented in Table 4. Lake Erie sport-fish consumption was not associated with risk of developing CRC (RR = 1.03, 95% CI: 0.50; 2.11), although the number of Lake Erie consumers with CRC was small (n=12). We observed an inverse association between Lake Ontario sport fish consumption and risk of CRC was observed regardless of Lake Erie sport fish consumption (Table 5).

4. Discussion

We found that consumption of contaminated sport fish from Lake Ontario was associated with a statistically non-significant decreased risk of CRC and a significantly decreased risk of colon cancer, which is consistent with a beneficial micronutrient hypothesis. Our results are inconsistent with the hypothesis that consumption of sport fish contaminated with POPs

is associated with increased risk of CRC. Sources of exposure to POPs other than Lake Ontario sport fish were not assessed in this study thus inferences regarding POPs and CRC are limited, although it was established in a subset of NYSACS participants that Lake Ontario sport fish consumers have higher serum concentrations of Mirex and PCB congeners (Bloom et al., 2005).

Associations between exposure to POPs and cancer risk are likely chemical specific. The chemicals that were positively associated with fish consumption among NYSACS participants (Mirex and PCB numbers, 138+163, 187, and 188 (Bloom et al., 2005)) have not previously been studied in association with CRC, thus our results are not directly comparable to prior studies. However, there have been studies of other POPs and risk of CRC that may provide useful background when contextualizing our findings. For instance, in a case-control study serum levels of PCB 28 and 118 above the limit of detection were associated with a higher odds of being a CRC case than those below the limit of detection (PCB 118 OR = 2.02,95% CI: 1.00; 4.08) (Howsam et al., 2004). It should be noted that the serum levels reported by Howsam et al. were generally higher than NYSACS participants. For instance, Howsam et al. reported the median concentration of PCB 118 to be 92 ng/g lipid(Howsam et al., 2004), while the median concentration of PCB 118 among a subset of 110 male NYSACS participants was 24.3ng/g lipid for consumers of Lake Ontario fish and18.3 ng/g lipid for non-consumers (Bloom et al., 2005). Researchers in Egypt found that 31 CRC cases had higher serum levels of OC insecticides than 17 controls (Soliman et al., 1997). Conversely, in a large prospective cohort study of pesticide applicators no association between risk of CRC and application of any OC insecticide was observed (Lee et al., 2007).

Carcinogenic contaminants in fish, including POPs, have been suggested as an explanation for inconsistencies across studies of fish consumption and risk of CRC (Sasazuki et al., 2011; Song et al., 2014b). Previous studies of fish consumption and risk of CRC have generally reported a weak inverse association (as reviewed by:(Yu et al., 2014)). Fish consumption was associated with a decreased odds of CRC (summary odds ratio= 0.88, 95% CI: 0.80; 0.95) in a meta-analysis of 22 prospective cohort and 19 case-control studies. In this analysis the inverse association was restricted to rectal cancer (OR = 0.79, 95% CI: 0.65; 0.97) and not colon cancer (OR = 0.93, 95% CI: 0.86; 1.01) (Wu et al., 2012). Epidemiologic studies of fish intake and CRC risk generally assess total fish intake without considering the source of fish. Our results of an inverse association between consumption of freshwater sport fish from Lake Ontario and risk of CRC are similar to the only prior study, to our knowledge, that considered freshwater fish separately. A stronger inverse association between risk of CRC and freshwater fish consumption than sea fish or dried/salted fish was observed in a case-control study conducted in China of 1189 CRC cases and 1189 controls. When compared with the lowest quartile of freshwater fish consumption those in the highest quartile of intake were at 53% lower odds of being a CRC case (OR = 0.47, 95% CI: 0.36; 0.60), the association comparing the highest quartile of sea fish consumption to the lowest was more modest (OR = 0.79, 95% CI: 0.62; 0.99) (Xu et al., 2015).

Dietary supplementation with fish oil has also been associated with reduced risk of CRC and further support the beneficial nutrient hypothesis. In a cohort study of 68,109 participants, the hazard ratio for developing CRC was 0.51 (95% CI: 0.26; 1.00) when those who took

fish oil supplements at least four days per week for at least three years were compared with those who did not take fish oil supplements(Kantor et al., 2014).

Experimental studies have demonstrated that n-3 PUFA inhibit colon carcinogenesis by up-regulating apoptosis of damaged cells (Cho et al., 2014). Furthermore, advisement to increase intake of n-3 PUFAs, including fish and fish oil supplements, was associated with a reduction in the incidence of colorectal tumors over 24 months among 104 polypectomized intervention participants when compared with 101 polypectomized control participants [hazard ratio (HR) = 0.81 (95% CI: 0.54; 1.21)] (Tokudome et al., 2015). In a prospective cohort study of Japanese individuals, a population that consumes high amounts of fish, self-reported dietary consumption of total n-3 PUFA was associated with decreased risk of proximal colon cancer, among men and women (HR fifth quintile of n-3 PUFA vs. first, men = 0.42, 95% CI: 0.18; 0.98 women = 0.55, 95% CI: 0.27; 1.11), but not distal colon or rectal cancer (Sasazuki et al., 2011).

As with all studies, ours has limitations that should be considered when interpreting our results. In spite of over 16 years of follow-up, NYSACS participants are still relatively young (mean age at censor = 48.2, SD=6.3). Consequently, a relatively small number of CRC cases have accrued, reducing statistical power and we cannot entirely rule out chance as an explanation for the observed inverse associations. We did not have information on fish consumption from non-Great Lakes sources, which introduces potential exposure misclassification. Previously, Great Lakes' sport fish consumers have reported eating more total fish meals from any source than non-Great Lakes' sport fish consumers (mean number of meals/year consumers = 53 non-consumers = 44, p-value= 0.04)(Imm et al., 2005). The average number of sport-fish meals consumers ate was 13, thus commercial fish consumption among the Great Lakes residents surveyed in that study did not vary by sport fish consumption (Imm et al., 2005). Additionally, while we assessed the duration of fish consumption, the amount of fish consumed during years other than 1991 was not assessed. We did assess the association between the number of servings per month participants reported consuming in 1991 and incidence of CRC and the results of an inverse association between Lake Ontario fish consumption and CRC were the same regardless of the amount consumed (results not shown). An additional source of exposure misclassification is that participants were asked to recall exposures from several decades in the past. These sources of exposure misclassification are likely non-differential with regards to CRC onset and may be attenuating the measures of association.

We used a linkage with the NYSCR to identify incident cases of CRC, which has a previously reported sensitivity of 77% for cases of breast cancer(Kato et al., 1999). We are unable to test the sensitivity of NYSCR to identify incident CRC cases in NYSACS, however it is plausible that the sensitivity would be higher, because unlike a study of women with breast cancer, the NYSACS is 63% male which decreases the number of participants that would not be identified because their name changed (Kato et al., 1999). Nonetheless, identification of CRC cases via linkage with NYSCR is still imperfect. The unidentified cases could be a source of non-differential outcome misclassification and potentially decreased the already limited statistical power in our study,

Uncontrolled confounding by physical activity, diet, diabetes, alcohol consumption, and body mass index is a possibility because these factors were not assessed at baseline. However, we conducted sensitivity analyses that indicated that if obesity, for instance, were associated with Lake Ontario sport fish consumption, a statistical adjustment for obesity would strengthen the observed inverse association. Furthermore, adjustment for the potential confounders that were assessed at baseline (i.e., age and pack years smoking) did not substantially change our point estimates. Therefore, uncontrolled confounding does not appear to be a likely alternative explanation for our results and could be attenuating the inverse association between Lake Ontario fish consumption and risk of CRC.

Loss to follow-up may have introduced a selection bias because nine percent of NYSACS participants moved out of New York State during follow-up. However, these losses were not associated with Lake Ontario sport fish consumption. Of those who were followed until the end of the study, 61% reported consuming Lake Ontario sport fish. Similarly, of those who were lost either due to moving out of NYS or death 59% reported consuming Lake Ontario sport fish. In addition, self-selection bias into the cohort is a possibility because only 30% of the 30,000 anglers sent a baseline questionnaire responded (Vena et al., 1996) and those who chose to enroll may be more healthy or health conscious than those who chose not to. However, we observed expected associations with other exposures and risk of CRC. Cigarette smoking was associated with increased risk of CRC and there was evidence that a higher number of pack-years was associated with increased risk (p for trend= 0.03). History of colon polyps was associated with an increased risk of developing CRC (RR=7.89, 95% CI: 1.90; 32.70). Additionally, Lake Ontario sport fish consumers were more likely to smoke than non-consumers (57% vs. 42%, respectively), which suggests that salubrious behaviors were not associated with Lake Ontario sport fish consumption.

We did not observe any association between consumption of Lake Erie sport fish and risk of CRC. Although the number of Lake Erie sport fish consumers with CRC is small, this is unexpected and we are unable to explain these findings. It is possible that differences in species of fish harvested from these two lakes coupled with differences in the distribution of pollutants and beneficial micronutrients in these fish explains this inconsistency with risk estimates. The mean n-3 PUFA:n-6 PUFA ratios were similar when lake trout sampled from Lake Erie in 2007 were compared with lake trout from Lake Ontario in 2008 (2.3±0.2 and 2.2±0.2, respectively)(Pantazopoulos et al., 2013), suggesting that the beneficial micronutrients do not vary by Great Lake. However, there are differences in the species of fish consumed by Great Lake source. In 1991, 3,761 Lake Erie fish consumers and 9,635 Lake Ontario fish consumers who participated in NYSACS completed a fish frequency questionnaire that queried the frequency of consumption of specific fish species. The most frequently reported fish species consumed by Lake Erie sport fish consumers were walleye, yellow perch, and rainbow trout. Conversely the most frequently reported fish consumed at least once per month by Lake Ontario consumers were yellow perch, lake trout, and Chinook salmon. Walleye is lower n-3 PUFA than salmon, which may partially explain the discrepancy between Lake Ontario and Lake Erie sport fish consumption (Raatz et al., 2013).

Our study also has several important strengths. The prospective design of NYSACS makes it unlikely that there are sources of exposure misclassification or factors influencing study participation that are differential with regards to developing CRC. All cases in these analyses had a histologically confirmed diagnosis of CRC that limits the potential for outcome misclassification. The relatively young age of NYSACS participants at enrollment reduces the potential for selection bias because it is unlikely that fish consumption was associated with mortality or onset of CRC among potential participants prior to initiation of the study (Weisskopf et al., 2015). Furthermore, we observed consistent associations between known CRC risk factors and CRC in this setting, including smoking, age, sex, and history of colon polyps.

In conclusion, we did not observe evidence that consumption of contaminated sport fish increases the risk of CRC in a large prospective cohort study. Although the methods used to estimate fish consumption in NYSACS were not designed to assess total fish consumption, our findings are consistent the hypothesis that fish consumption is inversely associated with incidence of colon cancer, but not rectal cancer. However, the relatively small number of CRC cases that have accrued and residual confounding by diet and possibly other risk factors that we were unable to adjust for remain as sources of concern. There may be other deleterious health effects of contaminated sport fish consumption and further research and additional follow-up in cohorts of Great Lakes' fish consumers are warranted.

Acknowledgments

Funding:

The New York State Angler Cohort Study was funded by: ATSDR/CDC R01TS000077. Catherine L. Callahan was supported by the National Cancer Institute (NCI) grant R25CA113951.

References

SEER Stat Fact Sheets: Colon and Rectum Cancer. 2016

Bloom MS, et al. Profiles of ortho-polychlorinated biphenyl congeners, dichlorodiphenyldichloroethylene, hexachlorobenzene, and Mirex among male Lake Ontario sportfish consumers: the New York State Angler Cohort Study. Environmental Research. 2005; 97:178–194. [PubMed: 15533334]

Boyle T, et al. Smoking, alcohol, diabetes, obesity, socioeconomic status, and the risk of colorectal cancer in a population-based case-control study. Cancer Causes & Control. 2014; 10:10.

Brown DP. Mortality of workers employed at organochlorine pesticide manufacturing plants--an update. Scand J Work Environ Health. 1992; 18:155–161. [PubMed: 1615289]

Buck GM, et al. Consumption of Contaminated Sport Fish from Lake Ontario and Time-to-Pregnancy: New York State Angler Cohort. American Journal of Epidemiology. 1997; 146:949–954. [PubMed: 9400336]

Cho Y, et al. Colon cancer cell apoptosis is induced by combined exposure to the n-3 fatty acid docosahexaenoic acid and butyrate through promoter methylation. Exp Biol Med (Maywood). 2014; 239:302–310. [PubMed: 24495951]

Ditraglia D, et al. Mortality study of workers employed at organochlorine pesticide manufacturing plants. Scand J Work Environ Health. 1981; 7(Suppl 4):140–146. [PubMed: 7330625]

Flegal KM, et al. Prevalence and trends in obesity among US adults, 1999–2000. JAMA. 2002; 288:1723–1727. [PubMed: 12365955]

Gribovskaja-Rupp I, et al. Obesity and colorectal cancer. Clin Colon Rectal Surg. 2011; 24:229–243. [PubMed: 23204938]

Hoar SK, et al. Herbicides and colon cancer. Lancet. 1985; 1:1277–1278.

Howsam M, et al. Organochlorine exposure and colorectal cancer risk. Environ Health Perspect. 2004; 112:1460–1466. [PubMed: 15531428]

Imm P, et al. Fish Consumption and Advisory Awareness in the Great Lakes Basin. Environmental Health Perspectives. 2005; 113:1325–1329. [PubMed: 16203241]

Kantor ED, et al. Long-chain omega-3 polyunsaturated fatty acid intake and risk of colorectal cancer. Nutr Cancer. 2014; 66:716–727. [PubMed: 24053119]

Kato I, et al. Comparison of active and cancer registry-based follow-up for breast cancer in a prospective cohort study. Am J Epidemiol. 1999; 149:372–378. [PubMed: 10025481]

Lauby-Secretan B, et al. Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls. Lancet Oncol. 2013 Apr; 14(4):287–288. 2013 Epub 2013 Mar 15. [PubMed: 23499544]

Le Marchand L, et al. Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. Cancer Res. 1997; 57:4787–4794. [PubMed: 9354440]

Lee WJ, et al. Pesticide use and colorectal cancer risk in the Agricultural Health Study. Int J Cancer. 2007; 121:339–346. [PubMed: 17390374]

Lo AC, et al. Lifestyle, occupational, and reproductive factors and risk of colorectal cancer. Dis Colon Rectum. 2010; 53:830–837. [PubMed: 20389219]

Ma Y, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One. 2013; 8:e53916. [PubMed: 23349764]

MacLennan PA, et al. Mortality among triazine herbicide manufacturing workers. J Toxicol Environ Health A. 2003; 66:501–517. [PubMed: 12712593]

Mallin K, et al. Cohort mortality study of capacitor manufacturing workers, 1944–2000. J Occup Environ Med. 2004; 46:565–576. [PubMed: 15213519]

Moser GA, McLachlan MS. The influence of dietary concentration on the absorption and excretion of persistent lipophilic organic pollutants in the human intestinal tract. Chemosphere. 2001; 45:201–211. [PubMed: 11572612]

Pantazopoulos P, et al. Fatty acids in Great Lakes lake trout and whitefish. Journal of Great Lakes Research. 2013; 39:120–127.

Porta M, et al. Monitoring concentrations of persistent organic pollutants in the general population: the international experience. Environ Int. 2008; 34:546–561. [PubMed: 18054079]

Purdue MP, et al. Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study. Int J Cancer. 2007; 120:642–649. [PubMed: 17096337]

Raatz S, et al. Issues of Fish Consumption for Cardiovascular Disease Risk Reduction. Nutrients. 2013; 5:1081. [PubMed: 23538940]

Ruder AM, et al. Mortality among 24,865 workers exposed to polychlorinated biphenyls (PCBs) in three electrical capacitor manufacturing plants: a ten-year update. Int J Hyg Environ Health. 2014; 217:176–187. [PubMed: 23707056]

Sasazuki S, et al. Intake of n-3 and n-6 polyunsaturated fatty acids and development of colorectal cancer by subsite: Japan Public Health Center-based prospective study. Int J Cancer. 2011; 129:1718–1729. [PubMed: 21120874]

Schlummer M, et al. Digestive tract absorption of PCDD/Fs, PCBs, and HCB in humans: mass balances and mechanistic considerations. Toxicol Appl Pharmacol. 1998; 152:128–137. [PubMed: 9772208]

Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf. 2006; 15:291–303. [PubMed: 16447304]

Schwartz B, Yehuda-Shnaidman E. Putative role of adipose tissue in growth and metabolism of colon cancer cells. Front Oncol. 2014; 4

Simon MS, et al. Racial differences in colorectal cancer incidence and mortality in the Women's Health Initiative. Cancer Epidemiol Biomarkers Prev. 2011; 20:1368–1378. [PubMed: 21602308]

Soliman AS, et al. Serum organochlorine pesticide levels in patients with colorectal cancer in Egypt. Arch Environ Health. 1997; 52:409–415. [PubMed: 9541361]

Song L, et al. p, p'-Dichlorodiphenyldichloroethylene induces colorectal adenocarcinoma cell proliferation through oxidative stress. PLoS One. 2014a; 9:e112700. [PubMed: 25386960]

Song M, et al. Dietary intake of fish, omega-3 and omega-6 fatty acids and risk of colorectal cancer: A prospective study in U.S. men and women. Int J Cancer. 2014b; 135:2413–2423. [PubMed: 24706410]

Tokudome S, et al. Dietary n-3/long-chain n-3 polyunsaturated fatty acids for prevention of sporadic colorectal tumors: A randomized controlled trial in polypectomized participants. Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA). 2015; 94:1–11.

Turyk ME, et al. Risks and Benefits of Consumption of Great Lakes Fish. Environmental Health Perspectives. 2012; 120:11–18. [PubMed: 21947562]

Vena JE, et al. The New York Angler Cohort Study: exposure characterization and reproductive and developmental health. Toxicol Ind Health. 1996; 12:327–334. [PubMed: 8843550]

Warner J, et al. Common classification schemes for PCB congeners and the gene expression of CYP17, CYP19, ESR1 and ESR2. Sci Total Environ. 2012; 414:81–89. [PubMed: 22119029]

Weisskopf MG, et al. Biased Exposure-Health Effect Estimates from Selection in Cohort Studies: Are Environmental Studies at Particular Risk? Environ Health Perspect. 2015; 123:1113–1122. [PubMed: 25956004]

Wu S, et al. Fish consumption and colorectal cancer risk in humans: a systematic review and meta-analysis. Am J Med. 2012; 125:551–559. [PubMed: 22513196]

Xu M, et al. Higher freshwater fish and sea fish intake is inversely associated with colorectal cancer risk among Chinese population: a case-control study. Sci Rep. 2015; 5:12976. [PubMed: 26264963]

Yang B, et al. Biospecimen long-chain N-3 PUFA and risk of colorectal cancer: a meta-analysis of data from 60,627 individuals. PLoS One. 2014; 9:e110574. [PubMed: 25375637]

Yang T, et al. N-3 PUFAs have antiproliferative and apoptotic effects on human colorectal cancer stem-like cells in vitro. J Nutr Biochem. 2013; 24:744–753. [PubMed: 22854319]

Yu XF, et al. Fish consumption and risk of gastrointestinal cancers: A meta-analysis of cohort studies. World J Gastroenterol. 2014; 20:15398–15412. [PubMed: 25386090]

Highlights

- Great Lakes fish consumption increases exposure to persistent organic pollutants
- Lake Ontario fish consumption inversely associated with colon cancer
- Lake Ontario fish consumption not associated with rectal cancer
- Lake Erie fish consumption was not associated with incidence of colorectal cancer

Table 1

Baseline characteristics by Lake Ontario sport fish consumption, New York State Angler Cohort Study, 1991

Baseline Characteristics	Non-Consumers (n=6,173)	Consumers (n=9,635)	
	n (%)		p^a
Education			0.35
<High school	266 (4.31)	404 (4.19)	
High school graduate	2563 (41.52)	4113 (42.69)	
>High school	3344 (54.17)	5118 (53.12)	
Age at baseline (years)			<0.001
≤30	2631 (42.62)	3684 (38.24)	
31–35	1951 (31.61)	3097 (32.14)	
≥36	1591 (25.77)	2854 (29.62)	
Sex			<0.001
Male	3182 (51.55)	6853 (71.13)	
Female	2991 (48.45)	2782 (28.87)	
Race			<0.001
Caucasian	6018 (98.09)	9323 (97.54)	
Other	117 (1.91)	235 (2.46)	
Ulcerative colitis			0.97
Yes	42 (0.68)	65 (0.67)	
No	6131 (99.32)	9570 (99.33)	
Cigarette smoking (pack-years)			<0.001
Never Smokers	2907 (47.09)	4117 (42.73)	
≤20	2796 (45.29)	4520 (46.91)	
>20	470 (7.61)	998 (10.36)	
Years of eating Lake Ontario fish			
≤3		2607 (27.06)	
>3 to ≤8		3892 (40.39)	
>8		3136 (32.55)	
	mean (SD)		p^b
Years of fishing in New York State	17.32 (9.31)	20.18 (8.54)	<0.001
Person-years of follow-up	16.42 (3.22)	16.53 (3.04)	0.04
	median (IQR)		p^c
Age at CRC diagnosis[d]	49.40 (5.89)	50.75 (9.54)	<0.001

Abbreviations: SD=standard deviation; IQR = inter-quartile range; CRC colorectal cancer.

[a] X^2 test of differences between strata.

[b] Student's t-test.

[c] Wilcoxon signed rank test.

[d] CRC cases only

Table 2

Rate Ratios (RR) and 95% confidence intervals (CI)[a] for colorectal cancer (CRC) by Lake Ontario sport fish consumption, New York State Angler Cohort Study, 1991–2008

	No. cases	Person-years	Unadjusted RR (95% CI)	Adjusted[b] RR (95% CI)
Colorectal cancer				
Ever ate L. Ontario fish				
No	18	101,366	1.00 (referent)	1.00 (referent)
Yes	23	159,251	0.81 (0.43; 1.51)	0.66 (0.35; 1.24)
Years of consumption				
Never	18	101,366	1.00 (referent)	1.00 (referent)
<3	9	59,618	0.85 (0.38; 1.89)	0.77 (0.35; 1.72)
4–7	6	34,106	0.99 (0.39; 2.50)	0.81 (0.32; 2.06)
>8	8	65,526	0.69 (0.29; 1.58)	0.51 (0.22; 1.18)
		p-trend	0.44	0.13
Colon Cancer				
Ever ate L. Ontario fish				
No	13	101,366	1.00 (referent)	1.00 (referent)
Yes	12	159,251	0.59 (0.27; 1.29)	**0.45 (0.20; 1.00)**
Years of consumption				
Never	13	101,366	1.00 (referent)	1.00 (referent)
<3	6	59,618	0.78 (0.30; 2.06)	0.69 (0.26; 1.83)
4–7	3	34,106	0.69 (0.20; 2.41)	0.52 (0.15; 1.85)
>8	3	65,526	0.36 (0.10; 1.25)	**0.24 (0.07; 0.87)**
		p-trend	0.10	0.02
Rectal cancer				
Ever ate L. Ontario fish				
No	5	101,366	1.00 (referent)	1.00 (referent)
Yes	11	159,251	1.40 (0.49; 4.03)	1.25 (0.43; 3.65)
Years of consumption				
Never	5	101,366	1.00 (referent)	1.00 (referent)
<3	3	59,618	1.02 (0.24; 4.27)	0.97 (0.23; 4.07)
4–7	3	34,106	1.78 (0.43; 7.46)	1.63 (0.39; 6.90)
>8	5	65,526	1.55 (0.45; 5.34)	1.30 (0.37; 4.58)
		p-trend	0.40	0.59

[a] Rate ratios (RR) and 95% confidence intervals were estimated using Poisson regression models

[b] Adjusted for age at baseline, sex, and pack-years of smoking

Table 3

Sensitivity analysis of potential impact of adjustment for obesity on estimates of Lake Ontario sport fish consumption and colorectal cancer rate ratios (RR), at the observed RR of 0.66

Prevalence of obesity among Lake Ontario sport fish consumers[a]	Obesity RR	Obesity-Adjusted RR
0.10	1.1	0.67
	1.5	0.68
	1.9	0.70
0.20	1.1	0.66
	1.5	0.65
	1.9	0.61
0.40	1.1	0.65
	1.5	0.60
	1.9	0.56
0.50	1.1	0.64
	1.5	0.57
	1.9	0.53
0.90	1.1	0.62
	1.5	0.50
	1.9	0.42

[a]Prevalence of obesity among non-consumers was held constant at 17.66%

Table 4

Rate Ratios (RR) and 95% confidence intervals (CI)[a] for colorectal cancer (CRC) by Lake Erie sport fish consumption, New York State Angler Cohort Study, 1991–2008

	CRC cases (n=32)	Person-years	Unadjusted RR (95% CI)	Adjusted[b] RR (95% CI)
Ever ate L. Erie fish				
No	20	116,860	1.00 (referent)	1.00 (referent)
Yes	12	62,621	1.12 (0.55; 2.29)	1.03 (0.50; 2.11)
Years of consumption				
Never	20	116,860	1.00 (referent)	1.00 (referent)
>7	5	35,652	0.82 (0.31; 2.18)	0.82 (0.31; 2.18)
8–14	3	10,797	1.62 (0.48; 5.46)	1.46 (0.43; 4.95)
>15	4	16,171	1.45 (0.49; 4.23)	1.13 (0.39; 3.30)
		p-trend	0.31	0.55

[a] Rate ratios (RR) and 95% confidence intervals were estimated using Poisson regression models

[b] Adjusted for age at baseline, sex, and pack-years of smoking

Table 5

Rate Ratios (RR) and 95% confidence intervals (CI)[a] for colorectal cancer (CRC) by Lake Ontario and Erie sport fish consumption, New York State Angler Cohort Study 1991–2008

Sport-fish consumption		CRC cases (n=32)	Person-years	Unadjusted RR (95% CI)	Model 1[b] RR (95% CI)
Lake Ontario	*Lake Erie*				
Non-consumer	Non-consumer	8	39,746	1.00 (referent)	1.00 (referent)
Non-consumer	Consumer	5	17,533	1.42 (0.46; 4.33)	1.19 (0.39; 3.66)
Consumer	Non-consumer	12	77,113	0.77 (0.32; 1.89)	0.67 (0.28; 1.67)
Consumer	Consumer	7	45,087	0.77 (0.28; 2.13)	0.64 (0.23; 1.78)

[a]Rate ratios (RR) and 95% confidence intervals were estimated using Poisson regression models

[b]Adjusted for age at baseline, sex, and pack-years of smoking