RESEARCH ARTICLE

Intake of Freshwater Fish and Associated Fatty Acids and Risk of Breast Cancer

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Abstract

To investigate the association between intake of freshwater fish and their fatty acids and the risk of breast cancer in Chinese women, we conducted a case-control study with 669 cases and 682 population-based controls in Jiangsu Province of China. A structured questionnaire was used to elicit detailed information. Unconditional logistic regression analysis was performed to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Total freshwater fish intake was linked to decrease in the adjusted OR for breast cancer, but without dose-dependence. Analyses by freshwater fish species showed that consumption of black carp and silver carp was inversely related to breast cancer risk, with adjusted-ORs for the highest intake category of black carp (\geq 500g/month) of 0.54 (95% CI=0.33-0.92; $P_{trend} < 0.002$) and for silver carp (\geq 1000g/month) of 0.19 (95% CI=0.11-0.33; $P_{trend} < 0.001$). In contrast, consumption of crucian carp was positively related to breast cancer risk, with an adjusted OR for the highest intake category (\geq 1000g/month) of 6.09 (95% CI=3.04-12.2; $P_{trend} < 0.001$). Moderate intakes of SFA, PUFA, n3-PUFA and n6-PUFA from freshwater fish may decrease the risk of breast cancer among premenopausal women. The findings of this study suggest that intake of freshwater fish and their fatty acids may modify risk of breast cancer, and that different species of freshwater fish could have a different actions on breast cancer risk. Future epidemiologic studies are needed to know the effects of freshwater fish intake on breast cancer risk and the cause of these effects.

Keywords: Freshwater fish - fatty acids - breast cancer - Chinese

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Introduction

Breast cancer constitutes the most common cancer in women and is an important public health concern worldwide. Although the incidence rate of breast cancer in China is lower than those in Western countries, there has been a marked increase in recent years (Parkin et al., 2005; Yang et al., 2005). In the past few decades, epidemiological studies (Brennan et al., 2010; Lambrechts et al., 2011; Gao et al., 2013) have suggested that a healthy diet and lifestyle is critical factor for the prevention of breast cancer. Many authors have analysed relationship between the fish intake and the risk of breast cancer, however the results have been inconsistent (Wirfalt et al., 2002; Terry et al., 2003; Hirose et al., 2006; Engeset et al., 2006; Brustad et al., 2007; Kim et al., 2009; Sala-Vila and Calder, 2011; Zheng et al., 2013).

Most previous studies on the association of breast cancer risk with fish did not analyze freshwater and marine fish separately. Dai et al. (2002) and Bao et al. (2012) found that intake of freshwater fish was related to an increased risk of breast cancer. Freshwater fish is one

of the staples of Chinese diet, especially in the non-littoral of China. To evaluate the relationship between intakes of freshwater fish and their fatty acids with breast cancer risk, we conducted this case-control study in Jiangsu Province, China.

Materials and Methods

Study subjects

We recruited breast cancer cases using data of the Cancer Registries in Taixing, Wuxi, Jintan and Huian Cities of Jiangsu Province of China, and also recruited cases who visited Jiangsu Province Cancer Hospital from these cities from June 2004 to December 2007. All cases were histopathologically diagnosed as having a primary breast cancer. Physicians at the hospital asked eligible cases to participate in our study, and doctors or nurses interviewed the participants after obtaining informed consent. Population-based controls were selected from healthy residents in eleven villages or towns of Taixing, Wuxi, Jintan and Huian Cities. Doctors of the public health centers randomly selected one or two controls

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Chang-Ming Gao et al

for each case, after matching for ethnicity and age within 2 years using the records of residents at the local governmental office, and then asked eligible residents for their participation. Interviews were performed as for the cancer cases. Total 669 cases and 682 controls completed interview. The ethics committee of Jiangsu Province Institute of Cancer Research approved this study.

Data collection

All participants completed an in-person interview that used a structured questionnaire. Dietary intakes were assessed using an 83-item food frequency questionnaire (FFQ), capturing 90% of food intake and covering nutrients constituting up to 90% of the nutrient intake in urban and rural areas of Jiangsu province (Wang et al., 2003). Each participant was asked about the frequency of a specific food that was eaten, followed by a question on the amount typically consumed. The FFQ listed 5 species of freshwater fish, including black carp (Mylopharyngodon piceus), finless eel (Monopterus albus), bream (Parabramis pekinensis), crucian carp (Crassius auratus) and silver carp (Hypopthalmichthys motitrix). Intakes of the fat and fatty acids (including total fatty acid, SFA, MUFA, PUFA, n3-PUFA and n6-PUFA) were calculated according to consumption of these freshwater fish, with Standard Food Composition Tables for China. (Yang et al., 2002).

Data analysis

Odds ratios (ORs) were used to measure the association of breast cancer risk with intakes of freshwater fish and their fatty acids. Unconditional logistic regression from the statistical package SAS were used to obtain maximum likelihood estimates of the ORs and their 95% confidence intervals (CIs), and used to the line trend test of ORs. All ORs were adjusted by age, status of marriage and menstruation, age of menarche and menopause, childbirth, body mass index (BMI), family history of breast cancer, income/month, status of the smoking and alcohol drinking, meats consumption, and intakes of the fruit and vegetables. Quarter distributions of intakes of the fat and fatty acids from freshwater fish among controls were used to categorize the variables.

Results

Table 1 shows comparisons of cases and controls on demographic factors, physiological and reproductive characteristics, and other known risk factors of breast cancer. Compared with controls, cases were younger at menarche and older at menopause. Cases were more likely to have a higher income, a family history of breast cancer among first-degree relatives. The statistically significant differences between cases and controls were observed for childbirth, status of the smoking and alcohol drinking, and usual consumption of the meats and fruit and vegetables. All of these variables were considered as potential confounders and adjusted for in subsequent analyses.

Data for associations between intakes of freshwater fish and breast cancer risk are presented in Table 2. As compared with women who never intakes of all freshwater fish, the adjusted OR for breast cancer among consumers of freshwater fish was 0.25 (95%CI: 0.11-0.57). Analyses by freshwater fish species showed that intakes of the black carp, finless eel, bream and silver carp significantly lowered the adjusted-ORs for breast cancer, the adjusted-ORs and their 95%CIs were 0.66 (0.51-0.84) for black carp, 0.47 (0.36-0.61) for finless eel, 0.54 (0.41-0.72) for bream and 0.46 (0.35-0.60) for silver carp, respectively.

Table 3 shows the dose-response relationship between the consumption of freshwater fish and the breast cancer risk. Among all study subjects, after adjusting for potential confounders, the ORs for breast cancer were significantly decreased with increasing consumption of the black carp and silver carp, with a statistically significant dose-response relation (P for trend =0.002 and <0.001, respectively). Reduced risk was also related to high consumption of finless eel (P for trend <0.001), but the adjusted-OR of the highest intake category (\geq 500g/month) was not statistically significant. With regard to intake of bream, compared with the never intake of bream, the second and the third intake categories all had a significant decreased adjusted-OR, but the adjusted-OR of the highest intake category (\geq 1000g/month) showed a clear increase

Table 1. Comparison of Cases and Controls by Selected Descriptive Characteristics

	Cases (n=669) C	χ^2	P	
Age at menarch	e (years)		8.11	0.004
≥14	479 (73.1)	541 (79.3)		
≤13	180 (26.9)	141 (20.7)		
Age at menopau	ise (years)		29.21	0.001
≤50	216 (60.0)	305 (78.2)		
< 50	144 (40.0)	85 (21.8)		
Childbirth			4.14	0.042
Never	25 (3.7)	13 (1.9)		
Have	644 (96.3)	669 (98.1)		
BMI			4.88	0.087
<22	225 (33.63)	244 (35.78)		
22-24.9	256 (38.27)	282 (41.35)		
≥25	188 (28.10)	156 (22.87)		
Family history	of breast cancer		15.31	0.001
No	638 (95.22)	674 (98.83)		
Have	32 (4.78)	8 (1.17)		
Income/month			30.79	0.001
Low	171 (25.56)	259 (37.98)		
Middle	230 (34.38)	232 (34.02)		
High	268 (40.06)	191 (28.01)		
Smoking status			8.07	0.018
Never	653 (97.61)	677 (99.27)		
Current	6 (0.90)	4 (0.59)		
Ever	10 (1.49)	1 (0.15)		
Alcohol drinkin	g status		7.50	0.023
Never	637 (95.22)	662 (97.07)		
Current	18 (2.69)	17 (2.49)		
Ever	14 (2.09)	3 (0.44)		
Meats intake (g.			9.44	0.024
<500	158 (23.62)	176 (25.81)		
500-999	202 (30.19)	212 (31.09)		
1000-1499	105 (15.70)	133 (19.50)		
≥1500	204 (30.49)	161 (23.61)		
Fruits intake (g/	8.21	0.042		
< 500	80 (11.96)	88 (12.90)		
500-999	145 (21.67)	151 (22.14)		
1000-1499	78 (11.66)	112 (16.42)		
≥1500	366 (54.71)	331 (48.53)		
Vegetables intal	45.59	0.001		
< 5000	240 (35.87)	311 (45.60)		
5000-9999	210 (31.39)	251 (36.80)		
≥10000	219 (32.73)	120 (17.59)		

(1.92,95%CI: 0.92-3.97). A significant increased trend in the risk of breast cancer with increasing consumption of crucian carp was observed (*P* for trend <0.001). Compared with the never intake of crucian carp, the highest intake category (≥1000g/month) had a significant increased adjusted-OR (6.09, 95%CI: 3.04-12.19). Increasing consumption of the total freshwater fish decreased ORs for breast cancer, but the test for linear trend was not statistically significant. In analyses by menopause status, the similar effect of freshwater fish intake was observed

in both post- and premenopausal women.

Table 4 shows the dose-response relationship between the consumption of fat and fatty acids from intakes of freshwater fish and the breast cancer risk. Among all study subjects, compared with the lowest quarter of intakes of the fat and fatty acids (including total fatty acid, SFA, MUFA, PUFA, n3-PUFA and n6-PUFA), women in other quarters all had a decreased adjusted-OR for breast cancer, but the tests for linear trend were not statistically significant (all *P* for trend > 0.05). Among premenopausal

Table 2. Freshwater Fish Intake and Breasd Cancer Risk

Fish intake		Cases n (%)	Controls n (%)	Crude OR (95%CI)	Adjusted OR* (95%CI)
Black carp	Never eaten	364 (54.4)	340 (49.9)	1.00	1.00
*	Eaten	305 (45.6)	342 (50.1)	0.83 (0.67-1.03)	0.66 (0.51-0.84)
Finless eel	Never eaten	378 (56.5)	273 (40.0)	1.00	1.00
	Eaten	291 (43.5)	409 (60.0)	0.51 (0.41-0.64)	0.47 (0.36-0.61)
Bream	Never eaten	233 (34.8)	174 (25.5)	1.00	1.00
	Eaten	436 (65.2)	508 (74.5)	0.64 (0.51-0.81)	0.54 (0.41-0.72)
Crucian carp	Never eaten	113 (16.9)	131 (19.2)	1.00	1.00
•	Eaten	556 (83.1)	551 (80.8)	1.17 (0.89-1.54)	0.95 (0.69-1.31)
Silver carp	Never eaten	278 (41.6)	146 (21.2)	1.00	1.00
1	Eaten	391 (58.5)	536 (78.6)	0.38 (0.30-0.49)	0.46 (0.35-0.60)
All freshwater fish	Never eaten	31 (4.6)	9 (1.3)	1.00	1.00
	Eaten	638 (95.4)	673 (98.7)	0.28 (0.13-0.58)	0.25 (0.11-0.57)

^{*}Adjusted by age, status of marriage and menstruation, age of menarche and menopause, childbirth; BMI, family history of breast cancer, income/month, status of smoking and alcohol drinking, intake of meats and fruit and vegetables

Table 3. Freshwater Fish Consumption and Breasd Cancer Risk

Fish intake	Total		Postmenopausal		Premenopausal	
(g/month)	Case/control (n)	OR (95%CI)	Case/control (n)	OR (95%CI)	Case/control (n)	OR (95%CI)
Black carp						
0,	364/340	1.00	194/197	1.00	170/143	1.00
1-499	259/294	0.66 (0.51-0.86)	144/165	0.77 (0.54-1.11)	115/129	0.59 (0.40-0.87)
≥500	46/48	0.54 (0.33-0.92)	23/28	0.42 (0.20-0.89)	23/20	0.66 (0.31-1.41)
P for trend		0.002		0.038		0.022
Finless eel						
0,	378/273	1.00	210/153	1.00	168/120	1.00
1-499	268/391	0.47 (0.36-0.61)	141/226	0.41 (0.29-0.59)	127/166	0.59 (0.41-0.86)
≥500	23/18	0.51 (0.23-1.11)	10/12`	0.50 (0.17-1.46)	13/6`	0.67 (0.20-2.18)
P for trend		< 0.001		< 0.001		0.023
Bream						
0,	233/174	1.00	120/101	1.00	113/73	1.00
1-499	288/403	0.52 (0.39-0.69)	149/226	0.50 (0.34-0.74)	139/177	0.53 (0.35-0.81)
500-999	71/91	0.37 (0.23-0.60)	46/53	0.41 (0.21-0.80)	25/38	0.30 (0.14-0.63)
≥1000	77/14	1.92 (0.92-3.97)	46/10`	1.92 (0.73-5.01)	31/4`	2.11 (0.62-7.21)
P for trend		0.251		0.574		0.240
Crucian carp						
0,	113/131	1.00	53/63	1.00	60/68	1.00
1-499	281/388	0.79 (0.56-1.10)	150/239	0.72 (0.44-1.18)	131/149	1.01 (0.61-1.66)
500-999	136/138	1.02 (0.66-1.56)	78/78	1.17 (0.62-2.20)	58/60	1.11 (0.59-2.08)
≥1000	139/25	6.09 (3.04-12.19)	80/10`	19.67 (5.76-67.23)	59/15	2.96 (1.07-8.17)
P for trend		< 0.001		< 0.001		0.003
Silver carp						
0,	278/146	1.00	155/63	1.00	123/83	1.00
1-499	273/322	0.47 (0.35-0.64)	138/182	0.32 (0.21-0.49)	135/140	0.70 (0.46-1.07)
500-999	85/145	0.39 (0.26-0.58)	45/92	0.53 (0.30-0.93)	40/53	0.84 (0.47-1.52)
≥1000	33/69	0.19 (0.11-0.33)	23/53	0.14 (0.07-0.29)	10/16`	0.35 (0.14-0.92)
P for trend		< 0.001		< 0.001		0.036
All freshwater fish						
1-499	192/173	1.00	99/90	1.00	93/83	1.00
500-999	158/227	0.60 (0.44-0.83)	81/134	0.49 (0.31-0.78)	77/93	0.81 (0.50-1.31)
1000-1499	113/119	0.65 (0.44-0.96)	55/66	0.57 (0.32-1.02)	58/53	0.91 (0.51-1.62)
≥1500	206/163	0.85 (0.58-1.26)	126/100	0.97 (0.57-1.66)	80/63	0.85 (0.46-1.55)
P for trend		0.292		0.992		0.738

^{*}ORs were adjusted by age, status of marriage and menstruation, age of menarche and menopause, childbirth; BMI, family history of breast cancer, income/month, status of smoking and alcohol drinking, intake of meats and fruit and vegetables

Table 4. Consumption of the Fat and Fatty Acid from Freshwater Fish and Breasd Cancer Risk

Fatty acids	Total		postmenopausal		premenopausal	
(g/month)	Case/control (n)	OR (95%CI)*	Case/control (n)		Case/control (n)	OR (95%CI)*
Fat						
0-16.2	175/174	1.00	92/92	1.00	83/82	1.00
16.3-29.7	139/168	0.78 (0.55-1.10)	74/102	0.63 (0.39-1.02)	65/66	1.04 (0.62-1.75)
29.8-51.6	132/172	0.60 (0.42-0.87)	57/89	0.43 (0.25-0.75)	75/83	0.91 (0.54-1.53)
≥51.7	223/168	0.95 (0.64-1.42)	138/107	1.03 (0.61-1.76)	85/61	0.85 (0.45-1.60)
P for trend		0.445		0.527		0.981
Fatty acid						
0-11.95	174/171	1.00	92/92	1.00	82/79	1.00
11.96-21.1	136/170	0.73 (0.52-1.04)	71/102	0.62 (0.38-1.00)	65/68	0.99 (0.58-1.67)
21.2-37.6	134/171	0.61 (0.42-0.88)	61/89	0.47 (0.27-0.82)	73/82	0.86 (0.52-1.51)
≥37.6	225/170	0.88 (0.89-1.30)	137/107	0.97 (0.57-1.65)	88/63	0.85 (0.45-1.60)
P for trend		0.420		0.603		0.890
SFA						
0-3.85	194/172	1.00	103/96	1.00	91/76	1.00
3.86-6.55	129/172	0.64 (0.45-0.90)	62/97	0.57 (0.35-0.92)	67/75	0.79 (0.47-1.32)
6.56-11.7	142/170	0.57 (0.40-0.82)	72/93	0.49 (0.29-0.83)	70/78	0.73 (0.43-1.24)
≥11.8	204/168	0.72 (0.49-1.06)	124/105	0.78 (0.46-1.31)	80/63	0.71 (0.38-1.31)
P for trend		0.060		0.289		0.253
MUFA						
0-4.80	176/173	1.00	93/93	1.00	83/80	1.00
4.9-8.9	145/169	0.77 (0.55-1.09)	74/100	0.63 (0.39-1.02)	71/69	1.07 (0.64-1.80)
9.0-15.4	122/170	0.54 (0.37-0.78)	55/91	0.39 (0.23-0.69)	67/79	0.78 (0.45-1.34)
≥15.5	226/170	0.90 (0.61-1.33)	139/106	1.05 (0.61-1.78)	87/64	0.81 (0.43-1.53)
P for trend	220/1/0	0.268	103,100	0.525	07701	0.630
PUFA		3 .2 33		0.020		0.000
0-2.4	182/184	1.00	93/96	1.00	89/88	1.00
2.45-4.2	129/165	0.74 (0.52-1.05)	67/104	0.52 (0.32-0.85)	62/61	1.20 (0.70-2.04)
4.3-7.2	128/164	0.65 (0.45-0.94)	60/86	0.52 (0.30-0.88)	68/78	0.89 (0.53-1.50)
≥7.3	230/169	0.98 (0.67-1.45)	141/104	1.07 (0.62-1.83)	89/65	1.00 (0.55-1.81)
P for trend	250/109	0.873	111/101	0.847	03703	0.981
n3-PUFA		0.072		0.017		0.501
0-0.78	176/171	1.00	89/88	1.00	87/83	1.00
0.79-1.35	129/174	0.69 (0.48-0.97)	68/109	0.51 (0.31-0.84)	61/65	1.04 (0.61-1.78)
1.36-2.35	133/166	0.65 (0.45-0.94)	63/87	0.54 (0.31-0.92)	70/79	0.86 (0.51-1.44)
≥2.36	231/171	0.95 (0.64-1.40)	141/106	1.06 (0.62-1.83)	90/65	0.92 (0.50-1.70)
P for trend	231/1/1	0.841	141/100	0.873	70/05	0.976
n6-PUFA		5.011		5.575		5.570
0-2.01	174/170	1.00	88/87	1.00	86/83	1.00
2.02-3.591	132/171	0.73 (0.51-1.03)	70/106	0.54 (0.33-0.89)	62/65	1.07 (0.64-1.83)
3.592-6.20	133/170	0.63 (0.44-0.90)	62/92	0.49 (0.28-0.83)	71/78	0.89 (0.53-1.49)
5.592-0.20 ≥6.21	230/171	0.94 (0.64-1.39)	141/105	1.04 (0.60-1.79)	89/66	0.95 (0.52-1.74)
P for trend	230/1/1	0.756	171/105	0.973	07/00	0.984

^{*}ORs were adjusted by age, status of marriage and menstruation, age of menarche and menopause, childbirth; BMI, family history of breast cancer, income/month, status of smoking and alcohol drinking, intake

women, there were significant reduction in breast cancer risk for the second and the third intake quartiles of the SFA, PUFA, n3-PUFA and n6-PUFA compared to the reference group who consumed the lowest quartile, but the adjusted ORs were not statistically significant in the highest intake quartile. Among premenopausal women, there were no significant association between intakes of the fat and fatty acids from freshwater fish and the risk of breast cancer.

Discussion

In this study, we analysed relationship between intakes of five common species of freshwater fish and the risk of breast cancer. We found that consumption of the black carp, finless eel, and silver carp were inversely related to

breast cancer risk, whereas consumption of crucian carp was positively related to breast cancer risk.

Freshwater fish provide a healthy source of high-quality proteins, essential vitamins, minerals and polyunsaturated fatty acids. Humans ingest eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) mainly through intake of fish. But, previous research also has shown that freshwater fish may have a high level of nocuous chemicals, such as methylmercury, polychlorinated dibenzo-p-dioxins, and dibenzofurans, organochlorine residues, and other contaminants (Dai et al., 2002; Watanabe et al., 2003; Hirunwatthanakul et al., 2006; Cheng et al., 2013; Eqani et al., 2013; Saengsawang et al., 2013; Wang et al., 2013; Lee et al., 2014), and some of them have been shown to be mutagens or animal carcinogens. Because contaminants and nutrients always coexist in freshwater fish, the risk

from contaminants and the benefit from nutrients are also concomitant via freshwater fish consumption.

Wang et al. (2013) calculated the benefit-risk quotient of the EPA and DHA vs. persistent organic pollutants via intakes of freshwater fish from Taihu Lake of China. They found that to achieve the recommended EPA and DHA intake of 250 mg/d for a healthy adult, the intakes of most fish species from the lake can cause cancer and non-cancer risks. However, the fish consumption at the rates of 44.9 g/d by Chinese would not lead to the risks for most of the fish species. Lee et al. (2014) measured seven organochlorine pesticides (OCPs) in river water of Yeongsan and Seomjin Rivers of Korea, and assessed the potential health risks of consuming OCPs from fish in the monitoring region by measuring the residual level of OCPs. They found that there is a high cancer risk associated with three OCPs. Thus, they indicated that individuals who consume large amounts of freshwater fish may be subject to a high risk of cancer. In our study, we found that when consumption of the bream and crucian carp were higher (≥1000g/month), the risk of breast cancer were clear increased. These results showed that the consumption of freshwater fish must be moderate.

Wang et al. (2013) found that the risk of consuming silver carp was generally lower than other freshwater fish species. In this study, we also found that consumption of silver carp was inversely related to breast cancer risk, whereas consumption of crucian carp was positively related to breast cancer risk. Our findings are consistent with results of Wang et al. Crucian carp is an omnivorous fish. Study results of Cheng et al. (2013) in Hong Kong showed that omnivorous fish accumulated higher concentrations of heavy metals from sediment in the pond or river than carnivorous fish. Zhuang et al. (2013) determined heavy metal accumulation in five carp species from two fishponds exposed to effluent waters from Dabaoshan mine of South China. They found that crucian carp (carassius auratus) accumulated the higher Pb, Cd, Zn, and Cu in the intestine compared with other fish species. Thus, individuals who consume large amounts of crucian carp have higher risk of breast cancer, may be associated with the contaminated degree of crucian carp by heavy metals.

Kim et al. (2009) investigated the association between fatty fish and their fatty acids intake and the incidence of breast cancer in Korean women. They found that high consumption of fatty fish is associated with a reduced risk for breast cancer, and that the intake of ω-3 fatty acids from fish is inversely associated with postmenopausal breast cancer risk. We also analysed relationship between the fat and fatty acids only from intakes of freshwater fish and the breast cancer risk. We found that moderate intakes of the SFA, PUFA, n3-PUFA and n6-PUFA from freshwater fish significantly decreased the risk of breast cancer among premenopausal women. Our results are partly similar to the finding of Kim et al. But we also found that the adjusted ORs were not statistically significant in the highest intake quartiles of the SFA, PUFA, n3-PUFA and n6-PUFA compared with the reference group who consumed the lowest quartile. Although chemical contaminants and nutrients coexist in freshwater fish may

partly explain the finding, further investigations into the dietary intake of OCPs or heavy metals and genetic factors will be important in clarifying the preventive effect of freshwater fish intake on breast cancer.

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